

Short survey
T-cell vaccination for autoimmune disease: a panorama

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Abstract

T-cell vaccination refers to a form of cell therapy, usually autologous, aimed at curing or ameliorating autoimmune diseases. This review considers five questions: What is TCV? How is it done? How does it work? Why does it work? And what is its future? © 2001 Elsevier Science Ltd. All rights reserved.

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1. What is T-cell vaccination (TCV)?

The rationale and practice of TCV against autoimmune disease is analogous, at least in some respects, to classical vaccination against infectious disease. I shall therefore occasionally refer in this review of TCV to concepts of classical vaccination against infectious pathogens. In general, vaccination can be described as a form of immune education in which exposure to an attenuated exemplar of a pathogen teaches the immune system to attack the pathogen in its virulent form. Most vaccinations against infectious agents are preventive, but some vaccinations, like rabies vaccination or tumor immunotherapy, can be curative. The vaccine might be composed of the whole pathogen or of a constituent of the pathogen that contains a vulnerable target antigen. TCV, like any other vaccination, activates a subject's immune system to neutralize a pathogenic agent. However, TCV differs from classical vaccination in that the agents to be resisted are populations of the subject's own T cells; the vaccine is devised using a component of the immune system itself.

TCV grew out of the studies of my colleagues and me which initially were directed to the etiologic agents of the disease known as experimental autoimmune encephalomyelitis (EAE). EAE can be actively induced by autoimmunization of experimental animals to myelin antigens such as myelin basic protein (MBP). It had been known that the disease was caused by autoimmune T cells, so we set out to isolate *in vitro* lines or clones of T cells specific for a myelin antigen that would be capable of

adoptively transferring EAE to naïve rats *in vivo* [1]. Once we succeeded in demonstrating that our cultured T cells were indeed pathogenic *in vivo*, we asked whether it might be possible to use the same T cells, suitably attenuated, to prevent EAE. Could the induction of an experimental autoimmune disease be inhibited by vaccinating the immune system against its own pathogenic T cells? The answer was positive; a single inoculation of irradiated anti-MBP T cells could vaccinate against EAE [2]. Successful vaccination, however, required that the T cells comprising the vaccine had to have been activated by culture with their specific antigen (or with a T-cell mitogen) before vaccination [3].

We and others extended TCV to other experimental autoimmune diseases in rats and mice such as adjuvant arthritis [4], experimental autoimmune thyroiditis [5], collagen-induced arthritis [6], experimental autoimmune uveitis [7], murine lupus [8], and type 1 diabetes [9]. The lupus and the diabetes models are spontaneous diseases arising in genetically susceptible mice, so TCV in these mice is done after the spontaneous onset of the autoimmunity; therapeutic TCV could be demonstrated in these models. TCV using T cells reactive against allo-antigens has also been shown to prolong skin allografts in experimental animals [10].

2. How is TCV done?

To be effective, a classical vaccine should supply two types of immune signals: an antigen and a suitable accessory signal. The vaccine has to contain a target antigen that can direct the immune system to the specific pathogen, and the vaccine has to provide the accessory signals needed to

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induce the type of immune response suitable for neutralizing the target pathogen. If, for example, eradication of a particular intra-cellular pathogen requires a T1 type of response, it would do no good and possibly cause harm to use a vaccine that induces a T2 type of response. Recognizing the antigen by itself is not sufficient to protect the host; antigen recognition has to elicit a biological response suited to the nature of the pathogen [11]. What then are the signals needed for effective TCV?

TCV, like classical vaccination, also requires the two sets of signals: target antigen signals and accessory signals. The target antigen is the T-cell receptor (TCR), or parts of it, that are representative of the autoimmune T cells responsible for the disease [9,12–16]. I say *representative* of the autoimmune T cells, because the TCR need not include all the autoimmune TCR types involved in the disease; even the TCR of a single clone of autoimmune T cells can vaccinate a strain of mice or rats against an autoimmune disease [17]. Indeed, even a single peptide from the TCR of a single clone can therapeutically vaccinate NOD mice suffering from autoimmune diabetes [9]. In addition to whole T cells or TCR peptides, TCV can be done using naked DNA that encodes part of a relevant TCR [18].

