SHORT ANALYTICAL REVIEW

Immunotherapy for neurological diseases

Pablo Villoslada a,⁎, Beatriz Moreno a, Ignacio Melero b, Jose L. Pablos c, Gianvito Martino d, Antonio Uccelli e, Xavier Montalban f, Jesus Avila g, Serge Rivest h, Laia Acairi, Stanley Appel j, Samia J. Khoury k, Patrick McGeer l, Isidro Ferrer m, Mario Delgado n, Jose Obeso a, Michal Schwartz o,⁎

a Department of Neuroscience, Center for Applied Medical Research, University of Navarra, Spain
b Hepatology and Gene Therapy, Center for Applied Medical Research, University of Navarra, Spain
c Servicio de Reumatología, Unidad de Investigación, Hospital 12 de Octubre, Madrid, Spain
d Neuroimmunology Unit, Institute for Experimental Neurology (INSPE). San Raffaele Hospital, Milan, Italy
e Neuroimmunology Unit, Department of Neurosciences, Ophthalmology and Genetics, University of Genoa, Italy
f Multiple Sclerosis Center of Catalonia, Vall d’Hebron University Hospital, Barcelona, Spain
g Centro de Biología Molecular "Severo Ochoa", Universidad Autónoma de Madrid, Spain
h Laboratory of Molecular Endocrinology, CHUL Research Center and Department of Anatomy and Physiology, Laval University, Québec, Canada
i Department of Cell Biology, Physiology and Immunology, Autonomous University of Barcelona, Spain
j Department of Neurology, Methodist Neurological Institute, Houston, Texas, USA
k Center for Neurologic Diseases, Department of Neurology, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA
l Kinsmen Laboratory of Neurological Research, Department of Psychiatry, University of British Columbia, Vancouver, Canada
m Institut Neuropatologia, IDIBELL-Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Spain
n Instituto de Parasitología y Biomedicina, CSIC, Granada, Spain
o The Weizmann Institute of Science, Rehovot, 76100, Israel

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Abstract The burden of neurological diseases in western societies has accentuated the need to develop effective therapies to stop the progression of chronic neurological diseases. Recent discoveries regarding the role of the immune system in brain damage coupled with the development of new technologies to manipulate the immune response make immunotherapies an attractive possibility to treat neurological diseases. The wide repertoire of immune responses and the possibility to engineer such responses, as well as their capacity to promote tissue repair, indicates that immunotherapy might offer benefits in the treatment of neurological diseases, similar to the benefits that are being associated with the treatment of cancer and autoimmune diseases. However, before applying such strategies to patients it is necessary to better understand the pathologies to be targeted, as well as how individual subjects may respond to immunotherapies, either in isolation or in combination. Due to the powerful effects of the

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⁎ Corresponding authors. P. Villoslada is to be contacted at Department of Neurology, Clinica Universitaria de Navarra and Center for Applied Medical Research, University of Navarra, Pio XII 36, 31008 Pamplona, Spain. Fax: +34 948 296500. M. Schwartz, fax: +972 8 9346018.
E-mail addresses: pvilloslada@unav.es (P. Villoslada), michal.schwartz@weizmann.ac.il (M. Schwartz).

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Introduction

Neurodegenerative diseases such as Alzheimer disease (AD), Parkinson disease (PD), Amyotrophic Lateral Sclerosis (ALS) and Multiple Sclerosis (MS) are among the most important health problems in developed countries. Due to the progressive aging of the population in western countries, the frequency of these diseases is reaching epidemic proportions, and they will cause an ever increasing social and economic burden on our societies. New treatments for AD are the biggest priority due to its prevalence in the aging population. Indeed, except for MS there are currently no therapies available to modify the progression of these diseases as existing therapies only treat the symptoms. In recent years, progress has been made in developing new therapies that target the immune system, or treatments that use components of the immune system as therapeutic agents (Table 1 and Fig. 1). Because the local immune response is sub-optimal or even destructive in neurodegenerative disease, it is reasonable to believe therapeutic immunomodulation might be beneficial in such circumstances.

