Pathophysiology of inflammation and tissue injury in multiple sclerosis: What are the targets for therapy

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ABSTRACT

Many new therapies have become available for multiple sclerosis patients during the last decade. They are mainly effective in the early relapsing stage of the disease. Despite this undisputed progress, there are still major deficits in the treatment of the patients. Effective anti-inflammatory treatments profoundly decrease disease activity, although this may occur on the expense of a partially impaired immune surveillance of the central nervous system. Furthermore, the clinical outcome of recent trials does not always meet the expectations of the neuroimmunological community. This suggests that preclinical testing in experimental models, although useful and necessary, has its limitations. For treatment of the progressive stage of the disease blood brain barrier penetration of drugs appears to be one crucial issue. Additionally, little is known on the immunological mechanisms of slow burning inflammation present in the brain of patients with progressive MS. Finally, it is suggested that neuroprotective strategies, which target mitochondrial injury and its downstream effects on neurons and axons are promising future therapeutic options.

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1. Introduction

Multiple sclerosis is a chronic inflammatory disease of the central nervous system, which results in the formation of focal demyelinated plaques in the white matter with partial axonal preservation [1]. In most patients disease starts with a relapsing remitting course, which is followed by a secondary progressive phase. In patients with primary progressive disease the relapsing stage of the disease is missed and patients show disease progression from the onset [2]. It is generally believed that inflammation starts the disease and drives demyelination and neurodegeneration. Thus, treatments targeting the inflammatory reaction are widely used [3]. They are mainly effective in the relapsing stage, and their efficacy seems to be related to their potency to suppress inflammation [4,5]. Interestingly, however, inflammatory components, which were thought to be perfect targets on the basis of our understanding of MS, have failed in clinical trials [6], while other targets, which were not thought to be important in MS pathogenesis, emerged to be attractive for therapy [7]. Furthermore, when patients enter the progressive phase of the disease, anti-inflammatory or immunomodulatory treatments become increasingly ineffective. These observations raise a number of fundamental questions, which can at least in part be addressed through studies of the pathology of the disease. Thus the nature of the inflammatory reaction in the brain and spinal cord has to be re-defined and the evidence for inflammation, being the driving force of the disease at all stages has to be reviewed. Finally, a deeper knowledge on the mechanisms of tissue injury in multiple sclerosis lesions could provide new clues on targets for neuroprotection.

2. Therapies targeting inflammation

There is no doubt that the inflammatory reaction in multiple sclerosis is dominated by lymphocytes and macrophages or activated microglia [1]. The global composition of inflammatory infiltrates is quite similar to that seen in experimental autoimmune encephalomyelitis (EAE) and in this experimental model inflammatory demyelination is induced, which in many respects resembles that seen in MS [8]. Thus, in the prevailing view inflammation in MS equals that seen in EAE. This implies that therapies, developed in EAE should also have a beneficial effect in MS patients. Although this is the case for some therapies, such as glatiramer acetate, β-interferone, natalizumab and others, perfect candidates, validated in EAE models failed. Examples for such failure are treatment with antibodies or reagents against CD4, against IL12/23 p40 [6] or against tumor necrosis factor alpha [9]. Thus, the nature of the inflammatory response between MS and EAE appears in part to be different, even, when the basic composition of lesion infiltrates by T-cells, B-cells and macrophages is essentially similar. One major difference is that in MS, in contrast to EAE Class I MHC restricted CD8 positive T-cells dominate the lymphocytic infiltrates at all stages of lesion formation and disease [10]. These cells in addition show the most profound and reproducible clonal expansion [10,11], suggesting that these are the T-cells in MS.

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patients, which are pathogenetically driven by a specific antigen [12]. This is different from most EAE models, where inflammation is mediated by Class II restricted CD4+ T-cells [3]. Whether the CD8+ T-cells drive disease and lesions in MS patients, is so far not proven. It may, however, become important in the future to test anti-inflammatory therapies not only in models of CD4+ T-cell, but also of CD8+ T-cell driven brain inflammation.

An unexpected finding in MS therapies was the pronounced treatment effect of Rituximab, a monoclonal antibody that targets B-lymphocytes [7,13]. B-lymphocytes are minor components of the inflammatory infiltrates in the lesions [14] and it is thus unlikely, that a blockade of these cells directly suppress the local inflammatory response. B-cells, however, besides other functions are potent antigen presenting cells and the elimination of B-cells also suppresses T-cell mediated immune responses and disease [15]. An alternative explanation for the therapeutic effectiveness of anti-B-cell therapy may be that killing B-cells also eliminates Epstein Barr Virus (EBV) infected cells. Since epidemiological data suggest a role of EBV in the induction of the disease [16] the elimination of this virus from the body may explain a therapeutic effect of B-cell directed therapies.

3. Therapeutic prospects for the progressive stage of the disease

It is an urgent problem in MS research to explain the failure of current treatment in patients, who have entered the progressive stage of the disease. Currently the most frequently proposed explanation is that the disease starts with inflammation, but with time converts into a neurodegenerative disease, which progresses independently from inflammation [17]. Pathological studies do not support this concept. They show that in patients with progressive disease pronounced inflammation is seen in the brain and spinal cord, which in quantitative terms (concerning T-cells, B-cells and macrophages) is quite similar to that seen in the early relapsing stage of the disease [14]. Thus, inflammation is unequivocally present, but does it drive the disease?

