Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy

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Multiple sclerosis is a chronic inflammatory disease of the nervous system in which a T-cell-mediated inflammatory process is associated with destruction of myelin sheaths. Although demyelination is the primary event, axons are also destroyed in the lesions, and the loss of axons correlates with permanent functional deficit. Here, we discuss evidence that demyelination and axonal destruction follow different pathogenetic pathways in subgroups of patients. This might, at least in part, explain the heterogeneity in genetic susceptibility, clinical presentation and response to treatment observed between individuals.

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Multiple sclerosis (MS) is the most common neurological disorder in young adults in the developed world. It is a chronic inflammatory disease of the central nervous system (CNS), which leads to large focal lesions of PRIMARY DEMYELINATION (see Glossary) with relative axonal preservation. It is considered to be an autoimmune disease that is induced when T HELPER 1 CELLS (Th1) recognize components of the myelin sheath. Activated, autoreactive T cells within the lesions are believed to drive the chronic inflammatory process and activate local or hematogenous macrophages that destroy myelin. However, we suggest that this pathogenetic scheme is oversimplified and cannot explain lesion formation. It is known that T-cell populations other than classical Th1 cells contribute to inflammation in MS and that amplification of demyelination in a chronic inflammatory reaction in the brain requires additional factors. Furthermore, the patterns of demyelination are different between different subgroups of MS patients, which suggests that the disease is heterogeneous. Depending upon the patient, factors that amplify demyelination can be either antibodies directed against surface components of myelin or factors that impair the metabolism of myelin-supporting oligodendrocytes. Although these insights are based mainly on pathological studies of biopsy or autopsy tissue, new clinical and paraclinical markers to distinguish these different patterns of demyelination look promising. The heterogeneity in the pathology of MS could form the basis of both the polygenic nature and the profound heterogeneity of the disease with respect to clinical presentation and response to therapy.

Basic features of MS lesions

The pathology of MS is distinguished from that of other inflammatory diseases of the nervous system by the presence of large, multifocal, demyelinated plaques with reactive glial scar formation[1,2]. This demyelinating process is accompanied by an inflammatory reaction with infiltrates composed mainly of T cells and macrophages. Although myelin sheaths are the primary target of tissue destruction, axons, nerve cells and astrocytes are also affected, although to a lesser degree. Active lesions, defined by the ongoing destruction of myelin, are heavily infiltrated by macrophages and activated microglial cells. These cells are closely associated with the disintegrating myelin sheaths and are responsible for the uptake and removal of myelin debris.

Although MS is a primary demyelinating disease with relative sparing of axons, the emphasis is on the term 'relative'. Acute axonal injury is frequent in actively demyelinating MS lesions[3], and this leads to a 50–70% reduction in neurite density in chronic plaques, compared with normal tissue. Although demyelination can be repaired, at least in part, by remyelination[2], axonal destruction is irreversible. Thus, in MS patients, the relapsing–remitting functional impairment is caused mainly by inflammation and demyelination, whereas the accumulation of an irreversible neurological deficit is caused mainly by axonal destruction and loss.

Is Th1-mediated autoimmunity against myelin the cause of inflammation in MS?

The pathology of inflammation in MS lesions is consistent with a T-cell-mediated immune reaction, leading to the recruitment of hematogenous macrophages and activation of microglia[4]. This is similar to the pathology of experimental autoimmune encephalomyelitis (EAE), a disease induced by immunization of animals with CNS tissue, myelin or myelin proteins. Several features of MS lesions suggest that, as in EAE, the inflammatory process in MS is driven by a Th1-mediated autoimmune response. For example, the number of autoreactive T cells with the cytokine spectrum of Th1 cells is increased in blood of MS patients compared with controls. Furthermore, within actively demyelinating lesions, Th1-related cytokines, such as interferon γ, tumour necrosis factor α (TNF-α) or interleukin 2, are expressed in invading leukocytes and local glial cells[5]. The spectrum of chemokines and chemokine receptors is also consistent with a Th1-driven inflammatory response[6], and MS is

