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REVIEW

Progressive multiple sclerosis

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Abstract Multiple sclerosis (MS) is a chronic inflammatory, demyelinating disease of the central nervous system, which starts in the majority of patients with a relapsing/remitting MS (RRMS) course , which after several years of disease duration converts into a progressive disease. Since anti-inflammatory therapies and immune modulation exert a beneficial effect at the relapsing/remitting stage of the disease, but not in the progressive stage, the question was raised whether inflammation drives tissue damage in progressive MS at all. We show here that also in progressive MS, inflammation is the driving force for brain injury and that the discrepancy between inflammation-driven tissue injury and response to immunomodulatory therapies can be explained by different pathomechanisms acting in RRMS and progressive MS.

Keywords Multiple sclerosis · Inflammation · Microglia · Neurodegeneration · Mitochondria · Age · Progressive MS · Relapsing/remitting MS

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, which is pathologically defined by the presence of confluent demyelinated plaques in the white matter [1]. In the majority of patients, it starts with a relapsing/remitting course, which after several years of disease duration converts into a progressive disease, which may or may not be superimposed by relapses. In about 15% to 20% of patients, a primary progressive course is seen, which manifests itself as a slowly progressive disease from the onset [2]. Relapsing/remitting multiple sclerosis (RRMS) appears to be largely driven by the inflammatory process. Newly formed lesions within the central nervous system (CNS) are associated with contrast enhancement in magnetic resonance imaging (MRI) scans, and this is reflected by profound inflammation within the lesions [3, 4]. Furthermore, anti-inflammatory therapies and immune modulation exert a beneficial effect at this stage of the disease [5]. In contrast, new and gadolinium (Gd)-enhancing lesions are rare or absent in patients with progressive disease (primary progressive multiple sclerosis, PPMS and secondary progressive multiple sclerosis, SPMS) and ongoing neurodegeneration, for instance, visualized by progressive loss of brain volume is not correlated with number and appearance of new focal white matter lesions [6–8]. Most importantly, current immunomodulatory or anti-inflammatory treatments have little or no beneficial effect in the progressive stage of the disease [5]. It has, thus, been suggested that neurodegeneration, which at least in part develops independent from inflammation drives chronic brain injury in patients with SPMS and PPMS [9].

In pathology, focal inflammatory demyelinating lesions with variable axonal destruction are the hallmark in the relapsing stage of the disease. Such lesions are also present in patients with SPMS and PPMS, and some of them may be very similar to classical active lesions seen in early MS. However, the majority of focal white matter lesions in progressive MS show either slow expansion at the lesion edges only or are inactive demyelinated plaques [10]. Besides focal white matter lesions, diffuse damage of the normal-appearing white matter (NAWM) and demyelinating lesions in the gray matter, in particular, in the cerebral

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and cerebellar cortex, are prominent [11–14] (Table 1). Since currently we have no therapeutic options for the progressive stage of the disease, future therapeutic strategies depend upon knowledge of the pathophysiology of brain and spinal cord damage in these patients. Key questions are whether inflammation or inflammation independent neurodegeneration drives damage in the CNS in this stage of the disease and what immunological or neurobiological mechanisms are involved.

Pathological evidence suggests that inflammation drives brain injury in progressive MS

It has been noted already in early studies of MS pathology that in the late progressive stage of the disease, pronounced diffuse brain and spinal cord injury is present, but the traditional interpretation postulated that this is a secondary consequence of tissue damage in focal white matter lesions. The spectrum of diffuse changes has been named "MS-encephalopathy," reflecting secondary (Wallerian) fiber degeneration following axonal transsection within plaques or neurodegenerative changes due to age or age-related confounding diseases [15]. However, recent quantitative studies in spinal cord pathology provided clear evidence that diffuse white matter changes cannot be solely explained by neurodegeneration in focal white matter plaques [16–19]. Similarly, focal lesion load in the brain only correlated poorly with the extent of diffuse white matter injury or cortical demyelination [12]. These data suggest that these three different types of MS pathology, at least in part, develop independently from each other, but they do not solve the question whether they are induced by inflammation or are inflammation independent neurodegenerative process.

