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Autoimmune maintenance and neuroprotection of the central nervous system

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Abstract

The genesis of immune privilege high in the evolutionary tree suggests that immune privilege is necessary, if not advantageous for the progressive development of the CNS. Upon reaching a certain degree of complexity, it seems as if the CNS was obliged to restrain the immune system from penetrating the blood–brain barrier. CNS autoimmunity against myelin proteins is known to be a contributory factor in the pathophysiology of multiple sclerosis and in the animal model of experimental autoimmune encephalomyelitis (EAE) (Wekerle, 1993). Such autoimmunity has therefore been regarded as detrimental and hence obviously undesirable. However, recent findings in our laboratory suggest that T-cell autoimmunity to CNS self-antigens (Moalem et al., 1999), if expressed at the right time and the right place, can do much good in the CNS. We shall review the experiments briefly, and then discuss their implications for our understanding of immune privilege and CNS maintenance after injury.

Keywords: Central nervous system; Central nervous system injury; Autoimmune maintenance

1. Neuroprotection by anti-MBP T-cells

An earlier experiment had shown that activated T-cells tended to accumulate at sites of CNS injury, an accumulation that was independent of the antigen specificity of the T-cells (Hirschberg et al., 1998; Moalem et al., 1999b,c). The question was whether autoimmune T-cells specific for CNS myelin antigens might function at the site of injury differently than did T-cells of other specificities. To study this question, we administered various activated T-cell lines ($CD4^+$) to rats that had just undergone a partial crush injury to an optic nerve, and observed the effects of the T-cells on the post-traumatic degeneration of the nerve (Moalem et al., 1999b). The T-cells specific for the foreign antigen ovalbumin or for a self peptide epitope of the 60 kDa heat shock protein (hsp60) had no effect on the nerve. In contrast, the anti-MBP T-cells enhanced by 2–3 fold the post-traumatic survival of the injured nerve, measured both functionally in nerve conduction and morphologically (Moalem et al., 1999b). This enhanced survival could be attributed to protection from secondary degeneration of the nerve cells that had escaped the initial crush Fig. 1. The anti-myelin autoimmune T-cells acted to inhibit the continuing spread of damage that usually amplifies CNS impairment beyond the initial site of local injury (McIntosh, 1993; Young, 1996; Yoles and Schwartz, 1998; Schwartz et al., 1999). Protection from secondary degeneration was produced equally well by a highly encephalitogenic T-cell line specific for the dominant MBP sequence 71–90 and by a weakly encephalitogenic T-cell line specific for the cryptic epitope 51–70. Significant protection did not seem to be associated with significant T-cell pathogenicity in naive rats.

More recently, we have extended the autoimmune protection experiments to study the effects of anti-MBP T-cell lines on spinal cord injury. Lewis rats that had undergone a calibrated contusion (Basso et al., 1996; Young, 1996) of the spinal cord were injected with 10^7 anti-MBP T-cells by the intraperitoneal route. Partial trauma of significant magnitude to the spinal cord can immediately trigger a complete loss of function, known as spinal shock. Over time, there may gradually occur a restoration of function that is limited by the extent of the initial damage and by the post-traumatic spread of secondary generation to initially undamaged tissue (Bazan et al., 1995; Beattie et al., 1997).

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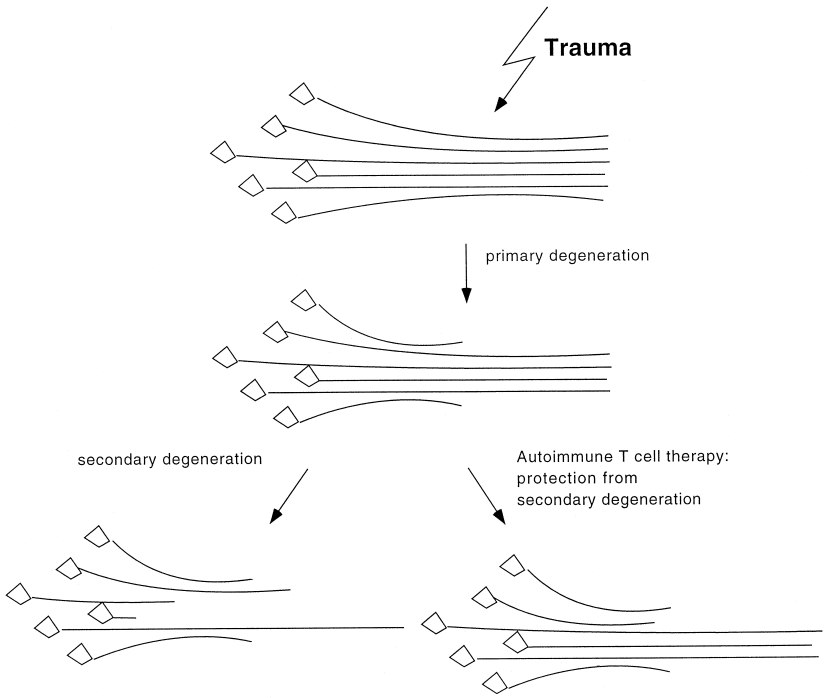

