Autoimmunity as a special case of immunity: removing threats from within

Uri Nevo1, Jonathan Kipnis2, Ido Golding3, Iftach Shaked2, Avidan Neumann4, Solange Akselrod1 and Michal Schwartz2

1School of Physics and Astronomy, Tel Aviv University, 69978 Tel Aviv, Israel
2Department of Neurobiology, The Weizmann Institute of Science, 76100 Rehovot, Israel
3Department of Molecular Biology, Princeton University, Princeton, NJ 08544, USA
4Department of Biology, Bar-Ilan University, 52900 Ramat Gan, Israel

The function of the adaptive immune response against exogenous (non-self) agents is to help the innate arm of the immune system (represented by phagocytic cells) to fight and eliminate these agents. We suggest that the body also protects itself against potentially harmful self components using mechanisms similar to those used for fighting and eliminating non-self agents, and that the protective immune activity against self-components competes with the activity of self-destructive compounds. Tolerance to self is thus not a lack of response to self, but the ability to tolerate an active defense response to self without developing an autoimmune disease.

It is widely believed that the principal function of the immune system is to protect the body against foreign pathogens [1–3]. Accordingly, successful operation of the immune system is generally thought to require the inhibition of any immune response against the self. Various theories have been formulated to explain how the body ensures that no anti-self response is evoked, either by accident or as part of a more global immune response [4–13]. Studies in our laboratory have provided strong evidence that an anti-self immune activity is an intentional physiological activity, aimed at protecting the injured CNS from damage associated with self-destructive compounds, even when no exogenous pathogens are involved [14,15].

It has been shown that CNS insults evoke a T-cell-mediated protective response, and that the protection conferred can be transferred by splenocytes to naive animals [16]. The ability to spontaneously produce this protective response is genetically controlled and, at least in part, inversely related to the inherent susceptibility of the individual to the development of an autoimmune disease [17]. Furthermore, a protective response can be induced by passive or active immunization directed against abundant self-compounds at the site of stress [18,19].

In this article, we suggest that autoimmunity should be viewed as a special case of immunity, and that the same cellular players participate in removing the source of a threat in both cases. This view might reconcile the inconclusive observations and conflicting interpretations from several studies regarding the role of the immune response after CNS injury, by suggesting that the controversy could arise from the fact that immune activity, although apparently destructive at an early stage after the insult, is beneficial later on. The concept focuses on T-cell-mediated autoimmunity; no experimental evidence exists with respect to humoral autoimmunity.

A ‘comprehensive immunity’ model of the events that follow tissue damage

After CNS damage caused, for example, by trauma, ischemic events, pathogenic infection, or local necrotic processes, the primary insult triggers a self-perpetuating process of tissue loss [20–24]. This destructive process is initiated by ‘violent’ cellular loss (e.g. necrosis), which leads to metabolic and oxidative stress, ionic imbalance, and excessive levels of physiological compounds that become toxic (e.g. nitric oxide and glutamate), inducing further oxidative stress.

In addition to eliciting self-perpetuating damage in the form of ongoing neuronal degeneration, the process of tissue loss triggers mechanisms that serve as ‘alarm signals’ [10] to the immune system, activating naive lymphocytes to acquire effector functions and to home to the site of damage [25].

Based on our experimental data, it appears that, in the case of pathogen-free insults, the triggered immune response is directed against self-antigen(s) residing at the site of injury [26,27], and facilitates an efficient clearance mechanism that is known to be important after injury [28–32].

We propose that the anti-self immune response also competes with the self-perpetuating destructive activity for the vulnerable tissue, eliminating healthy cells surrounding the lesion site, and thus reducing the availability of additional potentially harmful material. It is therefore possible that an early anti-self response not only allows T cells that home to the lesion site to become activated, but...
also attacks the self. A successful outcome of this immune activation is one in which the anti-self immune reactivity resolves the self-perpetuating tissue death, and then terminates itself rapidly enough to minimize further loss (Fig. 1).

The mechanism we suggest can be viewed in terms of a simple metaphor. Consider a fire burning its way through a forest. The firemen called upon to save the forest clear trees in the vicinity of the fire, including both the burning trees and trees that have not yet been burned. Their efforts might result in extinction of the fire or the loss of the forest, depending on the magnitude of the fire and their ability to control it (Fig. 2).