TCV, like classical vaccination, is also enhanced by adjuvants accessory signals. The accessory signals required for effective TCV depend on the actual vaccine used. Whole T cells, to serve as vaccines, need to have been activated by incubation with specific antigen or a T-cell mitogen [3]. T-cell activation appears to induce accessory signals termed *ergotopes*, which appear to be activation markers [19]; in the next section, we shall return to the role of the ergotope in TCV.

Treating the activated TCV cells with hydrostatic pressure can enhance their effectiveness as vaccines, possibly by modifying the structure of the lipid bilayer of the T-cell membrane [20]. The mechanism of the enhanced effect, however, is unknown. Hydrostatic pressure attenuates the T cells in the vaccine, but most studies, for convenience, use irradiation as the attenuator. Doses of autoimmune T cells lower than the numbers needed to adoptively transfer an autoimmune disease do not need attenuation; such inoculations can safely serve to vaccinate against subsequent attempts to induce the disease by otherwise effective means [12,21,22]. The activated T cells appear to provide adjuvant signals for their TCR.

TCR peptides need to be administered along with signals that induce a T1 type of phenotype among the responding T cells that mediate protection [9]. TCV will not be effective if the TCR peptide is administered in a way that results in a T2 response to the autoimmune TCR [23]. TCR–DNA vaccination is done with plasmids containing CpG motifs that activate T1 immunity to the autoimmune TCR [18]. We shall discuss more about T1 and T2 below. The point is that there are alternative ways to prepare effective T-cell vaccines; the key components are TCR epitopes combined with adjuvants that can be T1 inducers or ergotypic signals.

3. How does TCV work?

Early on it was concluded that TCV worked by activating T cells specific for the TCR of autoimmune T cells involved in the pathogenesis; anti-TCR T cells could mediate the effects of TCV [12] and TCR peptides could vaccinate [13]. But how TCV works at the molecular level is just now being sorted out. The works of Vippin Kumar and Eli Sercarz and Associates [16,23–25], and those of Hong Jiang and Len Chess and Associates [26] are revealing. A network that includes both CD4 and CD8 T cells is involved in responding to the autoimmune TCR epitopes. The CD8 T cells appear to be major suppressors of the autoimmune T cells [25,26]. There is also evidence that the autoimmune TCR epitopes are presented by Qa1 MHC restriction molecules [26]; but how this occurs is still being investigated.

It was once thought that CD8 regulatory T cells suppressed the autoimmune disease by killing the specific TCR-bearing autoimmune T cells [27]. However, cytotoxic killing of autoimmune clones cannot explain how vaccination with a single TCR clone can effectively suppress a disease caused by a multiplicity of different clones [9]; killing one of the autoimmune clones would not be expected to affect the others bearing diverse TCR. Indeed, T cells indeed, it now seems that TCV works by activating a shift in the cytokine phenotype of the autoimmune response. Shifts from pathogenic T1-type autoimmunity to suppressive T2-type autoimmunity has been reported to be induced by TCV in both the diabetes [9] and EAE models [18] in animals, and in the TCV of humans suffering from multiple sclerosis [28]. How the CD8 regulatory T cells can effect the cytokine shift of the autoimmune effector T cells has yet to be clarified.

It might seem strange that effective TCV induces a T1-type response directed to the autoimmune T cells; most organ-specific autoimmune diseases seem to be caused by autoimmune T cells that themselves are T1-type and produce tissue-damaging T1 cytokines such as IFN γ and INF α [29]. Nevertheless, TCV appears to work by activating T1-type regulatory cells that can block the T1 autoimmune T cells and switch the autoimmune response to a T2 phenotype [9,18,24]. In other words, T1 regulators convert a T1 autoimmune attack into a suppressive T2 response. However, we have no molecular information to explain how the induction of T1 anti-TCR immunity by TCV could induce a cytokine shift in the autoimmune response. But the shift to T2 autoimmunity is a reasonable explanation for the spreading of regulation induced by TCV to autoimmune clones not included in the vaccine; by-stander suppression [30] might be involved, although the molecular basis for this suppression too requires much more study. In short, we know that the TCR is one of the targets of the regulation activated by TCV and that a complex network of cells and molecules is involved in mediating the effect; but we do not know much more than this about anti-TCR regulation of immunity.

