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1 **Fatty acid metabolism in the progression and resolution of CNS disorders**

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25 **Abstract**

26 Recent advances in lipidomics and metabolomics have unveiled the complexity of fatty acid
27 metabolism and the fatty acid lipidome in health and disease. A growing body of evidence
28 indicates that imbalances in the metabolism and level of fatty acids drive the initiation and
29 progression of central nervous system (CNS) disorders such as multiple sclerosis, Alzheimer's
30 disease, and Parkinson's disease. Here, we provide an in-depth overview on the impact of the
31 β -oxidation, synthesis, desaturation, elongation, and peroxidation of fatty acids on the
32 pathophysiology of these and other neurological disorders. Furthermore, we discuss the impact
33 of individual fatty acids species, acquired through the diet or endogenously synthesized in
34 mammals, on neuroinflammation, neurodegeneration, and CNS repair. The findings discussed
35 in this review highlight the therapeutic potential of modulators of fatty acid metabolism and the
36 fatty acid lipidome in CNS disorders, and underscore the diagnostic value of lipidome
37 signatures in these diseases.

38

39 **Keywords**

40 Central nervous system, lipids, neuroinflammation, immunometabolism, neurodegeneration,
41 remyelination.

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43 **Declaration of interest**

44 None

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48

49 **Abbreviations**

50 ABCD1, ATP-binding cassette subfamily D member 1; ACC, acetyl CoA carboxylase; ALA,
51 α -linolenic acid; ARA, arachidonic acid; CNS, central nervous system; CPT1, carnitine
52 palmitoyl transferase 1; Δ 4,5,6,9D, delta-4,5,6,9 desaturase; DHA, docosahexaenoic acid;
53 DPA, docosapentaenoic acid; EAE, experimental autoimmune encephalomyelitis; EPA,
54 eicosapentaenoic acid; ELOVL, elongation of very long chain fatty acids proteins; FASN, fatty
55 acid synthase; FAO, fatty acid β -oxidation; HNE, 4-hydroxy-trans-2-nonenal; LA, linoleic
56 acid; LCFA, long-chain fatty acid; TLR, toll-like receptor; MCFA, medium-chain fatty acid;
57 mTORC1, mammalian target of rapamycin complex 1; MUFA, monounsaturated fatty acid;
58 NSPC, neural stem and progenitor cell; OPC, oligodendrocyte precursor cell; PUFA
59 polyunsaturated fatty acid; Th1/Th17, T helper 1 cell; Treg, regulatory T cell; SCD, stearyl-
60 CoA desaturase; SCFA, short-chain fatty acid; SFA, saturated fatty acid; SPM, specialized pro-
61 resolving mediator; SREBP, sterol regulatory element binding protein; VLCFA, very-long
62 chain fatty acids; X-ALD, X-linked adrenoleukodystrophy.

63

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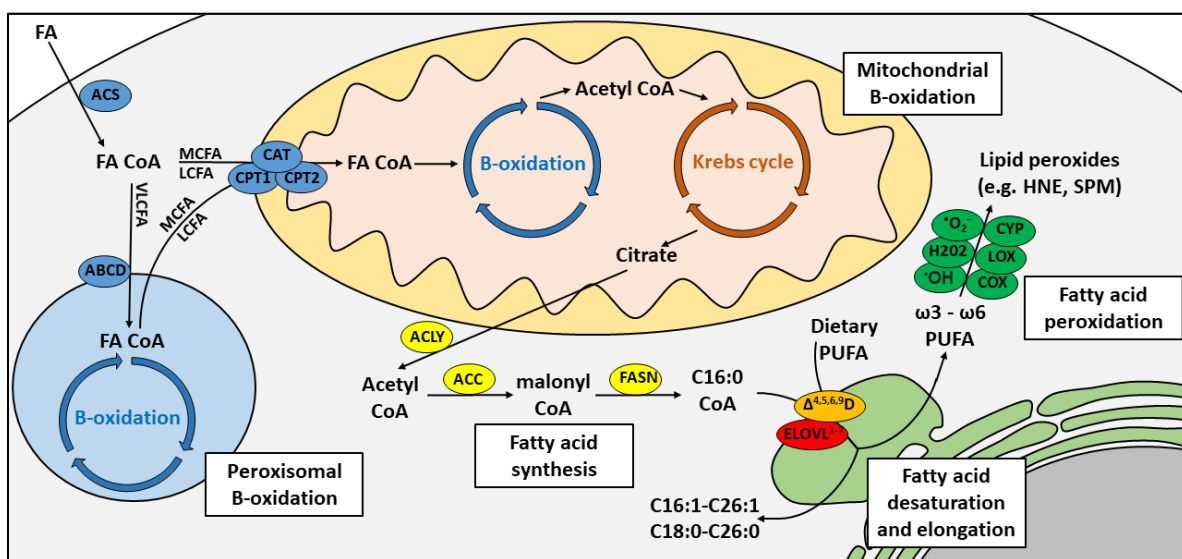
104 **1. Introduction**

105 Fatty acid metabolism consists of anabolic and catabolic processes that are necessary for energy
106 homeostasis as well as the formation of metabolic intermediates required for the maintenance
107 of cell membrane structure and function, storage of energy, and cell signaling. Recent
108 advances in technologies used to dissect and study fatty acid profiles and metabolism have shed
109 light on the pathogenic and protective role of fatty acid metabolism in health and disease. Not
110 surprisingly, given the abundance of fatty acids in the central nervous system (CNS), emerging
111 evidence indicates that fatty acid metabolism influences the pathophysiology of neurological
112 disorders, such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease. Alongside
113 the direct impact on neuronal and oligodendrocyte differentiation, function, and integrity, fatty
114 acid metabolism is key in driving both the disease-promoting and –resolving features of
115 peripheral and CNS-resident immune cell subsets. Based on these properties, modulation of
116 fatty acid metabolism is increasingly being recognized as a promising therapeutic strategy to
117 suppress neuroinflammation, prevent neurodegeneration, and even stimulate CNS repair. Here,
118 we summarize and discuss the current knowledge on the impact of fatty acid β -oxidation,
119 synthesis, desaturation, elongation, and peroxidation, on the pathology of CNS disorders.
120 Moreover, we will discuss if functional modulation of proteins and enzymes involved in these
121 metabolic processes is of therapeutic interest for CNS disorders. Finally, we will elaborate on
122 the inflammatory, neurotoxic, and neuroprotective features of individual fatty acids, as well as
123 the emerging role for their downstream bioactive lipid mediators called specialized pro-
124 resolving mediators in health and disease.

125 **2. Fatty acid β -oxidation**

126 Mitochondrial fatty acid β -oxidation (FAO) is an essential process for cellular energy
127 production, especially during fasting and intensive exercise. For FAO to initiate, fatty acids

128 first need to be activated to fatty acyl-CoAs by a family of acyl-CoA synthetases (Figure 1).
 129 Fatty acyl-CoAs are subsequently converted to acyl carnitine derivatives and transported into
 130 the mitochondrial matrix, reactions driven by the enzymes carnitine palmitoyl transferase 1
 131 (CPT1) and carnitine-acylcarnitine translocase, respectively. Within the mitochondrial matrix,
 132 CPT2 removes carnitine to regenerate fatty acyl-CoA esters, which are then repeatedly cleaved
 133 to produce acetyl-CoAs. Acetyl-CoAs are fed into the Krebs cycle and produce reducing
 134 equivalents for oxidative phosphorylation.



135
 136 **Figure 1. Schematic illustration of fatty acid anabolism and catabolism.** The β -oxidation of very long-chain
 137 fatty acids (VLCFAs) and medium- and long-chain fatty acids (MCFAs and LCFAs) is initiated in peroxisomes
 138 and mitochondria, respectively. For the initiation of fatty acid β -oxidation, fatty acids are converted to fatty acyl-
 139 CoAs (FA-CoAs) by a family of acyl-CoA synthetases (ACS). While ATP-binding cassette subfamily D (ABCD)
 140 transports VLCFA-CoAs into peroxisomes, carnitine palmitoyl transferases (CPT) and carnitine-acylcarnitine
 141 translocases (CAT) transport MCFAs and LCFAs into the mitochondrial matrix. Fatty acid synthesis
 142 starts in the cytosol with the conversion of acetyl-CoA to malonyl-CoA, a reaction driven by acetyl CoA
 143 carboxylases (ACCs) and ATP citrate lyase (ACLY, citrate to acetyl-CoA conversion). Fatty acid synthase (FASN)
 144 elongates FA-CoAs, which results in the formation of C16:0-CoA, the initial product of fatty acid synthesis.
 145 Subsequent elongation and desaturation steps, catalysed by elongases (ELOVL1-7) and desaturases (Δ 4,5,6,9D),
 146 form fatty acids of different carbon lengths and degrees of saturation. Lipid peroxidation products are formed as a
 147 consequence of oxidative stress (e.g. $\cdot\text{O}_2^-$, H_2O_2 , and $\cdot\text{OH}$) or after enzymatic conversion by cyclooxygenases

148 (COX), lipoxygenases (LOX), and cytochrome P450 (CYP). The peroxidation of unsaturated fatty acids,
149 especially PUFAs, results in formation of lipid peroxyl radicals and hydroperoxides, such as 4-hydroxy-trans-2-
150 nonenal (HNE), and specialized pro-resolving mediators (SPMs).

151 **2.1 Fatty acid β -oxidation in neuroinflammation**

152 In the last decade, it has become clear that pro-inflammatory immune cell subsets, such as
153 classically-activated M1 macrophages and T helper 1 (Th1) and 17 (Th17) cells, primarily use
154 aerobic glycolysis for sustaining their effector functions [1]. In contrast, regulatory T cells
155 (Tregs), alternatively activated M2 macrophages, and memory T cells largely rely on FAO for
156 sustaining their energy needs [1]. In line with this dichotomy, inactivation of aerobic glycolysis
157 markedly reduces neuroinflammation in animal models for Guillain-Barré syndrome, ischemic
158 brain injury, and multiple sclerosis [2-4]. Likewise, shifting microglia energy metabolism from
159 anaerobic glycolysis to oxidative phosphorylation alleviates neuroinflammation and A β burden
160 in two animal models of Alzheimer's disease [5]. Counterintuitively, mice treated with
161 etomoxir, an inhibitor of CPT1 and thus FAO, show reduced CNS inflammation and
162 demyelination in the experimental autoimmune encephalomyelitis (EAE) model, an animal
163 model of multiple sclerosis [6]. Here, etomoxir reduced inflammation by promoting apoptosis
164 of effector T cells, in particular upon glucose deprivation [6]. The mechanisms accounting for
165 the pro-apoptotic effect of etomoxir remain poorly understood. It has been proposed that
166 inhibition of FAO results in perturbations in proteins of the anti-apoptotic B cell lymphoma 2
167 family [7]. Another explanation is that etomoxir causes T cell apoptosis by reducing ATP
168 production and inducing oxidative stress [8]. Altogether, these studies indicate that FAO
169 impacts immune cell physiology, thereby likely affecting neuroinflammation.

170 **2.2 Fatty acid β -oxidation in neurodegeneration and demyelination**

171 While glucose is the main energy substrate in the CNS [9], increasing evidence supports a role
172 for FAO in neuronal and glial cell development and function. With respect to the latter, FAO

173 contributes up to 20% of the total brain energy requirement [10], and fatty acid-binding proteins
174 and carnitines are present in the CNS [11]. A recent study demonstrated that quiescent neural
175 stem and progenitor cells (NSPCs), which give rise to neurons and oligodendrocytes, rely on
176 FAO for survival and proliferation [12]. On that same note, functional peroxisomal FAO is
177 necessary to maintain glial cell integrity [13]. In X-linked adrenoleukodystrophy (X-ALD),
178 mutations in the fatty acid transporter ATP-binding cassette subfamily D member 1 (ABCD1)
179 lead to a reduced import of very-long chain fatty acids (VLCFAs) into peroxisomes and
180 decreased peroxisomal FAO. The resulting increase in intracellular VLCFAs induces
181 oligodendrocyte cell death and causes demyelination [13]. While these studies support a
182 protective role of FAO in maintaining NPSC and oligodendrocyte integrity and cell number, a
183 recent study showed that FAO can negatively impact glial cell and neuronal function as well.
184 In a mouse model of peripheral neuropathy, remodelling of lipid metabolism away from fatty
185 acid synthesis and towards oxidation depletes Schwann cells of important lipid myelin
186 components such as cerebroside and sulfatide [14]. Furthermore, elevated FAO markedly
187 increased the formation of long-chain acyl carnitines that increased axonal calcium levels and
188 promoted axon degeneration [14]. Collectively, these studies indicate that FAO is essential for
189 the function of neurons, glial cells, and NPSCs.

190 While modulation of FAO holds promise for treating neurological disorders, future studies
191 should address the abovementioned contradictions. Why does the induction of T cell apoptosis
192 by etomoxir outweigh its inflammatory impact on immune cell function, and does this still hold
193 up in experimental models that do not rely solely on T cells for induction? How does FAO
194 exactly impact the physiology of different CNS-resident cell types, and does the contribution
195 of FAO in these cells change in neurological disorders? In addition, given the reported off-
196 target effects of the golden standard FAO inhibitor etomoxir [15], there is also an urgent need
197 to develop more specific FAO inhibitors.

198 **3. Fatty acid synthesis**

199 The synthesis of fatty acids is a critical anabolic pathway in mammals. It occurs in the cytosol
200 and initiates with the carboxylation of acetyl-CoA to malonyl-CoA (Figure 1). This irreversible
201 reaction is the rate-limiting step in the synthesis of fatty acids and catalysed by acetyl CoA
202 carboxylases (ACCs). The serial condensation of seven malonyl-CoA molecules and one
203 acetyl-CoA by fatty acid synthase (FASN) eventually forms palmitate, the initial product of
204 fatty acid synthesis. Subsequent elongation and desaturation steps will produce fatty acids of
205 different lengths and degrees of desaturation, as described in section 4 and 5.

206 **3.1 Fatty acid synthesis in neuroinflammation**

207 Emerging evidence indicates that *de novo* fatty acid synthesis controls the fate of inflammatory
208 and immunosuppressive immune cell subsets. For instance, the inflammatory activation of
209 macrophages is closely associated with elevated fatty acid synthesis [16-20]. Similar,
210 impeding fatty acid synthesis, through inhibition of ACC1 and FASN, restrains the
211 development of Th17 cells and instead favors the induction of Tregs [21, 22]. In line with
212 these studies, inhibition of ACC1 and FASN attenuates the neuroinflammatory burden in the
213 EAE model by reducing the number of Th17 cells [21, 23]. Likewise, genetic depletion of
214 ACC1 in CD4⁺ T cells or pharmacological inhibition of ACC1 reduces neuroinflammation and
215 infarct volume after middle cerebral artery occlusion by altering the Treg/Th17 balance [24].
216 Indirect evidence also supports a role for fatty acid synthesis in driving neuroinflammation and
217 disease activity in Alzheimer's, Huntington's, and Parkinson's disease. In particular, the
218 mammalian target of rapamycin (mTOR), a master regulator of fatty acid lipogenesis [25], is
219 highly active in these disorders, and inhibition of mTOR complex 1 (mTORC1) signaling
220 reduces the neuroinflammatory burden and disease severity in preclinical models of these
221 neurodegenerative diseases [26-29]. However, given the pleiotropic functions of mTOR,

222 more research is warranted to define the relative contribution of reduced fatty acid synthesis
223 in the immunosuppressive and neuroprotective impact of mTOR inhibitors in these disorders.

224 **3.2 Fatty acid synthesis in remyelination**

225 Oligodendrocytes support signal transmission in the CNS by enwrapping axons with myelin,
226 which contains an exceptionally high content of fatty acid-containing glycolipids and
227 phospholipids [30]. Accurate formation of myelin is not only essential for proper developmental
228 myelination but also during remyelination that follows pathological demyelination in diverse
229 CNS disorders. While dietary fatty acids can be utilized to form myelin sheaths, increasing
230 evidence supports a role for fatty acid synthesis in this process. By depleting FASN in
231 oligodendrocyte precursor cells (OPCs), fatty acid synthesis was found to be essential for both
232 developmental myelination and remyelination after lysolecithin-induced focal demyelination
233 [31]. Likewise, while oligodendrocyte-specific deficiency of mTORC1 leads to developmental
234 hypomethylation [32], inhibition of mTOR using rapamycin impairs remyelination in the
235 cuprizone-induced remyelination model [33]. Conversely, oligodendrocyte-specific
236 hyperactivation of mTORC1 results in the formation of thinner myelin sheaths during
237 development and does not improve remyelination after lysolecithin-induced demyelination [25,
238 34]. This suggests that a precisely balanced regulation of mTORC1 in oligodendrocytes is
239 pivotal for CNS myelination and remyelination. In addition to affecting oligodendrocytes
240 directly, astrocytic fatty acid lipogenesis is key in providing OPCs with lipids for full myelin
241 membrane synthesis [35], which points towards the importance of horizontal lipid flux in
242 supplying OPCs with the necessary fatty acids for myelin formation. Collectively, these
243 findings indicate that fatty acid synthesis in oligodendrocytes and astrocytes controls the
244 formation of myelin, thereby likely influencing remyelination in CNS disorders.

245 **3.3 Fatty acid synthesis in neurogenesis and dendritogenesis**

246 Proper (re)myelination ensures efficient neuronal function and can protect axons from
247 degeneration in CNS disorders. Hence, by affecting the physiology of myelin-producing
248 oligodendrocytes, fatty acid synthesis can impact neuronal functioning. However, several
249 studies indicate that fatty acid synthesis not only changes neuronal function indirectly but also
250 in a cell-autonomous manner. For instance, FASN expression and activity is high in
251 proliferating NSPCs and its inhibition decreases NPSC proliferation [36]. By crossing
252 tamoxifen inducible nestin-promoter driven Cre mice with FASN-flox mice, the authors further
253 show that adult NSPCs require high levels of *de novo* lipogenesis for accurate neurogenesis
254 *in vivo*. Alongside promoting neurogenesis, fatty acid synthesis controls neuronal dendrite
255 expansion. Genetic knockdown of sterol regulatory element binding protein (SREBP), a crucial
256 regulator of fatty acid production, in dendritic arborization neurons decreases dendritic branch
257 length and the number of terminal endpoints, and promotes axon loss [37]. In summary, these
258 studies argue for fatty acid synthesis being essential for neuronal development, function, and
259 integrity.

260 The abovementioned studies indicate that pharmacological inhibition of fatty acid synthesis,
261 using FASN, ACC1, or mTORC1 inhibitors, may hold therapeutic promise to suppress
262 inflammation in CNS disorders. However, by doing so, one risks perturbing neurogenesis,
263 neuronal function, and remyelination, processes that are essential to prevent neurodegeneration
264 and stimulate CNS repair.

265 **4. Fatty acid elongation**

266 Fatty acid elongation occurs in the endoplasmic reticulum and relies on specific elongases
267 (Figure 1). Similar to cytosolic fatty acid synthesis, malonyl CoA is the source of added carbons
268 during elongation. In the first rate-limiting step, fatty acyl-CoAs are condensed with malonyl-
269 CoA, a reaction catalysed by elongases (elongation of very long chain fatty acids proteins,

270 ELOVL). Mammals have seven elongases (ELOVL1–7) that exhibit a tissue-specific
271 expression pattern and characteristic substrate specificity to different fatty acyl-CoAs.
272 Commonly, ELOVL1, 3, 5, 6, and 7 are involved in the elongation of monounsaturated
273 (MUFAs) and saturated fatty acids (SFAs), and ELOVL2 and 5 strictly elongate
274 polyunsaturated fatty acids (PUFAs). ELOVL4 catalyzes the formation of VLCFAs (>C26)
275 [38, 39]. While literature regarding the precise role of ELOVLs in CNS disorders is scarce,
276 mutations in ELOVLs are associated with CNS disorders such as Parkinson’s disease [40],
277 spinocerebellar ataxias [41], and neuro-ichthyotic syndrome [42]. Moreover, the expression and
278 activity of ELOVLs is closely linked to the pathophysiology of Alzheimer’s disease [43], X-
279 ALD [44], and multiple sclerosis [45].

280 **4.1 Fatty acid elongation in neuroinflammation**

281 Several studies indicate that elongases control the balance between pro- and anti-inflammatory
282 immune responses. While ELOVL1 is positively associated with the inflammatory status of
283 astrocytes in X-ALD [44], ELOVL6 reduces the inflammatory burden in preclinical models of
284 type 2 diabetes [46], non-alcoholic liver steatosis [47], and dermatitis [48]. These studies
285 suggest that inhibition of ELOVL1 and ELOVL6 may be an attractive therapeutic strategy to
286 reduce neuroinflammation. In contrast, ELOVL2-mediated synthesis of the ω 3 PUFA
287 docosahexaenoic acid (DHA) keeps macrophage and T cell polarization in check by
288 suppressing Th1/Th17 differentiation and M1 macrophage activation, and sustaining the
289 number and function of Tregs and M2 macrophages [49, 50]. Finally, the induction of T cell
290 proliferation is closely associated with an elevated expression of ELOVL5 [51]. However,
291 despite this elevated expression, ELOVL5 silencing does not impact T cell proliferation,
292 viability, or activation [51]. These studies indicate that the different elongases have a divergent
293 impact on immune cell function and that elongase-specific modulation is required to modulate
294 neuroinflammation.