Fig. 1. Schematic presentation of secondary degeneration following partial axonal injury and protection by autoimmune T-cell therapy.

The injured individual is left with whatever cord tissue remains after the combined primary and secondary losses. The question was whether rescue from spinal cord injury, like that following the partial crush of an optic nerve, could be influenced by anti-MBP T-cells.

Here too, the autoimmune T-cells proved beneficial; the treated rats manifested an earlier escape from spinal shock followed by a markedly greater restoration of spinal cord function, compared to control-treated rats with identical contusions (Hauben et al., 1999). The marked increase in spontaneous locomotion in the open field shown by the rats treated with anti-MBP T-cells was accompanied by a significantly greater preservation of spinal cord tissue in the area of injury (detected by MRI) and by a 5-fold increase in the number of neurons in the red nucleus of the brain that could be labeled by retrograde axonal transport through the area of contusion (Hauben et al., 1999). In short, the systemic administration of anti-MBP T-cells led to the preservation of spinal cord tissue, verified both anatomically and functionally. The autoimmune T-cells repressed the secondary damage perpetrated by the initial contusion. T-cells specific for a foreign antigen produced no such effects. A notable feature of the contusion model was a window of therapeutic opportunity; the anti-MBP T-cells could be of significant benefit even when administered a week after the spinal cord had been injured.

In summary, the experiments demonstrated that activated anti-MBP T-cells could enhance recovery from CNS trauma in two systems: the crushed optic nerve and the contused spinal cord. The desirable effects of cell treatment appeared to be at least as good, if not better, than those reported using pharmacological treatments. What could be the mechanisms of such effects?

2. Mechanisms of autoimmune T-cell neuroprotection

The experimental systems we have used are based on partial injury to the CNS in which viable tissue remains after primary injury. Therefore, we believe that the increase in function and in spared tissue produced by the anti-MBP T-cells is explained, at least in these systems, by neuroprotection (arrest of secondary degeneration), rather than by regeneration of nerve tissue de novo. Indeed, the effects of treatment occur too soon to attribute to the regeneration of lost nerve tissue. CNS regeneration of complete nerve transection has been detected following treatment with activated macrophages (Lazarov Spiegler et al., 1996; Rapalino et al., 1998). It remains to be seen whether T-cells too can stimulate regeneration, or whether the positive effects of anti-myelin autoimmune T-cells are restricted to neuroprotection. T-cells do activate macrophages, so it is not unlikely that anti-myelin T-cells will be found to have some effect on the process of CNS regeneration.

Activated T-cells do accumulate at sites of CNS injury (Hirschberg et al., 1998; Moalem et al., 1999b,c), so it is likely that the T-cell neuroprotection is produced locally. It seems, moreover, that the T-cells have to recognize a myelin antigen; autoimmune T-cells specific for the self-antigen hsp60 were not effective, even though hsp60 is expressed in areas of tissue stress (Birk et al., 1999). Our

working hypothesis is that myelin-specific T-cells are effective locally because they recognize their antigen at the site of damage. What could their effect be?

T-cells have been shown to express neurotrophins of various kinds (Gillis et al., 1978; Ehrhard et al., 1993; Santambrogio et al., 1994; Kerschensteiner et al., 1999) and we have found that our anti-MBP T-cells can actually secrete neurotrophins in response to MBP (Moalem et al., 1999a). So it is conceivable that the myelin-recognizing T-cells are activated at the site of injury to secrete neurotrophins which rescue the residual nerve tissue from spreading degeneration.

