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Targeting antigen presentation in autoimmunity☆

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ABSTRACT

Autoimmune diseases are heterogeneous group of disorders that together represent an enormous societal and medical problem. CD4+ T cells have critical roles in the initiation and pathogenesis of autoimmune disease. As such, modulation of T cell activity has proven to have significant therapeutic effects in multiple autoimmune settings. T cell activation is a complex process with multiple potential therapeutic targets, many of which have been successfully utilized to treat human disease. Current pharmacological treatment largely targets T cell intrinsic activities as a means of treating various autoimmune disorders. Here I review extant and potential therapeutic approaches that instead specifically target antigen presentation to CD4+ T cells as a critical checkpoint in autoimmune responses. In addition, the contribution of antigen modulation components in current therapeutic approaches is considered along with the impact of new antigen targeted treatment modalities. Finally, potential challenges are considered in the context of the potential for antigen specific targeting of the antigen presentation process.

1. Introduction

Although the exact number of disorders that can be considered autoimmune diseases remains an area of contention, dozens of disorders are recognized as including a self-directed adaptive immune component. One commonality of characterized and putative autoimmune disease is that T cell effector function is a critical component to disease initiation and/or continuation [1,2]. So it is not surprising that many of the current therapies for autoimmune disorders target T cell activation and effector function. Multiple components of T cell activity have been targeted in an effort to ameliorate disease, including depletion of lymphocyte subsets, direct modulation of intrinsic T cell signaling, blocking of costimulatory signals critical for productive antigen recognition, and targeting of effector molecules such as cytokines. While these approaches have certainly proven fruitful, they have also tended to be relatively generalized approaches to immunomodulation, with concomitant impacts on immunity to infectious agents. Thus, while these broad immunosuppressive approaches have been enormously successful in transplantation settings, they have proven less universally accepted in autoimmune settings that represent less immediate risks of mortality.

In addition to general immunosuppressive protocols, advances have also been made in modulation of antigen-specific autoimmune responses. Antigen specific modulation of autoimmunity is a highly sought goal, as it would allow therapeutic approaches that would not hinder immune reactivity to pathogens, preventing many of the adverse effects that limit current immune modulatory approaches to treatment of autoimmunity. Methods utilized often focus on targeting of T cells of known antigen specificity, either by directly targeting epitope specific lymphocytes or by induction or activation of regulatory cell populations that respond to the same antigen. The successes and challenges of these approaches have been extensively reviewed previously [3–6], and thus will not be covered in depth here. In addition several alternate approaches have been reported that attempted to directly target autoantigen presentation and/or antigen-presenting cells in autoimmunity, with varying efficacy.

2. Antigen presentation as a risk factor for autoimmunity

The use of twin studies and the explosion in available genetic data have revealed fascinating insights into the role of genetics in autoimmunity [7–10]. Perhaps because autoimmunity is such a broad categorization, the impact of genetics on individual autoimmune manifestations is wildly divergent, with genetic predisposition accounting for anywhere between 5% and 90% of established risk for individual disorders. However, while sensitive genetic techniques have now

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revealed multiple potential contributors to disease, factors involved in antigen presentation are among the most highly represented.

Antigen presentation is a complex biological process, with many molecular contributors, involving the production, peptide-loading, and localization of MHC molecules to the cell surface where the MHC/peptide complex can interact with passing or recruited T cells in a cognate manner. Specific alleles of the both MHC class I and MHC class II molecules were some of the first identified and remain by far the most significant genetic risk factor for multiple autoimmune diseases [11–15]. Further, there is evidence to suggest that the risk of disease associated with expression of specific MHC proteins is modified by complex interactions between multiple MHC alleles [16].

Genetic differences in other aspects of the antigen presentation pathway, particularly the molecular mechanisms responsible for the peptide processing and loading that results in epitope selection, have also been linked to increased risk for some autoimmune diseases. As an example, allelic differences in endoplasmic reticulum aminopeptidase proteins (ERAP), which result in subtle changes in the peptides displayed on MHC, are associated with significantly increased risk of ankylosing spondylitis [17,18]. Other changes in peptide production or display, including some induced by pathogen driven inflammatory conditions, have also been show to impact disease in multiple autoimmune settings [19,20]. Indeed, multiple studies have demonstrated that altering the ligands presented, often by providing large concentrations of modified peptides can greatly impact the T cell response [21–24].

