Major histocompatibility complex molecules on glial cells

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While glial cells of the central nervous system do not constitutively express class I or II major histocompatibility complex (MHC) molecules, astrocytes and microglial cells can be induced by a variety of factors to express these antigens. Oligodendrocytes have inducible class I but not class II elements. There are considerable differences in regulation of MHC antigen expression between glial cells from rodent and human brains, both in situ and in vitro. The consequence of glial cell MHC expression for immune interactions in the CNS is discussed in the context of glial cell antigen presentation capacity and neural cell susceptibility to cell-mediated immune effector mechanisms.

MAJOR histocompatibility complex (MHC) antigens comprise a highly polymorphic group of cell surface glycoproteins essential for the process of antigen recognition by T cells. Such recognition involves a trimolecular complex of *antigen*, in the form of a processed peptide, associated with (located in a groove or cleft formed by) an *MHC molecule*, which is presented to the *T-cell receptor* of T cells expressing the α and β chains of the receptor. The MHC recognition process is a requirement for initiation of the immune response through presentation of antigen to T helper (CD4^{+}) cells by specialized cells termed antigen-presenting cells, and for either CD4^{+} or CD8^{+} T cells to carry out effector responses dependent on cell-cell contact, particularly cytotoxic responses directed at specific cell targets.

The genes encoding MHC molecules are located on the short arm of chromosome 6 in human (HLA region) and on chromosome 17 in mice (H-2 region). These genes can be divided into 2 major classes,

class I and class II. Among the over 20 human class I genes are the HLA-A,B,C, genes (H2K,D,L in mouse) that encode a glycoprotein heavy chain that becomes associated with β_2-microglobulin; the latter polypeptide is encoded outside the MHC region. The class II gene region in human (HLA-D, corresponding to I-region in mouse) is comprised of at least 3 sub-regions, DP, DQ and DR, each of which encodes at least one of the α and one of the β chains that, together, comprise a class II MHC molecule. Genes outside the MHC region may also contribute to the overall process of immune recognition (minor histocompatibility antigens).

Class I MHC glycoproteins are 'normally' widely expressed on nucleated cells, except for endogenous cells within the central nervous system (CNS) (see discussion below); class II antigens are expressed primarily on cells involved in immune function, such as B cells, cells of the macrophage/monocyte lineage, dendritic cells, activated T cells in humans and specialized phagocytic cells within various tissues, e.g. Langerhan's cells in the skin. Usually, but not invariably, class I molecules are the MHC recognition molecules for CD8^{+} T cells (suppressor/cytotoxic) whereas class II molecules are recognized by CD4^{+} T cells (helper/inducer). The process of T cell recognition of antigen in the context of MHC molecules is a central means whereby an individual distinguishes self from non-self. Lack of class II MHC expression, as occurs in type II bare lymphocyte syndrome, results in severe immunodeficiency. At the other extreme, aberrant expression on normally class II-negative cells carries the risk of inappropriate presentation of self-antigens and is thought to be involved in the pathogenesis of many autoimmune diseases. Furthermore, individual susceptibility to a variety of autoimmune diseases in humans has been reported to be influenced by the genetically-determined MHC repertoire, particularly those of the class II MHC region.[1]

The CNS has traditionally been considered a relatively immunologically privileged site, partly because neural cells were thought not to express MHC antigens, based primarily on early immuno-

histochemical analyses of normal tissue in situ.[2,3] The selective advantage to the organism for such non-expression remains unexplained. Expression in human CNS of MHC antigens, both class I and class II, appears under pathological conditions, including not only those considered primarily inflammatory disorders[4,5] but also in neurodegenerative diseases where the pathogenesis is not thought to be immune-mediated.[6,7] Central issues raised by these observations include which CNS cells can be induced to express MHC molecules; what conditions regulate this expression; and what is the functional significance of such expression with regard to regulation of immune reactivity within the CNS and to endogenous CNS cells becoming susceptible targets of T cell-mediated immune effector mechanisms.

Here we focus on MHC antigen expression on glial cells within the CNS. We review how both technical and biological variables, including analyses in situ versus in vitro, normal versus pathological tissues, age and species factors, may have contributed to apparently discrepant observations. We present our experience with adult human glial cell cultures obtained from non-inflammatory surgical biopsies and consider the relevance of glial cell expression of MHC with regard to antigen-presentation and target-recognition. In particular we discuss how these may be related with susceptibility to cell-mediated autoimmune diseases of the CNS.

