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CHAPTER 22

Autoimmune involvement in CNS trauma is beneficial if well controlled

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Introduction

The central nervous system (CNS) has long been viewed as a site where any immune activity is detrimental. Moreover, if any immune activity is detected in the injured CNS, its effect was assumed to be negative. Yet, as is well known, the role of the immune system in general is to defend, to protect, and to repair. The question is: how can this apparent paradox be reconciled? Does it derive from a fundamental difference between the nervous system and the rest of the body with regard to their post-injury requirements for rescue and repair? Or is it an outcome of the immune system's ability to exert both beneficial and harmful effects, with the balance between them varying among different tissues? This article will summarize data suggesting that in cases of traumatic injury to the CNS, the role of the immune system is similar to its role in other tissues, but the unique nature of the CNS demands that immune involvement be more tightly controlled. Both innate and adaptive immune responses are needed for recovery after CNS axonal injury; macrophages are required for repair, and activated T-cells directed against CNS self-antigens are needed for protection. Immune cell therapy design should be based on timely intervention, with tight control of amounts and specificities so as to derive the maximal benefit with minimal risk.

In most tissues damaged by traumatic injury, the immune response has to do with the process of repair, a relatively simple task that does not require specificity to any particular pathogen and can therefore be mediated by the innate arm of the immune system, represented by the relatively non-specialized immune cells, the macrophages. These cells invade the injured tissue, remove dead cells and cell debris, and produce the factors needed to execute a myriad of processes that lead eventually to tissue repair (Clark, 1993a,b). This is the routine procedure when the insult is not pathogen-related and thus the primary need is for repair. The picture becomes more complicated, however, when pathogens are involved. The immune system must then provide not only repair and renewal of damaged tissues, but also defense against the infective organism and protection of the tissue from the progression of damage (Matzinger, 1994). In this case, the pathogen-induced damage evokes a 'stress' signal that recruits the acquired arm of the immune system, represented by the relatively more specialized T-cells.

It appears from our work that, at least in the CNS, even damage resulting from traumatic injury can benefit from the assistance of both arms of the immune system, the one involved in repair (macrophages) and the other concerned with defense and protection (T-cells). The T-cells mobilized in this case appear to be directed not against a specific

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pathogen, but against self-antigens expressed in the damaged CNS tissue (Schwartz et al., 1999). It thus appears, surprisingly, that what the CNS needs for recovery from trauma is not different from what is needed by other tissues, namely, the involvement of the immune system. Paradoxically, it also seems that the activity of the immune system in the injured CNS needs to be broader than in other injured tissues, while at the same time more stringently controlled. One possible reason for this, as discussed below, is the non-replicable character of the specialized nerve cells (neurons) in the CNS (Lotan and Schwartz, 1994; Cohen and Schwartz, 1999; Schwartz et al., 1999).

The role of macrophages in CNS regrowth and regeneration

Traumatic injury to CNS axons is followed by some immune activity, in the form of recruitment and activation of blood-borne monocytes and activation of resident microglia. However, this immune activity is limited to the site of injury in comparison with the massive spontaneous recruitment and activation of monocytes manifested by the process of Wallerian degeneration seen in injured peripheral nerves (Avellino et al., 1995). It is now clear that Wallerian degeneration, although apparently destructive in nature, is a prerequisite for subsequent regeneration (Brown et al., 1991; Lu and Richardson, 1991; Perry and Brown, 1992; Chen and Bisby, 1993; Perry et al., 1993; George and Griffin, 1994; La Fleur et al., 1996). The analogous process in non-nervous tissues is the clearing of dead cells and cell debris. In the nervous system, the process of tissue repair after axonal injury is not a matter of 'filling in' the space created by the damaged axon. This is because the damage is not intercellular but intracellular, involving axoplasmic disruption and therefore necessitating reconstruction of the axon all the way back to the target in the brain rather than mere bridging of the gap between the cut ends of the nerve. Thus, the apparently chaotic initial spread of damage to tissues beyond the site of the lesion is in fact a beneficial process — the price, so to speak, of preparing the tissue for repair. In the CNS, this spread of damage occurs more slowly than in the peripheral nervous system. The slow longitudinal degeneration in the CNS (i.e., along the injured axons themselves) may have both 'bad' and 'good' consequences. On the one hand, as proposed here and discussed below, it impedes the regeneration of damaged fibers. On the other hand, as a consequence of the above, it slows down the permeation of damage to viable neurons that escaped the primary injury.

