A reciprocal HLA-disease association in rheumatoid arthritis and pemphigus vulgaris

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1. ABSTRACT

Human leukocyte antigens (HLA) have been extensively studied as being antigen presenting receptors, but many aspects of their function remain elusive, especially their association with various autoimmune diseases. Here we discuss an illustrative case of the reciprocal relationship between certain HLA-DRB1 alleles and two diseases, rheumatoid arthritis (RA) and pemphigus vulgaris (PV). RA is strongly associated with HLA-DRB1 alleles that encode a five amino acid sequence motif in the 70-74 region of the DR beta chain, called the shared epitope (SE), while PV is associated with the HLA-DRB1*04:02 allele that encodes a different sequence motif in the same region. Interestingly, while HLA-DRB1*04:02 confers susceptibility to PV, this and other alleles that encode the same sequence motif in the 70-74 region of the DR beta chain are protective against RA. Currently, no convincing explanation for this antagonistic effect is present. Here we briefly review the immunology and immunogenetics of both diseases, identify remaining gaps in our understanding of their association with HLA, and propose the possibility that the 70-74 DR beta epitope may contribute to disease risk by mechanisms other than antigen presentation.

2. INTRODUCTION: HUMAN LEUKOCYTE ANTIGENS (HLA)

HLA genes represent the human major histocompatibility complex (MHC) and occupy a large region on the short arm of chromosome 6. This region consists of more than 200 highly polymorphic genes that encode for class-I and class-II HLA molecules, as well as many other proteins that have important roles in the immune system. Class-I and class-II HLA-encoded molecules are mostly known for their function in antigen presentation. Both HLA classes have important roles in the adaptive immune response and are essential for regulating immunity. HLA class-I molecules are expressed on the surface of all nucleated cells and present peptides that are derived from intracellular proteins, mostly following cell damage, or after viral infection, to cytotoxic T cells to induce clearance of the damaged or infected cell. HLA class-II molecules are typically expressed on the cell surface of antigen presenting cells, such as B cells, macrophages or dendritic cells, as well as activated T cells. These molecules present peptides derived from the extracellular space to T helper cells, which in turn stimulate B cells to produce antibodies towards that specific antigen, thereby enabling an antigen specific immune response.

2.1. HLA-disease association

For several decennia, strong associations have been observed between the HLA region and a large number of autoimmune diseases. The molecular mechanism of how certain HLA alleles predispose to autoimmune disease, a phenomenon commonly referred to as "HLA-disease association", has been the subject of a decades-long debate and is currently still unclear. Over the years many hypotheses have been proposed which commonly implicate aberrant antigen presentation of self-antigens (1, 2), cross reactivity with foreign or self- antigens (3, 4) or an immune response to "modified self" antigens (5). All these hypotheses propose that an immune response to putative foreign- or self-antigens is the basis of HLA-disease association. Despite their plausibility, however, presentation of specific antigens as a mechanism underlying HLA-disease association is difficult to reconcile with the mechanistic and epidemiologic evidence that is currently available.

- There are many cases of HLA alleles that are associated with more than one disease which involve completely different target tissues and pathogeneses. For example *HLA-DRB1*04:01*, which is best known for its association with rheumatoid arthritis (RA) is also associated with type-1 diabetes (6). Similarly, *HLA-DQB1*03:02* associates with both type-1 diabetes and celiac disease (7, 8). Moreover, there are certain HLA alleles, e.g. *HLA-DRB1*04:02*, which confer susceptibility to one disease (pemphigus vulgaris (PV)) but protect against another (RA).
- 2. T cell clonality, a feature that is commonly expected in antigen-specific immune responses, has not been convincingly demonstrated in HLA-associated diseases. Also, despite much research effort, for the majority of HLA-associated diseases the target antigen has not been identified.
- 3. The most significant class-II HLA-disease association to date has been found for the brain disorder narcolepsy, which is not known to involve antigen presentation (9). Also, HLA associations have been shown for traits that do not have any known immune basis, e.g. cognition (10).
- 4. Certain HLA molecules have been found to have other functions than antigen presentation, including olfaction and the activation of innate immune signaling (reviewed in (11)).
- Some disease-associated alleles have been shown to demonstrate species non-specificity, e.g. *HLA-DRB1*04:01* associates with human RA and also confers susceptibility to inflammatory arthritis in mice (12). Such 'cross-species susceptibility' is difficult to explain in terms of HLA-restricted antigen presentation.
- The allele-dose impact on disease severity that has been observed in RA (13-15), or the alleledose effects on concordance rates in monozygotic twins (16) are difficult to explain with antigen presentation-based hypotheses.

