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Mini-Review: ENTERIC GLIAL CELL HETEROGENEITY: IS IT ALL ABOUT THE NICHE?

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Abstract

Enteric glial cells represent the enteric population of peripheral neuroglia. According to their ‘glial’ nature, their principal function is to support enteric neurons in both structural and functional ways. Mounting evidence however demonstrates that enteric glial cells crucially contribute to the majority of enteric nervous system functions, thus acting as pivotal players in the maintenance of gut homeostasis. Various types of enteric glia are present within the gut wall, creating an intricate interaction network with other gastrointestinal cell types. Their distribution throughout the different layers of the gut wall translates in characteristic phenotypes that are tailored to the local tissue requirements of the digestive tract. This heterogeneity is assumed to be mirrored by functional specialization, but the extensive plasticity and versatility of enteric glial cells complicates a one on one phenotype/function definition. Moreover, the relative contribution of niche-specific signals versus lineage determinants for driving enteric glial heterogeneity is still uncertain. In this review we focus on the current understanding of phenotypic and functional enteric glial cell heterogeneity, from a microenvironmental and developmental perspective.

Keywords

Cellular plasticity; Enteric nervous system; Gastrointestinal; Neural crest; Neurogenic; Schwann cell precursors

Introduction

Enteric glia constitute a unique population of peripheral neuroglia involved in the regulation of gut function and gastrointestinal homeostasis. A growing body of evidence indicates that enteric glia are among the most dynamic cellular components of the digestive tract. Sensitive, and rapidly responding to changes in their microenvironment, enteric glia engage in crosstalk with a multitude of cell types and cellular systems within the gut [1-3]. Next to the bidirectional communication with enteric neurons [4-7], their evident companions within the enteric nervous system (ENS), enteric glial cells also interact with extrinsic nerves [8, 9], as well as with cells of the intestinal epithelium [10] and immune system [11]. The latter is reflected by their roles in barrier function and host defense, and is consistent with the notion that enteric glial cells are not confined to the perimeter of enteric ganglia. Accordingly, and in line with their high level of plasticity, enteric glial cells are implicated in a broad spectrum of gastrointestinal disorders [12]. In pathological states where the ENS is severely affected, enteric glial cells can serve as a source for new enteric neurons [13-17], underscoring their primary function in the gut, which is to support ENS activity and to ensure that enteric neurons can fulfil their tasks [18].

Classification of enteric glia

Considering this variegate set of functions, it is increasingly recognized that these are not executed by a single, multitasking type of enteric glial cell. Currently, the primary stratification of enteric glial cells is still based on their morphological characteristics, identifying four distinctive subtypes, called enteric glia type I, II, III and IV [19-21]. Although this classification is mainly based on enteric glia in the mouse ileum, these phenotypic subtypes and their compartmentalization seem to be preserved throughout the gastrointestinal tract [22], as well as in other species, such as zebrafish [23] and humans [24, 25]. Consistently, the morphological characteristics of enteric glia appear to be closely linked to their unique location within the gut wall (**Fig. 1**). Therefore, it is important to discriminate between for instance type I enteric glia residing within the myenteric plexus and those of the submucosal plexus [1]. Type I enteric glial cells are the only morphological glial subtype located within enteric ganglia where they closely associate with perikarya and engage in crosstalk with enteric neurons [5, 6, 26], amongst other activities. The location of type II enteric glial cells at inter-ganglionic connectives suggests roles in supporting axonal processes and in safeguarding nerve conduction. However, the varicose release nature of ENS connectivity and the fact that type II enteric glial cells project their processes parallel to neuronal fibers [19], withholds further analogy with oligodendrocytes. Enteric glial cells with type III morphology can be found in the lamina propria at the villus or crypt level, so-called ‘mucosal enteric glia’, and extra-ganglionically within both plexus layers. Some mucosal enteric glia residing within the villi are associated with enteroendocrine neuropod cells [27] and the vasculature [28], and their presence is dependent

on intestinal microbiota [28]. While their location presumes a role in mucosal functions, evidence for a task for this specific population in epithelial barrier integrity for example [10], is rather limited. Type IV enteric glia display a characteristic bipolar shape and exclusively localize to the muscular layers [19, 29]. To date, there is no general consensus on the functions these cells might cover. However, considering their location and shape, it is fair to assume that they assist enteric neurons in controlling the contractions and relaxations of the intestinal smooth muscle.

