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Molecular bases of the immune response to neural antigens
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Long-standing ideas about the immune response to neural antigens can now be revised. While the brain may be 'immunologically privileged', the privilege is not absolute; both immune and autoimmune responses can occur. While the blood–brain barrier contributes to this immunological isolation, other factors are also important. One is the normal absence of products of the major histocompatibility complex (MHC) from neural tissue. Without these cell surface proteins, neural cells are protected from T cell-mediated immune surveillance. MHC expression and modulation in neural tissue, and the implications for understanding and control of the immune response to neural antigens, are reviewed below.

Neural tissue is widely considered to be 'immunologically privileged'. Clinical findings that support this idea include the unusual growth patterns of viruses in the nervous system, the aggressive growth of neural tumors, and the successful growth of neural or intracranial transplants. Yet immune responses can occur in neural tissue. In some cases, such as certain anti-viral responses or autoimmune disorders, the immune response itself may be the cause of the observed pathology. Recent work has deepened our understanding of the mechanisms controlling the immune response to neural antigens, and how that response may be manipulated.

Barriers between the immune system and the nervous system

Traditionally, immune privilege and its abrogation have been interpreted in terms of physical barriers between the immune system and neural tissue. The brain's lack of conventional lymphatic drainage impedes transport of neural antigens to the lymphoid organs. Movement of material into the brain is impeded by the blood–brain barrier. This physical barrier is formed by specialized tight junctions between the endothelial cells in neural blood vessels, and in other locations. It prevents the passive entry of immunoglobulins, large immunomodulators, and immunocompetent cells.

Yet these physical barriers do not afford an absolute separation of the two systems. Although the brain lacks conventional lymphatic vessels, antigen can be carried from the brain via the CSF (Ref. 5). There are blood–brain-barrier-free areas even in normal neural tissue, such as the circumventricular organs. The blood–brain barrier is certainly broken in transplants, and it may be altered within tumors.

Nor can the physical barriers completely explain the immune–neural separation that does occur. The physical blood–brain barrier per se is unlikely to be the major impediment to the entry of lymphocytes into the brain. Leukocytes appear to leave the blood vessels in response to specific homing molecules or chemotactic factors, and then secrete degradative enzymes to cleave a passage through tissue. Thus, physical barriers alone cannot account for the immune–neural separation that does occur, nor is this separation complete. But there are other factors that can help to explain the unusual behavior of the immune system with respect to neural tissue.

Special properties of the neural cell surface also contribute to immune privilege

The work described below demonstrates that cell surface characteristics of the neural cells themselves also contribute to immune privilege, by preventing interactions with immunocompetent cells. Cell surface proteins that are required for T cell-mediated immune functions are lacking from both neurons and glia in normal neural tissue. Lacking these molecules, neural cells are unable to interact with immunocompetent T lymphocytes, even if lymphocytes have entered the brain, and neural cells bear viral, tumor-associated or other inappropriate antigens. These essential molecules are the class I and class II products of the major histocompatibility complex (MHC), as described below.

Lack of MHC expression contributes to neural immune privilege

Function and structure of the MHC complex

The structure and biology of the T cell receptor for antigen has been the focus of much recent work. Most relevant to this discussion is that T lymphocytes recognize antigen in association with a self-MHC product. In the usual case (A), the T cell and antigen-bearing cell are from the same individual. The T cell receptor recognizes antigen in association with a self-MHC product. In the case of a transplant (B), the T cell and antigen-bearing cell may express different MHC antigens. In that case, the T cell receptor can recognize the foreign MHC product alone; no additional antigen need be present.
do not recognize antigen alone, but rather must recognize antigen on a cell surface, in association with appropriate MHC proteins. This can occur in two ways. In the usual case, a T cell recognizes an antigen, such as a viral or tumor-associated antigen, on a cell surface in association with self-MHC determinants (Fig. 1A). This is known as T cell restriction. In the special case of a graft, T cells can respond to foreign MHC products on the grafted cells; no additional antigen is needed (Fig. 1B). There are two major families of MHC products that can mediate these interactions.

The class I MHC products are best known as the conventional major histocompatibility or transplantation antigens. These are the HLA-A, B, C molecules in man, and the H-2 molecules in the mouse. The class I molecules are highly polymorphic cell surface glycoproteins that were first identified as targets of graft rejection, as their name implies. Indeed, the high degree of class I polymorphism within the population is a major deterrent to achieving graft acceptance between unrelated individuals.

