Basic mechanisms of brain inflammation

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Summary. The mechanisms, how the immune system surveys the nervous tissue and how brain inflammation is regulated are essential questions for therapy of neuroimmunological diseases. The nervous system is continuously patrolled by hematogenous cells, which may pass the blood brain barrier in an activated state. When these cells find their respective target antigen in the CNS compartment, an inflammatory reaction is started through the secretion of proinflammatory cytokines. This leads to the upregulation of endothelial adhesion molecules and the local production of chemokines, which in concert facilitate the entry of inflammatory effector cells into the lesions. T-lymphocytes are effectively removed from inflammatory brain lesions by local apoptosis. In addition some lymphatic drainage of the nervous system allows the removal of effector cells from the lesions and their migration into regional lymph nodes. In summary these data suggest that the immune surveillance of the central nervous system is much more tightly controlled compared to that in other organs.

Introduction

Inflammation in the central nervous system is instrumental in a variety of human diseases, such as acute meningitis or encephalitis as well as multiple sclerosis or AIDS. To understand the pathogenesis of inflammatory brain diseases several basic questions have to be addressed. The immune system has to recognize the pathogen or autoantigen, that is sequestered in the nervous system. This implies, that immune cells have to get access to the normal nervous system and that the antigens have to be presented in a way that allows recognition. When antigen is recognized a cascade of events has to be started which leads to inflammation and elimination of the pathogen and which may be associated with additional tissue damage. Finally, during clearance of inflammation, inflammatory cells must be removed from the lesions. Since the regeneration capacity of the nervous system is very limited, all these processes have to be accomplished in a way, that keeps unspecific tissue damage at the lowest possible level. One of the central questions in neuroimmunology is thus to elucidate, how the immune system accomplishes this task.

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Immune privilege of the normal brain

In several immunological aspects the central nervous system differs from other organs. Due to the blood brain barrier immune cells, antibodies and immunological mediators have little access to the normal brain (Hickey et al., 1991). Yet, there are some hematogenous cells, in particular monocytes/macrophages and T-lymphocytes, present in the CNS tissue even under completely normal conditions (Hauser et al., 1983). Studies in bone marrow chimeras revealed that there is continuos turnover and replacement of monocytes and T-lymphocytes, mainly in the meninges and the perivascular space (Hickey and Kimura 1988; Hickey et al., 1992). Whereas at present it is not clear, how monocytes enter the CNS compartment, T-lymphocytes can traverse the normal blood brain barrier, when they are in a activated stage (Wekerle et al., 1986; Hickey et al., 1991). These data suggest, that it is the small pool of peripherally activated T-cells, that enter the CNS compartment for immune surveillance and are, thus, allowed to search for specific antigens or pathogens. Yet, when there is no peripheral T-cell activation, the respective antigens may hide in the CNS and escape detection by the immune system. Thus transplants may survive in the brain environment, in spite of a mismatch in histocompatibility antigens (Sloan et al., 1991; Broadwell et al., 1994), and by the same mechanism the brain protects itself against autoimmune reactions.

Another mechanism is the active suppression of the expression of major histocompatibility (MHC) antigens in the nervous system. Antigen recognition by T-lymphocytes requires the presentation of small peptides of the antigenic protein by antigen presenting cells in the context of MHC antigens. Thus, in the absence of MHC-antigens T-lymphocytes cannot recognize their target and, thus, do not activate the mechanisms, that finally lead to inflammation. MHC-expression in the normal brain is very low or even absent (Vass et al., 1986; Hart and Fabry, 1995). Its absence apparently does not reflect the lack of immunstimulatory signals, but is rather due to active suppression by electrically active nerve cells (Neumann et al., 1995). Damage of the nervous system, that blocks electrical activity, may induce MHC expression in neurons and possibly in neighboring glia cells. This allows T-cells to recognize their antigen, to induce inflammation or to eliminate their target through direct cytotoxicity.

The low expression of immune activation associated cell surface molecules in the CNS is not restricted to MHC-antigens. The expression of adhesion molecules, that are essential in cell-cell contacts during the migration of inflammatory cells (Bevilaqua, 1993; Springer, 1994), is low on endothelial cells of cerebral vessels as well as on local tissue elements (Sobel et al., 1990; Raine et al., 1990; Male et al., 1990; Lassmann et al., 1991; Rössler et al., 1992). Low expression is also found for CD 34, the receptor for lipopolysaccharide (LPS). Thus, induction inflammation by bacteria in the CNS, which is primarily mediated by LPS, is delayed in the brain and requires a very high bacterial load in comparison to that in peripheral organs (Quagliarello and Scheld, 1992; Lawson and Perry, 1995).