3. PV, DESMOGLEIN 3 AND HLA-DRB1*0402

Whereas the target antigen is unknown for the majority of HLA-associated diseases, in PV an autoantigen has been identified (17). PV, the most common type of pemphigus, is a potentially lethal blistering disease that affects the mucosal membranes and the skin, and is associated with antibodies against the desmosomal cadherins desmoglein 3 (Dsg3) and Dsg1 (17-20). These antibodies are believed to attack the desmosomes, thereby disrupting the adhesion between the keratinocytes in the epidermis, which is followed by accumulation of transudate fluid. This results in the formation of painful blisters in the skin and in the mucosal membranes. Although PV is relatively rare, with a reported prevalence of 0.1-0.7 per 100,000 individuals (21,22), it is associated with substantial morbidity and mortality (22). PV has long been shown to associate with particular HLA alleles of which HLA-DRB1*04:02 is one of the better-characterized alleles (23-25). In fact, over 95% of PV patients have been shown to carry either HLA-DRB1*0402 or HLA-DQB1*0503 (26-30). Both these HLA alleles have a higher incidence in certain ethnic groups, such as Jews, Iranians, Iraqis, and Indians, which is in agreement with an increased incidence of PV within these populations (31, 32). Although Dsg3 has been identified as the autoantigen for PV more than two decades ago and its function has been studied extensively, a clear understanding of its (possible) relation to the predisposing HLA alleles and the underlying mechanism that allows immune attacks to Dsg3 is still lacking.

3.1. Mouse models to investigate PV pathogenesis

Following the identification of Dsg3 as an autoantigen in PV, much research has been focused on the role of this protein in the epidermis and in PV pathogenesis. Various mouse models have been developed to decipher the role of Dsg3 and its autoantibodies in PV. Mice in which the Dsg3 gene was disrupted (*Dsg3^{-/-}* mice) were shown to mimic phenotypic features that are also seen in PV patients. These features included acantholysis, which is clinically used for differential diagnosis between PV and other types of pemphigus (33). Other models include autoimmune mouse models that involve repeated immunization of mice with (human) Dsg3 in combination with various types of adjuvant. Using a humanized HLA-DRB1*04:02 transgenic mouse model, it was recently shown that T cell recognition of Dsg3 is tightly associated with the HLA-DRB1*04:02 transgene. Additionally, it was shown that T cell-dependent B cell activation was critical for the induction of pathogenic IgG antibodies (34). However, as correctly stated by the authors, this mouse model is only suitable for investigating the effector phase of the autoimmune response in PV. In addition, whereas such immunized mouse models are practical, the observed immune responses largely depend on the mouse strain and the type of adjuvant that are used. Therefore, it is difficult to extrapolate these findings to the human disease (35). Another approach, using adoptive transfer of Dsg3^{-/-} splenocytes into immunodeficient (Rag2^{-/-}) mice resulted in the presence of pathogenic anti-Dsg3 IgG antibodies in the recipient mice, which subsequently displayed clinical, histological, and immunopathological phenotypes similar to those found in human PV (36). This model was shown to be a useful tool to investigate the pathophysiological mechanisms of blister formation by IgG autoantibodies and the immune mechanisms involved in B cells and T cell tolerance to Dsg3 (37).