But TCR-directed anti-idiotypic regulation is not the only effector of TCV; anti-ergotypic immunity is also involved. As I stated above, we learned at the outset that the T cells comprising the vaccine have to be activated to induce a regulatory effect [3]. The product(s) of T-cell activation required for TCV we called the ergotope (from the Greek word for activation). Indeed, we discovered that TCV led to the activation of regulatory T cells that seemed to recognize the ergotopes themselves [19]; in the course of TCV there arose T cells that proliferated in response to any syngeneic T-cell irrespective of its TCR. The only specific requirement for the anti-ergotypic response was that the stimulating T cells be activated (be ergotypic) and bear compatible MHC molecules [19]. Anti-ergotypic T cells were found to be functional; adoptive transfer of lines of anti-ergotypic T cells could down-regulate EAE in rats [19].

What is the ergotope? Many different molecules are associated with the activation of T cells, but we have found that at least some anti-ergotypic T cells recognize a peptide epitope present in the sequence of the alpha chain of the IL-2 receptor [31]. The alpha chain of the IL-2 receptor, also known as CD25 [32], is a prominent marker for activated T cells, and could function as a target ergotope. Indeed, a line of T cells responsive to a peptide of CD25 was found to down-regulate EAE [31].

The possibility that CD25 is a target ergotope in TCV is intriguing. T cells bearing CD25 have been reported to function as “non-specific” regulators of a variety of immune and autoimmune responses [33]. Although all activated T cells acquire the CD25 marker, the CD25-positive T cells present in naïve animals include these regulators. Note that the anti-ergotypic regulator T cells detected in TCV are both anti-CD25 and CD25 positive themselves (they are activated cells and respond to activated cells [19]). The anti-ergotypic regulators, like the CD25 regulators, could indeed function as “universal” regulators by virtue of a negative feed-back on T-cell activation. Perhaps the anti-ergotypic T cells discovered in TCV and the CD25 regulator T cells are members of a common cell family.

4. Why does TCV work?

The phenomenon of TCV, I believe, provides a functional insight into the internal organization of the immune system. TCV clearly shows us the complexity of this internal organization. The clonal selection theory (CST) of acquired immunity as enunciated by Burnet [34] had no need of any internal immune organization; the immune system was thought to be regulated entirely by only two factors: (1) the entry into the body of an antigen and (2) the presence in the body of at least one clone of lymphocytes bearing an antigen receptor capable of recognizing the antigen. The clones of lymphocytes “selected” by the antigen responded by destroying the antigen and the resulting disappearance of antigen shut off the response. The immune system was thus seen as a

simple stimulus-response loop, or better, as a chemical reaction regulated by the concentrations of the reactants—the reactants, in this case, being antigens and receptor-bearing clones. An important corollary of the CST view was the need to purge the immune repertoire of clones that bear receptors that could recognize self [35]. Strangely, this notion of the purging of autoreactivity, now called negative selection, has persisted to this day, despite a mass of data demonstrating the existence of autoimmune clones in healthy subjects [36]. The immune system is manifestly more complex than first envisioned by the classicists who sought chemical simplicity.

TCV, along with other immune phenomena, has uncovered networks of anti-idiotypic and anti-ergotypic T cells, the importance of autoimmune phenotypes, and the existence of naturally benign autoimmunity [37]. TCV has been an important element in the realization that the nature of the immune system, rather than being a simple reflex system [34], is a cognitive system with a complex internal organization [37] replete with an internal image of important self-antigens, the immunological homunculus [36]. Immunologists are beginning to come to terms with the complexity of the immune system that approaches that of the central nervous system. TCV works because it seems to activate the very mechanisms that the immune system uses naturally to modulate natural autoimmunity [38].

