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Immune modulation for autoimmune disorders: evolution of therapeutics

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ABSTRACT

Autoimmune disorders result from either congenital or acquired defects in central or peripheral immune tolerance. A genetic propensity may underlay the development of most such disorders, but an external trigger may be required for the eventual development of the autoimmune disease. The development of pharmacologic agents to treat such disorders by inducing self-tolerance has progressed over the last 60 years. Historically termed immunosuppressive agents, it is now understood that they may modulate the immune system in varied and unexpected ways. The goal of immunomodulation in autoimmune disease is to produce self-tolerance without global immunosuppression place the patient at increased risk of infection and loss of immune surveillance that prevents the development of secondary malignancies.

1. Immunity: recognition of non-self

The traditional classification of the human immune system divides the host response to external pathogens and transformed cells into innate immunity and adaptive immunity [1]. The innate immune system is comprised of neutrophils, monocytes, macrophages, dendritic cells, natural killer (NK) lymphocytes, and the plasma complement proteins. More recent definitions have expanded the innate immune system to include platelets, endothelium, and the coagulation cascade [1-4]. The innate immune system represents the first line of host defense against foreign pathogens. Innate immunity performs its immune surveillance function via Toll- like receptors that recognize conserved pathogen-associated molecular patterns (PAMPS) but also pattern-recognition receptors (PRRs) and NK receptors [5]. The initial response of the innate immune systems feeds into and directs the subsequent responses of adaptive immunity by antigen processing and cytokine production [1].

Adaptive immunity involves the expression of a targeted lymphoid response against foreign pathogens involving thymic [T] lymphocytes and antibody producing B lymphocytes. The targeted responses of the adaptive immune system can further recruit and amplify the cellular responses of the innate immune system [1]. This is performed in large part by antibody mediated pathogen clearance. Antibodies can also mediate complement lysis of pathogens and Fc-receptor phagocytosis of pathogens by neutrophils, monocytes, macrophages, and hepatic Kupffer cells. The cellular immune responses of the cytotoxic ($CD8^+$) T lymphocytes can clear viral infected and transformed cells. Both antibody and cellular immune responses are regulated by antigen specific helper/inducer ($CD4^+$) T lymphocytes. The CD4 lymphocyte can also function as an effector cell, enhancing the intracellular killing of pathogens by the production of interferon-γ.

2. Autoimmunity: loss of self-tolerance

During the development of mature B and T cells, lymphoid precursors highly attracted to self-antigens are eliminated. Lymphocytes in the bone marrow will become B cells and those that enter the thymus will become T cells. As they are maturing, those cells that are self-reactive will undergo apoptosis, in a process that is called central tolerance. Most of the deletion of strongly self-reactive T lymphocytes occurs in the thymus [6,7].

Most of the lymphocytes that recognize non-self (foreign) antigens will, therefore, enter the peripheral circulation occupying lymph nodes, spleen and bone marrow where they will expand when they meet antigen. A few self-recognizing lymphocytes with low-reactivity to self will also enter the peripheral circulation, where they will either remain inactive or be deleted when activated in order to prevent disease. This is called peripheral tolerance (6,7). Peripheral tolerance is mediated in large part by natural and inducible T regulatory cells (Tregs) [6-8].

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The existence of families with multiple individuals with autoimmune disorders, an increased risk of autoimmune disorders in siblings and the pronounced increased risk of such disorders in identical twins strongly speaks to a genetic propensity for autoimmune diseases [9,10]. Murine and human genome wide studies have found a number of genes associated with an increased risk of autoimmunity. While some genes are well known to be associated with immune regulation, genes in the major histocompatibility complex (MHC) region account for the greatest number of genetic associations with autoimmune disease [11]. Such changes in the MHC genes may account for the failure to delete some lower affinity self-reacting lymphocytes that can escape central deletion.

Environmental factors undoubtedly contribute to the development of autoimmunity. Even in identical twins the incidence of autoimmune disorders is only 40%–50% of the monozygotic sibling [12]. There are a number of environmental factors that have been shown capable of inducing autoimmune responses in genetically susceptible individuals. Epidemiologic studies have found associations between acute and chronic viral or bacterial infections, immunizations, environmental toxins, certain drugs, smoking, vitamin D deficiency, and even changes in the intestinal microbiome to potentially induce autoimmune disorders [9,10,13].

