Could TCR antagonism explain associations between *MHC* genes and disease?

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Alleles of *major histocompatibility complex* (*MHC*) loci are associated with certain types of diseases, including those of infectious and autoimmune origin. *MHC* products can promote susceptibility or resistance to disease by stimulating or inhibiting immune responses. Recent evidence suggests that MHC-associated peptides derived from self-proteins can act as antagonists of T-cell activation, thereby inhibiting immune responses to antigens. We suggest that self-peptide-promoted antagonism might explain some associations between *MHC* alleles and particular chronic diseases.

Immune responses are initiated when short peptide antigens derived from lysosomal or proteasomal proteolytic processing, in association with major histocompatibility complex (MHC) molecules, are presented to T lymphocytes. In every species analyzed to date, *MHC* genes are the most polymorphic genes found in the genome, and this polymorphism is maintained by selection [1]. Allelic variants of *MHC* gene products bind different peptides from any given protein (Fig. 1). The presence of multiple alleles in a population increases the probability of foreign-antigen presentation in at least some individuals (Fig. 2), and consequently enhances the likelihood of species survival [2]. Associations between *MHC* alleles and AUTOIMMUNE (see Glossary) diseases [3–6], infectious diseases [7], allergic disorders [8] and tumors [9–11] have been observed. One common characteristic of these diseases is their chronic nature, suggesting that MHC exerts its influence over relatively long time periods. Both susceptibility and resistance to disease can be mediated by stimulatory or inhibitory influences of MHC molecules on the intensity of the immune response, depending on the nature of the disease (Fig. 3 and Table 1).

Immune responses can contribute to either resistance or susceptibility to disease

Stimulation of an immune response can protect the host against infections or tumors, but can also promote autoimmune and/or inflammatory (IMMUNOPATHOLOGICAL) diseases. An illustrative example of MHC-mediated protection is resistance to the development of severe (cerebral) malaria [12]. Presentation of a peptide derived from *Plasmodium falciparum* by human leukocyte antigen (HLA)-B53 has enabled preferential survival of HLA-B53$^+$ individuals in areas of Africa in which severe malaria in endemic. *HLA* genes are also associated with the speed of development of AIDS following infection with HIV-1. Most untreated HIV-1-infected humans develop clinical AIDS within 5–10 years of initial infection [13]. However, a small group of seropositive long-term survivors develop benign disease with much slower progression to AIDS [14], and HLA-B57 and HLA-B27 are over-represented alleles in this group of individuals [15,16].

Productive immune responses can also be harmful. Some of the strongest associations between *HLA* and diseases are with autoimmune and/or immunopathological conditions. For example, >90% of patients with ankylosing spondylitis, coeliac disease, narcolepsy or birdshot chorioretinopathy are carriers of *HLA-B27*, *-DQ2*, *-DR2* or *-A29*, respectively (Table 1). Although associations between *MHC* genes and diseases could potentially be the result of 'squatter' genes placed by chance in the *MHC* locus, evidence for a specific and direct role for *MHC* alleles in disease has been provided in some cases. For example, in experimental animals transgenic for the appropriate allele, HLA-B27 [17,18] and HLA-A29 [19] promote the development of pathology that is

Glossary

Anergy: A state of unresponsiveness to antigen.
Autoimmunity: Damage done to the tissue as a consequence of an immune response to self antigens, which should not normally occur.
Determinant capture: Prevention of binding of an epitope to a major histocompatibility complex (MHC) molecule, caused by binding of the same epitope or its large portion to another MHC molecule.
Epitope: The portion of an antigen that interacts with antibody or the T-cell receptor (TCR).
Immunodominance: The capacity of an immune system to focus the response on one or few of the many potential epitopes.
Immunopathology: Damage done to the tissue as a consequence of a protracted immune response to foreign antigens.
Negative selection: Physical removal or functional silencing of autoreactive T cells, which occurs during maturation of T cells in the thymus.
Positive selection: Functional and phenotypic maturation of T cells in the thymus based on the ability of their TCRs to interact with self-peptide–MHC complexes.

