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REVIEW

Recognition of self and altered self by T cells in autoimmunity and allergy

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ABSTRACT

T cell recognition of foreign peptide antigen and tolerance to self peptides is key to the proper function of the immune system. Usually, in the thymus T cells that recognize self MHC + self peptides are deleted and those with the potential to recognize self MHC + foreign peptides are selected to mature. However there are exceptions to these rules. Autoimmunity and allergy are two of the most common immune diseases that can be related to recognition of self. Many genes work together to lead to autoimmunity. Of those, particular MHC alleles are the most strongly associated, reflecting the key importance of MHC presentation of self peptides in autoimmunity. T cells specific for combinations of self MHC and self peptides may escape thymus deletion, and thus be able to drive autoimmunity, for several reasons: the relevant self peptide may be presented at low abundance in the thymus but at high level in particular peripheral tissues; the relevant self peptide may bind to MHC in an unusual register, not present in the thymus but apparent elsewhere; finally the relevant self peptide may be post translationally modified in a tissue specific fashion. In some types of allergy, the peptide + MHC combination may also be fully derived from self. However the combination in question may be modified by the presence of other ligands, such as small drug molecules or metal ions. Thus these types of allergies may act like the post translationally modified peptides involved some types of autoimmunity.

KEYWORDS altered self, neoantigen, antigen presenting, T cell recognition, autoimmunity, allergy, diabetes, dermatitis, drug hypersensitivity

INTRODUCTION

The so-called alpha beta T cell receptors (TCRs) for foreign antigen are composed of two chains, alpha and beta. The genes coding for these chains are created by gene rearrangement in thymocytes. In mice, any given receptor may contain a TCR alpha chain (TCRα) made up of any one of between 70 and 107 Valphas (Vαs), and any one of about 50 Jalphas (Jαs). The number of combinations of these two elements is ~100 × 50 = 5,000, indicating that the germ line TCR alpha locus can code for about 5000 different TCRα chains. However, when Vα genes rearrange to lie next to a Jα gene, nucleotides can be removed or added, resulting in considerable variability in the DNA sequence, and therefore amino acid sequence, at this junction. This very variable junction lies within what is known as the CDR3 loop of the TCRα chain (Fig.1) and random DNA sequences in this junction increase the total number of possible TCRα chain protein sequences that can occur in an animal by several orders of magnitude, to ~10^7. Similar phenomena apply to rearrangements for the TCR beta (TCRβ) chain locus, leading to, again, a very large number of possible TCRβ chain sequences (Fig. 1).

These TCRs usually react with foreign antigens in the form of peptides from the foreign material bound to major histocompatibililty complex proteins (MHC). An example of the structure of the combination is shown in Fig. 2. The foreign peptide fills the groove of MHC and the TCR lies above the two in an approximately diagonal orientation, as previously reported (Garcia et al., 1996, 1998, 1999; Reiser et al., 2003;

