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Autoimmunity as the body's defense mechanism against the enemy within: Development of therapeutic vaccines for neurodegenerative disorders

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Insults to the central nervous system (CNS), whether of microbial or microbe-free origin, result in tissue damage. Until recently, it was generally believed that only microbe-related damage elicits an adaptive immune response, the purpose of which is to eliminate the offending microorganisms. Recent studies in the author's laboratory suggest, however, that the body exhibits an adaptive immune response to microbe-free injuries as well. The immune response in this case is directed against dominant self-antigens residing in the damaged site, where such an adaptive anti-self immune response reinforces the protective activity of local resident cells by providing them with factors that can augment and regulate their capacity for buffering troublemakers such as destructive self-compounds emerging from the injured neural tissue. Because the specificity of this autoimmune response apparently depends not on the type but on the site of lesion, the response can be boosted by therapeutic vaccination for acute and chronic neurodegenerative conditions irrespective of their primary etiology. The results have far-reaching implications, both for microbial infections and for neurodegenerative diseases of the CNS. *Journal of NeuroVirology* (2002) **8,** 480–485.

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Introduction

Neurodegenerative syndromes are commonly associated with ongoing neuronal losses in the central nervous system (CNS). In all of these disorders, regardless of their location in the CNS, the progressive neuronal loss follows a similar pattern and is perpetuated by similar toxic mediators (Hovda *et al*, 1991). It is interesting to note that destructive components that are common to neurodegenerative diseases, which mediate the toxicity causing secondary degeneration after acute CNS insults, have also been identified in autoimmune diseases that are viewed as myelin disorders, such as multiple sclerosis (Bjartmar and Trapp, 2001; Meyer *et al*, 2001; Olsson *et al*, 2000; Perry and Anthony, 1999). Among these components are excitatory amino acids (such as glutamate), nitric oxide, and free radicals, causing oxidative stress (Greenamyre *et al*, 1999; Hartwick, 2001; Rothstein, 1995a, 1995b). Immune activity is widely thought to have negative effects in all patients with neurodegenerative disorders (Asghar and Pasch, 2000; Burt *et al*, 2000; Choy, 2000; McMurray, 2001; Wimer, 1998), not only in those with definite etiology of autoimmune disease.

Studies in our laboratory have shown that immune cells in general, and autoimmune T cells in particular, play an essential role in protecting the injured CNS from the effects of destructive self-compounds

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(Fisher *et al*, 2001; Hauben *et al*, 2000a; Moalem *et al*, 1999; Schwartz, 2001). In certain strains of rats with partial crush injury of the optic nerve (Yoles and Schwartz, 1998), we found that passive transfer of autoimmune T cells reactive to myelin-related self-antigens confers a neuroprotective effect by reducing secondary degeneration of the damaged neural tissue (Fisher *et al*, 2001; Moalem *et al*, 1999), while at the same time inducing a transient autoimmune syndrome known as experimental autoimmune encephalomyelitis (EAE) (Ben-Nun and Cohen, 1982; Kim *et al*, 1998). Further studies by our group showed that protective autoimmunity is a physiological response to the insult (Yoles *et al*, 2001). The spontaneous ability to manifest a protective autoimmune response was found to vary among individuals, in apparent correlation with their ability to resist the induction (by myelin-associated antigens) of an autoimmune disease (Kipnis *et al*, 2001). We further observed that a T cell–dependent protective mechanism also operates when the CNS insult is of a biochemical rather than a mechanical nature (Kipnis and Yoles, 2001; Schori *et al*, 2001a; Schwartz and Kipnis, 2001). Thus, direct exposure of the eye to glutamate (by intravitreal injection) causes dose-dependent death of the retinal ganglion cells. In mice deprived of mature T cells, however, strain-related differences are wiped out, so that the relatively resistant strains lose their advantage. Interestingly, boosting of the T-cell response by myelin-associated antigens, though beneficial when the insult is inflicted on the myelinated axons, has no effect when the insult is directed to the retinal ganglion cells (Schori *et al*, 2001a, 2001b). These and other findings led us to postulate that protective autoimmunity is the body's mechanism of protection and repair in the case of insults by self-compounds, and that autoimmune disease is an outcome of failure to control this mechanism (Schwartz and Kipnis, 2001).