Finally the CNS is equipped with a particular tissue macrophage, the microglia (Germann et al., 1995). In the normal brain microglia in its resting

state seems to be immunologically inert. Although microglia can become activated by a variety of immunological and non-immunological stimuli, different levels of activation appear to exist, which may transform the cells in either pure scavengers or fully activated immunological effector cells. Furthermore these cell can produce both, immunostimulatory as well as immunosuppressive cytokines (Kiefer et al., 1995). Thus it is still unclear, whether the prime role of microglia in brain inflammation is to propagate or suppress the immune response.

Immune surveillance and the induction of initial brain inflammation

As mentioned before, activated T-lymphocytes can pass the normal blood brain barrier. Thus, peripheral stimulation of the immune system, for instance in the course of an infection, will allow a selected population of T-cells to enter the CNS and to search for their respective antigen. When the antigen or a cross reactive autoantigen is present in the CNS compartment, it will be presented to the T-lymphocytes on a population of meningeal and perivascular tissue macrophages, which constitutively express MHC antigens even under normal conditions (Vass et al., 1986; Hickey and Kimura, 1988). The initiation and propagation of brain inflammation can be mediated by antigen recognition on the tissue macrophages in the meninges and the perivascular space alone and does not require the participation of other cells of the CNS parenchyme, such as microglia and astrocytes (Hickey and Kimura, 1988; Lassmann et al., 1993).

The initial antigen recognition in the perivascular space triggers a cascade of secondary events, that lead to the development of brain inflammation. A key role in this process is played by cytokines, that are produced either by hematogenous cells or by local tissue elements. In acute T-cell mediated encephalomyelitis a characteristic temporal sequence of cytokine production has been observed. An initial peak of Interleukin 12 and gamma-interferon production is rapidly followed by pronounced synthesis of Interleukin 1 and Tumor Necrosis Factor alpha (Olsson, 1994). The latter correlates well with the peak of tissue infiltration with hematogenous cells. This process is associated with a pronounced upregulation of the expression of adhesion molecules on the endothelial cells of cerebral vessels (Lassmann et al., 1991; Cannella and Raine, 1995). The endothelial adhesion molecules apparently are required in the recruitment of secondary, non activated hematogenous effector cells, which are instrumental in the removal of pathogens but also in the induction of inflammatory tissue damage.

Amplification of the inflammatory response by local production of chemokines

Chemokines are small peptides, which are chemotactic for other inflammatory cells and play an important role in the secondary recruitment of leukocytes into an established inflammatory focus (Baggiolini et al., 1994). In brain

inflammation chemokines are not only produced by hematogenous cells but also and prominently by local cells such as astrocytes (Tani and Ransohoff, 1994). Liberated into the extracellular and perivascular space, they apparently modulate the inflammatory reaction by attracting additional monocytes or – in the case of bacterial meningitis – granulocytes into the lesions. In comparison to cytokines, the synthesis of chemokines in the lesions is much more prominent and less tightly controlled (Schlüsener and Meyermann, 1993). It has, thus, been suggested that chemokines are instrumental in the amplification of the inflammatory reaction and in the spread of inflammation into the parenchyme of the CNS.

Recently, however, it became clear, that not only the classical chemokines may exert chemotactic functions. Certain neuropeptides, as for instance Substance P, Vascular Intestinal Peptide or Secretoneurin, have been shown to be leucotactic for T-cells, monocytes or granulocytes (Carolan and Casale, 1993; Reinisch et al., 1993; Johnston et al., 1994). Interestingly, in acute T-cell mediated brain inflammation, a significant association between local expression of Secretoneurin with macrophage infiltration has been observed (Storch et al., 1996). This suggest, that in addition to classical chemokines the local milieu of neurotransmitters may modulate inflammation in the brain.

Mechanisms of immune-mediated tissue damage in inflammatory brain lesions

Immune effector cells, such as monocytes/macrophages, granulocytes or cytotoxic T-cells produce a variety of toxic factors, that are required for the destruction and elimination of foreign pathogens. These include cytotoxic cytokines (e.g. TNF-alpha, lymphotoxin), perforin or complement components, proteolytic and lipolytic enzymes and oxygen radicals. These toxic factors, however, not only destroy foreign pathogens but may also damage local tissue elements. In the central nervous system the myelin/oligodendroglia complex appears to be particularly vulnerable to the action of these toxic inflammatory mediators (Griot et al., 1990; Scolding et al., 1990; Selmaj and Raine, 1988). In vitro, in mixed culture systems, it is generally the oligodendrocyte with its myelin sheaths, that is damaged to a much larger extent as other CNS elements, such as astrocytes or neurons. This may in part explain, why chronic inflammatory conditions of the central nervous system in experimental autoimmune encephalomyelitis as well as in human conditions, as multiple sclerosis or HIV-encephalitis are accompanied by extensive white matter pathology.

