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Current Trends in Multiple Sclerosis Research:

An Update on Pathogenic Concepts

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Abstract

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) of presumed autoimmune origin which develops in a genetic susceptible individual triggered by additional environmental factors. In this review, we will provide an update of basic pathogenic concepts. In addition, we will discuss newly evolving concepts in MS pathogenesis such as pathogenic heterogeneity, importance of axonal loss and the role of $CD8^+$ T lymphocytes in tissue injury. In the last part of this review we will briefly describe currently approved MS treatments and summarize some promising therapeutic approaches that are currently under evaluation.

Keywords: multiple sclerosis, axonal injury, pathogenic heterogeneity

1. Clinical features

Multiple sclerosis (MS) is one of the most frequent causes of neurological impairment in young adults affecting 0.05-0.15% of Caucasians (1). The major pathological hallmark is the presence of sclerotic lesions or 'plaques', scattered throughout the central nervous system (CNS). These lesions are characterized by selective loss of myelin and oligodendrocytes leading to impaired or complete loss of axonal conduction (2). This demyelinating process is accompanied by an inflammatory reaction with infiltrates composed mainly of T cells and macrophages (3). Although almost any CNS region can be affected, there is a preference for ventricle surrounding tissue, optic nerves, brain stem and spinal cord. The most common disease symptoms include chronic and relapsing paralysis and problems of vision, sensation, strength and coordination (4). The multiplicity of clinical deficits is suggested to reflect the variety in location, size and number of lesions (5).

The diagnosis of MS is mainly based on clinical history combined with the detection of brain abnormalities, that is, demonstrating the scatter of CNS lesions in space and time (i.e. the occurrence of a second clinical episode at a different site in the CNS). Magnetic resonance imaging (MRI) of the brain and spinal cord is the most sensitive technique aiding the diagnosis of MS (6). Recently, an international panel published new diagnostic criteria for MS (McDonald criteria), suggesting that MRI evidence of dissemination in time and space is sufficient for the diagnosis of MS even before clinical deterioration has occurred (7).

The heterogeneity of the disease course resulted in a classification of MS in two major forms. Relapsing remitting (RR-) MS is the most frequent form (80-90%) and affects women twice as often as men. This form is characterized by a relapsing remitting illness with episodes of neurological dysfunction lasting several weeks, followed by substantial or complete recovery.

Many years after onset, the majority of relapsing remitting MS patients (RR-MS) develops a gradual clinical progression with or without clinical attacks superimposed. This is termed secondary progressive MS (SP-MS). A minority of patients (10-20%) display a primary progressive (PP-) MS, characterized by a gradual decline in neurological function and less evident inflammation on MRI (8). Heterogeneity of MS is not confined to disease course and clinical presentation, e.g. which areas are primarily affected. Morphological studies with MRI (9) and histopathological evaluation (10,11) revealed profound differences among MS patients. The factors underlying this heterogeneity are not completely understood but include a complex genetic trait that translates into different immune abnormalities, increased vulnerability of CNS tissue to inflammatory insult or reduced remyelinating capacity (12).

2. Role of genes and environment

The aetiology of MS remains unclear, but according to current data the disease develops in a genetic susceptible individual and requires additional environmental triggers (12). To establish a genetic component in a complex disease, familial aggregation studies serve as starting point. Population and family studies show that the prevalence of the disease is substantially increased in family members of MS patients with first degree relatives and daughters of affected mothers having the highest risk (13,14). Evidence originating from twin, adoption and half-sibling studies indicates that the familial segregation of MS is related to genetic sharing rather than to shared family environment. This evidence includes the difference in concordance rates between monozygotic (20-35%) and dizygotic (5%) twins (15,16), the similar recurrence risk between adoptive relatives of MS patients and the general population (17) and the lower occurrence risk for half-siblings (1.32%) compared to full-siblings (3.46%) (18). However, the quantitative genetic trait of MS has shown to be difficult to dissect. The only region consistently found to be associated with MS prevalence is the

MHC region. The MHC locus is a four mega-base region containing the classical HLA genes as well as at least 128 other genes (19). Within this region the HLA-DR2 (DRB1*1501, DQA1*0102 and DQB1*0602) haplotype was consistently shown to be associated with MS (20). In addition, MHC class I alleles may also contribute to disease susceptibility, although associations were much weaker (21). Current studies indicate that no single major susceptibility gene exists for MS and instead many loci are believed to confer overall MS susceptibility. However, genetic predisposition alone is not sufficient to develop MS, since other interacting factors including immunological and environmental factors have been shown to contribute to disease susceptibility.