Although the class I molecules were first defined as targets of graft rejection, they are now known to play a physiological role as T cell restriction elements, as described above. There are many subpopulations of T lymphocytes, serving different functions. Class I molecules most often serve as the restriction elements for cytotoxic T cells. Specifically, a class I-restricted cytotoxic T cell cannot kill an antigen-bearing target cell unless an appropriate class I MHC product is also present on the target. Many different cell types bear class I molecules, and can serve as targets of effector T cells.

The genetic organization of the MHC has been studied intensively. Most relevant here is that all of

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**Fig. 2. The structure of the class I MHC family in man, and a panel of monoclonal antibodies to different determinants on class I proteins.** (Left) Class I structure. The HLA-A, HLA-B, and HLA-C molecules are three different, but closely related protein families. All of the molecules have the same general structure, consisting of a 43 kDa heavy chain, the HLA chain, non-covalently linked to a 12 kDa polypeptide, β₂-microglobulin. The heavy chains are coded within the major histocompatibility complex (MHC), and are highly polymorphic within the population. Within an individual, the same class I alleles are expressed on all class I cells. The polymorphisms reside in the amino acid sequence variations of the HLA chains, and account for a relatively small proportion of the total amino acids (α, β, γ, etc.). Although the HLA-A, HLA-B and HLA-C heavy chains are similar to each other, chain-specific antigenic determinants (independent of the polymorphisms) exist (α, β, γ). (Right) Monoclonal antibodies used to analyse class I molecules. Antibodies to individual polymorphic specificities (HLA-A2, HLA-B7) can be used to identify single class I proteins. Other antibodies can be used as probes for the individual subfamilies (HLA-A, etc.). Still other antibodies react with all of the class I molecules, but identify different parts of the molecules: W6/32 recognizes a conformational determinant on the native molecules. Anti-HLA recognizes a sequential determinant on the HLA chain; it will react with the free HLA chain and the native molecules. L368 recognizes β₂-microglobulin; it reacts with both free β₂-m and the native molecules. The conventional anti-β₂-m serum is similar to L368 in its reactivity.

The class I molecules share a general two-chain structure, with the polymorphisms expressed as amino-acid sequence variations of the heavy chain. This co-existence of common and unique structural regions can be exploited for analysis by monoclonal antibodies (Fig. 2). For example, if the molecules are absent, it is possible to ask whether the entire class I family and the component chains are also absent. If the molecules are present, it is possible to ask whether they are present in their native conformation, and whether appropriate polymorphic specificities are expressed. Monoclonals have been particularly useful for analysis of the human molecules, for which the primary source of conventional antibodies was serum from multiparous women.

The second relevant family of MHC products are the class II molecules. These include the human HLA-D system, and the IA molecules in the mouse. The class II molecules share many general features with the class I family: they are also highly polymorphic glycoproteins, they also serve as targets for graft rejection, and they also play a physiological role as restriction elements in the immune response. Their restriction role complements that of the class I proteins: whereas class I proteins are the usual restriction elements for cytotoxic T cells, class II molecules are the usual restriction elements for helper T cells. That is, T cells that cooperate in the initiation of antibody production by B lymphocytes, that amplify the activity of cytotoxic T lymphocytes, or that initiate delayed-type hypersensitivity (DTH) responses usually recognize antigen in the context of class II molecules.

An important aspect of antigen presentation to helper T cells is that the antigen must usually be processed. Whereas many cell types can serve as effector T cell targets, only a few cell types can serve as antigen-presenting cells (APCs). These cells are able to process antigen that originally appeared either free or on other cells, and then present it to T cells in a class II-restricted manner. This property need not be constitutively expressed, but rather class II expression and antigen presenting function may vary in response to regulatory factors.

The class II molecules share a common general structure, and this is different from that of the class I proteins. As in the case of class I, a panel including monoclonals to both common and unique determinants is of value.

**MHC expression is under regulatory control**

Traditionally, class I molecules have been described as ubiquitous, and class II molecules as limited to a very few cell types. More recently, it has become clear that MHC expression is not fixed, and that for both class I and II, major changes can occur in response to
regulatory influences. It is only by microscopic examination in situ that a definition of MHC expression in normal and pathological neural tissue can be obtained.