295 **4.2 Fatty acid elongation in neurodegeneration and demyelination**

296 Increasing evidence points towards elongases being essential in controlling oligodendrocyte
297 and neuronal physiology in health and disease. In X-ALD patients, ELOVL1 is highly
298 expressed in oligodendrocytes and has been identified as the single elongase responsible for
299 catalyzing the toxic accumulation of VLCFAs [13, 52]. In accordance, the VLCFA-lowering
300 and neuroprotective impact of Lorenzo's oil in X-ALD partially depends on its suppressive
301 action on ELOVL1 activity [53]. In concert with the pathogenic impact of VLCFA in CNS
302 disorders, oligodendrocyte-specific *Dicer* mutant mice show abundant demyelination and
303 neuronal degeneration in the brain [54]. Elevated ELOVL7 activity was identified as one of the
304 primary molecular processes involved in driving the phenotype in these mice [54]. Of interest,
305 saturated VLCFAs formed by ELOVL4 were recently reported to prevent epileptogenesis and
306 neurodegeneration, and control presynaptic release kinetics [55, 56]. Collectively, these studies
307 indicate that excessive ELOVL1 and ELOVL7 activity promote demyelination and
308 neurodegeneration, and that ELOVL4 activity is essential to maintain synaptic transmission.

309 To date, the impact of fatty acid elongation on CNS disorders remains poorly understood. While
310 it is becoming clear that the divergent elongases impact immunity differently, the underlying
311 molecular mechanisms and fatty acids remain largely unresolved. In addition, while inhibition
312 of ELOVL1 and ELOVL7 represents a viable option to prevent neurodegeneration and
313 demyelination, its impact on CNS repair (e.g. remyelination and neuroregeneration) remains to
314 be determined. The absence of specific inhibitors of the different elongases, as well as the fact
315 that ELOVL1 and ELOVL4 knockout mice die shortly after birth [57, 58], likely explains the
316 lack of research on elongases.

317 **5. Fatty acid desaturation**

318 The desaturation of fatty acids is essential for the biosynthesis of UFAs (Figure 1). It relies on
319 specific desaturases, which require molecular oxygen and two electrons to insert double bonds
320 at specified positions within fatty acyl chains [59]. In mammals, four classes of desaturases are
321 described: delta-4 ($\Delta 4$ Ds), delta-5 ($\Delta 5$ Ds), delta-6 ($\Delta 6$ Ds), and delta-9 desaturases ($\Delta 9$ Ds), each
322 catalyzing the formation of a cis-double bond at the $\Delta 4$, $\Delta 5$, $\Delta 6$, and $\Delta 9$ position of fatty acyl-
323 CoAs, respectively. The $\Delta 4$ Ds, $\Delta 5$ Ds and $\Delta 6$ Ds are required for the formation of PUFAs, such
324 as DHA, eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and arachidonic acid
325 (ARA), from the dietary fatty acids linoleic acid (LA) and α -linolenic acid (ALA) [60]. The
326 formation of these PUFAs requires the successive actions by elongase and desaturase enzymes
327 [60]. The $\Delta 9$ Ds, also called stearoyl-CoA desaturases (SCD), catalyze the formation of MUFAs
328 (palmitoleoyl- and oleoyl-CoA) from SFAs (palmitoyl- and stearoyl-CoA) [61]. Unlike lower
329 animals and plants, mammals lack the $\Delta 12$ Ds and $\Delta 15$ Ds, which are needed to catalyse the
330 formation of linoleic acid (LA) and α -linolenic acid (ALA) [59]. Therefore, LA and ALA acid
331 are known as dietary essential fatty acids.

332 **5.1 Fatty acid desaturation in neuroinflammation**

333 Similar to the oxidation, synthesis, and elongation of fatty acids, fatty acid desaturation impacts
334 immune cell physiology. Deficiency of the $\Delta 9$ D SCD1 augments the inflammatory features of
335 effector T cells and macrophages [62-64]. Alternatively, while $\Delta 5$ D (FADS1) deficiency
336 reduces the number of Th17 cells in a colitis mouse model [65], it promotes and suppresses the
337 induction of M1 and M2 macrophage activation programs, respectively [66]. Alterations in the
338 levels of immunomodulatory $\omega 3$ and $\omega 6$ PUFAs, and pro-resolving and inflammatory lipid
339 mediators formed from these PUFAs (see section 8), likely underlie the impact of $\Delta 5$ Ds on
340 immune cell function and differentiation [65-67]. Several studies also reported a role for fatty
341 acid desaturases in controlling neuroinflammation. Transcriptomic analysis identified that
342 amyloid- β uptake by macrophages increases SCD1 expression in addition to a set of pro-

343 inflammatory genes [68]. In line with these findings, we found that myelin internalization
344 increases SCD1 expression in macrophages and that inhibition of SCD1 counters the
345 inflammatory phenotype of these cells *in vitro* and *in vivo* (unpublished data). Despite the
346 importance of ω 3 and ω 6 PUFAs in driving immune cell function (see section 7), it remains
347 unclear how changes in Δ 4D, Δ 5D, and Δ 6D activity influence neuroinflammation in CNS
348 disorders.

349 **5.2 Fatty acid desaturation in neurogenesis and neurodegeneration**

350 MUFAs and PUFAs are essential nutrients and fundamental components of neurons and
351 oligodendrocytes. Not surprisingly, desaturase activity correlates closely with the physiology
352 of these cells in health and disease. With respect to Δ 9D activity, SCD1 promotes the formation
353 of astrocytic oleic acid, which enhances neuron migration, and axon and dendrite growth [69,
354 70]. In contrast, while constitutive expression of human SCD5 promotes proliferation of mouse
355 Neuro2a cells, it suppresses retinoic acid-induced neuritogenesis and maturation [71]. These
356 findings indicate that SCD1 and SCD5 impact neuronal growth and maturation differently. In
357 yet another study, a direct link between SCD1 inhibition and synucleinopathies such as
358 Parkinson disease was demonstrated [72]. Here, inhibition of SCD1 enhanced the survival of
359 human neurons in the presence of toxic α -synuclein. To what extent these findings also hold up
360 for other CNS disorders characterized by the accumulation of toxic protein aggregates remains
361 to be determined. Yet again, while dietary supplementation with ω 3 and ω 6 PUFAs is well-
362 known to impact the integrity of neuronal and glial cells (see section 7), the importance of *de*
363 *novo* formation of PUFAs by Δ 4D, Δ 5D, and Δ 6D in this process remains unresolved. The
364 relative inactive desaturation in neurons as compared to endothelial cells and astrocytes might
365 indicate that neurons rely mainly on horizontal lipid fluxes for PUFAs [73], rendering Δ 4Ds,
366 Δ 5Ds, and Δ 6Ds redundant in these cells.

367 As clarified in the abovementioned paragraphs, the $\Delta 9$ D SCD1 represents a promising
368 therapeutic target to suppress neuroinflammation and neurodegeneration, and promote CNS
369 repair processes. Several small molecule inhibitors of SCD1 already progressed to early clinical
370 development for the treatment of metabolic disorders and cancer [74-76]. However, clinical
371 success remains to be attained, partially due the difficulty of translating lipid metabolism from
372 rodents to humans. Moreover, the accumulation of inflammatory SFAs poses a problem upon
373 prolonged treatment with SCD1 inhibitors [77]. Co-administration of PUFAs has been
374 proposed to prevent or reduce the deleterious side-effects stemming from this accumulation
375 SFAs [77]. In contrast to $\Delta 9$ Ds, evidence for the therapeutic applicability of $\Delta 4$ Ds, $\Delta 5$ Ds, and
376 $\Delta 6$ Ds to treat CNS disorders is rather limited. It is clear that the body converts the essential
377 fatty acids AL and ALA into the much needed $\omega 3$ and $\omega 6$ PUFAs. However, the relative
378 contribution of $\Delta 4$ Ds, $\Delta 5$ Ds, and $\Delta 6$ Ds in controlling $\omega 3$ and $\omega 6$ PUFAs levels in CNS-resident
379 and immune cells, as compared to dietary-derived $\omega 3$ and $\omega 6$ PUFAs, is poorly understood.

380 **6. Fatty acid peroxidation**

381 The process of lipid peroxidation occurs when oxidants such as free radicals interact with fatty
382 acids containing carbon-carbon double bonds, especially PUFAs (Figure 1). This interaction
383 involves hydrogen detachment from a carbon and oxygen insertion, and results in the formation
384 of lipid peroxy radicals and hydroperoxides [78]. Peroxidation can also be mediated by
385 enzymes such as lipoxygenases, cyclooxygenases, and cytochrome P450 [78] (Figure 1). Fatty
386 acid peroxidation products have both cytotoxic/inflammatory and cytoprotective/anti-
387 inflammatory effects. The eventual cellular outcome depends on the fatty acid substrate (e.g.
388 $\omega 3$ versus $\omega 6$ PUFAs) and pathway involved (e.g. enzymatic versus non-enzymatic) [78, 79].

389 **6.1 Fatty acid peroxidation in neuroinflammation**

390 The early observation that lipid peroxidation products are generated in atherosclerosis
391 suggested a link between fatty acid peroxidation and inflammation [80]. Indeed, aldehydes
392 derived from fatty acid peroxidation are implicated in a number of oxidative stress-induced
393 inflammatory conditions including diabetes [81], liver and kidney toxicity [82], cancer [83],
394 metabolic syndrome [84], aging [85], and ischemia [86]. Lipid peroxidation products can act as
395 precursors of important bioactive mediators of inflammation, such as the prostaglandins,
396 thromboxanes, and leukotrienes, following enzymatic conversion by cyclooxygenases,
397 lipoxygenases, and cytochrome P450 [87]. Likewise, 4-hydroxy-trans-2-nonenal (HNE), a
398 major lipid peroxidation-derived aldehyde, stimulates the inflammatory response in
399 macrophages and contributes to disease progression of atherosclerosis by inducing
400 cyclooxygenase 2 activity, prostaglandin formation, and NF- κ B activation [88, 89].
401 Alternatively, some of the lipid mediators generated from multistage enzymatic oxidation of
402 ω 3 PUFAs, such as resolvins, protectins, and maresins, support the resolution of inflammatory
403 processes (discussed in section 8) [90, 91]. Furthermore, reactive lipid oxidation products can
404 activate the anti-inflammatory peroxisome proliferator-activated receptor γ (PPAR γ) in
405 immune cells, thereby transrepressing inflammatory responses [92, 93]. In the EAE model, the
406 generation of oxidative-stress induced lipid peroxidation products seems mainly pro-
407 inflammatory as treatment with antioxidants ameliorates disease severity [94, 95]. Accordingly,
408 oxidative stress induced by lipid peroxidation precedes the inflammatory response in multiple
409 sclerosis patients [96]. Collectively, these studies indicate that lipid peroxidation products likely
410 affect neuroinflammation in CNS disorders. However, more research is needed to define the
411 fatty acid substrates and pathways involved in driving the formation of pro- and anti-
412 inflammatory lipid peroxidation products in CNS disorders.

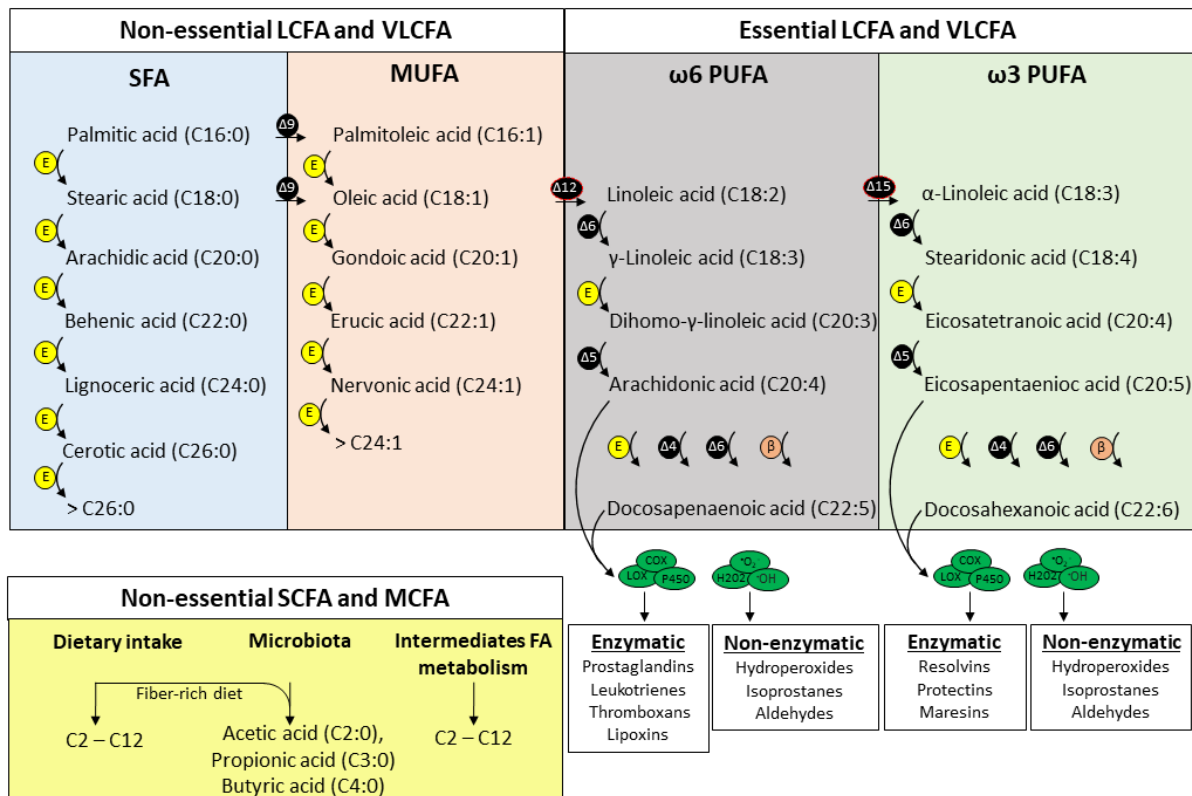
413 **6.2 Fatty acid peroxidation in neurodegeneration and CNS repair**

414 The high level of PUFAs in the brain makes it particularly vulnerable to oxidative stress and
415 fatty acid peroxidation [97]. With respect to the latter, relapsing-remitting multiple sclerosis
416 patients display heightened levels of biochemical markers of peroxidation, such as
417 malondialdehyde [96]. Lipid peroxidation products are also abundantly present in the brain,
418 cerebrospinal fluid, and plasma from patients with Alzheimer's disease [85]. Here, amyloid β
419 causes oxidative stress through its interaction with transition metal ions, such as Cu^{2+} and Zn^{2+} .
420 These metals are enriched in senile plaques ultimately leading to the formation of aggregates.
421 Hydrogen peroxide can be generated by Cu^{2+} - or Zn^{2+} -bound amyloid β using other electron
422 donors such as PUFAs, leading to the generation of toxic lipid peroxidation products such as
423 HNE [98]. An increase in lipid peroxidation products is also apparent in the substantia nigra in
424 Parkinson's disease [99]. Oligomeric α -synuclein was found to induce ROS production and the
425 peroxidation of PUFA residues within lipid membranes. The subsequent increase in lipid
426 peroxidation products is integral to α -synuclein-induced neuronal damage and neuronal death
427 [100]. Interestingly, lipid peroxidation products can be transported from neurons to
428 neighbouring astrocytes for detoxification or storage in lipid particles [101]. Horizontal transfer
429 of toxic lipid metabolites likely retains neuronal homeostasis in health and disease, but may
430 eventually also contribute to disease pathology in CNS disorders. While these studies show that
431 accumulation of oxidative stress-induced lipid peroxidation products causes neurodegeneration,
432 emerging evidence indicates that the enzymatic formation of oxygenated pro-resolving
433 mediators, such as resolvins, maresins, and protectins, reduces neuroinflammation and supports
434 CNS repair (discussed in section 8). On that same note, oxygenated derivatives of ω 3 PUFAs
435 called elovanoids were recently found to counteract oligomeric β -amyloid-induced gene
436 expression and protect photoreceptors [102]. Moreover, elovanoids protected neuronal cultures
437 undergoing either oxygen/glucose deprivation or receptor-mediated excitotoxicity, and were
438 neuroprotective in an experimental ischemic stroke model [103]. Therefore, increasing the level

439 of pro-resolving mediators and elovanoids, and decreasing that of oxidative stress-induced lipid
 440 peroxidation products is considered a promising strategy to reduce neurodegeneration and
 441 promote CNS repair.

442 7. Fatty acid chain length and saturation

443 In the previous sections, we focused on the impact of enzymes and proteins involved in the
 444 metabolism of fatty acids on CNS disorders. In the next sections, we will summarize and discuss
 445 the current knowledge on the impact of individual fatty acid species, formed through the
 446 anabolism and catabolism of fatty acids, obtained through the diet, or synthesized by the gut
 447 microbiota, on CNS disorders. We subdivided fatty acids based on their aliphatic carbon chain
 448 length. According to the chain length, fatty acids are classified as short-chain fatty acids
 449 (SCFAs, C1-6), medium-chain fatty acids (MCFAs, C7-12), long-chain fatty acids (LCFAs,
 450 C13-22), and very-long chain fatty acids (VLCFAs, > C22).



451

452 **Figure 2. Simplified figure of the origin and formation of individual fatty acids in the human body including**
453 **key enzymes involved in their synthesis.** Non-essential LCFAs and VLCFAs can be obtained from a variety of
454 dietary sources or endogenously synthesized from other fatty acids through successive desaturation (delta-9
455 desaturases, $\Delta 9D$) and elongation (E, ELOVL1, 3, 4, 6, and 7) steps. Non-essential SCFAs and MCFAs are
456 acquired through the diet, formed by the gut microbiota, or endogenously synthesized as intermediates during the
457 anabolism and catabolism of fatty acids. Given the lack of delta-12 and delta-15 desaturases ($\Delta 12D$ and $\Delta 15D$) in
458 humans, $\omega 3$ and $\omega 6$ PUFAs can only be obtained through the diet and, therefore, are called essential fatty acids.
459 Successive elongation (ELOVL2, 5, and 7), desaturation ($\Delta 4D$, $\Delta 5D$, and $\Delta 6D$), β -oxidation (β), and peroxidation
460 (enzymatic and non-enzymatic) steps result in the formation of complex polyunsaturated lipid species.

461 **7.1 Short-chain fatty acids**

462 SCFAs, such as acetic (C2:0), propionic (C3:0), and butyric acid (C4:0), are the primary end-
463 products of gastrointestinal fermentation of complex polysaccharides, found in fiber-rich diets
464 (Figure 2) [104]. Recent evidence indicates that these microbiota-derived SCFAs closely
465 regulate CNS homeostasis and neuroinflammation by affecting microglia activation and Treg
466 expansion [105, 106]. Furthermore, in experimental models of Alzheimer's disease, Parkinson
467 disease, stroke, traumatic brain injury, and infectious CNS disorders, SCFAs and derivatives
468 thereof were found to reduce amyloid β aggregation [107], protect neurons and
469 oligodendrocytes from cell death [108-111], restore blood-brain barrier permeability [112],
470 suppress neuroinflammation [111, 113], and improve memory and locomotor deficits [108, 111,
471 114, 115]. The neuroprotective impact of SCFAs likely depends in part on their ability to
472 reverse disease-associated reductions in histone deacetylation [108-111, 114-116].
473 Interestingly, multiple sclerosis patients display a depletion of bacterial species belonging to
474 clostridia XIVa and IV cluster, which produce SCFAs, such as propionate and butyrate [117].
475 Likewise, changes in gut microbiota are associated with a reduced presence of SCFAs in
476 patients with Parkinson's disease [118]. These microbial imbalances might promote the
477 neuroinflammatory burden in multiple sclerosis and Parkinson's disease. To what extent

478 microbial imbalances in these CNS disorders originate from environmental factors or disease-
479 associated processes remains to be determined. Collectively, these findings stress the beneficial
480 impact that gastrointestinal bacteria-derived SCFAs have on the healthy, inflamed, and
481 damaged CNS.

482 **7.2 Medium-chain fatty acids**

483 MCFAs, such as caprylic (C8:0), nonanoic (C9:0), capric (C10:0), and lauric acid (C12:0), are
484 mainly acquired through our diet by consumption of milk fat, coconut oil, and pelargonium oil
485 (Figure 2). MCFAs markedly increase the differentiation of Th1 and Th17 cells, and decrease
486 that of Tregs *in vitro* [106]. A lauric acid-rich diet mimics these immunological changes *in vivo*
487 and enhances CNS autoimmunity in the EAE model [106]. Gut microbiota were found to be
488 crucial in driving changes in the immunological landscape in these animals, likely by increasing
489 the concentration of MCFAs and LCFAs, and decreasing that of SCFAs. Aside from having a
490 direct impact on T cell polarization, caprylic acid can enhance the neuroinflammatory burden
491 by disrupting blood-brain barrier integrity [119]. While *in vivo* evidence is largely lacking,
492 MCFAs might boost neuroinflammation by activating the G-protein coupled receptor 84
493 (GPR84) [120]. GPR84 is highly expressed by T cells, neutrophils, macrophages, and microglia
494 [121], and its activation enhances the pro-inflammatory properties of these cells [120, 122-126].
495 Moreover, ample evidence indicates that GPR84 is highly expressed on activated microglia in
496 diverse animal models of CNS pathologies [122, 126-128]. Unexpectedly, while GPR84
497 deficiency reduces microgliosis, it accelerates the number of degenerating dendrites in
498 APP/PS1 mice [128]. The latter study indicates that GPR84, and thus likely MCFAs, are crucial
499 in maintaining dendritic homeostasis. In line with this protective role of MCFA, nonanoic and
500 capric acid enhance seizure control activity and provide protection against neuronal loss in
501 *in vitro* seizure and *in vivo* epilepsy models [129, 130]. These findings can partially explain
502 the therapeutic efficacy of a medium-chain triglyceride ketogenic diet on childhood epilepsy

503 [131], Alzheimer's disease [132, 133], and Huntington disease [134]. In summary, while
504 MCFAs promote inflammation, studies indicate that they maintain neuronal and
505 oligodendrocyte integrity in CNS disorders as well.