Several lines of evidence support the contribution of environmental factors to the aetiology of MS. These include the low concordance rate of identical twins (22,23), the increased prevalence of MS with distance from the equator (16,24) and studies showing that migration before puberty from a high to a low prevalence area results in a reduction in the risk to develop MS (25). The fact that first-degree adopted relatives of MS patients do not display an increased MS prevalence compared to the general population strongly suggests that MS is not purely a transmissible disease (17). Therefore, any environmental factor is likely to be ubiquitous and act on a population basis rather than within the family microenvironment (22). Both lifestyle influences and infectious agents have been proposed as risk factors (26). Substantial efforts were undertaken to identify an MS triggering virus (27,28). Although several viruses, including human herpes virus, 'MS-associated retrovirus' (MSRV), Epstein Barr virus, rabies and measles, have been claimed as potential candidate, none of the studied viruses could be univocally linked to disease (27,28).

The lack of hard proof for an MS causing virus does not rule out the possibility that infectious triggers are involved in disease initiation. According to the 'hit and run' hypothesis, persistence of an encephalitogenic virus is not necessary for the continuation of the disease process (29). It is possible that a transient viral CNS infection causes minor damage to myelin leading to the release of myelin epitopes and subsequent activation of myelin-reactive T cells (30,31). Alternatively, it is possible that autoreactive T cells become activated in the periphery after recognition of cross-reactive viral epitopes that mimic self peptides ('molecular mimicry') (32). Moreover, the profound heterogeneity of MS could reflect different triggering factors and thus explain why MS patients do not show universal positivity for a particular microorganism (33).

3. Multiple Sclerosis: a CNS specific autoimmune disease

Various lines of evidence suggest that MS is an autoimmune disease mediated by peripheral myelin reactive T cells (34,35). Indirect evidence for the possible autoimmune nature stems from the animal model experimental autoimmune encephalomyelitis (EAE). This experimental disease shares many clinical and histological features with MS and is induced by generating T cell-mediated immunoreactivity to CNS antigens (36). Adoptive transfer of myelin reactive T cells to naive recipients also induces EAE, demonstrating the T cell mediated autoimmune nature of this model (37,38). There is also direct evidence supporting MS as an autoimmune disease. For example, myelin reactive T cells accumulate in lesions and cerebrospinal fluid (CSF) of MS patients but not in the CNS of patients with other neurological diseases (39,40). The linkage of HLA class II genes such as HLA-DR2 to disease is another important argument, because HLA-DR2 determines the ability to recognize certain epitopes of potential autoantigens (41-43).

Although the exact event leading to the activation of myelin reactive T cells remains elusive, there are several mechanisms by which an infectious trigger may induce an autoimmune disease. The main postulated mechanism is molecular mimicry (32,44,45) in which autoreactive T cells are activated by a viral or bacterial epitope with structural or sequential similarity to the self peptide (46,47). Another proposed mechanism is bystander activation including both antigen-dependent and antigen-independent mechanisms (12). Antigen-independent mechanisms include activation of autoreactive T cells by bacterial or viral superantigens (48), Toll like receptor (TLR) triggering (49) and exposure to high concentrations of cytokines secreted during unrelated immune responses (50). Moreover, antigen-dependent activation can occur when myelin epitopes are released as a result of initial damage to the CNS, as illustrated in the Theiler virus-induced EAE model (30,51). In contrast to the above mentioned mechanisms that suggest activation in the periphery, recent evidence in several animal models for MS reveals that activation of autoreactive T cells can also be initiated in the CNS by a discrete population of vessel-associated dendritic cells (52,53). In this light, it was recently shown that besides activated T cells also naive T cells cross the blood brain barrier (BBB), bypassing the need for antigen priming in the periphery (52-54). This is probably facilitated by the increased expression of adhesion ligands (ICAM-1 and VCAM) during CNS inflammation in EAE (55).

Once activated, autoreactive T cells expand and traffic to the CNS (56). Migration through the endothelium of the BBB is facilitated by the expression of adhesion molecules, chemokines, their receptors and the release of pro-inflammatory cytokines (57-60). Once autoreactive T cells have extravasated through the endothelium, they have to pass through a barrier of extracellular matrix to enter the CNS. This is mediated by the secretion of matrix

metalloproteases (MMP-2 and MMP-9) following contact with collagen. These enzymes are not only involved in the proteolytic cleaving of extracellular matrix but can also cleave myelin components and thus generate immunogenic peptides (61-63). Thus, beside their role in opening the blood brain barrier these MMPs are also able to perpetuate inflammatory responses.

