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Antigen-specific tolerogenic and immunomodulatory strategies for the treatment of autoimmune arthritis

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Abstract

Objectives—To review various antigen-specific tolerogenic and immunomodulatory approaches for arthritis in animal models and patients in regard to their efficacy, mechanisms of action and limitations.

Methods—We reviewed the published literature in Medline (PubMed) on the induction of antigen-specific tolerance and its effect on autoimmune arthritis, as well as the recent work on B cell-mediated tolerance from our laboratory. The prominent key words used in different combinations included arthritis, autoimmunity, immunotherapy, innate immunity, tolerance, treatment, and rheumatoid arthritis (RA). Although this search spanned the years 1975 to 2007, the majority of the short-listed articles belonged to the period 1990 to 2007. The relevant primary as well as cross-referenced articles were then collected from links within PubMed and reviewed.

Results—Antigen-specific tolerance has been successful in the prevention and/or treatment of arthritis in animal models. The administration of soluble native antigen or an altered peptide ligand intravenously, orally, or nasally, and the delivery of the DNA encoding a particular antigen by gene therapy have been the mainstay of immunomodulation. Recently, the methods for in vitro-expansion of CD4+CD25+ regulatory T cells have been optimized. Furthermore, interleukin-17 has emerged as a promising new therapeutic target in arthritis. However, in RA patients, non-antigen-specific therapeutic approaches have been much more successful than antigen-specific tolerogenic regimens.

Conclusion—An antigen-specific treatment against autoimmune arthritis is still elusive. However, insights into newly emerging mechanisms of disease pathogenesis provide hope for the development of effective and safe immunotherapeutic strategies in the near future.

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INTRODUCTION

Rheumatoid arthritis (RA) is a multisystem autoimmune disorder affecting about 1% of the world's population (1). Despite advances in immune-based therapies in recent years, a much-desired antigen-specific therapy for this debilitating disease has been elusive. The induction of antigen-specific T cell tolerance has been extensively tested in various experimental models of autoimmune diseases, and several mechanisms associated with tolerance to combat potentially harmful autoimmune processes have been elucidated (2–5). In addition, the role of antibodies (pathogenic versus protective) in the pathogenesis of T cell-mediated diseases is gradually being realized (6–8). Although, most of the antigen-specific tolerogenic approaches are successful in the prevention of autoimmune diseases, the efficacy of these approaches against the ongoing disease is variable. Therefore, there is a pressing need to develop novel immunomodulatory approaches that are effective in the treatment of established autoimmune diseases (9–13,14). Nevertheless, significant advances have been made in this direction as discussed below.

Currently available therapeutic agents mainly treat the symptoms of autoimmune diseases and are only partially able to interfere with disease evolution, and thereby, fail to decrease the extent of physical impairment. Thus, the development of therapeutic strategies to limit tissue damage is imperative. Immunosuppressive drugs such as cyclosporine or steroids are widely used for inducing remission in the active phase of autoimmune diseases. While global immunosuppression may ameliorate an autoimmune disease, the immunocompromised state increases the susceptibility to infections. Thus, antigen-specific immunosuppression or tolerance induction is a highly desired goal for the treatment of autoimmune diseases.

METHODS

In addition to the classical tolerance-associated parameters such as T cell ignorance (15,16), anergy (17,18) and the T helper 1- T helper 2 cytokine balance (immune deviation) (19–21), the roles of the CD4+CD25+ T regulatory cells (Treg) (22,23) and the indoleamine -2, 3 -dioxygenase (IDO)-tryptophan pathway (24,25) in controlling autoimmunity have been elaborated in different animal models. Currently available methods for antigen-specific tolerance induction are listed in Tables 1 and 2.