Together, the studies discussed above provide strong evidence that MHC/T cell interactions are critical determinants of autoimmune disease. However, the genetic data cannot determine at what stage(s) of disease MHC/T cell interactions are required. Thus, an important question to consider is whether T cell/MHC interaction is required during disease initiation and/or on an ongoing basis throughout disease. To address this question early studies utilized antibodies specific for MHC class II molecules to both prevent and treat experimental autoimmune disease, suggesting that T cell/MHC interactions are important throughout the disease process [25–29]. Similarly, use of antibodies specific for the antigen receptor of clonal lymphocyte populations have been shown to modulate autoimmune disease [30,31].

In addition many other studies have made use of classic depletion methods to address the impact of different subsets of antigen presenting cells (APC) on disease induction and severity at different stages of disease. For instance, in models of the autoimmune disease type 1 diabetes, multiple types of APC appear to be critical to the initiation of disease [32,33]. However, it is important to note that these studies do not demonstrate the exact roles of the APC to disease development and thus the relative importance of antigen presentation, as opposed to other aspects of APC effector function to pathogenesis. Using a specific modulator of epitope generation and selection in diabetes models prevented pancreatic cell destruction, suggesting that antigen presentation is at least necessary to disease development [34–36]. Similarly, in experimental thyroiditis, use of a small molecule inhibits antigen presentation and subsequent disease [37].

3. Evidence of antigen presentation as a critical requirement for ongoing autoimmunity

Unfortunately, as neither patients nor physicians can accurately predict onset of autoimmunity, therapeutic intervention in established disease is typically required in the clinic. The critical requirements for T cell activity in disease initiation can make determining the impact of antigen-presentation in later phases of disease difficult. Because T cells generally rely on presentation of MHC/auto-antigen peptides within the target tissue to drive their effector functions, continued antigen presentation would appear to be a critical component in continuation of any established autoimmune setting that is known to be modulated with T cell targeted therapeutics. Excellent examples of such disorders would be RA and RRMS, both of which can be treated with T cell targeted therapeutics. Models developed to examine experimental depletion of specific APC subsets after development of disease reveal that the ongoing presence of antigen presenting cells within the target tissue [38] is essential for pathogenesis [39–42].

Again it is important to note that these findings do not necessarily demonstrate that antigen presentation itself is required for ongoing autoimmune disease, as APC can exert multiple impacts within a tissue beyond T cell activation. As such depletion methods may not accurately identify the actual role(s) antigen presentation plays in pathogenesis after autoimmune disease initiation. In support of an ongoing necessity for APC/T-cell interaction, in an autoimmune demyelination model, altered peptide ligands were found to modify T cell responses and ameliorate disease, suggesting that ongoing T cell activation is necessary for continued disease and could be targeted therapeutically [21–24]. Similar approaches were described in RA [43]. Further work has suggested several potential methods of modulating peptide usage in autoimmunity [44].

The nature of immune attack tends to result in increased antigen presentation during autoimmune inflammatory events [45]. During autoimmunity tissue destruction can result in antigen uptake and subsequent presentation, acting as a positive feedback loop to drive further autoimmunity through both increased antigen availability and production of new responses to previously unrecognized epitopes [46]. In several types of autoimmunity, these inflammation associated changes in presentation appear to be critical to the pathogenesis of disease [47]. The requirement for secondary responses to previously occult antigens, often called epitope spreading, in the pathogenesis of experimental neuroinflammation and arthritis models is a strong argument for the necessity of ongoing antigen presentation in established autoimmune disease.

4. Impact of current therapeutic approaches on antigen presentation

Given the heterogeneity of autoimmune disorders it is likely that blocking antigen presentation could be efficacious in some disorders while being completely ineffective in others. The efficacy of current therapeutics that are thought to work by modulating T cell activity would seem to be a reasonable guide. Broadly active therapeutics, such as corticosteroids, will have substantial effects on a multitude of cell types within the body, and have been shown to interfere with productive antigen presentation. Indeed any approach thought to act via modulation of innate immune parameters will most likely impact antigen presentation, as is clearly the case for newly recognized immunomodulators such as statins [48].

It is important to consider that, given the complex feedback mechanisms that regulate immunity, any therapeutic that modulates one aspect of the immune response, even by very narrow targeting of effector molecules, can have profound effects on other aspects of immunity. One example of this is the use of TNFα inhibitors in the treatment of multiple autoimmune disorders, including RA and Crohn's disease [49]. TNFα is a critical effector cytokine driving autoimmune pathology and as such its neutralization will have direct effects on disease outcomes [50]. In addition, TNFα is known to influence the antigen presentation capacity of antigen presenting cells. As such, TNFα inhibitors almost certainly have a secondary effect on antigen presentation [51], although the relative contribution of each effect of TNFα inhibition to disease amelioration is an open question.