The innate immune system also plays an important role in maintaining self-tolerance, However, an aberrant innate immune response to pathogens, drugs, toxins, or commensal microbiota can induce a severe inflammatory state presenting the adaptive immune system with auto-antigens derived from damaged tissues and inducing an adaptive T- and B-lymphocyte autoimmune reaction. Under such circumstances the presence of inflammatory-induce co-stimulatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) further drive the adaptive immune response by inhibiting Treg suppressor function leading to a chronic autoimmune state [9,10,14].

In susceptible individuals, the induction of autoimmunity pushes the T lymphocyte repertoire toward a pro-inflammatory state defined by a pattern of cytokines expressed by the subsets of thymic lymphocytes [9,10]. The inflammatory T_H1 $CD4^+$ helper lymphocyte repertoire is defined by the production of interferon-γ, IL-2, and TNF. The T_H17 lymphocyte repertoire is defined by the secretion of IL-17 and IL-22. A third pro-inflammatory repertoire termed T_{FH} lymphocytes express the $CD4^+$-inducible T-cell co-stimulator receptor and the C-X-C chemokine 5 receptor and secrete IL-21. T_{FH} lymphocytes support the expansion of autoantibody production. A T_H2 repertoire expresses the anti-inflammatory cytokine Il-10, along with IL-4, IL-5, IL-6, IL-9, and IL-13, which can invoke strong antibody responses and inhibit some neutrophil and macrophage effector functions [15]. Suppression of the pro-inflammatory lymphocyte repertoires requires reconstitution of Treg suppressor function [9,10,16].

The challenge for the clinician is to modulate the immune system in patients with autoimmune disease resulting in a therapeutic induced self-tolerance without inducing significant immune suppression, therefore, diminishing the patient's immune response to foreign pathogens and transformed cells. Also, the heterogeneity of the underlying pathophysiology may account for the variable responses to many treatment regimens.

3. Therapeutics for autoimmune disorders

The development of immune modulating therapies for autoimmune disorders has progressed rapidly since the first reports by Schwartz and Dameshek on the induction of immune tolerance in rabbits with 6-mecaptopurine (6-MP) [17,18]. Only 4 years after their initial reports; they subsequently reported on the use of the drug for treatment of patients with autoimmune hemolytic anemia [19]. Most often designated as immunosuppress drugs, a series of therapeutic agents have been developed that target one or more components of the immune system. They can be broadly defined as inhibitors of T lymphocyte activation and proliferation; inhibitors of B-lymphocyte activation and proliferation; inhibitors of the innate immunity, inhibitors of immune cell trafficking, cytokine inhibitors, and drugs that deplete T or B lymphocytes or both (Table 1).

Glucocorticosteroids (GC) were the first [20] and remain one of the most important agents for the treatment of autoimmune disorders with the broadest spectrum of immune modulatory effects [21]. The spectrum of their biologic effects can change with increasing doses. At low doses they affect immune cell trafficking, downregulate FcR expression on macrophages, and neutrophils and modulate cell signaling. With higher doses they can induce apoptosis of eosinophils and mast cells; inhibit dendritic cell differentiation, and suppress cytokine production from T lymphocytes, macrophages, endothelial cells, and smooth muscle cells. At very high doses, they can induce apoptosis of plasma cells, and T and B lymphocytes.

Compared to other immune modulating agents, the onset of action by glucocorticoids can be very rapid. Upon binding to the glucocorticoid receptor (GR), the complex of the receptor with the glucocorticoid (GR/GC) is rapidly transported to the nucleus where it binds to the glucocorticoid binding sites for transcription of

Table 1
Targets of immune modulating agents.

T lymphocyte	B lymphocyte	Monocyte, macrophage, dendritic cell	Inhibitors of immune cell trafficking	Cytokine & cytokine R inhibitors
Corticosteroids	Corticosteroids	Corticosteroids	Corticosteroids	Corticosteroids
Azathioprine	Azathioprine	Azathioprine	Natalizumab	**TNF inhibitors**
Cytoxan	Cytoxan	Cytoxan	PSI-697	Infliximab
Mycophenolate	Mycophenolate	Mycophenolate	GMI 1070	Adalimumab
Alemtuzumab	Alemtuzumab	IV-Ig		Golimumab
Cyclosporine	Rituxumab	Fostamatinib		Etanercept
Tacrolimus	Ofatumumab			**IL-1 inhibitors**
Sirolimus	Veltuzumab			Anakinra
Everolimus	Ocrelizumab			Canakinumab
BI655064				Rilonacept
BMS-986004				**IL-6 inhibitors**
				Tocilizumab
				11-17 inhibitors
				Secukinumab
				Ixekizumab
				Brodalumab