RESULTS

I. Antigen-specific tolerance induction and immunomodulation in experimental models of autoimmunity

Systemic administration of soluble antigen has been shown to prevent diseases such as experimental autoimmune encephalomyelitis (EAE) (26) and Type 1 diabetes mellitus (T1D) (4,27). Single or multiple intravenous or intraperitoneal injections of antigen in the absence of an adjuvant have been shown to induce antigen-specific immune tolerance. Fathman and colleagues showed that this tolerance was a result of induction of anergy in antigen-specific T cells (3). This anergic state resulted from T cell receptor (TCR) activation in the absence of a costimulatory signal that is generally provided by an adjuvant (28). Furthermore, it was shown that CD4+CD25+ regulatory T cells are generated after such a tolerization regimen (29). Although successful in animal models, the beneficial effects of systemic antigen administration in clinical settings are rather limited (30–32).

Weiner *et. al.* have demonstrated that oral administration of antigen prevents the induction of autoimmune diseases (33,34). The success of oral administration of the disease-related antigen in the control of the respective autoimmune disease has been shown for EAE, collagen-induced arthritis (CIA), adjuvant arthritis (AA), and T1D (33,34). Several mechanisms mediating the

effects of oral tolerance have been suggested, such as anergy/deletion of CD4 T cells and the induction of CD4+ regulatory T cells that produce interleukin-10 or transforming growth factor-β (35,36). Furthermore, the induction of oral tolerance can be enhanced by interleukin-4, interleukin-10, anti IL-12 antibody, transforming growth factor-β, cholera toxin B subunit and anti-CD40 ligand (37). It has been shown that peripheral blood mononuclear cells (PBMC) of RA patients respond well in vitro to collagen Type II (CII) 256–271 epitope and its overlapping variants (38). Using the CIA model, the oral administration of this CII peptide suppressed and suppression of the associated antigen specific T cell/antibody responses (39). In another study, the oral administration of CII induced interleukin-10-producing CD4+CD25+ regulatory T cells (40). These Treg mediate anti-inflammatory effect by reducing the production of interferon-g by CII-specific effector T cells. The role of Treg in CIA is further validated by the observation that the depletion of Treg in vivo increased the severity of CIA (41). Interestingly, the DQ8- HLA-transgenic (humanized) mice developed normal number of functional Treg (42,43). These results have implications in further understanding the pathogenesis of RA. Although the majority of animal studies have yielded positive results with oral tolerance regimen, under some circumstances, mucosal application of antigen may instead exacerbate the disease process (44).

An altered peptide ligand (APL) is a synthetic peptide similar to the pathogenic epitope of a self antigen, but with a change in 1 or 2 critical amino acids. Such a synthetic peptide has been shown to inhibit the activation of a T-cell clone (antagonistic activity) (45). APL administration prevents EAE in mice (46). Furthermore, a large variety of microbial agents might possess structural entities that mimic self epitopes, and thereby possess APL activity (47). The implication is that microbial immunity could modulate autoimmunity. This relationship between microbially-derived APL and autoimmunity could help understand the long-observed relationship between infection and triggering of autoimmunity or the relapse of ongoing autoimmunity. Another aspect of APL activity involves IDO, which is related to tolerance induction. Stimulation of myelin-reactive T cells with tolerogenic APL led to increased IDO transcription, which in turn induced suppression of both T cell proliferation and production of proinflammatory cytokines (48). Interestingly, the oral administration of a synthetic derivative of anthralinic acid (a tryptophan metabolite) reversed paralysis in mice with EAE, showing the significance of both APL and the tryptophan pathway in the treatment of autoimmunity (48).

The use of peptides/APL has been associated with a serious side effect, anaphylaxis. Attempts are being made to alter the solubility, dose, and route of administration of such peptides to minimize severe side effects. In this regard, one successful approach consisted of altering the isoelectric pH/point of the peptide by adding basic residues (arginine residues) to the carboxy-terminal of the peptide (49). This modification significantly reduced the side effect without affecting the disease modulating activity of the peptide.