However, as for most mouse models currently used, these studies focus on Dsg3 and the role of the adaptive immune system, but do not address the mechanistic basis of HLA alleles in PV pathogenesis.

3.2. T and B cells in PV

Following the identification of Dsg3 as the autoantibody for PV, substantial research effort has been focused on autoreactive T cells and their role in the induction and regulation of antibody production by B cells. In vitro stimulation of peripheral T cells from PV patients with Dsg3 has been shown to induce Dsg3-specific antibody secretion by B cells. However, in the absence of T cells there was no detectable autoantibody production by B cells (38), suggesting that T cells are necessary for the anti-Dsg3 antibody production by B cells. Indeed, recent in vitro and in vivo studies have shown that an interaction between T cells and B cells was necessary for autoantibody production in PV (34, 39). In addition, Dsg3specific T cells have been shown to be present at higher levels in the peripheral blood of PV patients compared to healthy controls (40). These findings illustrate the important role of the T cells in PV pathogenesis through their interaction with B cells; however, they do not explain their role in disease onset nor do they explain the role of the PV associated HLA alleles.

3.3. Current state of knowledge about the mechanistic role of *HLA-DRB1*04:02* in PV

It was recently shown that the PV associated HLA alleles, including HLA-DRB1*0402, are important drivers for the reactivity against autoantigen targets in PV (20). However, little is currently known about the mechanistic basis of the association of HLA-DRB1*04:02 with PV. One hypothesis attributes the association to the electric charge of certain Dsg3-derived epitopes and their ability to bind to distinct HLA alleles, thereby allowing recognition by autoreactive T cells. An interaction between HLA molecules and Dsg3-derived peptides has been described for HLA-DRB1*04:02 (41). A limited number of Dsg3 peptides with a positive charge were found to avidly bind to HLA-DRB1*04:02-coded molecules, which contain negatively charged aspartate (D) and glutamate (E) residues (41, 42). These amino acids of HLA-DRB1*04:02-coded molecules have been proposed to contribute to the shape and the charge of the HLA-DR molecule, and thereby play a role in effective binding of Dsg3-derived peptides and their presentation to auto-reactive T cells in PV (43, 44). Using a structure based model, another group proposed that HLA-DRB1*04:02-coded molecules bind in particular to peptides derived from the transmembrane and extracellular Dsg3 domains (45).

4. RA AND THE SHARED EPITOPE LIGAND HYPOTHESIS

Another disease that is well known for its association with certain *HLA-DRB1* alleles is RA, a

common immune-mediated disease that causes severe inflammation and destruction of the joints and affects 0.5-1.0% of the population (46, 47). Whereas the etiology of RA is currently still unknown, both genetic and environmental factors are thought to play major roles in RA onset and development. Of all genetic risk factors for RA, the HLA-DRB1 locus is the most significant one and accounts for 30% to 50% of the overall genetic risk for RA (48). The majority of RA patients carry HLA-DRB1 alleles that code for QKRAA, QRRAA or RRRAA sequences, collectively called the 'shared epitope' (SE), in position 70-74 of the DR beta chain (46). The SE not only confers a higher risk for RA, but it also increases the likelihood of developing earlier disease onset, more severe bone erosions (13-15, 49) and generation of anti-citrullinated (Cit) protein antibodies (ACPA) (50). Furthermore, there is evidence of a gene-dose effect, in which the severity of arthritis-associated bone destruction in RA has a positive correlation with the number of SE-coding HLA-DRB1 alleles (13-15).