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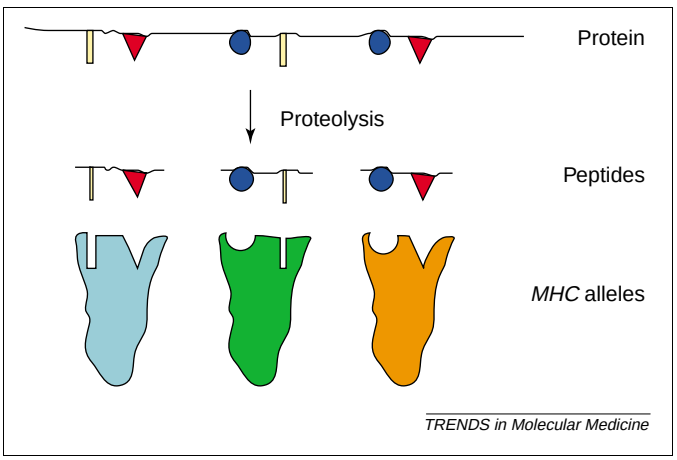

Fig. 1. Each peptide originating from a hypothetical protein binds to the protein product of different *major histocompatibility complex* (*MHC*) alleles. The specificity of peptide binding is determined by the presence or absence of specific amino-acid motifs in the products of proteolytic cleavage.

characteristic of ankylosing spondylitis and birdshot chorioretinopathy, respectively.

How can the immune response restricted by a given *MHC* allele contribute to a frequency of disease that is higher (autoimmunity or immunopathology) or lower (infectious diseases or tumors) than that found in the general population? In the case of autoimmune and immunopathological conditions, the disease-associated allele is thought to be uniquely capable of presenting the relevant antigen. For example, *HLA-DQ2* is the only HLA allele whose product presents peptides derived from gliadin, a causative agent of coeliac disease [20]. In addition, although the exact antigen responsible for induction of *HLA-B27*-associated ankylosing spondylitis has not been determined, peptide presentation by HLA-B27 is important; reducing the diversity of the presented-peptide repertoire by competition with an efficiently presented irrelevant EPITOPE prevents the disease in experimental *HLA-B27*-transgenic rats [21]. In the case of infections, the contribution of a given *MHC* allele to resistance against disease is determined by the relationship between IMMUNODOMINANT epitope presentation and mutations of infectious agents. Microorganisms are known to mutate frequently, and pressures

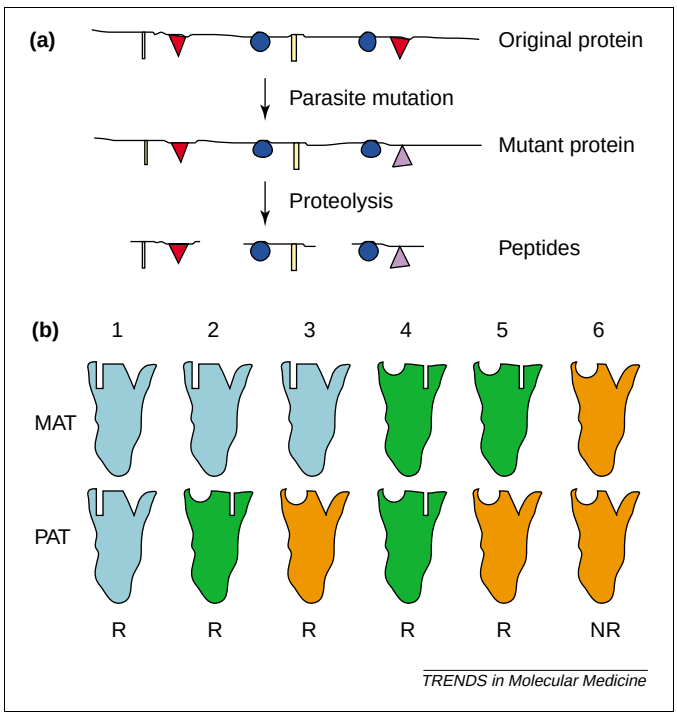

Fig. 2. Dynamics of the interaction between a microbe and the immune system of the host. (a) The major histocompatibility complexes (MHCs) and immune system of the host are useless when dominant antigenic epitopes are eliminated from the genome of the microbe. Hence, some microbes strive to create 'escape mutants'. (b) The host can increase the likelihood of responding (R) by heterozygosity at polymorphic *MHC* loci, which increases the chance of binding a presentable microbial peptide. Individuals homozygous for an *MHC* allele that cannot present mutant peptide do not develop an efficient immune response (NR). This could be deadly for the host, depending on the severity of the disease caused by the particular pathogen. Abbreviations: MAT, maternally inherited allele; PAT, paternally inherited allele.

exerted by [22–24] or unrelated to [25] the immune system can contribute to the selection of microbial variants with deleted or mutated immunodominant epitopes. The immune response against these variants is usually significantly reduced [22,26–30]. Therefore, the location of a crucial epitope in the genome of a particular microbe is of enormous practical importance for the control of infection. An epitope located in a region of the molecule that does not tolerate mutations (because that portion of the molecule is essential for survival, replication or