Within the CNS, T cells become reactivated when they encounter their specific myelin epitope presented by resident antigen presenting cells (APC). The nature of the APC responsible for antigen presentation is still subject of debate. Although astrocytes (64) and microglia (65-67) are capable of presenting antigen, recent evidence in EAE suggests that antigen presentation by perivascular dendritic cells and macrophages is sufficient to develop disease (53). Following reactivation, autoreactive T cells spread into the white matter and produce pro-inflammatory cytokines which trigger a cascade of immune reactions. During this inflammatory response, chemokines are released and the expression of adhesion molecules on endothelial cells is increased. This results in the recruitment of other immune cells including monocytes, T cells, mast cells and B cells. These inflammatory events ultimately lead to demyelination, astrogliosis and loss of oligodendrocytes and neurons. This tissue damage is induced by the combined effects of oxygen radicals, cytokines, autoantibodies, cytotoxic cells ($CD8^+$ T cells, γδT cells and macrophages), complement deposition and myelin phagocytosis (68,69). The decline of this inflammatory event is paralleled with the clearance of debris by macrophages and a relative dominance of Th2 cytokines. Surviving oligodendrocytes and oligodendrocyte precursors are activated and spontaneous myelin repair occurs in about 40% of plaques (70-72). Despite the fact that remyelination is wide spread, it is also clear that much of the myelin damage is not repaired (73). Especially lesions in patients with long standing disease display less pronounced

remyelination (74,75). This indicates that recurrent episodes of inflammation may exhaust the ability of oligodendrocytes to regenerate myelin (71) or lead to a milieu that is no longer favourable for remyelination (76). One of the challenges in MS research is to develop strategies that enhance inherent repair mechanisms, while simultaneously limiting immune-mediated damage.

4. New concepts in MS research

The view that MS is as a $CD4^+$ T cell driven demyelinating autoimmune disease is too simplistic. Indeed, accumulating evidence suggests a possible pathogenic role for $CD8^+$ T cells and besides demyelination also axonal degeneration is a prominent pathological feature. In addition, recent insights reveal a profound pathological heterogeneity among MS patients. These novel directions in MS research will be addressed in the next paragraphs.

4.1 Pathological heterogeneity

Recent evidence suggests that distinct pathological subtypes may exist in MS (77). The analyses of a large number of MS lesions in the active stage of demyelination revealed at least four distinct pathological patterns. These patterns differ in the extent of myelin and oligodendrocyte loss, the degree of humoral contribution (complement and antibody deposition) and the involvement of different immune cells. Pattern I and II share a number of similarities, such as prominent T cell and macrophage infiltration, location of lesions around venules and the occurrence of remyelination. Pattern II is distinguished from I by a prominent humoral component with deposition of antibodies and complement proteins. Based on parallels with focal cerebral ischemia, pattern III lesions are believed to be caused by a vasculitic mechanism. These lesions are characterized by a preferential loss of MAG

(myelin-associated glycoprotein), oligodendrocyte apoptosis and conservation of a rim of myelin surrounding venules. Pattern IV involves non-apoptotic oligodendroglial cell death. This pathological subtype has only been found in a small subset of patients with a primary progressive disease course (11). While in lesions of pattern I and II, the myelin sheath is the main target of the destructive process, patterns III and IV show primarily oligodendrocyte loss (78). It remains to be established whether these lesional patterns are constant along disease progression and whether these subtypes can be used for prognosis. Interestingly, different acute demyelinating lesions within one patient showed a similar pattern, indicating that lesion heterogeneity does not reflect different lesional stages, but rather distinct pathological mechanisms.

Subdividing MS patients based on their disease mechanism holds promise for more specific therapies. However, it remains to be established whether subdividing MS patients based on their lesional pattern is sufficient. Additional sub-classifications based on remyelinating capacity, responsiveness to treatment, amount of atrophy and other criteria may be needed. The identification of new MRI criteria (79,80), CSF markers (81) and molecular markers associated with heterogeneity, will allow tailoring specific treatments for a specific subgroup of MS patients.