MHC expression in studies of brain sections

Human brain sections

Initial immunohistochemical studies of normal human brain sections did not detect the presence of MHC-immunoreactive cells.[2,3] This has been corroborated by more recent reports.[4,5] In contrast, several studies have described class II MHC immunoreactivity on neural cells in normal human brain sections. The cell types expressing class II MHC molecules have been variably identified (either by morphology, ultrastructural features and/or immunohistochemistry) as astrocytes[8] or microglial cells;[7,9] oligodendrocytes and neurons have consistently been found to be negative for class II MHC antigen expression in situ.[5,10] The majority of examinations continue to report lack of expression of class I MHC molecules in normal neural tissue.[4,5,11]

Although the detection of MHC molecules in normal human brain tissue sections remains

equivocal, there is agreement that MHC expression is up-regulated (increased intensity of immunoreactivity and in proportion of immunoreactive cells) in many disease states. These include multiple sclerosis, where inflammatory processes are thought to be involved in the pathogenesis,[4,5] and in conditions where no classical inflammation is apparent, such as neurodegenerative diseases like Alzheimer's and brain tumors.[6-8,11] The cell types with up-regulated class I or II MHC expression remain controversial, with suggestions that these are either astrocytes[5] or microglial cells[6,9] or both.[10] The expression of MHC on glial cells has been used as an index that these cells have become 'activated' and are participating in the pathological reaction. In human disease states, oligodendrocytes and neurons remain MHC-negative.[5,10]

Technical differences may contribute to discrepant observations using tissue sections. MHC molecules are cell-surface antigens, which can be easily destroyed by inappropriate fixation. Prolonged exposure to formalin, used routinely to process postmortem human brain tissue, can mask or destroy the epitope.[7] Many studies have used frozen sections and often the morphology of cells was suboptimal, leading to possible misidentification of MHC immunoreactive cells. The choice of fixative (paraformaldehyde or Bouin's being preferred) and the duration of fixation have recently been highlighted as important determinants when assessing MHC expression in situ.[7] Class II MHC immunoreactivity can best be detected with fixation intervals of less than 5 h; staining intensity steadily declined with prolonged fixation until after 10 h, little or no immunoreactivity was observed.[7] Under the presumed optimal staining conditions, only microglia expressed class II MHC in the normal human brain.

Clinical variables may also influence the detection of MHC antigens in brain sections. Pre-mortem intercurrent systemic diseases, particularly infections, can affect class II MHC expression within the CNS (U. Traugot and P. Lebon, personal communication). In the presumed postmortem normal brain sections used for MHC detection, it is difficult to exclude the possibility that the tissue donors did not have any underlying pathology, such as subclinical viral infections, that could have modulated MHC antigen expression.

Rodent brain sections

A confounding factor in the reports of MHC expression in the CNS is species differences. Unlike

human brain sections, normal rodent brains *in situ* do not show immunoreactivity for MHC except on scattered endothelial cells of large blood vessels. Whereas class II MHC-positive astrocytes and microglia are observed in active lesions in multiple sclerosis, astrocytes in the lesions of experimental allergic encephalomyelitis (EAE), an animal model of multiple sclerosis, do not appear to express class II MHC (Ia) while microglia do;[12-14] astrocytes and microglia are both class I MHC immunoreactive in EAE. In Wallerian degeneration following eye enucleation or facial nerve resection, microglia but not astrocytes express Ia antigens;[15,16] following facial nerve resection microglia are also immunoreactive for class I MHC.[17] The majority of rat CNS cells newly induced to express MHC class II following 3 days of continuous intravenous administration of gamma-interferon, which is a potent inducer of class II antigens on astrocytes *in vitro* (see below), were found to be microglia and not astrocytes.[18] Normal mouse oligodendrocytes *in situ* have been reported to express class Ia,[19] although this was not confirmed by others.[18] One immuno-electron microscopic study[20] has described cytoplasmic reactivity for class Ia in a small proportion of oligodendrocytes in mice infected with Theiler's murine encephalomyelitis virus.

