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Animal Models of Demyelination

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Demyelination is a pathological feature that is characteristic of many diseases of the central nervous system (CNS) including multiple sclerosis (MS), sub-acute sclerosing panencephalomyelitis (SSPE), metachromatic leukodystrophy and Pelizaeus-Merzbacher disease. While demyelination is a pathological end-point that is common to all of these diseases, the cellular and molecular mechanisms responsible for this pathology are very different. These range from genetic defects that affect lipid metabolism in the leukodystrophies, cytopathic effects of viral infection in SSPE to the action of immunological effector mechanisms in MS and the viral encephalopathies. Irrespective of the initial cause of myelin degradation, many of these disorders are associated with some degree of CNS inflammation, as indicated by the local activation of microglia, recruitment of macrophages or the intrathecal synthesis of immunoglobulin. Many of these phenomena are now being duplicated in animal models, providing not only new insights into the pathogenesis of human demyelinating diseases, but also unexpected interrelationships between the immune response in the CNS and the pathogenesis of diseases such as Alzheimers disease and HIV encephalopathy. Autoimmune mediated models of inflammatory demyelinating CNS disease have proved particularly valuable in this respect as they allow the effects of defined immune effector mechanisms to be studied in the absence of CNS infection.

Immune Mediated Demyelination.

Demyelination in MS is believed to be mediated by an autoimmune response against CNS myelin. This concept is derived from studies of experimental autoimmune encephalomyelitis (EAE), an inflammatory demyelinating disease of the CNS induced in susceptible species following immunisation with CNS tissue or CNS myelin in Freunds complete adjuvant (74). Adoptive transfer experiments revealed that the initiation of clinical disease in EAE is dependent on the expansion and activation of a myelin-specific Th-1 subset $CD4^+$ T cell response. Once activated, this T cell population is able to cross the blood brain barrier and initiate an antigen-dependent, MHC class II restricted inflammatory response in the CNS (74). This results in a pronounced increase in the permeability of the blood brain barrier to serum proteins, edema and the recruitment of macrophages into the CNS. It is this macrophage population that is responsible for the neurological deficit associated with the inflammatory response (14). However, although CNS inflammation results in acute neurological dysfunction in EAE, it does not necessarily induce extensive primary demyelination. This is seen in both the Lewis rat and marmoset, species in which the adoptive transfer of encephalitogenic T cell lines or clones specific for the myelin basic protein (MBP) induce CNS inflammation, but virtually no demyelination (24, 27). In these species, the formation of confluent demyelinating lesions similar to those seen in MS is dependent on a myelin-specific autoantibody response to specifically direct immune effector mechanisms to attack the myelin sheath (43, 44). However this autoantibody response must be accompanied by an encephalitogenic T cell response in order that its pathogenic potential can be expressed (26).

In contrast to the resilience of the rat oligodendrocyte myelin continuum to a local inflammatory insult, the CNS of many other species are very sensitive to the local effects of inflammation. These can result in not only demyelination but also axonal degeneration as is seen in the CNS of the SJL/J mouse following the adoptive transfer of myelin-specific T cells (69). Tissue damage in this species is apparently antibody-independent and was originally described as "by-stander" demyelination. This was for many years loosely attributed to the action of pro-inflammatory and cytotoxic products of macrophages and T cells invading the CNS. Only now are the molecular details becoming clear through a combination of in vitro studies using cultured oligodendrocytes and transgenic rodents that develop chronic CNS inflammation as a result of the over-expression of pro-inflammatory cytokines in the CNS (7, 31, 51).

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Auto-Antibody Mediated Demyelination

Any autoantigen exposed at the outer most surface of the myelin sheath or oligodendrocyte must be considered as a potential target for a demyelinating autoantibody response. This has been demonstrated both in vivo and in vitro for autoantibodies specific for a number of myelin glycolipid and glycoprotein antigens exposed at the surface of the myelin membrane. The most striking clinical example is seen in patients with a demyelinating peripheral neuropathy associated with plasma cell dycrasia, many of who (60-70%) develop monoclonal IgM autoantibodies against a sulphated glucuronic acid epitope shared by P_0 protein, myelin associated glycoprotein (MAG) and several acidic glycolipids in PNS myelin. However, in the context of MS a demyelinating autoantibody response, if present, should ideally recognize a component expressed specifically on the surface of the myelin/oligodendrocyte continuum.

