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Visions & Reflections

Self and non-self discrimination is needed for the existence rather than deletion of autoimmunity: the role of regulatory T cells in protective autoimmunity

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Abstract. Autoimmune T cells have been viewed for decades as an outcome of immune system malfunction, and specifically as a failure to distinguish between components of self and non-self. The need for discrimination between self and non-self as a way to avoid autoimmunity has been repeatedly debated over the years. Recent studies suggest that autoimmunity, at least in the nervous system, is the body's defense mechanism against deviations from the normal. The ability to harness neuroprotective autoimmunity upon need is evidently allowed by naturally occurring CD4+CD25+ regulatory T cells, which are themselves controlled by brain-derived compounds. These findings challenge widely accepted concepts of the need for discrimination between self and non-self, as they suggest that while such discrimination is indeed required, it is needed not as a way to avoid an anti-self response but to ensure its proper regulation. Whereas a response to non-self can be self-limited by a decreased presence of the relevant antigen, the response to self needs a mechanism for strict control, such as that provided by the naturally occurring regulatory T cells.

Key words. Protective autoimmunity; neurodegeneration; autoimmune diseases; $CD4^+$ $CD25^+$ regulatory T cells; CNS injuries.

'Survival of the fittest' summarizes the essence of Darwinian evolutionary theory. In line with this theory and the pioneering theory of Metchnikoff in the 1890s [1, 2], followed by the 'clonal expansion' theory of Burnet in the 1950s [3–5], it was believed that discrimination of self from non-self, thymic education of T cells and deletion of autoimmune T cells in the thymus are the central features of immunology. Self-tolerance, defined as a state of non-responsiveness to self, was therefore viewed as the optimal condition and was assumed to enable the fittest to survive [6]. Studies carried out in rodent models of central nervous system (CNS) insults suggested a new concept according to which that autoimmunity is the body's defense mechanism against any self-derived threat to the tissue [7] and that only when the autoimmune response is poorly controlled will an autoimmune disease result. We therefore argue that defining tolerance to self in terms of non-responsiveness is incompatible with survival of the fittest. A more appropriate definition of tolerance to self would be the ability to tolerate an anti-self response without developing an autoimmune disease [8]. We suggest that just as the immune system fights off external pathogens, the autoimmune system fights off threats originating within the body itself (such as cancer, neurodegenerative conditions, tissue injuries), and also serves as a complementary defense mechanism against damage caused by external pathogens. Naturally occurring regulatory T cells (CD4+CD25+) serve as a physiological safety valve that can be modulated to maintain a fine balance between need and risk [8–10].

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Protective autoimmunity

The adaptive immune response has generally been considered as an immune activity evoked to enable the organism to cope with stressful conditions caused by pathogens. It was suggested that an adaptive immune response would be evoked unless the pathogen was recognized as self [11]. Opinions differ as to the mechanisms by which self becomes invisible to the immune system (for example by clonal deletion, anergy or tolerance) [12–20]. Some authors have proposed that autoimmunity, once established, might be harmless or even useful [21–24], but none has described a situation in which the body calls for help from an anti-self response.

Studies carried out by our research group have demonstrated that the passive transfer of T cells directed against self-antigens residing in a site of CNS damage reduces the posttraumatic loss of neurons and functional defects [25, 26]. In further studies we addressed the question of whether the observed beneficial effect of the autoimmune T cells represents a physiological response [27], and if so, what distinguishes between 'good' and 'bad' autoimmunity [28], and what determines response specificity [9]. The results provided persuasive evidence that autoimmunity is a defense mechanism which is spontaneously recruited under conditions that threaten the CNS, and that the recruited T cells are directed against self-antigens that reside in the threatened site [9]. Thus, specificity of the response is determined not by the type of threat but by its location, meaning that insults of different types (mechanical, ischemic, biochemical), if they occur at the same site, will recruit help from T cells of the same specificity [29]. Whether the effect of the autoimmune T cell response will be beneficial or harmful appears to depend, moreover, on the timing of its onset and shutoff [30]. A delayed or exaggerated response might not only lead to a lack of benefit but even result in an autoimmune disease. On the basis of these findings, we suggested that the anti-self immune activity evoked in response to insults in the CNS is a purposeful physiological event [27].