II. Immunomodulatory approaches tested in the adjuvant arthritis model

AA is inducible in the Lewis (LEW) rat by injecting subcuteneously heat-inactivated *Mycobacterium tuberculosis* H37Ra (Mtb), and it shares several features with human RA (50,51). Numerous immunologic approaches are effective in protection against AA **(**Table 2). In most of these approaches, attempts have been made to generate protective immunity against mycobacterial hsp65 (Bhsp65) and its self homolog, the rat hsp65 (Rhsp65). The administration of soluble recombinant Bhsp65 either intravenously/intraperitoneally (52) or orally (53,54) prevents subsequently induced AA. Systemically administered Bhsp65 induces suppression of antigen-specific T cell proliferation. This hypoproliferative state of T cells is reversible by interleukin-2, indicating that these T cells are anergic in nature. Interestingly, the protection against AA is associated with reduced production of IL-17 but enhanced anti-Bhsp65 antibody response (55). The latter is protective against AA (7,8). However, most of the soluble antigen-

based approaches in AA are ineffective against the ongoing disease with the exception of oral tolerance to Bhsp65 (53) and of tolerance induced by Bhsp65-expressing B cells (52).

III. Tolerogenic gene therapy for arthritis

Somatic gene therapy involves the introduction of new genetic material into a cell in to modify the function of the cell or to alter the level of expression of the corresponding protein within the cell (56–58). Although therapies based on the use of cytokine receptors, inhibitors, or antibodies are gaining widespread popularity in the treatment of autoimmune diseases, these treatment modalities suffer from limitations such as high expense, the need for repeated injections and unwanted side effects. Many of these limitations can be overcome by gene delivery (56–59).

B cell-mediated gene therapy—In the past several years, Scott and colleagues have developed a novel gene therapy approach for the induction of antigen-specific tolerance using antigen-Ig fusion protein delivered via a retroviral vector in B cells (60–64). In short, a fusion protein construct consisting of an immunodominant epitope or a full length antigen in-frame at the N-terminus of an IgG heavy chain was created. This fusion construct was then delivered into bone marrow-derived cells or lipopolysaccharide-stimulated B cell blasts via retroviral infection. The injection of these B cells into syngeneic recipients rendered them tolerant to a particular epitope or antigen (60–64). So far, the B cell-mediated gene therapy approach was successful in disease models such as experimental autoimmune uveitis (EAU) (62), EAE [induced either by myelin basic protein (MBP) or by myelin oligodendrocyte glycoprotein (MOG)] (64), and the non-obese diabetic (NOD) mouse model of diabetes (64,65). This approach has also been successful in inducing tolerance to factor VIII inhibitors in hemophilia A (66) and (in combination with BM transplantation) in the treatment of EAE (67). Our recent testing of the B cell-mediated gene therapy approach in the AA model (52) has not only extended the application of this therapeutic approach to a new model of autoimmune disease, arthritis, but also to another related species, the rat.

Adoptive cellular gene therapy of RA—Fathman and colleagues have developed the concept of adoptive cellular gene therapy of RA (68). In this approach, specific cell types (e.g., T cells or T cell hybridomas) that specifically migrate to the target organ in a particular autoimmune disease (e.g., the joints in arthritis) can be genetically modified to express a therapeutic product (e.g., interleukin-4) locally (69). Thus, the local delivery of an immunotherapeutic product is assured, which in turn limits the side effects inherent in the systemic delivery of cytokines and other biomolecules. This approach involving genetically engineered T cells expressing interleukin-4 was used successfully to prevent the development of CIA in mice (69). In addition to cytokines, agents that can prevent damage to cartilage and bone would constitute attractive molecules for targeted delivery. Other investigators have shown that direct local injection of the gene of interest (e.g., the tumor necrois factor-α receptor gene) in the paws can downmodulate arthritis in mice (70). Thus, an appropriately tailored adoptive cellular gene therapy approach using B cells, T cells, dendritic cells (DCs) and the desired gene can be applied for the treatment of multiple sclerosis (MS), RA, and insulin-dependent diabetes mellitus (IDDM or T1D).

