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RESEARCH ARTICLE

Vaccine Immunomodulation of Disease: Targeting the Treatment of Autoimmune Diseases

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ABSTRACT
Autoimmune disease disrupts the normal immunological balance by promoting a perpetual cycle of innate/immune/inflammatory responses that continues due to the continued presence of antigen. The disease cycle is in turn amplified and regulated by cycles of antigen-specific T cell mediated immune responses. Removal of the stimuli or regulation of the disease drivers can stop the cycle to allow rebalancing and prevent the progression or chronicity of disease. As an alternative to the current treatments for autoimmune and inflammatory disease, which reduce, inhibit or eliminate the triggers, drivers or antigens, newer approaches stimulate regulatory responses, or inhibit or repurpose the effector/inflammatory responses to control the immune disease cycle. LEAPS (Ligand Epitope Antigen Presentation System) therapeutic vaccines for rheumatoid arthritis are presented as examples of therapies that elicit antigen specific T cell modulation of autoimmune and inflammatory responses to treat disease.

Introduction

Disease results from a disruption of the normal balance of systems and functions within the body. This is especially true for the immune system which maintains a balance between the status quo (maintenance of homeostasis) and activation of effector and inflammatory responses.[1,2] Challenges from trauma, infections, neoplasms, and autoimmunity disrupt the normal balance by promoting a cycle of immune/inflammatory responses that continue as long as there are stimuli (tissue disruption, pathogenic microbes, antigens) and drivers (effector cells and molecules e.g. cytokines, chemokines, antibodies). The disease cycle is in turn amplified and regulated by cycles of antigen-specific T cell mediated responses. Removal of the stimuli or regulation of the disease drivers can stop the cycle to allow rebalancing and prevent the progression or chronicity of disease (Figure 1).