An overview of immunotherapy

To date, immunotherapies have been tested in chronic conditions such as cancer and autoimmune diseases. Hence, the experience with these diseases will benefit any attempts to develop immunotherapies for neurological diseases. Many different cell types are involved in chronic inflammatory diseases, including immune cells, endothelial cells and fibroblasts, reflecting the complexity of these diseases. In cancer, tumor cells are known to use multiple mechanisms to induce immune tolerance in order to facilitate immune evasion [1]. Indeed, tumor cells retain a complete copy of the human genome enabling them to fully exploit the range of immunomodulatory gene expression programs. Interestingly, it is becoming clear that many of the oncogenes responsible for the transformation and maintenance of tumor cells are also connected with immunosuppression. Thus, the knowledge accumulated in cancer immunology can serve as a base to understand the progression of neurodegenerative diseases, aiding in the development of immunotherapy that use the same molecular tricks that help tumors to escape the cellular immune response. There are several mechanisms that can be employed to evade the immune system, such as down modulating tumor antigen presentation, releasing immunosuppressive substances into the tumor microenvironment, disabling antigen presenting cells, inducing CD4 T cell tolerance, or enhancing the activity of regulatory T cells (Treg) [2]. Several immunotherapy approaches have been studied in cancer, including triggering immune responses against tumor antigens by vaccination, or by gene or cell therapy. Alternatively, boosting the immune response in a non-antigen specific way has been contemplated, both by using cytokines or blocking the suppressor activity of CTLA4. Significantly, interference with the immunosuppressive strategies adopted by the tumor seems to be essential for efficient therapeutic results. After several attempts, some of these immunotherapies have now entered the clinical phase of study and currently, there is a commercially available vaccine against melanoma. Indeed, several reports have indicated some success in controlling tumor cells in humans with various vaccination approaches. However, unwanted side effects, such as the induction of vitiligo in patients treated with an anti-CTLA4 antibody indicate that manipulation of the immune system must be carefully controlled [3]. The curative effect in cancer animal models of a monoclonal antibody directed against CD137 in mice appears to result from a strong cytotoxic T cell response, and this antibody is currently undergoing clinical trials [1]. Interestingly the same antibody ameliorates models of autoimmune diseases in mice, such as experimental autoimmune encephalomyelitis (EAE) [4], collagen induced arthritis and murine lupus, through a mechanism that involves the inhibition of pathogenic CD4 T cells.

In the case of autoimmune diseases, the development of new immunotherapies for rheumatoid arthritis (RA) exemplifies the opportunities offered by this approach [5,6]. New immunotherapies that have changed the natural history of RA include the use of antibodies against pro-inflammatory cytokines such as interleukin 6 (IL-6), interleukin 1 (IL-1) or tumor necrosis factor α (TNF-α), and CTLA 4 blocking strategies. Antibodies inhibiting IL-1 (Anakinra) and IL-6 (Tocilizumab) are effective in slowing disease activity and they are well tolerated by RA patients. TNF-α is a pleiotropic effector target due to its influence on multiple downstream pro-inflammatory pathways and given its regulatory role on effector and regulatory T cell activation. Anti-TNF (Infliximab and Adalimumab) and soluble TNF receptors (Etenecpt) are also widely used to treat RA. Abatacept is a CTLA4-Ig fusion protein capable of blocking CD28-B7 co-stimulation and it has recently been approved for use in RA. Downregulating autoantibody responses by depleting B cells with the anti-CD20 antibody Rituximab has also been shown to be remarkable effective in controlling the inflammatory process associated with RA and a variety of autoimmune diseases. However, when considering the benefits of immunotherapy for autoimmune disease we must bear in mind that they may have side effects, especially when used in combination, such as the susceptibility to opportunistic infections secondary to the potent immunosuppression induced by combined therapy [7,8].

Protecting neural tissue by controlled autoimmunity — a paradigm shift?

Autoimmunity has long been viewed as a destructive process and numerous therapies have been developed to halt the
However, there is evidence indicating that the immune response is beneficial rather than damaging after brain damage [9]. The studies from Schwartz and colleagues challenged the current dogma, suggesting that autoimmune T cells can evoke a purposeful response necessary in CNS maintenance and repair (Fig. 2). This response apparently effectively restores the balance when a small deviation from the homeostatic equilibrium occurs. In contrast, a severe deviation such as an acute insult, stress or ischemia, may lead to paralysis or chronic degeneration. Under such conditions either the evoked autoimmunity is insufficient or alternatively, it is out of control and leads to autoimmune disease. In animals susceptible to autoimmune diseases, the same autoimmune T cells are responsible for both neuroprotection and for disease development. The timing and strength of their activity will determine the effect produced and if the immune response is well controlled, T cell effectors could offer protection against axonal damage [9]. In the same way, the local innate immune response coordinated by activated microglia/macrophages can produce different phenotypes depending on the type of activation (Figs. 3 and 4). A more classic activation is