Tolerizing DNA vaccines—Recently, the success of another gene therapy approach in arthritis was reported: the tolerizing DNA vaccine encoding CII leading to the downmodulation of established CIA (71). The reduced severity of CIA was associated with decreased pro-inflammatory cytokines as well as reduced spreading of the antibody response (the latter was tested by arthritis microarray analysis) (71). Interestingly, the effect of DNA vaccination was significantly increased by atorvastatin, one of the statin drugs previously shown to suppress the severity of EAE (71).

IV. Current status of the antigen-specific tolerogenic/immunomodulatory approaches in clinical practice

Extensive efforts have been made in the past several years to transfer the promising bench-tested therapeutic approaches to the bed-side (translational research). The outcome of this transition has been mixed, with significant success for some approaches, but unexpectedly poor outcomes for others. We describe below an overview of the clinical application of various tolerogenic and immunomodulatory approaches in arthritis as the primary example. However, we also have included examples of other rheumatic diseases (e.g., systemic lupus erythematosus; SLE) as well as additional autoimmune diseases (e.g., MS and T1D) for sharing a broader perspective on the treatment of autoimmune diseases. Considering the availability of a relatively sizable literature on the use of biologics (such as anti-tumor necrois factor-α agents (infliximab, etanercept and adalimumab), interleukin-1-receptor antagonist (anakinra), cytotoxic T lymphocyte-associated antigen-4-immunoglobulin heavy chain (CTLA-4)-Ig (abatacept)) and anti-CD3 antibody in the treatment of autoimmune diseases or transplantation, this aspect of immunotherapy will not be further discussed.

CD4+CD25+ regulatory T cells (Treg)—CD4+CD25+ T cells play an important role in mediating peripheral tolerance and controlling the activity of potentially self-reactive T cells (72,73). Currently, several efforts are being made to induce and maintain tolerance by using therapeutic vaccination with CD4+CD25+ regulatory T cells, which can be done either directly or indirectly (through the use of anti CD3-antibody or antigen-directed immunotherapy) (72, 74,75). Treg are functionally compromised in RA (76) and SLE (77) patients. In RA patients, anti-tumor necrosis factor-α treatment increases the number as well as the function of Treg (76). Thus, the reduced function of Treg can be reversed/restored by treatment with a biologic agent.

Peptide/APL and tolerogenic DC therapy—Current therapeutic strategies that are based on global immune suppression or blocking of inflammatory pathways do not induce long-term disease remission, and have serious side effects, including infections. Thus, there is a need to develop antigen-/epitope-specific immunotherapy. Several immunomodulatory peptides have been identified as promising candidates for immunotherapy in various autoimmune diseases. Examples are heat-shock protein (hsp) peptides for the treatment of RA and juvenile chronic arthritis (JCA), and peptides derived from anti-DNA antibodies for the treatment of SLE (74, 78,79). The immune modulation with Hsp peptides was associated with the induction of Treg. In one pilot trial, immunization of RA patients with a peptide of a prokaryotic heat-shock protein led to the induction of Treg and disease improvement (75). Furthermore, small peptides that can interfere with cytokines or specific cell surface molecules have been developed, and can lead to the inhibition of autoimmune inflammatory reactions (80). Similarly, attempts have been made to block helper T cell responses by the use of competitor peptides whose in vivo efficacy had been increased by coupling to transferrin (81).

APLs are quite successful in controlling autoimmunity in animal models. However, the immune response to autoantigens in humans is polyclonal and a peptide that inhibits one clone may stimulate another. A clinical trial of an APL for the treatment of MS was halted because of disease exacerbation in a few patients (82). In 9% of the patients, the immune response deviated from T helper 1 type to a severe allergic (T_h2) type (83).