Consistent with their diverse expression levels of known glial markers [19, 21] enteric glial cells have turned out to be strikingly heterogeneous at the transcriptomic level [30-33]. Myenteric glia of the juvenile mouse small intestine cluster into six subgroups, together with a proliferating glia-type [32], recently confirmed by Guyer *et al* [17]. Small intestinal enteric glia display a *Hox* code, which is consistent with their vagal origin [32]. Whether enteric glia derived from another level of the neural crest, like those in the hindgut, express a different combination of *Hox* genes is currently not clear. Nevertheless, the molecular profile of enteric glia is likely intestinal region specific, as analysis of the myenteric plexus of the ileum and duodenum specifically, only identified two clusters within each region [30, 34]. Interestingly, in a model of helminth infection, the distribution of these two clusters changes in favor of the (reactive) enteric glia population expressing higher levels of glial fibrillary acidic protein (GFAP) and INFγ-related genes [34]. Single cell sequencing of the developing human ENS uncovered three principal groups of enteric glia, in addition to, again, a cluster of proliferating cells [33]. Human adult colonic enteric glia on the other hand, have been clustered into six populations [30]. Although it is not yet clear how the transcriptomically-defined enteric glia clusters fit the morphological classification scheme, specific marker expression can be, at least to some extent, related to their location and thus morphology [19, 21, 35]. While awaiting the outcome of spatial transcriptomic profiling efforts that promise to complete this picture, certain observations can be used to link morphological subtypes with typical gene expression sets. For instance, mucosal enteric glia from the human colon display an enhanced expression of ferritin genes, while those of the muscularis are enriched for cell adhesion molecules [30].

Functional heterogeneity and phenotypic plasticity

A limited number of studies have attempted to connect specific enteric glia phenotypes with their activity patterns. Purinergic receptor stimulation has been shown to evoke variable Ca^{2+} responses in distinct enteric glial subtypes. Specifically, myenteric type I and myenteric type II enteric glia both show Ca^{2+} transients that differ in amplitude, while only a reduced percentage of inter-ganglionic type III glia manifest responsiveness to purinergic receptor stimulation [19]. Recent *in-vitro* data also suggest that mucosal and submucosal enteric glia display stronger Ca^{2+} transients than myenteric glia [36]. Moreover, adding to this functional heterogeneity at

the level of local circuits, is the recently observed regional diversity. Compared to myenteric glia in the colon, duodenal myenteric glia exhibit different Ca^{2+} responses to cholecystokinin (CCK) and adenosine diphosphate (ADP). Based on their responsiveness and Ca^{2+} transient amplitude upon CCK and ADP, four intra-ganglionic myenteric glia profiles have been identified across the different gut regions [7]. Interestingly, the duodenal myenteric plexus displays an even distribution of these four subtypes, while the colonic myenteric plexus mainly contains enteric glia that are highly responsive to both CCK and ADP, or to ADP only [7]. Baghdadi *et al.,* [3] demonstrated that enteric glia with high GFAP expression residing in intestinal crypts are key players in the regulation of stem cell activity during homeostasis. This population specifically increases upon injury, and is proposed to represent a pool of enteric glia dedicated for mucosal regeneration. Highlighting the high degree of plasticity of enteric glia, it has been shown that their GFAP expression levels are very dynamic [19]. GFAP upregulation is also one of the hallmarks of enteric gliosis [34, 37] a particular glial phenotype in reaction to local stressors or damage [1]. Given the conflicting reports on the role of enteric glia in maintaining the epithelial barrier [38, 39], it remains to be elucidated how, and to what extent, enteric glial reactivity actually contributes to their capacity to support and repair the epithelium. Thus, while subtyping enteric glia based on molecular marker levels can be instrumental to study heterogeneity at the level of local circuits and within particular niches, it is probably less pertinent to evaluate enteric glia diversity between different gastrointestinal regions and activation status. Considering that enteric glia can express different isoforms of cellular markers [40], even adds another layer of complexity to molecular marker-based distinction.