The predicted outcome of the comprehensive immunity can be summarized as follows:

1. The immune response to a CNS injury, if it occurs early enough, reduces the self-perpetuating degeneration and simultaneously exacts an early price that is outweighed by the overall benefit in the long term. This price is not merely a negative by-product, but part of the mechanism.

2. If the immune response is evoked too late or is too weak to reduce the self-perpetuating degeneration, continuous and ongoing loss of tissue will occur.

3. As the immune response continues, irrespective of its intensity, the cost of the tissue loss begins to outweigh the neuroprotective benefit.

These predictions lead us to suggest that, in the context of the CNS, autoimmune disease and neurodegenerative conditions might be two extreme manifestations of the same risk factor, depending on which is dominant, the firemen or the fire, and whether the situation can be adequately controlled.
Possible manifestations of autoimmunity

Neuroprotection at a cost of minimal loss

We suggest that if the immune response is highly sensitive to increasing levels of the alarm signal, and if the anti-self response increases in strength once initiated, the resulting tissue loss will be minimal. A strong autoimmune response is one that successfully competes with the self-perpetuating destructive activity. If such an immune response is activated early enough by the alarm signal, it will cause minimal loss of healthy tissue, in addition to that produced by the primary insult. Hence, by reducing the amount of vulnerable tissue at the site of injury to below the threshold for self-perpetuating spread of damage, the tissue loss induced by the immune response prevents the damage from progressing.

For the autoimmune response to be protective, it must be well regulated, not only with regard to onset but also with regard to shut-off. We believe that the autoimmune process is self-limiting: as soon as the threat is removed, the immune response resolves itself. However, this does not rule out the involvement of common regulatory elements, such as naturally occurring CD4⁺ CD25⁺ regulatory T cells, in the self-limiting process [26,33].

Our view of comprehensive immunity predicts a brief early phase in which the immune cells contribute to some additional loss beyond the original insult-induced damage. This loss is an essential part of the process, required for the overall benefit rather than being an inevitable negative by-product of it. Our theory can explain the apparently conflicting experimental observations (with resulting erroneous conclusions) on the role of the immune response in CNS insults, assessed at an early post-injury stage before ‘steady state’ is reached. It can also explain why the use of immunosuppressive drugs, such as methylprednisolone, in patients with spinal cord injury protects the tissue from secondary loss only for a brief time after the insult [34–36]. In addition, it can explain why transgenic mice deprived of a pro-inflammatory cytokine (such as tumor necrosis factor) after brain injury show better recovery than wild-type animals soon after the insult, but worse recovery once a steady state is reached [37].

In cases where the immune response is evoked at a relatively late stage following injury, it might still be sufficient to halt the progression of damage, although by the time the damage is arrested the tissue will have experienced a more severe loss (caused both by the self-perpetuating damage and by the immune-induced loss required to halt it). This idea is supported by our finding that the passive transfer of autoimmune T cells to rats with restricted ability to produce an endogenous protective immunity after CNS insult causes a reduction in tissue loss, provided that the transfer is done within the therapeutic window [19,38,39]; delayed transfer does not confer any benefit [38].

The ability to harness autoimmunity for a beneficial outcome within the therapeutic window is genetically controlled [17], but these genetic aspects are not within the scope of our model. In this regard, it is important to note that not all individuals are capable of spontaneously producing a beneficial autoimmune response after injury. The difference between individuals was found to be related to the class-II major histocompatibility complex. In fact, paradoxically, animals that were relatively resistant to autoimmune disease were the most capable of harnessing a spontaneous T-cell-dependent protective response; differences were wiped out when the animals were deprived of mature T cells.

An immune response that is not strong enough: continuing degeneration

The comprehensive immunity model predicts that when the intensity of the evoked immune response is weaker than required (or when the initial loss is severe), the immune-dependent tissue clearance will fail to create conditions below the threshold needed to sustain self-perpetuating damage. The result will be ongoing damage propagation from both self-perpetuation and immune-induced death. The overall loss will be less than would have been sustained in the absence of the immune response, but its propagation will not be completely stopped. This scenario might explain the commonly encountered problem of massive secondary degeneration following severe CNS insult, even in animals that are inherently capable of manifesting protective autoimmunity [17,18]. It also fits with the experimental observation that even strains that are capable of spontaneously producing a protective autoimmunity are amenable to boosting of this response following severe optic nerve injury or spinal cord contusion [17,18]. Furthermore, in rats and mice devoid of mature T cells, neuronal survival after CNS injury is significantly lower than that seen in age- and strain-matched animals with normal immune systems [16,17,40,41].

