Autoimmunity can benefit self-maintenance

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Autoimmunity is usually considered only as a cause of disease; nevertheless, human T-cell repertoires are filled naturally with autoimmune lymphocytes. Here, we review evidence that autoimmune T cells can help heal damaged tissues, indicating that natural autoimmunity could also be a cause of health.

Maintenance

Maintenance is not as dramatic as defense because wear and tear is not as dramatic as sudden danger. Maintenance is beneficial when and where it is needed, and much else that is needed for body maintenance. Phagocytosis also contributes to maintenance processes. The nervous system joins the immune system in maintenance and repair by diverting blood flows and by supplying trophic factors and mediators when and where they are needed, and by insuring exercise, rest and caution. Neurobiologists should note that, here, processes that are traditionally seen as regeneration and neuroprotection are grouped together under the term maintenance.

Secondary degeneration in the CNS

Secondary degeneration refers to the tendency of damage in the CNS to spread from neurons injured in the primary insult to adjacent neurons that initially were spared. Secondary degeneration arises because injured CNS cells elaborate high levels of molecules that are toxic to neighboring cell bodies and cell processes. Thus, primary CNS injury is compounded by spreading secondary degeneration and what might have been a small primary deficit can become an overwhelming loss. The CNS, by its intense metabolic demands and its numbers reflect the numbers of intact axons that pass and neuroprotection are grouped together under the term maintenance.

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EXPERIMENTAL ANIMAL SYSTEMS HAVE BEEN DEVELOPED TO STUDY SECONDARY DEGENERATION RESULTS FROM GRADED CRASH INJURY TO THE OPTIC NERVE OR FROM CONTUSION OF THE SPINAL CORD. THE DEGREE OF INJURY AND ITS SPREAD CAN THEN BE ASCERTAINED AT VARIOUS TIMES BOTH MORPHOLOGICALLY AND FUNCTIONALLY. THE NUMBERS OF INTACT AXONS CAN BE ESTIMATED BY INJECTING A SUITABLE DYE DISTAL TO THE SITE OF INJURY; THE DYE IS TAKEN UP BY THE INTACT AXONS AND TRANSPORTED IN RETROGRADE FASHION TO THE NERVE CELL BODIES IN THE RETINA OR IN THE RED NUCLEUS IN THE BRAIN, AS THE CASE MAY BE. THE DYE-LABELED NERVE CELL BODIES ARE COUNTED, AND THEIR NUMBERS REFLECT THE NUMBERS OF INTACT AXONS THAT PASS...
through the area of the injury. The degrees of primary injury and secondary degeneration are quantified by counting the residual nerve cells at various times after injury, compared with the numbers of nerve cells in uninjured animals. The relative numbers of intact axons can also be evaluated electrophysiologically by stimulating a compound action potential in the isolated optic nerve, or by observing the recovery of spontaneous locomotion in animals after contusion of the spine.

**Autoimmune neuroprotection**

We used both the optic nerve injury and the spinal cord contusion models to study the effects of T cells on the progression of CNS secondary degeneration. The idea was to partially injure an optic nerve or contuse the spinal cord, inject lines of activated T cells intraperitoneally immediately after the injury, and measure the accumulation of the T cells at the site of injury and the effects of the injected cells on the progression of the CNS lesion. We used T-cell lines of four specificities in our study of optic nerve crush: one line was specific for a foreign antigen (ovalbumin), one line recognized a self-antigen not specific for myelin, an epitope of the 60 kDa heat shock protein (HSP60) known as p277 (Ref. 22) and two different lines were specific for two different epitopes of myelin basic protein (MBP, a myelin self-antigen). One anti-MBP T-cell line recognized the dominant peptide epitope MBP57–74 and was markedly pathogenic, and the other line, which was weakly pathogenic, was raised to a cryptic epitope MBP51–70 in the Lewis rat.

Activated T cells have been reported to penetrate the healthy blood–brain barrier and enter the CNS, but only those T cells that recognize CNS antigens accumulate in the intact CNS (Ref. 24). In contrast to the behavior of T cells in the healthy CNS, we have found that activated T cells tend, irrespective of their antigen-specificity, to accumulate at an axonal site of optic nerve injury. Indeed, T cells that were not specific for myelin could not be detected in the uninjured, contra-lateral optic nerve.

Although labeled T cells of the various specificities reached the site of damage, only the anti-MBP T cells had an effect on the progression of the damage. Two weeks after optic nerve injury, the rats injected with the anti-MBP T cells manifested, both morphologically and physiologically, two- to threefold more surviving neurons than the other groups of rats. In other words, the anti-MBP T cells rescued a significant number of retinal ganglion cells from secondary degeneration. Moreover, we observed that the relatively avirulent anti-cryptic epitope line did as well as the virulent anti-MBP line. Autoimmune virulence, thus, was neither a prerequisite for nor a hindrance to neuroprotection.

These results in the crushed optic nerve led us to investigate the effect of anti-MBP autoimmune recovery of rats from con-tusion injury of the spinal cord. Physiologically, we found that the administration of the autoimmune T cells was associated with significantly greater functional recovery of locomotion in the open field and with greater morphological integrity of the spinal cord tissue detected by histology and magnetic resonance imaging (MRI). Similar experiments in various strains of mice and rats (E. Hauben et al., unpublished) reproduced the results seen in the Lewis rat models.

