The HLA and kidney disease: from associations to mechanisms

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Abstract

Since the first association between HLA and diseases of native kidneys was described almost 50 years ago, technological and conceptual advances in HLA biology and typing, together with better case ascertainment, has led to an improved understanding of HLA associations with a variety of renal diseases. A substantial body of evidence now supports the existence of HLA genetic associations in the field of renal disease beyond the role of HLA in allogeneic responses in transplant recipients. HLA allomorphs have emerged as important risk factors in most immune-mediated renal diseases, which together with other genetic and environmental elements, lead to loss of tolerance and autoimmune-mediated renal inflammation. HLA associations have also been described for renal diseases that are less traditionally seen as autoimmune or immune-mediated. Here we review essential concepts in HLA biology and the association of HLA with diseases of the native kidneys, and describe current understanding of the epistatic and mechanistic bases of HLA-associated kidney disease. Greater understanding of the relationship between HLA and kidney function has the potential not only to further the understanding of immune renal disease at a fundamental level, but also to lead to the development and application of more effective, specific and less toxic therapies for kidney diseases.

The adaptive immune system has evolved to meet and manage infectious threats. A central component of this system is the contextual recognition of peptide antigens and differentiation of T cells, with the subsequent development of protective immunity. These key features occur through the recognition of peptides bound to major histocompatibility complex (MHC) (or in humans, human leukocyte antigen (HLA)) by T cells that bear unique, highly diverse T cell receptors (TCRs). The evolution of the adaptive immune system not only required the development of mechanisms to delete T cells that have a strong affinity for self-peptides and proteins, but also favored the development of a polygenic and highly polymorphic HLA system to enable the specific recognition of a diverse set of peptides for presentation to T cells.

A major cost of this powerful and specific system, however, is the aberrant recognition of self-peptides by TCRs, leading to the development of autoimmune disease. The risk associated with such mis-identification is highlighted by the fact that autoimmune diseases affect 7.6–9.4% of the world's population[1]. With some exceptions, autoimmune diseases are typically thought to evolve via a multistep process[2], involving loss of tolerance to one or more self-antigens owing to interactions between genetic susceptibility factors and environmental risk factors, followed by amplification of disease manifestations via the activation of positive feedback loops resulting from disordered immune responses. Tolerance is a state that in health is established and maintained by both central and peripheral mechanisms. Central tolerance involves the selection of T and B lymphocytes in the thymus and bone marrow, respectively. The selection of T cells, as well as their ability to recognize pathogenic peptides requires interactions between antigenic peptides bound to MHC (or HLA) molecules. Two classes of MHC molecules exist: MHC Class I molecules are found on the surface of all nucleated cells in the body and present peptides to CD8+ T cells. MHC II molecules are normally expressed only by antigen-presenting cells, such as dendritic cells, mononuclear phagocytes and B cells and present peptides to CD4+ T cells. MHC class I and class II molecules therefore define the repertoire of CD8+ and CD4+ T cells, respectively. Interestingly, almost all autoimmune diseases tend to occur in people with certain HLA types, highlighting the key role of HLA alleles in maintaining tolerance and conversely, in the development of autoimmunity. HLA is therefore a key genetic risk factor in autoimmune disease, and understanding the functions of HLA is fundamental to unravelling the pathogenesis of autoimmune diseases.

Since the initial studies of HLA and disease that essentially founded the field of immunogenetics, key advances have been made in our understanding of the immune system, including mechanisms involved in providing protection from infectious diseases, immunological memory, loss of tolerance and allorecognition[3]. In the last 10 years in particular, technical advances have led to the associations between HLA in disease being better defined and provided new insights into the underlying mechanisms[3]. This new understanding has the potential to identify better, more specific therapies for diseases involving HLA. This Review summarizes basic concepts pertaining to HLA and disease, and assesses the growing literature in the field of HLA in diseases of native kidneys. We review the mechanistic links underlying the associations between HLA and kidney diseases, and discuss how these links might provide insights into disease pathogenesis, as well as the clinical implications of these insights. Although HLA is a critical element of renal transplantation, the involvement of HLA and its role in allorecognition is mechanistically distinct from the mechanisms described in this Review[4–6] and is not discussed here.