Taken together, the results described above suggest that the immune system, via a well-regulated autoimmune response to a microbe-free insult in the CNS, can protect against the consequences of the insult. This raises some new questions: (1) What differentiates autoimmunity with a beneficial outcome (protective autoimmunity) from autoimmune disease? (2) What mechanism underlies the protection? (3) Does the protective mechanism apply also to viral infections in the CNS? (4) How can these findings be translated into a therapy?

Results and discussion

Well-controlled autoimmunity versus lack of autoimmunity

Our studies have shown that T cells of the same phenotype and specificity can potentially lead either to neuroprotection or to inflammatory neurodegenerative conditions. A neuroprotection outcome depends on the availability of T-helper 1 (Th1) cells and proper control of the intensity and duration of the autoimmune response, provided that the intensity and duration are well controlled (Kipnis *et al*, 2002b). Thus, whereas protection requires the participation of either dominant or cryptic epitopes for a given self-antigen, destruction is expressed by pathogenic self-epitopes that outweigh the protection. Because regulation controls the fine line between protection and destruction, the question arises: what determines this border?

Our experimental evidence strongly suggests that autoimmunity is controlled by naturally occurring $CD4^+CD25^+$ regulatory T cells. We demonstrated that nude mice show a greater ability to resist consequences of CNS insult if replenished with splenocytes deprived of $CD4^+CD25^+$ regulatory T cells obtained from wild-type mice, as compared to nude mice replenished with a complete splenocyte population obtained from wild-type mice. A more direct effect of $CD4^+CD25^+$ on the ability to resist consequences of CNS insult emerged from the experiments in which wild-type mice injected with $CD4^+CD25^+$ regulatory T cells showed a reduction in ability to resist consequences of CNS insult (Kipnis *et al*, 2000). We proposed that these regulatory T cells represent an evolutionary compromise between the need for autoimmunity with a low threshold for activation and the need to avoid autoimmune disease. It is possible that the regulatory T cells allow differential activation of autoimmune T cells, that is, the ones that are most easily activated are those with a low threshold (Schwartz and Kipnis, 2002a).

In line with this contention is our observation that neonatal immunization with myelin-associated antigens wiped out the ability to resist consequences of CNS insult as an adult (Kipnis *et al*, 2002a). Thus, depriving animals from the ability to mount an autoimmune response diminishes their ability to resist consequences of CNS axonal injury.

Is protective autoimmunity a general phenomenon restricted to nonmicrobial insults?

Our results suggest that the ability to cope with a CNS insult (when local buffering mechanism are inadequate) is reinforced by the innate immune response, which is amplified and controlled by T cells directed against self-antigens residing in the site of the insult (Shaked *et al*, unpublished data) (Butovsky *et al*, 2001). The data indicate that in the recruitment of this supportive autoimmune response and in determining its strength, the type or severity of the insult is less important than the site at which it occurs (Mizrahi *et al*, 2002; Schori *et al*, 2001a; Yoles *et al*, 2001).

We recently observed that retinal ganglion cells subjected to glutamate insult can benefit from

autoimmune T cells that are specifically reactive to antigens residing in the eye. It thus appears that for T cells to mediate a beneficial effect, they should be activated within the site of their activity. This means that they should recognize their antigen-presenting cells at that site (Mizrahi *et al*, 2002).

In view of our results, it seems that the presence of activated microglia or invading macrophages at the sites of CNS tissue damage in acute or chronic disorders cannot be used as an argument either for or against the contribution of such cells to the well-being of the damaged tissue. It is possible that these immune cells are recruited and activated to facilitate the clearance of cell debris and threatening self-compounds from the site, either by stimulating phagocytosis or by activating the resident microglia so as to increase their buffering capacity in a receptor-specific manner (Schwartz and Kipnis, 2002b). This means that different sites might require a different set of antigens. It also means that the same self-antigen will recruit a similarly effective response to that site regardless of whether the damage to the CNS is caused by a "sterile" lesion (Moalem *et al*, 1999) or biochemical insult (Schori *et al*, 2001a). If this is so, it is possible that the same mechanism will be applicable to microbial invasion.