Moreover, active immunization of rats or mice with MBP in adjuvant also led to enhanced neuroprotection (E. Hauben et al., unpublished); autoimmune neuroprotection was not exclusively a property of particular autoimmune T-cell lines. Thus, we could conclude that virulent populations of autoimmune T cells directed to a myelin antigen may not always be harmful, but can actually arrest the progression of secondary degeneration following traumatic injury to the CNS. Relatively avirulent anti-MBP T cells can also help maintain the CNS.

We are presently investigating the mechanisms by which anti-myelin autoimmune T cells arrest secondary degeneration. Nerve growth factors play a role in nervous system maintenance, and we find that T cells, upon recognizing their antigen, can secrete nerve growth factors into the environment. Such nerve growth factors appear to be critical for autoimmune neuroprotection, as their inhibition seems to significantly inhibit neuroprotection (G. Moseley et al., unpublished). Neuroprotective anti-myelin T cells also seem able to cause a temporary block in nerve conduction at the site of damage, which may lower metabolic needs, thereby reducing the metabolic sensitivity of the remaining nerve fibers. Autoimmune T cells thus provide a number of beneficial services to damaged CNS tissue. On its own behalf, damaged CNS white matter activates an anti-MBP T-cell response.

Obviously, the endogenous anti-MBP T cells were two- to three-fold less effective in maintaining the injured nerves than were the activated anti-MBP T-cell line we administered. The poor showing of the endogenous T cells may be a price paid by the CNS for being an immune privileged site in which the activity of endogenous immune cells is relatively restricted. By diminishing local inflammation, the CNS might escape undesirable inflammatory damage but, as a result of this privilege, it might also suffer from a deficiency of inflammatory maintenance. Biology operates on trade-offs. In any case, the administration of anti-myelin T cells appears to overcome some of the barriers to immune self-maintenance that might have been imposed by immune privilege.

**Autoimmune wound healing**

The CNS, as we have discussed above, is a privileged immune site. In fact, it is conceivable that the benefit produced by the exogenous anti-MBP T-cell lines was highlighted against the background of CNS endogenous immune privilege. Is autoimmune self-maintenance a peculiarity of the CNS, whose neurons are irreplaceable, or can regenerating tissues also enjoy the advantages of autoimmunity?

To test the generality of autoimmune self-maintenance, we have recently begun to examine the effects of transferred autoimmune T cells or of active autoimmunization on the healing of graded wounds in rodent skin. In contrast to the immune isolation of the CNS, the skin is one of the most immunologically accessible tissues in the body. Our experiments are still at a preliminary stage, but it appears that the closure of mouse skin wounds can be significantly accelerated by the intravenous administration of activated auto-immune T cells (E. Montero et al., unpublished). Note that in the case...
of the skin, the effective T-cell lines were not directed to myelin antigens. The range of self-antigens that can be associated with autoimmune enhancement of wound healing is in the process of investigation. Our idea is that each tissue, and perhaps each type of damage, may turn out to require a specific type of autoimmune repair. It is clear, however, that as it may, preliminary data suggest that autoimmune self-maintenance is not limited to the privileged CNS.

Implications

In the beginning, when the immune system was first discovered and for most of the 20th century, it was inconceivable to mainline immunologists that the immune agents of a healthy subject might ever be directed to self-antigens. In the past decade or so, however, sightings of autoimmune T cells and autoantibodies in healthy individuals have become commonplace, and natural autoimmunity can no longer be denied the status of an empirical fact. Indeed, the regularity of autoimmunity has been personified in the theory of the immunological homunculus. The concept of the immunological homunculus was based on the observation that T cells and B cells can mediate type 1 diabetes as well as help fight infection. Autoimmunity to particular members of the homuncular set of self-antigens may mediate particular functions. It remains to be seen how autoimmunity to other homuncular self-antigens may aid self-maintenance.

The healthy immune system, one may argue, could accommodate natural autoimmunity as long as it were harmless, but autoimmune disease would have to be forbidden absolutely. However, another implication of our present finding is that the boundary between pathogenic inflammation and beneficial inflammation may not be absolute. Virulent autoimmune T-cell populations can contribute to CNS maintenance as well as induce EAE. Thus, anti-HSP60 T cells can mediate type 1 diabetes as well as help fight infections. Indeed, macrophages strongly activated by tissue signals can trigger regeneration of the severed spinal cord. What then distinguishes damage? Of the skin, the effective T-cell lines were not directed to myelin antigens. The range of self-antigens that can be associated with autoimmune enhancement of wound healing is in the process of investigation. Our idea is that each tissue, and perhaps each type of damage, may turn out to require a specific type of autoimmune repair. It is clear, however, that as it may, preliminary data suggest that autoimmune self-maintenance is not limited to the privileged CNS.

Consider the idea that limited natural autoimmunity, the homunculus, might serve as the adaptive arm of the immune system that faces inward to aid maintenance. Occasional autoimmune disease may be the homunculus gone awry; the obverse side of the coin. Biology, as we said, operates through trade-offs; biological advantage to particular members of the homuncular set of self-antigens may mediate particular functions. It remains to be seen how autoimmunity to other homuncular self-antigens may aid self-maintenance.

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