Neuroprotective autoimmunity: Reappraising current therapeutic approach and future perspectives

REVIEW

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ABSTRACT

The immune system plays an essential role in the protection, repair, and healing of most tissues, although the central nervous system (CNS) does not have a classical exchange with the immune system. Preservating the integrity of the CNS is a complex and harmonizing act in which the immune system is involved. Although the immune response against CNS antigens has been considered deleterious, there are indications that the failure of the CNS to achieve a functional renewal after an injury is a consequence of an ineffective relation between the damaged tissue and the immune system. A disastrous effect of an injury to the CNS is that the primary insult triggers a self-destructive process of contiguous neurons, which were undamaged by the initial injury. The immune system recognizes the injury-associated-self compound as potentially damaging. Accordingly it elicits a protective anti-self response mediated by T cells that are specific to self-antigens. Thus, autoimmunity in the CNS may not always be detrimental, but could, under certain conditions, have a physiological role in protecting the damaged tissue. Beneficial autoimmunity is functionally discernible from autoimmune diseases and may even function as a protective mechanism. The immune system can be activated to cope with tissue damage, without the risk of autoimmune disease induction, rather than dealing exclusively with the danger associated with pathogens. A comprehensive understanding of the protective autoimmunity process will be instrumental in the generation of novel therapeutic approaches and for alternative therapeutic tools that will certainly meet vacant medical niches.

Keywords: neuroprotective autoimmunity, beneficial autoimmunity, CNS injury, neuroprotection

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RESUMEN

Autoinmunidad neuroprotectiva: Re-análisis de las aproximaciones terapéuticas actuales y de las perspectivas futuras. El sistema inmune (SI) tiene una función importante en la protección y cicatrización de la mayoría de los tejidos. Aunque el sistema nervioso central (SNC) ha sido considerado como un sitio inmunológicamente privilegiado porque en el no se evidencia una relación clásica con el sistema inmune, la preservación de su integridad requiere la participación del mismo. La respuesta inmune dirigida contra los tejidos del SNC ha sido considerada deletérea, sin embargo numerosas evidencias indican que el fallo del sistema nervioso en lograr una recuperación funcional después de una lesión, se debe a una relación torpida entre el tejido dañado y el sistema inmune. Las lesiones primarias en el SNC generan un proceso de degeneración que afecta a neuronas no involucradas en el insulto primario. El sistema inmune reconoce moléculas derivadas del daño y en consecuencia activa una respuesta protectora mediada por células T, antígeno específica. La respuesta autoinmune en el SNC no solo implica una reacción perjudicial, sino que bajo determinadas circunstancias es una respuesta fisiológica dirigida a proteger el tejido dañado. La autoinmunidad fisiológica es funcionalmente discernible de las enfermedades autoinmunes y funciona como un mecanismo de protección por ser auto-limitada. El sistema inmune no solo se activa ante la invasión de microorganismos patógenos, sino que puede ser activado para ayudar a reparar el tejido dañado, sin el riesgo de inducir autoinmunidad patológica que por naturaleza se amplifica y perpetúa. Una correcta interpretación de los procesos biológicos asociados a autoinmunidad neuroprotectiva o fisiológica, contribuiría a la generación de aproximaciones y herramientas terapéuticas novedosas en el área de la neuroprotección y neurorestauración, donde lamentablemente existe un enorme vacío terapéutico.

Palabras clave: autoinmunidad fisiológica, autoinmunidad neuroprotectiva, neuroprotección, neuroregeneración

*I*ntroduction

Autoimmunity has been currently defined as a direct destructive attack of the immune system against body tissues. However, the observations of a high proportion of autoimmune T cells found in healthy individuals and the fact that there is no correlation between disease severity and the number of autoimmune T cells [1-3] have demonstrated the inconsistency of this definition.

Protective autoimmunity is a new concept in the context of the Central Nervous System (CNS) repair, it is also a physiological response elicited by an alarming situation on the CNS. The response is beneficial but, if its operation is impaired, it can lead to an autoimmune disease. According to this view "Tolerance to Self" is considered, not as a state of non-responsiveness but,

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rather, as an ability to tolerate an autoimmune response to self-antigens without developing an autoimmune disease [4]. Consequently, autoimmune diseases may be viewed as a by-product of the malfunctioning of a physiological autoimmune response [5].