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manifested by phagocytic activity, production of nitric oxide (NO) and other oxidation products that can damage neurons at the site of the local immune response. Alternatively, while phagocytic activity is maintained, activated microglia/macrophages may produce growth factors such as BDNF and IGF-I without provoking toxicity [10,11]. Accordingly, autoimmunity is naturally regulated to serve as a safety valve, allowing injured individuals to benefit from protective autoimmunity without being exposed to the risk of developing autoimmune diseases. However, certain circumstances may lead individuals to lose control of this beneficial autoimmune response. The concept of neuroprotective autoimmunity calls for therapeutic protocols for neurodegenerative diseases to be revised, arguing in favor of therapies based on immunomodulation rather than immunosuppression. Such protocols would aim to maximize the beneficial component of autoimmunity without eliminating the immune effect altogether. Boosting autoimmunity without provoking a risk of developing an autoimmune disease is the treatment of choice and one option would be the use of altered peptide ligands [12].

**Immunomodulatory therapies for MS**

MS is a chronic inflammatory and neurodegenerative disease for which several immunomodulatory drug therapies have been established to try and control disease activity, including Interferon-beta, Glatiramer acetate, chemotherapy and Natalizumab. Observational and head-to-head studies have produced controversial results regarding the degree of efficacy of these products [13] and despite the efficiency reported, a large proportion of patients do not respond to treatment [14,15]. Nevertheless, this information is useful when considering the requirements of new treatments for MS, such as those being developed and those that adopt different approaches: therapies targeting T cell activation or migration; those inducing immune deviation; or cell-based therapies. Some of the promising therapies that are currently being assessed in phase III clinical trials include the use of Fingolimod, Rituximab, etc. Moreover, new therapeutic approaches are being studied that are based on the immunopathogenesis of MS, trying to block the T cell co-stimulatory signal, modulate the immune system by inhibiting inflammatory cytokines or vaccinating with brain antigens, adopting more neuroprotective strategies like restoring neuronal function, or promoting remyelination and axonal regeneration.

A promising new strategy to modulate the immune system involves targeting the intermediate metabolism. Statins, inhibitors of 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, modulate autoimmune activity by down-regulating the class II major histocompatibility complex molecules, co-stimulatory molecules and the Th1 cytokines, while pushing the immune response toward a Th2 response [16]. Indeed, in the initial clinical trials statins have shown promise in reducing disease activity in MS [17]. Recent research indicates that catabolites of the essential amino acid tryptophan can also modulate autoimmunity [18]. The kynurenines, breakdown products of tryptophan, can also modulate autoimmune activity by down-regulating the class II major histocompatibility complex molecules, co-stimulatory molecules and the Th1 cytokines, while pushing the immune response toward a Th2 response [16]. Indeed, in the initial clinical trials statins have shown promise in reducing disease activity in MS [17]. Recent research indicates that catabolites of the essential amino acid tryptophan can also modulate autoimmunity [18]. The kynurenines, breakdown products of tryptophan, can also modulate autoimmune activity by down-regulating the class II major histocompatibility complex molecules, co-stimulatory molecules and the Th1 cytokines, while pushing the immune response toward a Th2 response [16]. Indeed, in the initial clinical trials statins have shown promise in reducing disease activity in MS [17]. Recent research indicates that catabolites of the essential amino acid tryptophan can also modulate autoimmunity [18]. The kynurenines, breakdown products of tryptophan, can also modulate autoimmune activity by down-regulating the class II major histocompatibility complex molecules, co-stimulatory molecules and the Th1 cytokines, while pushing the immune response toward a Th2 response [16]. Indeed, in the initial clinical trials statins have shown promise in reducing disease activity in MS [17]. Recent research indicates that catabolites of the essential amino acid tryptophan can also modulate autoimmunity [18]. The kynurenines, breakdown products of tryptophan, can also modulate autoimmune activity by down-regulating the class II major histocompatibility complex molecules, co-stimulatory molecules and the Th1 cytokines, while pushing the immune response toward a Th2 response [16]. Indeed, in the initial clinical trials statins have shown promise in reducing disease activity in MS [17]. Recent research indicates that catabolites of the essential amino acid tryptophan can also modulate autoimmunity [18]. The kynurenines, breakdown products of tryptophan, can also modulate autoimmune activity by down-regulating the class II major histocompatibility complex molecules, co-stimulatory molecules and the Th1 cytokines, while pushing the immune response toward a Th2 response [16]. Indeed, in the initial clinical trials statins have shown promise in reducing disease activity in MS [17]. Recent research indicates that catabolites of the essential amino acid tryptophan can also modulate autoimmunity [18].
antioxidant effect in vivo, modulation of T cell activation, down-regulation of pro-inflammatory cytokines, enhancement of interleukin 10 (IL-10) production and modulation of NF-κB-mediated signaling [19]. The inhibition of methylation during the activation of signaling pathways seems to be responsible for such activity and this approach is becoming a powerful therapeutic strategy for several diseases. Indeed, recent studies using a synthetic drug that modulates methylation, mimicking the activity of MTA, have also shown that it has a powerful therapeutic strategy for several diseases. Indeed, the activity of T cells, including CD25+Foxp3+ and Tr1, is impaired in MS and other autoimmune diseases [24,25] and the loss of activity is not reversed by immunomodulatory therapy. Furthermore, not only is the suppressor function of T cells impaired but also their effector signaling pathways are dysfunctional in MS, such as the IL-10 receptor pathway [25], indicating the presence of resistance against peripheral immune tolerance mechanism in MS. Thus, cell therapies using T cells must recover these functions and the responses of the different signaling pathways involved.