4.2 Axonal pathology

Historically, MS has been considered an inflammatory demyelinating disease with a relative preservation of axons (82). Accordingly, research focused primarily on the inflammatory response and loss of myelin. New insights regarding the timing, extent and consequences of axonal loss in MS led to renewed attention for neurodegenerative processes. Axonal ovoids indicating recently transsected axons and APP (amyloid precursor protein) positive neurons

reflecting impaired axonal transport can be detected in lesions of patients with a short disease duration (83). Subsequent morphologic studies confirmed that axonal transsection is equally prominent in active lesions of patients with short disease duration and correlates with inflammatory activity in these lesions (84-86). In addition, acute axonal injury was also detected in inactive lesions (85). This is not observed in remyelinated lesions indicating that the myelin sheath itself may protect the axon against proinflammatory mediators released within the plaques (78) and oligodendrocytes may provide trophic support for the axon. The mechanisms of early axonal injury in MS are poorly understood, but may include deleterious effects of inflammatory mediators, T cells, oedema, glutamate, nitric oxide and genes involved in axonal responses to inflammation (87). This early axonal loss remains clinically silent for many years, suggesting that the CNS can compensate for neuronal loss (88). Irreversibly neurologic disability develops when a threshold of axonal loss is reached and the CNS compensatory mechanisms are exhausted (88-90).

4.3 A pathogenic role for $CD8^+$ T cells

MS is generally considered to be a $CD4^+$ Th1-mediated autoimmune disease (91). This view is based on the close similarities in pathology between MS and EAE (36,37,92). The role of $CD4^+$ T cells in MS is further supported by the association of MHC class II genes with the disease and the expression pattern of chemokines, cytokines and their receptors in MS lesions and CSF that is consistent with a $CD4^+$ Th1-mediated immune response (93-95). Other observations suggest an important role for $CD8^+$ T cells in the pathogenesis of MS. $CD8^+$ T cells have been shown to predominate in early MS lesions suggesting that their presence is not due to the recruitment of non-specific immune cells once inflammation has started (96,97). Clonal expansion was more frequently detected among $CD8^+$ T cells as compared to $CD4^+$ T cells in CSF of MS patients. In addition, increased numbers of memory $CD8^+$ T cells with

evidence for clonal expansion have been observed in the CSF and blood of MS patients as compared to controls (98,99). In the context of effector functions, $CD8^+$ T cells are better equipped to mediate direct CNS damage. Indeed, MHC class I molecules are, unlike MHC II molecules, expressed on CNS cells such as neurons, oligodendrocytes, axons and astrocytes (100,101). In addition, a number of HLA class I-restricted myelin epitopes have been described for myelin basic protein (MBP), proteolipid protein (PLP) and MAG (102-105). Myelin specific $CD8^+$ T cells are able to induce severe EAE upon adoptive transfer (106,107). Moreover, myelin reactive $CD8^+$ T cells have been isolated from MS patients and were able to specifically lyse oligodendrocytes and myelin pulsed target cells in vitro (100,103,105,108). $CD8^+$ T cells have also been found in MS lesions in proximity of axons and oligodendrocytes with their cytotoxic granules polarized toward the CNS target cells (109,110). Since there is no information on the antigen specificity of the infiltrated $CD8^+$ T cells it cannot be ruled out that these cells may be regulatory rather than pathogenic. Anti-idiotypic $CD8^+$ T cells for instance are part of the regulatory network that is thought to control autoreactive T cells by recognition of clonotypic determinants (111).

5. MS therapies: established treatments and new hopes

The increased understanding of the MS pathogenesis has led to the implementation of a number of immunotherapeutic approaches. The currently approved treatments and some promising therapeutic approaches that are currently under evaluation will be discussed below.

5.1 Established MS therapies

Interferon-β and glatiramer acetate are drugs currently approved for the treatment of RR-MS. IFN-β is a naturally occurring cytokine and is the most broadly used drug in MS therapy.

Three preparations of IFN-β (IFN-β1a: Avonex™, Rebif™ and IFN-β1b: Betaseron™) have shown efficacy in reducing the relapse rate and the number of active lesions in RR-MS (112-115). The predominant mechanism of action is unknown, but may involve the suppression of T cell proliferation and shifting of the T cell cytokine secretion from a pro-inflammatory Th1 profile towards a more protective Th2 profile (116). Other immunomodulatory activities include the induction of IL-10 and neurotrophic factors, blocking of BBB opening via inhibition of MMP-2 and -9 and reduction of cell adhesion to the BBB (12).

