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SHORT ANALYTICAL REVIEW

Immunotherapy for neurological diseases

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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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immune system, one priority is to avoid tissue damage due to the activity of the immune system, particularly considering that the nervous system does not tolerate even the smallest amount of tissue damage.

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 it 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 immune-based therapies 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 (Etanercept) 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