506 **7.3 Long-chain fatty acids**

507 LCFAs can be obtained from a variety of dietary sources or endogenously synthesized from
508 other fatty acids (Figure 2). The impact of LCFAs on neuroinflammation and
509 neurodegeneration largely depends on their saturation level. Hence, LCFAs were subdivided
510 into saturated, monounsaturated, and polyunsaturated LCFAs.

511 **7.3.1 Saturated long-chain fatty acids**

512 Saturated LCFAs such as myristic (C14:0), palmitic (C16:0), stearic (C18:0), arachidic (C20:0),
513 and behenic acid (C22:0) are generally regarded to promote the proliferation and differentiation
514 of inflammatory T cell, astrocyte, and microglia/macrophage subsets [106, 135-140]. In
515 accordance, dietary supplementation with saturated LCFAs promotes neuroinflammation in
516 diverse experimental animal models [106, 137, 140, 141]. Given the structural similarity
517 between saturated LCFAs and the lipid portion of bacterial lipopolysaccharide (LPS), they are
518 suggested to impact inflammation by ligating the toll-like receptor (TLR) 2 and 4 [138-140].
519 Several studies demonstrated that saturated LCFAs reduce neuronal and glial cell integrity in
520 health and disease as well. For instance, palmitic acid reduces the survival of NSPCs and
521 hypothalamic neurons, and negatively impacts hippocampal neurogenesis [142, 143]. Similar,
522 palmitic and stearic acid induce hyperphosphorylation of tau in cortical neurons by affecting
523 the secretory profile of astrocytes [144]. Finally, diets high in saturated fatty acids increase the
524 level of neurotoxic α -synuclein and amyloid β , and reduce the number of OPCs and mature
525 oligodendrocytes in experimental mouse models [145-147]. Altogether these studies provide
526 evidence that saturated LCFAs are inflammatory and neurotoxic, explaining the positive

527 correlation between LCFAs and disease progression in multiple sclerosis and Alzheimer's
528 disease [148, 149].

529 **7.3.2 Monounsaturated long-chain fatty acids**

530 In contrast to saturated LCFAs, the majority of studies report that monounsaturated LCFAs
531 such as palmitoleic (C16:1), oleic (C18:1), gondoic (C20:1), and erucic acid (C22:1) are anti-
532 inflammatory *in vitro* [150-153], and reduce neuroinflammation *in vivo* [154-156]. While direct
533 evidence is lacking, monounsaturated LCFAs may impact neuroinflammation through
534 activation of the anti-inflammatory receptors GPR120 and PPARs [156-159]. Oleic and
535 palmitoleic acid have also been extensively scrutinized for their neuroprotective effects.
536 Astrocytic oleic acid promotes neuronal differentiation and migration as well as
537 oligodendroglial myelination during brain development [35, 69, 70, 160]. On that same note,
538 oleic and palmitic acid increase the viability, proliferation, and stemness of embryonic neural
539 stem cells [161]. Finally, in experimental animal models of Alzheimer's disease, oleic acid
540 supplementation increases the non-amyloidogenic cleavage of amyloid precursor protein and
541 reduces amyloid β plaque load in the brain [162]. Despite of these protective properties,
542 monounsaturated LCFAs have neurotoxic features as well. By using a yeast
543 proteinopathy model, oleic and palmitoleic acid were found to promote α -synuclein toxicity
544 [72]. Furthermore, they stimulate the assembly of amyloid β and tau filaments, and the cytotoxic
545 aggregation of amyotrophic lateral sclerosis-linked superoxide dismutase 1 mutants *in vitro*
546 [163-165]. Collectively, these findings indicate that monounsaturated LCFAs can reduce
547 neuroinflammation and promote CNS repair. However, they can also stimulate the formation
548 of cytotoxic protein aggregates in CNS disorders. Future studies should correlate reported
549 changes in oleic acid levels in patients with Alzheimer's disease and multiple sclerosis to
550 disease progression and remission in these disorders [166-170].

551 **7.3.3 Polyunsaturated long-chain fatty acids**

552 In contrast to saturated and monounsaturated LCFAs, the brain primarily maintains levels of
553 polyunsaturated LCFAs via the uptake from dietary sources through diffusion over the blood-
554 brain barrier [171]. The general consensus is that ω 3 PUFAs, such as ALA (C18:3), EPA
555 (C20:5), and DHA (C22:6), are anti-inflammatory in CNS disorders. Dietary supplementation
556 with these ω 3 PUFAs reduces the neuroinflammatory burden in diverse experimental models
557 [172, 173], likely by suppressing the activation of the NLRP3 inflammasome [174], the
558 differentiation of Th17 cells [175], and the migratory capacity of leukocytes [176].
559 Accordingly, ω 3 PUFA supplementation is associated with a reduced inflammatory burden in
560 Alzheimer's disease [177], Parkinson disease [178], and multiple sclerosis [179]. Similar to
561 monounsaturated LCFAs, ω 3 PUFAs are hypothesized to reduce inflammation by activation of
562 GPR120 and PPARs [180, 181]. However, the anti-inflammatory effects of ω 3 PUFAs may
563 also be explained by the fact that they act as precursors of anti-inflammatory specialized pro-
564 resolving lipid mediators (discussed in section 8) [182, 183]. As opposed to ω 3 PUFAs, ω 6
565 PUFAs were for a long time considered to promote the inflammatory features of immune and
566 glial cells, mainly because ARA (C20:4) is a precursor of pro-inflammatory eicosanoids, such
567 as prostaglandins, thromboxanes, and leukotrienes [65, 184-187]. Indeed, by using the fat-1
568 mouse model, in which ω 3 PUFAs are endogenously formed from ω 6 PUFAs, a reduced
569 neuroinflammatory burden in experimental models for Alzheimer's disease and depression was
570 observed [188, 189]. Conversely, oral feeding of ω 6 PUFAs attenuates the disease course of
571 acute and chronic EAE [190], and emerging evidence indicates that ω 6 PUFAs have anti-
572 inflammatory properties in cardiovascular disorders [191, 192]. In concordance with these
573 studies, a Cochrane review of randomized dietary trials for multiple sclerosis did not observe a
574 significant effect of ω 6 PUFA supplementation on disease progression and relapse rate in
575 multiple sclerosis patients [193]. The latter findings might be explained by the wide variety of
576 the eicosanoids produced by ω 6 PUFAs, some of which possess pro-inflammatory features

577 [184]. Moreover, a biphasic activity of ω 6 PUFAs has been reported, with ω 6 PUFAs having a
578 role in both the initiation and resolution of inflammation and tissue repair [194], a process called
579 lipid mediator class switching [195]. Finally, stable isotope studies defined limited conversion
580 of dietary LA supplementation to AA in humans [196].

581 Approximately one-third of the lipids in the CNS are polyunsaturated LCFAs. Not surprisingly,
582 changes in the levels of these lipid species impact the formation, integrity, and function of glial
583 and neuronal cells in health and disease. For instance, ω 3 PUFAs promote the differentiation
584 of neurons [197-199], and support neurite growth in hippocampal, cortical, and sensory neuron
585 cultures [200, 201]. DHA was further found to stimulate oligodendrocyte progenitor maturation
586 and prevent the maturational arrest induced by TNF α [202, 203]. In accordance with these
587 studies, by using the fat-1 mouse model or dietary intervention, an increase in ω 3 PUFAs
588 improves neuronal and oligodendrocyte survival, and attenuates remyelination in experimental
589 animal models [188, 204-209]. In contrast to ω 3 PUFAs, ω 6 PUFAs such as ARA can induce
590 neuronal cell death through lipoxygenase- and cytochrome P450-catalyzed pathways [210].
591 Cellular release of ARA was even found to underlie neuronal cell death upon exposure to
592 soluble amyloid β peptides [210, 211]. An early study further demonstrated that ARA is also
593 an effective inhibitor of sodium currents and synaptic transmission in cultured striatal neurons
594 [212], which might cause maladaptive neurotransmission in CNS disorders. In support of these
595 studies, dietary ARA supplementation amplifies A β oligomer neurotoxicity and promotes
596 cognitive decline in animal models of Alzheimer's disease [213, 214]. However, ω 6 PUFAs are
597 also reported to have neuroprotective features. ARA supplementation can compensate for
598 changes in ω 6 PUFA levels and deficits in motor activity and coordination during development
599 in Δ 6D deficient mice [215, 216]. Even more, maternal ARA supplementation improves
600 neurodevelopment in young adult offspring [217]. These studies suggest that ω 6 PUFAs are

601 neurotoxic in excess but necessary for early brain development. On the other hand, these
602 findings might merely reflect the dual role that ω 6 PUFAs have on cell physiology [184, 194].

603 **7.4 Very long-chain fatty acids**

604 Saturated and monounsaturated VLCFAs, such as nervonic (C24:1), montanic (C28:0), and
605 cerotic acid (C26:0), are primarily derived through elongation of LCFAs. Polyunsaturated
606 VLCFAs are formed through the elongation and desaturation of the essential fatty acids ALA
607 and LA. Given the highly elevated levels of VLCFAs in X-ALD patients [218, 219], most
608 evidence concerning the role of VLCFAs in CNS disorders originates from studies in these
609 patients and analogous experimental models. For example, elevated plasma and CNS levels of
610 VLCFAs correlate with the level of inflammatory mediators in X-ALD patients [220, 221]. As
611 VLCFA metabolism is primarily affected in monocytes in X-ALD patients [222], the observed
612 inflammatory changes are likely due to an elevated inflammatory status of these cells.
613 Correspondingly, macrophages exposed to VLCFAs or deficient in ABCD1, the causative gene
614 in X-ALD, display an inflammatory phenotype, increased level of intracellular ROS, and
615 accumulation of inflammatory crystalline structures [223-226]. A number of studies further
616 demonstrated that the intracellular accumulation of VLCFAs promotes astrocytic generation of
617 TNF, IL1 β , NO, and ROS [227, 228]. Collectively, these studies provide evidence that
618 excessive accumulation of VLCFAs promotes the inflammatory activation of macrophages,
619 microglia, and astrocytes.

620 VLCFAs are well-documented to negatively impact neuronal and oligodendrocyte physiology.
621 Exposure to high levels of VLCFAs, such as C24:0 and C26:0, induces mitochondrial,
622 lysosomal, and peroxisomal dysfunction, and stimulates neuronal, astrocyte, and
623 oligodendrocyte cell death [229-232]. Of all CNS-resident cell types, oligodendrocytes are most
624 vulnerable to the cytotoxic effect of VLCFAs [13, 231, 232]. Interestingly, treatment with a
625 histone deacetylase inhibitor corrects the derangement of VLCFA levels and counteracts

626 oligodendrocyte loss [13, 232]. While these studies indicate that organelle dysfunction and
627 aberrant histone acetylation underlie the cytotoxic features of VLCFAs, other studies suggest
628 that VLCFAs can directly destabilize and permeabilize membranes [233], thereby promoting
629 necroptosis, a programmed form of necrosis [234]. Necroptosis is a common pathological
630 feature in CNS disorders, including multiple sclerosis, Alzheimer's disease, and Parkinson's
631 disease [235]. In line with the detrimental impact of VLCFAs on neuronal and glial cells *in*
632 *vitro*, extensive demyelination and neurodegeneration is apparent in the CNS of X-ALD
633 patients and associated animal models [236]. Although direct evidence for a disease-promoting
634 role of VLCFAs in other CNS disorders is lacking, VLCFA levels are increased in the serum
635 and CNS of patients suffering from multiple sclerosis and Alzheimer's disease [45, 237, 238].
636 Moreover, emerging evidence links peroxisomal dysregulation to these and other neurological
637 disorders [239]. Interestingly, while the latter studies indicate that long-term increases in
638 VLCFAs in the CNS can initiate or promote neurodegenerative events, recent studies indicate
639 that ω 3 PUFA-derived elovonoids and saturated VLCFA formed through ELOVL4 are
640 neuroprotective and essential for proper synaptic transmission [55, 56, 102, 103]. Future studies
641 should define whether the abundance of these newly identified protective VLCFA is associated
642 with disease remission in CNS disorders.

643 **8. Specialized pro-resolving mediators**

644 Fatty acids, and in particular essential PUFAs, are themselves precursors for a variety of
645 bioactive lipid mediators that have a broad range of biological functions. One of the most
646 important function is that they play a pivotal role in the control of both acute and chronic
647 inflammatory responses, a process known as the resolution of inflammation [90]. This
648 counteractive and tissue protective process is orchestrated by a new genus of bioactive lipids
649 called specialized pro-resolving mediators (SPMs), including lipoxins, resolvins, maresins, and
650 protectins [90, 240]. The biosynthesis of SPMs is initiated by the enzymatic addition of oxygen

651 to four dietary fatty acids, namely, ω 6 AA, ω 3 EPA, ω 3 DHA, and ω 3 DPA, by means of the
652 concerted action of lipoxygenase isozymes, cyclooxygenase 2, and, to a lesser extent,
653 cytochrome P450 (Figure 2) [240]. Initially, the resolution phase was thought to be a passive
654 process, but is now recognized as an active event initiated at the start of an inflammatory
655 response [241]. Similar to Virchow's cardinal signs of inflammation, like rubor (redness), calor
656 (heat), tumor (swelling), dolor (pain) and functio laesa (loss of function), there are five cardinal
657 signs of resolution [183, 242]. One of the key cardinal signs of resolution is cell clearance, in
658 which neutrophil apoptosis occurs and, as a consequence, efferocytosis through recruited
659 monocyte-derived macrophages ensues [243, 244]. The other four cardinal signs are cessation
660 of leukocyte recruitment, counter regulation of pro-inflammatory mediators, transition from
661 classical activated macrophages to a more alternative phenotype, restoration of vascular
662 integrity and re-entering of leukocytes in the vasculature and lymphatics [183, 242]. In general,
663 SPMs are potent resolution agonists that extinguish the eicosanoid-induced inflammation by
664 activating local resolution programs [245], via five separate G protein-coupled receptors;
665 ALX/FPR2, GPR32/DRV1, ChemR23/ERV, BLT1 and GPR18/DRV2 [246]. During
666 resolution of inflammation, the very same cells recruited to the inflammatory milieu, undergo
667 a temporal lipid mediator class switch, whereby they stop producing classical eicosanoids from
668 ω 6 AA and start to biosynthesize SPMs [195]. In addition, SPMs are produced in coordinated
669 waves, with lipoxins appearing earlier and resolvins, protectins, and maresins being produced
670 later during an inflammatory response [246]; therefore, they act in a time- and cell-dependent
671 manner.

672 Since the identification of SPMs in human samples relies on liquid chromatography-tandem
673 mass spectrometry (LC-MS-MS)-based approaches and internal standards have only recently
674 become available [247], it is now possible to consider that a failed resolution response may be
675 a universal cause of chronic (neuro-)inflammatory disorders [248]. For example, it has recently

676 been shown that LXA₄ is decreased in the brain and CSF of patients with Alzheimer's disease,
677 and that LXA₄ and RvD1 levels in the CSF positively correlate with mini-mental state
678 examination scores [249]. In line with these findings, levels of MaR1, PD1, and RvD5 are
679 reduced in the entorhinal cortex of patients with Alzheimer's disease [250], thereby providing
680 more evidence of a disturbed resolution pathway in Alzheimer's disease [251]. Moreover, our
681 recent findings indicate that such resolution defects are also apparent in multiple sclerosis and
682 that SPM signatures can be used to stratify patients according to their disease phase [252].
683 Further human studies are needed to reveal resolution defects in other neurological disorders
684 that are characterized by uncontrolled or chronic inflammation to facilitate clinical translation
685 of SPM supplementation. Results from preclinical disease models are encouraging and suggest
686 that treatment of inflammation-associated diseases might be possible with SPM agonists that
687 stimulate resolution and protect organs from collateral damage [253]. Moreover, in
688 experimental animal models of spinal cord injury, lamellar keratectomy, and Alzheimer's
689 disease, exogenous administration of SPMs, such as MaR1, PD1, and LXA₄, results in reduced
690 neuroinflammation, decreased levels of amyloid beta and phosphorylated-tau, neuroprotection,
691 and functional neurological recovery [254-257]. These studies indicate that treatment with
692 SPMs represents a promising therapeutic strategy to reduce neuroinflammation and stimulate
693 CNS repair simultaneously.

694 **9. Advances and challenges in lipidomics**

695 In contrast to genomics, transcriptomics, and proteomics, progress in developing global
696 lipidomics has fast-tracked only recently due to considerable advancements in the lipidomic
697 'pipeline'. Great progress has been made in defining solvents that recover lipid classes that
698 differ in polarity and abundance [258-260], and internal standards for uncommon lipid classes
699 are becoming available [247]. Also, the generation of publically available lipid databases and
700 tools to place lipidomics data in a biological context has been essential for progress in the field

701 [261-263]. Furthermore, the development of soft ionization mass spectrometry techniques, such
702 as electrospray ionization (ESI) [264], desorption electrospray ionization (DESI) [265],
703 and matrix-assisted laser desorption/ionization (MALDI) [266], has spurred the advent of
704 lipidomics. Soft ionization mass spectrometry techniques enabled researchers to quantitatively
705 and qualitatively define an unprecedented number of lipids species in biological samples, even
706 in crude lipid extracts without prior chromatographic separation, so called 'shotgun' lipidomics
707 [267]. Moreover, MALDI mass spectrometry imaging (MALDI-MSI) is becoming an important
708 tool to unravel the spatial distribution of lipid species in health and disease, and an increasing
709 number of studies apply MALDI-MSI to establish the regional distribution of lipids in the CNS
710 [268, 269]. In future studies, MALDI-MSI will undoubtedly be invaluable to confirm reported
711 brain region-specific differences in the presence and incorporation of ω 3 PUFA and
712 phospholipids in health and disease [270-273]. So far, the relatively low spatial resolution has
713 hampered single-cell analysis using MALDI-MSI. However, we recently managed to obtain
714 lipid spectra from pixels as small as 6 μ m in human post-mortem brain tissue [269]. This high
715 spatial resolution will pave the way for extensive single cell lipidomics in the healthy and
716 diseased brain in the near future.

717 Despite of these advances, there are still many hurdles to overcome. A first challenge is
718 associated with the immense complexity and structural diversity of lipids, and relates in part to
719 the inability of existing extraction, separation, and fractionation methods to fully resolve
720 individual lipids species in complex lipid extracts [274]. With respect to the latter, any single
721 extraction, separation, and fractionation procedure is bound to generate a bias toward particular
722 lipid species at the expense of others. Another challenge is related to the inability of current
723 mass lipidomics techniques to provide sufficient structural detail and resolution to distinguish
724 isomeric lipid populations and the location of double bonds [274, 275]. To date, this
725 shortcoming has prohibited the annotation of complex lipids including glycerophospholipids.

726 On a similar note, current mass spectrometry methods are not inherently quantitative, as lipid
727 ion abundance does not necessarily match its concentration but is also affected by experimental
728 factors, such as sample preparation and mass spectrometry steps [274]. Finally, there remains
729 substantial methodological diversity amongst different laboratories, and efforts to align
730 methodologies have proven challenging [276]. By overcoming the abovementioned challenges,
731 lipidome coverage and reproducibility between laboratories will significantly increase.

732 **10. Summary and therapeutic possibilities**

733 Advances in lipidomics and metabolomics have unveiled the complexity of fatty acid
734 metabolism and the fatty acid lipidome in CNS disorders. However, despite of these advances,
735 it remains challenging to modulate fatty acid metabolism in such a way that it reduces
736 neuroinflammation and neurodegeneration, and simultaneously promotes CNS repair. For
737 instance, while inhibitors of fatty acid β -oxidation (CPT1a), synthesis (ACC1 and FASN), and
738 desaturation (SCD1) hold great therapeutic promise to suppress neuroinflammation, studies
739 found that they also reduce neuronal and oligodendrocyte differentiation and integrity. By
740 using liposomes or nanoparticles, one could specifically target immune cells, thereby
741 circumventing the neurotoxic properties of these inhibitors. Alternatively, it would be
742 worthwhile to define whether the absence or accumulation of particular fatty acid species
743 underlies the detrimental impact of the abovementioned inhibitors on neuronal and
744 oligodendrocyte physiology. Combinatorial therapies might prove to be a promising strategy
745 to correct for such detrimental changes in the fatty acid lipidome. With respect to the latter, co-
746 administration of ω 3 PUFAs has been proposed to prevent or reduce the deleterious side-effects
747 originating from the accumulation SFAs upon treatment with an SCD1 inhibitor [77].