The only CNS myelin autoantigen known to satisfy the criteria of both specificity and localization is the myelin oligodendrocyte glycoprotein (MOG). MOG is a quantitatively minor myelin glycoprotein that comprises only 0.01 - 0.05 wt% of the total membrane protein (2, 29). Immunohistochemistry and in situ hybridization studies demonstrate that MOG is a specific product of the oligodendrocyte which is preferentially located at the outer surface of the myelin sheath and oligodendrocyte plasma membrane (7). The first indication that MOG was an immunodominant target for a demyelinating autoantibody was obtained in guinea pigs with EAE induced by immunisation with autologous spinal cord tissue (25, 28). Subsequently, MOG-specific mouse monoclonal antibodies were shown to mediate demyelination in vivo in rats with EAE (24, 27).

The cloning of rat and mouse cDNAs for MOG (11, 42) identified the mature protein as a highly conserved 218 residue member of the immunoglobulin superfamily which is encoded close to the class I MHC locus (23, 42, 58). Hydropathicity plots of the deduced amino acid sequence of MOG identified two potential transmembrane domains suggesting that the protein may be organized in the membrane with two distinct extracellular domains; a N-terminal IgG V-like domain and a 20 amino acid long C-terminal tail (11).

The relative importance of these two domains in the immunopathogenesis of autoimmune mediated demyelination has been established using synthetic MOG peptides and recombinant MOG fusion proteins. These studies have demonstrated that in the Lewis rat peptide epitopes in the N-terminal domain (a.a. 1-125) are responsible for the demyelinating autoantibody response (1, 16). However, this domain is unique among myelin proteins in that it not only contains B cell epitopes capable of inducing a demyelinating autoantibody response, but also encephalitogenic T cell epitopes for a large number of different species (3, 16 , 18, 31).

The direct consequence of this dual pathogenic capacity is that immunisation with a recombinant protein analogous to the IgG-like domain of rat MOG (a.a 1-125) (1) induces a demyelinating variant of EAE the pathology of which closely resembles MS in rats (1) and mice (3). The induction of an encephalitogenic T cell response by epitopes within the extracellular domain of the protein is crucial for the induction of this disease, as they initiate blood-brain barrier damage to allow antibodies to enter the CNS.

The pathological changes in the demyelinating lesions induced by active immunisation with MOG share several characteristics with those seen in MS, in particular complement and IgG deposition is associated with active demyelination at the leading edge of the lesions. It is also relevant to note that remyelination as well as demyelination is observed, once again a common feature of the early, active MS lesion.

The duality of the pathogenic autoimmune response in MOG-induced models has important consequences with respect to the development of therapeutic strategies for this disease model. Many novel treatment protocols for EAE, and by extrapolation MS, are based on the concept that disease induction involves only a Th-1 subset T cell response. In MOG-induced EAE, this concept breaks down as antibody and the associated Th-2 T cell subset are additional factors that must be considered when designing immunotherapies. In particular, strategies based on immune deviation - modifying the immune response to favor a non-inflammatory Th-2 T cell response, rather than a pro-inflammatory Th-1 T cell subset response may be ineffectual, as this will enhance the circulating antibody response without completely eliminating the inflammatory Th-1 component.

Cytokines as Mediators of Demyelination

Although autoantibodies can mediate selective demyelination in the CNS, studies in mouse models of EAE clearly demonstrate that the local inflammatory response can also initiate CNS demyelination in the absence of a specific autoantibody response. In vitro studies suggest that this may be due to a selective susceptibility of the oligodendrocytes to damage mediated by pro-inflammatory factors, including cytokines, complement and free radicals.

The most extensively studied of these potential effector mechanisms is mediated by TNFalpha (TNF). In tissue culture, exogenous TNF, as well as lymphotoxin is not only selectively cytotoxic for primary oligodendrocytes, but also causes myelin damage in myelinating CNS explants (63). Although several groups have attempted to analyse this effect in vivo by the injection of exogenous TNF, a more elegant approach is to generate transgenic animals that overexpress TNF in defined sets of cells in the CNS.

One such animal model was recently developed by Probert and coworkers (50), who produced a strain of transgenic mice specifically overexpressing TNF in a subpopulation of CNS neurons. TNF is a powerful proinflammatory cytokine (71) that is not only produced by monocytes, but also by neurons in the normal brain (6). TNF overexpressing transgenic mice spontaneously develop a chronic inflammatory demyelinating disease, which starts at 3-8 weeks of age. Affected animals develop progressively more severe neurological symptoms ranging from mild tremors to paralysis and premature death within ~8 months. Interestingly, as a consequence of expression of the transgene, $CD4^+$ and $CD8^+$ T cells are recruited into the meninges and CNS parenchyma of the transgenic mice, an event also seen in MS and EAE, where migration of T lymphocytes across the blood brain barrier plays a central role in disease pathogenesis.