Naturally occurring CD4+CD25+ regulatory T cells: a physiological safety valve

Naturally occurring CD4+CD25+ regulatory T cells constitute a subpopulation of CD4+ T cells which exists in naive animals, and to which researchers have attributed a role in warding off autoimmune diseases by keeping circulating autoimmune T cells in a state of tolerance [31–34]. To learn more about how the autoimmune T cells (effector T cells) exert a beneficial effect after CNS injury, we searched for a mechanism that can control the onset and shutoff of autoimmunity and is amenable to regulation according to need. We found that the naturally occurring CD4+CD25+ T cells are the cells that regulate autoimmunity, and are themselves amenable to regulation by brain-derived compounds [10]. Mice depleted of these regulatory T cells were found to cope more successfully with posttraumatic neuronal survival than normal mice [9] and to reject tumors more efficiently [35]. In some (but not all strains) of mice, depletion of this T cell subpopulation increases susceptibility to autoimmune diseases [36] and boosts graft rejection [37].

The mechanism underlying protective autoimmunity

There are many different subpopulations of CD4+ T cells, each responsible for a certain type of immune response. Th1 cells, for example, reinforce innate immunity and activate CD8+ T cells, whereas Th2 cells recruit and activate B cells. Studies have shown that the autoimmune CD4+ T cells (effector T cells) locally boost and control resident microglia and infiltrating blood-borne monocytes, helping them to acquire an activity that allows them to fight off degenerative conditions requiring removal of dead cells and cell debris, as well as to buffer toxic compounds without producing inflammation-associated compounds such tumor-necrosis factor (TNF)-α, nitric oxide (NO), or cyclooxygenase (COX)-2 [38–41]. Thus, according to our results, the role of CD4+ T cells directed against self-antigens (helper T cells, Th) is to activate the innate response, enabling it to recognize the threat to the tissue pathogen that it must destroy, but as a toxic substance that it must neutralize or buffer. In addition, the autoimmune T cells, upon encountering their specific antigens presented by antigen-presenting cells at the lesion site, can produce protective compounds such as growth factors and neurotrophins [42–44]. All of these tasks can be accomplished by a well-controlled response of helper T cells. These helper T cells, in order to perform their function, need to be locally activated by their specific antigens residing in the site of stress. Thus, antigenic specificity apparently dictates the homing of T cells to the site at which their local activation can occur. In line with this notion are our findings that T cells having the same antigenic specificity are protective against different types of threatening stimuli occurring at the same site, or against different threatening stimuli at different sites occupied by the same immunodominant self-proteins. As a corollary, if the same threatening stimulus is manifested at different sites that do not share common dominant self-antigens, those sites will not benefit from the same antigen-specific T cells [45].

Studies from several laboratories have shown that T cells patrol the healthy CNS, but do not accumulate there [46]. Our data suggest that in the event of an acute injury or chronic neurodegenerative conditions, T cells are recruited by and accumulate in the CNS [47, 48], where they

might rescue neurons from degeneration if the damage caused by the toxic biochemical environment is not yet irreversible; moreover, the recruited T cells will prevent further deterioration. It is also possible that this autoimmune protective mechanism also operates when the threat to the tissue comes from microbial infiltration. In such a case the individual might benefit from an anti-self response without even being aware of the threat, unless the harnessed autoimmunity gets out of control, in which case its effect is no longer beneficial but destructive, and might result in an autoimmune disease [49, 50]. This might be the situation in individuals who are predisposed to autoimmune disease development [28]. According to this view, and in line with our observations, the pathogenic self-proteins that have been implicated in autoimmune diseases are the very proteins against which a well-controlled T cell response is protective. This might help explain why autoimmune diseases are often attributed to viral infections in the brain. It might also explain the relatively low clinical prevalence of autoimmune diseases and their occurrence mainly in young adults rather than in the elderly population, whereas neurodegenerative diseases and cancer are common and significantly more prevalent in the elderly, in whom the immune system is deteriorating [51].