The finding that an autoimmune response can be beneficial implies that natural autoimmune T cells may have undergone positive selection at some stage in the ontogeny, as proposed by the theory of the "immunological homunculus" formulated by Irun Cohen [6]. Cohen states that these cells are not just a failure resulting from the escape of a negative T cell selection when identifying self-antigens; but rather, in healthy individuals the existence of autoimmune T cells has a biological significance in a "stand by" status, or promptness for protective action when required. Based on these studies, for neuroprotection the immune system must be instructed to drive inflammation as an internal repair mechanism, in an attempt to halt damage spreading.

Cellular mechanism of autoimmune-cell-mediated neuroprotection

Neurotrophins are a protein family that includes the Nerve Growth Factor (NGF), Brain-derived Nerve Growth Factor (BDNF), Neurotrophin 3 (NT 3) and Neurotrophin 4/5 (NT 4/5) [7]. Although they have been exhaustively characterized in terms of neural development, solid evidence demonstrates that neurotrophins also act on injured and degenerative nerve cells, indicating that they have a role in the response of neurons to traumatic or degenerative processes [8]. The Leukemia Inhibitory Factor (LIF), is a neuropoietic cytokine that is supplied by both resident CNS cells and infiltrating immune cells. It may also contribute to the neuroprotective effects of autoreactive T cells [9-11].

Additionally it has been demonstrated that some neurotrophins are produced and act in the immune system, with autocrine and paracrine mechanisms, and they therefore sustain a bidirectional dialog between the nervous system and the immune system [12].

The neuroprotective effect of autoimmune T cells is mediated by the release of neurotrophic factors [13]. Moreover other immune cells such as B-cells and macrophages also produce BDNF [14].

T cells upon activation, regardless of their antigenic specificity, produce neurotrophins, [15, 16]. Nerve growth factors play an important role in growth, differentiation, survival and regeneration of neurons after CNS damage [16-19], and they have an immunomodulatory effect on immune response and inflammation [20-22]. The secretion of neurotrophins by this T cells is antigen dependent [16, 23].

Another favorable effect of the accumulated autoimmune T cells, once activated, is the modulation of the local glial response to harmful conditions [24, 25], supporting the innate immune system in effectively clearing the tissue of dead cells and debris [16].

Unfortunately, it appears that neurotrophins secreted by immune cells under physiological conditions are not enough to avoid damage, and it is essential to find therapeutical approaches to develop the homing properties of the immune cells for targeting neurotrophins into the CNS.

Neuroprotective autoimmunity is determined by a genetically encoded autoimmune response

Neuroprotective autoimmunity is a rigorously regulated mechanism of tissue repair, which leads to an autoimmune disease only when the regulatory mechanisms are malfunctioning or absent [26]. There is a relation between the rate of neuronal survival after CNS damage and the resistance to autoimmune disease development. This relation is mediated by an injury-induced beneficial T cell response found only in genetically resistant animals, suggesting that the protective T-cell-dependent response and resistance to an autoimmune disease are regulated by a common mechanism [27].

The recovery from optic nerve injury in several strains of rats and mice with different predispositions to differentially predisposed to Experimental Autoimmune Encephalitis (EAE) induction, demonstrated that susceptible animals have a limited spontaneous ability to express a protective autoimmune response to CNS injury. In these susceptible animals the rate of post-injury neuronal survival was lower than in animals resistant to EAE [27].

In optic nerve injury experiments using adult Lewis rats, thimectomized at birth and therefore lacking endogenous T cells (including regulatory T cells), it was found that the adoptive transfer with T cells that are specific to the myelin antigen did not protect the damaged nerve. This suggests that protective autoimmunity includes both auto-reactive T cells and regulatory T cells, it also explains the correlation between beneficial autoimmunity and resistance to EAE [16, 28].

The same T-cells can either be beneficial or detrimental to neurons, depending on the regulatory environment and tissue context. T cells might be both potentially protective and potentially destructive and their expression depends on how they are regulated. Therefore, the ability to protect neuronal tissue apparently does not correspond to a lack of autoimmunity; instead, it reflects a well controlled autoimmunity [29].