DCs have been implicated in the induction of autoimmune diseases. These cells have been identified in lesions associated with several autoimmune inflammatory diseases, including RA (84). Unlike mature DC that are potent activators of naïve T cells, immature or semi-mature DC have the ability to tolerize T cells or prevent autoimmune reactions (85). Thus, current strategies exploiting the tolerogenic potential of DC or blocking their migration to the

inflammatory site by chemokine-blocking antibodies are attractive approaches for the treatment of RA and other autoimmune diseases (84–86).

Oral tolerance—Mucosal administration of antigen is an efficient way of tolerizing antigen-specific T cells. Oral tolerance has been tested in patients with RA, MS, uveitis, T1D, and allergies (35,36,87–90). No significant beneficial effect was observed in phase III clinical trials of oral bovine/chicken CII treatment in RA patients (87,88,91), or of oral myelin and glatiramer acetate in MS patients (37). Oral insulin treatment delays the onset of diabetes in a high-risk population (37,90). On the basis of animal studies, it has been suggested that the feasibility of the induction of oral tolerance to CII or other antigens in RA patients is high if prostaglandin levels are maintained normally in gut associated lymphoid tissue (92). Another report indicated that a cytotoxic T cell response could be induced by oral application of antigen, which could lead to the induction of an autoimmune disease (44). Thus, there is a possibility that oral tolerization may either have a beneficial effect or a detrimental effect, or no effect at all, depending on the dose, timing and other related conditions of testing (93).

DISCUSSION

The breakdown of self-tolerance results in autoreactivity, which if continued may result in autoimmune pathology. Several mechanisms have been described for the development of spontaneous autoimmunity. Genetic predisposition, especially the presence of a particular human leukocyte antigen (HLA) haplotype, plays an important role in susceptibility to arthritis and other autoimmune diseases (94–98). In addition, the background (non-major histocompatibility complex; non-MHC) genes also contribute to the disease process. For example, inbred rats of the same MHC haplotype display differential susceptibility to autoimmune diseases (99,100).

Deficiency in the number and/or function of CD4+CD25+ regulatory T cells (Treg) is associated with autoimmunity

Forkhead box p3 (Foxp3)-positive Treg have emerged as the central controllers of spontaneously-induced as well as experimentally-induced autoimmunity in a variety of animal models (22,23,101). Experimental cellular therapy using CD4+CD25+ T cells effectively delays and downmodulates the course of diabetes, colitis, gastritis, and graft-versus-host disease in animal models (22,23,101–103). An important question that is raised in autoimmunity is whether a deficiency of Treg is an essential component of the disease process. There is a relative deficiency of Treg in the NOD mouse compared to that of other mouse strains (104). However, a difference in the frequency of Treg may not explain the differential susceptibility of rat strains to an autoimmune disease (Satpute & Moudgil, unpublished data). Furthermore, it has recently been shown that the frequency of Treg in MS patients is comparable to that of healthy controls; however, the Treg of these patients are significantly less efficient in mediating the suppression of pathogenic effector T cells compared to the Treg from controls (105). Similarly, Treg defects have been reported in RA as well as SLE (76, 77). Thus, both the frequency as well as the efficacy of suppression of Treg needs to be considered in evaluating an autoimmune state. Interestingly, the number and function of Treg can be altered significantly by treatment with appropriate immunomodulatory peptides (75, 106).

IL-17 plays a critical role in the pathogenesis of autoimmunity

IL-17 is a pro-inflammatory cytokine produced by effector T cells (T helper 17; T_h17) distinct from T helper 1 cells (107,108). Interleukin-6 and transforming growth factor-β are essential for the differentiation of naïve CD4 cells into T_h17 effector cells (109,110). Ironically, transforming growth factor-β alone is required for Foxp3 expression in Treg (109). Therefore,

these new studies suggest that interleukin-6, which stimulates T_h17 differentiation but inhibits Treg development, might act as a master switch that determines the induction of immune response versus its regulation (111). Recently, a number of reports have described a reciprocal interaction between T helper 1 (interferon-γ) and T_h17 (IL-17) (112,113), as well as the role of interleukin-2 and interleukin-27 in the inhibition of T_h17 differentiation (114,115). Interestingly, retinoid-related orphan receptor-gamma (RORγt), an orphan nuclear receptor, is a transcription factor required for the differentiation of T_h17 lineage (116).