Fundamental aspects of HLA biology

The HLA is a fundamental component of adaptive immunity. Following their intracellular processing, self-peptides and non-self peptides are loaded into grooves within HLA complexes for presentation to TCRs. It is the combination of both the peptide and the MHC

complex that is recognized by the TCR. This specific recognition is a central tenet of antigen specificity, which itself the critical feature that defines the adaptive immune system.

HLA types and the HLA locus

The genes that encode the proteins of the MHC (or HLA in humans) are located on chromosome 6. The MHC region is the largest and most polymorphic area of the genome, containing several classes of genes that are important in immune function, including the antigen presenting MHC class I alleles (in humans the HLA-A, B and C alleles) and the MHC class II genes (in humans the HLA-DR, DP and DQ genes) (Fig. 1a). HLA Class I molecules are composed of a single **α** chain that is non-covalently bound to **β**2-microglobulin, with the **α**1 and **α**2 segments of the **α** chain forming the peptide binding cleft. By contrast, MHC class II molecules consist of both an **α** and a **β** chain, with the **α**1 and **β**1 segments forming the peptide binding cleft (Fig. 1b). The **α** chain of HLA-DR is essentially invariant, but functionally relevant polymorphisms exist in both the **α** and **β** chains for HLA-DQ and –DP (Table 1). Other genes within the HLA Class II region encode HLA-DO and HLA-DM, proteins that do not present peptides but are important to the process of loading peptides into HLA-DR, DP and DQ. HLA-DM is important in the loading of peptides into MHC class II whereas DO is a negative regulator of DM. Other MHC class I genes include the largely monomorphic HLA-E, -F and –G genes, which interact with NK cells and, in the case of HLA-G, help maintain immune tolerance to the fetus during pregnancy.

The MHC class I and class II genes are separated by the so-called MHC III region, which includes genes that encode complement components, Hsp70, tumor necrosis factor (TNF) and receptor for advanced glycation end-products (RAGE). These and other non-MHC I and MHC II genes within the MHC region have important biological functions in immune and nonimmune kidney diseases, and their presence within the broader MHC locus can complicate studies of the association between HLA and disease[7]. This Review focuses on the roles of the MHC class I and class II molecules that present antigen to T cells (that is, HLA-A, -B, C, -DR, -DQ and -DP) in kidney disease.

Humans inherit multiple MHC Class I and Class II alleles from each parent as a haplotype on chromosome 6. As of July 2018,9,341 different HLA-A -B and -C proteins and 5,355 different HLA-DR, -DQ and -DP proteins were known to exist, derived from polymorphisms in the HLA-A, B, C, DRA, DRB, DQA, DQB, DPA and DPB genes. Any individual can express up to six HLA Class I alleles and eight Class II alleles, highlighting the complexity of this system. With the exception of HLA-DP alleles, HLA alleles are often in strong linkage disequilibrium, tending to segregate together in specific haplotypes, such as the "8.1 ancestral haplotype"[8]. The most relevant HLA polymorphisms result in amino acid substitutions that predominantly involve peptide binding sites and/or potential TCR contact areas. It is therefore likely that this highly polymorphic and polygenic system evolved to favor the effective display of a broad array of infection-related and self-peptides to CD4+ and CD8+ T cells.

HLA and peptide presentation

Unlike antibodies, T cells do not recognize intact proteins. Rather, via their clonotypic **αβ** T cell antigen receptor, T cells bind to peptides presented by molecules encoded by the MHC (in humans, HLA). As mentioned above, self and foreign proteins are processed intracellularly. Classically, proteins that exist outside the cell and are degraded in endocytic vesicles via protease-mediated protein degradation bind to MHC Class II molecules, whereas peptides that bind to MHC Class I are derived from the processing of cytosolic proteins in the proteasome. In addition, exogenous proteins are presented by MHC Class I molecules on some antigen presenting cells, for example some dendritic cells, in a process known as cross-presentation[9]. Peptides are loaded onto MHC class I or MHC class II molecules within a

series of pockets located within the antigen-binding cleft. One or two pockets typically define the peptide binding preferences of a given MHC molecule. Although the two classes of MHC molecules have a similar overall three-dimensional architecture, differences exist within their peptide antigen binding clefts. Namely, the N-termini and C-termini of MHC class I molecules are "pinched off", favouring the binding of shorter length peptides (<10 amino acids), whereas the peptide binding grooves of MHC class II molecules are open-ended, thereby permitting peptides of much longer length to bind[10]. The polymorphic composition of the HLA locus enables each HLA allomorph to have a distinct peptide-binding preference through which it shapes the T cell repertoire. For example, the HLA-DR allomorphs HLA-DR1 and HLA-DR15 exhibit different peptide-binding characteristics, accounting for their ability to provide protection from, and increase the risk of Goodpasture's disease (also known as anti-glomerular basement membrane [GBM] disease), respectively[11].