There is good agreement between different neuropathological studies that inflammation is present in the CNS of patients with PPMS and SPMS, however, the extent of inflammation is highly variable between cases. We, thus, addressed the question regarding inflammation versus neurodegeneration in MS brain and lesions in a more systematic approach [20]. We found a highly significant correlation between inflammation (T cells, B cells, or macrophages) and acute axonal injury, determined by disturbance of fast axonal transport. In particular, patients with PPMS and SPMS with very rapid disease progression showed very pronounced inflammation, which was quantitatively similar to that seen in the relapsing stage. Such a correlation, however, does not prove that inflammation drives neurodegeneration. From these data, one cannot exclude that neurodegeneration secondarily provokes an inflammatory response. To adress this question further, we specifically selected a cohort of MS patients in whom inflammation on the level of T cells, B cells, and macrophages had declined to levels seen in age-matched controls. Such a scenario is seen in aged MS patients with very long disease duration [20]. Analyzing axonal injury in these patients, we observed that its degree, too, is reduced to levels as seen in age-matched controls, provided that the patients did not suffer from MS-unrelated but age-related confounding pathology, such as Alzheimer's disease or vascular lesions. If MS-related neurodegeneration continues in the absence of inflammation, further neurodegeneration would have to be seen in such a patient cohort. From these data, we conclude that neurodegeneration in MS is driven by inflammation, not only in the relapsing, but also in the progressive stage.

Inflammation in progressive MS becomes trapped within the CNS behind a closed (or repaired) blood brain barrier

There is a major discrepancy between neuropathological findings and data obtained by magnetic resonance imaging [21]. While inflammation is prominent in the brain of patients with progressive MS, contrast enhancement in MRI scans is rare or absent. Contrast enhancement reflects

Table 1 Differences between relapsing/remitting and progressive multiple sclerosis

	Relapsing/remitting multiple sclerosis	Progressive multiple sclerosis
Contrast enhancing lesions in magnetic resonance imaging	+++	(+)/−
Response to anti-inflammatory/immunomodulatory treatment	+++	−
Pathological changes:		
Focal inflammatory lesions with variable destruction of axons	+++	++(Slow expansion at lesion edge or inactive)
Diffuse damage of the normal-appearing white matter	+	+++
Demyelination in gray matter (cerebral and cerebellar cortex)	+	+++

disturbance of the blood brain barrier, which in patients with relapsing MS is apparently induced by waves of inflammatory cells, entering the CNS from the circulation. However, sensitivity of Gd-enhancement for the detection of blood brain barrier disturbance is low and does not depict the low grade disturbance of blood brain barrier, which is seen in pathology in all, including inactive MS lesions [21]. Furthermore, in MS, there is a discrepancy between inflammation and blood brain barrier damage. A leaky blood brain barrier is seen in active lesions of acute and relapsing MS, not only in inflamed vessels, but also in adjacent vessels without perivascular inflammatory cells. This may be due to the action of soluble inflammatory mediators, which by themselves may impair blood brain barrier permeability. In contrast, in progressive MS, many blood vessels are seen, which are surrounded by thick perivascular infiltrates, but do not show leakage of serum proteins or the expression of markers associated with increased endothelial permeability [22]. These data suggest that inflammation in MS may become trapped behind a closed (or repaired) blood brain barrier (Fig. 1). This view is further supported by the observation that in progressive MS lymph follicle-like structures (also known as tertiary lymphoid organs) are formed within the connective tissue compartments of the CNS, meninges, and large perivascular spaces [23, 24].