In the TNF transgenic mice, CNS inflammation is associated with extensive demyelination, which is most prominent in the white matter of the medulla oblongata and cervical spinal cord. In addition, the transgenic mice develop a pronounced reactive astrocytosis and microgliosis, a characteristic response of the adult CNS to inflammation which once again is also seen in MS (52) and EAE (67). Although the expression of TNF in the CNS clearly results in chronic inflammation and demyelination, it is still not possible to attribute the demyelinating response simply to a direct cytopathic effect of TNF production in the CNS on oligodendrocytes, similar to that described in vitro (55, 62,63). Alternative mechanisms may involve TNF acting in synergy with other proinflammatory cytokines (e.g. IL-1) to trigger the local production of other cytopathic mediators, such as nitric oxide, which also has toxic effects on oligodendrocytes (33, 40, 55). However, demyelination in this model may not be a direct consequence of the local over-production of TNF, but rather a consequence of the chronic inflammatory response induced in the CNS. It should be noted that both in this TNF model, as well as in transgenic mice engineered to overproduce IL-3 in astrocytes in the CNS (8), chronic CNS inflammation is associated with microglial activation and proliferation. The molecular mechanisms by which this inflammatory response mediates demyelination are as yet unknown, however the similarities between the two models suggest that chronic activation of the microglial population may play a key role in initiating demyelination. Irrespective of the molecular mechanisms that are responsible for demyelination in these animal models, it is important to note the dysregulation of TNF or IL-3 production in the CNS results in a pathology (CNS inflammation, reactive astrocytosis, microgliosis and myelin disruption) similar to that seen in MS lesions. Dysregulation of intrathecal cytokine production must therefore be considered as yet another potential mechanism in the immunopathogenesis of demyelination in human CNS disease.

Viral Models of CNS Demyelination

Autoimmune disease models have demonstrated that a complex spectrum of immune mechanisms can trigger CNS demyelination, but viral infection introduces a completely new level of complexity to this analysis. Viruses may not only be directly cytopathic for oligodendrocytes but virus-specific immune responses must also be expected to kill infected oligodendrocytes directly, or as described above in chronic CNS inflammation, indirectly by modifying the local CNS microenvironment and rendering oligodendrocytes more susceptible to the effects of the local inflammatory response. It is beyond the capacity of this short review to discuss fully the various models of virus induced demyelination in rodents, but two models have been particularly illuminating as they demonstrate that concepts derived from EAE are also applicable to the immunopathogenesis of viral infections of the CNS. Theiler's murine encephalomyelitis virus (TMEV) in mice and JHM hepatitis virus in rats have been studied for many years as virus models that produce a CNS pathology resembling that seen in MS. TMEV is a natural enteric picornavirus in mice, which following intra-cerebral infection will induce a chronic progressive, inflammatory demyelinating disease of the CNS in susceptible strains of mouse such as SJL/J. The pathology and clinical signs of affected animals are similar to those observed in patients with chronic progressive forms of MS and individual lesions show signs of both active immune-mediated demyelination and remyelination (57). The immunopathogenesis of TMEV is critically dependent on a TMEV-specific $CD4^+$ T cell response that mediates an inflammatory response in the CNS that is similar in many respects to that seen in adoptively transferred EAE in the mouse. In addition, virus antigen-specific $CD8^+$ T cell responses and demyelinating autoantibodies may also play a role in the immune pathogenesis of demyelination (75). Rodriguez and coworkers (57) analyzed the role of persistent CNS inflammation in the prevention of spontaneous remyelination in chronically infected SJL/J mice by treatment with either cyclophosphamide, or monoclonal antibodies specific for either CD4 or CD8. Both treatments resulted in significantly better remyelination than was seen in control animals (56), revealing a crucial role for T cells in the immunopathogenesis of demyelination/impaired remyelination in TMEV-infected mice. However, it should be noted that spontaneous remyelination in TMEV infected mice is limited and occurs rather late in the disease process, possibly reflecting a marked decrease in the expression of viral antigens in the CNS with time (10, 35). Unfortunately, as yet neither the effector mecha-

nisms nor the target antigens recognized by the T lymphocytes responsible for demyelination have been fully defined in TMEV.