In addition, however, the inflammatory response may directly affect neurons. Activated macrophages can produce significant amounts of quinolinic acid and other excitotoxins, which – at least in vitro – may destroy nerve cells through an NMDA-receptor mediated pathway (Giulian et al., 1993; Lipton et al., 1994; Espey et al., 1995). This mechanism may play a significant role in the induction of neuronal loss in HIV-encephalitis and may also contribute to axonal damage in multiple sclerosis lesions.

Clearance of inflammation

Inflammatory cells, that have entered the brain during inflammation, have to be removed from the lesions during recovery. In contrast to the mechanisms, that are involved in the induction of brain inflammation, those that operate during clearance are much less understood. Pender et al. (1991) first reported that in T-cell mediated inflammatory lesions of the brain abundant cells are locally destroyed by apoptosis. Later it became clear, that most of the apoptotic cells are T-lymphocytes and that the peak of T-cell apotosis correlates well with the clearance of the inflammatory lesions (Schmied et al., 1993). Both, direct as well as indirect evidence suggests, that it is the population of autoantigen-specific T-lymphocytes that are removed by programmed cell death in the brain (Tabi et al., 1994; Bauer et al., 1995). A similar destruction of T-cells by apoptosis has been identified in autoimmune neuritis (Zettel et al., 1994), corona virus induced demyelinating encephalomyelitis (Barac-Latas et al., 1995) and multiple sclerosis (Ozawa et al., 1995), but not in inflammatory diseases of peripheral organs (Bauer et al., 1995). Therefore, it appears that the nervous system has established a specific way to downregulate T-cell mediated immune responses through the local destruction of antigen-specific T-cells. The mechanisms of apoptosis induction in these conditions are still poorly understood.

Although apoptosis is sometimes also encountered in macrophages (Nguyen et al., 1994) and granulocytes, its incidence in inflammatory brain lesions is too low to explain their removal by this mechanism. Therefore some drainage of secondary effector cells from the brain into the blood vessels or the local lymphatic tissue has to be considered. The existence of lymphatic drainage pathways in the nervous system has for long been controversial. Recently, however, it has been shown that antigens or particulate material, that were injected into the cerebrospinal fluid may reach regional lymph systems at areas, where cranial and spinal nerves and blood vessels pass the meningeal barrier (Weller et al., 1992; Zenker et al., 1994). Such intrathecally injected antigens may elicit a local immune response for instance in the deep cervical lymph nodes (Cserr et al., 1992). We have recently studied the migration routes of macrophages, that have taken up brain proteins in inflammatory demyelinating lesions and found evidence for a drainage pathway through the spinal meninges into the epidural lymphatic vessels and the paraaortal lymph nodes. In addition, some macrophages were also found to migrate through the walls of inflamed vessels into the circulation and could then be identified in the spleen. Thus, these data suggest that there is indeed a lymphatic drainage of the central nervous system. In contrast to lymphatic drainage in other organs, however, the time, required for macrophages to reach the lymph nodes was much longer. Thus, the transport of antigens from the CNS into the lymphatic tissue may be limited by the fact, that most antigens will already be degraded when the macrophages accumulate in the lymphatic environment.

Conclusions

In summary the mechanisms of brain inflammation in many respects follow the same basic patterns, that operate in inflammation at other sites of the body. Yet, the brain has developed a variety of protective mechanisms, which secure an efficient immune surveillance while keeping undesired immune mediated tissue damage at a lowest possible level. These protective mechanisms are partly accomplished by the blood brain barrier, that allows the entry of immune effector cells, immune mediators and antibodies only when damage already has occurred. Furthermore, the low expression of histocompatibility antigens and other immune associated cell surface receptors and the efficient elimination of antigen-specific T-lymphocytes from the brain in general prevents overheated local immune responses, that could be deleterious for brain function. Yet, when very severe proinflammatory stimuli are provided the full immunological repertoire of inflammation can be activated. Thus, in the CNS inflammation is a graded response, that secures an immune surveillance at the lowest level, that is just appropriate for the defense against pathogens. Obviously, a dysregulation of this process, which may take place in certain infectious diseases or in autoimmunity has deleterious effects on brain integrity.

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