Under the neuroprotective autoimmunity paradigm, autoimmune T cells are on the alert to maintain the organisms defenses against the ubiquitous agents of self-destruction. When a pathological situation arises such as that caused by traumatic injury for example, intervention by the autoimmune T cells is needed urgently, although it is apparently insufficient and must be boosted to be effective. Boosting can be achieved by up-regulating the effector autoimmune T cells by active immunization [26]. Indeed, it has recently been demonstrated that immunization with a myelin-associated peptide modified to evoke a T cell-mediated response without inducing EAE was beneficial to rats with optic nerve or spinal cord injury [26]. Currently, several clinical trials using the myelin basic protein altered peptide ligand (APL) or a DNA vaccination strategy are under way [27]. However, previous experiences with APL have shown contrasting effects, including reactivation of MS [28]. Hence, the careful development of such therapies will be necessary to avoid side effects, which can vary between patients due to individual differences in the generation of the immune response that in turn, depends on both the genetic background and immune memory.

**Therapeutic plasticity of neural stem cells and mesenchymal stem cells**

Neural stem cells/precursor cells (NPCs) are a heterogeneous population of mitotically-active, self-renewing, multipotent cells that exist in both the developing and the adult central nervous system (CNS) that show complex spatio-temporal patterns of gene expression [29]. NPCs can exert a therapeutic effect by cell replacement but they can also promote CNS repair through their intrinsic neuroprotective capacity, releasing neuroprotective agents at the site of tissue damage in a manner that is temporally and spatially adjusted to the environmental needs. The neuroprotective molecules involved may be immunomodulatory substances, neurotrophic growth factors and/or stem cell regulators that are...
Figure 3  Heterogeneity of the microglial response to stimuli. Changes in microglial morphology in control animals (A), and following massive neuronal death induced by acute excitotoxicity resulting from the injection of an exogenous glutamate analogue into the immature rat brain (B-H). Microglia are visualized using tomato lectin histochemistry (TL). Microglia display very rapid morphological changes (B, 4 h post-lesion) and the fully developed response to injury involves reactive ramified forms (C) or ameboid to round microglia/macrophagic morphologies (D), which express MHC class II (E) and several pro-inflammatory molecules like cyclooxygenase-2 (COX2) (F), interleukin 1 beta (IL-1β) (G) or interleukin-6 (IL-6) (H). A single immune stimulus (LPS) induces transient de novo transcriptional activation of the Toll-like receptor-2 (TLR2) in microglia (I, J) as demonstrated by Iba-1 immunohistochemistry (J, K). TLR2 is only induced when microglia cells are activated and this transcript is not expressed under basal conditions. Indeed, when this transcript is induced in most case of acute immune stimuli, there is no neurodegeneration, suggesting that it might have a neuroprotective effect. Photographs courtesy of Prof. L. Acarin and S. Revest.
constitutively expressed by NPCs to maintain tissue homeostasis both during development and in adulthood. NPCs might also induce apoptosis of inflammatory T lymphocytes by up-regulating the membrane expression of certain death receptor ligands, as triggered by pro-inflammatory (interferon-γ, IFN-γ, IL-1β and TNF-α), but not anti-inflammatory (IL-4, IL-5 and IL-13) cytokines. NPCs can also promote remyelination driven by endogenous oligodendrocyte progenitors.