The underlying mechanisms by which the SE affects susceptibility to - and severity of - RA are unknown. The most common hypothesis postulates that the SE allows presentation of putative self or foreign arthritogenic antigens (51); however, the identities of such target antigens remain elusive. Our group has recently demonstrated that the SE acts as a signaling ligand that interacts with cell surface calreticulin, activates Th17 polarization and induces osteoclast differentiation with resultant aggravation of inflammatory, bone-destroying arthritis in an experimental RA mouse model (52-54). These findings suggest that irrespective of whether or how presentation of arthritogenic antigens by SE-coding HLA-DRB1 alleles plays a role in RA etiology, the SE ligand's function could account for (at the least most of) the mechanistic basis of the SE-RA association.

It is worth mentioning that recent genomics data suggest that in addition to residues 70-74, which are located in the α helical rim of the DR beta chain and are classically defined the "SE", residues 11 and/or 13 which are located inside the 'floor' of the HLA-DR groove are associated with RA susceptibility as well (55, 56). This suggests that presentation of peptidic antigens may play a role in RA etiology. However, it should be noted that while this hypothesis awaits experimental validation, the relevance of these statistical data to RA etiology has been recently questioned (57). Be that as it may, the SE ligand hypothesis does not exclude the possible involvement of antigen presentation in RA etiology; it rather explains aspects of RA that cannot be explained by antigen presentation alone. It is conceivable that while presentation of specific antigen(s) determines the sites of the immune attack, it is the SE ligand that polarizes the immune response and thereby facilitates bone damage with the resultant severe erosive RA development (discussed in (58, 59)). This scenario may be consistent

with the fact that the SE alone is not sufficient to cause RA and a secondary factor seems necessary. For example, the SE was shown to confer a risk particularly in those RA patients that were positive for anti-citrulline antibodies (60). Furthermore, there is ample evidence for gene (SE)-environment interaction in RA (61, 62). For example, individuals that smoke and carry one or two SE-coding *HLA-DRB1* alleles are, respectively, 7.5 times or 15.7 times more likely to develop RA than their non-smoking counterparts with the same genetic predisposition (60). In addition, not all individuals that are SE positive develop RA.

4.1. RA-protective HLA-DRB1 alleles

Interestingly, while the HLA alleles that encode QKRAA, QRRAA or RRRAA sequences in position 70-74 of the DR beta chain increase the risk for RA, those HLA alleles that code for D instead of Q or R in position 70 are protective (46, 63-66). In particular, the 70-DERAA-74 sequence that is encoded by several alleles, including DRB1*13:01, DRB1*13:02 and DRB1*04:02 exerts a protective effect (65, 67). Presence of one DERAA-coding HLA-DRB1 allele provides protection against RA even in individuals that carry a SE-coding allele (67). This dual role of HLA-DRB1*04:02 in HLA-disease association, being protective in RA on the one hand, and being a genetic risk factor in PV on the other is currently not understood. A recent study proposed that the negative association in RA is due to cross-reactivity between citrullinated vinculin and microbial proteins and due to the presentation of the DERAA sequence by DQB molecules coded by alleles that are in linkage disequilibrium with SE-coding DRB1 alleles (4). However, besides the fact that this intriguing hypothesis requires experimental validation, it seems to contradict published data by the same group indicating that DERAA-coding alleles are protective against RA, independent of the presence of a SE-coding DRB1 allele (67). Also, it has been shown that there is a dominant protective effect of a DERAA-expressing transgene on collagen-induced arthritis development in mice, independent of DQ molecules (68). Moreover, this hypothesis does not explain why SE-positive haplotypes cannot mount a similar immune protective effect in individuals without DERAA-coding alleles upon exposure to the DERAA sequence, which is ubiquitously expressed by microbial proteins. Finally, DERAA-coding HLA-DRB1 alleles have been shown to be protective against several other autoimmune diseases besides RA, including systemic lupus erythematosus and scleroderma (69, 70). This suggests an antigen-nonspecific modulatory effect, rather than an antigen presentation-based mechanism.

