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REVIEW



# Vaccination against autoimmune diseases moves closer to the clinic

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**ABSTRACT**

Biologicals, e.g. TNF inhibitors, have improved dramatically the efficacy of medical interventions in autoimmune diseases, such as in rheumatoid arthritis (RA). However, although progressive inflammation can be halted in this way, no drug-free remissions or lasting cures are reached. For this to become real, therapies based on induction antigen-specific immune tolerance are sought. This review describes mechanisms of tolerance and the current possibilities for induction of therapeutic tolerance through antigen-specific vaccination approaches. And despite the fact that for various diseases the search for appropriate autoantigens is ongoing, pioneering studies are now already developed that use more broadly inflammation associated antigens. Through their capacity to preferentially induce regulatory T cells, heat shock proteins are an attractive source of such broadly inflammation associated antigens.

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## Immunological tolerance

Although the Nobel Prize for immunological tolerance was awarded in 1960 to Burnet and Medawar, the realization that the immune system was capable of adopting a state of non-responsiveness to foreign tissues was already made by the pioneering observations by Ray Owen in the 1940s.[1] Genetically different twin calves with a common placenta became tolerant to one another's tissues. Only later in the 1950s, Medawar showed that foreign tissues transplanted into embryo's led to tolerance, while Burnet contributed with the idea of clonal deletion, the process whereby potentially reactive lymphocytes are removed from the system: negative selection as a mechanism of tolerance induction.[2] Thus principles of tolerance have been known for many decades. However, true induction of tolerance in the mature immune system for allotransplantation or the reversal of autoimmunity has remained until now a much sought 'holy grail'.

Recently it has become evident that negative selection occurs to a very incomplete extent.[3] Removal of too many potentially dangerous clonotypes would lead to too many holes in the repertoire, and this, therefore, seems to have led to leakiness in the process of negative selection. In the process of negative selection, autoreactive cells are pruned and certainly not eliminated. Experimental models of autoimmune diseases have shown that autoreactive T cells are present in the repertoire of healthy individuals, and that those T cells can be aroused experimentally to produce an autoimmune disease.[4] In the case of type I diabetes, it was demonstrated that islet-reactive cytotoxic CD8+ T cells home to the pancreas but circulate at similar frequencies in patients and healthy controls.[5] Moreover, other studies have shown that frequencies of T cells recognizing endogenous peptides equaled more or less the frequencies of T cells recognizing foreign epitopes.[6] And up to about 20% of the mature and circulating B cells were found to be self-reactive. Therefore, avoidance of self-reactivity must be regulated functionally and not negated axiomatically by the elimination of risky clones. We have to accept the idea that many self-reactive lymphocytes are present in the periphery and that they are kept at bay by peripheral tolerance mechanisms, such as anergy, exhaustion, lack of tissue homing and, last but not least, regulatory T cells (Treg). Given the variety of such mechanisms, further detailed understanding of mechanisms of peripheral tolerance and their relative contributions to tolerance will be key to further development of innovative tolerance therapies.

## T cell recognition of antigens and immunological tolerance

Most autoimmune diseases are genetically associated with MHC II alleles. This means that HLA class II alleles predispose to an increased susceptibility to disease. The straightforward interpretation is then that certain HLA molecules either cause impaired negative selection of potentially autoimmune T cells or lead to the presentation of risky self-antigens to potentially pathogenic T cells. However, upon analysis, it appears that such interpretation in many cases is too simple. The well-known textbook example is diabetes type 1. Whereas the damaging effects on the insulin-producing beta cells are, most likely, caused by MHC I restricted CD8+ cytotoxic T cells, the HLA association is with MHC II molecules HLA-DR or -DQ. Also, enigmatic has remained the strong association of HLA-B27 with both reactive arthritis, an arthritic disease, sometimes with conjunctivitis/uveitis, elicited by infections with Salmonella, Shigella or Campylobacter species and ankylosing spondylitis or