Recent studies of the intravenous or intra-cerebroventricular administration of syngenic NPCs in different mouse models of MS demonstrated a clear therapeutic effect in both chronic-progressive and relapsing-remitting EAE [30,31]. NPCs specifically enter the affected regions of the CNS where they promote a marked reduction in demyelination, axonal loss and astrogliosis, accompanied by an almost complete restoration of neurological function. NPCs display such a selective regional tropism for inflamed areas because they express a number of molecules that are also expressed by and that are important for the function of immune cells, such as the high-affinity cell adhesion molecules CD44 and the very late antigen 4 (VLA-4). Again, the therapeutic potential of NPCs could be explained by cell replacement or, CNS repair may be promoted through a bystander effect exerted by the release of neuroprotective and immunomodulatory molecules at the site of tissue damage by undifferentiated "stem" cells in response to environmental stimuli. Thus, the concept of "therapeutic plasticity" of NPCs reflects the capacity of somatic stem cells to adapt their fate and functions to specific environmental needs as a result of different pathological conditions.

The bone marrow is composed of a stromal component that interacts closely with osteoblasts and endothelial cells to create the proper microenvironment for the survival of hematopoietic stem cells. Such a stromal scaffold is formed by cells of mesenchymal origin, named mesenchymal multipotent progenitor cells or mesenchymal stem cells (MSCs) because of their capacity to differentiate into multiple tissues of a mesenchymal origin. MSCs can inhibit the proliferation of T, B and dendritic cells by inducing the arrest of cell division [32]. MSCs can also inhibit the proliferation of NK cells and impair dendritic cell maturation, as well as antigen presentation [32]. These features provide the conceptual support for their use in vivo in immune-mediated diseases. Recently, MSCs were shown to ameliorate EAE, since their intravenous injection into mice immunized with the 35–55 peptide of myelin oligodendrocyte glycoprotein (MOG) significantly improved the clinical severity of EAE, decreasing CNS inflammation and demyelination by inhibiting peripheral pathogenic T cells [33]. Later, these data were further validated by demonstrating that MSC can also ameliorate relapsing-remitting EAE and inhibit pathogenic antibodies [34]. Thus, the therapeutic benefits of MSCs do not arise through tissue repair sustained by regeneration of

Figure 4 Neuroprotection mediated by activated microglia. Microglial activation induced by inflammatory mediators such as LPS induced a more efficient removal of debris and recruitment of oligodendrocyte precursor cells (OPC), promoting the survival of myelin sheaths and neurons (reproduced by permission from Glezer I, Lapointe A, Rivest S. Innate immunity triggers oligodendrocyte progenitor reactivity and confines damages to brain injuries. FASEB J. 2006 Apr; 20(6):750-2).
damaged neurons and oligodendrocytes but instead, they are
due to the modulation of the autoimmune attack on myelin [35]. Moreover, MSCs are currently used in clinical practice to
treat acute myocardial infarction, graft versus host disease,
or Crohn's disease with no obvious side effects. Indeed, they
can be easily obtained from the bone marrow of the patient
(autologous) or commercial preparations can even be used
(allogenic). All these facts make MSCs a promising cell
therapy in the short term, encouraging their use in patients
with neurological disease.