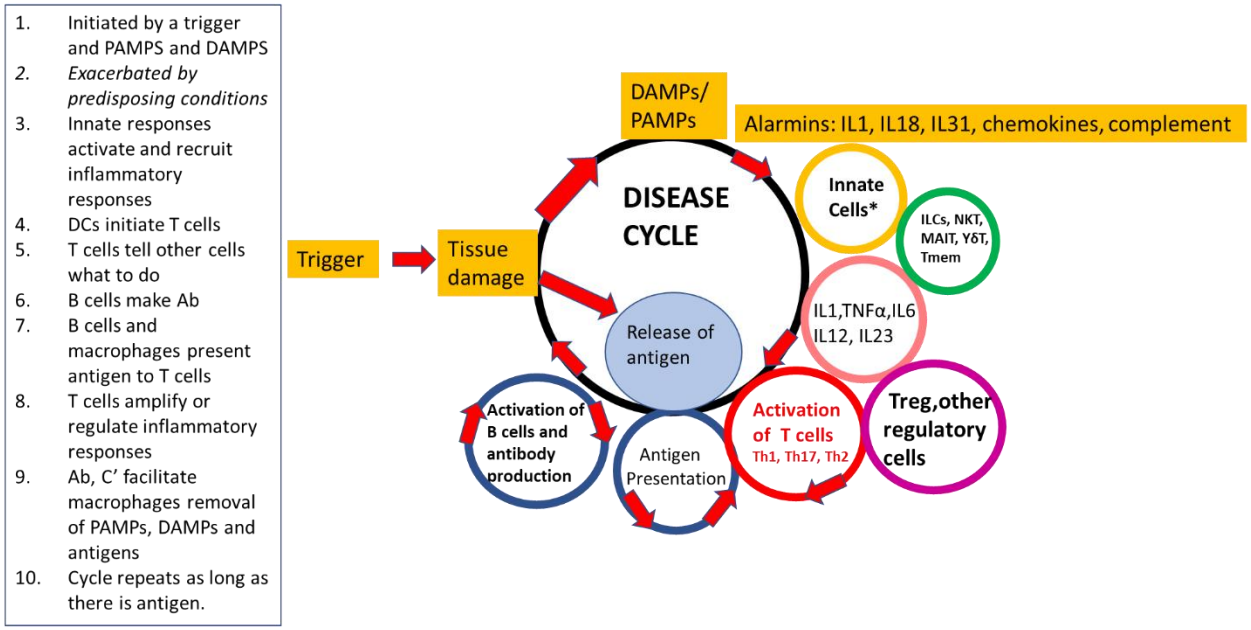

Figure 1. The immune disease cycle. Immunologic disease is initiated by a trigger such as trauma or infection which causes tissue damage, which releases damage associated molecules (DAMPs) and potentially infection by normal or other microbes and exposure to their pathogen associated molecular patterns (PAMPs). The damage, DAMPs, and PAMPs activate receptors and expression of alarmins, cytokines, chemokines and potentially activation of the complement cascade which recruit and activate innate cells (yellow circle), including dendritic cells (DCs), macrophages and neutrophils. Alternative lymphocytes (green circle), including innate lymphoid cells (ILC), invariant natural killer T cells (NKT), mucosal associated invariant T (MAIT), and γδT cells, and memory αβT cells, if present (Tmem) reinforce the local innate responses. These cells also produce acute phase and bridging cytokines (pink circle) which activate inflammation and DCs to generate proinflammatory Th1 and Th17 cells (red circle). These T cells activate neutrophils, macrophages and B cells. Th2 cells are generated and with Th1 cells activate B cells to switch production to IgG, IgE and IgA antibody to the antigen released by tissue damage and with other APCs present antigen to T cells to maintain T cell activation (blue circles). Effector and inflammatory functions are regulated by Tregs, iTregs and other cells (purple circle). The cycle continues as long as antigen, and damage are present.

The classical example of the immunological disease cycle occurs for infections (see Figure 1). Infections initiate the immune disease cycle by exposing microbial structures (pathogen associated molecular patterns (PAMPs)[3] and releasing cellular debris upon tissue damage (damage associated molecular patterns (DAMPs)) to be detected by epithelial, neutrophil, macrophage, dendritic cells (DCs), and other cells. These cells initiate local inflammation and the DCs activate T cells. The cycle is amplified by the cytokine conversations and actions of proinflammatory Th17 and Th1 T cells (Figures 2 and 3). As long as the microbe and the inflammatory response to the microbe continue to produce DAMPs, PAMPs and microbial or other antigens, the cycle of the immune and inflammatory response will continue. Upon resolution of the infection, the production of damage and antigens stops, macrophages facilitate the clearance of DAMPs, PAMPs and antigen, and effector cells dissipate or are regulated by T cells and other cells

(see Figures 2 and 3) to allow the system to return to its balance and heal.

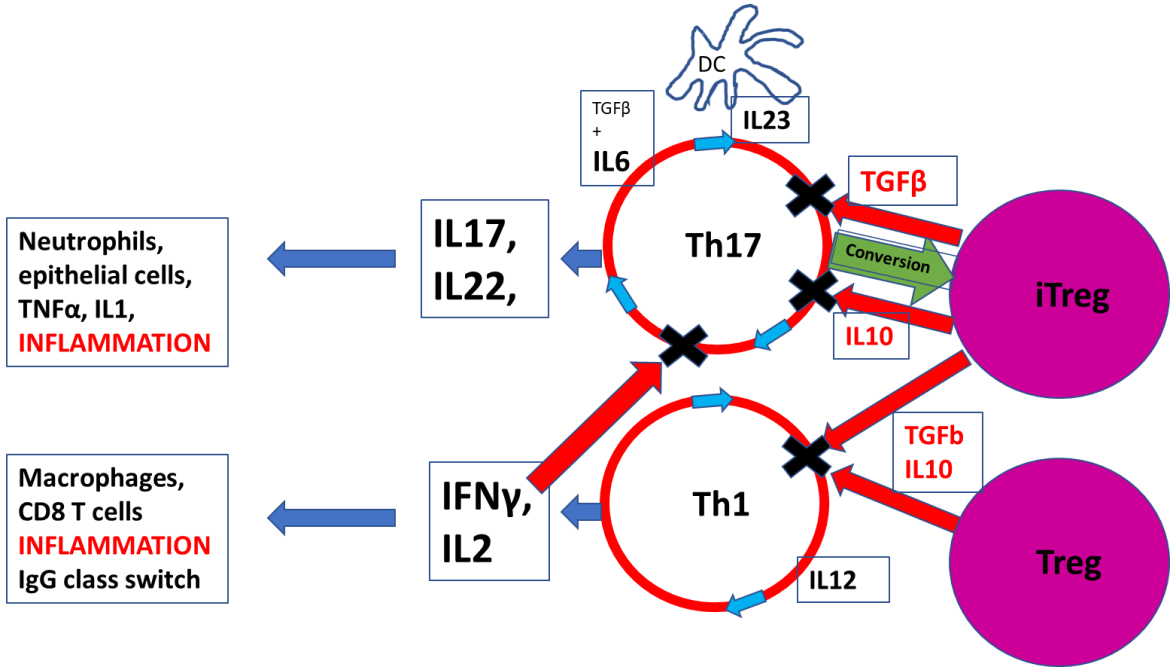

Figure 2. Activation and control of proinflammatory Th17 and Th1 responses. Th17 responses are initiated by antigen presentation by activated dendritic cells (DC) in the presence of IL6 and small amounts of TGFβ and the response matures by IL23 action produced by DCs. Th1 responses are initiated by DCs activated by small amounts of IFNγ and IL12. Th17 and Th1 responses are inhibited by IL10 or large amounts of TGFβ which can promote their conversion into inducible Treg (iTreg) cells. Interferon gamma (IFNγ) also inhibits Th17 responses.