These findings give relevant information on beneficial autoimmunity, which only appears to be expressed by individuals with a genetic background determining resistance to autoimmune diseases; thus, the result of identical CNS damage will diverge in individuals who differ in their susceptibility to autoimmunity. Resistance or susceptibility, in terms of the development of autoimmune diseases after active immunization with self-antigens, is related to the existence and functioning of regulatory T-cells. Regulatory cells help sustain a balance between the ability to express an autoimmune response, required for neuroprotection, and the need to prevent autoimmune diseases [30]. Individuals with a limited ability to regulate the autoimmune response are often unable to benefit from protective autoimmunity [29, 31, 32]

The genetically determined predisposition to autoimmune diseases seems to be essential not only for predicting an increase in damage after CNS injury, but also for scheduling personalized therapy, because treatments that are appropriate to resistant individuals might not be applicable to susceptible persons.

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Neuroprotective autoimmunity is a physiological response to both CNS trauma and neurodegenerative disorders

A self-propagating process of secondary degeneration, of initially undamaged neurons, often follows traumatic or degenerative damage produced by injury to the CNS. The role of protective autoimmunity that evolves under non-infectious conditions (as in these cases) probably arrests progressive degeneration [27, 33].

The traumatic and neurodegenerative event at the CNS sends a stress signal to the immune system, to help the damaged nerve cope with the hazard of progressive degeneration. After a harmful event, the CNS spontaneously evokes a beneficial T cell-dependent immune response that reduces the spread of the injury-induced damage and conversely, the recovery is worse in the absence of T-cells [26, 27, 33, 34].

The evidence supporting a protective autoimmunity after CNS injury was found during studies on the response to CNS insults; it was discovered that the immune system provides protection against a self-destructive process. Experiments in rats using a partial crush injury of the optic nerve, followed by the adoptive transfer with myelin-specific T cells, demonstrated that the number of surviving neurons and fibers was significantly higher in rats treated with myelin specific T-cells than in those treated with T cells specific to an irrelevant antigen, or not treated at all [35]. The ability of autoimmune T cells to diminish the post-traumatic neuronal failure was confirmed both morphological and functionally in experimental models of axonal trauma of the optic nerve and spinal cord [35-38].

In an animal model of optic nerve injury, the surviving neurons are significantly higher if preceded by spinal cord injury, as compared to animals without a previous contusion. Here the neuroprotective response is detectable by the improved recovery after a subsequent CNS lesion at another site; moreover the neuroprotective effect can be successfully transferred to recipient rats by splenocytes activated ex vivo with myelin basic protein. In contrast, adult rats thimectomized at birth and therefore devoid of mature T cells, lack endogenous protective autoimmunity, indicating that protective autoimmunity is not induced by experimental or therapeutical interventions but it is a physiological response to CNS injury [33].

On the other hand, neonatally induced tolerance to myelin antigens significantly reduces the ability of adult rats to resist axonal injury, indicating that the spontaneous T-cell dependent protection, evoked as a reaction to wounds of myelinated axons, is myelin specific [30, 39]. The discovery of neuroprotection in transgenic mice over-expressing a T cell receptor for myelin basic protein peptides, but not in mice overexpressing a T cell receptor for ovoalbumin peptides, also supports the concept that antigenic specificity is essential for neuroprotection [33].

These T cell-dependent neuroprotective responses, although beneficial if stringently regulated, may not be sufficiently effective, as a result of the immune-privileged character of the CNS [40, 41].

Due to the impairment of neurogenesis, the poor regeneration ability of injured axons and the destructive series of injury-induced events that result in the lateral and longitudinal spread of the damage to neurons that escaped the direct initial damage, the injury to CNS often produces an irreversible functional deficit [42]. The impracticality of CNS regeneration can be overridden with a clear interpretation of the contribution of the immune system during the recovery process after CNS injury, which leads to a new therapeutic approach; this would take into consideration that immunization with CNS-related antigens leads to a more effective management of immune cells for therapy and perhaps for disease healing, driving the inflammatory reaction towards a beneficial, rather than a harmful situation.