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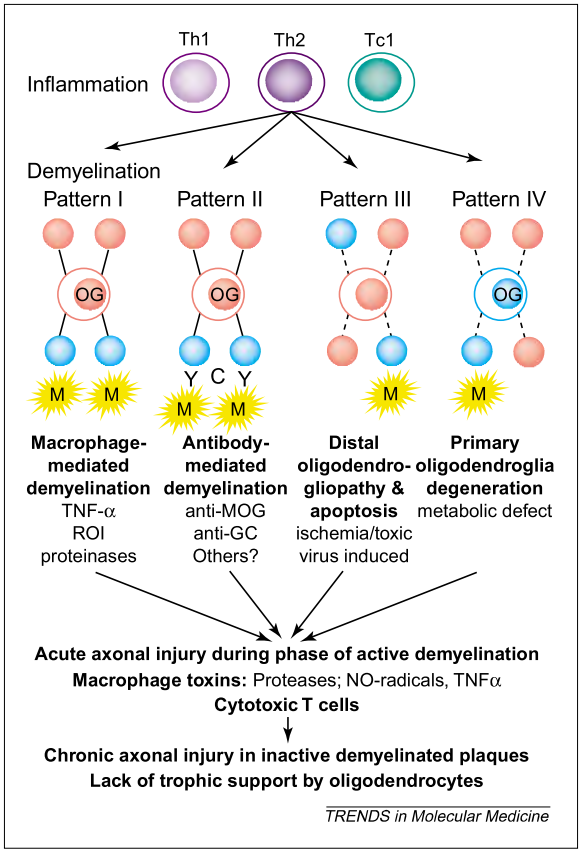

Fig. 1. Summary of pathogenetic mechanisms involved in the formation of multiple sclerosis lesions. Inflammation: evidence indicates that T helper 1 (Th1) cells have a role in inducing inflammatory reactions in the central nervous system. Proinflammatory cytokines released from Th1 cells activate macrophages, which are responsible for the majority of demyelination and axonal injury. In addition, however, T helper 2 (Th2) cells and cytotoxic, CLASS I-RESTRICTED CYTOTOXIC T CELLS (TC1) might modify the outcome of the lesions. Demyelination: myelin sheaths and oligodendrocytes (OG) can be destroyed, possibly by different mechanisms in different individuals. This results in distinctly different patterns of demyelination in active lesions. Demyelination may be induced by macrophages (M) and/or their toxic products (resulting in pattern I), by specific demyelinating antibodies and complement (C, resulting in pattern II), by degenerative changes in distal processes, in particular those of periaxonal oligodendrocytes (distal oligodendrogliopathy), followed by apoptosis (resulting in pattern III) or by a primary degeneration of oligodendrocytes followed by myelin destruction (resulting in pattern IV). Possible mediators of myelin and oligodendrocyte destruction include tumor necrosis factor α (TNF-α), reactive oxygen intermediates (ROI), antibodies against myelin oligodendrocyte glycoprotein (anti-MOG) or galactocerebroside (anti-GC). Axonal injury: axonal injury follows acute destruction of myelin sheaths. In the active phase of demyelination, axonal injury is likely to be induced by macrophage toxins or by the direct effects of cytotoxic T cells. The chronic axonal injury observed inactive plaques may be caused by a lack of trophic support by glial cells, such as oligodendrocytes, but could also involve inflammatory mediators, produced by macrophages, that persist in most active chronic lesions.

associated with certain major histocompatibility complex class II haplotypes[7]. Thus, it is generally believed that the immunological mechanisms responsible for inflammation in MS are similar to those in EAE, an experimental paradigm of Th1-mediated autoimmune disease, and that immunomodulatory therapeutic strategies that work in EAE should also be beneficial in MS. Unfortunately, in many instances this approach has been disappointing[8].