**Expression of class I and II MHC products in neural tissue**

Although the regulation, structure, expression and function of class I and II MHC products have been studied in great detail, relatively little of this work has focused on neural tissue. It had been established by absorption studies that brain homogenates express little of either protein family, as compared to most other organs. It is only recently, with the availability of monoclonal antibodies and sensitive immunocytochemical techniques, that a more precise analysis of the cellular distribution of MHC products has been possible.

Immunocytochemical analysis of normal brain from animals and humans has given a consistent picture of class I expression in many laboratories. Neither class I molecules nor their component chains have been detected in neurons, glia, oligodendrocytes, microglia, or any other parenchymal cells when analysed with monoclonal probes. Class I activity is also lacking from many tumors of neural origin. The only reproducible class I activity seen in normal brain has been in blood vessel walls (Fig. 3A, B). This appears as a continuous stain of all small and medium vessels, and serves as a useful internal positive control in the assays. However, even this activity may reflect the adsorption of serum-borne antigen to the vessel walls, rather than an endogenous class I expression.

There is general agreement that class II molecules are also lacking from most parenchymal cells, and also from most blood vessels in normal brain. Some laboratories have detected rare class II + cell bodies within normal brain (Fig. 4). By their morphology, these cells might include reactive astrocytes, microglia, or oligodendrocytes, but not neurons or quiescent astrocytes. Class II activity has also been observed as a discontinuous stain in rare blood vessel walls (Fig. 3C). This is in striking contrast to the continuous class I stain that is seen in all brain blood vessels in frozen sections. The infrequency of the class II + cells and vessels suggests that they may represent local modulation, perhaps in response to insult, rather than constitutive class II + populations in normal adult brain.

To summarize, neither class I nor class II restriction elements are detected in the great majority of parenchymal cells in normal brain. This implies that most brain cells would be unable to present antigen to helper T cells (which are usually class II-restricted). It also implies that most brain cells would be protected from T cell-mediated cytotoxicity even if they bear viral, tumor-associated, or other inappropriate antigens. In different contexts, the lack of MHC products could be an important factor in the successful growth of neural transplants, but could also be a factor in the successful growth of infected or transformed cells.

At the same time, the brain's protection from T cell surveillance is not absolute; T cell-mediated immune responses can certainly occur in pathological conditions. How can this be understood in terms of the lack of T cell restriction elements in normal neural tissue?

**Neural MHC expression is under regulatory control**

The most complete evidence for neural MHC modulation comes from studies in vitro. Neuronal cell lines show increased class I expression after exposure to interferon (IFN). Glial lines show strong
class I expression even without IFN addition\textsuperscript{26,27}. For both neuronal and glial lines, the class I molecules can be expressed by every cell in the population, they have the appropriate structure, and, where tested, can express appropriate polymorphic specificities\textsuperscript{24,26,28} (Fig. 5). Cultured glial, but not neuronal, cells and cell lines are also able to express class II, and these molecules can present antigen, the predicted class II restriction function, in vitro\textsuperscript{29,30}. Thus, it appears that cells of both neuronal and glial origin can synthesize bona fide MHC products. The essential questions to be asked now are: In what developmental or pathological situations is this biosynthetic potential expressed in vivo? Under what therapeutic conditions might greater MHC expression be induced? When MHC induction is undesirable, as in the case of a graft, how can it be prevented? When there is a change in MHC expression, what are the immunological consequences?

When is MHC expression modulated in vivo?

In brain, most parenchymal cells are protected from passive exposure to blood-borne antigens, immunomodulators, and immunocompetent cells by the blood–brain barrier. It is possible, then, that neural cells in barrier-free regions might express MHC products. In practice, class I expression is not seen in the area postrema (a barrier-free circumventricular organ)\textsuperscript{31}, within most glial tumors in brain (where the blood–brain barrier could be altered)\textsuperscript{15,16}, in the free nerve endings of olfactory neurons\textsuperscript{32}, or in neuronal tumors growing in peripheral sites (such as adrenal gland or lymph node)\textsuperscript{33}. Thus, passive exposure to blood-borne elements is apparently not sufficient to induce neural class I expression. In most of these cases, class II expression has not yet been examined.