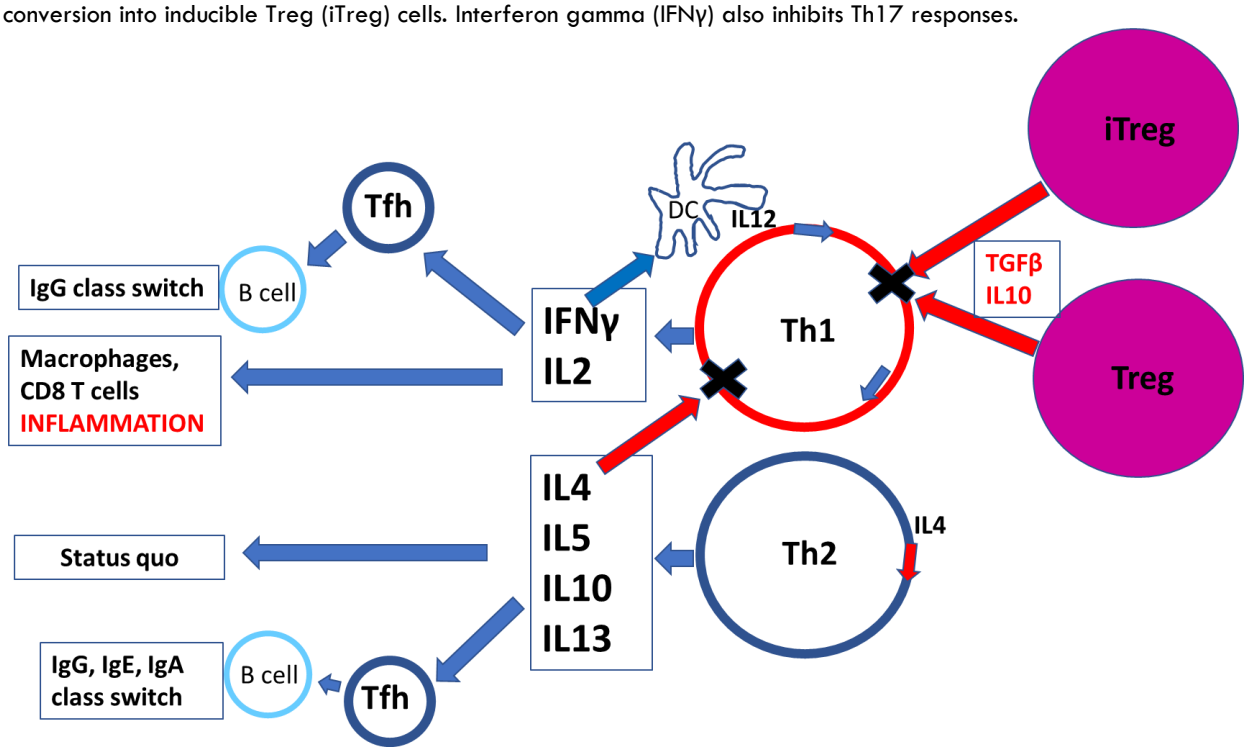

Figure 3. Activation and control of proinflammatory Th1 responses. Th1 responses are initiated by antigen presentation by dendritic cells (DC) that are stimulated by small amounts of interferon gamma (IFNγ) to produce IL12. The absence of IL12 or an abundance of IL4 promotes Th2 responses. Th1 cells are controlled by IL10 and TGFβ. Th1

and Th2 responses also activate and direct T follicular helper cells (Tfh) to promote B cells to undergo immunoglobulin class switch.

During chronic infections, the microbe is not eliminated, and hence the immune stimuli remain to continue the immune disease cycle with continued inflammation, tissue damage or systemic disruption. The disease presentation is likely to be different than for acute disease due to differences in the response to PAMPs and DAMPs and changes in the activity, numbers and interactions of the effectors and regulators. Similarly, once initiated by an activator of DCs, for an autoimmune disease, the disease cycle is maintained by an unlimited supply of autoantigens.