Summary of CNS studies in situ

MHC antigens have been detected on a variable proportion of neural cells, particularly microglia, in the presumed normal human brain. Inducible expression on astrocytes and microglia has been shown in a range of diseases. In the non-human system, the prevailing view is that normal CNS cells, including microglia, do not show constitutive expression of MHC. The lack of MHC on microglia of laboratory rodents, generally bred in a controlled clean environment, suggest that the findings of class II MHC on human microglia might be related to sub-clinical factors (e.g. latent viral infections) to which humans are generally exposed, rather than reflecting constitutive expression. In disease states in rodents, especially EAE, inducible Class II MHC expression is seen on microglia but not on astrocytes, in contrast to the human disease. Oligodendrocytes and neurons do not show constitutive or inducible MHC expression. In Table 1, we summarize an apparent

Table 1. 'Consensus' for MHC antigen expression by glial cells in CNS tissue section or tissue culture studies: basal verus activated conditions (e.g. multiple sclerosis or EAE in sections, or gamma-interferon-treatment in culture)

	Class I	Class II	Class I	Class II
A. Brain section studies				
	'Normal' brains		In MS or EAE brains	
Human				
Astrocytes	–	–	+	+
Oligodendrocytes	–	–	–	–
Microglia	–	+	+	+
Rodent				
Astrocytes	–	–	+	–
Oligodendrocytes	–	–	–	–
Microglia	–	–	+	+
B. Cultured cell studies				
	Basal culture		Plus gamma-interferon	
Human				
Astrocytes	+	+	+	+
Oligodendrocytes	+	–	+	–
Microglia	+	+	+	+
Rodent				
Astrocytes	+	–	+	+
Oligodendrocytes	–	–	+	–
Microglia	+	–	+	+

Absent – ; present + . Neurons are negative for class I and II molecules under all conditions.

consensus regarding MHC antigen expression in the CNS *in situ*.

MHC expression in tissue culture studies

Rodent cultures

In view of the many potential difficulties of experiments *in vivo*, cultured cells have been used to address the issue of expression of MHC on neural cells. Here, live cells can be subjected to immunohistochemical protocols without prior fixation, and the cell type of interest can be reliably identified by using cell type-specific antibodies in double immunofluorescence analyses. Bulk isolated cultures also allow for more detailed analyses using molecular biology tools.

By immunohistochemical analyses largely performed using cells cultured from neonatal animals, the consensus for rodent cells is that under basal culture conditions class I MHC antigens are expressed on a substantial number of astrocytes[21,22] and microglial cells[23] but not oligodendrocytes.[22,25] Class I can be induced on rodent oligodendrocytes by viral infections and gamma-interferon.[24,25] Immunoreactive expression of class II MHC (Ia) on rodent astrocytes, microglia or oligodendrocytes in basal culture conditons appears to be absent or negligible.[21,26-30] Analyses at the messenger RNA level similarly reveal that cultured astrocytes do not constitutively express mRNA for class II MHC.[31] Induction of Ia on rodent astrocytes occurs after treatment with gamma-interferon,[26,27,29,32] tumor necrosis factor[33] and certain strains of viruses.[29] The administration of gamma interferon *in vivo* results in the detectable expression of Ia antigens on rodent astrocytes when isolated and cultured, even when none are detected *in vivo*.[27] Similarly, gamma-interferon treatment of mouse or rat microglia *in vitro* results in Ia expression;[23,30] neonatal or adult brain-derived microglia respond in a similar manner.[23] The gamma-interferon-induced Ia expression on glial cells seems to be mediated by the protein kinase C signal transduction pathway.[34]

In contrast to astrocytes and microglia, rodent oligodendrocytes appear refractory to Ia expression even when stimulated with gamma-interferon, or supernatants derived from activated mononuclear cells or virus-infected cells.[25,26] It is of interest to note that the O-2A progenitor cell (which gives rise to the type-2 astrocytes and oligodendrocytes at least *in vitro*) and the type-2 astrocytes can be induced by

gamma-interferon to express Ia; oligodendrocytes are refractory.[35] These authors suggest that differentiation of the O-2A progenitor cells along the oligodendrocyte pathway is associated with a loss of inducibility of Ia antigens.