Table 1. Some examples of associations of *HLA* genes with diseases

HLA	Disease	Association	Mechanism	Ref.
B53	Severe malaria	Resistance	Stimulatory	[12]
B27, B57	AIDS	Resistance	Stimulatory	[15,16]
DR2	Hepatitis B	Resistance	Stimulatory	[7]
*DRB1*1101, DQB1*0301*	Hepatitis C	Resistance	Stimulatory	[7]
B27	Ankylosing spondylitis	Susceptibility	Stimulatory	[4]
A29	Birdshot chorioretinopathy	Susceptibility	Stimulatory	[6]
DQ2	Coeliac disease	Susceptibility	Stimulatory	[3]
DR2	Narcolepsy	Susceptibility	Stimulatory	[81]
*DQB1*0602*	Multiple sclerosis	Susceptibility	Stimulatory	[35]
A29, B35	AIDS	Susceptibility	Inhibitory	[16,31]
DR2, A10, B8	Pulmonary tuberculosis	Susceptibility	Inhibitory	[7]
DR2	Leprosy	Susceptibility	Inhibitory	[7]
DR7	Chronic hepatitis B	Susceptibility	Inhibitory	[7]
*DRB1*0701, DRB4*0101*	Hepatitis C	Susceptibility	Inhibitory	[7]
*DR2 (DRB1*1501-DQB1*0602)*	HPV-type-16-induced cervical cancer	Susceptibility	Inhibitory	[10]
*DQB1*0602*	Type-I diabetes	Resistance	Inhibitory	[33]

Abbreviations: HLA, human leukocyte antigen; HPV, human papillomavirus.