Neuroinflammation in neurodegenerative
diseases: Targeting microglia and
blood-born monocytes/macrophages

Microglia are the immune system cells resident in the CNS
that are in a continuous process of extension and retraction,
even under normal conditions, providing permanent surveil-
ance of the extracellular environment [36]. Following
changes in the CNS parenchyma, like chronic or acute neuro-
degeneration, microglia cells are activated and respond by
undergoing morphological changes, migrating, proliferating
and changing their patterns of gene expression to augment
the expression of inflammatory compounds such as cytokines,
chemokines and their receptors. These are well-established
features of the innate immune response that is responsible
for tissue repair in the periphery. However, far from being
stereotyped, the microglial response is highly dependent on
the CNS region, the type of insult, the degree of tissue
damage, the presence of neuronal debris, the state of the
blood-brain barrier, and the presence or absence of an
immune challenge triggering the immune adaptive response.
Accordingly, recent evidence suggests that the microglial
response can either have a protective or detrimental role
depending on the pathological condition and the context in
which it develops (Figs. 3 and 4). Indeed, these cells are able
to display a large array of responses in order to maintain the
homeostatic equilibrium in the brain and to promote brain
repair [37]. Microglia can impede the invasion of infectious
agents, provide trophic support and protection to neurons,
eliminate neurons that are irreparable destined to die, and
assist in glial scar formation and tissue repair. However,
excessive, chronic or unregulated microglia activation may
be harmful to neurons.

In this sense, microglia are becoming one of the main
immunotherapeutic targets for neurological diseases, and
several approaches are under study to target the activation
of microglia. Anti-inflammatory therapies, such as the use
of non-steroidal anti-inflammatory drugs (NSAIDs) that can
antagonize the neurotoxic products of scavengers, antago-
nists of reacting-oxygen species (ROS), NO and inflam-
matory compounds seem to provide neuroprotection in
different pathologies [38,39]. However, these neurotoxic
products are neither exclusively produced by microglia/
macrophages nor do they constitute a unique feature of the
microglia cell response. Thus, neuroprotective strategies
should target individual facets of the microglial response in
order to modulate the activation of this cell type rather
than deplete its activity, which may be devastating due
to the diminished phagocytosis and deregulation of the
inflammatory response [40], among other factors. Accord-
ingly, in certain experimental models it has been suggested
that neuroprotection can be achieved in conjunction with
increased microglial activation. New strategies, like Toll-
like receptor (TLR) subtype deficiencies can produce
selective reduction of lesion-induced cytokine and chemokine
expression, as well as delayed T cell recruitment and
microglia proliferation in several experimental injuries
[41].

Immunotherapy for Alzheimer and
Parkinson disease

Senile plaques and neurofibrillary tangles are the pathologi-
cal hallmarks of AD. Plaque material consists mostly of
extracellular aggregates of beta-amyloid protein (Aβ), while
the neurofibrillary tangles mostly consist of intracellular
aggregates of phosphorylated tau. Severe inflammation
develops around both the extracellular Aβ deposits and neu-
rofibrillary tangles, and activated microglia produce a variety
of toxic material, including free oxygen radicals and pro-
teases. Accordingly, therapeutic strategies should be direc-
ted at reducing the level of inflammation and to achieve this,
the toxic effects of over stimulated microglia should be
attenuated. This is the presumed role of anti-inflammatory
agents, including NSAIDs, whose main effect is to inhibit the
cyclooxygenase (COX) activity that is up-regulated in AD
microglia cells, although they can also target several
secretes involved in the amyloid cascade [42]. In multiple
epidemiological studies, NSAIDs have been found to amelio-
rate AD and they reduce behavioral and pathological deficits
in transgenic models of AD in a dose dependent manner.

Many of the highly ramified microglia found within the
core of amyloid plaques in the transgenic mouse models of
AD originate from the bone marrow, and the Aβ-amyloid 40
and 42 isoforms are able to trigger this chemoattraction.
These newly recruited cells also exhibit a specific immune
reaction to both exogenous and endogenous Aβ-amyloid in
the brain, as well as having the ability to eliminate amyloid
deposits by a cell-specific phagocytic mechanism. The fact
that newly recruited blood-born monocytes are more effi-
cient than their resident immune cell counterparts is clearly
beneficial in restricting the progression of AD. Thus, a novel
strategy to improve such a process and target it towards Aβ-
amyloid deposits could lead to the elimination of toxic senile
plaques by bone marrow stem cells capable of differentiating
into microglia in the CNS. These cells might also be modified
to express trophic factors and amyloid precursor protein
degrading enzymes [43].