748 As touched upon in this review, fatty acids can have both beneficial and detrimental effects
749 on CNS disorders, depending on the carbon chain-length and degree of desaturation. SCFAs,

750 monounsaturated LCFAs, ω -3 PUFAs, elovanooids, and SPMs are suggested to resolve
751 neuroinflammation, prevent neurodegeneration, and even stimulate CNS repair. Hence, dietary
752 supplementation with these fatty acids may reduce disease severity in CNS disorders. In
753 contrast, given their inflammatory and neurotoxic features, excessive consumption of MCFAs,
754 saturated LCFAs, and VLCFAs should be avoided. However, one should keep in mind that
755 these findings stem primarily from *in vitro* and *ex vivo* culture models, and *in vivo* animal
756 models. As species-specific differences in fatty acid metabolism are reported, care should be
757 taken when extrapolating findings to humans. To illustrate, despite abundant evidence in
758 experimental models, a systematic review found that ω 6 PUFA and ω 3 PUFA supplementation
759 does not significantly impact disease progression in multiple sclerosis patients [193]. In
760 addition, emerging evidence indicates that the lipid class in which fatty acids are incorporated
761 (e.g. phospholipids, sphingolipids, and ceramides) affects their impact on CNS disorders.
762 Hence, future studies should define to what extent fatty acids present in different lipid classes
763 modulate the pathology of CNS disorders. Finally, while CNS disorders show considerable
764 overlap in their lipidome signatures, disease-associated changes in particular fatty acid-
765 containing lipid species are reported. These lipid imbalances might call for disease-specific
766 dietary interventions or lipid-based therapies.

767 To date, numerous randomized, double-blinded, placebo-controlled clinical trials have been
768 undertaken to study the impact of fatty acid supplementation on neurodegenerative disorders,
769 often with mixed results. To illustrate, in Parkinson's disease, supplementation with ω 3 PUFAs
770 from fish oil (180 mg EPA and 120 mg DHA) in combination with vitamin E reduced
771 depressive symptoms but did not impact the level of disability [277]. Conversely,
772 supplementation with ω 3 PUFAs (1000 mg total) from flaxseed oil in combination vitamin E
773 did reduce the level of disability Parkinson's disease patients [278]. In subjects with mild to
774 moderate Alzheimer's disease, daily ω 3 PUFAs supplementation (1720 mg DHA and 600 mg

775 EPA) did not improve cognitive function but ameliorated depressive symptoms in non-APOE ϵ 4
776 carriers [279, 280]. By using different doses and source of ω 3 PUFA, other clinical trials studied
777 either corroborated or contradicted these studies [281-284]. Of interest, supplementation with
778 Souvenaid, a complex mixture including ω 3 PUFAs and choline, improved memory
779 performance in drug-naïve Alzheimer's disease patients but not in an alike patient population
780 taking FDA-approved symptomatic treatments [285-289]. Also in multiple sclerosis and
781 Huntington disease, clinical trials reported conflicting outcomes on the impact of ω 3 PUFAs
782 on pathological and disability measures [193, 290, 291]. Potential causes for the controversial
783 outcome of the abovementioned clinical trials, as well as those using other fatty acid containing
784 lipid species such as ω 6 PUFAs, phospholipids, and ketogenic diets [292, 293], include
785 differences in 1) the source (*e.g.* plant versus animal) and dosing of lipids, 2) supplementation
786 of co-factor mixtures, 3) patient population characteristics (*e.g.* age, disease status, and
787 treatment regime), 4) trial duration and clinical endpoint measures, and 5) potential disease-
788 associated disturbances in lipid metabolism. Also, the relatively small patient populations used
789 in the majority studies makes it challenging to draw meaningful conclusions. Another major
790 issue concerns the relative lack of knowledge about the spatial distribution of lipids in the
791 healthy and diseased CNS. Increasing evidence indicates brain region-specific differences in
792 the presence and incorporation of fatty acids in disease and following dietary supplementation,
793 respectively [270-273]. An extensive analysis of region- and cell-specific lipidome signatures
794 using MALDI-MSI in the healthy and diseased CNS is likely to enable researchers to pinpoint
795 exact lipid requirements and formulate well-founded, disease-specific dietary formulas.

796 Changes in the fatty acid lipidome are apparent in plasma and CSF samples of patients with
797 neurological disorders, as discussed in sections 7 and 8. Hence, fatty acid profiling has the
798 potential to become a viable method to monitor the prognosis, diagnosis, and response to
799 therapies in these disorders in the near future. However, gender-, ethnic-, gut microbiota-, and

800 diet-induced alterations in fatty acid composition complicate the identification of disease- and
801 therapy-specific lipidome signatures. Moreover, applying lipidomics to monitor these disease-
802 and therapy-associated changes in the clinic requires the development of standard operation
803 procedures (e.g. protocols, lipid standards, data handling and quantification). However, to date,
804 there remains substantial methodological diversity amongst different laboratories, and efforts
805 to align methodologies have been rather limited [276]. Once these methodological issues are
806 resolved, lipidomics will become an important diagnostic approach in the clinic.

- 808 [1] L.A. O'Neill, R.J. Kishton, J. Rathmell, A guide to immunometabolism for immunologists, *Nature*
809 *reviews. Immunology*, 16 (2016) 553-565.
- 810 [2] M.D. Kornberg, P. Bhargava, P.M. Kim, V. Putluri, A.M. Snowman, N. Putluri, P.A. Calabresi, S.H.
811 Snyder, Dimethyl fumarate targets GAPDH and aerobic glycolysis to modulate immunity, *Science*, 360
812 (2018) 449-453.
- 813 [3] R.T. Liu, M. Zhang, C.L. Yang, P. Zhang, N. Zhang, T. Du, M.R. Ge, L.T. Yue, X.L. Li, H. Li, R.S. Duan,
814 Enhanced glycolysis contributes to the pathogenesis of experimental autoimmune neuritis, *Journal of*
815 *neuroinflammation*, 15 (2018) 51.
- 816 [4] Y. Li, B. Lu, L. Sheng, Z. Zhu, H. Sun, Y. Zhou, Y. Yang, D. Xue, W. Chen, X. Tian, Y. Du, M. Yan, W.
817 Zhu, F. Xing, K. Li, S. Lin, P. Qiu, X. Su, Y. Huang, G. Yan, W. Yin, Hexokinase 2-dependent
818 hyperglycolysis driving microglial activation contributes to ischemic brain injury, *J Neurochem*, 144
819 (2018) 186-200.
- 820 [5] R.Y. Pan, J. Ma, X.X. Kong, X.F. Wang, S.S. Li, X.L. Qi, Y.H. Yan, J. Cheng, Q. Liu, W. Jin, C.H. Tan, Z.
821 Yuan, Sodium rutin ameliorates Alzheimer's disease-like pathology by enhancing microglial amyloid-
822 beta clearance, *Sci Adv*, 5 (2019) eaau6328.
- 823 [6] L.P. Shriver, M. Manchester, Inhibition of fatty acid metabolism ameliorates disease activity in an
824 animal model of multiple sclerosis, *Sci Rep*, 1 (2011) 79.
- 825 [7] I. Samudio, R. Harmancey, M. Fiegl, H. Kantarjian, M. Konopleva, B. Korchin, K. Kaluarachchi, W.
826 Bornmann, S. Duvvuri, H. Taegtmeier, M. Andreeff, Pharmacologic inhibition of fatty acid oxidation
827 sensitizes human leukemia cells to apoptosis induction, *The Journal of clinical investigation*, 120
828 (2010) 142-156.
- 829 [8] L.S. Pike, A.L. Smift, N.J. Croteau, D.A. Ferrick, M. Wu, Inhibition of fatty acid oxidation by
830 etomoxir impairs NADPH production and increases reactive oxygen species resulting in ATP depletion
831 and cell death in human glioblastoma cells, *Biochimica et biophysica acta*, 1807 (2011) 726-734.
- 832 [9] U. Funfschilling, L.M. Supplie, D. Mahad, S. Boretius, A.S. Saab, J. Edgar, B.G. Brinkmann, C.M.
833 Kassmann, I.D. Tzvetanova, W. Mobius, F. Diaz, D. Meijer, U. Suter, B. Hamprecht, M.W. Sereda, C.T.
834 Moraes, J. Frahm, S. Goebbels, K.A. Nave, Glycolytic oligodendrocytes maintain myelin and long-term
835 axonal integrity, *Nature*, 485 (2012) 517-521.
- 836 [10] D. Ebert, R.G. Haller, M.E. Walton, Energy contribution of octanoate to intact rat brain
837 metabolism measured by ¹³C nuclear magnetic resonance spectroscopy, *The Journal of neuroscience*
838 *: the official journal of the Society for Neuroscience*, 23 (2003) 5928-5935.
- 839 [11] R.W. Mitchell, G.M. Hatch, Fatty acid transport into the brain: of fatty acid fables and lipid tails,
840 *Prostaglandins Leukot Essent Fatty Acids*, 85 (2011) 293-302.
- 841 [12] M. Knobloch, G.A. Pilz, B. Ghesquiere, W.J. Kovacs, T. Wegleiter, D.L. Moore, M. Hruzova, N.
842 Zamboni, P. Carmeliet, S. Jessberger, A Fatty Acid Oxidation-Dependent Metabolic Shift Regulates
843 Adult Neural Stem Cell Activity, *Cell reports*, 20 (2017) 2144-2155.
- 844 [13] J. Singh, M. Khan, A. Pujol, M. Baarine, I. Singh, Histone deacetylase inhibitor upregulates
845 peroxisomal fatty acid oxidation and inhibits apoptotic cell death in *abcd1*-deficient glial cells, *PLoS*
846 *one*, 8 (2013) e70712.
- 847 [14] A. Viader, Y. Sasaki, S. Kim, A. Strickland, C.S. Workman, K. Yang, R.W. Gross, J. Milbrandt,
848 Aberrant Schwann cell lipid metabolism linked to mitochondrial deficits leads to axon degeneration
849 and neuropathy, *Neuron*, 77 (2013) 886-898.
- 850 [15] C.H. Yao, G.Y. Liu, R. Wang, S.H. Moon, R.W. Gross, G.J. Patti, Identifying off-target effects of
851 etomoxir reveals that carnitine palmitoyltransferase I is essential for cancer cell proliferation
852 independent of beta-oxidation, *PLoS Biol*, 16 (2018) e2003782.
- 853 [16] G.M. Tannahill, A.M. Curtis, J. Adamik, E.M. Palsson-McDermott, A.F. McGettrick, G. Goel, C.
854 Frezza, N.J. Bernard, B. Kelly, N.H. Foley, L. Zheng, A. Gardet, Z. Tong, S.S. Jany, S.C. Corr, M.
855 Haneklaus, B.E. Caffrey, K. Pierce, S. Walmsley, F.C. Beasley, E. Cummins, V. Nizet, M. Whyte, C.T.
856 Taylor, H. Lin, S.L. Masters, E. Gottlieb, V.P. Kelly, C. Clish, P.E. Auron, R.J. Xavier, L.A. O'Neill,

857 Succinate is an inflammatory signal that induces IL-1beta through HIF-1alpha, *Nature*, 496 (2013)
858 238-242.

859 [17] K.R. Feingold, J.K. Shigenaga, M.R. Kazemi, C.M. McDonald, S.M. Patzek, A.S. Cross, A. Moser, C.
860 Grunfeld, Mechanisms of triglyceride accumulation in activated macrophages, *Journal of leukocyte*
861 *biology*, 92 (2012) 829-839.

862 [18] M.Z. Cader, K. Boroviak, Q. Zhang, G. Assadi, S.L. Kempster, G.W. Sewell, S. Saveljeva, J.W.
863 Ashcroft, S. Clare, S. Mukhopadhyay, K.P. Brown, M. Tschurtschenthaler, T. Raine, B. Doe, E.R.
864 Chilvers, J.L. Griffin, N.C. Kaneider, R.A. Floto, M. D'Amato, A. Bradley, M.J. Wakelam, G. Dougan, A.
865 Kaser, C13orf31 (FAMIN) is a central regulator of immunometabolic function, *Nature immunology*, 17
866 (2016) 1046-1056.

867 [19] X. Wei, H. Song, L. Yin, M.G. Rizzo, R. Sidhu, D.F. Covey, D.S. Ory, C.F. Semenkovich, Fatty acid
868 synthesis configures the plasma membrane for inflammation in diabetes, *Nature*, 539 (2016) 294-
869 298.

870 [20] R.G. Carroll, Z. Zaslona, S. Galvan-Pena, E.L. Koppe, D.C. Sevin, S. Angiari, M. Triantafilou, K.
871 Triantafilou, L.K. Modis, L.A. O'Neill, An unexpected link between fatty acid synthase and cholesterol
872 synthesis in proinflammatory macrophage activation, *The Journal of biological chemistry*, 293 (2018)
873 5509-5521.

874 [21] L. Berod, C. Friedrich, A. Nandan, J. Freitag, S. Hagemann, K. Harmrolfs, A. Sandouk, C. Hesse,
875 C.N. Castro, H. Bahre, S.K. Tschirner, N. Gorinski, M. Gohmert, C.T. Mayer, J. Huehn, E. Ponimaskin,
876 W.R. Abraham, R. Muller, M. Lochner, T. Sparwasser, De novo fatty acid synthesis controls the fate
877 between regulatory T and T helper 17 cells, *Nature medicine*, 20 (2014) 1327-1333.

878 [22] D. Cluxton, A. Petrasca, B. Moran, J.M. Fletcher, Differential Regulation of Human Treg and Th17
879 Cells by Fatty Acid Synthesis and Glycolysis, *Frontiers in immunology*, 10 (2019) 115.

880 [23] K.E. Young, S. Flaherty, K.M. Woodman, N. Sharma-Walia, J.M. Reynolds, Fatty acid synthase
881 regulates the pathogenicity of Th17 cells, *Journal of leukocyte biology*, 102 (2017) 1229-1235.

882 [24] X. Wang, Y. Zhou, D. Tang, Z. Zhu, Y. Li, T. Huang, R. Muller, W. Yu, P. Li, ACC1 (Acetyl Coenzyme
883 A Carboxylase 1) Is a Potential Immune Modulatory Target of Cerebral Ischemic Stroke, *Stroke; a*
884 *journal of cerebral circulation*, 50 (2019) 1869-1878.

885 [25] M. Laplante, D.M. Sabatini, mTORC1 activates SREBP-1c and uncouples lipogenesis from
886 gluconeogenesis, *Proceedings of the National Academy of Sciences of the United States of America*,
887 107 (2010) 3281-3282.

888 [26] J.S. Talboom, R. Velazquez, S. Oddo, The mammalian target of rapamycin at the crossroad
889 between cognitive aging and Alzheimer's disease, *NPJ Aging Mech Dis*, 1 (2015) 15008.

890 [27] Y.C. Liu, X.X. Gao, L. Chen, X.Q. You, Rapamycin suppresses Abeta25-35- or LPS-induced neuronal
891 inflammation via modulation of NF-kappaB signaling, *Neuroscience*, 355 (2017) 188-199.

892 [28] W.M. Pryor, M. Biagioli, N. Shahani, S. Swarnkar, W.C. Huang, D.T. Page, M.E. MacDonald, S.
893 Subramaniam, Huntingtin promotes mTORC1 signaling in the pathogenesis of Huntington's disease,
894 *Sci Signal*, 7 (2014) ra103.

895 [29] D. Masini, A. Bonito-Oliva, M. Bertho, G. Fisone, Inhibition of mTORC1 Signaling Reverts
896 Cognitive and Affective Deficits in a Mouse Model of Parkinson's Disease, *Front Neurol*, 9 (2018) 208.

897 [30] T. Harayama, H. Riezman, Understanding the diversity of membrane lipid composition, *Nature*
898 *reviews. Molecular cell biology*, 19 (2018) 281-296.

899 [31] P. Dimas, L. Montani, J.A. Pereira, D. Moreno, M. Trotsmuller, J. Gerber, C.F. Semenkovich, H.C.
900 Kofeler, U. Suter, CNS myelination and remyelination depend on fatty acid synthesis by
901 oligodendrocytes, *Elife*, 8 (2019).

902 [32] F. Lebrun-Julien, L. Bachmann, C. Norrmen, M. Trotsmuller, H. Kofeler, M.A. Ruegg, M.N. Hall, U.
903 Suter, Balanced mTORC1 activity in oligodendrocytes is required for accurate CNS myelination, *The*
904 *Journal of neuroscience : the official journal of the Society for Neuroscience*, 34 (2014) 8432-8448.

905 [33] H.H. Sachs, K.K. Bercury, D.C. Popescu, S.P. Narayanan, W.B. Macklin, A new model of cuprizone-
906 mediated demyelination/remyelination, *ASN Neuro*, 6 (2014).

907 [34] E.P. Harrington, C. Zhao, S.P. Fancy, S. Kaing, R.J. Franklin, D.H. Rowitch, Oligodendrocyte PTEN is
908 required for myelin and axonal integrity, not remyelination, *Annals of neurology*, 68 (2010) 703-716.

909 [35] N. Camargo, A. Goudriaan, A.F. van Deijk, W.M. Otte, J.F. Brouwers, H. Lodder, D.H. Gutmann,
910 K.A. Nave, R.M. Dijkhuizen, H.D. Mansvelder, R. Chrast, A.B. Smit, M.H.G. Verheijen, Oligodendroglial
911 myelination requires astrocyte-derived lipids, *PLoS Biol*, 15 (2017) e1002605.

912 [36] M. Knobloch, S.M. Braun, L. Zurkirchen, C. von Schoultz, N. Zamboni, M.J. Arauzo-Bravo, W.J.
913 Kovacs, O. Karalay, U. Suter, R.A. Machado, M. Rocco, M.P. Lutolf, C.F. Semenkovich, S. Jessberger,
914 Metabolic control of adult neural stem cell activity by Fasn-dependent lipogenesis, *Nature*, 493
915 (2013) 226-230.

916 [37] A.B. Ziegler, C. Thiele, F. Tenedini, M. Richard, P. Leyendecker, A. Hoermann, P. Soba, G.
917 Tavosanis, Cell-Autonomous Control of Neuronal Dendrite Expansion via the Fatty Acid Synthesis
918 Regulator SREBP, *Cell reports*, 21 (2017) 3346-3353.

919 [38] H. Guillou, D. Zdravec, P.G. Martin, A. Jacobsson, The key roles of elongases and desaturases in
920 mammalian fatty acid metabolism: Insights from transgenic mice, *Prog Lipid Res*, 49 (2010) 186-199.

921 [39] A. Jakobsson, R. Westerberg, A. Jacobsson, Fatty acid elongases in mammals: their regulation
922 and roles in metabolism, *Prog Lipid Res*, 45 (2006) 237-249.

923 [40] G. Li, S. Cui, J. Du, J. Liu, P. Zhang, Y. Fu, Y. He, H. Zhou, J. Ma, S. Chen, Association of GALC,
924 ZNF184, IL1R2 and ELOVL7 With Parkinson's Disease in Southern Chinese, *Front Aging Neurosci*, 10
925 (2018) 402.

926 [41] K. Ozaki, H. Doi, J. Mitsui, N. Sato, Y. Iikuni, T. Majima, K. Yamane, T. Irioka, H. Ishiura, K. Doi, S.
927 Morishita, M. Higashi, T. Sekiguchi, K. Koyama, N. Ueda, Y. Miura, S. Miyatake, N. Matsumoto, T.
928 Yokota, F. Tanaka, S. Tsuji, H. Mizusawa, K. Ishikawa, A Novel Mutation in ELOVL4 Leading to
929 Spinocerebellar Ataxia (SCA) With the Hot Cross Bun Sign but Lacking Erythrokeratoderma: A
930 Broadened Spectrum of SCA34, *JAMA Neurol*, 72 (2015) 797-805.

931 [42] H. Mir, S.I. Raza, M. Touseef, M.M. Memon, M.N. Khan, S. Jaffar, W. Ahmad, A novel recessive
932 mutation in the gene ELOVL4 causes a neuro-ichthyotic disorder with variable expressivity, *BMC Med*
933 *Genet*, 15 (2014) 25.

934 [43] L.K. Hamilton, M. Dufresne, S.E. Joppe, S. Petryszyn, A. Aumont, F. Calon, F. Barnabe-Heider, A.
935 Furtos, M. Parent, P. Chaurand, K.J. Fernandes, Aberrant Lipid Metabolism in the Forebrain Niche
936 Suppresses Adult Neural Stem Cell Proliferation in an Animal Model of Alzheimer's Disease, *Cell stem*
937 *cell*, 17 (2015) 397-411.

938 [44] J. Singh, M. Khan, I. Singh, HDAC inhibitor SAHA normalizes the levels of VLCFAs in human skin
939 fibroblasts from X-ALD patients and downregulates the expression of proinflammatory cytokines in
940 Abcd1/2-silenced mouse astrocytes, *Journal of lipid research*, 52 (2011) 2056-2069.

941 [45] V.K. Senanayake, W. Jin, A. Mochizuki, B. Chitou, D.B. Goodenowe, Metabolic dysfunctions in
942 multiple sclerosis: implications as to causation, early detection, and treatment, a case control study,
943 *BMC neurology*, 15 (2015) 154.

944 [46] H. Zhao, T. Matsuzaka, Y. Nakano, K. Motomura, N. Tang, T. Yokoo, Y. Okajima, S.I. Han, Y.
945 Takeuchi, Y. Aita, H. Iwasaki, S. Yatoh, H. Suzuki, M. Sekiya, N. Yahagi, Y. Nakagawa, H. Sone, N.
946 Yamada, H. Shimano, Elov6 Deficiency Improves Glycemic Control in Diabetic db/db Mice by
947 Expanding beta-Cell Mass and Increasing Insulin Secretory Capacity, *Diabetes*, 66 (2017) 1833-1846.