Progressing to other types of conditions, parenchymal class I expression was also not detected in regions of physical trauma (needle wound) (Nicklaus, K., Siegel, G., Whelan, J. P. and Lampson, L. A., unpublished observations), in the presence of reactive astrocytes\textsuperscript{34}, or in the area surrounding glial tumors\textsuperscript{15}. In contrast, greater numbers of class II cells have been found in the vicinity of brain tumors.\textsuperscript{15,20} Both class I and class II induction have been reported on cells of glial origin following exposure to viruses\textsuperscript{33,34}. Besides affecting the cells’ potential to participate in T cell-mediated immune reactivity, the MHC products may themselves serve as viral receptors\textsuperscript{35}.

The most promising situations in which to look for MHC modulation might be when T cell infiltration would be predicted, or has already occurred. Class II modulation is seen as an early event in the development of MS plaques\textsuperscript{23,26}, and class I is also increased\textsuperscript{44}. Further studies of inflamed tissue, as well as transplanted and infected tissue are now essential.

Still another context in which to look for MHC modulation is during neural differentiation or development, where the molecules have been hypothesized to play a role in non-immunological cellular interactions\textsuperscript{35}. However, class I induction is not seen in reactive astrocytes\textsuperscript{15}, in either the developing neurons or supporting cells in olfactory epithelium\textsuperscript{36}, nor in the developing neural tube or other neural tissue of the developing embryo\textsuperscript{39}. Nor does the presence or absence of class I molecules appear to affect the spectrum of morphological forms, or the ability to form cell–cell contacts of neuroblastoma cells in culture\textsuperscript{54,59}. Thus, the available evidence does not support a role for class I modulation during normal differentiation or development of neural cells. A role for class II has not yet been examined.

MHC induction in vivo

Interferon, which induces MHC expression in neural cells in vitro, can also induce MHC expression when injected directly into the brains of neonatal mice\textsuperscript{25}. These findings provide further evidence that MHC modulation is not solely a property of neural cells in vitro, and raise the possibility that induction might be possible in a therapeutic context. They also help to focus the questions that must be asked once in-vivo MHC induction has been seen: Which of the cells actually synthesize the MHC products that they express, as opposed to having adsorbed or endocytosed antigen secreted by other cell types? Will biochemical studies confirm that molecules that were first detected immunocytochemically are in fact MHC products, and do the molecules have the same structure as their counterparts on lymphoid cells? Are the molecules able to perform their predicted restriction functions? Finally, if all of these answers are positive, will induction of MHC products on cells that do not usually bear them lead to autoimmune reactivity against normal cell surface antigens?

Implications

Situations in which neural MHC induction occurs are only now being defined. Greater MHC expression has been reported in MS plaques, in the vicinity of neuronal tumors, after viral infection, and following intracerebral injection of interferon. This modulation does not occur easily. Class I expression was not found to be increased by passive exposure to blood-borne antigens or immunocompetent cells, following physical trauma, or as a normal part of neural development or differentiation. Taken together, the existing evidence implies that when neural MHC induction is seen, there has been a major change in the immunoregulatory environment. Thus, in pathological conditions in which the existence of an immune etiology is controversial, analysis of MHC expression in situ could be informative.

The interaction between MHC-restricted and other immune effector functions

MHC-restricted T cell-mediated functions re-
Fig. 5. Induction of class I proteins in human neuronal cell lines. (A) Immunoblot analysis of class I proteins. The neuroblastoma cell line IMR-5 was grown in the absence or presence of γ-interferon. Detergent extracts were analysed on an immunoblot, using monoclonal antibodies to HLA chains (lanes 2 and 4), to actin (lanes 3 and 5), or negative controls (lanes 1 and 6)24. The quantity of HLA chains is greatly increased following exposure to interferon, but the actin is not increased. The class I + B cell line RAJI (not treated with interferon) was included as a positive control. (B) Distribution of class I proteins within the population. IMR-5 cells grown in the absence (panel 1) or presence (panel 3) of γ-interferon were assayed for class I expression using monoclonal antibody L368 (see Fig. 2) in the peroxidase-anti-peroxidase (PAP) assay24. The cells had been harvested from culture and embedded in agarose blocks, which accounts for their round shape. The figure shows that class I was increased within every cell of the population. The class I + B cell line RAJI, not treated with interferon, is shown for comparison (panel 2).

present only a part of the body’s potential to respond to foreign or inappropriate antigens. MHC restriction is not required for neutrophil- or macrophage-mediated inflammatory reactions, nor for natural killer (NK) cell activity. Neural cell lines that are not susceptible to T cell killing are excellent NK targets40.