This is in contrast to coronavirus MHV-JHM CNS infections in the rat in which at least one mechanism of immune mediated demyelination is relatively well understood. MHV-JHM mediates the formation of sub-acute demyelinating lesions in a significant number of infected rats. Histopathology and immuno-electron microscopy in this model suggest that an anti-viral spike protein antibody response may play a major role in demyelination (75). Spike protein is displayed on the surface of infected oligodendrocytes in the lesions, which are associated with complement activation/deposition, together with high numbers of B cells and plasma cells. These observations suggest that demyelination is mediated by the humoral response to this viral protein, anti-S protein antibodies targeting the oligodendrocyte in the same way as has been described in MOG-mediated EAE (78).

Clearly the balance of humoral v. T cell immune effector mechanisms in virus mediated models of demyelination is dependent on the nature of the infectious agent and the host. CD4+ T cells and antibody responses are without doubt involved in many cases, but as yet very little hard evidence is available with respect to the capacity of CD8+ T cells to mediate demyelination during viral CNS infections.

Dissection of the effector mechanisms responsible for demyelination is also complicated by the observation that tissue damage during the course of a CNS viral infection stimulates the expansion of CNS autoantigen specific T cell clones in the periphery. This secondary, autoimmune response can it self be pathogenic as described in rats with MHV-induced SDE, or sub-acute measles encephalomyelitis. In both models encephalitogenic MBP-specific T cells can be recovered from the spleens of infected animals and be shown to transfer EAE to naive syngeneic recipients (73). A similar observation has also been reported in mice in the later stages of TMEV infection suggesting that a gradual switch from predominantly viral-specific to autoimmune effector mechanisms may be a common occurrence during viral infections of the CNS.

Although such a specificity-switch is a very attractive mechanism to account for the induction of chronic demyelinating diseases that continue long after virus is cleared from the CNS, alternative mechanisms should also be considered to account for the incomplete remyelination of the CNS seen in both MS and animal models such as chronic infection with TMEV. In one possible scenario, oligodendrocytes and possibly more importantly their precursors may just simply be depleted in the lesions. Indeed, in chronic MS lesions surviving oligodendrocytes are located predominantly at the periphery of the lesions and are rare in the center (53). Such findings may also be explained by a lack of those factors within lesions that are necessary to sustain and promote oligodendrocyte growth, differentiation and migration. Candidates for such factors are fibroblast growth factor, insulin-like growth factor-1, or platelet-derived growth factor, all of which are ubiquitous factors influencing oligodendrocyte growth in vitro (41). However, it remains to be established whether or not this concept is applicable to any demyelinating disease of the CNS.

Genetic Defects Leading to Demyelination

In contrast to MS which is often first diagnosed in the second to fourth decades of life, demyelination associated with genetic disorders, such as the leukodystrophies, normally manifest themselves clinically during childhood and are inevitably fatal. Although the genetic basis of the majority of these disorders involves defects in genes involved in lipid metabolism, several exhibit a selectively detrimental effect on CNS function which in X-linked adrenoleukodystrophy (ALD) is characterized by progressive demyelination of the cerebral white matter. ALD provides an interesting link between a metabolic defect affecting CNS white matter and inflammatory CNS disease, as demyelinating lesions in ALD are associated with an intense inflammatory response. Infiltrating macrophages and reactive astrocytes are particularly conspicuous at the active edge of the lesions, the frequency of the latter appearing to correlate directly with the intensity of inflammatory demyelination. In contrast, T lymphocytes and plasma cells are concentrated in perivascular cuffs, but not in the parenchyma. In fact, the perivascular cuffs in ALD display a very similar cellular composition as those found in active MS or EAE lesions, containing CD4+ and CD8+ T lymphocytes, macrophages, and, to a lesser degree, B cells and plasma cells (12, 46, 47). These similarities frequently resulted in ALD and MS being considered similar entities (60), and the suggestion that demyelination in ALD was also immune mediated. However, there appears to be no specific primary immunopathogenic mechanism operating in ALD. Unlike MS lesions where T cells are found at the active demyelinating edge of the lesion, in ALD inflammation appears to be secondary to myelin destruction (60). Moreover, although increased levels of IgA and IgG were found in ALD tissues (4, 70) and high levels of myelin-specific antibodies were detected in sera of ALD patients (61), it is not characteristic for ALD cerebrospinal fluid to contain elevated IgG levels as typically seen in MS.

