Glial Cells and Products of Activated Inflammatory Cells: Implications for Pathogenesis and Treatment of Multiple Sclerosis

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Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system of unknown etiology, but a disease in which immunopathologic events are likely important [1]. It is a chronic disease, frequently with an clinically relapsing course [2], but the pathologic processes may actually be continuous, although accentuated at times [3]. It also has a restricted age distribution, with the peak onset between 20 and 40 years of age. In addition to the inflammation, which is predominantly made up of monocyte-macrophage-microglia and lymphocytes and/or their progeny, and demyelination, the other characteristic pathologic feature is gliosis [4]. This gliosis relates to the astrocytes, although there is some controversy as to whether these cells become more prominent, increase in number, or both.

There has been considerable interest in the possibility that MS is an autoimmune immunopathologic disease with a component of myelin/oligodendrocyte, the target for an antibody and/or cellular response. To date, the evidence is indirect [5, 6] and the antigen has certainly not been unambiguously identified [7]. More recently, there has been increasing interest in other interactions between the immune and nervous systems. This has been made possible by several scientific advances, including the ability to identify, purify, and study the function of subsets of cells of both the immune and nervous system as well as to purify and characterize secretory products of cells of both systems. In addition, genetic engineering has allowed the production of single products of inflammatory cells, and the use of monoclonal antibodies allows the unequivocal identification of epitopes of important surface and cytoplasmic components of cells of the nervous system on the immune system. Much of this recent activity has centered on interactions between products of activated inflammatory cells (cytokines=lymphokines+monokines) and glial cells [oligodendrocytes, astrocytes, macrophages, microglia (brain phagocytic cells)] and brain vascular endothelial cells [8, 9]. These cytokines are clearly present in the nervous system and CSF of patients with MS [10]. An extension of this line of investigation is the study of glial cells serving functions traditionally associated with cells of the immune system such as presentation of antigen [11], production of monokines [12, 13], phagocytosis [14], and production of enzymes such as proteases which could contribute to myelin breakdown and even act as stimulators of B-cell proliferation and differentiation [15]. Although much has been learned, there are many unanswered questions of considerable neurobiologic, immunologic, and pathologic importance.

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Which products of activated inflammatory cells are mitogenic for which types and subtypes of glial cells?

The work of several groups [8, 9, 16, 17] makes it clear that unfractionated supernatants from activated inflammatory cells induce proliferation of astrocytes and CNS origin fibroblasts in vitro. As noted earlier, there is clearly gliosis associated with long-standing lesions of patients with MS, with the suggestion that astrocytes may undergo swelling, show an increase in intermediate filaments, and perhaps proliferate. In acute experimental allergic encephalomyelitis (EAE) as well as in the chronic and relapsing forms of the disease, astrocytes are also similarly affected. We do not know whether all astrocytes are affected equally [18]. Type II astrocytes, which in rats seem to arise from the same precursor glioblasts as oligodendrocytes [19, 20], are more numerous in white matter and some may be intimitely related to the paranodal region of the myelinated CNS axon [21]. Thus, it is conceivable that changes in this subclass of astrocyte, including proliferation, changes in phenotypic markers and functions, swelling, and failure to perform normal astrocytic functions, could lead to changes in CNS nerve conduction and result in symptoms. If the changes do not lead to demyelination or gliosis, it is possible that there might be rapid improvement in symptomatology. Could this be one of the mechanisms responsible for the rapid and often clinically complete recovery seen after exacerbations, especially during early phases of the disease?

Fontana's group [8, 16, 22, 23] performed preliminary studies on activated supernatants and identified a factor which seemed to induce astrocyte proliferation. There has been no further published work characterizing the factor further, which seemed to be a product of T cells, nor do we know is it has any effect on oligodendrocytes, microglia, or Schwann cells. Is it the only mitogen for astrocytes produced by T cells? It most likely is not the only mitogen produced by inflammatory cells since it has been shown that interleukin-1 (IL-1) (produced by macrophages and perhaps microglia and astrocytes themselves) induces astrocyte proliferation [17, 24]. It is of some interest that Schwann cells, at least cells from neonatal rat sciatic nerves, do not proliferate in direct response to IL-1 in vitro [25].