Our model suggests that as long as the insult is modest, the spontaneous protective autoimmune response is an adequate response mechanism. In such a case, the individual might not even be aware of either the damage or the protective measures taken. In agreement with this notion, we have observed that apparently non-toxic levels of glutamate can cause neuronal loss in animals that are deprived of mature T cells [40,42].

However, after severe trauma or stroke, when the demand for protective autoimmunity exceeds the capacity of the immune system to supply it, a boosting mechanism is required. Peptide derived from any abundant protein at the site of stress can, in principle, boost protective autoimmunity.

Our data suggest that immunization with weak self-reacting peptides, such as cryptic epitopes derived from abundant proteins, or non-pathogenic peptides derived from pathogenic epitopes that have lost their pathogenicity by being altered, can induce protective autoimmunity without the risk of inducing the strong autoimmunity that leads to autoimmune disease [18,19,27,43].

Immunity that lasts too long; lack of control and possibly autoimmune disease development

Our model of comprehensive autoimmunity predicts that when the intensity of the immune response is sufficiently high to compete with the self-perpetuating destructive activity, but is maintained for too long, the net effect will be an increased tissue loss. The damage caused by the
immune system will add to (and might even replace) the original self-perpetuating damage.

Excessive tissue loss is also predicted when the intensity of the immune response is adequate but is shut off before the threat is completely eliminated. In this case, the self-perpetuating tissue loss is significantly reduced but not completely stopped, and resumes as soon as the immune-induced damage resolves itself. As a result, damage increases again, followed by a resumption of the autoimmune response and possibly a continuing cycle of self-perpetuating death — response — transient shut-off — resumed self-perpetuating death. Experimentally and clinically, this scenario might correspond to a multiphasic loss of tissue and an oscillatory pattern of the immune response that is much like the relapsing–remitting pattern seen in patients with multiple sclerosis [44,45]. It might also explain how an autoimmune disease can be triggered following a severe CNS insult [46].

This scenario highlights a problem with the therapeutic measures commonly used to suppress inflammatory and autoimmune responses: the suppression of the autoimmune response effectively causes its premature shut-off, initiating neuronal loss by mechanisms other than autoimmunity, producing the relapsing–remitting pattern and thus exacerbating tissue loss.

It is important to note that all cases of CNS injury lead to local inflammation [47,48] but not necessarily to autoimmune disease; the autoimmune response evoked by the insult even in susceptible strains is insufficient to cause autoimmune disease. However, when these autoimmune cells are isolated, exposed \textit{ex vivo} and re-introduced to syngeneic naive animals, they can cause autoimmune disease [49].

\textbf{Where does ‘self’ become a target?}

So far, we have only addressed the temporal regulation of the autoimmune response. However, this leaves the question of how self-tissue that should be eliminated is differentiated from self that should not. According to our hypothesis, the differentiation is defined by the stress signal; stress-free self-tissue will not be eliminated. In a focal insult, the role of the homing T cells (effectors and regulators) is to demarcate the site of the lesion [47], thereby reducing the interaction between healthy tissue and the source of the threat. Hence, we believe that multifocal degeneration is a reflection of multifocal primary insults. As a corollary, an apparent spread of autoimmune disease can be caused by malfunctioning autoimmunity following multisite primary insults (e.g., viral infection).

According to our model, the role of the autoimmune T cells, at least in part, is to remove some healthy tissue to allow the rest to be spared. This can be achieved if the effector autoimmune cells are either CD4+ or CD8+ T cells. If the effector autoimmune cells are CD4+ (Th1) cells (as our results have suggested [50]) then, upon encountering their relevant self-antigens at the site of the lesion, they might become activated and release cytokines that induce innate immunity by orchestrating resident microglial activity (I. Shaked \textit{et al.}, unpublished). Hence, the adaptive immune response provides a means of amplifying the innate response, and the clearance process itself is carried out by the innate system. The activated microglia, in addition to their role as buffering cells, might facilitate the rapid removal of healthy cells at the perimeter of the lesion site, where the ‘competition’ between degeneration induced by destructive self-compounds and tissue clearance resulting from the immune-induced response should take place.