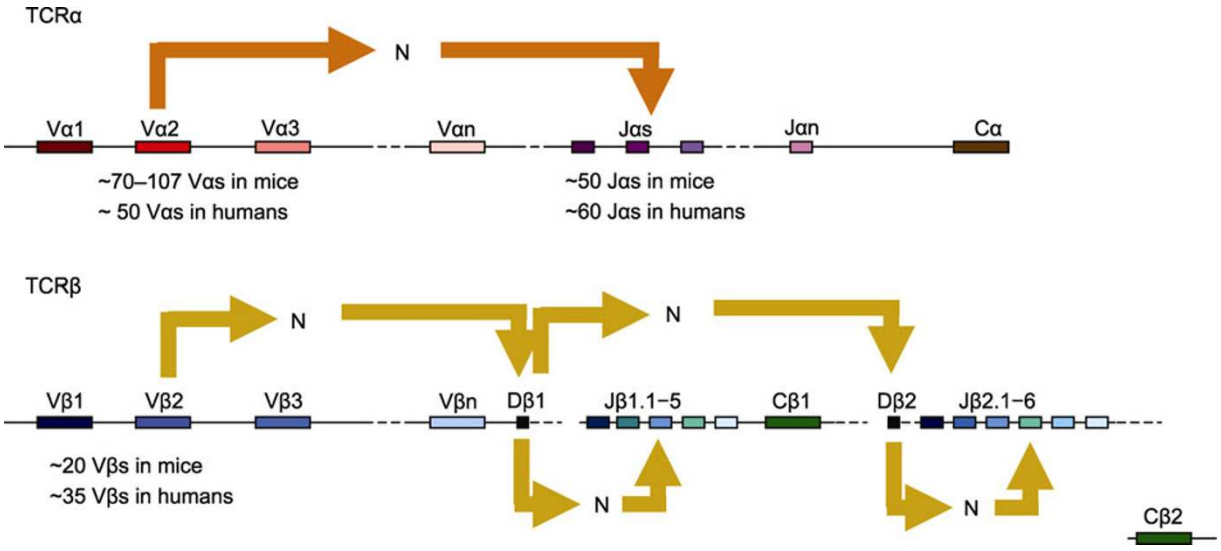

Figure 1. Diagram of the rearrangements that give rise to genes coding for T cell receptor alpha and beta polypeptides. Shown are diagrams of the arrangement of variable (V), diversity (D), joining (J) and constant (C) regions for T cell receptor alpha and beta chains. Arrows indicate rearrangement patterns and N indicates the sites at which nucleotides are removed or added. Also indicated are the approximate numbers of each genetic element in the mouse and human genome.

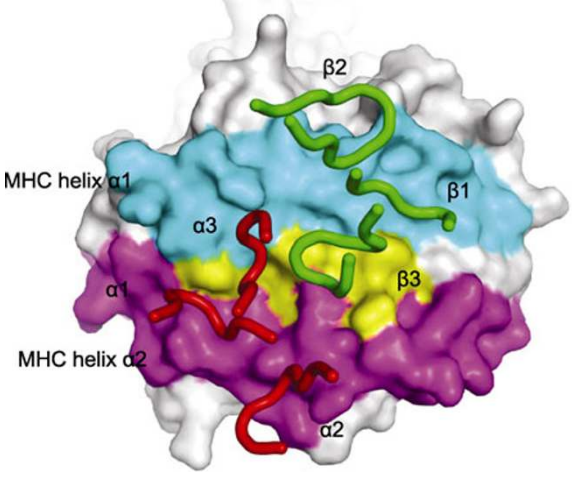

Figure 2. Illustration of the position of T cell receptor CDR regions on an MHC + peptide ligand. Shown are the positions of the TCR alpha and beta chain CDR regions (α1–α3 and β1–β3 respectively) of the YAe62.8 TCR bound to the mouse MHCI protein, K^b and the pWM peptide. The CDR loops are colored red (CDRα1–3) and green (CDRβ1–3). The alpha helices of K^b are colored cyan (α1) and magenta (α2) and the pWM peptide is colored yellow. The peptide has been truncated in the Figure to remove amino acid residues of the linker that covalently binds the peptide to K^b. This Figure is a modified version of a Figure in Yin et al. (2011a).

Maynard et al., 2005; Tynan et al., 2005; Colf et al., 2007; Feng et al., 2007; Tynan et al., 2007; Dai et al., 2008; Marrack et al., 2008; Garcia et al., 2009; Burrows et al., 2010; Day et al., 2011; Yin et al., 2011a). This allows the loops at the ends of the TCRα and TCRβ beta strands to contact both MHC and foreign peptide, with the CDR1 and CDR2 sequences (which are encoded in the germ line DNA for Vα and Vβ respectively) contacting mostly the alpha helices of the MHC proteins themselves. However, the CDR3 regions of TCRα and TCRβ (which are encoded by the random, non germline sequences that are created by gene rearrangement) make many contacts with the foreign peptide.