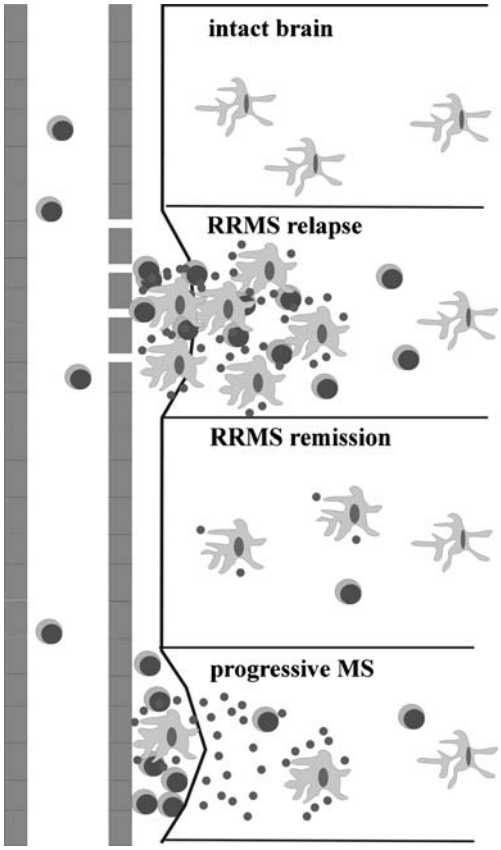

Fig. 1 Inflammation of the central nervous system (CNS) in progressive multiple sclerosis (MS) differs from inflammation of relapsing/remitting multiple sclerosis (RRMS). In RRMS at relapse, the blood brain barrier is open, and large numbers of bloodborne T cells and monocytes/macrophages enter the CNS parenchyma and locally release proinflammatory factors. In RRMS during remission, the blood brain barrier is repaired, and the numbers of intraparenchymal T cells is dramatically decreased as is the degree of microglial cell activation. In progressive MS, inflammation is trapped behind a closed blood brain barrier, and damage of the CNS parenchyma is provoked by the action of diffusible factors acting on microglia cells and a few intraparenchymal T cells

Lymph follicle-like structures in progressive MS

Organized lymphoid structures that resemble secondary lymphoid organs in tissues often form, as a result of chronic inflammatory processes. Their formation is a dynamic process, which starts with sparse lymphocytic infiltration and eventually, organizes in secondary B cell follicles with germinal centers and distinct T cell areas containing dendritic cells and high endothelial venules [25]. Ectopic lymph follicles in MS patients share with those observed in other chronic inflammatory diseases the presence of CD21+ CD35+ follicular dendritic cells, or germinal centers, but clearly differ from follicles of those other diseases, by the absence of T cell aggregates with CCL19+ CCL21+ stromal cells, dendritic cells, and high endothelial venule-like vessels [25]. It is assumed that the same signaling pathways, which orchestrate the organogenesis of lymphoid organs like lymph nodes and spleens are also used for the formation of ectopic lymph follicles. For example, the development of secondary lymphoid organs like spleen and lymph nodes crucially depends on signaling through the lymphotoxin-beta receptor [26], the accumulation of leukocytes in nonlymphoid tissues is promoted by the expression of CCL19 and CXCL12 [27], and the pathways culminating in segregation of B and T cells at these sites are driven by CCL21 or CXCL13 [28, 29]. All of these molecules are also found in chronically inflamed tissues harboring lymphoid-like structures. Hence, the formation of ectopic lymph follicles seems to involve a complex interplay of adhesion molecules, lymphoid chemokines like CCL19, CCL21, CXCL12, and CXCL13 induced in follicle-organizing stromal cells in response to lymphotoxin, and a tissue specific response program controlled by the functional diversity of stromal cells at a given anatomical site [25]. This tissue specific response program might be responsible for the formation of ectopic lymph follicles in the meningeal compartment and not in the CNS parenchyma of patients with secondary progressive MS: Meninges are fibroblast-rich structures, and activated fibroblasts have the ability to support lymphocyte adhesion and survival [30, 31]. Moreover, changes of local fibro-

blasts or the differentiation of fibroblast precursors could give rise to the population of follicular dendritic cells found in the ectopic lymph follicles [25, 32]. Germinal centers of ectopic lymph follicles contain proliferating B cells and the networks of follicular dendritic cells needed for B cell proliferation, maturation, and survival. This could be one contributing factor to the intrathecal antibody production in MS patients, although, it has to be mentioned in this context that intrathecal antibodies are a diagnostic hallmark of MS and are already present at the onset of the disease while the course is not yet progressive.

The consequences of ectopic lymph follicles for progressive MS

Ectopic lymph follicles are almost exclusively found adjacent to large subpial cortical lesions and in the meninges entering the cerebral sulci with underlaying inflammation and demyelination [24], and evidently form in response to chronic inflammatory processes within the adjacent tissue. However, their presence is associated with large and actively demyelinating subpial cortical lesions [24], and they may, thus, contribute to and possibly, even massively amplify inflammation in the underlaying tissue. This assumption is based on some structural peculiarities of ectopic lymph follicles in progressive MS, which sets them apart from other secondary or tertiary lymphoid organs.