Glossary

Primary demyelination: destruction of myelin sheaths with relative sparing of axons.
T helper 1 cells (Th1): MHC class II-restricted T cells that secrete a spectrum of cytokines including interleukin 2, interferon γ and lymphotoxin α, and elicit a delayed-type hypersensitivity reaction.
T helper 2 cells (Th2): MHC class II-restricted T cells that secrete mainly interleukins 4, 5, and 6. They stimulate antibody production and are involved in allergic reactions.
Class I-restricted cytotoxic T cells (Tc1): cells that secrete a similar spectrum of cytokines to Th1 cells.

One possible reason for this might be that the pathogenesis of MS lesions is more complex than a pure Th1-mediated CNS autoimmune disease. There is evidence that cells other than classical Th1 cells contribute to the inflammatory response in MS lesions (Fig. 1). Numerically, CD8, class I-restricted T cells outnumber CD4 cells[9]. Furthermore, class I-restricted T cells are predominant at the site of tissue destruction in actively demyelinating lesions, whereas CD4 cells are retained mainly in perivascular inflammatory infiltrates[10]. Recent studies using PCR to analyze single cells show that clonal expansion is much more prominent in the CD8 population than in the CD4 T-cell population[10]. Additionally, the extent of axonal injury and tissue destruction correlates better with the number of macrophages and CD8 cells in the lesions than with CD4 cells. Taken together, these data suggest that class I-restricted T cells could play an important role in the pathogenesis of MS.

Another feature of inflammation in MS that is incompatible with the concept of a purely Th-1-mediated disease is the abundance of granulocytes and eosinophils in active lesions of acute and fulminate variants, in particular in Marburg's type of acute MS and Devic's type of neuromyelitis optica. An inflammatory reaction similar to that found in Devic's disease can be induced by transfer of Th2-polarized autoreactive T cells to immunocompromised animals[11]. These data suggest that T HELPER 2 CELL (TH2)-mediated mechanisms might contribute to inflammation in subsets of patients with MS (Ref. 12).

Additional demyelinating amplification factors are required to form demyelinated plaques

In most vertebrates, including rats, guinea pigs and primates, pure T-cell-mediated inflammation of the brain does not lead to demyelination. An exception to this is the mouse, in which extensive activation of macrophages and microglia in EAE, or in certain transgenic models, is associated with primary destruction of myelin. In these mouse models, signaling through TNF receptor 1 is required for the destruction of myelin and oligodendrocytes[13].

Pure inflammatory T-cell-mediated encephalomyelitis can, however, become an MS-like demyelinating disease in the presence of specific demyelinating amplification factors. One such factor, which has been extensively characterized recently, is

Box 1. Multiple sclerosis cases included in a study of the heterogeneity of multiple sclerosis lesions[a]

As the mechanisms of demyelination can only be studied in MS lesions in which myelin is at the stage of disintegration, observations on the heterogeneity of demyelination are from studies of active lesions (Table I). Because active lesions are more common in patients with fulminate acute disease, such as that in acute MS or in biopsies from early MS, these conditions are over-represented in our material. Thus, the study contains an inherent bias towards patients with exceptionally severe disease. Also included, however, are samples from 18 patients with different forms of chronic MS, which have a similar spectrum of lesional patterns.

Undoubtedly, the full spectrum of pathology within active MS lesions is best recognized following autopsy, where large areas of the lesions plus surrounding brain tissue can be analyzed. However, the different patterns of demyelination, described here (Table II), can be identified unequivocally even in small stereotactic biopsies, provided an area of active demyelination is present and appropriate care is taken in staging of the lesions.