In conjunction with studies of MHC induction, down-regulation of MHC expression has also been examined. For rodent astrocytes, the induction of Ia by gamma-interferon or tissue necrosis factor is inhibited by adrenaline through β_2-adrenergic mechanisms,[36] vasoactive intestinal peptides or by transforming growth factor-β_1 and -β_2.[37]

Most studies of MHC antigen expression to date, including analyses *in situ* and *in vitro*, have used antibodies to recognize MHC determinants. Previously, we have observed that cytotoxic T cells could recognize class I MHC on murine astrocytes (i.e. functional recognition), although expression of such molecules was not convincingly demonstrated by antibody immunolabelling.[38] These findings could reflect not only the lack of sensitivity of the immunohistochemical techniques used to detect MHC but also that the determinants recognized by antibody and those recognized by T cells need not be identical. The latter possibility could account at least in part for the failure of some antibodies to MHC molecules to block cytotoxic T cell responses directed against specific cell targets.

Human cultures

A much more limited number of studies have explored whether human glial cells *in vitro* are immunoreactive for MHC antigens. In two studies using autopsy-derived human adult cells, the large proportion (close to 100% in some cases) of astrocytes and oligodendrocytes expressed class I MHC molecules (HLA-A,B,C) whereas a smaller proportion of cultured astrocytes (9-24%) from all 12 donors expressed class II MHC (HLA-DR). Of interest, 4-16% of oligodendrocytes from 6 of the 12 donor preparations were immunoreactive for HLA-DR.[39,40] In contrast, a study using cells from two autopsy adult samples[28] and another reporting on one autopsy case,[41] did not find HLA-DR expression on astrocytes.

To circumvent possible post-mortem effects and the variability introduced by pre-mortem intercurrent systemic infections that may affect MHC antigen expression (see above) we have been using glial cells cultured from brain samples surgically

resected during treatment for intractable epilepsy. Except for the seizures, these subjects were normal. Their young age group (25 ± 3 years) corresponds to one that is at risk for developing suspected auto-immune diseases such as multiple sclerosis. For class I MHC molecules, close to 100% of oligodendrocytes, astrocytes and microglia were immunoreactive.[42-45] For HLA-DR, virtually all microglia showed positivity; no oligodendrocytes were found to express HLA-DR (Figure 1). The analyses of HLA-DR

expression on biopsy-derived adult human astrocytes showed that this class II MHC molecule was detected on all 15 human biopsy-derived cultures; however, different series of human astrocytes expressed HLA-DR bearing astrocytes remained relatively constant when analysed at different time points, up to 125 days *in vitro*.[45] The differential level of expression of HLA-DR between human series was not correlated with the age of the human subjects, the extent of gliosis in the resected material or the duration for
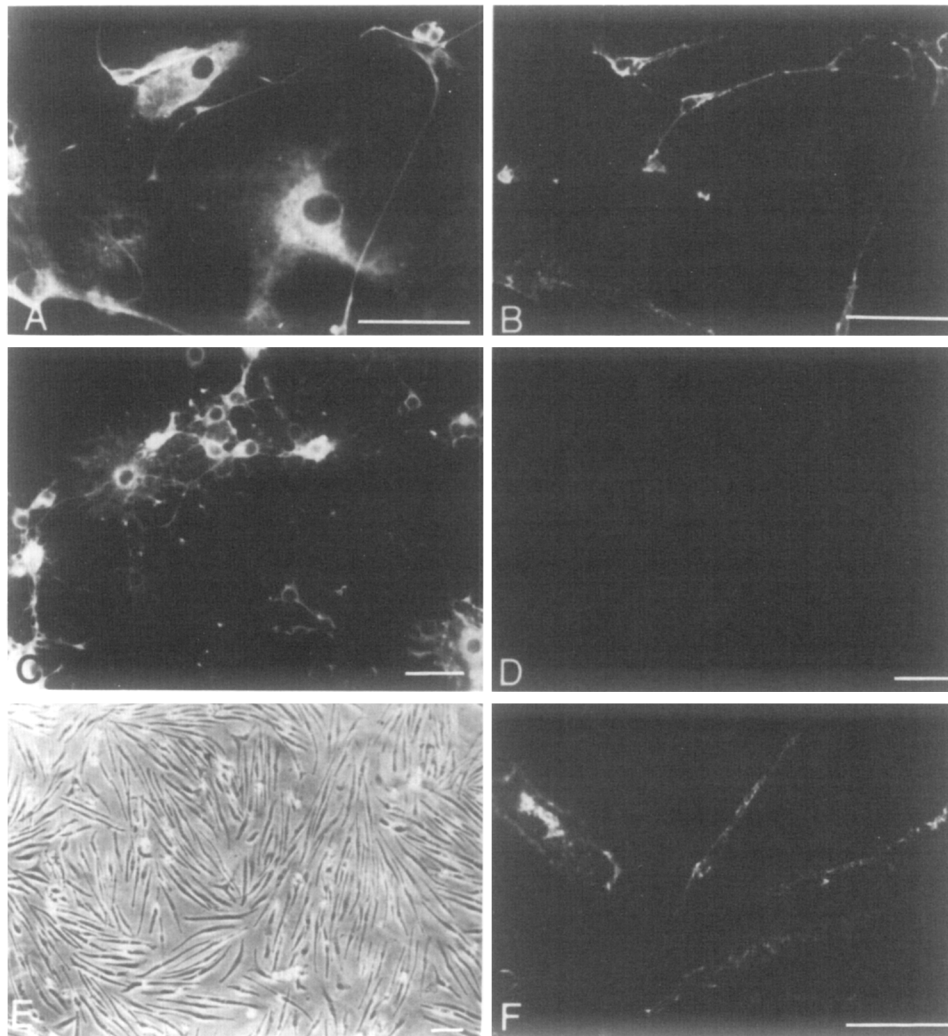