To cope with the myriad of peptide–MHC complexes that are presented on the surface of cells, the TCR itself is highly variable. The **αβ**TCR is composed of two chains, each of which is comprised of multiple gene segments encoded within the Variable domain. Moreover, the existence of non-nucleotide encoded additions and/or deletions at gene junctional boundaries increases the sequence diversity of TCRs. Current estimates suggest that up to 1×10^{15} different TCRs exist in the human body which, after thymic selection, is reduced to 1×10^{8} TCRs[12].

Interaction between the TCR and the peptide–MHC complex involves the specific and simultaneous co-recognition of the peptide and the MHC molecule in a phenomenon known as MHC restriction (Fig. 1c), and is the critical event that determines effective T cell immunity. Structural studies over the past 20 years have provided fundamental insights into the molecular determinants of this key recognition event and illuminated key facets of immunology, for example, by providing insights into how MHC polymorphisms shape TCR recognition, T cell cross-reactivity, alloreactivity and autoreactivity, as well as mechanisms of biased TCR usage and viral immunity[10]. Although much remains to be learned in the field of antigen recognition, our ability to harnessing these mechanisms holds promise for the future, including the development of diagnostics centered on TCR repertoire usage and precision medicine approaches.

HLA typing and nomenclature

Changes to HLA nomenclature and methods for HLA typing have had implications for studies of HLA associations with disease (Box 1). The origins of HLA typing date back to the 1960s, with the generation of antibodies that recognized HLA complexes on the cell surface, such as HLA-A2, in which the "2" describes a distinct variant or allomorph in HLA-A[13]. The advent of molecular typing enabled the identification of genes expressing HLA class I **α** chains, HLA Class II **α** chains and HLA Class II **β** and provided insights into the complexity of HLA Class II. Use of this technology enabled the nomenclature of HLA to become both more complex and more accurate, by including a four-digit descriptor for each chain: this nomenclature was later expanded to accommodate the discovery of synonymous coding and non-coding HLA polymorphisms. (Fig. 1d)[14]. In a research setting, single nucleotide polymorphism (SNP)-based typing of HLA encoding genes with allelic imputation is common. Most genotyping methods result in some genotyping and allelic ambiguity in that results might be consistent with several alleles at a particular locus. Fortunately, however, this ambiguity often does not have major implications for association studies of immune-mediated kidney diseases, as it often pertains to polymorphisms outside of peptide binding and TCR contact regions or to very rare alleles. The characteristics of the antigen-presenting HLA Class I proteins (HLA-A, -B and -C) and HLA class II proteins (HLA-DR, -DQ and -DP) are summarized in Table 1.

HLA and kidney disease

HLA types give rise to risk alleles, protective alleles and dominantly protective alleles, which are important in several aspects of disease. Different autoimmune kidney diseases arise from the interactions of self-peptides with specific HLA molecules, as evidenced by the association of HLA types with specific diseases. The first association of HLA with renal disease was reported in 1969[13]. Early studies of the association between HLA and kidney disease often involved small numbers of patients; in the past decade, larger studies have been better able to dissect the contributions of individual HLA types in linkage disequilibrium within a haplotype to disease. HLA associations with disease have most commonly been studied by comparing HLA types among patients with a disease with those of individuals within a control cohort. However, simply comparing HLA types in patients with disease to those without, particularly without detailed clinical phenotyping, might miss some of the important but subtle potential effects of HLA types, including the influence of HLA on the age of disease onset, disease severity, disease phenotype and rates of disease triggering events. Some kidney diseases, for example, membranous nephropathy mediated by autoimmunity to the phospholipase-A2-receptor (PLA2R) and anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis have a clear immunological basis[15] and relatively logical mechanisms by which different HLA types might modify disease risk. In other kidney conditions, including end-stage renal disease in general, linkage disequilibrium with other inflammation-related genes in the MHC III region might confound the HLA data. Although the association of HLA types to disease can be similar across ethnic groups (as in the increased risk of Goodpasture's disease conferred by the expression of HLA-DR15)[16–18], they can also differ (as reported for HLA risk alleles in the context of membranous nephropathy)[19–22]. Of note, in addition to changes in HLA nomenclature and HLA typing methods (Box 1), changes in diagnostic criteria and classification of kidney diseases has further complicated studies of the association of HLA alleles with kidney diseases.