In order for T cells to divide and be activated to perform their various functions, cell killing, cytokine production etc., the TCR on the T cell must engage its ligand, a ligand that is composed, as discussed above, of a self MHC protein bound to a foreign peptide and "presented" on the surface of an antigen presenting cell. At the beginning stages of the T cell response, the antigen presenting cell is usually a dendritic cell (Steinman and Inaba, 1985; Steinman et al., 1988; Inaba et al., 1990; Banchereau and Steinman, 1998). The reaction delivers so-called Signal 1 to the T cell. Signal 1 alone is not usually sufficient to trigger the T cell into full activity, however. T cells usually need to receive additional, so-called co-stimulatory signals, with so-called Signal 2 delivered by interaction between proteins such as CD28 on the T cell and B7-related proteins on the antigen presenting cell (Alarcon et al.; Watts; Lafferty and Cunningham, 1975; Jenkins and Schwartz, 1987; Bluestone, 1995; Sharpe, 2009) and Signal 3 coming from some inflammatory stimulus, cytokines such as IL-1, IL-6, TNFα and their relatives or perhaps from engagement of Toll like receptors and other systems for generic detection of invading organisms (Hintzen et al., 1994; Dinarello, 2002; Dolfi and Katsikis, 2007; Croft, 2009) (Fig 3).

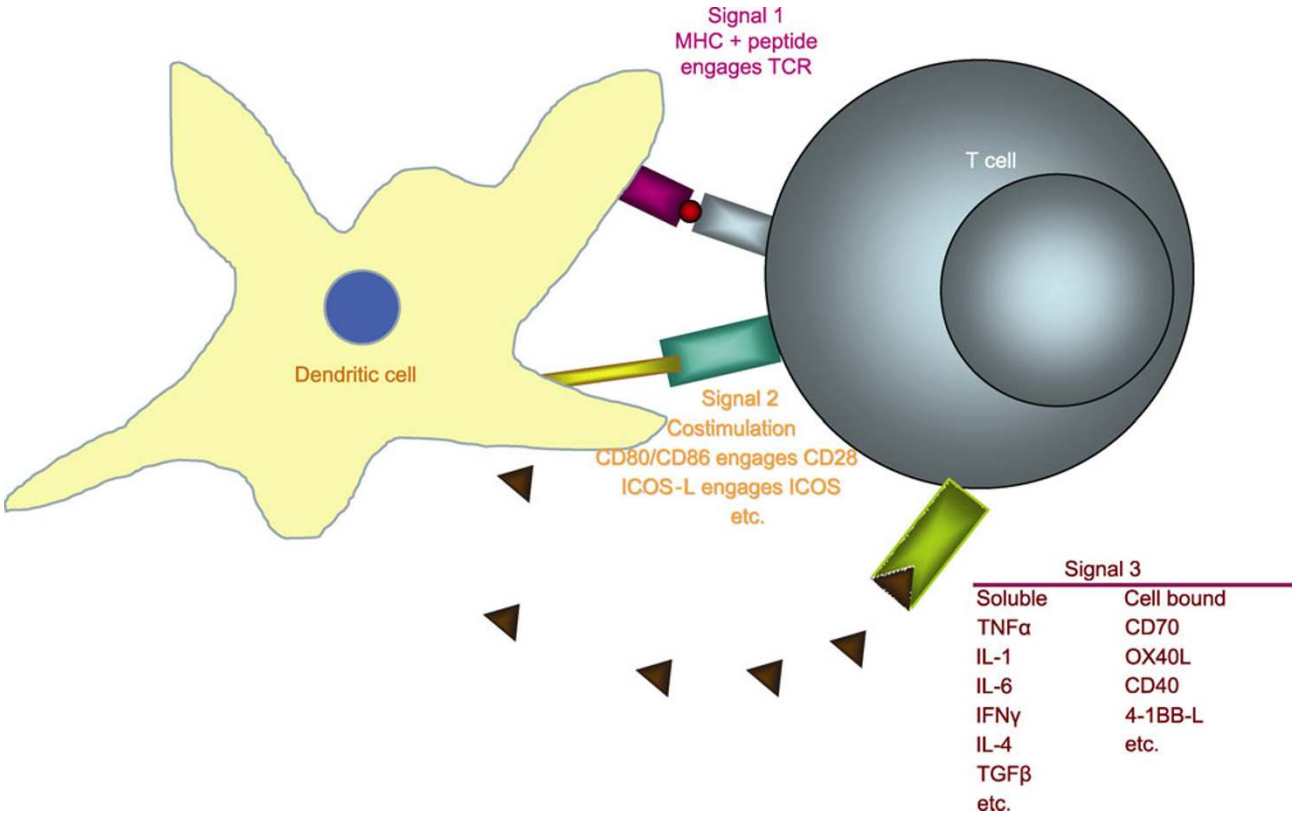

Figure 3. T cells need three signals for productive responses. Shown are the three signals that are thought to be needed for T cells to respond well to antigen. These include Signal 1, derived from engagement of the T cell's TCR, Signal 2, thought to be often delivered through receptors on the T cell surface such as CD28 and ICOS and Signal 3, thought to be often derived from cytokines or cell bound ligands that are produced in response to inflammation.