Studies involving the modulation of IL-17 or interleukin-23 have revealed that these cytokines are critical in EAE (117,118), CIA (119,120), inflammatory lung disease (113), and T1D (121,122). Through these studies, it has been suggested that the IL-17/interleukin-23 axis is required to initiate tissue-specific autoimmune diseases. IL-17 has been associated with RA pathology, as IL-17 can be found in the synovium of RA patients, and acts in concert with interleukin-1 to stimulate interleukin-6 production by synovial fibroblasts (123).

Mechanisms underlying tolerance induction by B cell-mediated gene therapy

Immunoglobulins are efficient antigen-carriers for the induction of T- and B-cell tolerance, and B cells are among the most potent tolerogenic antigen-presenting cells (APCs) (60–64). Gene therapy with DNA fragment encoding an antigen (in the absence of an IgG scaffold) produces hyporesponsiveness and affords protection against disease (124). However, the level of hyporesponsiveness induced is significantly higher when the antigen is expressed within the IgG scaffold. Moreover, such tolerance is maintained for a much longer duration compared to the transient tolerance offered by antigen/DNA alone (61). A recent study has demonstrated that the assembly of the IgG heterodimer may contribute to the efficacy of tolerance induction (125). The advantages of B cell-mediated gene therapy protocol over other methods include the following: the tolerance induced is antigen-specific, the effective tolerance is maintained for as long as 6 months (62), the tolerance can be induced not only in the peripheral lymphoid organs, but also in the target organ, and the tolerogenic regimen is capable of ameliorating the ongoing disease, simulating application in the clinical setting for patients (62,64,65).

The precise mechanisms of tolerance induction by B cell-delivered antigen are not fully defined. The question whether B-cell mediated tolerance occurs via the secretion of chimeric antibody molecules, or via B cells acting as APCs for the presentation of IgG-peptide, has been examined through studies based on specific gene knock-out mice (63,64). B cells were critical APCs for this tolerance induction. MHC class II expression by the presenting B cells was essential for the tolerogenic effect, but the Fc receptors (FcRs) were not required (63). A high level of expression of B7, especially B7.2 costimulatory molecule, was required for the induction of tolerance by negative regulatory signaling through CTLA-4 (126). T helper 1/T helper 2 deviation was not observed following tolerance induction, and interleukin-10 was not required as the mediator for tolerance (64). However, the expression of Fas ligand (FasL) on the tolerogenic B cell was required for the induction of tolerance (64). Song et al have recently demonstrated that transforming growth factor-β was upregulated in long-term tolerant NOD mice treated with B cells expressing glutamic acid decarboxylase-IgG (65). Furthermore, the frequency of CD4+CD25+ T cells in the spleen of the experimental group of mice was significantly higher than that of the control mice, and these regulatory T cells suppressed the proliferative response of $CD4^+CD25^-$ T cells *in vitro* (65). The role of Treg in B cell-mediated tolerance has been corroborated by subsequent studies in hemophilia (66) and in the NOD mouse model of T1D (127).