Sites of HLA expression

HLA is clearly critical within lymphoid organs, where HLA–peptide complexes participate in the selection of T and B lymphocytes to establish central tolerance, and to activate naïve T cells or maintain them in a quiescent state (Fig. 2). Kidney disease can arise from the effects of HLA in the lymphoid or in the kidney. Naïve CD4+ and CD8+ T cells are activated in secondary lymphoid organs including lymph nodes and spleen, where antigen specific CD4+ T cells also have an essential role in antibody production by interacting with peptides presented by HLA class II molecules on B cells. Effector CD8+ T cells, as well as both T_H1 and T_H17 CD4+ T cells can injure the kidney, both by recognizing intrarenal antigens, including at least for CD4+ T cells, antigens presented within the glomerular microvasculature[23–25] (Fig. 3). The expression of HLA Class I molecules on nucleated cells within the kidney enables effector CD8+ T cells to recognize cells that have been infected with virus and cells displaying peptides derived from intracellular antigens. The role of HLA Class II molecules in antigen recognition by effector or regulatory CD4+ cells within the kidney is more complex. Resident and infiltrating antigen presenting cells within the kidney — also known as renal mononuclear phagocytes — constitutively express MHC II and are prominent in the tubulointerstitium.[26,27] In the tubulointerstitium MHC II is also present on B cells and tubular epithelial cells. In glomeruli, MHC II is expressed by luminal monocytes[24], and on infiltrating macrophages and dendritic cells under inflammatory conditions.[28] Non-phagocytic intrinsic glomerular cells, including endothelial cells and podocytes can also be induced to express MHC II in response to a variety of inflammatory stimuli, potentially allowing them to present antigen to effector CD4+ T cells.[29,30] Moreover, tubulointerstitial B cell aggregates are present in at least some types of glomerulonephritis;

and activated antigen-specific B cells are highly effective antigen presenting cells and express MHC II[31,32].

Under physiologic conditions, MHC II expression by tubular cells and perhaps intrinsic glomerular cells might help maintain peripheral tolerance**,** but might exert pro-inflammatory effects in under certain conditions[33–35]. Thus in addition to the effects of HLA in lymphoid organs, it is plausible that HLA allomorphs expressed by renal cells or renal mononuclear phagocytes might contribute mechanistically to renal disease.

From association to mechanistic insights

Improved understanding of the molecular sequence and structure of most HLA molecules has enabled comparison of the commonalities and differences between risk, neutral and protective alleles[36]. This comparative approach has been frequently applied to the study of risk alleles in autoimmune disease, including Goodpasture's disease and membranous nephropathy[16,19]. Individual amino acid differences in HLA alleles can dictate structural determinants that define peptide binding and therefore antigen presentation — features that can be interrogated in functional and structural studies[11,37]. However, intermolecular and intramolecular epitope spreading complicates assessment of HLA–peptide interactions in autoimmune disease, as the multiplicity of epitopes in more than one autoantigen makes definitive identification of the critical autoantigenic peptides difficult. Some systemic autoimmune diseases, such as systemic lupus erythematosus (SLE) feature loss of tolerance to multiple autoantigens. Even organ-specific autoimmune diseases where one might expect only one autoantigen can often involve loss of tolerance to multiple autoantigens; for example, type 1 diabetes mellitus (T1DM) features loss of tolerance to multiple pancreatic **β**-cell antigens[38]. However, several autoimmune renal diseases, including Goodpasture's disease, proteinase 3 anti-neutrophil cytoplasmic antibody associated vasculitis (PR3-AAV), myeloperoxidase-ANCA associated vasculitis (MPO-AAV) and PLA2R-induced membranous nephropathy seem to involve a single or at least a dominant autoantigenic target, at least according to our current knowledge of disease pathogenesis.