The spread of degeneration (secondary degeneration) in the injured CNS has been shown to result from an extracellular imbalance in neuron-associated transmitters and other essential components, which become noxious when their physiological levels are exceeded owing to buffering impairment. Compounds such as glutamate and nitric oxide play a pivotal role in the maintenance and performance of the normal nervous system, but pose a threat when their levels exceed the system's buffering capacity. It is still a matter of debate whether immune involvement at an early post-traumatic stage has any negative effects on the delayed degeneration in the CNS (Popovich et al., 1999). The beneficial effect of methylprednisolone administration soon after spinal cord injury could be interpreted as an indication that local inflammation in the very early stages after trauma, even if mild, is bad for recovery (Blight, 1992; Constantini and Young, 1994). Somewhat later, however, when the process of degeneration becomes necessary for repair, the advantage of inflammation overrides the early disadvantage, but its mildness now makes it insufficiently effective (Lu and Richardson, 1991; Lazarov-Spiegler et al., 1996, 1998a,b; Prewitt et al., 1997; Lazar et al., 1999).

We have shown that after complete transection of the rat optic nerve or spinal cord, local administration of macrophages, following their activation by exposure to peripheral nerve tissue, promotes axonal regrowth (Lazarov-Spiegler et al., 1996; Rapalino et al., 1998). In the case of the spinal cord, treatment with the activated macrophages was effective even when applied as late as two weeks or one month after transection. Macrophage implantation resulted in partial recovery of function as well as some tissue restoration, indicated morphologically by fiber tracing, diffusion magnetic resonance imaging (MRI), and immunohistochemistry. All of the tests showed evidence of neural tissue bridging the gap between the cut ends of the nerve. How far the fibers grow, and what makes the macrophage-

treated tissue amenable to regrowth and restoration of function, are still open questions. It seems clear, however, that the macrophages, as in all other injured tissues, prepare the CNS tissue for repair. Among the factors produced by the macrophages are cytokines and growth factors. In the context of CNS trauma, it is still a matter of controversy whether cytokines have a beneficial or a detrimental effect on the injured tissue, and there is evidence to support both of these possibilities (Hirschberg et al., 1994; Bethea et al., 1999). We suggest that viewing cytokine activity after brain and CNS trauma as 'good' or 'bad' is misleading, and we would do better to focus our attention on individual cytokines and other factors that may exert distinctive and possibly opposing effects, depending on the phase of recovery and on whether rescue or regrowth is predominantly required. Phase and requirements may be related, as treatment for protection has a narrower post-injury time window than treatment for growth. If properly regulated, local treatment of the damaged axons with a well controlled quantity of suitably activated macrophages, in a time window when the threat to the rescue of spared neuronal tissue is still low, might enable the damaged tissue to 'talk' with the macrophages in a way that allows them to self-regulate their activities according to need, while avoiding the undesirable effects of each factor. In cases of partial lesion of the nerve fibers rather than complete transection, it may be necessary to make suitable adjustments to the timing of macrophage application in order to exploit the optimal therapeutic window (Lazarov-Spiegler et al., 1998a).