An independent therapeutic strategy, with the same goal
of recruiting blood-born monocytes, thereby minimizing
plaque formation and encouraging cell renewal, has been
applied using T cell- based vaccination in a double transgenic
AD mouse model. The approach is based on the concept of
‘protective autoreactivity’, whereby T cells recognizing brain
proteins are needed for CNS maintenance, repair and re-
newal under conditions where the levels, timing and
phenotypes are well controlled [12]. In an AD mouse
model, boosting the levels of T cells that can weekly cross-
react with brain antigens using Glatiramer acetate reduced
plaque formation and cognitive loss, while enhancing
neurogenesis [10]. The underlying mechanism was
associated with the modulation of the microglia/macrophage phenotype associated with the plaques [10] and the recruitment of blood-born monocytes locally expressing this phenotype.

Another important aspect of AD treatment is the prevention of Aβ misfolding and the disruption of Aβ aggregation through different approaches, including the use of selective small molecules, synthetic peptides, chaperones and Aβ-binding proteins, as well as Aβ immunization. Immunization with Aβ peptides and vaccination with antibodies against Aβ have emerged as important strategies to treat AD, both aimed at reducing Aβ aggregation and the burden of β-amyloid plaques [44]. In terms of improved behavior and reduced plaque formation positive results were obtained following active and passive Aβ immunization in AD transgenic mice. Pioneering trials in moderate AD cases showed a variable clinical improvement and a decrease in the β-amyloid plaques with this approach, although β-amyloid angiopathy and the hyperphosphorylated tau pathology were maintained. However, this trial was stopped due to the appearance of meningoencephalitis in a subset of patients as a result of T cell-mediated immune responses in addition to the expected antibody-related immune response [45]. These results prompted the development of new approaches aimed at reducing the side effects, such as encephalitis and microhemorrhages, and at optimizing immunization. Different approaches geared to optimizing immunization have been adopted by engineering phages expressing specific peptides. In an attempt to reduce the adverse effects, recombinant adeno-associated viral Aβ vaccine expressing a fusion protein containing Aβ1-42 and the cholera toxin B subunit was assayed in a mouse model of AD [46]. Immunization resulted in reduced behavioral impairment and a reduction in the number of Aβ cortical plaques in transgenic mice [46]. Together, such experimental designs have defined Aβ immunization as a potent therapeutic tool in the early stages of the disease, either when administered alone or more probably, in combination with other drugs [47].

Tau phosphorylation and aggregation also participates in AD. Tau is a microtubule-associated protein that accumulates in a phosphorylated and aggregated form not only in AD, but also in other pathologies known as tauopathies. Analyzing the role of tau phosphorylation and tau aggregation in a transgenic mouse overexpressing GSK-3beta and FTDP-17 tau, phosphorylation of tau but not its aggregation appears to be involved in the cognitive impairment found in this model [48]. Recent studies indicate that immunization with amyloid-beta has a positive effect in transgenic mouse models of AD by reducing the levels of pathological tau [49]. This represents a challenge since tau is mainly intracellular, suggesting that tau immunotherapy might work by stimulating neuroprotective autoimmune.

Parkinson disease (PD) is a CNS disease that produces severe difficulties in movement control and cognitive impairment, and current therapies are aimed at restoring dopaminergic activity in the brain [50]. PD is characterized by the presence of intracytoplasmic inclusions or protein aggregates called Lewy bodies and the depletion of pigmented DA-containing neurons in the substantia nigra pars compacta. Several factors are believed to be involved in the pathogenesis of PD, including inflammation. The COX enzyme, as well as inflammatory mediators such as NO are thought to be increased in PD and indeed, the non-selective COX inhibitor, Aspirin, and the preferential COX-2 inhibitor, Meloxicam, seems to confer neuroprotection in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced DA depletion in mice [51]. Tetracycline derivatives are other anti-inflammatory agents that offer neuroprotection in experimental models of PD. As such, minocycline treatment inhibits iNOS and NADPH oxidase expression, modulates the microglial response and prevents the degeneration of dopamine containing neurons induced by MPTP [52]. VIP can also act by blocking microglial activation and through a neuroprotective effect in the MPTP mouse model [53]. The involvement of abnormal α-synuclein (α-syn) folding in the pathogenesis of PD suggests that immunization with human α-syn might represent a potential therapy. Accordingly, human α-syn transgenic mice were vaccinated with human α-syn to demonstrate that the vaccination is effective in reducing neuronal accumulation of human α-syn aggregates, which may be further developed to treat PD [54]. Glatiramer acetate was also tested in MPTP mice, producing an accumulation of T-cells within the substantia nigra pars compacta, suppression of microglial activation, and increased local expression of astrocyte-associated glial cell line-derived neurotrophic factor. This immunization resulted in significant protection of nigrostriatal neurons against MPTP neurodegeneration [55]. However, the value of these experimental findings to predict the potential of its therapeutic application for patients with PD is questionable. Indeed, animal models may not faithfully mimic the pathology of PD in terms of pattern and rate of cell death, and Lewy bodies do not actually form. Significantly, the role of Lewy body formation (i.e. protective or deleterious) in the pathogenesis of PD is still not clear.