Origin of enteric glia

Microenvironmental cues instructed by local tissue requirements and pathological insults represent major driving forces that control phenotypic and functional characteristics of enteric glial cells [14]. Whether and how genetic and epigenetic factors contribute to determining the set of enteric glial phenotypes has not been elucidated. During development, the vast majority of ENS precursors arise from the vagal neural crest and colonize the developing gut rostro-caudally. Sacral neural crest cells enter via the hindgut and contribute to the formation of enteric neurons and glia in the distal colon and rectum [41]. In addition, Schwann cell precursors have entered the limelight as ENS progenitors [42, 43]. Arising from the rostral somites of the vagal neural crest, Schwann cell precursors are fundamental for the innervation of the esophagus and stomach [44]. Importantly, Schwann cell precursors maintain their neurogenic and gliogenic potential into postnatal stages [42, 45] and employ it in pathological conditions [46, 47]. The contribution of Schwann cell precursors to gliogenesis specifically, has not been investigated in detail, and it is unknown whether the glial progeny of Schwann cell precursors allocate to specific enteric glial cell types. Overall, and because of their extensive

plasticity, discriminating between enteric glia located within a given intestinal segment based on neural crest level origin, is maybe superfluous. By the same token, Schwann cell precursors present within the adult ENS could just be considered enteric glial cells.

Which enteric glial cells have neurogenic potential?

It has become increasingly evident that enteric glial cells should not be considered as a static population of neuroglia. In hindsight, this may not be that surprising considering the unique and temperamental complexity of the digestive tract. Given the notion that astrocyte heterogeneity seems to be driven by the need to keep the brain “resistant” [48], enteric glial heterogeneity and plasticity might be explained by the requirement to keep the ENS “resilient”. In agreement with this concept, and adding an extra level to their plastic demeanor, is the fact that enteric glial cells have the ability to generate new enteric neurons in adulthood [14]. Even though it is known that enteric glia only engage their neurogenic potential once the ENS gets compromised, at least in mammals [23], it is still debatable whether this is a capacity of all enteric glia or of a specific subtype. Extra-ganglionic cells expressing canonical glial markers, like enteric glia type II, III and IV, have been suggested to migrate into the myenteric plexus and differentiate into neurons via 5-hydroxytryptamine receptor 4 signaling [49]. Recent single-cell multiome sequencing data indicate that specific enteric glia subsets, in particular $GFAP^{+}$ enteric glia, are characterized by a chromatin state consistent with neurogenic potential [17]. Within eight transcriptionally-distinct myenteric glia clusters, two display an accessible chromatin structure and a higher expression of genes encoding transcription factors associated with neuronal differentiation such as *Phox2b*, *Hand2*, *Tbx3*, and *Ascl1*. While restricted to a subpopulation of myenteric glia *in vivo*, this chromatin and expression profile appears to become the standard for the majority of myenteric glia upon dissociation and primary culture. This is in agreement with earlier lineage-tracing experiments [15] and a recent report demonstrating that adult enteric glia preserve the neurogenic properties of early ENS progenitors [50]. Similar studies focusing on the submucosal plexus have yet to be reported, and the outcome of those might be different given the findings by Parathan and colleagues, who identified enteric glial cells positive for either Sox10 or S100β that co-express the pan-neuronal marker Hu [51]. Although *in-vitro* analyses show that the human lamina propria contains bipotential enteric precursors [52], mucosal enteric glia have also not been investigated in this context. One could, of course, question whether the intestinal mucosa is a niche where new neurons need to be generated. Nevertheless, since progenitors, from which the clonal descendants get arranged in a columnar fashion, first settle at the level of the myenteric plexus [53], it is likely that this remains the prime location for cells pre-configured with the ability for ENS repair.

Conclusion and future perspectives

Enteric glia comprise a diverse set of highly-specialized cells with remarkable plasticity. Going forward, and trying to unravel the full extent of enteric glial cell diversity on a functional level, it will be important to better understand the mobility and interchangeability of these cells. The identification of molecular IDs that allow tracing and perturbation of specific enteric glia populations in both physiological and pathological settings, would be a great asset in this context. Hopefully, and in keeping with the plasticity and versatility of enteric glial cells, this will soon be possible. Taking into consideration the complexity of the gastrointestinal environment, the current literature firmly supports a model wherein enteric glial heterogeneity is mostly induced by local tissue requirements. Those demands differ within specific intestinal segments (intra-regional heterogeneity). For example, mucosal enteric glia are assumed to have a different job package than type IV enteric glial cells within the *muscularis externa*. Likewise, local requirements ought to vary between gastrointestinal regions (inter-regional heterogeneity). Colonic enteric glial cells, for instance, face a highly distinct luminal environment compared to enteric glia residing in the stomach wall. Moreover, these needs also alternate in time and change because of injury or disease. Therefore, we argue that even if lineage determinants contribute to enteric glial cell diversity, such phenotypic or functional traits are likely overruled by the niche.