Figure 1. Adult human astrocytes and microglia but not oligodendrocytes express MHC class II molecules (HLA-DR) *in vitro*. Astrocytes are identified by immunoreactivity for the specific marker, glial fibrillar acidic protein (A), with the corresponding HLA-DR labelling shown in (B). Note that HLA-DR is more readily detected on process-bearing astrocytes than on the flat forms. In (C), oligodendrocytes immunolabelled for 2',3'-cyclic nucleotide phosphohydrolase do not display HLA-DR immunoreactivity, see (D). Microglial cells, identifiable by their bipolar morphology in (E) using inverted phase contrast microscopy, or by Leu-M5 staining by immunohistochemistry (not shown), are immunoreactive for HLA-DR (F). Scale bars: 25 μm.

which the cells have been maintained in culture. When adult human astrocytes were subclassified by morphology (these did not fall neatly into the type-1 and type-2 astrocytes characterized in rodent), HLA-DR expression was prevalent on process-bearing rather than the flat astrocytes (Figure 1).[44]

The expression of HLA-DR on cultured adult human glial cells in our studies probably represents an induction process in vitro, because freshly isolated cells did not have detectable HLA-DR and because the type of serum (example, human AB) and its concentration in the culture medium affected the proportion of astrocytes that expressed HLA-DR.[45] It would be of interest to determine whether the individual variability of HLA-DR expression on human astrocytes reflects a genetically determined property, as seems to be the case with rodents where inducibility of Ia molecules on cultured astrocytes correlates with susceptibility to EAE (see below).

In contrast to their human counterparts, rat astrocytes in our hands did not express class II MHC when isolated and maintained in identical culture conditions to the adult human cells.[45] This result is in agreement with the multitude of reports cited above that rat astrocytes have undetectable levels of Ia under baseline culture conditions. Thus, whereas the expression of MHC on adult human cells probably represents an induction process in vitro, rodent cells are not similarly induced; this suggests differences in inductive capability, probably at the molecular level, of MHC between species. Such a result would reflect the observations in situ (see above) that MHC antigens are more readily detected on human neural cells than those of rodents.