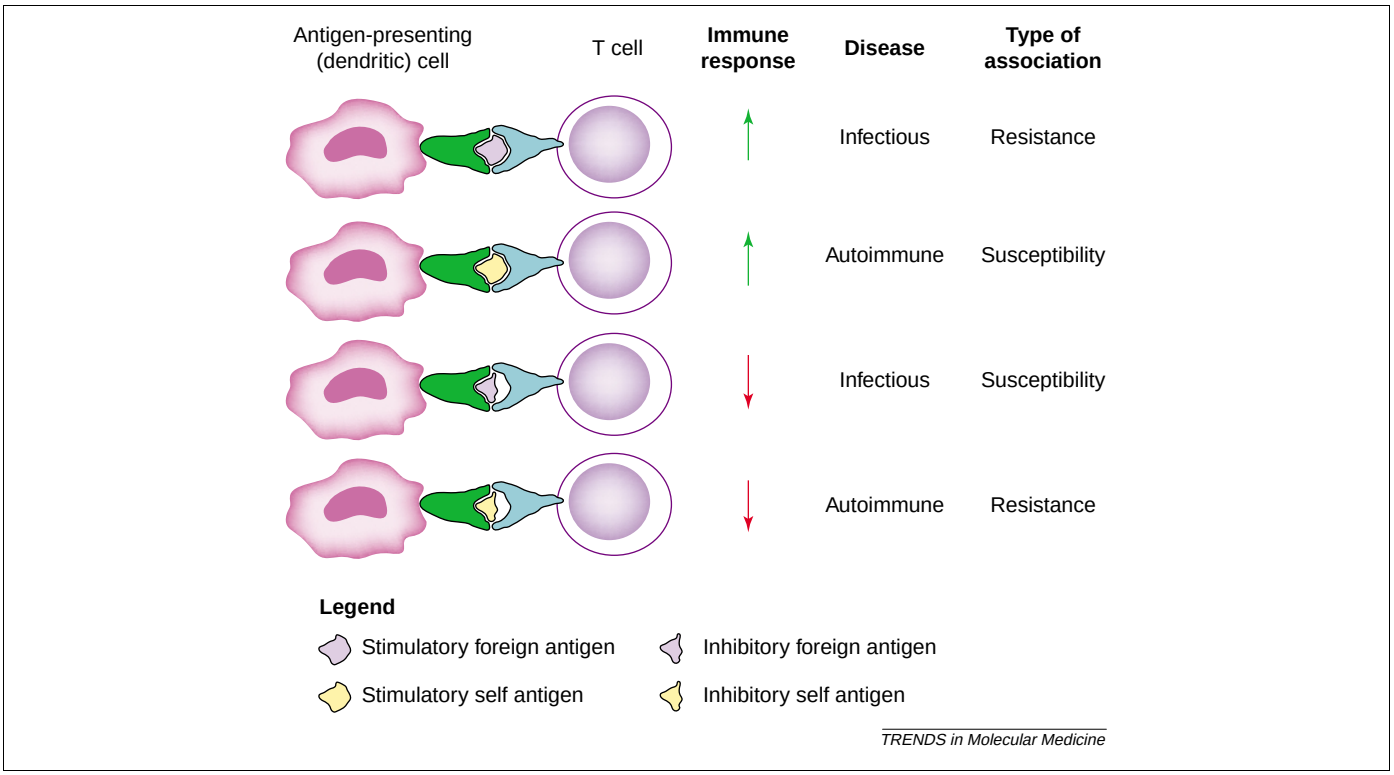

Fig. 3. Both stimulation and inhibition of immune responses by major histocompatibility complex (MHC)–peptide complexes can underlie susceptibility or resistance to disease. The binding of complexes of MHC (green) and antigen on the surface of antigen-presenting (dendritic) cells (pink) to T-cell receptors (blue) on the surface of T cells (purple) can stimulate or inhibit the immune response depending on the nature of the antigen being presented. This immune response can either clear or initiate disease.

infectivity of the microbe) offers more efficient protection against infection than an epitope located in a region with dispensable function.

Associations between *MHC* genes and disease can be caused by inhibition of immune responses

Some associations between *MHC* and disease follow the inverse pattern to that resulting from stimulation of immune responses (Table 1). In the case of infectious agents, this can mean higher susceptibility to disease for carriers of particular alleles. For example, *HLA-B35* [16,31] and *HLA-A29* [16] are associated with rapid progression to AIDS. Interestingly, a single amino-acid change in HLA-B35 can make the difference between the allele being neutral or deleterious [32]. Another example is the association of *HLA-DR2* with human-papilloma-virus-type-16-induced cervical carcinoma [10]. In the case of autoimmune and immunopathological diseases, a negative influence of *MHC* genes is beneficial for the host. For instance, several human *MHC class-II* alleles are associated with reduced frequency of type-1 diabetes mellitus relative to the general population [33]. Hence, it appears that MHC molecules can inhibit as well as stimulate immune responses. It can sometimes be difficult to distinguish whether susceptibility to a particular infection is the result of inhibition of an immune response, or promotion of autoimmunity or immunopathology by an active immune response. However, the fact that transgenic expression of certain *MHC class-II* alleles reduces the incidence and severity of diabetes caused by autoreactive T cells in non-obese diabetic mice [5] provides direct evidence that *MHC* alleles can be linked with disease by promoting inhibition of the immune response.

The regulation of immune responses by particular *MHC* alleles could be related to their role in peptide presentation or to a more general mechanism (Table 2). An example of the latter might include the consequences of interaction of MHC class-I molecules with inhibitory natural killer (NK) receptors on NK cells and $CD8^+$ T cells [34]. However, MHC class-II molecules do not affect the activity of NK cells, but are associated with various diseases. Furthermore, *HLA* alleles do not usually exhibit 'across the board' stimulatory or inhibitory influences. For example, *HLA-A29* promotes the development of birdshot chorioretinopathy (by stimulating an immune response) [6], but also renders individuals susceptible to rapid development of AIDS (via an inhibitory mechanism) [16]. Another *HLA* allele with a disease-specific influence is

Table 2. Possible mechanisms of inhibitory function of MHC on immune response

(a) Unrelated to peptide presentation
Inhibition of NK-cell function
(b) Related to peptide presentation
(i) Antigen presentation
Anergy
Changing the effector phenotype of T cells
DETERMINANT CAPTURE
TCR antagonism
(ii) Self-peptide presentation
Positive selection of regulatory T cells
NEGATIVE SELECTION of antigen-specific T cells
TCR antagonism

Abbreviations: MHC, major histocompatibility complex; NK, natural killer; TCR, T-cell receptor.

*HLA-DQB1*0602*, which is considered protective for diabetes [33] but is a risk factor for multiple sclerosis [35]. Similarly, in mice, an *MHC class-II* transgene protected against type-1 diabetes, but produced a more severe form of experimental allergic encephalomyelitis (an experimental model of multiple sclerosis) [36]. The specificity of the influence of *MHC* favors peptide presentation as an explanation for associations between *MHC* genes and disease.

Potential mechanisms of peptide-dependent negative influence of MHC on disease have been most extensively studied in animal models of diabetes. These can be broadly divided into those that depend on presentation of foreign antigens or of self-peptides (Table 2). Evidence for or against most of these mechanisms has been obtained in various experimental models and is listed in Ref. [37]. Strangely, T-cell receptor (TCR) antagonism has received little serious consideration as a potential mechanism even though the concept fits intuitively with the described negative effects of *MHC* genes.