As an alternative to the current treatments for autoimmune and inflammatory disease, which reduce, inhibit or eliminate the triggers, drivers or antigens, newer approaches stimulate regulatory responses, or inhibit or repurpose the effector/inflammatory responses to control the immune disease cycle. LEAPS (Ligand Epitope Antigen Presentation System) therapeutic vaccines for rheumatoid arthritis (RA) are presented as examples of therapies that elicit antigen specific T cell modulation of autoimmune and inflammatory responses to treat disease.[4-7]

The Immunological Disease Cycle

The PAMPs and DAMPs generated by infection, trauma or life's abuses trigger the start and determine the nature of the immune disease cycle. The innate and antigen-specific systems reinforce these responses through cell-cell interactions, cytokines, chemokines and other molecules. Depending upon the triggers, specific and distinct cytokine/chemokine conversations direct the nature of the responses (Table 1). Following tissue damage and bacterial infection, the cycles are initiated by alarmins (interleukin (IL)1, IL18, IL31, IL8, etc.)[8] and progress to acute phase cytokines (IL1, TNFα, IL6), and then bridging cytokines which activate proinflammatory T cell responses (IL12, IL23). Following exposure to abnormal RNA or DNA, such as from a viral infection, the cycle starts with type I and III interferon production and progresses differently to Th1 and CD8 T cell responses.[9] Neutrophils are first responders and promote inflammation but are short lived[10] whereas macrophages[11] and dendritic cells (DC)[12] have more diverse activities, are long lived and can extend the length of the response.[12] As phagocytes, these cells provide antimicrobial actions, the elimination and recycling of molecular trash and promote remodeling of tissue following the challenge. The innate responses are guided by innate lymphoid cells (ILC), alternative T cells (γδ T cells, NKT, MAIT), and memory T cells, if present.

The transition to classical αβT cell responses is initiated by activated DCs producing the bridging cytokines IL12 or IL23 and presenting antigen to naïve T cells.[12] Activation of antigen presenting cells (APCs) upregulates cell surface molecules to enhance T cell activation. DCs, including Langerhans cells in the epidermis of the skin, are the most potent of the APCs and the only cell type that can initiate a new T cell response from a naïve T cell. DCs constantly phagocytize local proteins and particles (including cells and microbes) and elicit tolerizing signals unless activated by PAMPs, DAMPs or the cytokines produced by surrounding cells. Activated DCs cease phagocytosis, travel to the draining lymph node and present peptides digested from phagocytized proteins to CD4 and CD8 T cells within the lymph node. DCs are also adept at cross-presenting peptides from phagocytosed proteins to CD8 T cells. In addition to DCs, macrophages, and B lymphocytes, are also APCs. They proteolytically process the proteins that they phagocytize and present peptides on major histocompatibility complex antigens (MHC I, MHC II). DCs and macrophages in the lymphatics and at the site of the challenge can extend T cell activation by antigen presentation, especially when they are activated by TNFα and IFNγ. B cells can also accumulate at the site of challenge and are very potent antigen presenting cells for the specific antigenic protein captured by its cell surface antibody. The internalized antigen is then processed and presented at a high concentration and in a limited repertoire to potently activate CD4 T helper cells which can maintain and amplify the immune response. B cells are therefore major drivers of T cell responses in autoimmune disease.

Which antigenic peptides get presented to T cells is determined by the individual's MHC I and II molecules. The antigenic peptide is anchored within a cleft at or near the top of these molecules to display its epitope to T cells.[13] The ability of a peptide to bind to the cleft can determine whether an immune response can occur. Certain MHC types bind autoantigenic peptides better than others leading to MHC associations with these diseases.[13] Each cell can present at least 6 different endogenous (intracellular and cross presented

extracellular proteins) peptides on its MHC I molecules, two HLA-A, two HLA-B and two HLA-C, to CD8 T cells. APCs, and on occasion other cells, can also express 6 different peptides on their MHC II molecules, two HLA DR, two HLA-DP and two HLA-DQ, to CD4 T cells. In addition, the MHC antigens are part of a large gene complex that encodes other immunological activities and mutations in these genes affecting the immune disease cycle may be genetically associated with certain MHC types.[14]

Antigen recognition by B cells and T cells is determined by the B cell receptor (immunoglobulin molecule (BCR)) or T cell receptor (TCR). Each clone of these cells expresses a different BCR or TCR. These genes are generated by random recombination of gene segments to produce a large repertoire of antigen binding molecules which can include nonsense and recognition of autoantigens. Most of the lymphocytes with self-reacting BCRs or TCRs are selected for elimination but some auto-reactive cells escape the selection systems and are not eliminated. The selection process for T cells occurs in the thymus with a subset of the self-reactive T cells becoming regulatory T cells (Tregs). In addition to the 'escapees' and Tregs, self-reacting IgM antibodies (rheumatoid factor) are generated to facilitate clearance of immune complexes and antimicrobial protections but may also contribute to autoimmune diseases.[15,16]