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Table I. Multiple sclerosis cases included in this study[b]

Definition of clinical MS courses	Number of cases
Acute multiple sclerosis (Marburg's Type): Fulminate inflammatory demyelinating disease with typical multiple sclerosis pathology leading to patient's death within one year after onset.	14 autopsies
Early multiple sclerosis (biopsies): Patients with severe acute neurological disease with atypical clinical and MRI presentation (e.g. large monofocal lesions; no intrathecal immunoglobulin synthesis); Biopsy taken generally during the first months after disease onset with pathology of inflammatory demyelinating disease resembling MS; 77% of these patients develop clinically definite MS in follow up (average follow up time: 37 months).	51 biopsies
Chronic active multiple sclerosis: Patients with clinically definite chronic multiple sclerosis (relapsing-remitting; primary progressive or secondary progressive); At least one actively demyelinating lesion present within the CNS.	18 autopsies
Chronic inactive multiple sclerosis: Patients with clinically definite multiple sclerosis; (relapsing-remitting; primary progressive or secondary progressive); No actively demyelinating lesions in whole CNS.	not included

Table II. Defining demyelinating activity[c]

Definition of demyelinating activity	Number of lesions
Active lesions: Lesions with infiltration by macrophages, which contain intracytoplasmic granules, immunoreactive for all myelin proteins, including minor myelin components such as myelin oligodendrocyte glycoprotein	173 lesions in autopsies 62 lesions in biopsies
Inactive lesions: Demyelinated or remyelinated lesions, with or without macrophage infiltration; Macrophages do not contain degradation products, immunoreactive for minor myelin proteins;	152 lesions in autopsies 9 lesions in biopsies

the presence of demyelinating antibodies directed against epitopes expressed on the surface of myelin sheaths and oligodendrocytes[14]. In this experimental paradigm, brain inflammation, mediated by T cells, induces local activation of hematogenous macrophages or microglia, and impairs the blood–brain barrier. The latter allows circulating demyelinating antibodies and complement components to enter the CNS and destroy myelin, either by complement activation or an antibody-dependent cellular cytotoxicity reaction. The pathological hallmark of such lesions is the local precipitation of the lytic terminal complement complex on the surface of myelin sheaths and oligodendrocytes.

However, other mechanisms that have been identified could induce myelin damage during the course of an inflammatory process in the CNS. These include direct T-cell-mediated cytotoxicity[15] and metabolic impairment of oligodendrocytes through ischemia[16], toxins[17] or virus infection[18]. Thus, a major challenge for future research, is to define which of these mechanisms operate in actively demyelinating MS plaques.

Heterogenous patterns of demyelination in MS

A major restriction of pathogenetic studies of MS is the limited material available from actively demyelinating lesions, and it has required a large international effort to collect sufficient specimens to perform such a study[19,20] (Box 1). A detailed immunopathological investigation of this material has revealed a profound heterogeneity in the patterns of demyelination between different patients, although active plaques from the same patient were very

Table 1. Essential characteristics of different patterns of demyelination in multiple sclerosis

Patterns of demyelination	Pathology	Putative mechanisms
(I) Macrophage mediated	Perivenous distribution of lesions; Radial expansion of the lesions; Inflammatory infiltrates composed of T-cells and macrophages; Activated macrophages and microglia associated with degenerating myelin.	T-cell-mediated inflammation with macrophage/microglia activation; Demyelination induced by macrophage toxins.
(II) Antibody mediated	Similar lesions as in I but additional deposition of immunoglobulin and activated complement at sites of active myelin destruction	T-cell-mediated inflammation with macrophage/microglia activation; Complement mediated lysis of antibody-targeted myelin
(III) Distal oligodendrogliopathy	Inflammation by T-cells and macrophages; Small vessel vasculitis with endothelial cell damage and microvessel thrombosis; Degeneration of distal oligodendrocyte processes, followed by oligodendrocyte apoptosis and demyelination	T-cell-mediated small vessel vasculitis with secondary ischemic damage of the white matter
(IV) Primary oligodendrocyte damage with secondary demyelination	Similar lesion as in (I), but prominent oligodendrocyte degeneration in a small rim of periplaque white matter	T-cell-mediated inflammation with macrophage/microglia activation; Demyelination induced by macrophage toxins on the background of metabolically impaired oligodendrocytes; Genetic defect of oligodendrocytes?

similar. All actively demyelinating lesions were associated with an inflammatory process, with the inflammatory infiltrates composed mainly of T cells and macrophages. Despite the similarities in the inflammatory reaction the lesions segregated into four patterns of myelin destruction (Table 1, Figs 1,2).