Any given animal could contain a very large number of different TCRs, each expressed on a different T cell. How is it that these TCRs don't recognize self peptides, peptides from the proteins of their own host, bound to the host's MHC proteins? Several phenomena prevent such potentially lethal interactions. Of these the first to be firmly established was the phenomenon of clonal deletion in the thymus. Thymocytes bearing TCRs that react too well with MHC + peptide combinations and other ligands that appear in the thymus die (Kappler et al., 1987; Bluthmann et al., 1988). Thus these cells cannot convert into mature functional T cells and hurt their hosts. In spite of clonal deletion, some potentially autoreactive T cells escape the thymus. These are held in check by at least three controls: regulatory T cells (Wildin et al., 2002; Gambineri et al., 2003; Ramsdell, 2003); clonal exhaustion, induced by prolonged exposure to antigen (Wherry et al. 2007) or anergy, a state of unresponsiveness induced by a failure to deliver signal 2 or signal 3 (Sloan-Lancaster and Allen, 1995; Wherry et al., 2007) (Fig. 3). This last controlling mechanism has been harnessed recently in cancer therapies, in which blockade of CTLA4 or PD1, proteins that inhibit co-stimulation by Signal 2 (Fig. 3) allows resumed autoattack by T cells of tumor cells (Callahan et al., et al., 2010; Pardoll, 2012).

WHAT ALLOWS T CELLS TO REACT WITH SELF ANTIGENS AND THUS DRIVE AUTOIMMUNITY?

Autoimmune disease occurs in spite of the many ways in which potentially autoreactive T and B cells are deleted or inactivated. Sometimes disease occurs because one or more of the controlling mechanisms fails. For example, mice and humans lacking Fas, a protein that contributes to the death of activated lymphocytes, develop lymphadenopathy and autoimmunity (Dhein et al., 1995; Sneller et al., 1997). Likewise animals lacking AIRE, a protein that affects T cell tolerance in the thymus, develop what is known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED). This disease drives the appearance of autoantibodies against the products of many tissues and thus autoattack on many different organs of the body. Interestingly, APECED patients also produce antibodies against cytokines such as IL-17A, IL-17F and IL-22, a phenomenon that might be the cause of their frequent infection with candida (Browne and Holland; Heino et al., 2001; Anderson et al., 2002; Ramsey et al., 2002).

In humans, most autoimmunity is not caused by mutations in single genes. Rather, the problem seems to be driven by contributions from a number of genetic polymorphisms (Allanore et al.; Bogdanos et al.; Brand and Gough; Depaz et al.; Deshmukh et al.; Rainbow et al., 2008). Many genes related to immune function have been identified in the past and in recent genome wide association studies (GWAS) of individuals with autoimmune diseases. Amongst these are PTPN22, CTLA-4, IL-2/IL-21 and, most often, particular MHC alleles, and variants of antigen processing genes (Grumet et al., 1971; McDevitt and Bodmer, 1974; Evnouchidou et al., 2012; Fierabracci et al., 2012; Guerini et al., 2012; Ireland and Unanue, 2012). Why do these variants act together to cause autoimmunity? The consensus is that particular MHC alleles, coupled, in some disease, with variants in the antigen processing machinery, lead to over expression of particular combinations of MHC bound to particular self peptides, which themselves then engage TCRs. Polymorphic variants of other genes then increase the sensitivity of T lymphocytes to engagement of their TCRs and/or reduce the likelihood that aberrant lymphocyte responses will be prevented. Together, these two phenomena contribute to the likelihood of an individual acquiring an autoimmune disease.