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Bechterew's disease. The same strong HLA association for both diseases, but still no understanding of a connection for infection with the origin of ankylosing spondylitis. Another illustrative study was the extensive analysis of narcolepsy.[7] Narcolepsy is an autoimmune disease, presenting with excessive daytime sleepiness, cataplexy, hypnagogic hallucinations and sleep paralysis, strongly associated with HLA-DQB1*06:02. The disease got much attention since, in the 2009 influenza pandemic, an adjuvanted flu vaccine was found to cause a rising incidence of narcolepsy in children of some Northern European countries. The study of Latorre convincingly showed the enhanced presence of autoimmune CD4+ T cells responding to a critical hypothalamic protein called hypocretin in narcoleptic patients. However, despite the almost 100% association of the disease with HLA-DQ, the hypocretin responding T cells were HLA-DR restricted, while the hypocretin-producing neurons are known to be HLA class II negative. Most responding T cell lines were responding to various hypocretin derived peptides and not to any influenza antigens. Interestingly, hypocretin peptide-specific T cells were not responding to the full hypocretin protein processed and presented by autologous monocyte-derived DC or B cells. This failure to generate the correct T cell epitopes out of the full protein has been seen also in other systems. It was seen for T cell clones isolated from diabetic mice[8] and also for our TcR transgenic T cells responding to a specific epitope of HSP70.[9] Created from a T cell responding to a self-homolog peptide of mycobacterial HSP70 epitope B29, the transgenic T cells never responded to the full HSP70 mammalian protein. Such T cells, also known as type B T cells, apparently recognize unique conformations generated by peptide binding to MHC II in late endosomal compartments or to cell-surface or recycling MHCII. It is possible that this sort of extracellular processing and unconventional presentation may be a route to escape thymic negative selection and to produce autoreactive T cells.[8,10]

It is self-evident that further mechanistic understanding of the nature of antigen recognition by autoimmune T cells will help the development of novel ways to produce therapeutic tolerance.

## Therapeutic tolerance

Development of immune tolerance therapies will depend on the progress that transcends individual diseases or single technology platforms. Until now, clinical development of antigen-specific immunotherapy (ASIT) for allergy has been instructive. Although prolonged allergen administration regimens were needed, typically up to 5 years for reaching durable tolerance, tolerance induction for allergen immunotherapy has become a reality. Positive clinical effects were obtained by subcutaneous, sublingual, oral and epicutaneous routes of administration. However, also, in this case, limited understanding of CD4 T cell epitope/determinant hierarchies and modulatory T cell interactions hamper the further rational design and monitoring of ASIT. Encouraging results in animal models using vaccines based on pathogenic T cells or the autoantigen have prompted the design of novel and selective immune-based therapies for human autoimmune diseases. Pathogenic T cells have been used as vaccines with the idea to elicit T cell receptor (TcR) specific anti-idiotypic T cell responses with regulatory activity. This idea of T cell vaccination was coined by Cohen and first shown to be effective in the model of experimental autoimmune encephalomyelitis (EAE).[11] Since then, T cell vaccination was pioneered in RA, where T cells were collected from the inflamed synovial fluids, expanded with antigens such as collagen type II, proteoglycans and mycobacterial antigens such as HSP60 and then attenuated by chemical fixation or irradiation. One patient developed a measurable T cell response to the vaccine and this patient showed a clear decrease in disease activity.[12] A more recent study on vaccination with collagen II reactive T cells in RA showed a favorable immunological effect with raised levels of activated Foxp-3+ Treg's.[13] Another study with a significant clinical effect of T cell vaccination was carried out with irradiated myelin basic protein (MBP) specific T cells in patients with progressive multiple sclerosis (MS).[14] Along similar lines, my group had carried out some underpinning research on T-T cell interactions the rat model. A CDR1 T-cell receptor beta-chain peptide obtained from an arthritogenic T cell clone was found to induce MHCII restricted T cells that recognized the relevant rDNA TcR proteins and the arthritogenic T cell itself. The latter finding indicated that activated T cells can process and present their own T cell receptor in the context of MHCII and that TcR peptides are recognized by TcR variable gene-specific T cells.[15] In follow-up studies, it was shown that TcR peptides can have the capacity to protect against arthritis in the experimental model upon *in vivo* nasal administration.[16] Although with the relatively recent revival of interest in T cell regulation the focus of research has been on therapeutic applications of Treg, also the regulatory B cell or the Breg may have the potential for tolerance induction. Although Breg was known to downregulate immune responses by secretion of IL-10 and IL-35, the origin of Bregs had remained a bit unclear. Now a recent report showed that LAG3+ CD138$^{hi}$ plasma cells were natural regulatory elements by producing IL-10 in response to TLR triggering. The cells were probably self-antigen specific, normally in a quiescent state and becoming fully regulatory upon bacterial infections. They were found to express PD-L1, PD-L2, and CD200, which is compatible with their suppressive nature.[17] In addition to this, earlier studies by my group had already identified the suppressive nature upon TLR triggering of so-called B-1a cells, innate-like B cells that produce polyreactive natural antibodies.[18]