TABLE 1. Cytokine Conversations that drive Immune responses

Response	Main Sources	Conversation	Outcome
Alarmins	Epithelial and initial challenged cells; inflammasome	IL1, IL18, IL33, IL18, TSLP*, IL25, chemokines, complement, etc.	Activation and recruitment of innate responses, macrophages, neutrophils
Type I and III interferons	Virus infected cells and plasmacytoid DCs	IFNα,β,ε	Antiviral response, CD8 T cell response, etc.
Acute phase	Macrophages, etc.	IL1, TNFα, IL6	Inflammation, fever, acute phase liver responses, activation of macrophages and neutrophils, etc.
Bridge cytokines	DCs, Macrophages	IL12, IL23	Activate Th1, Th17 responses, respectively
Th1	ILC 1, CD4 and other T cells**	IFNγ, IL2, LT	Cell mediated lymphocyte responses, activation of macrophages, proinflammation, IgG class switch.
Th17	ILC3, CD4 and other T cells	IL17, IL22, TNFα	Activate neutrophils, antimicrobial peptides, proinflammation, epithelial maintenance
Th2	ILC2, CD4 and other T cells	IL4, IL5, IL10, IL13	Humoral responses, IgG, IgE, IgA class switch, activation of mast cells, eosinophils
Treg	ILCreg, CD4 and other T cells	IL10, TGFβ	Regulation of effector cells, autoimmune responders, and inflammation

*Abbreviations: TSLP: Thymic stromal lymphopoietin; IL: interleukin, LT: lymphotoxin, ILC: innate lymphoid cells, TGF: transforming growth factor, TNF: tumor necrosis factor.
**Other T cells include CD8 T cells, invariant natural killer T cells (NKT), MAIT and γδ T cells.

The immune disease cycle is amplified by the cell-cell interactions and cytokine conversations of CD4 helper T cells and other T cells[17] (see Figures 2 and 3). The status quo response to a bolus of antigen would initiate a Th2 humoral response driven by IL4, IL5, IL10 and IL13 to promote production of immunoglobulin G (IgG), IgE and IgA and activation of mast cells and eosinophils. DCs that acquire

antigenic proteins in the presence of IL6 and normal levels of TGFβ or produce IL23 will promote a proinflammatory Th17 response. The cytokine conversation of a Th17 response, IL17, IL22 and TNFα, promotes neutrophil activity and epithelial cell functions. DCs experiencing small amounts of interferon (IFN) γ and bacterial PAMPs, such as LPS, produce IL12 which promotes the proinflammatory Th1 response and generates IL2, larger amounts of IFNγ and lymphotoxin (LT). These cytokines promote cell mediated responses and also act on B lymphocytes to promote class switch to IgG antibody. IL2 promotes T cell and NK cell proliferation while IFNγ promotes the activation of macrophages to M1 activated macrophages which have enhanced antigen presenting ability, increased antimicrobial activity and ability to promote inflammation. The long lifespan of macrophages and B cells and their ability to present antigen to T cells can reinforce and extend Th17 and Th1 responses as long as antigen is present.

Regulation of the Immune Cycle

Once established, an antigen specific response must be tightly controlled since it represents a commitment to lymphocyte cell clones which develop lifelong memory that can be reactivated and expanded upon future rechallenge. Most lymphocytes with self-reactive antigen receptors (TCR, BCR) are eliminated in the thymus or bone marrow but autoimmune cells do escape from selection and autoreactive Treg cells have the potential to convert into effector cells due to the plasticity of T cell responses (see next section).

In the periphery, initiation of a new T cell response in naïve T cells is restricted by requiring three signals: 1. a strong recognition by the TCR for the MHC:antigenic peptide complex; 2. sufficient numbers of B7 co-receptors bound to CD28 to override CTLA4 inhibition; and 3. cytokines or other stimuli to activate and determine the nature of the response.[18] Activated DCs upregulate cell surface expression of MHC and B7 molecules for this purpose. Once activated, the expansion of autoimmune or overzealous T effector cells is further regulated by Tregs, inducible T regs (iTreg), Th3 cells, other regulatory T cells, innate lymphoid cells (ILC), competing responses and myeloid and other suppressor cells.[19-21]

Regulatory T cells and ILCs control autoreactive and excessive responses with cytokines, by activating suppressor macrophages and DCs, by direct cell-cell interactions and by killing activated lymphocytes.[19,21] Although T cells are antigen specific, the IL10, TGFβ and IL16 that they release can disseminate to suppress inflammatory effector cells or stimulate suppressive functions from macrophages and DCs.[21] Stimulation of suppressor/regulatory macrophages and DCs can promote production of indoleamine2,3 dioxygenase (IDO) which depletes the supply of tryptophan and prevents T cell proliferation.[22,23]

Classical CD4 regulatory T cells are generated in the thymus[24] whereas the plasticity of T cells [24] allows generation of iTregs and CD8 regulatory/suppressor T cells (CD8Ts)[25] in the periphery in the absence of inflammatory stimuli or in the presence of large amounts of the regulatory cytokines, IL10 and TGFβ.