Several observations suggest that the immune system is organized during development to down-regulate autoimmune T cells. Firstly, the immune system seems to be primed for TCV; TCV can be effected by very small numbers of autoimmune T cells, as few as 100–1000 cells [12,20,21]. Such numbers of foreign T cells would not elicit much of a response. Indeed, the induction of EAE, by itself, seems to induce the activation of the very anti-idiotypic T cells induced by TCV [24]. Intra-thymic injection of a key TCR peptide to “tolerize” the system to its own anti-idiotypic regulators was found to accelerate the development of diabetes in NOD mice [9]. Finally, the capacity to mount a particular autoimmune response is a pre-requisite for a response to TCV; TCV seems to be possible only when the autoimmune reaction to be regulated is naturally prominent. TCV was found not to be effective in animals that were non-responders to the self-antigen recognized by the T-cell vaccine [39]. This suggests that specific anti-idiotypic regulatory T cells develop as a consequence of the natural development of particular autoimmune T cells [37]: no autoimmunity, then no anti-idiotypic regulatory cells and no TCV.

If autoimmunity exists, then it is certainly naturally regulated; but why must it exit? Why is there a “carrier state” for autoimmune T cells? The CST has tended to see autoimmunity as an aberration, an accident [35]. Since physiology deals with regularities and not with accidents, autoimmunity was a subject for pathologists only. But if we conclude that autoimmunity is natural, and not only pathogenic, then natural autoimmunity must serve some function [38]. Recently, we have discovered that autoimmune T cells, the very T cells

that can in some situations cause EAE, can also serve to protect the central nervous system against the consequences of trauma [40]. Body maintenance just might be one of the gifts of natural autoimmunity [37]. Regulation, like that uncovered by TCV, would serve to allow autoimmune lymphocytes to become activated in response to body damage to fine-tune the inflammatory response required for healing, angiogenesis and regeneration [37,38]. Autoimmune self-maintenance requires self-regulation to prevent the emergence of autoimmune disease.

Most importantly, whatever may be one's sectarian conviction regarding autoimmunity, TCV seems to offer an approach to medical therapy. Where do we go from here?

5. The future

In November 1999, there was held in Israel an international workshop on TCV in which investigators from Europe, USA, Israel and South America presented their experience and plans for clinical trials using TCV. It seems that over 100 persons suffering from multiple sclerosis have been treated with TCV using vaccines composed of attenuated (irradiated) autologous, autoimmune T cells responsive to myelin antigens. The results of human TCV confirm and even extend our immunological information about TCV. Humans too show down-regulation of their autoimmune reactivity [41,42], anti-idiotypic and anti-ergotypic reactivity [41,42], and T2 enhancement [28,43]. The clinical responses have been encouraging; the participants reported a lessening of clinical attacks and stabilization of the lesions visualized by imaging techniques in the treated patients without undue side-effects ([44,45], and reported at the workshop, 1999). However, these studies have been based on historical controls, and to date, no study has been done in a blinded fashion. Thus, future studies must be blinded, whatever the inconvenience, if we are to ever prove the efficacy of TCV as a treatment of multiple sclerosis or any other disease.

Of course, technical details of vaccine composition (whole cells, TCR, TCR peptides, anti-ergotypic cells, ergotopes, etc.), antigen specificity of the T cells, dose of T cells and dose schedule must be optimized for the persons treated, and TCV may have to be tailored to the particular disease and the state of the patient. Scaling-up and automation of procedures should be worked out. TCV is a process and lacks the ease of administration characteristic of pharmaceutical agents. Considering, however, the enormous cost of developing pharmaceuticals, TCV may turn out to be the most cost-effective way of treating the large numbers of people whose lives are ruined by autoimmune disease. The cure may be had by activating the natural mechanisms of regulation accessible within the human patient. T-cell vaccination is notable example of the attempt to cure autoimmune disease by inducing active regulation rather than by suppressing the immune system [46].

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