948 [47] T. Matsuzaka, A. Atsumi, R. Matsumori, T. Nie, H. Shinozaki, N. Suzuki-Kemuriyama, M. Kuba, Y.
949 Nakagawa, K. Ishii, M. Shimada, K. Kobayashi, S. Yatoh, A. Takahashi, K. Takekoshi, H. Sone, N. Yahagi,
950 H. Suzuki, S. Murata, M. Nakamuta, N. Yamada, H. Shimano, Elov6 promotes nonalcoholic
951 steatohepatitis, *Hepatology*, 56 (2012) 2199-2208.

952 [48] Y. Nakamura, T. Matsuzaka, S. Tahara-Hanaoka, K. Shibuya, H. Shimano, C. Nakahashi-Oda, A.
953 Shibuya, Elov6 regulates mechanical damage-induced keratinocyte death and skin inflammation, *Cell*
954 *Death Dis*, 9 (2018) 1181.

955 [49] E. Talamonti, A.M. Pauter, A. Asadi, A.W. Fischer, V. Chiurchiu, A. Jacobsson, Impairment of
956 systemic DHA synthesis affects macrophage plasticity and polarization: implications for DHA
957 supplementation during inflammation, *Cell Mol Life Sci*, 74 (2017) 2815-2826.

958 [50] V. Chiurchiu, A. Leuti, J. Dalli, A. Jacobsson, L. Battistini, M. Maccarrone, C.N. Serhan,
959 Proresolving lipid mediators resolvin D1, resolvin D2, and maresin 1 are critical in modulating T cell
960 responses, *Sci Transl Med*, 8 (2016) 353ra111.

961 [51] P.P. Robichaud, J.E. Munganyiki, E. Boilard, M.E. Surette, Polyunsaturated fatty acid elongation
962 and desaturation in activated human T-cells: ELOVL5 is the key elongase, *Journal of lipid research*, 59
963 (2018) 2383-2396.

964 [52] R. Ofman, I.M. Dijkstra, C.W. van Roermund, N. Burger, M. Turkenburg, A. van Cruchten, C.E. van
965 Engen, R.J. Wanders, S. Kemp, The role of ELOVL1 in very long-chain fatty acid homeostasis and X-
966 linked adrenoleukodystrophy, *EMBO molecular medicine*, 2 (2010) 90-97.

967 [53] T. Sassa, T. Wakashima, Y. Ohno, A. Kihara, Lorenzo's oil inhibits ELOVL1 and lowers the level of
968 sphingomyelin with a saturated very long-chain fatty acid, *Journal of lipid research*, 55 (2014) 524-
969 530.

970 [54] D. Shin, J.Y. Shin, M.T. McManus, L.J. Ptacek, Y.H. Fu, Dicer ablation in oligodendrocytes
971 provokes neuronal impairment in mice, *Annals of neurology*, 66 (2009) 843-857.

972 [55] B.R. Hopiavuori, F. Deak, J.L. Wilkerson, R.S. Brush, N.A. Rocha-Hopiavuori, A.R. Hopiavuori, K.G.
973 Ozan, M.T. Sullivan, J.D. Wren, C. Georgescu, L. Szweda, V. Awasthi, R. Towner, D.M. Sherry, R.E.
974 Anderson, M.P. Agbaga, Homozygous Expression of Mutant ELOVL4 Leads to Seizures and Death in a
975 Novel Animal Model of Very Long-Chain Fatty Acid Deficiency, *Mol Neurobiol*, 55 (2018) 1795-1813.

976 [56] F. Deak, R.E. Anderson, J.L. Fessler, D.M. Sherry, Novel Cellular Functions of Very Long Chain-
977 Fatty Acids: Insight From ELOVL4 Mutations, *Frontiers in cellular neuroscience*, 13 (2019) 428.

978 [57] T. Sassa, Y. Ohno, S. Suzuki, T. Nomura, C. Nishioka, T. Kashiwagi, T. Hirayama, M. Akiyama, R.
979 Taguchi, H. Shimizu, S. Itoharu, A. Kihara, Impaired epidermal permeability barrier in mice lacking
980 elovl1, the gene responsible for very-long-chain fatty acid production, *Molecular and cellular biology*,
981 33 (2013) 2787-2796.

982 [58] V. Vasireddy, Y. Uchida, N. Salem, Jr., S.Y. Kim, M.N. Mandal, G.B. Reddy, R. Bodepudi, N.L.
983 Alderson, J.C. Brown, H. Hama, A. Dlugosz, P.M. Elias, W.M. Holleran, R. Ayyagari, Loss of functional
984 ELOVL4 depletes very long-chain fatty acids (> or =C28) and the unique omega-O-acylceramides in
985 skin leading to neonatal death, *Hum Mol Genet*, 16 (2007) 471-482.

986 [59] J.M. Lee, H. Lee, S. Kang, W.J. Park, Fatty Acid Desaturases, Polyunsaturated Fatty Acid
987 Regulation, and Biotechnological Advances, *Nutrients*, 8 (2016).

988 [60] M.T. Nakamura, T.Y. Nara, Structure, function, and dietary regulation of delta6, delta5, and
989 delta9 desaturases, *Annu Rev Nutr*, 24 (2004) 345-376.

990 [61] C.M. Paton, J.M. Ntambi, Biochemical and physiological function of stearoyl-CoA desaturase, *Am*
991 *J Physiol Endocrinol Metab*, 297 (2009) E28-37.

992 [62] B.S. Yeoh, P. Saha, V. Singh, X. Xiao, Y. Ying, J.K. Vanamala, M.J. Kennett, K.J. Harvatine, B. Joe,
993 M. Vijay-Kumar, Deficiency of stearoyl-CoA desaturase-1 aggravates colitogenic potential of
994 adoptively transferred effector T cells, *Am J Physiol Gastrointest Liver Physiol*, 311 (2016) G713-G723.

995 [63] J.M. Brown, S. Chung, J.K. Sawyer, C. Degirolamo, H.M. Alger, T. Nguyen, X. Zhu, M.N. Duong,
996 A.L. Wibley, R. Shah, M.A. Davis, K. Kelley, M.D. Wilson, C. Kent, J.S. Parks, L.L. Rudel, Inhibition of
997 stearoyl-coenzyme A desaturase 1 dissociates insulin resistance and obesity from atherosclerosis,
998 *Circulation*, 118 (2008) 1467-1475.

999 [64] E. Erbay, V.R. Babaev, J.R. Mayers, L. Makowski, K.N. Charles, M.E. Snitow, S. Fazio, M.M. Wiest,
1000 S.M. Watkins, M.F. Linton, G.S. Hotamisligil, Reducing endoplasmic reticulum stress through a
1001 macrophage lipid chaperone alleviates atherosclerosis, *Nature medicine*, 15 (2009) 1383-1391.

1002 [65] J.M. Monk, H.F. Turk, Y.Y. Fan, E. Callaway, B. Weeks, P. Yang, D.N. McMurray, R.S. Chapkin,
1003 Antagonizing arachidonic acid-derived eicosanoids reduces inflammatory Th17 and Th1 cell-mediated
1004 inflammation and colitis severity, *Mediators of inflammation*, 2014 (2014) 917149.

1005 [66] A.D. Gromovsky, R.C. Schugar, A.L. Brown, R.N. Helsley, A.C. Burrows, D. Ferguson, R. Zhang, B.E.
1006 Sansbury, R.G. Lee, R.E. Morton, D.S. Allende, J.S. Parks, M. Spite, J.M. Brown, Delta-5 Fatty Acid
1007 Desaturase FADS1 Impacts Metabolic Disease by Balancing Proinflammatory and Proresolving Lipid
1008 Mediators, *Arterioscler Thromb Vasc Biol*, 38 (2018) 218-231.

1009 [67] W. Stoffel, B. Holz, B. Jenke, E. Binczek, R.H. Gunter, C. Kiss, I. Karakesisoglou, M. Thevis, A.A.
1010 Weber, S. Arnhold, K. Addicks, Delta6-desaturase (FADS2) deficiency unveils the role of omega3- and
1011 omega6-polyunsaturated fatty acids, *EMBO J*, 27 (2008) 2281-2292.

1012 [68] S. Uryu, S. Tokuhira, T. Oda, beta-Amyloid-specific upregulation of stearoyl coenzyme A
1013 desaturase-1 in macrophages, *Biochem Biophys Res Commun*, 303 (2003) 302-305.

1014 [69] E. Polo-Hernandez, V. Tello, A.A. Arroyo, M. Dominguez-Prieto, F. de Castro, A. Tabernero, J.M.
1015 Medina, Oleic acid synthesized by stearoyl-CoA desaturase (SCD-1) in the lateral periventricular zone
1016 of the developing rat brain mediates neuronal growth, migration and the arrangement of prospective
1017 synapses, *Brain research*, 1570 (2014) 13-25.

1018 [70] A. Tabernero, E.M. Lavado, B. Granda, A. Velasco, J.M. Medina, Neuronal differentiation is
1019 triggered by oleic acid synthesized and released by astrocytes, *J Neurochem*, 79 (2001) 606-616.

1020 [71] D.I. Sinner, G.J. Kim, G.C. Henderson, R.A. Igal, StearoylCoA desaturase-5: a novel regulator of
1021 neuronal cell proliferation and differentiation, *PLoS one*, 7 (2012) e39787.

1022 [72] B.M. Vincent, D.F. Tardiff, J.S. Piotrowski, R. Aron, M.C. Lucas, C.Y. Chung, H. Bacherman, Y.
1023 Chen, M. Pires, R. Subramaniam, D.B. Doshi, H. Sadlish, W.K. Raja, E.J. Solis, V. Khurana, B. Le
1024 Bourdonnec, R.H. Scannevin, K.J. Rhodes, Inhibiting Stearoyl-CoA Desaturase Ameliorates alpha-
1025 Synuclein Cytotoxicity, *Cell reports*, 25 (2018) 2742-2754 e2731.

1026 [73] S.A. Moore, Polyunsaturated fatty acid synthesis and release by brain-derived cells in vitro, *J Mol*
1027 *Neurosci*, 16 (2001) 195-200; discussion 215-121.

1028 [74] Z. Zhang, N.A. Dales, M.D. Winther, Opportunities and challenges in developing stearoyl-
1029 coenzyme A desaturase-1 inhibitors as novel therapeutics for human disease, *Journal of medicinal*
1030 *chemistry*, 57 (2014) 5039-5056.

1031 [75] G. Liu, Recent advances in stearoyl-CoA desaturase 1 inhibitors for dyslipidemia and obesity,
1032 *Curr Top Med Chem*, 10 (2010) 419-433.

1033 [76] R.A. Igal, Stearoyl CoA desaturase-1: New insights into a central regulator of cancer metabolism,
1034 *Biochimica et biophysica acta*, 1861 (2016) 1865-1880.

1035 [77] J.M. Brown, L.L. Rudel, Stearoyl-coenzyme A desaturase 1 inhibition and the metabolic
1036 syndrome: considerations for future drug discovery, *Curr Opin Lipidol*, 21 (2010) 192-197.

1037 [78] A. Ayala, M.F. Munoz, S. Arguelles, Lipid peroxidation: production, metabolism, and signaling
1038 mechanisms of malondialdehyde and 4-hydroxy-2-nonenal, *Oxid Med Cell Longev*, 2014 (2014)
1039 360438.

1040 [79] G. Poli, G. Leonarduzzi, F. Biasi, E. Chiarotto, Oxidative stress and cell signalling, *Curr Med*
1041 *Chem*, 11 (2004) 1163-1182.

1042 [80] C. Smith, M.J. Mitchinson, O.I. Aruoma, B. Halliwell, Stimulation of lipid peroxidation and
1043 hydroxyl-radical generation by the contents of human atherosclerotic lesions, *Biochem J*, 286 (Pt 3)
1044 (1992) 901-905.

1045 [81] N.J. Pilon, M.L. Croze, R.E. Vella, L. Soulere, M. Lagarde, C.O. Soulage, The lipid peroxidation by-
1046 product 4-hydroxy-2-nonenal (4-HNE) induces insulin resistance in skeletal muscle through both
1047 carbonyl and oxidative stress, *Endocrinology*, 153 (2012) 2099-2111.

1048 [82] S.C. Kang, H.W. Kim, K.B. Kim, S.J. Kwack, I.Y. Ahn, J.Y. Bae, S.K. Lim, B.M. Lee, Hepatotoxicity and
1049 nephrotoxicity produced by 4-hydroxy-2-nonenal (4-HNE) following 4-week oral administration to
1050 Sprague-Dawley rats, *J Toxicol Environ Health A*, 74 (2011) 779-789.

1051 [83] P. Karihtala, S. Kauppila, U. Puistola, A. Jukkola-Vuorinen, Divergent behaviour of oxidative stress
1052 markers 8-hydroxydeoxyguanosine (8-OHdG) and 4-hydroxy-2-nonenal (HNE) in breast
1053 carcinogenesis, *Histopathology*, 58 (2011) 854-862.

1054 [84] M.P. Mattson, Roles of the lipid peroxidation product 4-hydroxynonenal in obesity, the
1055 metabolic syndrome, and associated vascular and neurodegenerative disorders, *Exp Gerontol*, 44
1056 (2009) 625-633.

1057 [85] D.A. Butterfield, M.L. Bader Lange, R. Sultana, Involvements of the lipid peroxidation product,
1058 HNE, in the pathogenesis and progression of Alzheimer's disease, *Biochim Biophys Acta*, 1801 (2010)
1059 924-929.

1060 [86] E. McCracken, D.I. Graham, M. Nilsen, J. Stewart, J.A. Nicoll, K. Horsburgh, 4-Hydroxynonenal
1061 immunoreactivity is increased in human hippocampus after global ischemia, *Brain Pathol*, 11 (2001)
1062 414-421.

1063 [87] D.A. Pratt, K.A. Tallman, N.A. Porter, Free radical oxidation of polyunsaturated lipids: New
1064 mechanistic insights and the development of peroxy radical clocks, *Acc Chem Res*, 44 (2011) 458-
1065 467.

1066 [88] T. Kumagai, N. Matsukawa, Y. Kaneko, Y. Kusumi, M. Mitsumata, K. Uchida, A lipid peroxidation-
1067 derived inflammatory mediator: identification of 4-hydroxy-2-nonenal as a potential inducer of
1068 cyclooxygenase-2 in macrophages, *J Biol Chem*, 279 (2004) 48389-48396.

1069 [89] U.C. Yadav, K.V. Ramana, Regulation of NF-kappaB-induced inflammatory signaling by lipid
1070 peroxidation-derived aldehydes, *Oxid Med Cell Longev*, 2013 (2013) 690545.

1071 [90] C.N. Serhan, Pro-resolving lipid mediators are leads for resolution physiology, *Nature*, 510 (2014)
1072 92-101.

1073 [91] B. Yang, R. Li, C. Michael Greenlief, K.L. Fritsche, Z. Gu, J. Cui, J.C. Lee, D.Q. Beversdorf, G.Y. Sun,
1074 Unveiling anti-oxidative and anti-inflammatory effects of docosahexaenoic acid and its lipid
1075 peroxidation product on lipopolysaccharide-stimulated BV-2 microglial cells, *Journal of*
1076 *neuroinflammation*, 15 (2018) 202.

1077 [92] R.L. Schild, W.T. Schaiff, M.G. Carlson, E.J. Cronbach, D.M. Nelson, Y. Sadovsky, The activity of
1078 PPAR gamma in primary human trophoblasts is enhanced by oxidized lipids, *J Clin Endocrinol Metab*,
1079 87 (2002) 1105-1110.

1080 [93] L. Nagy, P. Tontonoz, J.G. Alvarez, H. Chen, R.M. Evans, Oxidized LDL regulates macrophage gene
1081 expression through ligand activation of PPARgamma, *Cell*, 93 (1998) 229-240.

1082 [94] S. Ljubisavljevic, I. Stojanovic, D. Pavlovic, M. Milojkovic, D. Sokolovic, I. Stevanovic, A. Petrovic,
1083 Suppression of the lipid peroxidation process in the CNS reduces neurological expression of
1084 experimentally induced autoimmune encephalomyelitis, *Folia Neuropathol*, 51 (2013) 51-57.

1085 [95] R.A. Sosa, C. Murphey, R.R. Robinson, T.G. Forsthuber, IFN-gamma ameliorates autoimmune
1086 encephalomyelitis by limiting myelin lipid peroxidation, *Proceedings of the National Academy of*
1087 *Sciences of the United States of America*, 112 (2015) E5038-5047.

1088 [96] P. Wang, K. Xie, C. Wang, J. Bi, Oxidative stress induced by lipid peroxidation is related with
1089 inflammation of demyelination and neurodegeneration in multiple sclerosis, *Eur Neurol*, 72 (2014)
1090 249-254.

1091 [97] J.M. Braugher, E.D. Hall, Involvement of lipid peroxidation in CNS injury, *J Neurotrauma*, 9 Suppl
1092 1 (1992) S1-7.

1093 [98] A.I. Bush, R.E. Tanzi, Therapeutics for Alzheimer's disease based on the metal hypothesis,
1094 *Neurotherapeutics*, 5 (2008) 421-432.

1095 [99] D.T. Dexter, C.J. Carter, F.R. Wells, F. Javoy-Agid, Y. Agid, A. Lees, P. Jenner, C.D. Marsden, Basal
1096 lipid peroxidation in substantia nigra is increased in Parkinson's disease, *J Neurochem*, 52 (1989) 381-
1097 389.

1098 [100] P.R. Angelova, M.H. Horrocks, D. Klenerman, S. Gandhi, A.Y. Abramov, M.S. Shchepinov, Lipid
1099 peroxidation is essential for alpha-synuclein-induced cell death, *J Neurochem*, 133 (2015) 582-589.

1100 [101] M.S. Ioannou, J. Jackson, S.H. Sheu, C.L. Chang, A.V. Weigel, H. Liu, H.A. Pasolli, C.S. Xu, S. Pang,
1101 D. Matthies, H.F. Hess, J. Lippincott-Schwartz, Z. Liu, Neuron-Astrocyte Metabolic Coupling Protects
1102 against Activity-Induced Fatty Acid Toxicity, *Cell*, 177 (2019) 1522-1535 e1514.

1103 [102] K.V. Do, M.I. Kautzmann, B. Jun, W.C. Gordon, R. Nshimiyimana, R. Yang, N.A. Petasis, N.G.
1104 Bazan, Elovans counteract oligomeric beta-amyloid-induced gene expression and protect
1105 photoreceptors, *Proceedings of the National Academy of Sciences of the United States of America*,
1106 116 (2019) 24317-24325.

1107 [103] S. Bhattacharjee, B. Jun, L. Belayev, J. Heap, M.A. Kautzmann, A. Obenaus, H. Menghani, S.J.
1108 Marcell, L. Khoutorova, R. Yang, N.A. Petasis, N.G. Bazan, Elovans are a novel class of homeostatic
1109 lipid mediators that protect neural cell integrity upon injury, *Sci Adv*, 3 (2017) e1700735.

1110 [104] J.L. Sonnenburg, F. Backhed, Diet-microbiota interactions as moderators of human metabolism,
1111 *Nature*, 535 (2016) 56-64.

1112 [105] D. Erny, A.L. Hrabé de Angelis, D. Jaitin, P. Wieghofer, O. Staszewski, E. David, H. Keren-Shaul, T.
1113 Mhlakoiv, K. Jakobshagen, T. Buch, V. Schwierzeck, O. Utermohlen, E. Chun, W.S. Garrett, K.D.