The T-cell response to CNS damage

As discussed above, where damage to the tissue is of pathogenic origin, the specialized immune cells, the T-cells, are recruited to protect the tissue from the spread of damage. Studies have indicated that spinal cord injury triggers the activity of autoimmune T-cells. As these T-cells have traditionally been considered detrimental to CNS tissue, it was assumed that their effects on the damaged spinal cord are negative (Popovich et al., 1996). However, in a recent study showing that axonal injury in the CNS is followed by a transient, nonselective accumulation of T-cells at the site of injury, we made the astonishing discovery that of all the accumulated T-cells, only those which display immunity to a CNS self-antigen affect the damaged tissue in a manner that is not destructive, but protective (Moalem et al., 1999a, 2000a,b). Adoptive transfer of autoimmune T-cells directed against a cryptic epitope of the CNS antigen reduced the injury-induced spread of damage and thus resulted in a significantly improved outcome, manifested both functionally and morphologically, after optic nerve or spinal cord injury (Moalem et al., 1999a; Hauben et al., 2000). Thus, for example, a single injection of T-cells directed against myelin basic protein reduced the loss of fibers after partial lesion of the rat optic nerve or promoted recovery from partial injury (contusion) of the rat spinal cord. We found that after injury, the damaged nerve tissue became permissive to the accumulation of T-cells, regardless of their antigen specificity (Hirschberg et al., 1998; Moalem et al., 1999b), but only those T-cells directed against myelin-associated proteins had any effect on the damaged nerve, and that effect was beneficial, i.e., neuroprotective. T-cells of other specificities had no effect on the injured nerve. The neuroprotective effect could be achieved not only by passive immunization (transfer of T-cells) but also by active immunization, i.e., vaccination with relevant antigens.

This unexpected effect of the autoimmune T-cells challenges our understanding of autoimmunity in general and CNS autoimmunity in particular. We suspected, and recently proved, that the spontaneous autoimmune response triggered by the injury is potentially beneficial, but too weak to be effective, and therefore in need of therapeutic boosting. This would indicate that the autoimmune response triggered by injury to CNS tissue is analogous to the T-cell response triggered in other tissues by pathogen-associated damage. Just as the signal for this T-cell immune response is tissue stress, so the damage to the CNS is sufficiently threatening to justify the triggering of a T-cell response, even at the risk of its being directed against the self. Such a response would obviously need to be rigorously controlled to avoid incurring an autoimmune disease (see scheme in Fig. 1). In line with this view, it is tempting to suggest the existence of two potential stress signals in the CNS: (1) the threat of irreversible damage spread due to nerve-derived mechanisms of toxicity and the

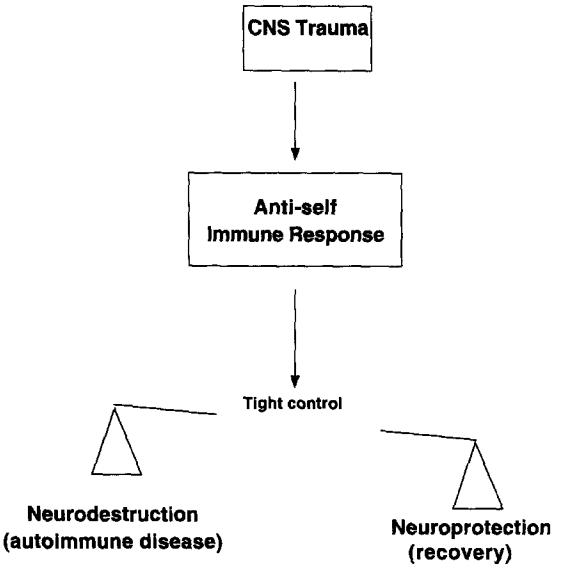

Fig. 1. Injury to CNS axons triggers an immune response against self that is neuroprotective rather than neurodestructive if well controlled, but is too weak to be effective and needs to be amplified.

irreplaceable character of the neural tissue, and (2) the threat of immune activity, including excessive autoimmune activity. We believe that the evolutionary development of limitation on immune activity in the CNS, in the form of immune privilege, came about because of the potentially harmful modulation of the intricate network of the healthy CNS as a result of any immune-related intervention. Thus, it seems that the mammalian brain developed physiological barriers to immune intervention, and that this development resulted in the acquiring of its status as an immune-privileged site. After injury, although the CNS may be in need of its protective immunity (in the form of autoimmunity), such autoimmunity is limited by the same mechanisms that limit immune activity in general in the CNS (Schwartz et al., 1999). Indeed, perhaps the existence of autoimmune T-cells to certain epitopes should be interpreted not as a failure of deletion of 'self', but rather as an indication that the individual needs those T-cells as part of its 'protective repertoire' (Cohen, 1992). If this is so, research efforts should be directed toward discovering how to regulate autoimmunity by awakening a protective response without incurring the risk of autoimmune disease.

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