On the basis of these findings, we suggest that the entry of pathogenic microorganisms into the CNS by direct invasion or via a "Trojan horse" (Poluektova *et al*, 2002) will send signals alerting the immune system to take defensive action against the microbes as well as against destructive self-components (such as glutamate, oxygen free radicals, and others) unleashed by the primary virus-induced insult (Schwartz and Kipnis, 2002b).

According to this view, the autoimmune response can be viewed as the individual mechanism's need for amplifying the innate local response to any CNS insult, whether caused by exogenous invading microorganisms, mechanical trauma, or destructive self-compounds evoked by stress originating within the body itself. Autoimmune disease can then be viewed as one extreme situation, where the autoimmune response overshoots and gets out of control. The other extreme is a degenerative disorder, where the autoimmune response is not strong enough for effective protection, and degeneration therefore continues. Thus, inflammation might be seen in both of these pathological conditions, being distinctive in the former and beneficial yet insufficient in the latter, and therefore will require distinct therapeutic handling in each case (Nevo *et al*, unpublished observations).

Therapeutic T cell–based vaccination

To translate the protective response into a therapeutic vaccine, it is necessary to find a way to boost the T-cell response to self-antigens residing at the site of damage while avoiding the development of an autoimmune disease. In seeking a potent antigen that would fulfill the requirement of activating self-reactive T cells without risking healthy tissue, we tested Galatiramer acetate (Cop-1) (Kipnis *et al*, 2000; Schori *et al*, 2001a), a compound that (when administered according to a different regimen) has proved useful as a treatment for patients with the relapsing-remitting form of multiple sclerosis (Sela, 1999a, 1999b).

Our initial assumption was that Cop-1, by cross-reacting with myelin basic protein (MBP) or other components of myelin, might enable Cop-1–specific T cells to recognize the damaged tissue, accumulate at the site of the damage, and undergo activation resulting in neuroprotection (Kipnis *et al*, 2000).

After partial crush injury of the rat optic nerve, myelin epitopes are exposed at the site of injury, and peripheral lymphocytes—regardless of their antigenic specificity—enter the CNS (Owens *et al*, 2001; Schmidt *et al*, 1997). T cells reactive to myelin proteins are activated at the site of injury or in the cervical lymph nodes, where the drainage of CNS antigens probably takes place (Aloisi *et al*, 2000).

Recent studies in our laboratory showed that activation of autoimmune T cells after injury is a prerequisite for neuroprotection, and that such activation can be boosted by immunization with self-antigens (in this case myelin proteins) (Fisher *et al*, 2001; Hauben *et al*, 2000a, 2000b). These findings led us to suggest that upon passive transfer of Cop-1–specific T cells or active immunization with Cop-1, T cells arriving at the site of injury will serve a dual role: First they will trigger proinflammatory activity, and later they will terminate their own activation (Kipnis *et al*, 2000). Examination of this possibility indeed showed that Cop-1–reactive T cells accumulate in the normal (undamaged) optic nerve, where only myelin-specific T cells can accumulate, but that their numbers are smaller than those of the accumulated myelin-specific T cells. These findings pointed to cross-reactivity of Cop-1–activated T cells with myelin proteins *in vivo*. Activated Cop-1–reactive T cells produce neurotrophic factors, but their pattern of neurotrophin expression differs from that of MBP-reactive activated T cells (Kipnis *et al*, 2000). Accordingly, the mechanism we suggested was that Cop-1–reactive T cells, after arriving at the site of the injury, are weakly reactivated by self-antigens residing at the lesion site. Such reactivated T cells were shown to produce cytokines associated with both Th1 (interferon-gamma, INF-γ) and Th2 (interleukin-4, IL-4), indicating that Cop-1–reactive T cells have the potential for self-regulation. We suggest that the reactivated proinflammatory Cop-1 cells in turn activate the resident microglia, as suggested above, facilitating their ability to clear the lesion site of toxic compounds in a receptor-specific manner, as well as to display enhanced phagocytic activity for nonspecific clearance. The activated T cells also produce neurotrophic factors and activate microglia to produce neurotrophic factors (Barouch and Schwartz, 2002). We have preliminary

studies suggesting that exposure of microglial cells to Th1-activated T cells increases the capacity for glutamate uptake by the microglia (Shaked *et al*, unpublished observations). Thus microglial cells can provide dual standby activity as antigen-presenting cells and as cells capable of buffering activity when the site of injury becomes deprived of astrocytes, the major "cleaner" in resting tissue.