Pattern I (macrophage-associated demyelination) closely resembles myelin destruction in mouse models of autoimmune encephalomyelitis. In these models, toxic products of activated macrophages, such as TNF-α (Ref. 13) or reactive oxygen species, are mainly responsible for the destruction of myelin sheaths[21]. Lesions similar to pattern II (antibody-mediated demyelination) are found in models of EAE that are induced by sensitization with myelin oligodendrocyte glycoprotein (MOG). In this model, demyelination is induced by cooperation between encephalitogenic T cells, which are responsible for inflammation, and demyelinating anti-MOG antibodies[14]. So far, patterns III and IV have not been identified in experimental models of demyelinating disease. Distal oligodendrogliopathy-associated demyelination (pattern III), however, is commonly found in virus-induced human white-matter diseases[22] and is also seen in the penumbra region of white-matter strokes (Rauschka *et al.*, unpublished). Preliminary evidence from our laboratory suggests that white-matter ischemia is a major pathogenetic factor for demyelination and tissue damage in such lesions. The mechanisms responsible for pattern IV lesions (primary oligodendrocyte degeneration), which are the most infrequent in the MS population and are restricted to a subset of patients with primary progressive disease[20], are not clear. It is tempting to speculate that, in these patients, a genuine metabolic disturbance of oligodendrocytes could render these cells particularly vulnerable to the toxic action of inflammatory mediators.

The heterogenous patterns of pathology so far could only be related to a specific clinical disease variant in patients with most acute and fulminate disease course. All patients with Devic's type of neuromyelitis optica had antibody-mediated tissue damage[23] (pattern II), whereas all patients with Balo's type of concentric lesions had lesions of distal oligodendrogliopathy (pattern III). Furthermore, primary oligodendrocyte degeneration (pattern IV) has only been found in a small subset of patients with primary progressive disease. Except for this segregation in the most severe disease variants, no specific association between the pattern of demyelination and clinical disease was found.

Axonal injury and loss: a consequence of inflammatory demyelination

Early descriptions of the pathology of MS, published in the early 1900s, emphasized the functional importance of axonal destruction in the lesions, which led to secondary (Wallerian) tract degeneration and brain atrophy[3]. This aspect of MS pathology has received increased attention recently, as serial magnetic resonance imaging (MRI) investigations indicate that axonal loss within the lesions and brain atrophy correlate with permanent, progressive functional deficits. Axonal injury in MS plaques occurs in two stages[24]. A high incidence of acute axonal injury is found in lesions during the active stage of myelin destruction[25,26]. Thus, even during the earliest stages of the disease, every newly formed plaque is associated