Besides the further identification of cellular elements involved in regulation, development of therapeutic tolerance in humans seems to depend, at least in part, on the proper identification of critical autoantigens. Definitive identification of pathogenic T cell antigens as is now done in celiac disease, for example, will facilitate rational design of tolerance therapies for human autoimmune diseases.[19]

## Antigens to be developed for therapeutic tolerance

Steadily rising incidences of autoimmune diseases in developed countries have led to the realization that reduced contacts with microbes, possibly due to lowered exposure to infection, may be a causative factor in this. This idea, also known as the hygiene hypothesis, may underlie a generalized reduced capacity of the immune systems of disease-prone individuals to maintain a tolerance for self-antigens. The possible importance of innate immune receptors, such as TLR, in mediating the protective

effects of microbes on autoimmunity has been discussed recently.[20] Alternatively it is possible that microbial antigens have a natural tendency to contribute to self-tolerance. A recent analysis of shared risk factors for type 1 diabetes and celiac disease concluded that besides the shared high-risk HLA class II haplotypes for both diseases, there is a shared role of microbial exposure especially in early life.[21] The analysis suggested that recent environmental changes have increased disease penetrance in individuals carrying HLA types that previously afforded disease protection. In other words, reduced contact with critical microbial antigens may have led to an insufficient level of self-tolerance.

A potentially interesting group of candidate microbial antigens that qualify as inducers of T cell regulation are heat shock proteins (HSP) or stress proteins. When bacteria are sampled by mucosal DCs in the gut, the consequential stress response of the ingested microbes will ensure upregulated processing and presentation of prokaryotic HSP by the mucosal DC. Due to their unique degree of evolutionary conservation, such overexpressed HSP peptides must lead to the induction and propagation of self-HSP cross-reactive T cells. With their gut mucosa acquired tendency to promote tolerance, such self-HSP reactive T cells will adopt a regulatory phenotype. The experimental models have provided ample evidence that such locally induced Treg can drive tolerance, also in a systemic manner. Orally administered microbial HSP was found to protect against arthritis. For example OM-89, an *E. coli* derived bacterial extract with a dominant presence of HSP70 protected against adjuvant arthritis in rats.[22] Similarly, mycobacterial HSP60 when given orally to rats in the early phase of a developing adjuvant arthritis, was clearly suppressing disease development. In the same treated rats, a reduced number of activated and pro-inflammatory T cells was observed. Also, the locally upregulated expression of endogenous (self-) HSP70 in mucosal lymphoid tissues in mice was found to produce HSP70 specific arthritis inhibitory T cells. This latter finding was made by oral feeding of the HSP co-inducing substance carvacrol, which upregulated HSP70 expression in Peyer's patches. Analysis of the T cell responses of the treated mice revealed raised HSP70-specific T cell responses, and adoptive transfer of CD4+ T cells from treated animals also suppressed disease in diseased recipients. Carvacrol administration also increased the number of CD4 + CD25 + FoxP3+ T cells, systemically in the spleen and locally in the joints (Wieten et al. A&R 2010). Based on these observations we have proposed that HSP induced Tregs will target the self-HSP molecules in the tissues. And then preferentially the tissues with HSP over-expressed by the stress of inflammation. This capacity of microbial HSP to promote the presence and function of regulatory T cells leading to enhanced peripheral tolerance and suppression of inflammatory disorders has been discussed previously.[23–25]