Proinflammatory responses can also be inhibited by activation of a counterbalancing T helper response. The Th2 cytokine conversation includes IL4, which will reinforce the Th2 response and prevent expression of the Th1 phenotype,[26] and also IL10 which is immunosuppressive.[27,28] IFNγ, the key cytokine of the Th 1 conversation, can also stimulate Treg cell function, inhibit Th17 responses and also neutrophil trafficking, and stimulate certain regulatory responses, including production of IDO by DCs and macrophages.[29] These T cell regulatory networks are especially important at mucosal epithelial borders of the body that receive constant microbial challenge and for controlling potential autoimmune responses.

Chronic Immunological Disease Cycles

Immunological disease occurs when the normal functions of the immune system are excessive, unregulated, dysregulated, activated inappropriately or to the wrong molecule. For inflammatory and autoimmune diseases, such as RA, celiac disease, type 1 diabetes, multiple sclerosis (MS), Crohns disease and psoriasis, to name the more commonly recognized diseases, the omnipresence of a self-antigen or a chronic stimulus will overpower the normal regulatory mechanisms to allow continuation of the immune disease cycle and prevent the rebalance of the immune system.[7,30] These diseases often start with a triggering response, such as an infection, trauma, or even vaccination which activates DCs and also provides self or related antigens to initiate the autoimmune disease cycle (see Figure 1). The cytokines produced by the activated DCs then promote proinflammatory Th17 and/or Th1 responses to amplify and maintain the disease cycle (see Figures 2 and 3).

The immunological balance is shifted towards inflammation and inflammatory diseases by the accumulation of life's challenges (immunobiography) with aging, termed Inflammaging.[31,32] The aging and shrinkage of the thymus reduces the generation of Tregs which contributes to the inflammaging. This increases the systemic levels of inflammatory cytokines and lowers the set point for development of autoimmune disease.

Specific MHC types increase the risk for autoimmune disease by their ability to bind and present the autoantigen to T cells.[33] The risk is converted into autoimmune disease by highly activated DCs, possibly as a result of the cytokine storm produced by a superantigen or viral infection that overrides regulatory signals. Autoimmune responses may be elicited towards an autoantigen released by tissue damage, a chemically modified peptide, as for citrullinated peptides, or a microbial peptide that resembles an autoantigenic peptide (antigenic mimic), as for the Epstein Barr Virus (EBV) EBNA1 protein and myelin proteins.[34-36] In addition, slippage in the TCR recognition of the peptide-MHC complex can expand the numbers of T cell clones that can recognize self-antigens, a process termed epitope spreading.[37] Once initiated towards the autoantigen, immune stimulation continues since the supply does not disappear. APCs maintain the stimulation of T cells to extend the chronic condition. Although the constant stimulation may exhaust some of the lymphocytes or make them anergic or senesce,[38] the response develops into chronic inflammatory disease.

For RA, antigens derived from connective tissue proteins and their citrullinated versions provide a constant stimulus for inflammatory responses.[39,40] For celiac disease, it is responses to deamidated gluten from grains and human transglutaminase-2 protein that continue the cycle.[41] For type 1 diabetes, the self-antigens include glutamic acid decarboxylase (GAD), insulinoma-associated antigen-2 (IA-2) and zinc transporter 8 (ZnT8) of the pancreatic islets,[42] and for MS, it includes myelin basic protein (MBP), proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG).[43] For psoriasis, it may be the Pso p27 antigen[44,45] and for Crohns disease, bacterial flagellin. [46]

The classic example of an autoimmune disease is RA. The autoantigens associated with RA include collagen II, IX and XI, proteoglycan (PG or aggrecan), vimentin, filaggrin, fibrinogen, heat shock proteins (HSP), nuclear proteins and citrullinated and other modified versions of these and other proteins.[7,43,46-52] Generation of citrullinated peptides within connective tissue proteins can occur as a consequence to smoking. DCs present these proteins with IL12 or IL23 to initiate Th1 and Th17 proinflammatory responses. The disease progresses with production of the inflammatory cytokines, TNFα, IL1, IL6 and receptor activator of NF-κB ligand (RANKL) produced by activated macrophages, osteoclasts and other cells. Th1 and Th17 responses drives activation of neutrophils, macrophages, B cells, other T cells and osteoclasts that promote the disease cycle.[52,53] The chronic disease cycle is maintained by the release of antigen following inflammatory tissue damage and osteoclast activation, phagocytosis by macrophages, DCs and antigen-specific B cells and protein processing and presentation to T cells. The chronic disease cycle continues and is prolonged by the proinflammatory T cells due to the unending supply of antigen.