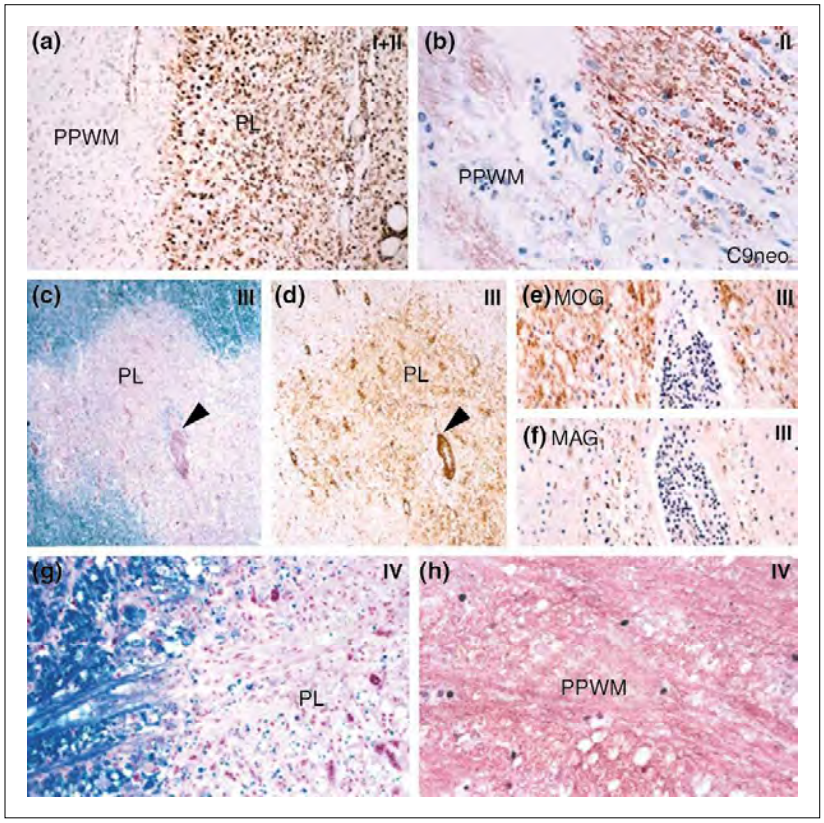

Fig. 2. Histopathology of different patterns of demyelination in multiple sclerosis. (a) Actively demyelinating lesion following patterns I and II. The active plaque (PL) is filled with activated macrophages and microglia. There is a sharp demarcation between the actively demyelinating lesions and the periplaque white matter (PPWM). Immunocytochemistry for CD68 (to identify activated macrophages/microglia). Magnification × 200. (b) Actively demyelinating plaque of pattern II that shows massive deposition of complement C9neo-antigen (brown staining) on degenerating myelin sheaths and in myelin degradation products taken up by macrophages in the zone of active demyelination (ADM). There is faint C9neo reactivity on myelin sheaths in the PPWM. Immunocytochemistry for C9neo-antigen. Magnification × 500. (c) Actively demyelinating lesion following pattern III. Myelin staining using Luxol fast blue shows an ill-demarcated demyelinated plaque (PL). In the centre of the lesion is an inflamed blood vessel surrounded by a small rim of preserved myelin (arrow). Magnification × 30. (d) The same lesion as shown in (c) stained with the leukocyte marker CD45. Myelin around the central vessel has a lower density of inflammatory cells compared to the rest of the lesion (arrow). In addition, this lesion has an indistinct boundary compared with the lesion in panel (a). Immunocytochemistry for CD45. Magnification × 30. (e) Higher magnification of the area indicated by the arrow in panels (c) and (d) stained for myelin-oligodendrocyte glycoprotein (MOG, brown staining). There are numerous MOG-reactive fibers preserved in the lesion. Magnification × 300. (f) Higher magnification of the area indicated by the arrow in panels (c) and (d) stained for myelin associated glycoprotein (MAG). There is very little MAG immunoreactivity. Magnification × 300. (g) Actively demyelinating lesion following pattern IV. The plaque contains numerous macrophages containing myelin degradation products (stained blue with the Luxol fast blue myelin stain) and has a sharply demarcated edge. Magnification × 300. (h) The periplaque white matter of the lesion in (g). The myelin appears vacuolated and contains numerous oligodendrocytes with fragmented DNA (black nuclei) identified using an *in situ* tailing reaction for DNA fragmentation. Magnification × 400.

with a significant loss of axons. In this phase, the extent of axonal injury correlates with the number of macrophages and class I-restricted T cells in the lesions, and is apparently mediated by toxic products of macrophages and T cells. A few mediators have been identified, such as nitric oxide and proteases, that can induce axonal injury *in vitro* or *in vivo*[27,28]. In addition to axonal degeneration in active plaques, there is also a low level of continuous axonal destruction and loss in chronic inactive demyelinated plaques[24]. This is not seen in inactive, remyelinated lesions, so the lack of trophic support by oligodendrocytes in demyelinated lesions might render axons vulnerable to progressive damage. Although the initial event that triggers axonal damage can differ, the final pathway of axonal destruction appears to be similar in all conditions of cerebral damage; alterations in ion-channel permeability disturb calcium homeostasis within the axons, which leads to activation of calcium-dependent proteases, local degradation of cytoskeletal elements, blockade of axonal transport and, finally, axonal disruption[29].