In secondary lymphoid organs like lymph nodes, fibroblast reticular cells form the conduit system, which is an interconnected network of collagen fibres that are wrapped by extracellular matrix sheaths and are completely surrounded and enfolded by podoplanin-expressing fibroblastic reticular cells [33–35]. The diameter of these conduits is too small to transport cells, but allows the coordinated and directed transport of signal molecules like chemokines, cytokines, and antigen. This is especially important for the chemokines CCL19 and CCL21, which are produced by fibroblastic reticular cells and associate with the basement membrane (and hence, the inside) of the conduit. In the absence of conduits, as seen in the ectopic lymph follicles of secondary progressive MS (Lassmann and Kerjaschki, unpublished observation), these chemokines are not locally confined. Instead, they could easily diffuse, become available to macrophages and microglia cells in the subpial cortex, and possibly modify the function and behavior of these cells in the course of inflammatory processes. Such a scenario has recently been described for human monocytes [36]: CCL19 and CCL21 per se do not act on monocytes and do not compete with other chemokines for binding to the chemokine receptor CCR2 on monocytes. And yet, in the presence of CCL19 and CCL21, monocytes need much lower concentrations of the CCR2 agonists CCL2 and CCL7 to initiate cell and migration responses (in the case of CCL7, ~100 times lower concentrations!) than in their absence because CCL19 and CCL21 prevent the degradation of chemokines by the decoy receptor D6 and thus, modify one important control mechanism to dampen inflammatory responses [36].

Not only chemokines like CCL19 or CCL21 could become available to the cerebrospinal fluid and the subpial cortex, but also the follicular dendritic cell-derived cytokines, IL-15 and IL-6. The availability of IL-15 would have different effects on memory and effector CD8+ T cells. The Il-15 induces the antigen-independent proliferation and enhances the antigen-specific stimulation of CCR7+ central memory CD8+ T cells [37] which dominate in the cerebrospinal fluid of MS patients [17], but has only marginal effects on CCR7− effector memory CD8+ T cells, which represent the major cell type of T cell infiltrates in the CNS parenchyma of MS patients [37, 38]. Increased concentrations of IL-6 in the subpial cortex, however, could induce the synthesis of the proinflammatory prostaglandin E(2) in astrocytes [39] and hence, exacerbate neuroinflammation.

Taken together: The chronically inflamed brain may create a local environment that favors the retention of inflammatory cells within this compartment and the aberrant formation of lymphatic structures. The failure of current immunosuppressive or immunomodulatory treatments in patients with SPMS and PPMS may, thus, be more related to their inability to pass the blood brain barrier and to reach therapeutically relevant concentrations within the CNS compartment.

Cortical lesions: a tool to study the pathophysiology of tissue injury in progressive MS

While both perivascular and parenchymal infiltration of T cells is a characteristic feature of active lesions in acute and relapsing MS, the pattern of inflammation is different in the progressive stage. In lesions and NAWM of patients with progressive MS inflammatory cells are dominantly seen in perivascular cuffs, while their dispersion into the parenchyma is sparse. Thus, there is a topographical mismatch between lymphocyte infiltration and tissue injury. This is even more pronounced in active lesions in the cerebral or cerebellar cortex [40]. There, T cells, B cells, and plasma cells are nearly exclusively located in the meninges [20], and the severity of meningeal inflammation or lymph follicle formation correlates with the activity of the cortical lesions [24]. Active tissue injury and demyelination in the cortex is associated with profound microglia activation [11]. However, shape and topographical orientation of cortical lesions are closely related to meningeal inflamma-

tory infiltrates, and areas with low circulation of the cerebrospinal fluid, such as cortical sulci and deep invaginations of the brain surface (such as the insular cortex), are predilection sites for cortical lesions [12]. These data suggest that soluble factors produced by meningeal inflammatory cells diffuse into the cortical tissue and induce demyelination and tissue injury either directly or indirectly through microglia activation. Studies in experimental autoimmune encephalomyelitis, a model which can give rise to very similar cortical lesions [41, 42], suggest that specific demyelinating (anti-myelin oligodendrocyte glycoprotein) antibodies are one candidate for such a soluble factor. However, immunoglobulin and complement deposition on cortical myelin at sites of demyelination in MS are generally not seen [43]. Thus, the nature of the putative soluble factor, which drives tissue injury in cortical lesions is so far unidentified.