1114 McCoy, A. Diefenbach, P. Staeheli, B. Stecher, I. Amit, M. Prinz, Host microbiota constantly control
1115 maturation and function of microglia in the CNS, *Nature neuroscience*, 18 (2015) 965-977.
1116 [106] A. Haghikia, S. Jorg, A. Duscha, J. Berg, A. Manzel, A. Waschbisch, A. Hammer, D.H. Lee, C. May,
1117 N. Wilck, A. Balogh, A.I. Ostermann, N.H. Schebb, D.A. Akkad, D.A. Grohme, M. Kleinewietfeld, S.
1118 Kempa, J. Thone, S. Demir, D.N. Muller, R. Gold, R.A. Linker, Dietary Fatty Acids Directly Impact
1119 Central Nervous System Autoimmunity via the Small Intestine, *Immunity*, 44 (2016) 951-953.
1120 [107] L. Ho, K. Ono, M. Tsuji, P. Mazzola, R. Singh, G.M. Pasinetti, Protective roles of intestinal
1121 microbiota derived short chain fatty acids in Alzheimer's disease-type beta-amyloid
1122 neuropathological mechanisms, *Expert review of neurotherapeutics*, 18 (2018) 83-90.
1123 [108] R. St Laurent, L.M. O'Brien, S.T. Ahmad, Sodium butyrate improves locomotor impairment and
1124 early mortality in a rotenone-induced *Drosophila* model of Parkinson's disease, *Neuroscience*, 246
1125 (2013) 382-390.
1126 [109] S. Sharma, R. Taliyan, S. Singh, Beneficial effects of sodium butyrate in 6-OHDA induced
1127 neurotoxicity and behavioral abnormalities: Modulation of histone deacetylase activity, *Behav Brain*
1128 *Res*, 291 (2015) 306-314.
1129 [110] B. Langley, M.A. D'Annibale, K. Suh, I. Ayoub, A. Tolhurst, B. Bastan, L. Yang, B. Ko, M. Fisher, S.
1130 Cho, M.F. Beal, R.R. Ratan, Pulse inhibition of histone deacetylases induces complete resistance to
1131 oxidative death in cortical neurons without toxicity and reveals a role for cytoplasmic p21(waf1/cip1)
1132 in cell cycle-independent neuroprotection, *The Journal of neuroscience : the official journal of the*
1133 *Society for Neuroscience*, 28 (2008) 163-176.
1134 [111] H.J. Kim, D.M. Chuang, HDAC inhibitors mitigate ischemia-induced oligodendrocyte damage:
1135 potential roles of oligodendrogenesis, VEGF, and anti-inflammation, *Am J Transl Res*, 6 (2014) 206-
1136 223.
1137 [112] V. Braniste, M. Al-Asmakh, C. Kowal, F. Anuar, A. Abbaspour, M. Toth, A. Korecka, N. Bakocevic,
1138 L.G. Ng, P. Kundu, B. Gulyas, C. Halldin, K. Hultenby, H. Nilsson, H. Hebert, B.T. Volpe, B. Diamond, S.
1139 Pettersson, The gut microbiota influences blood-brain barrier permeability in mice, *Sci Transl Med*, 6
1140 (2014) 263ra158.
1141 [113] C.L. Sherry, S.S. Kim, R.N. Dilger, L.L. Bauer, M.L. Moon, R.I. Tapping, G.C. Fahey, Jr., K.A.
1142 Tappenden, G.G. Freund, Sickness behavior induced by endotoxin can be mitigated by the dietary
1143 soluble fiber, pectin, through up-regulation of IL-4 and Th2 polarization, *Brain, behavior, and*
1144 *immunity*, 24 (2010) 631-640.
1145 [114] N. Govindarajan, R.C. Agis-Balboa, J. Walter, F. Sananbenesi, A. Fischer, Sodium butyrate
1146 improves memory function in an Alzheimer's disease mouse model when administered at an
1147 advanced stage of disease progression, *J Alzheimers Dis*, 26 (2011) 187-197.
1148 [115] P.K. Dash, S.A. Orsi, A.N. Moore, Histone deacetylase inhibition combined with behavioral
1149 therapy enhances learning and memory following traumatic brain injury, *Neuroscience*, 163 (2009) 1-
1150 8.
1151 [116] P.M. Smith, M.R. Howitt, N. Panikov, M. Michaud, C.A. Gallini, Y.M. Bohlooly, J.N. Glickman,
1152 W.S. Garrett, The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell
1153 homeostasis, *Science*, 341 (2013) 569-573.
1154 [117] S. Miyake, S. Kim, W. Suda, K. Oshima, M. Nakamura, T. Matsuoka, N. Chihara, A. Tomita, W.
1155 Sato, S.W. Kim, H. Morita, M. Hattori, T. Yamamura, Dysbiosis in the Gut Microbiota of Patients with
1156 Multiple Sclerosis, with a Striking Depletion of Species Belonging to Clostridia XIVA and IV Clusters,
1157 *PloS one*, 10 (2015) e0137429.
1158 [118] M.M. Unger, J. Spiegel, K.U. Dillmann, D. Grundmann, H. Philippeit, J. Burmann, K. Fassbender,
1159 A. Schwiertz, K.H. Schafer, Short chain fatty acids and gut microbiota differ between patients with
1160 Parkinson's disease and age-matched controls, *Parkinsonism Relat Disord*, 32 (2016) 66-72.
1161 [119] D.A. Trauner, R.S. Garrett, Effect of octanoate injection on rat blood-brain barrier, *Pediatr*
1162 *Neurol*, 1 (1985) 20-22.
1163 [120] J. Wang, X. Wu, N. Simonavicius, H. Tian, L. Ling, Medium-chain fatty acids as ligands for orphan
1164 G protein-coupled receptor GPR84, *The Journal of biological chemistry*, 281 (2006) 34457-34464.

1165 [121] E. Alvarez-Curto, G. Milligan, Metabolism meets immunity: The role of free fatty acid receptors
1166 in the immune system, *Biochemical pharmacology*, 114 (2016) 3-13.

1167 [122] C. Bouchard, J. Page, A. Bedard, P. Tremblay, L. Vallieres, G protein-coupled receptor 84, a
1168 microglia-associated protein expressed in neuroinflammatory conditions, *Glia*, 55 (2007) 790-800.

1169 [123] L.S. Nicol, J.M. Dawes, F. La Russa, A. Didangelos, A.K. Clark, C. Gentry, J. Grist, J.B. Davies, M.
1170 Malcangio, S.B. McMahon, The role of G-protein receptor 84 in experimental neuropathic pain, *The*
1171 *Journal of neuroscience : the official journal of the Society for Neuroscience*, 35 (2015) 8959-8969.

1172 [124] C. Venkataraman, F. Kuo, The G-protein coupled receptor, GPR84 regulates IL-4 production by T
1173 lymphocytes in response to CD3 crosslinking, *Immunology letters*, 101 (2005) 144-153.

1174 [125] C. Recio, D. Lucy, G.S.D. Purvis, P. Iveson, L. Zeboudj, A.J. Iqbal, D. Lin, C. O'Callaghan, L.
1175 Davison, E. Griesbach, A.J. Russell, G.M. Wynne, L. Dib, C. Monaco, D.R. Greaves, Activation of the
1176 Immune-Metabolic Receptor GPR84 Enhances Inflammation and Phagocytosis in Macrophages,
1177 *Frontiers in immunology*, 9 (2018) 1419.

1178 [126] K. Gamo, S. Kiryu-Seo, H. Konishi, S. Aoki, K. Matsushima, K. Wada, H. Kiyama, G-protein-
1179 coupled receptor screen reveals a role for chemokine receptor CCR5 in suppressing microglial
1180 neurotoxicity, *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 28
1181 (2008) 11980-11988.

1182 [127] A. Bedard, P. Tremblay, A. Chernomoretz, L. Vallieres, Identification of genes preferentially
1183 expressed by microglia and upregulated during cuprizone-induced inflammation, *Glia*, 55 (2007) 777-
1184 789.

1185 [128] J. Audoy-Remus, L. Bozoyan, A. Dumas, M. Filali, C. Lecours, S. Lacroix, S. Rivest, M.E. Tremblay,
1186 L. Vallieres, GPR84 deficiency reduces microgliosis, but accelerates dendritic degeneration and
1187 cognitive decline in a mouse model of Alzheimer's disease, *Brain, behavior, and immunity*, 46 (2015)
1188 112-120.

1189 [129] P. Chang, N. Terbach, N. Plant, P.E. Chen, M.C. Walker, R.S. Williams, Seizure control by
1190 ketogenic diet-associated medium chain fatty acids, *Neuropharmacology*, 69 (2013) 105-114.

1191 [130] P. Chang, K. Augustin, K. Boddum, S. Williams, M. Sun, J.A. Terschak, J.D. Hardege, P.E. Chen,
1192 M.C. Walker, R.S. Williams, Seizure control by decanoic acid through direct AMPA receptor inhibition,
1193 *Brain : a journal of neurology*, 139 (2016) 431-443.

1194 [131] E.G. Neal, H. Chaffe, R.H. Schwartz, M.S. Lawson, N. Edwards, G. Fitzsimmons, A. Whitney, J.H.
1195 Cross, A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment
1196 of childhood epilepsy, *Epilepsia*, 50 (2009) 1109-1117.

1197 [132] M.K. Taylor, D.K. Sullivan, J.D. Mahnken, J.M. Burns, R.H. Swerdlow, Feasibility and efficacy
1198 data from a ketogenic diet intervention in Alzheimer's disease, *Alzheimers Dement (N Y)*, 4 (2018) 28-
1199 36.

1200 [133] M. Ota, J. Matsuo, I. Ishida, H. Takano, Y. Yokoi, H. Hori, S. Yoshida, K. Ashida, K. Nakamura, T.
1201 Takahashi, H. Kunugi, Effects of a medium-chain triglyceride-based ketogenic formula on cognitive
1202 function in patients with mild-to-moderate Alzheimer's disease, *Neuroscience letters*, 690 (2019)
1203 232-236.

1204 [134] F. Mochel, S. Duteil, C. Marelli, C. Jauffret, A. Barles, J. Holm, L. Sweetman, J.F. Benoist, D.
1205 Rabier, P.G. Carlier, A. Durr, Dietary anaplerotic therapy improves peripheral tissue energy
1206 metabolism in patients with Huntington's disease, *Eur J Hum Genet*, 18 (2010) 1057-1060.

1207 [135] M. Angela, Y. Endo, H.K. Asou, T. Yamamoto, D.J. Tumes, H. Tokuyama, K. Yokote, T. Nakayama,
1208 Fatty acid metabolic reprogramming via mTOR-mediated inductions of PPARgamma directs early
1209 activation of T cells, *Nat Commun*, 7 (2016) 13683.

1210 [136] S. Gupta, A.G. Knight, S. Gupta, J.N. Keller, A.J. Bruce-Keller, Saturated long-chain fatty acids
1211 activate inflammatory signaling in astrocytes, *J Neurochem*, 120 (2012) 1060-1071.

1212 [137] M. Valdearcos, M.M. Robblee, D.I. Benjamin, D.K. Nomura, A.W. Xu, S.K. Koliwad, Microglia
1213 dictate the impact of saturated fat consumption on hypothalamic inflammation and neuronal
1214 function, *Cell reports*, 9 (2014) 2124-2138.

1215 [138] Z. Wang, D. Liu, F. Wang, S. Liu, S. Zhao, E.A. Ling, A. Hao, Saturated fatty acids activate
1216 microglia via Toll-like receptor 4/NF-kappaB signalling, *Br J Nutr*, 107 (2012) 229-241.

1217 [139] H. Shi, M.V. Kokoeva, K. Inouye, I. Tzamelis, H. Yin, J.S. Flier, TLR4 links innate immunity and fatty
1218 acid-induced insulin resistance, *The Journal of clinical investigation*, 116 (2006) 3015-3025.

1219 [140] M. Milanski, G. Degasperi, A. Coope, J. Morari, R. Denis, D.E. Cintra, D.M. Tsukumo, G. Anhe,
1220 M.E. Amaral, H.K. Takahashi, R. Curi, H.C. Oliveira, J.B. Carnevali, S. Bordin, M.J. Saad, L.A. Velloso,
1221 Saturated fatty acids produce an inflammatory response predominantly through the activation of
1222 TLR4 signaling in hypothalamus: implications for the pathogenesis of obesity, *The Journal of*
1223 *neuroscience : the official journal of the Society for Neuroscience*, 29 (2009) 359-370.

1224 [141] S. Duthiel, K.T. Ota, E.S. Wohleb, K. Rasmussen, R.S. Duman, High-Fat Diet Induced Anxiety and
1225 Anhedonia: Impact on Brain Homeostasis and Inflammation, *Neuropsychopharmacology*, 41 (2016)
1226 1874-1887.

1227 [142] H.R. Park, J.Y. Kim, K.Y. Park, J. Lee, Lipotoxicity of palmitic Acid on neural progenitor cells and
1228 hippocampal neurogenesis, *Toxicol Res*, 27 (2011) 103-110.

1229 [143] C.M. Mayer, D.D. Belsham, Palmitate attenuates insulin signaling and induces endoplasmic
1230 reticulum stress and apoptosis in hypothalamic neurons: rescue of resistance and apoptosis through
1231 adenosine 5' monophosphate-activated protein kinase activation, *Endocrinology*, 151 (2010) 576-
1232 585.

1233 [144] S. Patil, C. Chan, Palmitic and stearic fatty acids induce Alzheimer-like hyperphosphorylation of
1234 tau in primary rat cortical neurons, *Neuroscience letters*, 384 (2005) 288-293.

1235 [145] J. Schommer, G. Marwarha, K. Nagamoto-Combs, O. Ghribi, Palmitic Acid-Enriched Diet
1236 Increases alpha-Synuclein and Tyrosine Hydroxylase Expression Levels in the Mouse Brain, *Front*
1237 *Neurosci*, 12 (2018) 552.

1238 [146] J.Y. Kim, H.J. Lee, S.J. Lee, Y.H. Jung, D.Y. Yoo, I.K. Hwang, J.K. Seong, J.M. Ryu, H.J. Han, Palmitic
1239 Acid-BSA enhances Amyloid-beta production through GPR40-mediated dual pathways in neuronal
1240 cells: Involvement of the Akt/mTOR/HIF-1alpha and Akt/NF-kappaB pathways, *Sci Rep*, 7 (2017)
1241 4335.

1242 [147] H. Yoon, A. Kleven, A. Paulsen, L. Kleppe, J. Wu, Z. Ying, F. Gomez-Pinilla, I.A. Scarisbrick,
1243 Interplay between exercise and dietary fat modulates myelinogenesis in the central nervous system,
1244 *Biochimica et biophysica acta*, 1862 (2016) 545-555.

1245 [148] G.M. Hon, M.S. Hassan, S.J. van Rensburg, S. Abel, R.T. Erasmus, T. Matsha, Membrane
1246 saturated fatty acids and disease progression in multiple sclerosis patients, *Metab Brain Dis*, 24
1247 (2009) 561-568.

1248 [149] M.L. Nasaruddin, C. Holscher, P. Kehoe, S.F. Graham, B.D. Green, Wide-ranging alterations in
1249 the brain fatty acid complement of subjects with late Alzheimer's disease as detected by GC-MS, *Am*
1250 *J Transl Res*, 8 (2016) 154-165.

1251 [150] M.E. Passos, H.H. Alves, C.M. Momesso, F.G. Faria, G. Murata, M.F. Cury-Boaventura, E.
1252 Hatanaka, S. Massao-Hirabara, R. Gorjao, Differential effects of palmitoleic acid on human
1253 lymphocyte proliferation and function, *Lipids Health Dis*, 15 (2016) 217.

1254 [151] Y.T. Oh, J.Y. Lee, J. Lee, H. Kim, K.S. Yoon, W. Choe, I. Kang, Oleic acid reduces
1255 lipopolysaccharide-induced expression of iNOS and COX-2 in BV2 murine microglial cells: possible
1256 involvement of reactive oxygen species, p38 MAPK, and IKK/NF-kappaB signaling pathways,
1257 *Neuroscience letters*, 464 (2009) 93-97.

1258 [152] C.O. Souza, A.A. Teixeira, L.A. Biondo, L.S. Silveira, P.C. Calder, J.C. Rosa Neto, Palmitoleic acid
1259 reduces the inflammation in LPS-stimulated macrophages by inhibition of NFkappaB, independently
1260 of PPARs, *Clin Exp Pharmacol Physiol*, 44 (2017) 566-575.

1261 [153] D.M. Pereira, G. Correia-da-Silva, P. Valentao, N. Teixeira, P.B. Andrade, Anti-inflammatory
1262 effect of unsaturated fatty acids and Ergosta-7,22-dien-3-ol from *Marthasterias glacialis*: prevention
1263 of CHOP-mediated ER-stress and NF-kappaB activation, *PLoS one*, 9 (2014) e88341.

1264 [154] M. Cappa, C. Bizzarri, A. Petroni, G. Carta, L. Cordeddu, M. Valeriani, C. Vollono, L. De Pasquale,
1265 M. Blasevich, S. Banni, A mixture of oleic, erucic and conjugated linoleic acids modulates
1266 cerebrospinal fluid inflammatory markers and improve somatosensorial evoked potential in X-linked
1267 adrenoleukodystrophy female carriers, *J Inher Metab Dis*, 35 (2012) 899-907.

1268 [155] J. Song, Y.S. Kim, D.H. Lee, S.H. Lee, H.J. Park, D. Lee, H. Kim, Neuroprotective effects of oleic
1269 acid in rodent models of cerebral ischaemia, *Sci Rep*, 9 (2019) 10732.

1270 [156] D.E. Cintra, E.R. Ropelle, J.C. Moraes, J.R. Pauli, J. Morari, C.T. Souza, R. Grimaldi, M. Stahl, J.B.
1271 Carvalheira, M.J. Saad, L.A. Velloso, Unsaturated fatty acids revert diet-induced hypothalamic
1272 inflammation in obesity, *PloS one*, 7 (2012) e30571.

1273 [157] T.E. Johnson, M.K. Holloway, R. Vogel, S.J. Rutledge, J.J. Perkins, G.A. Rodan, A. Schmidt,
1274 Structural requirements and cell-type specificity for ligand activation of peroxisome proliferator-
1275 activated receptors, *J Steroid Biochem Mol Biol*, 63 (1997) 1-8.

1276 [158] M.A. Altinoz, A. Ozpinar, PPAR-delta and erucic acid in multiple sclerosis and Alzheimer's
1277 Disease. Likely benefits in terms of immunity and metabolism, *Int Immunopharmacol*, 69 (2019) 245-
1278 256.

1279 [159] H.E. Xu, M.H. Lambert, V.G. Montana, D.J. Parks, S.G. Blanchard, P.J. Brown, D.D. Sternbach,
1280 J.M. Lehmann, G.B. Wisely, T.M. Willson, S.A. Kliewer, M.V. Milburn, Molecular recognition of fatty
1281 acids by peroxisome proliferator-activated receptors, *Mol Cell*, 3 (1999) 397-403.

1282 [160] E. Polo-Hernandez, F. De Castro, A.G. Garcia-Garcia, A. Taberner, J.M. Medina, Oleic acid
1283 synthesized in the periventricular zone promotes axonogenesis in the striatum during brain
1284 development, *J Neurochem*, 114 (2010) 1756-1766.

1285 [161] M. Ghareghani, K. Zibara, H. Azari, H. Hejr, F. Sadri, R. Jannesar, G. Ghalamfarsa, H. Delaviz, E.
1286 Nouri, A. Ghanbari, Safflower Seed Oil, Containing Oleic Acid and Palmitic Acid, Enhances the
1287 Stemness of Cultured Embryonic Neural Stem Cells through Notch1 and Induces Neuronal
1288 Differentiation, *Front Neurosci*, 11 (2017) 446.

1289 [162] Z. Amtul, D. Westaway, D.F. Cechetto, R.F. Rozmahel, Oleic acid ameliorates amyloidosis in
1290 cellular and mouse models of Alzheimer's disease, *Brain pathology*, 21 (2011) 321-329.

1291 [163] Y.J. Kim, R. Nakatomi, T. Akagi, T. Hashikawa, R. Takahashi, Unsaturated fatty acids induce
1292 cytotoxic aggregate formation of amyotrophic lateral sclerosis-linked superoxide dismutase 1
1293 mutants, *The Journal of biological chemistry*, 280 (2005) 21515-21521.

1294 [164] Y. Liu, L. Yang, K. Conde-Knape, D. Beher, M.S. Shearman, N.S. Shachter, Fatty acids increase
1295 presenilin-1 levels and [gamma]-secretase activity in PSwt-1 cells, *Journal of lipid research*, 45 (2004)
1296 2368-2376.

1297 [165] D.M. Wilson, L.I. Binder, Free fatty acids stimulate the polymerization of tau and amyloid beta
1298 peptides. In vitro evidence for a common effector of pathogenesis in Alzheimer's disease, *The*
1299 *American journal of pathology*, 150 (1997) 2181-2195.

1300 [166] Z. Guan, Y. Wang, N.J. Cairns, P.L. Lantos, G. Dallner, P.J. Sindelar, Decrease and structural
1301 modifications of phosphatidylethanolamine plasmalogen in the brain with Alzheimer disease, *Journal*
1302 *of neuropathology and experimental neurology*, 58 (1999) 740-747.

1303 [167] M.O. Trepanier, K.D. Hildebrand, S.D. Nyamoya, S. Amor, R.P. Bazinet, M. Kipp,
1304 Phosphatidylcholine 36:1 concentration decreases along with demyelination in the cuprizone animal
1305 model and in post-mortem multiple sclerosis brain tissue, *J Neurochem*, 145 (2018) 504-515.

1306 [168] S.G. Snowden, A.A. Ebshiana, A. Hye, Y. An, O. Pletnikova, R. O'Brien, J. Troncoso, C. Legido-
1307 Quigley, M. Thambisetty, Association between fatty acid metabolism in the brain and Alzheimer
1308 disease neuropathology and cognitive performance: A nontargeted metabolomic study, *PLoS*
1309 *medicine*, 14 (2017) e1002266.

1310 [169] A.N. Fonteh, M. Cipolla, J. Chiang, X. Arakaki, M.G. Harrington, Human cerebrospinal fluid fatty
1311 acid levels differ between supernatant fluid and brain-derived nanoparticle fractions, and are altered
1312 in Alzheimer's disease, *PloS one*, 9 (2014) e100519.

1313 [170] L. Noguerras, H. Gonzalo, M. Jove, J. Sol, A. Gil-Sanchez, J.V. Hervas, P. Valcheva, C. Gonzalez-
1314 Mingot, M.J. Solana, S. Peralta, R. Pamplona, L. Brieva, Lipid profile of cerebrospinal fluid in multiple
1315 sclerosis patients: a potential tool for diagnosis, *Sci Rep*, 9 (2019) 11313.

1316 [171] M. Ouellet, V. Emond, C.T. Chen, C. Julien, F. Bourasset, S. Oddo, F. LaFerla, R.P. Bazinet, F.
1317 Calon, Diffusion of docosahexaenoic and eicosapentaenoic acids through the blood-brain barrier: An
1318 in situ cerebral perfusion study, *Neurochemistry international*, 55 (2009) 476-482.