It has been reported that T-cell products stimulate oligodendrocytges to proliferate in vitro [26]. A 30000 mol. wt. protein is said to induce proliferation of oligodendrocytes and no other CNS, PNS, or non-NS cells [27]. Based on the mol. wt. of 30000, as well as its reported very restricted selectivity as a mitogen, it seems unlikely to be IL-1, interleukin-2 (IL-2), or Fontana's glial proliferative factor. We have been unable to demonstrate that unfractioned activated supernatants, IL-2, or γ-interferon (γ-IF) induce proliferation of oligodendrocytes [28]. Others have reported that IL-2 is mitogenic for oligodendrocytes [29], but at a very high concentration. Although cloned IL-2 has been used by both our group as well as those who detect a proliferative effect, the results differ. The need for very high concentrations to induce proliferation suggests either an effect of some carrier material or that oligodendrocytes have either very low density of IL-2 receptors or low-avidity receptros. Neonatal Schwann cells do not proliferate in vitro in response to IL-2, although they proliferate in response to the unfractionated supernatants of activated inflammatory cells [30]. It is not clear why these differences in results occur, but species and in vivo age of animals as well as in vitro age of cultures may explain some but not all of the conflicts. The question of the effect of age may be

important in consideration of which products of activated inflammatory mononuclear cells are capable of induction of major histocompatibility complex (MHC) antigens and which glial cells are susceptible to MHC antigen induction. Since the onset of MS shows age restriction and the pattern of clinical disease may differ in part related to the patient's age, the possible effect of age and the response to cytokines may be important.

Supernatants obtained from activated mononuclear cells have been reported to induce MHC type I antigens (HLA-A, B, C in man) on oligodendrocytes, astrocytes, and microglia-macrophages [28, 31–35]. The demonstration that type I antigens can be induced on a cell type which ordinarily does not bear such antigens is not trivial since it has been demonstrated that T-cell-mediated antigen-specific cytotoxic reactions against cellular antigens, including viral antigens in such cells, can only occur if the cells bear MHC type I antigens [36]. If glial cells serve as targets for such antigen-specific cytotoxic reactions in MS and other diseases, it would be required that type I MHC antigens be induced by a lymphokine, such as γ-IF, or by a viral infection [37]. There is much written about the search for type II (Ia) MHC antigens on glial cells in lesions of patients with MS but little about type I antigens on such glial cells. Parenthetically, such studies are likely forthcoming and we will need to remember that in a disease like MS that has periods of varying activity and a chronic course we may expect variable reports from different groups. The may be studying different lesions in different patients, or indeed different lesions in the same patient [38].

There is also interest in the question of which cells in the CNS naturally bear or can be induced to bear MHC type II (Ia) antigens (DR, DQ in man). It has been reported that activated antigen-specific T-cell lines, which would be capable of production and secretion of lymphokines including γ-IF, and γ-IF itself can induce Ia on astrocytes [8, 9, 11) which are ordinarily la negative [39]. These astrocytes can then present myelin basic protein (MBP) to the T-cells. It is a "requirement" for antigen-presenting cells to have type II on their surface. Recently, it has been reported that oligodendrocytes can have an accessory function on in vitro T-cell mitogenesis [40], but this is a different phenomenon from specific antigen presentation and antigen-specific proliferation. There is little evidence, if any, that oligodendrocytes become la positive in vitro or in vivo [39, 41, 42]. It has been reported, however, that astrocytes in MS and EAE lesions are type II MHC positive [10, 43]. Based on the earlier described in vitro evidence, it has been postulated that antigen presentation by astrocytes may contribute to propagation of inflammatory lesions in the CNS. Astrocyte lysis by MBP-specific T-cells has also been described [44].

The situation regarding astrocytes is not as straight forward as it had seemed. In EAE lesions in rats, macrophages become strongly positive before a relatively small percentage of astrocytes become Ia positive [45, 46]. We and others have not found induction of Ia on most astrocytes in vitro [28, 35]. Microglia-macrophages are the predominant Ia-positive cells in normal cultures [35,39] and after induction [28, 35]. MHC antigens are glycoproteins and may be found on cells adjacent to the cell that is actually producing la; i. e., it may be very difficult to localize la [35]. Disparity between immunofluorescence and immunoperoxidase techniques, and light and electron microscopic localization of Ia has been reported in other organs [47]. Cells

which are passively Ia positive likely do not function as antigen-presenting cells. Therefore, it will be important to determine, both in vitro and in vivo, if astrocytes or even oligodendrocytes actually can be induced to become la positive and which cytokines induce the antigens. It will likely require molecular biologic techniques, such as in situ hybridization combined with immunohistology, ultimately to settle the question.