The extent of axonal damage in MS lesions is variable and depends upon the severity of the inflammatory process during the active stage of demyelination. Other factors that influence the degree of axonal injury are the pathogenetic mechanism of demyelination and, possibly, heterogeneity in the susceptibility of individual patients. Within the MS population, axonal loss appears to be most important in patients with either primary or secondary progressive disease courses.

These data provide support for the concept that the mechanism of demyelination and tissue destruction is heterogenous between different subgroups of patients, and could have profound consequences for our understanding of disease pathogenesis and for the future design of novel therapeutic strategies.

Is inflammation in MS lesions always deleterious?

As previously discussed, T-cell-mediated inflammation is the apparent driving force behind the pathological process in MS lesions. More recent data, however, indicate that inflammation might also be neuroprotective, or have a role in the repair of damaged tissue within the CNS. For example, autoimmune T cells protect neurons in the optic nerve from secondary degeneration after injury by partial crushing[30]. The presence of macrophages stimulates remyelination in organ culture[31], an observation that could be particularly relevant for MS lesions. Furthermore, inflammatory cells within MS lesions synthesize neurotrophic factors, such as brain-derived neurotrophic factor[32]. These data suggest that the inflammatory response within demyelinated plaques of MS patients might also have a role in the repair process and, thus, complete blockage of all inflammatory processes within the lesions could be counterproductive.

Clinical identification of subgroups of MS patients

The heterogenous patterns of demyelination in individuals with MS patients are defined by the pathology of active lesions. However, we expect that clinical diagnosis and therapy would be aided by developing clinical and paraclinical markers to identify patient subgroups according to their pathogenetic pathways of lesion formation. As the association between clinical forms of the disease and pathological subtypes is limited, this approach will largely depend upon the development of suitable paraclinical markers.

It is possible that subsets of MS patients will be identified using MRI and magnetic resonance

Outstanding questions

- What immunological and neurobiological mechanisms underlie the heterogenous patterns of MS pathology?
- Which are the most suitable clinical and paraclinical markers to define patient subgroups with different pathogenetic pathways in the formation of demyelinated plaques?
- Do patients with different pathogenetic pathways of demyelination require subtype-specific therapy?
- Are recent therapies developed against specific mechanisms of demyelination or axonal injury effective in MS patients?

spectroscopy. These techniques focus on two major issues: determining the imaging correlate of basic histopathological MS features, such as inflammation, demyelination–remyelination, gliosis and axonal loss; and identifying different demyelination pathways. From their pathological appearance[20], it is predicted that pattern I and II lesions, which reflect classical autoimmunity, will be characterized by their sharp borders, and early and pronounced contrast enhancement as a reflection of damage to the blood–brain barrier. By contrast, lesions that involve oligodendrocytes (patterns III and IV) expand more diffusely into the white matter. Thus, these lesions have ill-defined borders and less pronounced and delayed blood–brain barrier damage. Lesions with these features have been described in subgroups of MS patients[33] and preliminary evidence indicates that they correlate with the respective pathological patterns.