5. SUMMARY OF KNOWLEDGE GAPS

Despite the identification of Dsg3 as a target antigen in PV, the underlying immunological response that leads to anti-Dsg3 antibody production is still unclear and requires further research. Little is known about the mechanistic basis of HLA-DRB1*0402 association with PV pathogenesis. Research of this association is currently mostly driven by hypotheses addressing the antigen presentation theory, due to the identification of Dsq3 as a target for autoantibodies in PV. Since its discovery, the roles of Dsg3 and of Dsg3-antibodies have been studied extensively and PV is generally regarded a Dsg3 autoantibody-mediated disease. However, the antithetic hypothesis stating that production of anti-Dsg antibodies might be a result, rather than a cause of epidermal blistering (71) deserves further consideration. The underpinnings of this unorthodox hypothesis relate to several observations, including that Dsg3 antibodies are not unique to PV. For example some patients with silicosis, a disease that does not involve blisters, develop antibodies to Dsg1 and/or Dsg3 (72). Furthermore, there are several studies that show that the antibody titers for Dsg1 and/or Dsg3 do not necessarily correlate with the disease activity and that a subset of PV patients lack detectable anti-Dsg antibodies (73-75). Moreover, there is increasing evidence that antibodies against targets other than desmogleins might play a role in PV (76-78). In addition, Dsg3-specific T cells can also be detected in the peripheral blood of healthy carriers of PV-associated HLA alleles (26). Such healthy individuals that carry the HLA-DRB1*0402 allele display T-cell responses against the same epitopes of Dsg3 as patients with active PV, yet they do not suffer from PV (26, 40). These findings were recently supported by a study in which multiplexed autoantigen microarrays were used that showed that when grouped based on the presence of PV associated HLA alleles, those that were positive (first or second degree related or unrelated) showed autoantibody profiles similar to active PV, supporting the notion that PV associated HLA alleles may underlie the autoantibody production (20). Because of these findings, it seems unlikely that loss of T-cell tolerance alone leads to PV and that additional processes may play a role as well.

As discussed above, most research on PV pathogenesis has been focused on Dsg3 and the adaptive immune response, in particular the role of T cells, while largely disregarding a potential role of the innate immune system. HLA gene products are expressed on the cell surface of antigen presenting cells, and the best-characterized role of these molecules is to present antigenic peptides to T cells in an MHC-restricted fashion (79). It is therefore understandable that most research efforts to decipher the role of HLA molecules in PV and RA to date have focused on self-antigenspecific recognition by T cells. However, there are strong indications that HLA molecules may also perform a variety of other important biologic functions that are not related to antigen presentation (11). The evidence discussed above demonstrate that HLA-DRB1*04:01-encoded SE can activate innate cell signaling and osteoclastogenesis (52-54, 80). This is one of several examples of HLA molecules with non-antigen presentation roles (discussed

in (59)). It is therefore conceivable that in addition to their roles in the adaptive immunity, other disease associated HLA alleles, including *HLA-DRB1*04:02*, also may contribute to the development of or the resistance to autoimmune diseases through allele-coded ligands that activate aberrant signaling events.

6. CONCLUSION

*HLA-DRB1*04:02* epidemiologic associations with PV susceptibility on the one hand, and protection against RA on the other are well documented; however, little mechanistic knowledge exists about the basis of these associations. Understanding how *HLA-DRB1*0402* exerts its reciprocal effects in these two diseases will likely provide new insights into the multifactorial nature of HLA-disease association, and could open the door to novel and more efficient therapies for many diseases.

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Abbreviations: ACPA, Anti-citrullinated Protein Antibodies; CIA Collagen Induced Arthritis; Cit, Citrinullated; CRT, Calrticulin; Dsg3, Desmoglin 3; HLA, Human Leukocyte Antigen; MHC, Major Histocompatibility Complex; OC, Osteoclast; PBMCs Peripheral Blood Mononuclear Cell; PV, Pemphigus Vulgaris; RA, Rheumatoid Arthritis; SE Shared Epitope

Key Words: HLA-DRB1, Pemphigus Vulgaris, Rheumatoid Arthritis, Shared Epitope, Review

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