Differential modes of Cop-1 administration in patients with multiple sclerosis and with neurodegenerative disorders

We recently found that Cop-1 acts as an antigen that can activate with low affinity a wide range of self-reacting T cells. The questions arise in connection with the optimal therapeutic regimens of Cop-1 for different conditions. In the case of autoimmune disease, where the regulation of autoimmunity is malfunctioning, there is a need to shut off the autoimmune clones. In the case of acute CNS injury or chronic neurodegenerative disorders, on the other hand, there is a need for neuroprotection, initially requiring the participation of active autoimmune clones and subsequently needing tight control to shut off the autoimmune response at the right time.

Reports indicate that multiple sclerosis patients treated with Cop-1 initially show a Th1-type response, which later switches towards a Th2-type response (Farina *et al*, 2001; Neuhaus *et al*, 2001), considered to be a favorable phenotype in such patients. From this stage onward, each application of Cop-1 boosts the Th2-type response and weakens the Th1-type response (Duda *et al*, 2000; Neuhaus *et al*, 2000).

In acute neurodegenerative disorders, the aim of therapy is to boost the local immune response at the lesion site in a well-regulated way. Accordingly, a weak Th1 (effector) response is a welcome phenomenon, essential for stopping the process of damage caused by self-destructive compounds. It can be achieved by Cop-1 vaccination, which allows an induced Th1 (effector) immune response to be accompanied by a regulatory response. In patients with chronic neurodegenerative disorders, the timing and amount of each booster application should incorporate the Th1 phase. During this phase (which is probably very short) the affinity of the Th1 cells for self-epitopes is relatively low, so the development of an autoimmune disease during the Th1 phase window is avoided, whereas the desired activation of phagocytes for clearing of myelin debris is probably achieved.

The mediators of toxicity are common to many neurodegenerative disorders. Thus, regardless of the primary risk factors (many of which are not yet known), in patients with degenerative diseases, the loss of neurons continues even after the risk is diminished. Considerable research attention has therefore been directed to neutralizing the mediators of continuing degeneration, of which glutamate is one of the most prominent. The finding by our group that vaccination with Cop-1 protects neurons from the consequences of direct glutamate insults suggested that this might be a promising therapy for chronic insults in the CNS, including those associated with viral infection.

Concluding remarks

On the basis of a series of experiments carried out in our laboratory, we suggest that the T cell–mediated protective response evoked by a CNS insult is harnessed by the body to assist local innate immune mechanisms to cope with the insult-induced secretion of destructive self-compounds (Schwartz and Kipnis, 2001). This T cell–mediated response needs to be rigorously regulated in order to provide protection without risk of inducing an autoimmune disease. Vaccination with Cop-1 appears to provide a safe way to both regulate and boost the response. Degeneration is a chaotic process, involving the activity of numerous physiological compounds. Some of these compounds (for example glutamate), though normally essential for CNS function, become toxic when (as a result of the insult) their normal concentrations are exceeded. Pharmacological intervention aimed at reducing the toxicity of a particular compound is likely to be accompanied by an undesirable disruption of that compound's normal functioning, and might also interfere with the functioning of other compounds. Protective autoimmunity appears to be the body's own mechanism of coping with conditions of stress, such as those caused by CNS insults of various types. Taken together, the findings of our group and those of others further support our contention that the immune response evoked by CNS trauma is always at least potentially beneficial, but it needs to be properly regulated for the beneficial effect to be expressed. If properly regulated and suitably boosted, protective autoimmunity, such as that supplied by vaccination with Cop-1, is therefore likely to provide a physiological and global therapeutic effect for neurodegenerative disorders, as well as for toxic infiltration or microbial invasion of the CNS.

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