Tailoring treatment for autoimmune and inflammatory diseases

In order to treat an autoimmune or inflammatory disease, the immune cycle of disease must be broken to allow restoration of the immune balance. For infections, the cycle can be broken by elimination of infection, its PAMPs and antigens and the cessation of tissue damage and its DAMPs. Reduction in the infectious load by antimicrobial drugs allows the immune system, which may have been initiated by a vaccine, to clear the infection and its antigens. For most autoimmune diseases, the cycle continues because the source of antigen cannot be eliminated and regulatory mechanisms are either subverted or overpowered. Classical treatments are therefore directed towards inhibiting or eliminating the immune molecules, cytokines or cells that are driving the autoimmune and inflammatory responses. In contrast to infections, therapeutic vaccines are being considered to activate antigen specific Tregs or redirection of the disease driving proinflammatory T cell responses. The challenge, however, is to elicit therapy and not elicit antibody, T cell or hypersensitivity reactions that may exacerbate disease. For autoimmune diseases that are initiated and maintained by immune responses to latent and recurring viruses, such as Epstein Barr virus, or endogenous retroviruses, e.g., HERV, an antiviral vaccine may be therapeutic.[36,54]

For RA, treatment usually starts with attempts to alleviate pain and then progresses to use of Disease Modifying Antirheumatic Drugs (DMARDS) which suppress the expression of inflammatory responses

(low dose methotrexate, corticosteroids); kill or inhibit the growth or function of effector cells; or ablate the action of the effector cells or their cytokines.[7,55,56] Most of these treatments also suppress or eliminate important immune responses which increase the risk of the patient for intracellular infections and some cancers.

Ablative therapies include neutralizing monoclonal antibodies or soluble receptor antagonists that target specific cytokines. The targeted cytokines include the mediators of inflammation and acute phase response (TNFα, IL1, and IL6), the bridge cytokine inducers of proinflammatory T cell responses (IL12, IL23) and IL17, of the proinflammatory Th17 response.[55-57] Alternatively, small molecule inhibitors of the intracellular Janus tyrosine kinases (JAK1, JAK2, JAK3 or TYK2) stop the transmission of signals between cytokine receptors and gene expression to limit expression of proinflammatory mediators. These inhibitors (to be referred to as "-nibs") target one or more of these kinases and to different extents. As such, different -nibs will inhibit different sets of cytokines and their actions.[58-61] The immunological disease cycle can also be broken by reducing the number of antigen-presenting B cells by inducing killing with monoclonal antibodies targeted at the cell surface CD20 protein.[62]

Alternative approaches to these ablative therapies attempt to rebalance the immune response by lowering systemic inflammation metabolically, by targeting the microbiome,[63] or by addressing the proinflammatory effector T cells that amplify the disease cycle. These immunotherapies attempt to modulate, regulate or redirect the disease promoting responses[7,64-66] by stimulating new or existing Tregs or CD8Ts,[24,25] by inhibiting the Th17 or Th1 proinflammatory T cells or repurposing them into iTreg.[25] Induction of Th2 responses block the development of other T helper responses with IL4 and IL10. IL4 produced by Th2 responses drives more production of IL4 to reinforce the Th2 response.[67] The IL10 will suppress proinflammatory responses.[68,69] Generation of IFNγ,[70] in addition to activating macrophages, can stimulate Treg function, inhibit Th17 responses, neutrophil trafficking, and stimulate certain regulatory responses, including production of IDO by DCs and macrophages.[22,23] Although the CD4 Tregs, iTregs and CD8 T suppressor cells are antigen specific, the regulatory cytokines IL10, TGFβ and IL16 released by these cells can disseminate locally and elicit a bystander effect to suppress other tissue specific T cells and activate suppressive functions from macrophages and DCs.

Various means have been used to elicit antigen specific therapeutic responses [reviewed in [64-66,71-75]] but are limited by our understanding of how to activate regulatory responses. These include use of DNA vaccines, peptide or protein vaccines, use of certain adjuvants[76,77] or carriers,[78] or by adoptive transfer of laboratory expanded Tregs or antigen loaded tolerogenic DCs.[79] Alternate routes or means of antigen delivery, such as oral or dermal delivery of the antigen, can also promote immunoregulation.[80,81] For example, oral delivery of live attenuated salmonella expressing pre-proinsulin combines the alternate route with a unique delivery system to promote immunotolerance.[82] Reviews and examples of vaccine immunotherapies are provided for T1D,[83-85] MS,[86] celiac disease,[87] and for RA.[88-92]

LEAPS vaccine modulation of proinflammatory T cells

The LEAPS platform for vaccine development provides a means for custom designing antigen specific activation of either Th1 or Th2 and Treg responses to optimize the subsequent prophylactic and therapeutic outcomes. LEAPS peptide vaccines have been shown to treat on-going disease in animal models of RA and encephalomyelitis by modulating the ongoing proinflammatory T cell responses.[4-7,93] The LEAPS vaccines consist of an immune cell binding ligand (ICBL), termed either DerG or J, attached to a disease related T cell antigen containing peptide.

