REVIEW

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Treatment of autoimmune disease: time for a paradigm shift?

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Abstract

Current treatment of human autoimmune diseases (AIDs) was developed empirically and relies mostly on non-selective suppression of the immune system. Traditional non-selective immunosuppressants such as corticosteroids, cyclophosphamide, and methotrexate and more novel means such as monoclonal antibodies to CD3, CD4, or CD25 do not discriminate between pathogenic and beneficial T cells. Importantly, the severe side effects seen with current therapies are related to the fact that these treatments not only suppress the pathogenic disease-inducing cells, but also cells influential in combating infections and killing malignant cells. Severe infections and malignancies are the inevitable result of non-selective immune suppression. Many of the novel forms of therapy of AID were developed in experimental animals, and their translation to the human disease was associated with the revelation of unexpected and sometimes catastrophic side effects. These surprises underscore the major differences between the relative simplicity of the experimental model and the complexity of the human disease. How can this current state of treatment of AID be improved? Which principles should guide us in the design of new treatments? This review attempts to offer a new look at these questions.

Key words: autoimmune disease, immune regulation, immune suppression, regulatory T cells.

Abbreviations: AID – autoimmune disease, EAE – experimental autoimmune encephalomyelitis, MS – multiple sclerosis, TCV – T cell vaccination, RA – rheumatoid arthritis, TCR – T cell receptor, APL – altered peptide ligand.

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AUTOIMMUNE DISEASE IS AN IMMUNE RESPONSE

In the last decades, knowledge in the field of immunology has grown exponentially. Major achievements in other fields of biology, such as the gene-chip technology [47] or novel *in vivo* imaging [63], were swiftly applied to the study of the immune system [46]. Following a short lag, new insights gained on the principles of operation of the immune system are translated into a better understanding of the autoimmune reaction [38]. As our insights of the operation of the immune system improve, novel therapies are added to the arsenal against autoimmune disease (AID).

The most important participant in many experimental and clinical AID is the $CD4^+$ effector T cell [34]. In addition to its direct pathogenic effects [72], this cell orchestrates and affects B cells [22], induces anti-idiotypic [36] and anti-ergotypic [39, 50] T cells, and affects antigen-presenting cells (APCs) [37] (Fig. 1). These $CD4^+$ T cell effectors, that are not deleted in the thymus [48], circulate the immune system in a quiescent state until they meet their peptide presented on a professional APC, such as a dendritic cell [20]. This leads to the full activation and differentiation of the effector cell, enhancing its migratory potential to non-lymphoid tissues [29]. The secondary activation in the target tissue leads to immune-mediated destruction and loss of function, translating as the clinical symptoms of a specific disease [2]. The effector T cells are controlled by cytokines, chemokines, and the recently described various regulatory T cells [13, 15]. In other words, the simplistic model of the tri-molecular complex (peptide-MHC-TCR) governing the autoimmune response [5] has been updated to include several kinds of regulatory T cells capable of turning off autoimmune inflammation [4, 13, 15, 33, 67].

A major point to emphasize is that mechanistically there is no difference between an immune response to

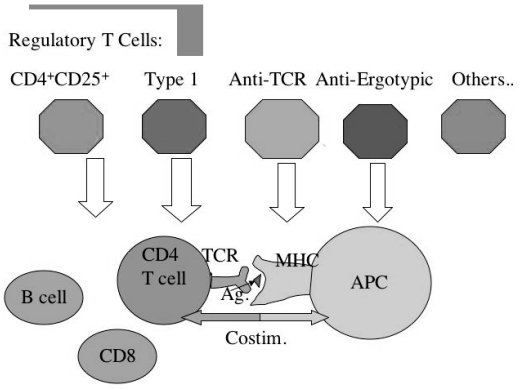

Fig. 1. Participants in the autoimmune response. The major player is the $CD4^+$ effector T cell, recognizing its antigenic peptide (designated Ag.) in the cleft of a class II MHC molecule on an APC. This interaction is affected by various costimulatory molecules (Costim.). Additional players are B cells [68] and CD8 T cells [25]. The upper row of cells represents the various kinds of regulatory T cells affecting the CD4 effectors. The best characterized are the $CD4^+CD25^+$ Tregs [51]. In addition, some Tregs are specific for TCR determinants (anti-TCR) [33], others are against T cell activation-induced molecules [39] (anti-ergotypic). Another member of the regulatory cell family is the type 1 Treg [67], characterized by the secretion of IL-10, and others (designated Others..), which might include the Th3 type cells secreting TGFβ and IL-10 [69] and additional types of Tregs to be characterized in the future.