Inhibition of immune responses by altered peptide ligands

T-cell epitopes with point mutations, known as altered peptide ligands (APLs), can elicit only a fraction or subset of T-cell responses induced by wild-type epitopes [38]. A special category of APLs not only fail to induce full responses, but can also inhibit responses to the original epitope *in vitro* [39,40] and *in vivo* [41]. These APLs are referred to as TCR antagonists (Fig. 4a). Because of their specific inhibitory capacity, it was originally thought that TCR-antagonist ligands might be useful for

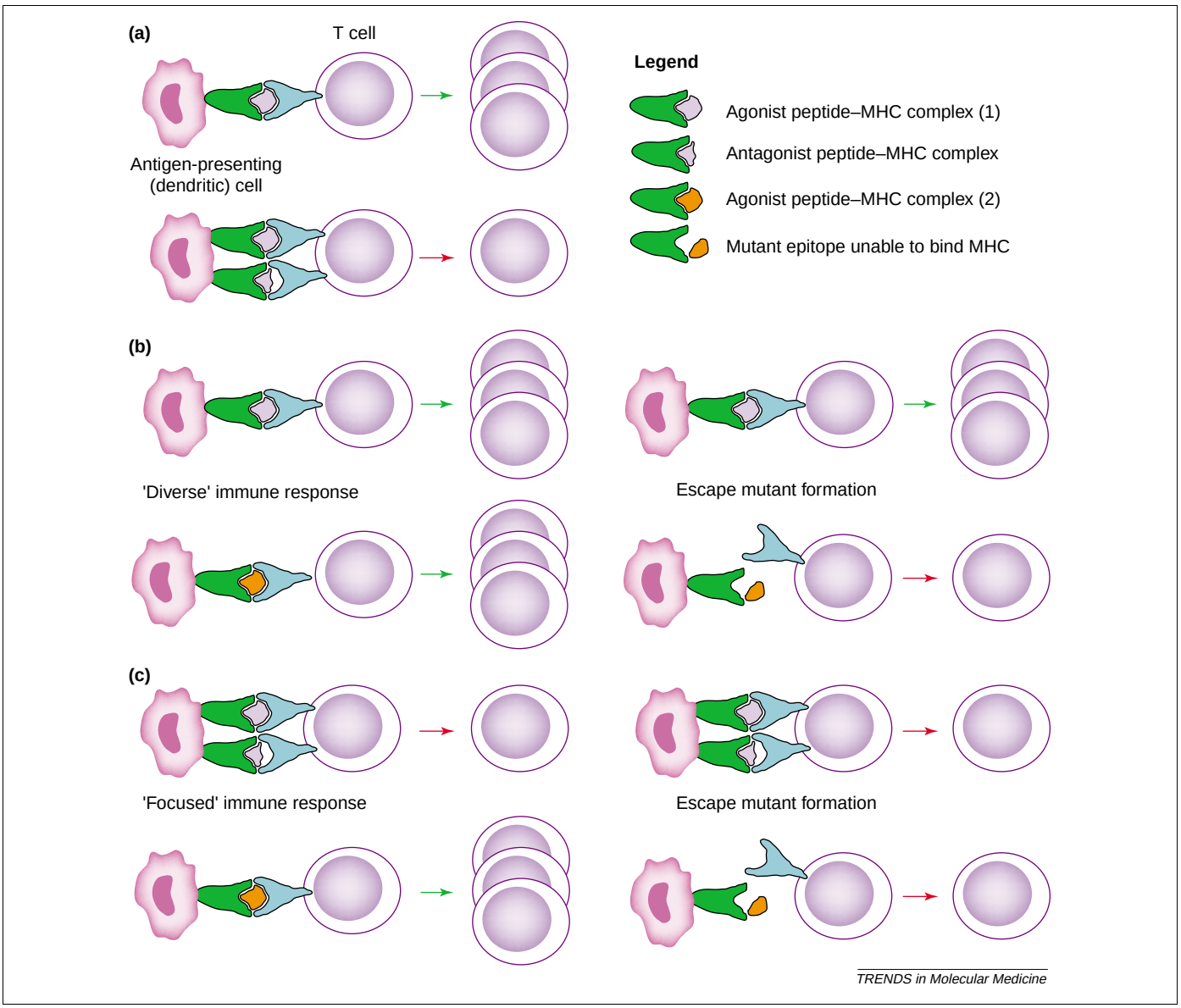

Fig. 4. Potential influence of T-cell receptor (TCR) antagonism on the outcome of infection. (a) TCR (blue) peptide ligands bound to major histocompatibility complexes (MHCs) (green) can have agonist or antagonist activity. Agonists (top) promote proliferation and effector functions of T cells (green arrow), whereas antagonist ligands (bottom) inhibit agonist-induced responses (red arrow) in a specific manner. (b,c) A potential impact of TCR antagonism on resolution of infection. (b) Initially, T-cell response is directed to two (or more) epitopes. Hence, an escape mutation that creates one epitope that is no longer able to bind MHC molecules (bottom) does not have a serious impact on the overall immune response to the microorganism. (c) If TCR antagonism (top)'focuses' the response to a single epitope (bottom), escape mutation of that epitope leads to nonresponsiveness to the microbe and progression of infectious disease.

treating T-cell-mediated diseases [42]. However, TCR-antagonist APLs, as initially described, are clone-specific and require excessive antagonist:agonist ratios for inhibition of TCR responses [39,40]. These properties cast serious doubt over the use of specific inhibition of polyclonal antigen-specific responses *in vivo* [43]. Nevertheless, there are at least two reasons to suggest that antagonism might affect the outcome of immune responses despite these shortcomings. First, even though T-cell responses might not be completely inhibited, TCR antagonism can still play a decisive role in the outcome of an infection. Microbial escape mutants are preferentially selected in the presence of monospecific T-cell responses with limited TCR diversity [44], and TCR diversity is essential for resistance to viral infection [2]. Therefore, the focusing of T-cell responses by TCR antagonism to reduced number of epitopes might interfere with the effective clearance of infection, by creating conditions favorable for escape-mutant selection (Fig. 4b). Such a TCR-antagonist-mediated narrowing of the immune response has been described in T-cell responses to malaria [45]. Second, not all TCR-antagonist ligands are clone-restricted: polyclonal immune responses have been inhibited by a single antagonist APL in several experimental models [46–49]. Interestingly, many suggested mechanisms of TCR antagonism that is not clonally restricted are similar to proposed mechanisms of inhibitory influence of *MHC* on development of autoimmune diseases: the induction of ANERGY [50,51], modulation of the cytokine secretion pattern [52], and stimulation of immunoregulatory cells [53]. In addition, one antagonist ligand has been reported to alter the structure of the presenting MHC class-I molecule [54].