With such ideas in mind three hypotheses can be put forward. One suggests that autoimmune disease is most strongly linked to particular MHC alleles because certain MHC alleles bind very strongly to certain self peptides (Ada and Rose, 1988). Under these circumstances, the individual contains an overabundance of such MHC+peptide combinations, thus increasing the likelihood of stimulating a T cell, even if that cells bears a TCR with relatively low affinity for the MHC + peptide in question. Thymocytes that can react strongly with MHC + peptides that are present in the thymus die in that organ, and never appear in the periphery (Kappler et al., 1987; von Boehmer et al., 1989), therefore, in order for this idea to be correct the relevant peptide must be at low concentrations in the thymus but high concentrations elsewhere. This could happen because the concentration is higher in certain tissues of many proteins, for example insulin in the pancreas and myelin basic protein in the nervous system, than in the thymus.

Another hypothesis suggests that particular MHC alleles bind poorly to particular self peptides (Suri et al., 2008). Consequently such MHC + peptide combinations are present at very low levels in the thymus and cannot effectively cause the death of thymocytes bearing TCRs that react with them. The potentially autoreactive cells mature and appear in the periphery where they may encounter the MHC + peptide combination at higher concentrations because the protein source of the peptide in question is produced at very high levels in particular tissues. In this situation, the appearance of the autoreactive T cells in the periphery may even be helped by low levels of their stimulating MHC + peptide ligands in the thymus, since there is evidence that stimulatory MHC + peptide combinations can, under some circumstances, contribute to positive selection of T cells (Bevan and Hunig, 1981).

A third idea, which could be thought of as a variation of the second hypothesis, suggests that some autoantigenic peptides are not just straightforward breakdown products of their parent protein. Rather, the peptides in question are generated by processes that do not function in the thymus. For example, in some cases tissue specific proteolysis may give rise, in a particular tissue, to a peptide that is not generated in the thymus. If this peptide binds an MHC allele present in the animal it could drive T cell responses against the tissue in question. Under other circumstances a particular tissue may produce a modified version of a self peptide which, when bound to MHC, engages some TCRs with high affinity. Alternatively, the modifications could allow the peptides in question to bind to particular MHC alleles more strongly, or in a different register, with the amino acid residues that point out of the MHC groove towards the TCR different from those that were involved in tolerance induction in the thymus. As noted above, the idea that post translationally modified peptides contribute to autoimmunity is particularly likely if the modifications in question are the result of a tissue specific process, a process that occurs in some peripheral tissues but not in the thymus (Marrack and Kappler, 2012; Stadinski et al., 2010a, 2010b). This idea is also bolstered by the structural finding that many autoimmune TCRs bind to their MHC + self peptide ligands with unusual orientations (Hahn et al., 2005; Li et al., 2005; Sethi et al., 2011; Yin et al., 2011b).

If this last hypothesis about autoimmunity is correct, such diseases are not necessarily failures of any tolerance mechanisms. Rather they are caused by modifications of proteins and/or their peptide products in tissue specific fashions, to give rise to self peptides that are produced only in particular tissues or tissue specific post translational modifications of peptides. In either case the responsible peptides can be viewed as “altered self” or “neoantigens”.

Of course any of these hypotheses may apply, under different circumstances. Moreover, regardless of which hypothesis is relevant, a productive T cell response to the autoantigen will require simultaneous recognition of antigen and delivery of signals 2 and 3 (Fig. 3) to the autoreactive T cells

EVIDENCE FOR AUTOIMMUNITY CAUSED BY LOW AFFINITY BINDING OF PEPTIDE TO MHC

As mentioned in the Introduction, TCRs usually engage MHC + foreign peptide ligands in a diagonal orientation with the CDRs of the TCR placed in fairly reproducible positions on the MHC + peptide ligand. Over the last 10 years, however, a number of reports have supported the idea that autoimmunity can involve engagement of MHC + peptide + TCRs in unusual configurations. These unusual configurations could involve unexpected registers for peptide binding to the groove of MHC and/or, unexpected alignments of autoimmune TCRs on MHC + peptide combinations.