Of course, the vast majority of infiltrating T cells are not specific to self, even though only the anti-self T cells are relevant. Indeed, no effect was seen when memory T cells specific to ovalbumin were transferred to animals subjected to CNS insult [18,19,38].

\textbf{Discussion}

In the above we suggested that autoimmunity is a special case of immunity: a defense mechanism that has similar goals, players and operational methods to those of immunity in general. This proposed view of comprehensive immunity is almost antithetical to the common view of autoimmunity, which suggests that an anti-self response is an unwanted event. Since protective autoimmunity was first described [19], attempts have been made to explain how a mechanism with obviously destructive effects can be beneficial, and why the beneficial effect has not been observed. In the past, we have proposed that harnessed autoimmunity helps local innate immune cells (microglia and invading macrophages) to remove from the site of injury cell debris and self-compounds that exceed their physiological levels. In addition, we have demonstrated that the autoimmune T cells, either directly or indirectly, serve as a means of providing neurotrophic factors to the damaged nerves [51,52].

Here we present an alternative or additional view, in which the response to self is needed to arrest the spread of damage after CNS injury. We suggest that three different end results — autoimmunity with beneficial outcome, neurodegeneration as a result of inefficient autoimmunity, and true autoimmune disease — are manifestations of the same basic immune response to the self (Fig. 3). This notion is strongly supported by the finding that a protective autoimmune response can be stimulated by the same antigens that in another context cause an autoimmune disease [38]. Furthermore, the amounts of autoimmune T cells or antibodies present in patients suffering from autoimmune diseases are similar to those found in healthy subjects [53,54]. Our findings also imply that histological examination might reveal the presence and activity of reactive immune components (either beneficial or harmful) at all sites of CNS insult. These components should not be mistaken for, and defined as, the exclusive cause of the ongoing tissue loss. It is only in the case of harmful autoimmunity that the autoimmune response itself is a cause of unwanted tissue loss. This scenario, if it exists in a clinical or experimental situation, is a true autoimmune disease.

Our model includes no assumptions about the nature of the self-derived insult or the nature of the damaged tissue. Hence, it might be valid for any type of insult in which self-compounds constitute a threat to a tissue, and in which an immune response against potentially destructive antigens provides an effective way of eliminating the threat (as in
the case of damage induced by external pathogens). Although the theory of comprehensive immunity is based on results obtained in the study of CNS injury, its predictions are applicable to scenarios of post-injury degeneration in other tissues [27].

The question then arises as to how this concept accommodates the notion of tolerance to self. If we assume that the immune response is able to minimize tissue destruction, then according to our concept, a state of tolerance to self will be an autoimmune mechanism that an individual can tolerate without developing an autoimmune disease. According to this view, an autoimmune response that is well regulated (i.e., occurs immediately after an insult, and is of short duration and of suitable intensity) will resolve the destructive process rapidly and with a minimum loss of tissue. This mechanism would be a suitable means of preventing tissue loss caused by imperceptible mini-traumas on a daily basis, and might therefore be the true way in which the body facilitates tolerance to self: through activity rather than by nonresponsiveness.

This suggested manifestation of self-tolerance as an anti-self response of short duration could explain why the protective side of autoimmunity has been ignored for so long: the response resolves itself too rapidly for us to notice it. Hence, observations of the protective autoimmunity that follows an acute insult [16–19] serve as a magnifying glass through which the nature of autoimmunity is revealed.

We postulate a direct connection between autoimmune disease, protective autoimmunity and tolerance, and degenerative disorders: they are the respective outcomes when the mechanism operates too strongly, properly and insufficiently. According to our view, it is possible that at least some of the known autoimmune diseases have a protective ‘counterpart’ manifestation that operates via the same disease-causing immune effector cells in healthy individuals, either systemically or in the affected organ [55].

Our results call for reassessment of the use of non-specific immunosuppressive therapy, and argue in favor of immunomodulatory therapies [15,38,42,56] for neurodegenerative diseases (such as multiple sclerosis and Alzheimer’s disease), degenerative disorders, diseases characterized by recurrent inflammation, and any other disease that can be exacerbated by non-pathogenic secondary degeneration (e.g., myocardial infarcts, stroke, glaucoma, optic myelopathy, traumas and graft rejection). It is possible that, in many of these cases, our long-standing declaration of war on the autoimmune response is actually a fight against the windmills that our minds have turned into giants.

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