Boosting of protective autoimmunity by T-cell-based vaccination

Elimination of regulatory T cells or downregulation of their activity can be viewed as a means of boosting a physiological protective autoimmunity [8, 10]. In addition, it should be possible to boost the autoimmune T cell population, which is needed to fight off neurotoxic self-agents, by immunization with a non-pathogenic agonist of the relevant self-antigens, or alternatively by weakening the mechanism that normally keeps autoimmunity suppressed [52]. In seeking a suitable agonist we considered copolymer-1 (Cop-1), a synthetic oligopeptide that was originally designed to mimic the binding site of a dominant epitope of myelin basic protein to T cell receptors, and was serendipitously found, in experiments with rodents, to induce T cells that prevent the development of experimental autoimmune encephalomyelitis [53–55]. Cop-1 is now an approved drug for the treatment of multiple sclerosis [56]. It was used in our laboratory to vaccinate rats or mice subjected to different types of acute or chronic CNS injury, and was found by others as well as by us to act as an agonist of a wide variety of self-antigens [57–59]. Significantly more neurons survived in the vaccinated rodents than in similarly injured controls [60]. A beneficial effect of the vaccination was also obtained in rodent models of abnormal behavior in cases of mental stress or cognitive impairment, substantiating the contention that T cells are needed to assist the innate resident immune cells safeguard the physical, mental and cognitive activities controlled by the brain [61]. Deviations from normal activity, due either to peripheral immune deficiency or to local transmitter imbalance or brain damage, require systemic intervention by boosting of T cells [61]. Thus, T-cell-based vaccination might be viewed as a means of recharging the immune system to meet the needs imposed by age and other risk factors [59].

Darwinism and autoimmunity

In the early 1990s it became evident that there is little difference, if any, between the T cell repertoires of healthy individuals and of patients suffering from autoimmune diseases [62]. At around the same time it was suggested that the sole function of a group of suppressor T cells newly identified as CD4+CD25+ was to inhibit the anti-self aggression of any autoimmune T cells that (presumably owing to an evolutionary mistake) had left the thymus and taken up residence in the periphery [31, 32]. It is contrary to Darwinian theory, however, to propose that two cell populations exist in the same organism for the sole purpose of inhibiting each other's activity. Survival of the fittest implies that unwanted features, especially if harmful, will disappear, while beneficial features will be transferred to future generations [63–65]. Thus, since all humans possess a similar repertoire of autoimmune cells [66, 67], Darwinian theory would presuppose that these cells have a physiological function.

Theoretically, complete elimination of autoimmune T cells would be the best way to prevent autoimmune disease development, whereas uninhibited autoimmunity would be the best way to counteract neurodegenerative disorders and cancer. A Darwinian resolution of these opposing immunological scenarios might have led, as a compromise between risk and benefit, to the concomitant presence of autoimmune T cells and the regulatory T cells that normally suppress them [8]. Based on present knowledge of the role of autoimmunity in the devastating conditions of cancer [35, 68] and neurodegeneration [9], it seems unlikely that even the most ardent disciple of Burnet would suggest that complete deletion of autoimmunity favors survival of the fittest. Hence our belief that CD4+CD25+ regulatory T cells do not exist in a permanently suppressive state that keeps autoimmune T cells unresponsive to self-antigens, but are amenable to modulation by physiological signals that weaken or strengthen their suppressive activity according to need. This hypothesis is in line with our suggestion that tolerance to self be redefined as the ability to tolerate an anti-self response without sustaining the risk of autoimmune disease.

We recently showed that activity of regulatory T cells can be controlled by a brain-derived neurotransmitter, which

we identified as belonging to a family of brain-derived compounds that are released in situations of stress and can control the weakening or the strengthening of the regulatory T cells [10]. Discovery of such a family of compounds opens the way to a better understanding of how the brain controls and is controlled by the immune system. It might also allow us to learn how the brain contains neurotoxicity of endogenous origin. Moreover, these findings suggest that there is a need to distinguish between self and non-self, not as a way to avoid an anti-self response but to ensure its proper regulation. Whereas a response to non-self can be self-limited by a decreased presence of the relevant antigen, the response to self cannot afford the luxury of self-limitation and needs to be limited instead by the naturally occurring regulatory T cells.

Many of the questions raised by the revelations of our study have still to be addressed. It remains to be determined, for example, whether the basic principles governing protective autoimmunity in CNS are applicable to other tissues. Once the implications of our findings are fully explored and understood, we can anticipate the introduction of novel approaches to the treatment of chronic and acute disorders in the CNS.

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