Of the professional antigen presenting cells, B cells have been the focus of many recent studies. The capacity to deplete mature B cells has suggested that B cells contribute to multiple forms of autoimmune inflammation [52]. B cells can utilize multiple mechanisms in autoimmune responses, including production of antibody and cytokines [53,54], but recent data suggests that B cells may also have critical

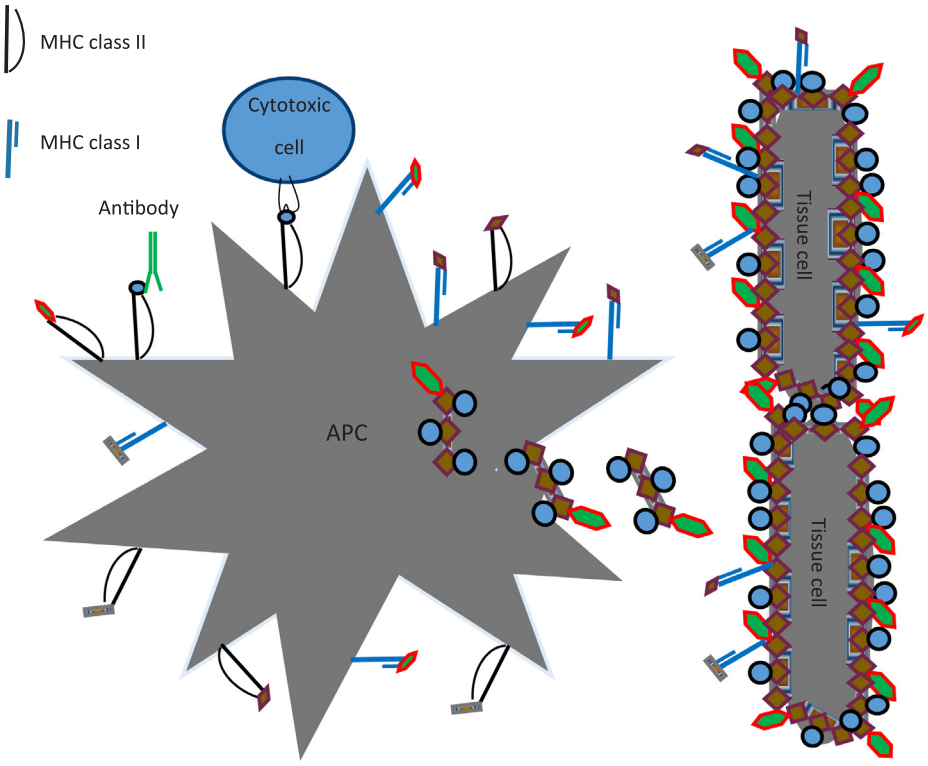

Fig. 1. Targeting known MHC/peptide can also block presentation of additional associated tissue proteins. Proteins sampled from tissue cells will tend to be taken up as a complex resulting in multiple epitopes from a tissue being presented by the same antigen presenting cell. Targeting a single MHC class II/peptide can block presentation of multiple associated peptides while sparing MHC class II negative tissue cells.

antigen presenting roles in some forms of autoimmunity [55–57]. Examination of the role of specific B cell activities in autoimmune disease is extremely difficult, however studies using experimental autoimmune animal model systems have provided some important data. For instance, B cell antigen presentation appears to be a critical component to the initiation of spontaneous type I diabetes in the NOD model [58,59]. As a consequence depletion of B cells using a variety of methods results in reduced diabetes onset [60–63]. As an additional example, in MS the therapeutic success of anti-B cell antibody treatment [64,65] has suggested that B cells must play a critical role in ongoing neuroinflammation, however the exact mechanism is still unclear. Studies done in the experimental autoimmune encephalomyelitis model of MS has suggested that the critical role for B cells may be antigen presentation, with the caveat that B cell involvement in EAE disease is highly system dependent [66,67]. However, additional studies in EAE have suggested that B cell antigen presentation is sufficient to drive EAE responses when other APC are not present [68,69], suggesting that these cells can be a critical antigen presenting cell population during neuroinflammation.

Together, these data indicate that some current therapeutic approaches may partially rely on inhibition of antigen presentation to produce clinical benefit. This suggests that antigen presentation is a reasonable target for ongoing attempts to modulate immunity. Given the already mentioned advantages of antigen specific regulation, modulation of antigen presenting cell activity, in an antigen dependent manner, would appear to be an exciting goal.