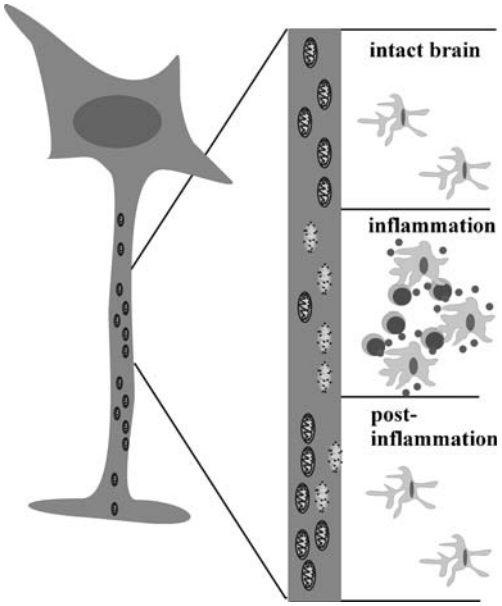

Fig. 2 Axons found in active lesions of chronic multiple sclerosis contain functionally disturbed mitochondria. Once inflammation has declined, an increase of mitochondrial mass, as well as of respiratory chain activity is seen in axons found in inactive lesions. This may reflect attempts to compensate inflammation-induced mitochondrial dysfunction

Mitochondrial injury is a major factor of driving demyelination and neurodegeneration in progressive MS

Primary demyelination with destruction of mature oligodendrocytes together with variable axonal injury is defined as the hallmark for multiple sclerosis lesions. Axonal injury, preferentially, involves small caliber axons [44]. Thus, in chronic MS lesions the quantitative profile of axonal diameter is shifted towards thick axons, and the preservation of unusually thick axons with high reactivity for phosphorylated neurofilament is frequently seen. Thus, considerations on the mechanisms of tissue injury in MS lesions have to take into account the differential vulnerability of oligodendrocytes and thin axons in relation to other cellular components of the lesions.

Interestingly, a similar preferential affection of oligodendrocytes and thin axons is also seen in hypoxic lesions of the white matter, and a pattern of tissue injury closely similar to that in white matter stroke has been observed in a setting of fulminate active MS lesions. In such lesions, profound mitochondrial alterations consisting of a predominant loss of COX1, the heme-containing protein of Complex IV of the respiratory chain, suggest that hypoxia-like tissue injury is driven by mitochondrial injury [45, 46]. Similar changes in mitochondrial proteins [47] and their messenger RNAs [48] have also been observed in chronic MS associated with active lesions [47]. Furthermore, in inactive lesions, an increase of mitochondrial mass, as well as of respiratory chain activity is seen, apparently reflecting an attempt to compensate the defect when inflammation has declined [46] (Fig. 2). In contrast to the situation for oligodendrocytes, the consequences of mitochondrial dysfunction in axons is well understood [48, 49]. Energy failure impairs the clearance of sodium ions from the axoplasm of spiking axons. Accumulated Na+ in the axoplasm is replaced by Ca++ ions through reverse operation of the sodium/calcium exchanger. This, together with activation of Ca++ channels, leads to Ca++ overload of the axons and axonal degeneration. Small caliber axons are much more vulnerable for energy deficiency due to their high energy demand and low numbers of mitochondria. Whether similar mechanisms are involved in oligodendrocyte destruction remains to be resolved.

A major question, which is largely unresolved today, is what induces mitochondrial dysfunction in MS lesions. Possible candidates are reactive nitric oxide intermediates [50]. Inducible nitric oxide synthase, the enzyme responsible for the formation of nitric oxide (NO) radicals, is expressed in MS lesions. The NO radicals can directly bind to and inactivate the heme-containing COX 1 of the mitochondrial respiratory chain. Reactive oxygen species, too, can induce mitochondrial dysfunction, although, less selectively than nitric oxide [45, 51]. Whether radicals are the only mediators involved in mitochondrial injury is currently not known.