a foreign antigen (infection) and an immune response to a self antigen (AID). In other words, the hundreds or thousands of molecules participating in the inflammatory process, such as cytokines, chemokines, and their receptors, the signaling pathways in APCs T cells and B cells, and the molecules orchestrating the regulatory phase of the immune response are similar in infection-induced and autoimmune inflammation. The only specific key that may enable selective control of autoimmune inflammation is the use of the specific antigen [14] or the antigen-specific T cell clones reactive to it [6] that is targeted by the immune system in AID. A recently described antigen-specific regulatory T cell may represent another sophisticated level to control AID [9, 17, 23, 24, 43].

THE EXPERIMENTAL-CLINICAL DIFFERENCE

One of the most promising ways to study human diseases is to investigate an animal model for etiology, pathogenesis, and therapy. Most common human AIDs have experimental counterparts in animals that serve as models for their study. Multiple sclerosis (MS), rheumatoid arthritis (RA), type I diabetes mellitus, lupus, uveitis, thyroiditis, myocarditis, neuritis, nephritis, orchitis, colitis, and many others have their experimental models that, being genetically simplified (most models are in genetically MHC-identical mice or rats), are considerably easier to study. Some of the effective treatments in human AIDs were developed in these models. Glatiramer acetate [60], natalizumab [62], and mitoxantrone [26] in MS and anti-tumor necrosis factor (TNF)-α in RA [41] were developed in experimental animals. However, due to the relative ease and simplicity in curing or ameliorating the experimental disease [61] and the complexity of shutting off human disease, there are many frustrations as one tries to make the jump from the experimental to the human disease. The paradoxical exacerbation of MS by altered peptide ligands (APL) [7] and the adverse outcome of treatment with interferon γ [53] are examples. Unexpected severe side effects, such as the development of progressive multifocal leukoencephalopathy in recipients of adhesion molecule blocker in MS [3, 56] or the life-threatening massive T cell activation in volunteers treated with stimulatory anti-CD28 antibodies [64], serve as examples that highlight the large gap in our knowledge and dictate a more humble and cautious approach as we implement knowledge gained from mice to humans. At a more basic level, the problem relies on the heterogeneity of the human disease and in our incomplete understanding and control over the tolerization effect, thus, in a minority of recipients treated, the tolerizing therapy (oral tolerance [8], T cell receptor (TCR) peptide immunization [19], costimulation blockade [54], DNA vaccination [57, 58], administration of APL [7]) may actually have an immune induction effect resulting in disease relapse or progression.

THE SELECTIVITY OF TREATMENT

The ideal therapy for AID should affect the pathogenic clone or clones specifically without suppressing the entire immune system, it should be devoid of toxicity, and it should be easily administered. While there are considerable efforts in improving the treatment of AID, none of the current immunosuppressive therapies are satisfactory.

As previously stated, one of the most important qualities of a treatment for AID is its selectivity. Put in other words, how will the given treatment affect innocent bystanders cells (which are important in the defense against infection and in killing malignantly transformed cells) in comparison to pathogenic cells. Despite considerable efforts to try to find specific mechanisms or pathways used selectively by autoimmune T cells, to date there are no convincing data to support a valid difference between pathogenic and protective T cells (except for the TCR of pathogenic cells). The choice of a cytokine [41], chemokine [44], signaling molecule [52], or adhesion receptor [56] may be appealing at first glance, based on the knowledge of their suggested importance in the autoimmune inflammation. However, as many other important beneficial immune reactions use the same molecules, the risk of significant side effects is built into the decision to use them.

The success of treating RA and Crohn's disease with anti-TNF-α antibodies may seem at first glance to be

a contradiction to the selectivity principle suggested. However, the lack of real remission with such treatment (stopping treatment is associated with the relapse of disease [40]) and the reports of mycobacterial infections and malignancies arising in these patients [10] reinforce the claim that nonselective treatment is likely to be accompanied by significant side effects.

Following the selectivity principle, the most selective treatments would be those based on the auto-antigen or the T cells recognizing it. The treatment principle would be to use the auto-antigen to manipulate the immune system to lose its reactivity to it, i.e. induce tolerance to the auto-antigen. Oral tolerance is a well-characterized mode of tolerizing the immune system to a given antigen. Myelin basic protein [31], collagen type II [65], and insulin [42] were given orally or nasally as effective treatments of experimental autoimmune encephalomyelitis (EAE), collagen-induced arthritis, and type I diabetes mellitus, respectively, in experimental animals. Based on the positive results in experimental models, human oral tolerance trials were initiated with much less impressive results [70]. An additional caveat was that in some cases the introduction of antigen by the oral route might result in immune activation rather than immune suppression, potentially leading to exacerbation of AID [8]. Additional ways to induce antigen-specific tolerance were introduced (thymic injection [32], co-stimulation blockade [71], DNA vaccination) and remain to be tested in humans.