Author contributions

All authors participated in conceptualization of the manuscript and final editing. GS wrote the initial draft. WB acquired funding.

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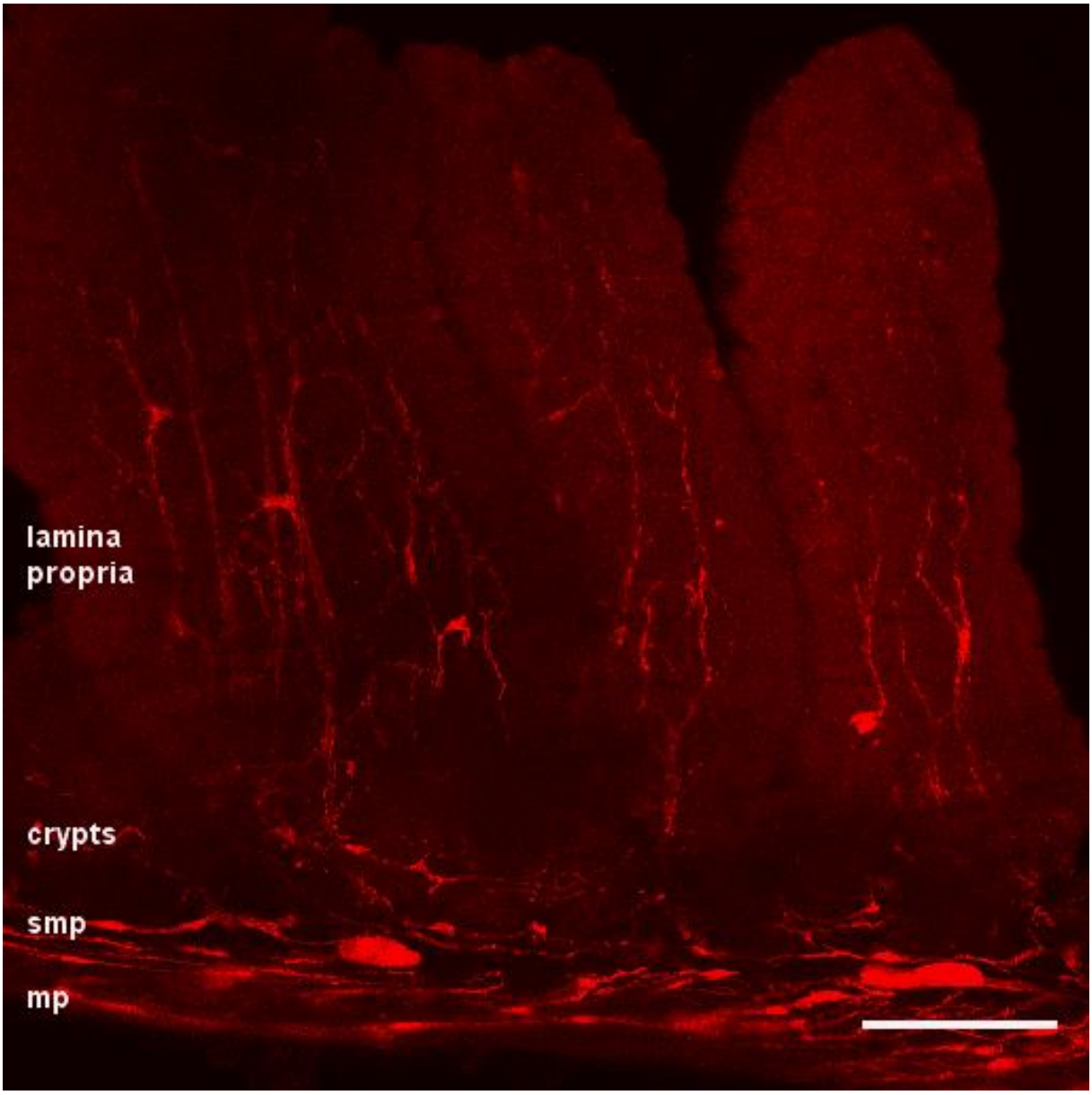

Fig. 1. Different types of enteric glia can be found throughout the gastrointestinal wall. S100β immunolabelling of a transverse section of the mouse duodenum. Enteric glial cells are present within and outside the ganglia of the myenteric (mp) and submucosal (smp) plexus. In addition, they localize to the smooth muscle layers and the lamina propria. Depending on their location, enteric glia show a distinct morphology. Scale bar: 100µm.

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