Profound microglia activation at the sites of injury in the MS brain and the close association of these cells with degenerating oligodendrocytes and axons suggest that they play a key role in mediating demyelination and neurodegeneration [52–54]. In addition, the highly significant correlation between T cell infiltration in the brain and

meninges with neurodegeneration in progressive MS [20] suggests that microglia activation is driven by products from activated T cells (and possibly, B cells). Interestingly, mitochondrial injury is induced in mixed glial cultures when exposed to a mixture of proinflammatory cytokines [55] further supporting the view that tissue damage in MS is indeed driven by the inflammatory process. However, as will be discussed below, microglia activation is a complex process, which may result in both protective and cytotoxic functions.

The microglial response to degeneration and apoptosis

Degenerated myelin, degenerating neurons, and oligodendrocytes, as well as apoptotic infiltrate cells must be engulfed and removed by microglia cells and activated macrophages to prevent further damage. For example, if myelin debris is not cleared off, it could inhibit the remyelination by oligodendrocytes [56] and could further activate the complement system to form membrane attack complexes, which would add to the destruction of myelin sheaths and axons [57–59]. Microglia cells can efficiently remove such debris, and they are uniquely equipped with a battery of receptors to perform this function: For example, with receptors recognizing the constant portion of immunoglobulins (FcγR), which require the prior opsonization of myelin by antimyelin antibodies [60]; with the complement receptor-3 (CR3/MAC-1) and the scavenger receptor-AI/II (SRAI/II), which do not have this requirement, but crucially rely on the presence of the β galactoside binding lectin galectin-3/MAC-2 [57]; with the triggering receptor expressed on myeloid cells-2 (TREM2) needed to clear apoptotic neurons [61] and cellular debris resulting from inflammatory processes in active demyelinating lesions from MS patients [62] and corresponding animal models [61]; and finally, with phosphatidylserine receptors and receptors of the Tyro3/Axl/Mertk receptor tyrosine kinase family [63], which aid in the recognition of apoptotic cells and membrane vesicles and regulate their phagocytic elimination. Signaling through these receptors induces an anti-inflammatory phenotype in microglia cells by inhibiting the production of nitric oxide synthase-2 (NOS2, iNOS) and by decreasing the transcription of proinflammatory cytokines [64–66].

Neurotoxic microglia cells may be the end result of myelin loss and neurodegeneration

Many studies in vitro and in vivo suggest that microglial neurotoxicity might not only result from the presence of noxious stimuli, but that it may also be caused by the absence of key molecules regulating microglial responses. A very attractive class of molecules involved in this process are neurotransmitters. Microglia cells carry the appropriate receptors, for example gamma-aminobutyric acid receptors, A3 adenosine receptors, cannabinoid receptors, adrenergic receptors, and dopamine receptors (for review see [67]). Under pathological conditions, neurotransmitters can become available to microglia cells by ectopic release from neurons or after synapse stripping [68]. In many, but not all cases, interactions of such neurotransmitters with their cognate receptors on microglia cells induce an anti-inflammatory phenotype in microglia cells by attenuating the microglial production and release of proinflammatory cytokines and nitric oxide [67]. For example, under ischemic conditions, norepinephrine is released in excess into the extracellular space [69–72]. On one hand, this molecule is intensely neurotoxic [71, 73] because it increases the neuronal metabolism and aggravates the ischemia-associated glutamate excitotoxicity [74, 75], but on the other hand, it blocks the production of proinflammatory cytokines from stimulated macrophages and CD8+ T cells [76, 77], and it favors the production of the anti-inflammatory cytokine TGF-β [78, 79]. A similar function is ascribed to acetylcholine, which does not only interact with conventional acetylcholine receptors on neurons, but also with the extrasynaptic nicotinic alpha7 acetylcholine receptor on microglia cells. Again, interaction of acetylcholine with its microglial receptor stimulates anti-inflammatory responses, the so-called cholinergic anti-inflammatory pathway. It effectively counteracts the excessive production of proinflammatory cytokines in lipopolysaccharide (LPS)-activated microglia cells and macrophages in vitro [80–85]. The last example is provided by the recently discovered neuropeptide urocortin, a member of the corticotropin-releasing hormone family that localizes to neurons in a variety of brain regions and has its corresponding receptors on neurons and microglia cells [86]. Even in ultra low (femtomolar concentrations), urocortin regulates excessive inflammatory microglial responses as evidenced by the inhibition of the production of proinflammatory cytokines and NO in LPS-stimulated microglia cells in vitro [86].