An alternative approach to using the antigen was to use the reacting T cell [6, 49] or its receptor [66] to enhance regulation over pathogenic T cells. T cell vaccination (TCV) was developed and successfully applied in several animal models of AIDs [16]. Based on the positive results in animals, TCV was tested in humans, mostly in MS and RA by several groups in Europe [28], the US [27], and Israel [1], with positive results (lowering the attack rate and lesion burden by MRI [73, 74]). TCR peptide vaccination was also tried in human MS [11]. Thus, despite the theoretical advantage of selective immuno-suppression based on the auto-antigen or the T cell reactive to it, the overall performance of this approach in treating human disease is not optimal. Indeed, the recent description of success in raising antigen-specific Treg cells [17] opens the arena of specific immune suppression to a new player with significant capacities to turn off the experimental autoimmune response.

THE CURRENT PARADIGM

Most novel treatments for human AIDs were developed and tested in experimental animals. Rarely, target molecules were identified in human MS tissue and later verified in EAE as treatment modality [38]. The current treatment paradigm is based on the linear concept of disease pathogenesis, which starts with pathogenic T cell activation, acquisition of effector function, followed by migration to target tissue and induction of tissue damage (by direct contact or cytokines). In the chronic or relapse phases, pathogenic T cell reactivity can be shifted to other epitopes in the same auto-antigen (a phenomenon called intra-molecular "determinant spreading" [35]) or to other proteins (inter-molecular "determinant spreading" [45]). In the healing phase, pathogenic cells undergo apoptosis [59] or a change in cytokine pattern [31] or develop anergy, either spontaneously or following regulation by several types of T regulatory cells. Following this linear concept of pathogenesis, various single means are tested to interrupt the autoimmune reaction. The various modalities can be divided mechanistically according to their suggested site of action: T cell-activation inhibitors, migration blockers, cytokine or chemokine antagonists, etc. If we assume that the immune attack is mediated by several kinds of pathogenic cells (CD4 [34], CD8 [25], and γδ T cells [55], B cells [21], and macrophages [18]) induced by more than one self peptide and acting in concert, the approach of targeting a single molecule to shut off the complex autoimmune response may be somewhat naïve.

THE MULTI-HIT APPROACH

We have to admit that despite a huge increase in our knowledge of the immune system in recent years, we have not acquired the capacity to block an ongoing AID without adversely affecting our allies in the war against infection and malignancy. In sharp contrast to the multitude of ways to stop experimental autoimmunity, our weapons to stop human disease are for the most part both ineffective in inducing complete remission and in exerting their effects selectively on the pathogenic effector T cells. Based on the assumption that the autoimmune process is complex and its progress is not dependent on a single molecule to be attacked, I propose that the approach to treatment should be based on pathophysiology and rely on the attack of more than one target. In analogy to the treatment of malignant disorders, the selection of several targets for treatment, if properly selected, may have synergistic effects and a greater impact on halting the autoimmune process. An example for the selection would be using the antigen to induce antigen-specific suppression [70] or TCV with another means to prevent the epitope-spreading phenomenon [35], thus preventing the perpetuation of disease on another antigen. Another example would be to combine two methods of tolerization: oral tolerance and TCV. Naturally, the development of synergistic treatment protocols will necessitate testing in experimental animals and validation in clinical trials. The actual selection of agents will depend on an increase in our knowledge of the actual escape mechanisms used by the autoimmune process to evade the first-hit treatment effect. Thus, first remission could be induced with one agent and treatment of the relapse should be tailored by the knowledge of the molecular events leading to the relapse [30].

There is an inherent problem with this approach as the different treatment modalities might have emerged from different researchers (sponsored by different companies) and their combined application will thus demand a significant level of cooperation. As the enemy (human AID) turns out to be much more sophisticated and difficult to beat, we should try to tailor the therapy to several of its pathogenic mechanisms to win the war against it. Indeed, such combination treatment approaches are already being tested [12]. On theoretical grounds, the use of several synergistic modes of treatment will enable the use of smaller doses of each therapeutic modality, thus minimizing side effects.

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