As far as unexpected MHC + peptide registers are concerned, one of the first examples came from work studying the reaction of T cells with a peptide from the N terminus of myelin basic protein (MBP) and the mouse MHCII protein, IA^u, a reaction that drives experimental autoimmune encephalomyelitis (EAE) the experimental model in mice for multiple sclerosis (MS) in humans. The N terminal amino acid (an alanine) of MBP is a naturally acetylated, a phenomenon which was mimicked in the crystal preparations of the MHC + peptide + TCR complex by an upstream glycine residue. The crystal structure revealed that the N terminal alanine is bound to IA^u at what is usually the P3 position, the position in the MHC groove that is usually occupied by the third amino acid of the bound peptide (Maynard et al., 2005). The glycine replacing the acetyl group is at P2 and some residues from the construct used to express the MHC + peptide combination lie upstream of P2. Hence, the peptide that contributes to EAE in IA^u-expressing mice probably begins its engagement with IA^u at P2, via the acetyl group, leaving, presumably, the P1 position empty, an unusual and perhaps unstable configuration.

Similar conclusions, that recognition of MHC + peptide combinations that bind weakly to each other can lead to multiple sclerosis in humans, have been reached recently, although in this case the weakly binding peptide appears to occupy the MHC groove entirely, as do most antigenic peptides (Yin et al., 2011b).

Studies on the insulin peptides that contribute to type 1 diabetes in NOD mice lead to related conclusions. Insulin has long been thought to be the source of autoantigenic peptides that are required for induction of type 1 diabetes, in mice at least (Levisetti et al., 2007 Mohan et al., 2007; Nakayama et al., 2007; Jarchum and DiLorenzo, 2009). Although the portion of insulin that contains the culprit peptide has long been known, the precise insulin peptide that drives disease was for many years unknown. It turns out that the crucial product is unexpected, a peptide that binds poorly rather than well to IA^{g7} (Stadinski et al., 2010b). In fact the predicted culprit binds so poorly to IA^{g7} that structural studies of its engagement to MHCII can only be performed with peptide and/or IA^{g7} mutants that have been constructed to improve the reaction between the peptide and IA^{g7}. How then, can the peptide bind MHCII and engage TCRs at significant levels in vivo? Two factors probably contribute. The first is that insulin is present at extremely high levels in the islets of Langerhans, levels that might allow sufficient peptide to be produced to allow detectable levels of the IA^{g7} + peptide complex to be present. The second is that islet beta cells might cleave insulin differently than the other cells of the body do, causing removal of amino acid residues of insulin that inhibit binding of the peptide in the diabetogenic register to IA^{g7} and modifying the peptide such that it binds more efficiently to the MHCII protein in question.

The direct consequence of these unstable configurations of peptides binding to MHC is a destabilization of the whole TCR-MHC-peptide complex. This may allow autoimmune TCRs that react with this MHC+peptide combination to escape negative selection.

EVIDENCE FOR AUTOIMMUNITY CAUSED BY ENGAGEMENT WITH UNUSUAL TOPOLOGY OF MHC + PEPTIDE BY TCRS

There are now several examples of autoreactive TCRs that bind to their MHCII + self peptides ligands at an unusual angle. Amongst these are two human TCRs, Ob.1A12 and 3A6, from the T cells of patients with multiple sclerosis that react with DRB1*1501 bound to a peptide included in MBP 85–101 (Hahn et al., 2005; Li et al., 2005). In both of these cases the TCR engages primarily the N-terminal end of the peptide and that portion of MHCII which surrounds that part of the peptide. Hence the TCR rotated is heavily tilted towards what is normally illustrated to be the left hand end of the MHC protein (Fig. 2). Recent work on TCRs, Ob.2F3 and Ob.3D1, from one of the same donors indicated that these TCRs also bind the N terminal end of the peptide (Kato et al., 2010). These TCRs may have low affinity for their self MHC/self peptide ligands, however, they may also escape tolerance mechanisms in the thymus because their angle of approach to MHC lowers the ability of CD4 to contribute to signaling within the T cell (Adams et al., 2011; Yin et al., 2012a).

Another version of engagement of an autoreactive TCR with MHC + self peptide is illustrated by the HY.1B11 TCR, that binds DQ1+ MBP85-99 (Sethi et al., 2010). In this case the TCR is dramatically tilted on its ligand, such that the germ line encoded Vα loops of the TCR do not contact the DQ protein. Whether this unusual orientation of the TCR on MHC contributed to the ability of the T cell bearing this TCR to escape thymic deletion remains to be discovered.