It is also essential to consider the rationality and application scheme of anti-inflammatory or immunosuppressor compounds after injury, since, although they may appear to have a beneficial effect [43-46] they may be ineffective and possibly detrimental in terms of neuroregeneration [47-51].

Neuroprotective autoimmunity is elicited during CNS stress mediated by glutamate toxicity

Glutamate is an essential neurotransmitter in the CNS. Synaptic activity induces a transient local increase in glutamate concentrations in the synaptic cleft, but the transporter mediated uptake restores glutamate homeostasis [52, 53]. During CNS stress, significant alterations in glutamate concentrations make it toxic to the point of self destruction [54-58].

The excessive amount of glutamate in situ during CNS stress is a sign of the body recruiting help from the peripheral immune system in the form of T cells specific to immunodominant antigens that reside at the site of the glutamate-induced stress [29]. A systemic immune response can thus assist the overburdened local coping mechanisms of the CNS. The inflammatory immune response in CNS is accompanied by the activity of macrophages and microglia cells, which play an active role in brain pathology by releasing glutamate [59]. However, both cells have also been shown to express glutamate transporters and take up glutamate [60-62], thereby apparently contributing to protection against glutamate toxicity. Moreover, activation of macrophages and microglia can result in a phenotype that may or may not maintain a dialog with adaptive immunity. The former phenotype is associated with the expression of the major histocompatibility complex class II proteins (MHC-II); the latter is associated with little or no expression at all, and cannot derive any benefit from the adaptive immune response [4].

A particular attribute of protective autoimmunity is that antigen specificity is required for targeting the T cells to the stress site. The recruitment of T cells, including T helper 1and 2 (Th 1 and Th 2, respectively) cells that are targeted at specific antigens residing at the lesion site, leads to a further activation of microglia cells, with a resulting increase in the secretion of interferon gamma. Interferon gamma can affect the number of glutamate receptors expressed by astrocytes as well as by microglia, re-moving the toxicity endangering the tissue [63-65]. So, resident microglia

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have a dual function, as antigen-presenting cells and as cells that clear the damaged site of potentially harmful material [4, 66].

On the other hand, it has been demonstrated in the animal model for optic nerve injury, where glutamate is injected into the vitreous humor of mice, that the myelin proteins and peptides fail to boost the T-cells dependent protection, [29, 67]; in contrast vaccination with antigens that are immunodominant at the eyes led to significant protection [29, 68, 69]. It strongly suggests that a peptide that boosts beneficial autoimmunity resides at the site of the stress and is derived from a protein that is also potentially capable of inducing an autoimmune disease at that same site. This suggestion is supported by the strong evidence in the case of uveitis, where the tissue-specific self pathogen is the same protective self antigen [29].

Therapeutic vaccination that boosts a physiological mechanism for the regulation of glutamate might prove to be a possible strategy for the therapeutic protection against glutamate-associated neurodegenerative or mental disorder.

Neuroprotective autoimmunity in demyelinating diseases

The pathogenic role of autoreactive T-cells recognizing CNS antigens in both multiple sclerosis and its animal model EAE), has centered the attention of research and consequently much effort has been given to emergent multiple sclerosis therapies in order to abrogate auto-immune T cells or shift the balance from presumed pathogenic Th1 to the assumed beneficial Th2 pheno-type of T cells.

However, clinical observations primarily associated to the "clinical radiological paradoxes", as well as experimental evidence specifies that the suppression of deviated immune response may be an inappropriately simplistic method. Some of these irrefutable clinical and experimental observations are listed below:

- Multiple sclerosis inflammatory lesions do not predict later changes in impairment or disability [70].

- In both primary progressive and secondary progressive clinical forms of multiple sclerosis, associated with increasing disability, there have been less inflammatory changes than in the relapsing-remitting disease [71].

- Currently available immunomodulatory and immunosuppressive treatments of multiple sclerosis have a much more pronounced effect on inflammatory activity than on the clinical disease [71]. The non-selective immunosuppressive treatment often fails to have a realistic clinical benefit [72, 73]; suppressive therapy may fail when the beneficial effect on the inflammatory reaction prevails over its negative consequences [8].