Mutations in HIV-1 [55,56], hepatitis B virus [57], hepatitis C virus [58–60], *P. falciparum* [61], and lymphocyte choriomeningitis virus [62] can produce natural antagonist APLs. In these studies, co-infection with the mutant microorganism protected infected cells against attack by $CD8^+$ T cells with specificity for the wild-type epitope. An important characteristic of these natural antagonist APLs is their potency. They are effective at one tenth or even one hundredth of the concentration of the agonist peptide, whereas 'conventional' antagonist APLs must be at a 10–100-fold excess over the agonist peptide. Could natural antagonist APLs explain the inhibitory influence of certain MHC molecules on immune responses? Consistent with this idea, it has been proposed that TCR antagonism might be a mechanism by which HIV-1 escapes immune recognition [63]. However, as attractive as this possibility might appear, it has a major flaw: the so-far identified antagonist APLs produced by mutant microbial strains are not presented by *HLA* alleles associated with susceptibility to the respective infectious disease. In addition, given that auto-antigens are unlikely to mutate at the same rate and speed as microbes, we still need to explain how *MHC* alleles can have inhibitory effects on autoimmune diseases.

Self-peptides with TCR-antagonist activity

In the absence as well as the presence of antigen presentation, MHC molecules are occupied by a wide variety of peptides derived from the degradation of self-proteins. It is becoming increasingly clear that self-peptide–MHC complexes are not immunologically inert: they have been shown to enhance [64] or reduce [65–67] responsiveness to the antigen, depending on the experimental model. Could inhibition of the immune response be mediated by antagonist self-ligands? It has been proposed that self-peptides might have TCR-antagonist activities [68]. Reasoning that antagonist self-peptides would have to be in some way similar to the cognate antigen, several laboratories have devised homology-based strategies for identifying self-peptides with biological activities [69–71]. In these experiments, self-peptides that could have antagonist activity were readily identified in diverse antigenic systems of both humans and experimental animals. Subsequently, two self-peptides with antagonist activity were shown to be presented *in vivo* [72,73]. Mice heterozygous at the *MHC* locus encoding the product that presents an antagonist self-peptide responded to antigen more strongly than homozygous animals [65]. The response to antigen of homozygous mice was characterized by poor cytolytic activity in the presence of cytokine secretion and a weak proliferative response. This pattern was generated by co-stimulation-mediated selective rescue of cytokine secretion in the context of an otherwise overall poor response [65].