Evidence for autoimmunity caused by T cell recognition of altered self

The idea that post translational modifications to proteins and, hence, their peptide products, can lead to autoimmunity. Given the tremendous number of post translational changes to proteins that can occur this is a very attractive idea. For example, a lot of attention has been focused on protein citrullination, a process catalysed by the peptidylarginine deiminase enzymes, that converts arginine in proteins to citrulline. The contribution of citrullination to autoimmunity is supported by the fact that antibodies against various citrullinated proteins are found in a number of autoimmune diseases (van Boekel et al., 2002; Rubin and Sonderstrup, 2004; Kuhn et al., 2008). However, T cells specific for these post translationally modified peptides have been difficult to find, partly because the target peptides cannot be screened by conventional genetic means. A recent example comes from studies of type 1 diabetes in non obese diabetic (NOD) mice. The TCR

BDC2.1 is often used in experiments dealing with the disease. After many years of searching, the protein source of the peptide target of BDC2.1 has been identified. It is chromogranin, a protein that accumulates and is processed in the granules of cells such as the beta cells of the pancreas and in neuroexocrine cells in the brain. A peptide product of the processing of this protein binds to IA^{g7} and contributes to type 1 diabetes (Stadinski et al., 2010a). However, the exact nature of the responsible peptide is still unknown. It appears to be a post translationally modified form of a peptide product of the chromagranin protein, a modification that is peculiar to pancreatic beta cells (Haskins and Cooke, 2011).

ALTERED SELF AND ALLERGY

Metal ions

At first thought, the idea that allergy involves recognition by T cells of altered self seems unlikely. After all, allergens, such as those provided by ragweed pollen, cat saliva and peanuts are clearly foreign peptides, produced from foreign proteins and recognized, bound to MHC, by host T cells. However, for other allergens the idea of altered self is not so inconceivable. Most straightforwardly, allergies to metal ions, which clearly are not foreign peptides, probably involve T cell recognition of self MHC bound to a self peptide(s) and simultaneously engaging in an MHC and peptide specific fashion, the metal ion in question. In such cases the metal ion could be involved in a number of ways. It might bind to the self peptide, to some combination of peptide and MHC or be engaged in sufficient amounts only when the self peptide, MHC and TCR are present. The metal ion might be involved in some other way, buried beneath the peptide and distorting its upper surface such that the peptide appears "foreign" to the TCR (Fig. 4).

Our recent experiments on T cell responses to the very common human allergen, Ni++, and the very damaging metal ion, Be++, suggest such reactions. We have previously shown that Ni++ binds strongly to a combination of the human MHCII protein, DR52c, and some still unknown human peptide. When Ni++ is present, this combination is recognized by a TCR, ANi-2.3, from a human individual who is allergic to Ni++. We have solved the structure of ANi-2.3 bound to DR52c and a peptide that mimics the combination of the unknown human peptide plus Ni++. The structure suggests that the TCR will bind DR52c + self peptide + Ni++ with the conventional orientation. The structure predicts that the Ni++ ion will be bound to a combination of amino acid residues from the MHC and peptide and thus probably converts the DR52c + self peptide combination from a complex that is not recognized by self T cells to one that represents a form of "altered self" that is recognizable by certain TCRs in Ni++ sensitive individuals (Yin et al., 2012b).

We have come to similar conclusions in collaborative studies with Dr. Andrew Fontenot's laboratory on recognition of Be++ by human T cells. Immunity to Be++ occurs in individuals who are involved in machining beryllium and requires expression in the patient of DP2 or some related DP protein. Berylliosis is a serious and potentially lethal lung disease. We have shown that Be++ binds very strongly to DP2 and our preliminary Xray crystallographically solved structures of DP2 + a mimitope peptide plus Be++ with a TCR from a beryllium-sensitive patient indicate, again, that the metal ion converts a combination that is not seen by T cells to a form of "altered self" that is immunogenic. As in the case of Ni++, the beryllium ion is predicted to be bound to a combination of amino acids from both DP2 and the self peptide lying in the groove. In this state it then participates in engagement of a DP2 + Be++ specific TCR (Clayton et al., in preparation).