What is the role of vascular endothelial cells in the initiation of and self-propagation of immunopathologic reactions with the CNS?

There is growing evidence that the endothelial cells of cerebral blood vessels may play an active rather than passive role in immunopathologic reactions within the CNS [9]. There have been reports of DR (Ia) on CNS endothelial cells in the CNS of animals with EAE [45, 46]. However, this has not been a universal finding and, more recently, it has been suggested that it is actually perivascular dendritic (microglia) that are the positive cells in the CNS vessels [49]. It has been reported that similar Ia localization is seen in MS lesions [50, 51], but, again, the exact nature of the positive cells in uncertain. It would not be surprising if a macrophage-microglial cell among the endothelial cells were induced to become Ia positive and interact with circulating T-cells, even presenting antigen [52]. It should be noted that how T-cells circulating at a high flow rate interact with endothelial or dendritic cells is still not clear. Changes in the endothelium could also allow passage of nonspecific inflammatory cells or serum proteins which could induce demyelination [53–55]. On the other hand, some of the changes reported in CNS vasculature in MS are seen in classic passive transfer delayed hypersensitivity reactions. Further comparative studies of passive and active EAE are clearly of importance here as are in vitro studies of endothelial cell-cytokine interactions and lymphocyte-endothelial cell interactions. It must also be remembered that the frequency of CNS antigen-specific T-cells is probably very different in animals with actively induced EAE, passively transferred EAE, and EAE passively transferred with T-cell lines or clones. Moreover, T-cell lines and clones, especially after reactivation or restimulation, may differ quantitatively and qualitatively from "normal" T-cells in many in vitro and in vivo characteristics.

For the most part, I have emphasized the potential pathogenic importance of the interactions of cytokines and glial cells, and I belive we are just beginning to understand this important area. Clearly, there are tremendous therapeutic implications. It has been traditional to consider how drugs and modifiers of biologic reactions would interact with the classic cells of immunopathologic reactions (T-cells, B-cells, monocyte-macrophages, and, more recently, K and NK-cells). The reports of some [56–59] but not all groups [60–62] of a defect of NK-cell function associated with (or perhaps caused by) a decreased γ-IF production in patients with MS lead to the suggestion that γ-IF might be of benefit in MS. Recently, a therapeutic study demonstrated that γ-IF was associated with an increase in exacerbations [63]. This might relate to activation of circulating cells of the immune system, but it is also possible that immunologic cells within the nervous system or glial cells were affected directly by γ-IF crossing a damaged blood-brain barrier [64]. Since glial cells have been postulated to produce IL-1 [8, 12] and proteases (which could interact with B-cells) [15], activation of glial cells by systemically administered lymphokines could also have a deleterious effect in an indirect fashion. Rather than

looking for biologic modifiers for treatment of MS, we may need antibodies directed against the modifier or its receptor.

There are other possible cytokine-glial cell interactions that have therapeutic implications. α- and β-IF inhibit cellular proliferation, as does γ-IF, under certain circumstances [65]. If the astrocytic response in MS is deleterious, then an inhibitory effect by one of the interferons or other biologic modifier might have a long-term beneficial effect in MS. However, if oligodendrocyte or oligodendrocyte precursor proliferation were inhibited by an exogenously administered agent, that might prove to be harmful. It has been reported that IL-2 induces synthesis of myelin-specific constituents, such as MBP, by oligodendrocytes [29]. Thus, inhibition of IL-2 production or blocking of IL-2 receptors, if present, on glial cells would be potentially harmful, even if inhibition of the effect of IL-2 on T or B-cells might be potentially helpful. Until we know more about the in vivo and in vitro effects of the many cytokines, as well as the effects of inhibition of the cytokines and their receptors, we are guessing in planning therapeutic studies.

Although there is no substitute for eventually performing well-controlled studies in patients, we need to learn much more about in vitro and in vivo effects of various potential biologic agents on glial cells before embarking on more and more treatment studies in patients.

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