Where MHC-restricted T cell activity does play a role, the effects need not be limited to the original MHC+ cells. Although helper T cell participation is required for most antibody formation, once formed, the circulating immunoglobulins are only prevented from entering the brain by the physical blood–brain barrier6. Although effector T cells must recognize antigen on a cell surface, in association with an appropriate MHC product, secreted effector molecules may act directly on adjacent cells. These effector molecules can also indirectly affect cells over a broader area, by mediating the recruitment of additional effector cells, and by release of new cytokines and immunomodulators51. This cascade of events is the basis of the delayed type hypersensitivity (DTH) response that, for example, is believed to account for much of the demyelination in an MS plaque52. Thus, to understand the role of the MHC in the immune response to neural antigens, it is necessary to consider the role of T cells in initiating or amplifying a cascade of immunological responses as well as in directly mediating effector functions.

As discussed above, the lack of MHC expression in normal brain may represent a regulatory control rather than a constitutive lack of expression in parenchymal cells. In view of the functional interactions discussed above, MHC expression may be critical in initiating or amplifying an immune response in neural tissue even when this expression is limited to only a few cells or cell types11,23,25,29.

Concluding remarks
Despite the physical, homing and cell surface barriers to immune–neural interactions, immune responses and, in particular, T cell-mediated immune responses can occur in the brain. Destruction of the blood–brain barrier, novel expression of leukocyte homing molecules and chemotactic factors, induction of MHC molecules, and interactions between MHC-restricted and non-restricted effector functions can each play a role. An understanding of the function and regulation of neural MHC products is one essential aspect of being able to predict, and control, these responses.

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An Introduction to the Mathematics of Neurons
by F. C. Hoppensteadt, Cambridge University Press, 1986. £9.95/$17.95 (xv + 175 pages) ISBN 0 521 31574 3

In his introduction to this book, Professor Hoppensteadt clearly states the perspectives that dominate the text:

'For example, the most sophisticated model of neurons to date remains the Hodgkin–Huxley model.'

'By adopting the point of view that neurons deal with phase, or frequency, information much like frequency-modulated (FM) radios do.'

'This book introduces some modelling techniques that are useful in studying time and clocks from neurons to higher levels.'

'It is intriguing that phase information stores memory and governs the psychological response of networks, and there remains many interesting and untouched aspects of this kind of information storage and processing by neural networks.'

'Arguing (as others have done previously) that the Hodgkin–Huxley model is too complicated to be used profitably as the element of neural-network models, Hoppensteadt introduces a simpler surrogate — the Voltage Controlled Oscillator analog of a Neuron (VCON). In addition to its simplicity, the chief advantage of the VCON is the fact that its output is described in terms of phase, allowing the modeller to treat small and large networks of these devices on the basis of phase interaction. This should remind neural modellers of the celebrated paper of Perkel, Schulman, Bullock, Moore and Segundo (Science 1964, 145, 61–63), which beautifully exploited phase interaction in analysing two-neuron models, and of the subsequent work by Winfree, applying phase-interaction analysis to oscillator populations. In a text written largely, I believe, for students, Hoppensteadt carefully develops the notion of phase interaction and shows the reader how it might be applied to small and large network models. Along the way, he introduces a wide variety of well-known concepts that, in my opinion, should be part of the intellectual arsenal of all neurobiologists seriously interested in networks of neurons. These concepts range from basic electrical network devices and dynamics, to phase- or state-plane dynamics and energy surfaces. Each chapter ends with a series of exercises, often general and open-ended, appropriate for intellectually mature students. Since some of the exercises are computer based, and since chaos is so easily demonstrated computationally in the phase-interaction equations of coupled oscillators, I was surprised not to see that concept developed (although it was mentioned).'

Many classic neuron and neural-network models and much of the classical neural modelling literature are not mentioned in the book. For example, the integrate and fire model is described in detail; but the far more successful and nearly as simple (two-time-constant) model of Hill, Rasshevsky, and Monnier is not mentioned. McCulloch and Pitts are not mentioned, nor are the notions of lateral inhibition or reciprocal inhibition; and in spite of the fact that an entire chapter is devoted to synchronization of neuronal firing in large networks, the rich early literature in that field is largely ignored. However, all of this older material has been covered in other texts and review articles, so its omission here is reasonable. However, it does require that the book be supplemented extensively if it is...