Interestingly, a functional phenotype like that of 'naturally antagonized' T cells [65] can be found in late phases of the immune response to HIV-1 [74], Epstein–Barr virus [75] or melanoma antigens [76]. Could these suboptimal immune responses be due to persistent work of antagonist self-peptides? In support of this notion, many but not all self-peptides that induce POSITIVE SELECTION exhibit antagonist activity for mature T cells [72,73]. Hence, antagonist self-peptides could have a defined role in T-cell development. Furthermore, some of the self-peptides with putative TCR-antagonist activity [69–71] might be presented *in vivo*. Thus, self-peptides with TCR-antagonist activity might influence immune responses as a rule, rather than as an exception. If indeed antagonist self-ligands are relatively common, their number and potency could vary for different epitopes and *MHC* alleles. This could explain the inhibitory effects of certain *MHC* alleles on immune responses.

A model explaining inhibitory influences of MHC molecules on immune responses

Based on the information described above, we propose a model to explain the inhibitory influence of *MHC* genes on immune responses (Fig. 5). The two central tenets of this model are (1) that TCR-antagonist activity exerted by self-peptides modulates immune responses, and (2) that the antagonist activity of self-peptides applies to a wide variety of epitope specificities. Depending on their relative abundance and frequency, self-peptides could exert antagonist activity during the induction of the immune response, or at a later stage when the antagonist:agonist ratio becomes favorable, owing to a reduced antigenic load as a result of the actions of the maturing immune response. In the case of infections, we consider the latter scenario more likely, for two reasons. First, the chronic nature of the

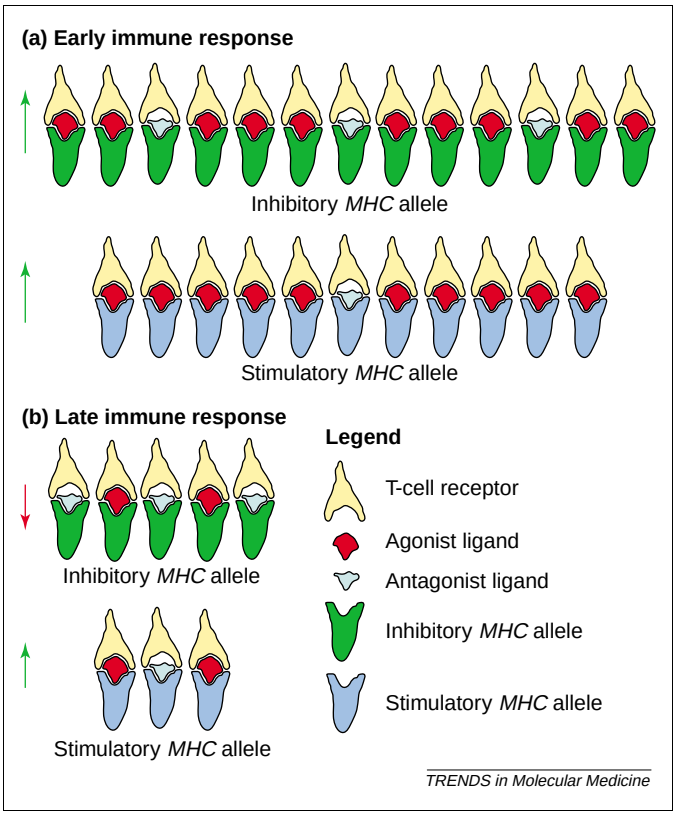

Fig. 5. A model of major histocompatibility complex (MHC)-specific self-peptide-induced T-cell receptor (TCR) antagonism as a regulator of long-term immune responses to infectious agents. (a) In the early stages of an immune response restricted by a stimulatory or inhibitory *MHC* allele, the agonist:antagonist ratio is heavily in favor of agonist ligands. As a result, relatively efficient immune responses are raised leading to a reduced pathogen load. (b) The subsequent decrease in epitope presentation opens up the possibility of dominance of antagonist ligands. However, this only occurs if antagonist ligand(s) are abundant, which is the case with inhibitory *MHC* alleles. Arrows indicate the overall influence of the ligands on immune response. For simplicity's sake, we have assumed that the amount of antagonist self-peptide remains static. In reality, it could fluctuate as a result of the influence of cytokines and other inflammation mediators, although to a much lesser degree than the agonist ligands. We have also assumed a rapid initial increase in epitope numbers, allowing only a limited time in which the antagonist:agonist ratio is unfavorable to induction of immune responses. Dendritic cells are depicted as the cell type essential for inducing and maintaining the immune responses. However, antagonist:agonist ratios would probably be different between dendritic cells and various cell types that are targets for $CD8^+$-T-cell lysis. Note that the designation of inhibitory and stimulatory alleles is dependent on the specificity of the immune response: an inhibitory allele in one response can be stimulatory in another.