In correspondence with rodent cells, class II MHC expression on human adult astrocytes can be up-regulated by treatment with gamma-interferon;[45,46] this effect can be blocked by treatment with beta-interferon.[46] More recently, it has been shown that interleukin-1β can decrease constitutive expression of class II MHC in a glioblastoma multiforme line.[47]

Human fetal cells have also been examined for expression of MHC molecules. This literature is small but it seems that both class I and II MHC can be detected on fetal astrocytes;[48] a small proportion of microglia were immunoreactive for HLA-DR (class I was not examined).[49] Oligodendrocytes and neurons in human fetal cultures were negative for MHC expression.[48]

Summary of tissue culture studies

Expression of MHC antigens by glial cells is more readily detected in tissue culture studies than in the brain in situ (Table 1). Although one explanation may be the feasibility of determinations in vitro, it is more likely that the induction of MHC molecules is a result of cell culture. Another possibility is that in culture as yet uncharacterized in situ inhibitors of MHC antigen expression are lost. Class II MHC expression on astrocytes and microglia in the human system is observed under baseline culture conditions, unlike in rodent cells (Table 1); we speculate that the molecular factors that control inducible elements of MHC gene expression in the human system are less tightly regulated than those in rodent cells. However, in response to treatment with gamma-interferon, a potent cytokine, induction of MHC seems to be similar across species (Table 1). There does not appear to be changes in MHC expression due to age factors, from the limited number of studies currently available.[23,48,49]

Significance of MHC expression by glial cells

Antigen presentation

Neonatal murine astrocytes and microglia, especially after gamma-interferon treatment, can present antigen, e.g. myelin basic protein, to previously sensitized CD4+ T cell lines in an MHC class II-restricted manner.[22,30,50,51] Astrocytes, even after treatment with gamma-interferon, are, however, unable to induce activation of primary CD4+ T cells in a mixed lymphocyte reaction;[52] such responses were achieved by 'professional' antigen presenting cells, such as dendritic cells and activated B cells. Microglial cells prepared from human brain biopsies are also able to induce a response by previously non-activated human peripheral blood-derived T cells in a mixed lymphocyte reaction. The capacity of endogenous glial cells to present antigen probably contributes to the observed persistence of activated myelin-sensitized T cells within the CNS, as compared to non-neural antigen-reactive T cells.

Target-cell recognition

Immune-mediated injury to oligodendrocytes or its myelin membrane is postulated to account for the

demyelination which characterizes the acquired human disease multiple sclerosis, the induced human disease acute disseminated encephalomyelitis (post-vaccination, post-infectious encephalomyelitis) and the induced animal disease EAE. In the last, the disease can be passively transferred using myelin antigen-reactive CD4^{+} T cells. The mechanisms through which oligodendrocyte/myelin injury occurs are not precisely defined; mechanisms implicated include direct CD4^{+} T cell-mediated injury, cell-mediated injury by other T and non-T (macrophage/microglia) cells recruited to the lesion sites, and injury mediated by soluble factors released by the accumulated inflammatory cells.

Rat T cells, reactive to myelin basic protein and comprised predominantly of CD4^{+} T cells (or CD4^{+} T cell hybridomas), have been shown to be cytotoxic to cultured rat oligodendrocytes in a strain-, presumably MHC-, restricted manner.[53] The cytotoxic effect of the CD4^{+} T cell lines require the presence of antigen presenting cells, which possibly enhance effector-target interactions; the effect could not be reproduced by soluble factors. Myelin basic protein-reactive CD4^{+}-T cells can acquire cytotoxic capability, at least *in vitro*, and have been shown to lyse cells expressing histocompatible class II MHC antigens (e.g. B cells transformed with Epstein-Barr virus) in the presence of myelin basic protein. The target oligodendrocytes did not express class II MHC although they were induced to express class I antigens when cocultured with T cells.[5] The presumably small number of CD8^{+} T cells in the MBP-reactive CD4^{+} T cell lines[53] could also have contributed to oligodendrocyte lysis, consistent with our previous observations that allo-reactive CD8^{+}-T cells can lyse human oligodendrocytes *in vitro* in an MHC class I restricted manner.[43] A further potential mechanism whereby CD4^{+}-T cells may be cytotoxic to non-MHC class II expessing cells, such as oligodendrocytes, involves the possibility of their acquiring cytotoxic capability following prolonged activation while losing their MHC restriction; such cells have been generated *in vitro* and termed promiscuous killers. We have found that T-α/β chain-expressing CD4^{+} and CD8^{+} T cells can induce promiscuous killing of human oligodendrocytes (T.C.G. Ruijs, E.A. Brown and J.P. Antel, unpublished). The conditions for generating these cells involves maintaining persistent activation with interleukin-2; such conditions *in vitro* may well parallel those found *in vivo* in the chronic inflammatory lesions characteristic of multiple sclerosis. The

promiscuous cytotoxic effect canot be reproduced with supernatants from such cultures.

