VIEWPOINT
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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.

We have recently discovered that populations of T cells that can cause experimental autoimmune encephalomyelitis (EAE) are also capable of protecting the CNS from some of the consequences of axonal injury[1–4]. This finding demonstrates the functional importance of context[5]: autoimmune T cells may cause a disease in one context, yet the same population of cells can help heal the body in another context[4]. Further, natural autoimmunity may have earned its place in the healthy repertoire by serving body maintenance[6].

Defense

To endure the hazards of existence, the individual needs to be defended. Evolution of the species has generated various physiological systems that defend, but two systems bolster innate defense with individual experience: the nervous and the immune. The nervous system keeps us out of trouble by its organs that sense, see, smell and hear, and by its brain that learns, anticipates and plans. The immune system defends us against dangers that are beyond the knowledge of the nervous system: infectious agents, foreign cells and molecules, and abnormal cells arising within our own bodies. Like the nervous system, the individual immune system learns and remembers. There is no argument about the importance of defense; its lack is felt acutely. But defense is not enough. The integrity of the body also demands maintenance[7].

Maintenance

Maintenance is not as dramatic as defense because wear and tear is not as dramatic as sudden danger. Maintenance is not much appreciated unless, that is, you have a wound or a bed-sore that needs healing, blood vessels or nerves that need sprouting, a liver that needs regeneration, worn-out cells that need disposal, or traumatic damage that needs repair. Maintenance, in short, is required to resist the grind of existence. Defense and maintenance share a common goal, but differ in aspect. Taking the self as the point of reference, defense is directed outward – a defense system ejects from the self the dangerous alien. Maintenance is directed inward – a maintenance system examines and repairs the self.

The immune system is an important player in body maintenance, one might argue the major player. Cytokines and other molecules produced by immune system cells regulate wound healing, angiogenesis, connective tissue formation, apoptosis, tissue regeneration and much else that is needed for body maintenance[6,8,9]. Phagocytosis also contributes to maintenance processes[8–11]. The nervous system joins the immune system in maintenance and repair by diverting blood flows and by supplying tropic 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[12].

Maintenance, directed inward to the self, has been associated with macrophages and other agents of the innate immune system. However, until recently, innate immunity was less appreciated and immunology was mostly focused on antigen recognition and adaptive immunity. Adaptive immunity was thought to be directed outward only, to defend the self against foreign dangers. Indeed, it was taught that the healthy antigen receptor repertoire could not look inward, and thus could not recognize the self[13]. If self-recognition is forbidden, there can be no antigen-specific self-maintenance, by definition.

But body maintenance, despite expectations, does seem to involve the receptor repertoire; autoimmune T cells, as we have now observed[1–3], can protect the CNS from the sequela of axonal trauma called secondary degeneration[3,4,14].

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[14–16]. Secondary degeneration arises because injured CNS cells elaborate high levels of molecules that are toxic to neighboring cell bodies and cell processes[17–19]. Thus, a 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 activity, makes life more difficult for itself.

Experimental animal systems have been developed to study secondary degeneration resulting from graded crush injury to the optic nerve[14] or from contusion of the spinal cord[2]. 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

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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[14]. The relative numbers of intact axons can also be evaluated electrophysiologically by stimulating a compound action potential in the isolated optic nerve[1,14,20,21], or by observing the recovery of spontaneous locomotion in animals after contusion of the spine[2,8,9].

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[1–3]. 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 MBP73–84 and was markedly pathogenic, and the other line, which was weakly pathogenic, was raised to a cryptic epitope MBP51–70 in the Lewis rat[23].

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[25]. Indeed, T cells that were not specific for myelin could not be detected in the uninjured, contra-lateral optic nerve[1,25,26].

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 did the other groups of rats[1,27]. In other words, the anti-MBP T cells rescued a significant number of retinal ganglion cells from secondary degeneration[1,3,27]. 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 nor a hindrance to neuroprotection.

These results in the crushed optic nerve led us to investigate the effect of anti-MBP autoimmunity on the recovery of rats from contusion injury of the spinal cord[2]. 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)[2]. Similar experiments in various strains of mice[28] 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[29–31], 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. Moalem *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[1,32]. 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[33].