Immunotherapy for Amyotrophic Lateral Sclerosis

ALS is a neurodegenerative disease that affects adult motor neurons. A small proportion of familial cases are caused by dominant mutations in the ubiquitously expressed Cu²⁺/Zn²⁺ superoxide dismutase (SOD1), which has led to the generation of transgenic models of ALS. The only currently available therapy for this devastating disease is Riluzole, which slightly modifies the disease course. Thus, developing new therapies that can halt the evolution of ALS is a priority. Recent studies suggest that microglia also play an important role in this disease contributing to motorneuron injury in animal models of familial ALS [56]. Indeed, the expression of mutant SOD microglia in the CNS contributes to motorneuron injury. Compared with wild type microglia, the mutant cells produce and release more superoxide and nitrite, and they induced more neuronal death [57]. Hence, microglia act as a double-edged sword, highlighting the importance of targeting microglia to minimize cytotoxicity and maximize neuroprotection in neurodegenerative diseases. Several attempts have been made to target neuroinflammation in ALS. For example, Glatiramer acetate (only when used in a specific regimen and specific adjuvant), and other formulations and variants of the original compound, can ameliorate the disease course in animal models of ALS [58]. Importantly, the use of Glatiramer acetate without adjuvant in a regime that was effective in animal models of AD [10], was not effective in mouse models of ALS. For this reason, a clinical trial with Glatiramer acetate should not be commenced until the regime has been carefully
selected. The regime that is effective in MS patients (daily injection of Glatiramer acetate) was only mildly effective in male mice suffering from ALS and it was destructive in their female counterparts (M. Schwartz, in preparation). Other strategies are being tested, such as the inhibition of the key mediator of inflammation, COX-2. Rofecoxib, administered by intraperitoneal injection in the SOD1 (G93A G1H) mouse model induced a small but significant delay in locomotor impairment, however survival was not affected by the treatment [59]. Despite all these positive experimental results, we have to be careful before proposing anti-inflammatory therapies in ALS patients, since modulating the innate immune system in the brain has failed to change the outcome of different mouse models of ALS [60]. Moreover, inhibiting pro-inflammatory signaling (e.g., MyD88) in bone marrow-derived microglia might dramatically accelerate disease progression in SOD1 (G37R) mice (Kang and Rivest, submitted).

Conclusions

Immunotherapies are powerful strategies to treat chronic diseases. However, to apply these approaches we must better understanding the involvement of the immune system in the pathogenesis of neurological diseases. The capacity of the immune system to target damaged tissue and restore the integrity of the tissue provides an excellent opportunity to treat patients suffering chronic and disabling brain diseases. However, several considerations need to be satisfied before immunotherapies can be considered. First, the treatment of choice should be carefully selected and we must consider differences between individuals in terms of the immune system response in order to predict the response to therapy and to identify patients at risk of developing side effects. Second, in addition to modulating the immune response, immunotherapies might have a well-defined neuroprotective effect. Third, we must be careful when combining therapies due to the unexpected alterations of the immune system that may compromise its normal function, leading to adverse events. Finally, the same compound may not work in all neurodegenerative diseases or alternatively, the same compound may only be effective for different diseases under distinct regimes, since the precise immune response may depend on the dose and timing of treatment. Thus, although neurodegenerative diseases share a characteristic malfunctioning of the immune response, which may serve as a therapeutic target, the way to achieve it such modifications should be carefully selected for each separate disease in order to maximize the benefits from immunotherapies and reduce the risk of side effects. Finally, treatments should be applied as early as possible to maximize their potential therapeutic value. This by itself represents a challenge in the treatment of neurodegenerative diseases.

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