diseases associated with *HLA* suggests that the inhibitory influence requires time to exert its effect. Second, antagonist self-peptides discovered to date require a high molar excess relative to the agonist ligand. The antagonist:agonist ratio favoring inhibition of an immune response can occur early in infection but is of limited duration because epitope production and presentation increases rapidly. Therefore, it is likely that antagonist self-ligands exert their largest influence at a later stage of infection, after some or most of the antigen has been cleared by an initial wave of immune response. Mutant epitopes with antagonist activity generated during the course of an infection could also contribute, but we believe that this would be sporadic.

In the case of autoimmune diseases, the dynamics of epitope presentation are somewhat different from those of infectious agents. The level of auto-antigen presentation by dendritic cells is likely to be a function of tissue destruction. Hence, the initial increase in epitope density is likely to be steadier than in infections, and immunity will lead to an increase rather than a decrease in epitope presentation during the later stages of the response. Therefore, by contrast with infectious diseases, the antagonist activity of self-peptides in autoimmune diseases is more likely to occur early.

Antagonist peptide(s) might work by reducing the diversity of the immune response, thereby allowing easier selection of escape mutants in the case of infectious diseases, or reducing the tissue damage and consequently the new antigen supply in the case of autoimmune diseases. Alternatively, a dominant mechanism, such as induction of regulatory T cells, immune deviation, or another mechanisms listed in Table 2 might apply. Allelic variations in self-peptides can account for the formation of antagonistic or neutral self-ligands, which together with other genetic influences could complicate associations between *MHC* and disease. The preferential association of endogenous antagonist activity with certain *MHC* alleles in responses to a given pathogen, and vice versa, within a spectrum of *MHC*-allele-restricted responses could potentially be explained by a preference of *MHC* alleles for certain amino acids at defined positions in the peptide [77]. For example, HLA-B*3503 and HLA-B*3501, the former associated with rapid development of AIDS and the latter not [32], have a preference for alanine and methionine, respectively, at peptide position one [77]. In a hypothetical scenario, the presence of alanine, which is capable of forming hydrogen bonds, in many self-peptides could contribute to weak engagements with a subset of HLA-B*3503-restricted TCRs of various epitope specificities, resulting in antagonist activity. By contrast, self-peptides associated with HLA-B*3501, with methionine (which does not form hydrogen bonds) at position one, would rarely exhibit antagonist activity. In another hypothetical scenario, frequent C-terminal tyrosine in self-peptides binding HLA-B27 subtypes that are associated with ankylosing spondylitis (HLA-B*2705), but not in those binding subtypes that are not associated with the disease (HLA-B*2706 and HLA-B*2709), could contribute to antagonist activity specific to a subset of HLA-B*2705-restricted TCRs [4]. In this case, tyrosine acts as an anchor residue buried deep into the peptide-binding cleft and, hence, its contribution to the induction of antagonist activity would have to be more indirect, possibly by influencing the overall peptide conformation. Although the absence of tyrosine as a C-terminal anchor in peptides that bind another disease-promoting allele, HLA-B*2707, is considered to be evidence against the central role of C-terminal tyrosine in disease progression [4,78], it is possible that different HLA-B27 subtypes contribute to antagonist activity and autoimmune disease progression using distinct self-peptide features. Another complicating issue in identifying possible sources of HLA-B27-mediated antagonist activity at the molecular level is the unique ability of this molecule to dimerize [78]. The role of this process in the development of disease remains uncertain, as does its impact on the characteristics of peptides that bind the homodimeric structure.

The identification of self-peptide sequences with cognate-antigen-specific antagonist activity using homology-based searches [69–73], and the defining of their abundance and potency, should help to explain associations between *MHC* genes and disease. In addition, self-peptides with antagonist activity might prove useful for treatment of T-cell-mediated diseases. One likely advantage of these antagonists is that, unlike other APLs [79,80], they will probably not induce immune responses to themselves.

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