Anti-MBP T-cells could also contribute to neuroprotection by putting nerve tissue to rest. It is thought that the metabolic hyperactivity of CNS tissue renders the CNS susceptible to poisoning by toxic molecules released from dead and dying nerve cells (Ransom et al., 1990; Liu et al., 1994; Lynch and Dawson, 1994; Sanner et al., 1994; Povlishock and Jenkins, 1995; Agrawal and Fehlings, 1996; Schwab and Bartholdi, 1996). Some years ago, we reported that anti-MBP T-cells in contact with an optic nerve could transiently inhibit nerve conduction in an in vitro system (Yarom et al., 1983). Now, we find that anti-MBP T-cells cause a transient augmentation of paralysis in the injured optic nerve over and above the paralysis caused by the crush injury (Moalem et al., 1999b). Fortunately, this amplified paralysis, noted 1 week after injury, is replace by the markedly increased recovery seen at 2 weeks and later. In other words, rescue from secondary degeneration seems to be preceded by a transient period of paralysis. This suggests that anti-myelin T-cells might aid the injured CNS by a local inhibition of nervous metabolic activity — a kind of localized, physiological ''hypothermia''. Surprisingly, the T-cells specific for the cryptic epitope, 51–70, also caused transient paralysis in the injured optic nerve, although these T-cells were poorly encephalitogenic in the intact rat (Moalem et al., 1999b). Perhaps trauma to myelin exposes cryptic epitopes. In any case, local inhibition of nerve activity might also allow the nerve to respond more efficiently to T-cell neurotrophins. Nerve activity has been shown to down-regulate the expression by nerves of molecules involved in immune signaling, such as major histocompatibility complex molecules (Neumann et al., 1998). Thus, transient arrest of nerve conduction might facilitate beneficial interactions between the nervous and immune systems during the critical period for the immune maintenance of the injured tissue. Obviously, neuroprotection emerges from a combination of mechanisms. But what is immune maintenance?

3. Autoimmune maintenance

Immunologists usually emphasize the role of the immune system in defense of the body against the dangers of infectious agents (Matzinger, 1994). However, it is now common knowledge that cytokines and other immune molecules are key agents in wound healing, angiogenesis, connective tissue growth and regeneration in susceptible organs. The immune system, in short, not only defends the body, it maintains the body (Cohen, 1999; Schwartz et al., 1999).

It has been taught that the adaptive immune system — the T-cells and B cells — does not recognize the self (Burnet, 1959), so that any immune contribution to body maintenance, which requires self-recognition, would have to be performed exclusively by the innate immune system — the macrophages and their kind. However, our observation of CNS maintenance performed by autoimmune T-cells indicates that the adaptive lymphocytes, too, could play a role in immune maintenance (Schwartz et al., 1999). One could imagine that physiological autoimmunity encoded in the immunological homunculus (Cohen, 1992) could well serve maintenance functions, among its other roles (Birk et al., 1999), by supplying factors needed for healing and growth to sites of injury. In any case, our observations of autoimmune maintenance in the CNS should direct attention to the question of autoimmune maintenance in other tissues. Anti-MBP T-cell lines inaugurated the use of such T-cells as probes to study autoimmune disease (Ben Nun et al., 1981), they initiated the field of T-cell vaccination therapy (Ben Nun and Cohen, 1981), and now they serve to raise the question of autoimmune maintenance (Moalem et al., 1999b).

4. Physiology or opportunity?

As with most first observations, the questions are far more numerous than are the answers. Anti-MBP T-cells have been shown to be activated by CNS trauma (Popovich et al., 1996, 1998). If such cells arise physiologically in the body of the injured subject, why do not the endogenous cells suffice for optimal neuroprotection? Why have we to administer anti-MBP T-cell lines to arrest secondary degeneration? It is likely that CNS immune privilege, which reduces immune intervention generally, is responsible for the sub-optimal activation of neuroprotective myelin autoimmunity. The trade off for the exclusion of inflammatory damage to the delicate CNS appears to be deficient immune neuroprotection. Perhaps CNS damage to higher organisms in the wild left insufficient time for survivors to benefit from neuroprotection or regeneration that could have taken place after the injury; evolution simply may not have had any selective return for investing in the long-term repair of CNS damage. The advantage was on the side of blanket privilege. Now that we have evolved intensive care, human culture may be able to find a way to endow the CNS with the capacity for immune maintenance and regeneration found in other, less complicated tissues. In contrast to the stiffness of drug therapy, the resilient T-cell knows when and where it is needed, homes to the site, and produces a dynamically regulated pharmacopoeia of agents.

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