Another molecule involved in the communication between microglia cells and neurons is fractalkine (CX3CL1). This molecule is produced and released by intact neurons [87, 88], and its interaction with the fractalkine receptor (CX3CR1) on microglia cells suppresses microglial neurotoxicity both in vitro [89] and in vivo [88].

Finally, electrically active neurons secrete neurotrophins which efficiently prevent the transformation of microglia cells to MHC classII+ antigen-presenting cells [90] and reduce their production of iNOS, NO, and proinflammatory molecules in response to activation [91].

From all these different examples listed above one, can easily deduce that intact neurons produce a large number of molecules with anti-inflammatory properties that could maintain microglia cells in a hyporesponsive state and that the loss of these molecules could remove this braking system and might permit microglia activation [86]. Placed in the context of multiple sclerosis, one could speculate that this source of restraint could be gradually lost in the course of the disease due to neuronal degeneration. Probably, this loss is still below a critical threshold in patients with relapsing/remitting disease and above this threshold when the disease changes to a secondary progressive course. Then, even subtle changes in the environment—either provided by cytokine producing CD8+ T cells in the parenchyma or by diffusible factors produced in the meningeal compartment—might be sufficient to lift the brakes on microglia cell activation (Fig. 3). Under these conditions, microglia cells would overreact to stimulation, upregulate the expression of neurotoxic molecules, and eventually, aggravate neuronal loss as long as the stimulating triggers are present.

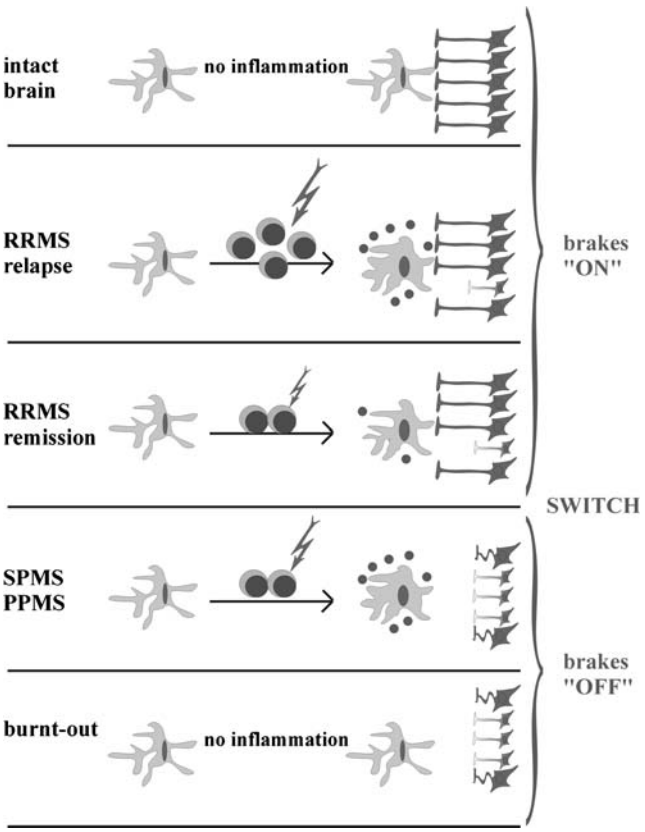

Fig. 3 Neurodegeneration lifts the brakes of microglia cells and renders them more susceptible to inflammation. Then, fewer numbers of activated T cells seem to be required in both secondary and primary progressive multiple sclerosis patients to trigger a similar production of neurotoxic factors by microglia cells than needed earlier in patients with relapsing/remitting multiple sclerosis at relapse

What are the triggers for microglia cell activation in progressive MS?

First of all, these triggers could be provided by inflammatory responses in the CNS parenchyma of patients with PPMS and SPMS. Inflammation is associated with the production and release of TNF-α and interferon-γ by inflammatory TH1 cells and of interleukin-17 by TH17 cells. All these molecules induce the production of proinflammatory cytokines, the expression of iNOS, and the release of NO by microglia cells [92, 93].