B cell tolerance and the protective effect of antibodies in arthritis

Most of the examples discussed above have focused on the tolerization of T cells. However, it is conceivable that the tolerization of B cells that are the potential source of arthritogenic

antibodies would also serve a useful therapeutic purpose. In a recent study based on the K/BXN model of arthritis, it was shown that multiple mechanisms were operative in the tolerization of B cells depending on the affinity of the B cell receptor (BCR) for the ligand, glucose-6-phosphate isomerase (GPI) (128). The B cells bearing high affinity-BCR for GPI were negatively selected, with receptor editing contributing to this process. However, several B cells escaped tolerance induction through the expression of an additional light chain. Furthermore, B cells bearing low affinity-BCR for GPI were 'ignored' (immune ignorance) (128). Considering that anti-GPI antibodies serve as a good marker for extra-articular RA (129), the detailed understanding of the tolerization of B cells specific for GPI would contribute towards better understanding of the pathogenesis of RA as well as for designing novel antigen-specific therapeutic approaches for this disease.

Increasing evidence suggests that antibodies to certain disease-related antigens might be regulatory in nature (7,8,130,131). We and others have shown that arthritic Lewis (LEW) rats develop antibodies to Bhsp65 during the peak and recovery phase of AA (7,8). These antibody responses are seen early after Mtb immunization in AA-resistant rat strains such as the Wistar Kyoto rat (WKY) (7), the Fischer F344 rat and the Brown Norway (BN) rat (131). Interestingly, the transfer into naïve LEW rats of serum derived from the late phase arthritic LEW rats or the AA-resistant BN rats offered protection against subsequent AA in the recipient rats (7,131). Furthermore, the Bhsp65 peptides 31–46, 211–226, and 349–364 represent the epitopes that were recognized by the late antibodies from both WKY and LEW rats (7).

The role in innate immune mechanisms in the pathogenesis of autoimmunity

Rapid advancements in the field of innate immunity have brought to focus the interactions between innate and adaptive immune effectors mechanisms in infection and host immune response (132–136). It is increasingly being realized that the molecules and receptors that were initially assumed to be restricted to the microbial agents in regard to their origin or response are also capable of recognizing and responding to certain self components. This, along with the observations showing the involvement of the Toll-like receptors (TLRs) in the activation of macrophages, dendritic cells, T cells and B cells (132–136), begin to provide one of the rationales for the long-observed association between infection and autoimmunity. Furthermore, mast cells that were typically viewed in the context of allergies, only are now coming to the forefront constituting one of the effector mechanisms of autoimmune inflammation (137,138). Similarly, the perturbations of the complement pathway-components and their impact on self reactivity and autoimmune damage are gaining significance (139, 140).

Several recent studies have highlighted the role of various innate immune mechanisms in rheumatic diseases. The role of complement components and mast cells in effector mechanisms of arthritis is exemplified by studies in the K/BXN model of arthritis (128,138,140). In RA patients, synovial tissue expresses TLRs (e.g., TLR 2 and 4), which affect macrophage activation, cytokine production and chemokine expression (141–143). In regard to antibody responses, TLRs (e.g., TLR 7 and 9) are involved in the production of autoantibodies in murine lupus (134,144). Some of the innate immune pathways are also being targeted for therapeutic purposes. For example, in experimental models, arthritis can be suppressed by inhibitors of the innate pathways by using, for example, a tylophorine analog, anti-complement 5 antibodies, or a TLR 4-antagonist (145–147).

Concluding remarks

Two major realizations that have emerged in experiments from animal models and in clinical trials in patients with autoimmune diseases are (2,9–14,148)-: **a**) Non-antigen-specific immunomodulatory approaches (e.g., biologics and costimulation blockade) have been far

more successful than the antigen-specific tolerogenic approaches (9,10). However, newer therapeutic strategies may have to harness the beneficial aspects of both approaches (9,10); and **b**) There is increasing emphasis on restoring a functional balance across the immune system among the critical subsets of T/B cells involved in autoimmune processes, including the naïve, effector, memory, and regulatory cells (13,14). Thus, newer therapies would be aimed at controlling or deleting effector cells, and at shifting the profile of the immune homeostasis of patients towards a healthy type (148).