Cases of MS in which antibody-mediated demyelination occurs could, additionally, be identified by the presence of serum-demyelinating antibodies. Such antibodies have been found in the serum of a subset of MS patients[34]. One of the major targets of demyelinating antibodies is MOG. Although anti-MOG antibodies occur in serum and cerebrospinal fluid of MS patients, a classification of MS patient subsets on the basis of their presence or absence is not yet possible[35,36]. An additional complication is that these antibodies are also found in control patients without MS and in patients with other neurological diseases. Furthermore, not all anti-MOG antibodies induce demyelination *in vivo* and *in vitro*: most anti-MOG antibodies recognize regions of MOG that are not exposed on the extracellular surface of oligodendrocytes and are therefore not targets for antibodies *in vivo*. Lastly, MOG is only one of the possible target antigens for antibody-mediated demyelination. More precise analysis of demyelinating anti-MOG antibodies, and the identification of other potential targets of pathogenic autoantibodies, should lead to tools that allow a more detailed categorization of MS patient subsets.

Consequences of MS therapy

Demyelination in MS develops by a T-cell-driven inflammatory process. Thus, the primary nature of inflammation is undisputed and will remain central for treatments that modulate the immune system[8]. There are, however, several aspects that limit the therapeutic efficacy of strategies directed exclusively against the inflammatory component of the disease. Currently, immune suppression is unable to stop the inflammatory reaction in the CNS and immune modulatory regimes using interferon β or co-polymer I decrease, but do not abolish, inflammation. It is not possible to intervene more specifically in the inflammatory process because neither the trigger of inflammation (virus induced versus autoimmunity) nor the specific target antigen in the CNS of affected patients is known. It should also be remembered that, in MS, evidence that inflammation is driven by a Th1 response is circumstantial, and a role for other T cells, for example a response mediated by class-I-restricted cells, is likely.

These uncertainties indicate the importance of identifying supplementary therapeutic strategies to prevent demyelination and tissue destruction in MS. Possible approaches include blocking macrophage responses or specific macrophage toxins, the elimination of specific demyelinating antibodies, neuroprotective therapies to prevent axonal injury or the consequences of brain ischemia, and stimulation of remyelination. Although attractive conceptually, these strategies have so far failed. It is possible that this is because of the heterogeneity in the pathogenetic mechanisms that leads to the formation of demyelinated plaques in this disease, which we have described earlier.

Thus, a major challenge for MS research is to develop paraclinical markers that identify the heterogenous pathogenetic components involved in the formation of MS plaques in individuals at different stages of their disease. This could lead to the stratification of MS patients into smaller subgroups with common, defined mechanisms of inflammation, demyelination and tissue damage, and to subtype-specific therapy.

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Molecular basis of partial lipodystrophy and prospects for therapy

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Lipodystrophy is characterized by altered partition of adipose tissue. Despite heterogeneous causes, which include genetic, autoimmune and drug-induced forms, lipodystrophy syndromes have similar metabolic attributes, including insulin resistance, hyperlipidemia and diabetes. The mechanisms underlying the insulin resistance are unknown. One form of lipodystrophy, namely Dunnigan-type familial partial lipodystrophy (FPLD) was shown to result from mutations in the *LMNA* gene, which encodes nuclear lamins A and C. Although the relationship between the mutations in the nuclear envelope and insulin resistance is unclear at present, these findings might eventually be shown to have relevance for the common insulin resistance syndrome and for drug-associated lipodystrophies.

The compensatory hyperinsulinemia that is required to maintain glucose tolerance in people with insulin resistance is associated with a cluster of metabolic abnormalities, which usually presents before the onset of diabetes mellitus[1,2]. This metabolic cluster is referred to as 'metabolic syndrome X' or 'insulin resistance syndrome'[1,2]. This disorder is frequently seen in individuals with android obesity, and is characterized by glucose intolerance, dyslipidemia and hypertension[1,2], which together contribute to accelerated atherosclerosis. Defining the underlying mechanisms of insulin resistance might help to develop preventative and/or treatment strategies. One approach to understand a common complex phenotype is to study a genetically extreme form. An extreme monogenic form of insulin resistance is DUNNIGAN-TYPE FAMILIAL PARTIAL LIPODYSTROPHY (FPLD) (see Glossary).

Clinical attributes of FPLD

In the 1940s, Lawrence reported a diabetic patient with atrophic fat stores and hyperlipidemia[3].

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