1319 [172] S.K. Orr, M.O. Trepanier, R.P. Bazinet, n-3 Polyunsaturated fatty acids in animal models with
1320 neuroinflammation, *Prostaglandins Leukot Essent Fatty Acids*, 88 (2013) 97-103.

1321 [173] S. Laye, A. Nadjar, C. Joffre, R.P. Bazinet, Anti-Inflammatory Effects of Omega-3 Fatty Acids in
1322 the Brain: Physiological Mechanisms and Relevance to Pharmacology, *Pharmacol Rev*, 70 (2018) 12-
1323 38.

1324 [174] Y. Yan, W. Jiang, T. Spinetti, A. Tardivel, R. Castillo, C. Bourquin, G. Guarda, Z. Tian, J. Tschopp,
1325 R. Zhou, Omega-3 fatty acids prevent inflammation and metabolic disorder through inhibition of
1326 NLRP3 inflammasome activation, *Immunity*, 38 (2013) 1154-1163.

1327 [175] M.J. Allen, Y.Y. Fan, J.M. Monk, T.Y. Hou, R. Barhoumi, D.N. McMurray, R.S. Chapkin, n-3 PUFAs
1328 reduce T-helper 17 cell differentiation by decreasing responsiveness to interleukin-6 in isolated
1329 mouse splenic CD4(+) T cells, *J Nutr*, 144 (2014) 1306-1313.

1330 [176] A. Ferrante, D. Goh, D.P. Harvey, B.S. Robinson, C.S. Hii, E.J. Bates, S.J. Hardy, D.W. Johnson, A.
1331 Poulos, Neutrophil migration inhibitory properties of polyunsaturated fatty acids. The role of fatty
1332 acid structure, metabolism, and possible second messenger systems, *The Journal of clinical*
1333 *investigation*, 93 (1994) 1063-1070.

1334 [177] I. Vedin, T. Cederholm, Y. Freund Levi, H. Basun, A. Garlind, G. Faxen Irving, M.E. Jonhagen, B.
1335 Vessby, L.O. Wahlund, J. Palmblad, Effects of docosahexaenoic acid-rich n-3 fatty acid
1336 supplementation on cytokine release from blood mononuclear leukocytes: the OmegaAD study, *Am J*
1337 *Clin Nutr*, 87 (2008) 1616-1622.

1338 [178] O.R. Tamtaji, M. Taghizadeh, E. Aghadavod, A. Mafi, E. Dadgostar, R. Daneshvar Kakhaki, J.
1339 Abolhassani, Z. Asemi, The effects of omega-3 fatty acids and vitamin E co-supplementation on gene
1340 expression related to inflammation, insulin and lipid in patients with Parkinson's disease: A
1341 randomized, double-blind, placebo-controlled trial, *Clin Neurol Neurosurg*, 176 (2019) 116-121.

1342 [179] V. Ramirez-Ramirez, M.A. Macias-Islas, G.G. Ortiz, F. Pacheco-Moises, E.D. Torres-Sanchez, T.E.
1343 Sorto-Gomez, J.A. Cruz-Ramos, G. Orozco-Avina, A.J. Celis de la Rosa, Efficacy of fish oil on serum of
1344 TNF alpha , IL-1 beta , and IL-6 oxidative stress markers in multiple sclerosis treated with interferon
1345 beta-1b, *Oxid Med Cell Longev*, 2013 (2013) 709493.

1346 [180] G. Schmitz, J. Ecker, The opposing effects of n-3 and n-6 fatty acids, *Prog Lipid Res*, 47 (2008)
1347 147-155.

1348 [181] D.Y. Oh, S. Talukdar, E.J. Bae, T. Imamura, H. Morinaga, W. Fan, P. Li, W.J. Lu, S.M. Watkins,
1349 J.M. Olefsky, GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and
1350 insulin-sensitizing effects, *Cell*, 142 (2010) 687-698.

1351 [182] P. Kohli, B.D. Levy, Resolvins and protectins: mediating solutions to inflammation, *British*
1352 *journal of pharmacology*, 158 (2009) 960-971.

1353 [183] M.C. Basil, B.D. Levy, Specialized pro-resolving mediators: endogenous regulators of infection
1354 and inflammation, *Nature reviews. Immunology*, 16 (2016) 51-67.

1355 [184] J.K. Innes, P.C. Calder, Omega-6 fatty acids and inflammation, *Prostaglandins Leukot Essent*
1356 *Fatty Acids*, 132 (2018) 41-48.

1357 [185] H. Chen, J. Qin, P. Wei, J. Zhang, Q. Li, L. Fu, S. Li, C. Ma, B. Cong, Effects of leukotriene B4 and
1358 prostaglandin E2 on the differentiation of murine Foxp3+ T regulatory cells and Th17 cells,
1359 *Prostaglandins Leukot Essent Fatty Acids*, 80 (2009) 195-200.

1360 [186] J. Kumar, R. Gurav, V. Kale, L. Limaye, Exogenous addition of arachidonic acid to the culture
1361 media enhances the functionality of dendritic cells for their possible use in cancer immunotherapy,
1362 *PloS one*, 9 (2014) e111759.

1363 [187] D. Xu, T. Omura, N. Masaki, H. Arima, T. Banno, A. Okamoto, M. Hanada, S. Takei, S.
1364 Matsushita, E. Sugiyama, M. Setou, Y. Matsuyama, Increased arachidonic acid-containing
1365 phosphatidylcholine is associated with reactive microglia and astrocytes in the spinal cord after
1366 peripheral nerve injury, *Sci Rep*, 6 (2016) 26427.

1367 [188] K.E. Hopperton, M.O. Trepanier, V. Giuliano, R.P. Bazinet, Brain omega-3 polyunsaturated fatty
1368 acids modulate microglia cell number and morphology in response to intracerebroventricular
1369 amyloid-beta 1-40 in mice, *Journal of neuroinflammation*, 13 (2016) 257.

1370 [189] M. Gu, Y. Li, H. Tang, C. Zhang, W. Li, Y. Zhang, Y. Li, Y. Zhao, C. Song, Endogenous Omega (n)-3
1371 Fatty Acids in Fat-1 Mice Attenuated Depression-Like Behavior, Imbalance between Microglial M1
1372 and M2 Phenotypes, and Dysfunction of Neurotrophins Induced by Lipopolysaccharide
1373 Administration, *Nutrients*, 10 (2018).

1374 [190] L.S. Harbige, L. Layward, M.M. Morris-Downes, D.C. Dumonde, S. Amor, The protective effects
1375 of omega-6 fatty acids in experimental autoimmune encephalomyelitis (EAE) in relation to
1376 transforming growth factor-beta 1 (TGF-beta1) up-regulation and increased prostaglandin E2 (PGE2)
1377 production, *Clin Exp Immunol*, 122 (2000) 445-452.

1378 [191] F. Marangoni, C. Agostoni, C. Borghi, A.L. Catapano, H. Cena, A. Ghiselli, C. La Vecchia, G.
1379 Lercker, E. Manzato, A. Pirillo, G. Riccardi, P. Rise, F. Visioli, A. Poli, Dietary linoleic acid and human
1380 health: Focus on cardiovascular and cardiometabolic effects, *Atherosclerosis*, 292 (2020) 90-98.

1381 [192] M. Marklund, J.H.Y. Wu, F. Imamura, L.C. Del Gobbo, A. Fretts, J. de Goede, P. Shi, N. Tintle, M.
1382 Wennberg, S. Aslibekyan, T.A. Chen, M.C. de Oliveira Otto, Y. Hirakawa, H.H. Eriksen, J. Kroger, F.
1383 Laguzzi, M. Lankinen, R.A. Murphy, K. Prem, C. Samieri, J. Virtanen, A.C. Wood, K. Wong, W.S. Yang,
1384 X. Zhou, A. Baylin, J.M.A. Boer, I.A. Brouwer, H. Campos, P.H.M. Chaves, K.L. Chien, U. de Faire, L.
1385 Djousse, G. Eiriksdottir, N. El-Abbadi, N.G. Forouhi, J. Michael Gaziano, J.M. Geleijnse, B. Gigante, G.
1386 Giles, E. Guallar, V. Gudnason, T. Harris, W.S. Harris, C. Helmer, M.L. Hellenius, A. Hodge, F.B. Hu, P.F.
1387 Jacques, J.H. Jansson, A. Kalsbeek, K.T. Khaw, W.P. Koh, M. Laakso, K. Leander, H.J. Lin, L. Lind, R.
1388 Luben, J. Luo, B. McKnight, J. Mursu, T. Ninomiya, K. Overvad, B.M. Psaty, E. Rimm, M.B. Schulze, D.
1389 Siscovick, M. Skjelbo Nielsen, A.V. Smith, B.T. Steffen, L. Steffen, Q. Sun, J. Sundstrom, M.Y. Tsai, H.
1390 Tunstall-Pedoe, M.I.J. Uusitupa, R.M. van Dam, J. Veenstra, W.M. Monique Verschuren, N. Wareham,
1391 W. Willett, M. Woodward, J.M. Yuan, R. Micha, R.N. Lemaitre, D. Mozaffarian, U. Riserus, H. Cohorts
1392 for, A. Aging Research in Genomic Epidemiology Fatty, C. Outcomes Research, Biomarkers of Dietary
1393 Omega-6 Fatty Acids and Incident Cardiovascular Disease and Mortality, *Circulation*, 139 (2019)
1394 2422-2436.

1395 [193] M. Farinotti, L. Vacchi, S. Simi, C. Di Pietrantonj, L. Brait, G. Filippini, Dietary interventions for
1396 multiple sclerosis, *Cochrane Database Syst Rev*, 12 (2012) CD004192.

1397 [194] J.R. Silva, B. Burger, C.M.C. Kuhl, T. Candreva, M.B.P. Dos Anjos, H.G. Rodrigues, Wound Healing
1398 and Omega-6 Fatty Acids: From Inflammation to Repair, *Mediators of inflammation*, 2018 (2018)
1399 2503950.

1400 [195] B.D. Levy, C.B. Clish, B. Schmidt, K. Gronert, C.N. Serhan, Lipid mediator class switching during
1401 acute inflammation: signals in resolution, *Nature immunology*, 2 (2001) 612-619.

1402 [196] N. Hussein, E. Ah-Sing, P. Wilkinson, C. Leach, B.A. Griffin, D.J. Millward, Long-chain conversion
1403 of [¹³C]linoleic acid and alpha-linolenic acid in response to marked changes in their dietary intake in
1404 men, *Journal of lipid research*, 46 (2005) 269-280.

1405 [197] E. Kawakita, M. Hashimoto, O. Shido, Docosahexaenoic acid promotes neurogenesis in vitro
1406 and in vivo, *Neuroscience*, 139 (2006) 991-997.

1407 [198] H. Hejr, M. Ghareghani, K. Zibara, M. Ghafari, F. Sadri, Z. Salehpour, A. Hamedi, K. Negintaji, H.
1408 Azari, A. Ghanbari, The ratio of 1/3 linoleic acid to alpha linolenic acid is optimal for
1409 oligodendrogenesis of embryonic neural stem cells, *Neuroscience letters*, 651 (2017) 216-225.

1410 [199] M. Katakura, M. Hashimoto, T. Okui, H.M. Shahdat, K. Matsuzaki, O. Shido, Omega-3
1411 polyunsaturated Fatty acids enhance neuronal differentiation in cultured rat neural stem cells, *Stem
1412 Cells Int*, 2013 (2013) 490476.

1413 [200] F. Calderon, H.Y. Kim, Docosahexaenoic acid promotes neurite growth in hippocampal neurons,
1414 *J Neurochem*, 90 (2004) 979-988.

1415 [201] L.G. Robson, S. Dyal, D. Sidloff, A.T. Michael-Titus, Omega-3 polyunsaturated fatty acids
1416 increase the neurite outgrowth of rat sensory neurones throughout development and in aged
1417 animals, *Neurobiology of aging*, 31 (2010) 678-687.

1418 [202] A. Bernardo, M.L. Giammarco, C. De Nuccio, M.A. Ajmone-Cat, S. Visentin, R. De Simone, L.
1419 Minghetti, Docosahexaenoic acid promotes oligodendrocyte differentiation via PPAR-gamma
1420 signalling and prevents tumor necrosis factor-alpha-dependent maturational arrest, *Biochim Biophys
1421 Acta Mol Cell Biol Lipids*, 1862 (2017) 1013-1023.

1422 [203] N. Lewkowicz, P. Piatek, M. Namiecinska, M. Domowicz, R. Bonikowski, J. Szemraj, P.
1423 Przygodzka, M. Stasiolek, P. Lewkowicz, Naturally Occurring Nervonic Acid Ester Improves Myelin
1424 Synthesis by Human Oligodendrocytes, *Cells*, 8 (2019).

1425 [204] E. Siegert, F. Paul, M. Rothe, K.H. Weylandt, The effect of omega-3 fatty acids on central
1426 nervous system remyelination in fat-1 mice, *BMC Neurosci*, 18 (2017) 19.

1427 [205] O. Torkildsen, L.A. Brunborg, F. Thorsen, S.J. Mork, M. Stangel, K.M. Myhr, L. Bo, Effects of
1428 dietary intervention on MRI activity, de- and remyelination in the cuprizone model for demyelination,
1429 *Experimental neurology*, 215 (2009) 160-166.

1430 [206] R.E. Ward, W. Huang, O.E. Curran, J.V. Priestley, A.T. Michael-Titus, Docosahexaenoic acid
1431 prevents white matter damage after spinal cord injury, *J Neurotrauma*, 27 (2010) 1769-1780.

1432 [207] W.L. Huang, V.R. King, O.E. Curran, S.C. Dyllal, R.E. Ward, N. Lal, J.V. Priestley, A.T. Michael-
1433 Titus, A combination of intravenous and dietary docosahexaenoic acid significantly improves
1434 outcome after spinal cord injury, *Brain : a journal of neurology*, 130 (2007) 3004-3019.

1435 [208] C. Luo, H. Ren, J.B. Wan, X. Yao, X. Zhang, C. He, K.F. So, J.X. Kang, Z. Pei, H. Su, Enriched
1436 endogenous omega-3 fatty acids in mice protect against global ischemia injury, *Journal of lipid
1437 research*, 55 (2014) 1288-1297.

1438 [209] C.Y. Chang, Y.H. Kuan, J.R. Li, W.Y. Chen, Y.C. Ou, H.C. Pan, S.L. Liao, S.L. Raung, C.J. Chang, C.J.
1439 Chen, Docosahexaenoic acid reduces cellular inflammatory response following permanent focal
1440 cerebral ischemia in rats, *J Nutr Biochem*, 24 (2013) 2127-2137.

1441 [210] K.J. Kwon, Y.S. Jung, S.H. Lee, C.H. Moon, E.J. Baik, Arachidonic acid induces neuronal death
1442 through lipoxygenase and cytochrome P450 rather than cyclooxygenase, *Journal of neuroscience
1443 research*, 81 (2005) 73-84.

1444 [211] B. Kriem, I. Spohne, A. Fivre, C. Malaplate-Armand, K. Lozac'h-Pillot, V. Koziel, F.T. Yen-Potin, B.
1445 Bihain, T. Oster, J.L. Olivier, T. Pillot, Cytosolic phospholipase A2 mediates neuronal apoptosis
1446 induced by soluble oligomers of the amyloid-beta peptide, *FASEB journal : official publication of the
1447 Federation of American Societies for Experimental Biology*, 19 (2005) 85-87.

1448 [212] D.D. Fraser, K. Hoehn, S. Weiss, B.A. MacVicar, Arachidonic acid inhibits sodium currents and
1449 synaptic transmission in cultured striatal neurons, *Neuron*, 11 (1993) 633-644.

1450 [213] Z. Amtul, M. Uhrig, L. Wang, R.F. Rozmahel, K. Beyreuther, Detrimental effects of arachidonic
1451 acid and its metabolites in cellular and mouse models of Alzheimer's disease: structural insight,
1452 *Neurobiology of aging*, 33 (2012) 831 e821-831.

1453 [214] M.H. Thomas, C. Paris, M. Magnien, J. Colin, S. Pelleieux, F. Coste, M.C. Escanye, T. Pillot, J.L.
1454 Olivier, Dietary arachidonic acid increases deleterious effects of amyloid-beta oligomers on learning
1455 abilities and expression of AMPA receptors: putative role of the ACSL4-cPLA2 balance, *Alzheimers
1456 Res Ther*, 9 (2017) 69.

1457 [215] E. Hatanaka, A. Harauma, H. Yasuda, J. Watanabe, M.T. Nakamura, N. Salem, Jr., T. Moriguchi,
1458 Essentiality of arachidonic acid intake in murine early development, *Prostaglandins Leukot Essent
1459 Fatty Acids*, 108 (2016) 51-57.

1460 [216] A. Harauma, H. Yasuda, E. Hatanaka, M.T. Nakamura, N. Salem, Jr., T. Moriguchi, The
1461 essentiality of arachidonic acid in addition to docosahexaenoic acid for brain growth and function,
1462 *Prostaglandins Leukot Essent Fatty Acids*, 116 (2017) 9-18.

1463 [217] J. Zhao, M.R. Del Bigio, H.A. Weiler, Maternal arachidonic acid supplementation improves
1464 neurodevelopment in young adult offspring from rat dams with and without diabetes, *Prostaglandins
1465 Leukot Essent Fatty Acids*, 84 (2011) 63-70.

1466 [218] C. Theda, A.B. Moser, J.M. Powers, H.W. Moser, Phospholipids in X-linked
1467 adrenoleukodystrophy white matter: fatty acid abnormalities before the onset of demyelination,
1468 *Journal of the neurological sciences*, 110 (1992) 195-204.

1469 [219] P. Sharp, D. Johnson, A. Poulos, Molecular species of phosphatidylcholine containing very long
1470 chain fatty acids in human brain: enrichment in X-linked adrenoleukodystrophy brain and diseases of
1471 peroxisome biogenesis brain, *J Neurochem*, 56 (1991) 30-37.

1472 [220] D.P. Marchetti, B. Donida, C.E. Jacques, M. Deon, T.C. Hauschild, P. Koehler-Santos, D. de
1473 Moura Coelho, A.S. Coitinho, L.B. Jardim, C.R. Vargas, Inflammatory profile in X-linked

1474 adrenoleukodystrophy patients: Understanding disease progression, *J Cell Biochem*, 119 (2018) 1223-
1475 1233.

1476 [221] A.S. Paintlia, A.G. Gilg, M. Khan, A.K. Singh, E. Barbosa, I. Singh, Correlation of very long chain
1477 fatty acid accumulation and inflammatory disease progression in childhood X-ALD: implications for
1478 potential therapies, *Neurobiology of disease*, 14 (2003) 425-439.

1479 [222] F.D. Weber, C. Wiesinger, S. Forss-Petter, G. Regelsberger, A. Einwich, W.H. Weber, W. Kohler,
1480 H. Stockinger, J. Berger, X-linked adrenoleukodystrophy: very long-chain fatty acid metabolism is
1481 severely impaired in monocytes but not in lymphocytes, *Hum Mol Genet*, 23 (2014) 2542-2550.

1482 [223] N. Yanagisawa, K. Shimada, T. Miyazaki, A. Kume, Y. Kitamura, K. Sumiyoshi, T. Kiyanagi, T.
1483 Iesaki, N. Inoue, H. Daida, Enhanced production of nitric oxide, reactive oxygen species, and pro-
1484 inflammatory cytokines in very long chain saturated fatty acid-accumulated macrophages, *Lipids*
1485 *Health Dis*, 7 (2008) 48.

1486 [224] H.H. Schaumburg, J.M. Powers, C.S. Raine, K. Suzuki, E.P. Richardson, Jr.,
1487 Adrenoleukodystrophy. A clinical and pathological study of 17 cases, *Archives of neurology*, 32 (1975)
1488 577-591.

1489 [225] F.S. Eichler, J.Q. Ren, M. Cossoy, A.M. Rietsch, S. Nagpal, A.B. Moser, M.P. Frosch, R.M.
1490 Ransohoff, Is microglial apoptosis an early pathogenic change in cerebral X-linked
1491 adrenoleukodystrophy?, *Annals of neurology*, 63 (2008) 729-742.

1492 [226] T. Karasawa, A. Kawashima, F. Usui-Kawanishi, S. Watanabe, H. Kimura, R. Kamata, K.
1493 Shirasuna, Y. Koyama, A. Sato-Tomita, T. Matsuzaka, H. Tomoda, S.Y. Park, N. Shibayama, H.
1494 Shimano, T. Kasahara, M. Takahashi, Saturated Fatty Acids Undergo Intracellular Crystallization and
1495 Activate the NLRP3 Inflammasome in Macrophages, *Arterioscler Thromb Vasc Biol*, 38 (2018) 744-
1496 756.

1497 [227] N. Kruska, P. Schonfeld, A. Pujol, G. Reiser, Astrocytes and mitochondria from
1498 adrenoleukodystrophy protein (ABCD1)-deficient mice reveal that the adrenoleukodystrophy-
1499 associated very long-chain fatty acids target several cellular energy-dependent functions, *Biochimica*
1500 *et biophysica acta*, 1852 (2015) 925-936.