The principal biochemical abnormality in ALD is due to an accumulation of very long chain fatty acids in the adrenal cortex and in the brain (15), as a result of impaired beta-oxidation of these acids in peroxisomes (65). A two-stage pathogenetic scheme has been put forward to explain the CNS lesions of ALD. The primary phase of ALD involves the accumulation

of very long chain fatty acids which causes myelin instability and ultimately myelin breakdown. This is then enhanced by a secondary inflammatory response in the CNS which induces further demyelination (45, 47). In this respect the chronic immunopathogenesis of ALD resembles to some extent the pathology of transgenic mice specifically overexpressing TNF in CNS neurons.

It was only recently, that the gene responsible for ALD was cloned and the affected protein identified as a peroxisomal membrane protein, ALDP, a member of the ATP binding cassette (ABC) transporter superfamily (36). Hopefully, with the identification of the genetic basis of ALD, ALDP-knock-out mice and ALDP-knock-in mutants should become available in the near future. It is anticipated that it will then be possible to elucidate the different biochemical and immunological events involved in causing demyelination in ALD and identify a suitable therapeutic regimen for the management of ALD patients.

In contrast to the situation with ALD, spontaneous mutants are available in mouse (19), rabbit (71), rat (76) and dog (77) that provide animal models for another human leukodystrophy, Pelizeus Merzbacher Disease (PMD). PMD is the oldest known X-linked dysmyelinating disorder of the central nervous system (34, 39). It is associated with hypomyelination of the CNS and a reduced number of mature oligodendrocytes (59), while the peripheral nervous system remains unaffected. Approximately 25% of cases of PMD have been ascribed to mutations within the coding region of the PLP/DM-20 gene. These can take the form of missense mutations (49), in-frame deletions (20), as well as insertions leading to frameshift mutations (22) and, in principal virtually any exons of the PLP gene can be affected (Exon 2 (13, 49), exon 3 and 4 (20), exon 5 (48), exon 6 (50), or exon 7 (22)). However, other PMD cases appear to be due to an overexpression of PLP/DM-20 transcripts (9). In such cases the severity of the phenotype appears to be strongly related to the level of overexpression of the protein.

Many of the PLP mutations seen in PMD patients have their direct counterparts in the spontaneous mutants described mice, rats, rabbits or dogs. As in PMD the severity of the clinical phenotype and the degree of dys- or demyelination is dependent on the nature of the mutation, although X-linkage, a relative preservation of axons in the CNS and integrity of PNS myelin are features common to all of the mutations. Two of the most extensively characterized natural mutants are the jimpy (jp/Y) mouse and myelin deficient (md/Y) rat. The jp/Y mutation involves the deletion of the fifth exon, spanning 74 bp of the PLP gene (38), due to an A to G conversion at a conserved AG residue of the 3'-splice site (30, 37). The ensuing shift of the reading frame leads to a PLP protein with an altered C-terminal sequence, that is toxic to oligodendrocytes even in the presence of transgenic, wildtype PLP (61). In md rats, an A to C point mutation in exon III is involved in a single amino acid substitution (Thr 75 -> Pro) of PLP (6).

The phenotypic expression of these two distinct mutations is most pronounced in jp/Y mice which normally die as a consequence of chronic seizures between 20 and 30 days of age. In contrast, some md/Y mutant rats can survive for up to two months of age (21). In both of these mutants oligodendrocyte maturation is impaired and gliosis is readily visible at light microscopic level. An extensive immunocytochemical analysis of myelin proteins in these mutants was made by Koeppen and coworkers (21) and yielded a number of interesting findings that may help explain why the phenotype differs.

Compared to normal littermates, immunocytochemical staining of the brains of both jp/Y and md/Y revealed a greatly reduced level of reaction product when stained with antisera to MBP, MAG, and CNP. Immunochemical reaction products were located in clusters and revealed cells (oligodendrocytes) with delicate projections connected to the myelin-like sheaths. In contrast, antiserum to PLP failed to reveal any immunoreactive structures in the white matter. Using anti-transferrin antibodies as a marker, some oligodendrocytes of normal morphology could be detected in md/Y rats, but were completely absent in jp/Y mice. Koeppens findings suggest that cells differentiate along the oligodendrocyte lineage in these mutants up to a particular point in their developmental program, but fail to survive as mature cells. This is thought to be due to either a lack of PLP, or alternatively the cytopathic effects of hydrophobic peptides derived from the proteolysis of the aberrant protein product. Interestingly regardless of the mechanism of cell death, it is also associated with variable reductions in other myelin proteins such as MBP, CNP and MAG in both jp/Y mice (19) and md/Y rats (75).