The derG LEAPS peptide vaccines activate humoral (Th2) and regulatory responses by interacting with CD4 T cells.[94,95] The derG ICBL consists of the DGQEEKAGVVSTGLI peptide from the beta chain of the MHC II molecule. Immunomodulatory vaccines developed for RA include CEL-4000, which incorporates the ATEGRVRVNSAYQDK (PG70) proteoglycan peptide, and a related LEAPS vaccine, which incorporates the citrullinated PG275 proteoglycan peptide, MDMCSAGWLAD{Cit}SVR.[94,95] Immunization with either of these vaccines or a combination of the two vaccines elicited antigen-specific responses that stopped the progression of on-going disease in the proteoglycan induced PGIA and GIA models of RA. These models[96-98] resemble human RA more than other animal models in that disease is induced in older female mice, and anti-citrullinated protein (ACC), autoantibody to anti-citrulline peptide (ACPA) (such as in humans) and rheumatoid factor (Rf) are produced. Neither the DerG-ICBL nor the

antigenic peptides alone were therapeutic. Treatment with the derG-LEAPS vaccines curtailed the Th1 driven disease progression in this mouse model, reduced the Th1 and Th17 related cytokine and inflammatory responses and promoted T regulatory responses by acting on memory and effector T cells, including those in the spleen, to increase expression of anti-inflammatory IL-4, IL-10 and TGF-β cytokines and Treg numbers while decreasing the expression of pro-inflammatory IFN-γ and IL-17.[94,95]

The J LEAPS peptide vaccines activate IFNγ mediated responses by activating the maturation of mouse or human precursors to rapidly become IL12 producing DCs.[93,99,100] The J-LEAPS responses include Th1 related cytokines and CD8 cytotoxic T cells and favor cell-mediated responses but also include immunomodulation. The J ICBL consists of the DLLKNGERIEKVE peptide from beta-2-microglobulin of MHC I. Attachment of the J-ICBL to a peptide containing a CD8 T cell antigen elicits CD8 and CD4 responses producing IFNγ.[93, 99-101] Treatment with CEL-2000, which incorporates the TGGKPGIAGFKGEQGPKGEP epitope from human type II collagen, curtailed on-going disease progression in the collagen induced arthritis (CIA) mouse model of RA.[102] Disease in these mice is driven by Th17 proinflammatory responses. Mice immunized with CEL-2000 had greatly reduced levels of IL17 and TNFα and increased levels of IFNγ and IL10 indicative of immunomodulation of the disease. Similarly, the J-My-1 LEAPS conjugate, incorporating a myocarditogenic peptide of cardiac myosin (MyHCα334-352 (My-1)), prevented or treated Th17 driven experimental autoimmune myocarditis in mice.[103] In these autoimmune disease models, J-LEAPS vaccine activation of DCs producing IL12 induce T cells to produce IFNγ and IL10 and immunomodulate the disease driving Th17 proinflammatory responses to stop progression of disease. In addition to their immunomodulatory activity, J-LEAPS peptide vaccines have been developed that provide protection against HSV-1 infection[93,99-101,104] and protection and therapy for HER-2/neu breast cancer in mouse models.[105] Adoptive transfer of DCs prepared using J-LEAPS vaccines protected against HSV-1 infection[99,100] and protected and treated H1N1 influenza infection with reduced expression of inflammatory cytokines.[106] For Th17 driven diseases, such as psoriasis, a J-LEAPS vaccine or adoptive transfer of autologous derived J-LEAPS vaccine DCs, may provide the antigen-specific immunomodulation necessary to break the disease cycle and rebalance the immune response.

CONCLUSION

Autoimmune disease continues as a cycle of inflammatory responses that is maintained by tissue damage and amplified by and regulated by the cytokine conversations of T cell mediated antigen-specific immune responses. Inhibition or ablation of the mediators that maintain or amplify the immune cycle of disease can treat the disease but also compromises certain immune protections. Activation of regulatory responses or redirection of the disease driving proinflammatory T cell responses are reasonable alternatives but are challenged with the choice of an appropriate antigen and means for eliciting the immune modulating response to the therapy without activating a disease exacerbating response. The LEAPS vaccines provide an approach which rebalances the immune response in autoimmune diseases by redirecting proinflammatory responses and stimulating regulatory responses, as demonstrated in animal models of RA disease. Immunomodulation with LEAPS or other vaccines may become the treatment of RA, T1D, MS, Crohns disease and other autoimmune diseases, with increased understanding of the cycles of T cell activation and regulation.

Conflicts of Interest Statement

KSR is an inventor of one or more LEAPS patents and has no other
conflict. DHZ is an officer of CEL-SCI, a stockholder and inventor
of one or more LEAPS patents.

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