5. Antigen specific targeting of antigen presenting cells

Early attempts to target antigen specific cell populations relied on antibody responses to unique determinants within the variable regions of clonal antigen receptors [30,31]. This is an effective method for targeting individual clonotypes, but requires identification of the specific idiotypes of dominant clones and the production of antibodies to those idiotypes. Conversely, there are several examples of the production of antibodies specific for peptide in the context of MHC [70]. These reagents should allow one to target specific antigen displayed on APC in the context of MHC.

MHC class I molecules are ubiquitously expressed while MHC class II molecules have a highly limited distribution. As outlined above, presentation of MHC class II (MHCII)/myelin peptides to $CD4^+$ T cells within target tissue is thought to be a critical component of initiation and continuation of autoimmune inflammation. As such emerging protocols that would allow antibody mediated direct visualization and targeting of defined peptide/MHC II complexes may provide us with new ways to approach autoimmune treatment.

Recent work has delineated methods for successfully introducing new antigen receptors into mature cytotoxic T cells [71]. These cells have been found to be efficacious for antigenic cell elimination in a variety of settings. Antigen specificity was provided via transgenic expression of either cloned MHC class I/peptide responsive TCR or engineered antigen receptors that recognized native antigen without MHC restriction. The emergence of T cells transduced with defined antigen receptors has opened up new possibilities for targeting autoimmunity in an antigen specific manner [3,5]. Indeed, several exciting studies have emerged demonstrating T cell directed therapies produced by transduction of regulatory T cells [72].

While multiple groups examined the consequences of expressing a MHC class I restricted TCR in mature $CD4^+$ T cells [73–75] no one has yet reported the functional consequences of expressing a MHCII restricted TCR in mature $CD8^+$ cells. Interestingly, functional MHCII restricted $CD8^+$ T cells have been reported in circumstances of CD4 deficiency [76] or viral pathogenesis [77] and there is evidence that cytotoxicity can occur without CD8 co-receptor activation [78]. Further, cytotoxic $CD8^+$ T cells have been shown to modulate ongoing antigen presentation by killing antigen-decorated antigen presenting cells (APC) in a variety of systems [79–86]. These findings suggest that introduction of a MHCII/peptide responsive TCR into mature $CD8^+$ T cells may allow cells to recognize and lyse cells bearing the cognate antigen, providing a new method for targeting APC displaying specific epitopes.

Regardless of the method used, one major advantage of targeting specific antigen(s) displayed on APC is that the targeted APCs would be expected to present multiple self-derived peptides from the same tissue,

due to the nature of antigen processing from phagocytized or endocytized complex material. Importantly, that would mean that targeting APC for modulation with a single defined antigen, using either antibody or transgenic cytotoxic cells, would also impact the presentation of any additional tissue specific antigens that APC would present (Fig. 1). This is critical as the inability to determine what antigenic responses are actually responsible for ongoing autoimmunity is one of the great challenges currently facing T cell targeted approaches to antigen specific tolerance induction.

6. Potential challenges

While there is clear evidence that failure of central tolerance can drive autoimmunity [87,88] there is also a growing understanding that at least some forms of autoimmunity are not the result of rare failures in central tolerance of lymphocytes, but rather represent a failure in the control of autoreactive cells that typically occur in the normal immune repertoire [89–92]. Further, there are indications that adaptive immune auto-reactivity is involved in normal physiological responses, suggesting that autoimmune reactions could, at least in some cases, represent dysregulation of otherwise beneficial biology [93,94]. Further, lessons from transplantation suggest that blockade of specific costimulatory molecules can decrease the capacity of naturally occurring regulatory mechanisms to modulate ongoing inflammation [95,96]. This data is supported in multiple other model systems that have demonstrated that blocking antigen presentation can also block the initiation of homeostatic peripheral tolerance mechanisms [97–101], even leading to *de novo* autoimmunity [102,103]. Any attempts to modulate antigen specific APC would also have to consider the emerging role of B cells as immune regulatory cells, with the capacity to modulate ongoing responses either through the production of cytokines such as IL-10 or by direct modulation of T cell function [104].

Given this data, it seems clear that attempts to modulate immune responses would have to be careful to avoid interference with active homeostatic regulatory processes. However, given the potential of this approach targeting tissue specific antigens displayed by antigen presenting cells appears to represent an emerging field of interest.

7. Conflict of interest statement

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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