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Table 1

Immuno-specific tolerogenic approaches tested in animal models of autoimmune diseases

Mode of delivery of the native antigen	Examples		Reference
	Model	Antigen (route)	
Soluble antigen (injected intravenously or intraperitoneally)	EAE	MBP	(3)
	CIA	CII	(149)
	AA	Bhsp65 peptide	(150)
Antigen coupled to splenocytes (injected intravenously)	EAE	MBP	(151,152)
Antigen-IgG fusion protein expressed in B cells (injected intravenously or intraperitoneally)	EAE	MBP-IgG	(64)
	T1D	Glutamic acid decarboxylase-IgG	(64)
	-		-
	EAU	IRBP peptide-IgG	(62)
	AA	Bhsp65-IgG	(55)
Antigen emulsified in adjuvant (injected subcutaneously, intradermally, intratesticularly, or intracamerally)	AA	Bhsp65 peptide	(153)
	AA	Bhsp65 peptide	(154)
	DIA	Bhsp65 peptides	(155)
	AA	Mtb	(156)
	AA	Mtb	(156)

AA= Adjuvant arthritis; Bhsp65= Mycobacterial heat-shock protein 65; CII= Collagen type II; CIA= Collagen-induced arthritis; DIA= Dimethyl Diammonium Bromide (DDA)-induced arthritis; EAE= Experimental autoimmune encephalomyelitis; EAU= Experimental autoimmune uveitis; IRBP= Interphotoreceptor retinoid-binding protein; MBP= Myelin basic protein; Mtb= *M. tuberculosis*, heat-killed; T1D= Type 1 diabetes.

Table 2

Antigen-specific approaches for the prevention/treatment of autoimmune arthritis in animal models

The form of the antigen used	Model	Antigen	Reference
Native protein	AA	Bhsp65, Bhsp70, Bhsp10, Rhsp65, CII	(157–160)
	PIA	Bhsp65	(161)
	CIA	CII, Bhsp65	(40,162)
	SCWIA	Bhsp65	(163)
	AvIA	Bhsp70	(158)
Synthetic peptides representing native amino acid sequences	AA	Peptides of Bhsp65, Rhsp65, Hhsp60	(8,99,153,154, 164–167)
	-	-	
	AvIA	Bhsp65 peptide	(167)
	DIA	Bhsp65 peptides 120–134 and 213–227	(155)
	CIA	CII peptide 250–270	(39)
	PIA	Bhsp65 peptide 261–271	(168,169)
Altered peptide ligands having altered TCR- or MHC-contact residues	AA	Bhsp65 peptide 180–188 with an alanine substituted at position 183	(170,171)
	-		-
	CIA	Core CII determinant 256–270/276	(172)
	PGIA	Aggrecan peptide	(173)
DNA vaccination	AA	Construct encoding Hhsp60	(174)
Recombinant vaccinia virus expressing the antigen	AA	Bhsp65, Hhsp60	(175,176)
B cells expressing the DNA construct encoding the Bhsp65-IgG fusion protein	AA	Bhsp65	(55)
Bacille Calmette Guérin	AA	Bhsp65 and other bacterial antigens	(177)
Mycobacterium vaccae	PIA	Bhsp65 and other bacterial antigens	(178)
Mycobacterium tuberculosis	AA	Bhsp65 and other bacterial antigens	(156)

AA= Adjuvant arthritis; AvIA= Avridine-induced arthritis; Bhsp65= Mycobacterial heat-shock protein 65; Bhsp70= Mycobacterial hsp70; Bhsp10= Mycobacterial hsp10; CII= Type II collagen; CIA= Collagen-induced arthritis; DIA= Dimethyl Diammonium Bromide (DDA)-induced arthritis; Hhsp60= Human hsp60; IgG= IgG heavy chain; MHC= Major histocompatibility complex; PGIA= Proteoglycan-induced arthritis; PIA= Pristane-induced arthritis; Rhsp65= Rat hsp65; TCR= T cell receptor.