Obviously, the endogenous anti-MBP T cells were two- to threefold 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[3,34–37]. 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[11]. 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[3]. 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 autoimmune 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. Be 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[13]. 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[38]. Indeed, the regularity of autoimmunity has been personified in the theory of the immunological homunculus[6,39,40]. The concept of the immunological homunculus was based on the observation that T-cell and B-cell autoimmunity, both in health and disease, seems to be focused on a limited number of dominant self-antigens. The global analysis of natural autoantibodies in rodents[41] and in humans[42] confirms that the B-cell autoimmune repertoire recognizes a limited and stereotypic set of self-antigens.

Now, it is an article of evolutionary theory that, in the long run, the advantages of a universally prevalent phenotype must outweigh its disadvantages. This implies that each of the particular self-antigens expressed in the immunological homunculus ought to provide some service in the struggle for existence, and not only produce disease. The findings that anti-MBP T cells can help maintain the integrity of the injured CNS (Refs 1, 2) and that anti-HSP60 autoimmunity can help regulate allograft rejection[43], suggest that natural autoimmunity to MBP and to HSP60 can be advantageous. Indeed, anti-HSP60 autoimmune T cells can provide help for antibody production to T-independent bacterial capsular antigens[44]. Thus, 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 (Refs 1, 2), and anti-HSP60 T cells can mediate type 1 diabetes[22] as well as help fight infection[44]. Indeed, macrophages strongly activated by tissue signals can trigger regeneration of the severed spinal cord[8,9]. What then distinguishes between healthy autoimmune self-maintenance and pernicious autoimmune disease?

In physiological terms, the output of the immune system is not defense against danger or self/nonself discrimination, such terms describe teleological ends. In molecular terms, the output of the immune system, by both its innate and adaptive arms, is inflammation[7]. Consider the idea that immune danger may be contextual and circumstantial; when, where and how long an inflammatory response occurs may be no less important to survival than the kind of response phenotype that is activated. In view of the positive contribution of inflammation to ongoing body maintenance and repair, it seems reasonable that the immune system makes its decisions by integrating multiple signals in an ongoing dialogue with the tissues[45]. It is likely that the tissues themselves provide signals that trigger the type of inflammation they require for self-maintenance and repair. For example, we find that the damaged CNS upregulates its expression of B7-2 molecules (M. Schwartz and I.R. Cohen, unpublished). In any case, a self-limited, local attack of EAE may be a reasonable price for arresting secondary degeneration; angry macrophages at a site of injury may be a tolerable prerequisite for regeneration. A disease in one context may be a boon in another[46] (see Fig. 1).

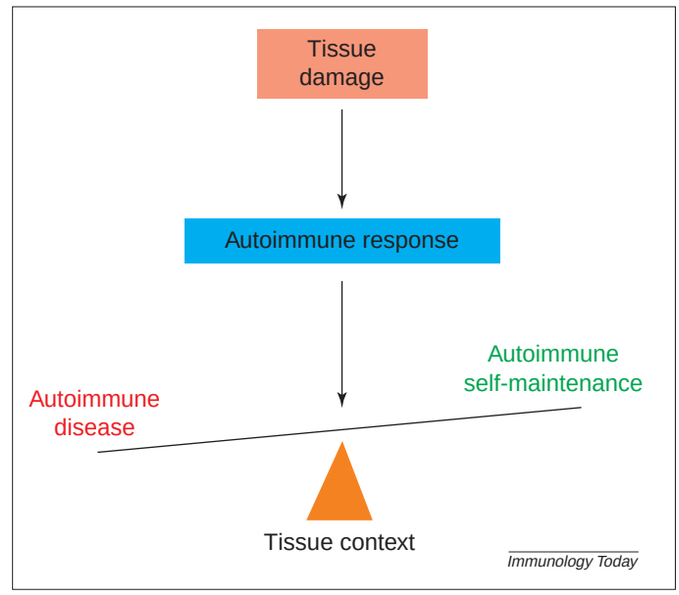

Fig. 1. *Autoimmunity can be destructive or protective depending on the tissue context[46]: the inflammatory outcome can thus be viewed as a balance.*

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 valuable coin[39,40]. Biology, as we said, operates through trade-offs; evolution merely makes do[6]. Be that as it may, the finding of autoimmune neuroprotection suggests that it is worth discovering how to enhance a protective autoimmune response without inducing autoimmune disease[46]. We are now exploring the clinical applicability of autoimmune neuroprotection in spinal cord injury.

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