1501 [228] J. Singh, M. Khan, I. Singh, Silencing of *Abcd1* and *Abcd2* genes sensitizes astrocytes for
1502 inflammation: implication for X-adrenoleukodystrophy, *Journal of lipid research*, 50 (2009) 135-147.

1503 [229] A. Zarrouk, A. Vejux, T. Nury, H.I. El Hajj, M. Haddad, M. Cherkaoui-Malki, J.M. Riedinger, M.
1504 Hammami, G. Lizard, Induction of mitochondrial changes associated with oxidative stress on very
1505 long chain fatty acids (C22:0, C24:0, or C26:0)-treated human neuronal cells (SK-NB-E), *Oxid Med Cell*
1506 *Longev*, 2012 (2012) 623257.

1507 [230] M. Baarine, K. Ragot, A. Athias, T. Nury, Z. Kattan, E.C. Genin, P. Andreoletti, F. Menetrier, J.M.
1508 Riedinger, M. Bardou, G. Lizard, Incidence of *Abcd1* level on the induction of cell death and organelle
1509 dysfunctions triggered by very long chain fatty acids and TNF-alpha on oligodendrocytes and
1510 astrocytes, *Neurotoxicology*, 33 (2012) 212-228.

1511 [231] S. Hein, P. Schonfeld, S. Kahlert, G. Reiser, Toxic effects of X-linked adrenoleukodystrophy-
1512 associated, very long chain fatty acids on glial cells and neurons from rat hippocampus in culture,
1513 *Hum Mol Genet*, 17 (2008) 1750-1761.

1514 [232] M. Baarine, C. Beeson, A. Singh, I. Singh, ABCD1 deletion-induced mitochondrial dysfunction is
1515 corrected by SAHA: implication for adrenoleukodystrophy, *J Neurochem*, 133 (2015) 380-396.

1516 [233] L.R. Parisi, S. Sowlati-Hashjin, I.A. Berhane, S.L. Galster, K.A. Carter, J.F. Lovell, S.R. Chemler, M.
1517 Karttunen, G.E. Atilla-Gokcumen, Membrane disruption by very long chain fatty acids during
1518 necroptosis, *ACS Chem Biol*, (2019).

1519 [234] L.R. Parisi, N. Li, G.E. Atilla-Gokcumen, Very Long Chain Fatty Acids Are Functionally Involved in
1520 Necroptosis, *Cell Chem Biol*, 24 (2017) 1445-1454 e1448.

1521 [235] J. Yuan, P. Amin, D. Ofengeim, Necroptosis and RIPK1-mediated neuroinflammation in CNS
1522 diseases, *Nature reviews. Neuroscience*, 20 (2019) 19-33.

1523 [236] J. Berger, S. Forss-Petter, F.S. Eichler, Pathophysiology of X-linked adrenoleukodystrophy,
1524 *Biochimie*, 98 (2014) 135-142.

1525 [237] J. Kou, G.G. Kovacs, R. Hoftberger, W. Kulik, A. Brodde, S. Forss-Petter, S. Honigschnabl, A.
1526 Gleiss, B. Brugger, R. Wanders, W. Just, H. Budka, S. Jungwirth, P. Fischer, J. Berger, Peroxisomal
1527 alterations in Alzheimer's disease, *Acta neuropathologica*, 122 (2011) 271-283.

1528 [238] E. Gray, C. Rice, K. Hares, J. Redondo, K. Kemp, M. Williams, A. Brown, N. Scolding, A. Wilkins,
1529 Reductions in neuronal peroxisomes in multiple sclerosis grey matter, *Multiple sclerosis*, 20 (2014)
1530 651-659.

1531 [239] D.S. Jo, D.H. Cho, Peroxisomal dysfunction in neurodegenerative diseases, *Arch Pharm Res*, 42
1532 (2019) 393-406.

1533 [240] C.N. Serhan, B.D. Levy, Resolvins in inflammation: emergence of the pro-resolving superfamily
1534 of mediators, *The Journal of clinical investigation*, 128 (2018) 2657-2669.

1535 [241] C.N. Serhan, A search for endogenous mechanisms of anti-inflammation uncovers novel
1536 chemical mediators: missing links to resolution, *Histochem Cell Biol*, 122 (2004) 305-321.

1537 [242] J.N. Fullerton, D.W. Gilroy, Resolution of inflammation: a new therapeutic frontier, *Nature*
1538 *reviews. Drug discovery*, 15 (2016) 551-567.

1539 [243] C.N. Serhan, S.D. Brain, C.D. Buckley, D.W. Gilroy, C. Haslett, L.A. O'Neill, M. Perretti, A.G. Rossi,
1540 J.L. Wallace, Resolution of inflammation: state of the art, definitions and terms, *FASEB journal* :
1541 official publication of the Federation of American Societies for Experimental Biology, 21 (2007) 325-
1542 332.

1543 [244] M.A. Sugimoto, L.P. Sousa, V. Pinho, M. Perretti, M.M. Teixeira, Resolution of Inflammation:
1544 What Controls Its Onset?, *Frontiers in immunology*, 7 (2016) 160.

1545 [245] V. Chiurchiu, A. Leuti, M. Maccarrone, Bioactive Lipids and Chronic Inflammation: Managing the
1546 Fire Within, *Frontiers in immunology*, 9 (2018) 38.

1547 [246] N. Chiang, C.N. Serhan, Structural elucidation and physiologic functions of specialized pro-
1548 resolving mediators and their receptors, *Mol Aspects Med*, 58 (2017) 114-129.

1549 [247] R.A. Colas, M. Shinohara, J. Dalli, N. Chiang, C.N. Serhan, Identification and signature profiles
1550 for pro-resolving and inflammatory lipid mediators in human tissue, *Am J Physiol Cell Physiol*, 307
1551 (2014) C39-54.

1552 [248] I. Tabas, C.K. Glass, Anti-inflammatory therapy in chronic disease: challenges and opportunities,
1553 *Science*, 339 (2013) 166-172.

1554 [249] X. Wang, M. Zhu, E. Hjorth, V. Cortes-Toro, H. Eyjolfsdottir, C. Graff, I. Nennesmo, J. Palmblad,
1555 M. Eriksdotter, K. Sambamurti, J.M. Fitzgerald, C.N. Serhan, A.C. Granholm, M. Schultzberg,
1556 Resolution of inflammation is altered in Alzheimer's disease, *Alzheimers Dement*, 11 (2015) 40-50
1557 e41-42.

1558 [250] M. Zhu, X. Wang, E. Hjorth, R.A. Colas, L. Schroeder, A.C. Granholm, C.N. Serhan, M.
1559 Schultzberg, Pro-Resolving Lipid Mediators Improve Neuronal Survival and Increase Abeta42
1560 Phagocytosis, *Mol Neurobiol*, 53 (2016) 2733-2749.

1561 [251] M. Fiala, G. Kooij, K. Wagner, B. Hammock, M. Pellegrini, Modulation of innate immunity of
1562 patients with Alzheimer's disease by omega-3 fatty acids, *FASEB journal* : official publication of the
1563 Federation of American Societies for Experimental Biology, 31 (2017) 3229-3239.

1564 [252] G. Kooij, C. Derada Troletti, A. Leuti, P.C. Norris, I. Riley, M. Albanese, S. Ruggieri, S. Libreros,
1565 S.M.A. van der Pol, B. van Het Hof, Y. Schell, G. Guerrera, F. Buttari, N.B. Mercuri, D. Centonze, C.
1566 Gasperini, L. Battistini, H.E. de Vries, C.N. Serhan, V. Chiurchiu, Specialized pro-resolving lipid
1567 mediators are differentially altered in peripheral blood of patients with multiple sclerosis and
1568 attenuate monocyte and blood-brain barrier dysfunction, *Haematologica*, (2019).

1569 [253] C.N. Serhan, N. Chiang, Resolution phase lipid mediators of inflammation: agonists of
1570 resolution, *Curr Opin Pharmacol*, 13 (2013) 632-640.

1571 [254] I. Francos-Quijorna, E. Santos-Nogueira, K. Gronert, A.B. Sullivan, M.A. Kopp, B. Brommer, S.
1572 David, J.M. Schwab, R. Lopez-Vales, Maresin 1 Promotes Inflammatory Resolution, Neuroprotection,
1573 and Functional Neurological Recovery After Spinal Cord Injury, *The Journal of neuroscience* : the
1574 official journal of the Society for Neuroscience, 37 (2017) 11731-11743.

1575 [255] H.C. Dunn, R.R. Ager, D. Baglietto-Vargas, D. Cheng, M. Kitazawa, D.H. Cribbs, R. Medeiros,
1576 Restoration of lipoxin A4 signaling reduces Alzheimer's disease-like pathology in the 3xTg-AD mouse
1577 model, *J Alzheimers Dis*, 43 (2015) 893-903.

1578 [256] R. Medeiros, M. Kitazawa, G.F. Passos, D. Baglietto-Vargas, D. Cheng, D.H. Cribbs, F.M. LaFerla,
1579 Aspirin-triggered lipoxin A4 stimulates alternative activation of microglia and reduces Alzheimer
1580 disease-like pathology in mice, *The American journal of pathology*, 182 (2013) 1780-1789.

1581 [257] M.S. Cortina, J. He, T. Russ, N.G. Bazan, H.E. Bazan, Neuroprotectin D1 restores corneal nerve
1582 integrity and function after damage from experimental surgery, *Invest Ophthalmol Vis Sci*, 54 (2013)
1583 4109-4116.

1584 [258] A. Reis, A. Rudnitskaya, G.J. Blackburn, N. Mohd Fauzi, A.R. Pitt, C.M. Spickett, A comparison of
1585 five lipid extraction solvent systems for lipidomic studies of human LDL, *Journal of lipid research*, 54
1586 (2013) 1812-1824.

1587 [259] M.A. Lopez-Bascon, M. Calderon-Santiago, J. Sanchez-Ceinos, A. Fernandez-Vega, R. Guzman-
1588 Ruiz, J. Lopez-Miranda, M.M. Malagon, F. Priego-Capote, Influence of sample preparation on
1589 lipidomics analysis of polar lipids in adipose tissue, *Talanta*, 177 (2018) 86-93.

1590 [260] G. Vale, S.A. Martin, M.A. Mitsche, B.M. Thompson, K.M. Eckert, J.G. McDonald, Three-phase
1591 liquid extraction: a simple and fast method for lipidomic workflows, *Journal of lipid research*, 60
1592 (2019) 694-706.

1593 [261] J. Chong, D.S. Wishart, J. Xia, Using MetaboAnalyst 4.0 for Comprehensive and Integrative
1594 Metabolomics Data Analysis, *Curr Protoc Bioinformatics*, 68 (2019) e86.

1595 [262] E. Fahy, S. Subramaniam, R.C. Murphy, M. Nishijima, C.R. Raetz, T. Shimizu, F. Spener, G. van
1596 Meer, M.J. Wakelam, E.A. Dennis, Update of the LIPID MAPS comprehensive classification system for
1597 lipids, *Journal of lipid research*, 50 Suppl (2009) S9-14.

1598 [263] T. Kind, K.H. Liu, D.Y. Lee, B. DeFelice, J.K. Meissen, O. Fiehn, LipidBlast in silico tandem mass
1599 spectrometry database for lipid identification, *Nat Methods*, 10 (2013) 755-758.

1600 [264] X. Han, R.W. Gross, Global analyses of cellular lipidomes directly from crude extracts of
1601 biological samples by ESI mass spectrometry: a bridge to lipidomics, *Journal of lipid research*, 44
1602 (2003) 1071-1079.

1603 [265] Z. Takats, J.M. Wiseman, B. Gologan, R.G. Cooks, Mass spectrometry sampling under ambient
1604 conditions with desorption electrospray ionization, *Science*, 306 (2004) 471-473.

1605 [266] B. Fuchs, J. Schiller, MALDI-TOF MS analysis of lipids from cells, tissues and body fluids, *Subcell
1606 Biochem*, 49 (2008) 541-565.

1607 [267] F.F. Hsu, Mass spectrometry-based shotgun lipidomics - a critical review from the technical
1608 point of view, *Anal Bioanal Chem*, 410 (2018) 6387-6409.

1609 [268] J.H. Hong, J.W. Kang, D.K. Kim, S.H. Baik, K.H. Kim, S.R. Shanta, J.H. Jung, I. Mook-Jung, K.P. Kim,
1610 Global changes of phospholipids identified by MALDI imaging mass spectrometry in a mouse model
1611 of Alzheimer's disease, *Journal of lipid research*, 57 (2016) 36-45.

1612 [269] A.P. Bowman, J.F.J. Bogie, J.J.A. Hendriks, M. Haidar, M. Belov, R.M.A. Heeren, S.R. Ellis,
1613 Evaluation of lipid coverage and high spatial resolution MALDI-imaging capabilities of oversampling
1614 combined with laser post-ionisation, *Anal Bioanal Chem*, (2019).

1615 [270] A. Lamaziere, D. Richard, U. Barbe, K. Kefi, P. Bausero, C. Wolf, F. Visioli, Differential
1616 distribution of DHA-phospholipids in rat brain after feeding: A lipidomic approach, *Prostaglandins
1617 Leukot Essent Fatty Acids*, 84 (2011) 7-11.

1618 [271] I. Carrie, M. Clement, D. de Javel, H. Frances, J.M. Bourre, Specific phospholipid fatty acid
1619 composition of brain regions in mice. Effects of n-3 polyunsaturated fatty acid deficiency and
1620 phospholipid supplementation, *Journal of lipid research*, 41 (2000) 465-472.

1621 [272] M. Chavko, E.M. Nemoto, Regional differences in rat brain lipids during global ischemia, *Stroke;
1622 a journal of cerebral circulation*, 23 (1992) 1000-1004.

1623 [273] J.O. Ojo, M. Algamal, P. Leary, L. Abdullah, B. Mouzon, J.E. Evans, M. Mullan, F. Crawford,
1624 Converging and Differential Brain Phospholipid Dysregulation in the Pathogenesis of Repetitive Mild
1625 Traumatic Brain Injury and Alzheimer's Disease, *Front Neurosci*, 13 (2019) 103.

1626 [274] Y.H. Rustam, G.E. Reid, Analytical Challenges and Recent Advances in Mass Spectrometry Based
1627 Lipidomics, *Anal Chem*, 90 (2018) 374-397.

1628 [275] S. Agatonovic-Kustrin, D.W. Morton, V. Smirnov, A. Petukhov, V. Gegechkori, V. Kuzina, N.
1629 Gorpinchenko, G. Ramenskaya, Analytical Strategies in Lipidomics for Discovery of Functional
1630 Biomarkers from Human Saliva, *Disease markers*, 2019 (2019) 6741518.

1631 [276] J.A. Bowden, C.Z. Ulmer, C.M. Jones, J.P. Koelmel, R.A. Yost, NIST lipidomics workflow
1632 questionnaire: an assessment of community-wide methodologies and perspectives, *Metabolomics*,
1633 14 (2018) 53.

1634 [277] T.M. da Silva, R.P. Munhoz, C. Alvarez, K. Naliwaiko, A. Kiss, R. Andreatini, A.C. Ferraz,
1635 Depression in Parkinson's disease: a double-blind, randomized, placebo-controlled pilot study of
1636 omega-3 fatty-acid supplementation, *J Affect Disord*, 111 (2008) 351-359.

1637 [278] M. Taghizadeh, O.R. Tamtaji, E. Dadgostar, R. Daneshvar Kakhaki, F. Bahmani, J. Abolhassani,
1638 M.H. Aarabi, E. Kouchaki, M.R. Memarzadeh, Z. Asemi, The effects of omega-3 fatty acids and vitamin
1639 E co-supplementation on clinical and metabolic status in patients with Parkinson's disease: A
1640 randomized, double-blind, placebo-controlled trial, *Neurochemistry international*, 108 (2017) 183-
1641 189.

1642 [279] Y. Freund-Levi, M. Eriksson-Jonhagen, T. Cederholm, H. Basun, G. Faxen-Irving, A. Garlind, I.
1643 Vedin, B. Vessby, L.O. Wahlund, J. Palmblad, Omega-3 fatty acid treatment in 174 patients with mild
1644 to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial, *Archives of*
1645 *neurology*, 63 (2006) 1402-1408.

1646 [280] Y. Freund-Levi, H. Basun, T. Cederholm, G. Faxen-Irving, A. Garlind, M. Grut, I. Vedin, J.
1647 Palmblad, L.O. Wahlund, M. Eriksson-Jonhagen, Omega-3 supplementation in mild to moderate
1648 Alzheimer's disease: effects on neuropsychiatric symptoms, *Int J Geriatr Psychiatry*, 23 (2008) 161-
1649 169.

1650 [281] C.C. Chiu, K.P. Su, T.C. Cheng, H.C. Liu, C.J. Chang, M.E. Dewey, R. Stewart, S.Y. Huang, The
1651 effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: a
1652 preliminary randomized double-blind placebo-controlled study, *Prog Neuropsychopharmacol Biol*
1653 *Psychiatry*, 32 (2008) 1538-1544.

1654 [282] J.F. Quinn, R. Raman, R.G. Thomas, K. Yurko-Mauro, E.B. Nelson, C. Van Dyck, J.E. Galvin, J.
1655 Emond, C.R. Jack, Jr., M. Weiner, L. Shinto, P.S. Aisen, Docosahexaenoic acid supplementation and
1656 cognitive decline in Alzheimer disease: a randomized trial, *JAMA : the journal of the American*
1657 *Medical Association*, 304 (2010) 1903-1911.

1658 [283] L. Shinto, J. Quinn, T. Montine, H.H. Dodge, W. Woodward, S. Baldauf-Wagner, D. Waichunas, L.
1659 Bumgarner, D. Bourdette, L. Silbert, J. Kaye, A randomized placebo-controlled pilot trial of omega-3
1660 fatty acids and alpha lipoic acid in Alzheimer's disease, *J Alzheimers Dis*, 38 (2014) 111-120.

1661 [284] M.A. Phillips, C.E. Childs, P.C. Calder, P.J. Rogers, No Effect of Omega-3 Fatty Acid
1662 Supplementation on Cognition and Mood in Individuals with Cognitive Impairment and Probable
1663 Alzheimer's Disease: A Randomised Controlled Trial, *Int J Mol Sci*, 16 (2015) 24600-24613.

1664 [285] P. Scheltens, P.J. Kamphuis, F.R. Verhey, M.G. Olde Rikkert, R.J. Wurtman, D. Wilkinson, J.W.
1665 Twisk, A. Kurz, Efficacy of a medical food in mild Alzheimer's disease: A randomized, controlled trial,
1666 *Alzheimers Dement*, 6 (2010) 1-10 e11.

1667 [286] P. Scheltens, J.W. Twisk, R. Blesa, E. Scarpini, C.A. von Arnim, A. Bongers, J. Harrison, S.H.
1668 Swinkels, C.J. Stam, H. de Waal, R.J. Wurtman, R.L. Wieggers, B. Vellas, P.J. Kamphuis, Efficacy of
1669 Souvenaid in mild Alzheimer's disease: results from a randomized, controlled trial, *J Alzheimers Dis*,
1670 31 (2012) 225-236.

1671 [287] H. de Waal, C.J. Stam, M.M. Lansbergen, R.L. Wieggers, P.J. Kamphuis, P. Scheltens, F. Maestu,
1672 E.C. van Straaten, The effect of souvenaid on functional brain network organisation in patients with
1673 mild Alzheimer's disease: a randomised controlled study, *PloS one*, 9 (2014) e86558.

1674 [288] H. Soininen, A. Solomon, P.J. Visser, S.B. Hendrix, K. Blennow, M. Kivipelto, T. Hartmann, g.
1675 LipiDiDiet clinical study, 24-month intervention with a specific multinutrient in people with
1676 prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial, *Lancet*
1677 *Neurol*, 16 (2017) 965-975.

1678 [289] R.C. Shah, P.J. Kamphuis, S. Leurgans, S.H. Swinkels, C.H. Sadowsky, A. Bongers, S.A. Rappaport,
1679 J.F. Quinn, R.L. Wieggers, P. Scheltens, D.A. Bennett, The S-Connect study: results from a randomized,
1680 controlled trial of Souvenaid in mild-to-moderate Alzheimer's disease, *Alzheimers Res Ther*, 5 (2013)
1681 59.

1682 [290] W.A. AlAmmar, F.H. Albeesh, L.M. Ibrahim, Y.Y. Algindan, L.Z. Yamani, R.Y. Khattab, Effect of
1683 omega-3 fatty acids and fish oil supplementation on multiple sclerosis: a systematic review, *Nutr*
1684 *Neurosci*, (2019) 1-11.

1685 [291] S. Morsy, S.M. Khalil, M.F. Doheim, M.G. Kamel, D.S.M. El-Basiony, H.I. Ahmed Hassan, A.A.
1686 Eisa, C.T. Anh Ngoc, N.P. Dang, K. Hirayama, N.T. Huy, Efficacy of ethyl-EPA as a treatment for
1687 Huntington disease: a systematic review and meta-analysis, *Acta Neuropsychiatr*, 31 (2019) 175-185.

1688 [292] D. Kullenberg, L.A. Taylor, M. Schneider, U. Massing, Health effects of dietary phospholipids,
1689 *Lipids Health Dis*, 11 (2012) 3.

1690 [293] D. Wlodarek, Role of Ketogenic Diets in Neurodegenerative Diseases (Alzheimer's Disease and
1691 Parkinson's Disease), *Nutrients*, 11 (2019).

1692