Drugs

A clear example of altered self generated by a drug came from the recent studies of Illing et al. (2012). The scientists examined reactivity to the drug Abacavir, a small molecule used to treat HIV infections. Individuals who express HLA-B*57:01 can become sensitive to the drug and develop Abacavir hypersensitivity syndrome (AHS). Illing et al. showed that Abacavir binds to the bottom of the HLA-B*57:01 groove, changing the spectrum of peptides that can bind the groove. They obtained similar results with carbamazepine, an anti-epileptic drug that causes hypersensitivity in HLA-B*15:02 expressing individuals. Thus in both cases the severe hypersensitivity reactions are probably due to massive activation of CD8 T cells to self MHC bound to a collection of self peptides to which the T cells were not tolerized in the thymus. How frequently these findings will extend to other drug allergens, such as aspirin, remains to be seen. Nevertheless the current findings describe dramatic examples of the consequences of recognition of altered self by T cells. They perhaps support the findings, years ago, by Bevan and Hunig

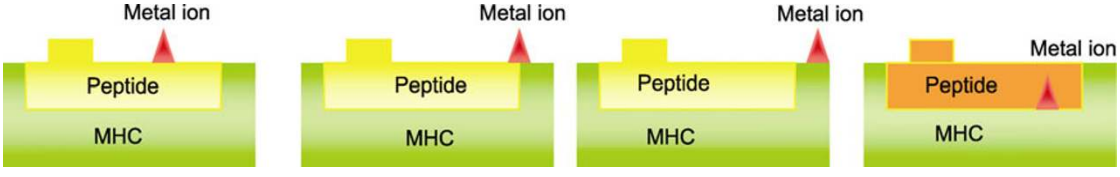

Figure 4. Small molecules such as metal ions may change the structure of self MHC + self peptide complexes in various ways. Metal ions or drugs may be able to bind to and change the aspect of self MHC + self peptides by binding to the upper surface of the peptide, by binding to a combination of peptide + MHC, by binding just to the MHC, or by engaging the groove of the MHC protein, thus changing the spectrum of self peptides bound to the MHC, rendering the MHC + peptide combination now "foreign".

that T cells react more powerfully to self MHC bound to altered peptides than to foreign MHC (Bevan and Hunig, 1981).

CONCLUSIONS

A great number of post translation modifications of proteins that are possible, phosphorylation, glycoslyation, conversion of amino acids such as asparagines to aspartic acid, acetylation, lipidation, sulfation, methylation, the list of possibilities is tremendously long. Given this, it is perhaps surprising that autoimmunity caused by recognition of post translationally modified peptides is not more common that it is. Perhaps the fact that such diseases are rare is a tribute to the efficiency of thymic tolerance, perhaps all these modifications occur in the thymus and can thus usually participate in deletion of potentially autoreactive thymocytes. Alternatively, T cells that can react with all these post translationally modified peptides may be held down by the processes of peripheral tolerance, such as regulatory T cells or anergy induction. Whatever the processes are that usually prevent T cell reaction with "altered self", they usually operate very effectively.

The parallels between autoreactivity caused by recognition of "altered self" peptides and allergy caused by modifications of self MHC+self peptides by small molecule allergens are interesting. Both can involve recognition by T cells of self MHC + a self peptide. For autoreactivity, the self peptide may be modified by post translational process, for small molecule driven allergy, the self peptide bound to MHC may be affected by the small molecule itself. Some years ago, experiments suggested that the mature T cells in an individual are more likely to react strongly with MHC proteins that are closely related to the MHC expressed in the individual. That is, some element of relationship between MHCs affects the likelihood that T cells will cross react with the unfamiliar target. Perhaps this argument applies also to autoreactivity and small molecule allergy. That is, although most potentially autoreactive T cells are deleted in the thymus, those that survive might be more likely to react with self MHC + a peptide related to self (an altered self peptide) in the periphery. The same argument might apply to allergic reactions in which the small allergen, a metal ion or drug, slightly alters the aspect of self MHC + self peptide. Only further experiments will test these ideas.

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