The CNS of patients with progressive MS is not only characterized by inflammation, but also by damage to myelin sheaths. Disrupted myelin could abnormally release sulfatide (sulfated galactocerebroside), which causes a dose-dependent increase of iNOS expression and NO release by microglia cells and stimulates their production of inflammatory cytokines and chemokines [94].

Then, increasing evidence suggests that strong/chronic inflammation could trigger the expression of components of the W family of human endogenous retroviruses in MS patients [95, 96]. One of these components, the glycoprotein syncytin, not only causes toxicity to oligodendrocytes by inducing the production and secretion of nitric oxide by astrocytes [97], but is also recognized by myeloid cells like monocytes, macrophages, dendritic cells, and microglia cells expressing the appropriate pattern recognition receptor TLR4/CD14 [98]. Upon interaction with this receptor, microglia cells and macrophages become activated and produce proinflammatory cytokines. And last, microglia cell activation in patients with progressive MS might also be the result of ageing.

Age, a contributing factor to lesion development in progressive MS

As described above, MS starts in the majority of patients with a relapsing/remitting course (RRMS), which after several years of disease duration converts into a progressive disease (SPMS). In about 15% to 20% of patients, typically presenting with first symptoms of MS in a higher age, a primary progressive course is seen (PPMS), which manifests itself as a slowly progressive disease from the onset [2]. These observations suggest that the aging brain plays an important role in the course of progressive MS.

Recent publications indicate that this may indeed be the case: The aging brain is not only characterized by an increase in oxidative stress and a decline in neurotransmission [99–101], but also by the activation of microglia cells and astrocytes [102–105]. In general, microglia cells of the aged brain have some morphological features of activation in that they have shorter cellular processes and larger gaps

between adjacent cells [106]. In addition, they express more antigen-presenting molecules, primarily in the CNS white matter [102–105]. Interestingly, in the aged brain, not only microglia cells are activated. Also astrocytes become hypertroph, increase the expression of glial fibrillary acidic protein, and assume an activated phenotype [102–105]. The activated phenotypes of both types of cells are accompanied with quite dramatic changes in the expression of inflammatory genes in different brain regions, leading to increased levels of TNF-α and IL-6 in the aged cortex and of IL-1β and IL-6 in the aged striatum [107]. Such differences between the adult and the aged CNS could influence responses of the aged brain to pathological stimuli [106–109] and could significantly contribute to the progressive phase of MS.

Concluding remarks

There is no doubt that the driving force for brain injury in MS patients is inflammation, independent of whether the patients experience a relapsing/remitting or progressive course of their disease. Nevertheless, the response to anti-inflammatory treatments is radically different in both groups of MS patients. This discrepancy between inflammation-driven tissue injury and response to immunomodulatory therapies can be explained by different pathomechanisms acting in RRMS and progressive MS. In RRMS, inflammatory lesions are characterized by an open blood brain barrier, and new lesions flare up as a result of distinct waves of brain infiltrating inflammatory cells entering the CNS parenchyma from the blood stream. As a result of inflammatory activity, besides other mechanisms of tissue damage, mitochondrial dysfunction develops, which drives the loss of myelin and neurons. As long as sufficient numbers of intact neurons remain, the activation of microglia cells remains controllable. Once the number of intact neurons falls below a critical threshold, the brakes on microglia cell activation may be lifted. Then, these cells may become hyperreactive in response to stimulation. On top of this process, age-related changes in microglia cells and astrocytes could create a proinflammatory environment. This is possibly the time–point when RRMS turns into a progressive disease course. In progressive MS, inflammation is trapped behind a closed (or repaired) blood brain barrier, and most inflammatory activity is found in the meningeal compartment, occasionally, even associated with ectopic lymph follicle-like structures. Diffusible factors released from this compartment become available to intraparenchymal hyperreactive microglia cells, the CNS parenchyma, which produce excess amounts of neurotoxic factors.

Hence, the distinct pathomechanisms acting in progressive MS explain the failure of immunomodulatory treatments and reveal additional targets for the design of novel therapies.

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