The classic antigen-restricted T cell expresses the α and β chain of the T cell receptor, as indicated previously. A T cell population identified by expression of the γ/δ chains of the T cell receptor has been observed to accumulate in excess numbers in regions of demyelination in CNS brains.[54] These cells can mediate potent cytotoxicity of human oligodendrocytes *in vitro*. These T-γ/δ cells are not restricted by either classical class I or II MHC molecules. The recognition molecule of these cells remains unknown, with much interest focused on heat shock proteins. However, further candidates may be class I-like molecules such as CD1 or possible equivalents of the mouse Qa and TL gene products.[55]

MHC expression and neurological diseases

A potential link between MHC class II up-regulation on glia and genetic susceptibility to autoimmune disease was suggested by findings that astrocytes from rodent strains susceptible to EAE expressed higher levels of MHC class II after exposure to gamma-interferon *in vitro* than do astrocytes from resistant strains,[56] although this has recently been disputed.[57] Glia from EAE susceptible mouse strains are more potent presenters of MPB to sensitized T cells than are glia from EAE resistance mice; no differences were found in this function using spleen cells.[58] Susceptibility to immune-mediated encephalomyelitis initiated by JHM-virus infection in rats is a function of inducibility of Ia (but not class I) antigen on astrocytes.[59] Such observations have raised speculations that exposure to cytokines (especially gamma-interferon) or viruses could contribute to CNS cells becoming capable of presenting auto-antigen to infiltrating T cells or becoming susceptible targets of such T cells. For human adult astrocyte cultures, it remains to be determined whether the differential expression of HLA-DR by various specimens[45] could be correlated with particular HLA haplotypes associated with genetic susceptibility to the development of auto-immune diseases of the CNS, such as multiple sclerosis (DR2 locus). Whether the observed deleterious effect of systemically administered gamma-interferon on the course of relapsing multiple sclerosis reflects effects on the CNS as well as on the systemic immune system, remains speculative.[60]

A novel means of inducing overexpression of MHC molecules in the CNS *in vivo* involves the creation of transgenic animals. A transgenic mouse line created by insertion of a class I MHC gene under control of the myelin basic protein promoter, with resultant restricted expression of the transgene to oligodendrocytes, displayed marked dysmyelination but without inflammation.[61] This model may be more akin to genetic models of impaired myelin production, rather than to immune-mediated myelin destruction as claimed.

Summary of functional significance of MHC antigen expression on glia

MHC antigen expression on glia has been linked with susceptibility to development of autoimmune CNS diseases. The potent inducers of MHC expression on glia include viruses and immune system-derived soluble factors (cytokines), which themselves are the suspected initiators or mediators of such diseases. MHC expression on glial cells is of functional significance with regard to these cells acquiring the capacity to present antigen to T cells and thus promoting (or conversely, potentially inhibiting) immune reactivity, and to these cells themselves becoming susceptible targets of specific immune effector mechanisms.

Conclusions and future directions

The dynamic expression of MHC molecules within the CNS contributes both to the capacity of endogenous glial cells to regulate immune reactivity within this compartment and to such cells becoming susceptible targets of immune effector responses. The functional importance of MHC molecules in antigen-specific T cell responses is well illustrated by the potent effects of systemically administered anti-class II MHC antibodies, which inhibit the development and disease course of EAE. The increasing availability of molecular genetic techniques to manipulate expression of MHC *per se* within the CNS provides new opportunities to assess the role of these molecules in influencing neural-immune interactions. With regard to human immune-mediated CNS disease, optimal immunotherapies would be those which are organ-specific, i.e. spare overall systemic immune capability. The apparent effect of biological response modifiers on MHC expression on glial cells implicate

them as potential selective therapies. It still has to be defined whether down-regulation of MHC can be more readily achieved on CNS cells with their inducible rather than constitutive expression of MHC, than on systemic antigen-presenting cells that constitutively express them. Conversely, in some circumstances, up-regulation may be of advantage, for example to augment glial tumor-directed immune responses. As the molecular mechanisms regulating MHC expression in the CNS are further defined, additional means will hopefully become available for therapeutic manipulation of this dynamic system.

Acknowledgements

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