It is now apparent that not only mutations of the PLP gene, but also the overexpression of PLP/DM-20 transcripts can result in severe dysmyelination, or in some cases milder forms of demyelination. This has been observed in several lines of PLP/DM20 transgenic mice and rats that were produced over the last few years. In DM-20 overexpressing transgenic mice (65) that carry 70 copies of a transgene cassette encompassing a human PLP gene promoter element and human DM-20 cDNA, life span is shortened and demyelination is seen in the CNS. Abnormalities in these DM-20 transgenic animals became apparent at ~ 3 months and included an unsteady gait that progressively worsened with time, and an increasing frequency of seizures. Death occurred at 8-10 months of age. These clinical symptoms correlated with CNS demyelination. At 3 months of age, when DM-20 overexpressing transgenic mice were phenotypically still asymptomatic, no pathological changes could be observed in the CNS. However, 7 months later a dra-

matic decrease in the overall amount of CNS myelin was evident, many axons in the optic nerve were thinly myelinated or even completely denuded of myelin. Moreover, many of the surviving myelin sheaths were abnormal or exhibiting signs of disruption and axonal degeneration. These changes were associated with a prominent astrogliosis and the presence of lymphocytic infiltrates (31). The mechanism of demyelination in DM-20 overexpressing mice is not known, but could be due to the downregulation of PLP synthesis by the DM-20 transgene. Alternatively, elevated levels of DM-20 may result in a block in myelin synthesis/maintenance following completion of the initial phase of neonatal myelinogenesis. Intriguingly, a premature arrest of myelin formation was also reported for transgenic mice with an increased proteolipid protein gene dosage (17, 54).

Demyelination was associated with moderate increases of the PLP gene dosage, as seen in heterozygous transgenic animals (17): Initially, myelination was observed and the white matter tracts appeared essentially normal for a period of several weeks. During this time the trangenic animals were clinically normal and indistinguishable in behavior from wild-type littermates. However, after 2-3 months of age, a progressive degeneration of the myelin sheaths could be observed in the CNS. This abnormality was clinically asymptomatic until an age of about six months at which time heterozygous transgenic mice displayed tremors and ataxia, followed by severe convulsions. These symptoms coincided with a rapid degeneration of myelin sheaths, associated with a very marked survival of oligodendrocytes and axonal sparing. These highly selective demyelinating lesions were extensively infiltrated by "microglia-like cells" (microglia or macrophages). This selective and abrupt destruction of myelin was ascribed to a systemic immune response, possibly involving the production of autoantibodies, rather than to a direct affect of the transgene on the oligodendrocyte. In this scenario, the initial slow degeneration of myelin eventually triggered a myelin-specific autoimmune response, culminating in demyelination in the absence of chronic inflammation. It should however be noted that this pathology was not observed in other lines of heterozygous PLP overexpressing transgenic mice produced by Readhead and coworkers (54). These workers reported that although isolated uncompacted myelin structures and a slight overall reduction of myelin thickness occurred in aged heterozygous animals, there was no evidence for the extensive degeneration of myelin sheaths or destruction of oligodendrocytes. In contrast, homozygous animals exhibit a dysmyelinating pheneotype in which oligodendrocytes were only rarely engaged in myelination (17, 54), and microglia-like cells with inclusions (17), or astrogliosis (54) were prominent features.

Conclusions

Destruction of the myelin sheath is a common theme in a wide range of neurological disorders, but the underlying causes are many fold. In some cases, immune responses to antigens expressed by oligodendrocytes are primary events. In this situation activated antigen-specific T cells cross the endothelial blood brain barrier, initiate a local inflammatory response and pave the way for other blood borne cells and molecules such as antibodies to enter the CNS. Destruction of myelin sheaths can then be mediated by either antibody, or the local action of inflammatory cytokines. In contrast, in adrenoleukodystrophy, immune responses are secondary to myelin degeneration. In this and related disorders, damage to myelin sheaths occurs first as a consequence of genetic defects that preferentially affect cells in the CNS. Only in later stages of disease do inflammatory cells become evident and mediate myelin disruption. The availability of novel animal models that mimic these pathologies provide us for the first time with the basic tools to elucidate the many different mechanisms that can result in the selective destruction of CNS myelin in human disease.

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