- Lymphocytes of multiple sclerosis patients have an increased amount of BDNF transcripts, indicating that autoimmune T cells have beneficial effects on neural tissue [74]. The endogenous expression of neurotrophins in early multiple sclerosis lesions is greater than that of the older chronic multiple sclerosis plaque. This finding explains the ongoing axonal degeneration in these plaques in the chronic progressive stage of the disease [8].

- In animal models after a crush injury of the optic nerve or contusion of the spinal cord, activated T-cells that are specific for the basic myelin protein (but not against non-CNS antigens) protect the injured nervous system tissue from secondary degeneration and promote its repair [35]. This neuroprotective effect is mediated by the release of neurotrophic factors from autoimmune T-cells, while B cells and macrophages produce neurotrophic factors as well [13, 14, 75].

- In multiple sclerosis lesions, detailed immunohistochemical analyses have shown the presence of BDNF and its receptor, suggesting a role for this neurotrophin in multiple sclerosis physiopathology [76].

All the clinical and experimental evidence sustains the hypothesis of "a double role" of the immune system in demyelinating diseases, highlighting the favorable effects of inflammation. The concept of neuroprotective autoimmunity will have important consequences for the pathogenesis and treatment of multiple sclerosis, because it is necessary to combine neuroprotective and immunomodulatory agents, preserving the endogenous protective potential of inflammation. Unfortunately, in multiple sclerosis it is not clear whether there is a phase of the disease in which the inflammatory response is more favorable than dangerous [8].

CNS-antigens vaccination protocols: Therapeutic challenge

After the injury to the CNS, therapeutic vaccination may guarantee the immediate recruitment of immunocompetent cells making it possible to protect the in-dividual from the pathological consequences of the damage. Active vaccination may be a way of protecting individuals from the devastating effects of secondary degeneration, because unlike antibody response, the response of T cells to immunization with a suitable antigen starts within the time period required for a neu-roprotective effect, whereas antibody production takes longer [77]. As the vaccination is designed to protect the individual from insultinduced endogenous toxicity, the antigen will be a self-protein and the immune reaction is therefore an autoimmune response [16].

The choice of antigens for therapeutic vaccination should be based on safety considerations, ensuring that it promotes neuroprotection without inducing an autoimmune disease. Vaccination with non-pathogenic peptides, such as those derived from myelin basic protein or synthetic polymers that cross-react with self-proteins, have shown better motor recovery without autoimmune disease development in spinally injured rats [31, 77] and in experimental models of chronic injuries of the optic nerve [67, 78, 79]. Vaccination with altered encephalitogenic peptides in treating CNS injury or neurodegenerative disorders offer an approach with the potential advantage of avoiding the risk of developing an autoimmune disease [67, 78, 79]. This type of therapeutical approach is also beneficial in that it stimulates a physiological mechanism that is evoked by the insult, but at a level that is too low to be completely effective [16].

Conclusions

The criteria on the uselessness of CNS regeneration can be revoked if we are able to understand the con-

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tribution of the immune system, through the recovery process after CNS injury.

Research on neuroprotection requires efforts to command the immune system in shifting inflammation as an internal repair mechanism, in an attempt to halt damage spread. Neuroprotective autoimmunity is a new concept leading to the analysis of whether current therapeutic methods used to attenuate the inflammatory immune response in the CNS after a traumatic injury, or even during an autoimmune attack, are truly effective or deleterious.

The evidence of beneficial autoimmunity points to the possible development of therapeutic vaccination with self-antigens, or with antigens that are cross-reactive with self-antigens, in order to increase autoimmunity without inducing an autoimmune disease, thus providing a safe method for aborting degeneration. Autoimmune protection would be a valuable boosting resource for therapeutic purposes and solely requires the appropriate homing of tools within the CNS. It may be a suitable way to gear a direct and efficient T cell compartmentalization as a local neurotrophin bioreactor.

The fact that autoimmune diseases stand as genetically pre-determined processes will require a personalized therapy since therapeutic approaches that may be appropriate to resistant patients could be harmful to susceptible persons. The personalized therapy toward CNS repair should be based on safety considerations, ensuring that it promotes neuroprotection without inducing an autoimmune disease.

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