## Current status of tolerance therapies by antigen-specific vaccination

A disease in which potentially relevant autoantigens were defined, and antigen-specific tolerance would be a possible therapeutic approach is type I diabetes. A first clinical trial with positive results was carried out with the C19-A2 proinsulin peptide, a peptide that is restricted by T1DM-associated HLA-DRB1*0401. The peptide was shown to modulate autoreactive CD4 T cells in patients expressing this same class II allele. In recently diagnosed individuals (within 100 days), administration of the peptide led to higher C-peptide plasma concentrations without systemic or local hypersensitivity. The biomarker levels were associated with the expansion of IL-10 and Foxp3 expressing Treg cells.[26]

Patients with uveitis have in many cases shown immunity toward retinal S-antigen. For this reason, clinical trials were carried out with oral feeding of such patients with this antigen,[27] or alternatively with an HLA peptide cross-reacting with S-antigen.[28] Although initial results were encouraging, further studies are required to examine the therapeutic usefulness of the procedure in more detail. A possible problem, in this case, is that the specific antigens that serve as molecular targets for uveitis are not yet sufficiently known.

Relevant in the case of poorly defined inciting self-antigens, is that tissue-specific bystander suppression, where T cells specific for one antigen may suppress responses to other antigens in the same tissue environment, could be exploited possibly to get around this limitation. Also, here dependable self-antigens that may serve as a possible surrogate by-stander antigen to target inflammation are heat shock proteins. Their capacity to drive anti-inflammatory Tregs has been shown in a wide spectrum of experimental models, that included different inciting autoantigens.[23–25] In addition, HSP70 has been administered intravenously in patients with rheumatoid arthritis (RA).[29] The latter trial showed significantly prolonged remissions at the highest protein concentrations administered (5 and 15 mg), which suggested the induction of Treg, supporting the original hypothesis regarding the therapeutic action of HSP.

In two recent open-label trials in relapsing multiple sclerosis (MS) with ATX-MS-1467, which is a mixture of HLA-DR binding MBP peptides, patients were repeatedly vaccinated intradermally or subcutaneously in different time schedules and with increasing dosages. Relatively slow ATX-MS-1467 titration and a longer full-dose i.d. treatment period were shown to be associated with a reduction in lesions and a sustained effect post treatment[30] providing some perspectives on tolerance therapies for MS.

However, at this early juncture of tolerance therapy development, it can be attractive to make use of the synergistic effects of combining distinct approaches, such as, for example, tolerant dendritic cells (tolDC) and Treg inducing peptides. Such combinations would work by turning off effector cells and promoting Tregs at the same time. Tolerant DCs have been pioneered in an RA, open-label, trial where tolDC were created with an NFκB inhibitor and loaded with citrullinated peptide antigens. Eighteen Patients were treated once intradermally. Apart from the safety that was shown, as a measure of efficacy DAS28 was seen to decrease within 1 month in treated patients with active disease.[31] A more recent study, carried out by our collaborators in Newcastle, UK, showed that dexamethasone and Vitamin D3 treated tolDC loaded with synovial fluids, had some local positive effects by stabilizing knee symptoms when injected into inflamed joints of RA patients.[32] In order to collect synovial fluids and monitor therapeutic effects in joints,

this latter study had its focus on RA patients with advanced and active disease. This, however, is not the easiest patient group for tolerance induction. We are planning now a phase I-II, unblinded, longitudinal study with RA patients in remission or with low disease activity under conventional therapy.[33] In our case the dexamethasone and Vit D3 tolerized DC will be loaded with a well-characterized HSP70 derived peptide, which is called HSP70-B29.[34] Peptide HSP70-B29 is conserved, and T cells were shown to cross-respond between the microbial and the self-peptide both in mice and in humans. The peptide triggered the expansion of disease suppressive Tregs, and it showed promiscuous binding affinities for a majority of human MHC class II molecules. With tetramers, a repertoire of HSP70-B29 T cells, including Tregs, was shown to exist in humans.[35] It is hoped that therapeutic interventions based on such combinations of tolDC and a Treg inducing peptide may possibly lead to the ultimate goal of reaching a lasting self-tolerance and a permanent form of drug-free cure. Successful monitoring of the mechanistic pathways associated with the induction of such lasting tolerance may then possibly pave the way for preventive vaccination in early disease or even genetically predisposed healthy individuals.

## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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