Glatiramer acetate (Co-polymer 1: Copaxone™) is a random polymer of 4 amino acids (L-glutamic acid, L-lysine, L-alanine and L-tyrosine) that mimics MBP. Its main mechanism of action involves the induction of a Th1-Th2 shift. Other activities of GA include the induction of anergy of MBP-reactive T cells, cross-reactivity with myelin epitopes, polyclonal activation of T cells leading to bystander suppression and induction of neurotrophic factors such as BDNF (117-120).

However, treatment with GA or IFN-β has substantial limitations. Although the annual relapse rate is decreased by about one third (121-123), their long-term clinical effect is uncertain (124). Recent papers report negligible effects of the above treatments on disability in chronic stages of the disease, implying that their effects on axonal damage are probably very limited (113,125). Available data on IFN-β treatment suggest that it might be more effective when given early, maybe even at the first clinical presentation of the disease; long-term data are awaited (126-128).

Mitoxantrone is an anthracyclin-based chemotherapeutic that is approved for the treatment of secondary progressive and progressive relapsing MS. Treatment with mitoxantrone resulted

in significantly fewer lesions, reduced relapse rate and reduced progression of disability (129,130). Proposed mechanisms of action are suppressing T and B cell responses, but also inducing apoptosis in antigen presenting cells and macrophages (131).

Acute exacerbations of MS are generally treated with high doses of glucocorticoids, such as methylprednisolone (132-134). The above described approved MS therapies are all directed at suppressing or modulating immune responses. They are only partially effective in controlling MS and were introduced before there was an understanding of their mode of action. Elucidation of the mechanisms by which these therapeutics exert their protective effects and further insights in pathogenic pathways of MS have led to new therapeutic strategies.

5.2 New therapeutic approaches

Future immunotherapies can be classified into 3 broad categories (135). The first are antigen-specific therapies. These include T cell vaccination (111,136), T cell receptor (TCR) vaccination (137), oral tolerance, altered peptide ligands (91) and MHC blockers. Importantly, these approaches require detailed knowledge of all involved autoantigens and effector cells. A second class of novel immunotherapies relies on targeting well defined pathogenic mechanisms. Promising examples of these approaches are daclizumab, a monoclonal antibody specific for the subunit of the interleukin-2 receptor influencing activation of peripheral $CD4^+$ T cells (138); natalizumab, a monoclonal humanized antibody directed against VLA-4 inhibiting cell adhesion to the BBB (139), and modulators of cAMP levels in the brain and in immune cells (140). The last class of new immunotherapies are agents with broad immunomodulatory activities. These include for example alemtuzamab, a humanized monoclonal antibody directed against CD52 that is intended to deplete T and B cells, monocytes and macrophages (141), statins, currently approved cholesterol lowering

agents with immunomodulatory properties (142-144), pregnancy related hormones (145) and haematopoietic stem cell transplantation.

Besides the immunologic aspects, attention has in recent years focused on the enhancement of repair and regeneration mechanisms as targets for therapy especially in secondary progressive MS. There are two broad approaches for promoting myelin repair (76). Transplanting cells with myelinogenic capacity represents the first approach. This approach has made significant progress in animal models for MS (146-148). The second approach is directed at promoting the endogenous protective pathways from the brain and immune system. For this approach, a number of strategies have shown an effect in animal models (149) and await validation in MS.

All therapeutics summarized here are in different stages of development. While one important goal is to develop new therapeutics, there is also a growing appreciation that some MS therapeutics may be beneficial when given in combination (150). The prerequisite of combination therapy is that both drugs have an additive or synergistic effect, but not overlapping toxicities (151).

6. Summary

Multiple sclerosis (MS) is generally considered a $CD4^+$ T cell-mediated autoimmune disease that is triggered by unknown exogenous agents in subjects with a specific genetic background. New tools, such as gene expression profiling with cDNA microarrays and LD-based maps may help us identify disease-risk alleles. Despite major efforts, the precise cause of MS remains unknown and many aspects of MS pathogenesis have become more complicated. Whereas demyelination was originally thought to be relevant for the lasting neurological deficit, it is now commonly accepted that the extent of axonal loss dictates the degree of permanent clinical disability. How axonal damage can be prevented remains elusive. In addition, new insights on the prominent role of $CD8^+$ T cells indicate that the concept of MS as $CD4^+$ driven autoimmune disease should be revisited. Finally, different patterns of tissue damage have been shown in active MS lesions, suggesting that the mechanisms of injury are distinct in different subgroups of patients. The classification of pathogenic mechanisms in an individual patient may be necessary to provide better targeted therapies.

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