One observation, suggesting an active role of inflammation in the induction of tissue injury, is the highly significant correlation between the extent of inflammation and of active axonal degeneration [14]. The other important observation is that in some patients inflammation may decrease to levels seen in age matched controls. Interestingly in these patients also acute axonal injury declines to that seen in controls [14]. Both of these observations suggest that inflammation is important in driving neurodegeneration, but they are not the final proof. Ultimately it has to be shown that therapies, which stop inflammation in the nervous system, also stop the progressive disease process. This has so far not been achieved and there are several potential explanations for this unsatisfactory situation.

First, it seems that in the progressive stage of the disease inflammation is no longer induced by active invasion of inflammatory cells from the circulation into the brain. Although even in the progressive phase there is increased blood brain barrier permeability compared to that seen in the normal brain, the blood brain barrier damage is mild and apparently not reflected by gadolinium enhancement in magnetic resonance imaging. In addition, brain inflammation is frequently encountered in the lesions of patients with progressive MS, which is not associated with protein leakage through the blood brain barrier or the expression of markers for increased trans-endothelial transport [18]. The formation of lymph follicle like structures in the meninges, which can be seen in the brain of patients with progressive MS [19], also supports the view that the inflammatory response is compartmentalized within the central nervous system. In such a situation, anti-inflammatory or immunomodulatory drugs would have to be designed, which can pass the intact blood brain barrier in an amount, which is sufficient to exert their effects. This does not seem to be the case for most drugs currently used for MS therapy. Thus, from a theoretical point of view, intrathecal anti-inflammatory or chemotherapy is an attractive option for treatment of patients with progressive MS, in a similar way as it is currently used for central nervous system prophylaxis in patients with leukemia or lymphomas (in particular primary CNS lymphomas) [20,21]. However, such treatments are associated with adverse effects on the CNS tissue itself, which may even be more profound in the pre-damaged nervous tissue of MS patients. Whether intrathecal therapies with specific monoclonal antibodies such as for instance anti-CD20 antibodies [22] may become a future option is currently unresolved.

An alternative explanation could be that the functional state of inflammatory cells within the brain lesions is different from that, which allows the cells to enter the brain and start the inflammatory process. Since a slow burning inflammatory process, as it is typically seen in the brains of patients with progressive MS, is currently not reproduced in experimental models, little is known on the activation and functional state of inflammatory cells in this condition. Further research is urgently needed, which defines the functional state of inflammatory cells within the brain in progressive MS and identifies new potential targets for therapy.

The alternative for treatment in progressive MS is to develop neuroprotective and repair strategies. Although many different immunological mechanisms can induce damage in oligodendrocytes, myelin and axons [23], there seems to be one mechanism, which is particularly promising as a target for therapy. Currently the mechanism, which can best explain chronic tissue injury in MS lesions in the progressive stage is mitochondrial injury leading to a state of "virtual hypoxia" [24,25]. Such a mechanism satisfactorily can explain key characteristics of the lesions, including demyelination and oligodendrocyte death [26], preferential destruction of thin axons [27,28], impairment of remyelination and increased susceptibility of the target tissue in the chronic progressive stage of the disease [29]. In particular, mitochondrial impairment in axons leads to tonic imbalance in the course of action potential propagation, resulting in increased axoplasmic calcium concentration and axonal degeneration. This is further amplified by the action of excitatory amino acids, such as glutamate and aberrant expression of Ca-channels in the membrane of dystrophic axons. Blockade of these mechanisms is neuroprotective in experimental models, not only in MS like inflammatory disease but also in ischemia [27]. First clinical studies in MS patients have been initiated to assess the feasibility of such therapeutic strategies in patients. Whether the beneficial clinical effects, seen in patients treated with 4-aminopyridine, a potassium channel blocker [30], are due to neuroprotection or just reflect a symptomatic functional improvement is currently unresolved.

In multiple sclerosis lesions mitochondrial injury is associated with T-cell and B-cell inflammation and microglia or macrophage activation [25]. Pro-inflammatory cytokines may induce mitochondrial injury in vitro [31] and reactive oxygen or nitric oxide species interact with proteins of the mitochondrial respiratory chain, leading to energy deficiency [28]. Oxidised and nitrosylated proteins and lipids have been found in active MS lesions, suggesting radical mediated injury [32,33]. The mechanisms of radical production in MS lesions are currently unresolved, but myeloperoxidase, produced by microglia cells [34,35] as well as iron accumulation within the human brain, which is even more pronounced in MS lesions, may play a role [36]. Further research is needed to test a potential role of radical scavengers in neuroprotection in MS.

4. Conclusions

Currently a large number of new therapies are tested in multiple sclerosis patients in clinical trials. Most of them target the inflammatory component of the disease and have been developed and pre-clinically tested in models of EAE. Outcomes of recently completed trials show variable success of this strategy, suggesting that the mechanisms of inflammation between EAE and MS are similar in...
many, but different in important aspects. A key issue for the treatment of progressive MS is that in contrast to the situation in relapsing MS therapies have to be designed, which reach the pathological process in sufficient concentration within the brain behind a partially closed blood brain barrier. Such therapies should target both, the inflammatory as well as the neurodegenerative component of the disease.

References