HLA types may predispose an individual to, or protect an individual from the development of autoimmune disease through multiple mechanisms such as through changes in the expression or stability of HLA, antigenic peptide modifications, shifts in the peptide binding register between different HLA molecules or the development of a pathogenic or protective antigen-specific T cell repertoire[3,11,37,39–41]. Thus, the relationship between HLA–peptide complexes, autoreactive TCRs and cellular phenotype is of utmost importance in determining whether an interaction will induce tolerance or autoimmunity, and whether it could potentially be harnessed for therapeutic purposes**.** However, in general little is known about how HLA allomorphs, and the differences in peptide binding to different HLA allomorphs, affects the deletion, selection and subsequent activation of T cells bearing autoreactive TCRs. In autoimmune diseases, knowledge of immunodominant peptide epitopes and their binding to different HLA molecules is critical to understanding mechanisms by which different HLA allomorphs influence the risk of disease. Various techniques have therefore been developed to define the mechanisms of HLA associations (Box 2). Although human studies are critical in any mechanistic study of HLA associations, HLA transgenic mice have emerged as important tools in in vivo studies.

Goodpasture's disease is a useful prototypic model for mechanistic studies of renal autoimmune disease, due to the presence of a dominant autoantigen (non-collagenous domain of the **α**3 chain of type IV collagen; **α**3(IV)NC1) with defined T cell and B cell epitopes, high sequence homology between human and mouse **α**3(IV)NC1, strong positive (HLA-DR15) and dominant negative HLA associations (HLA-DR1 and -DR7) and clear diagnostic criteria[16,42]. Loss of tolerance to **α**3(IV)NC1 and the development of Goodpasture's disease has been

studied in HLA-DR transgenic mice lacking murine MHCII, wherein the CD4+ T cell repertoire is based on the interactions of mouse proteins with human HLA-DR[11,43,44]. These transgenic mice have been engineered to express the invariant HLA-DRA1*01:01 allele, with either DRB1*15:01 (DR15+), DRB1*01:01 (DR1+) or both HLA-DRB1 alleles (DR15+DR1+). Consistent with sentinel studies in humans[45], an epitope derived from **α**3(IV)NC1, **α**$3_{135–145}$ (mouse **α**$3_{136–146}$) was established as the critical and disease-inducing epitope in disease-sensitive mice DR15+ mice. However, in the presence of the dominantly protective HLA-DR1 allele, the **α**$3_{135–145}$ epitope does not induce pro-inflammatory responses in mice or in humans, explaining the dominantly protective effect of HLA-DR1 on the risk conferred by DR15 (Fig. 4a)[11,44].

This phenomenon of dominant HLA-mediated protection against autoimmunity could conceivably involve several mechanisms, including the deletion or activation-induced cell death of autoreactive T cells, epitope capture by the protective HLA allomorph, or the induction of epitope specific regulatory T (Treg) cells. In both HLA transgenic mice and in humans, dominant protection against autoreactivity to **α**3(IV)NC1 is dependent on polymorphisms that distinguish DR15 and DR1 and affect the presentation of the **α**$3_{135–145}$ epitope, causing a shift in the binding register[11]. The structure of the DR15 and DR1 peptide binding pockets change the presentation of **α**$3_{135–145}$ to CD4+ T cells, leading to fundamental differences in their associated TCR repertoires and phenotype. Indeed, **α**$3_{135–145}$-specific CD4+ cells in naïve mice and in healthy humans show proinflammatory capacities in the context of DR15, but generate predominantly Treg cells in the context of DR1 (Fig. 4a). The power of antigen-specific Treg cells in inducing tolerance was demonstrated by in vitro findings in humans and mice and in vivo findings in mice, showing that Treg cells generated in response to HLA-DR1-presentation of **α**$3_{135–145}$ suppressed the effects of autoreactive conventional T cells generated in response to HLA-DR15[11]. Similar processes might operate in other diseases. In particular, HLA-DQ6 exhibits a similar dominantly protective effect on the risk conferred by DQ8 in T1DM, with studies in diabetes-prone NOD mice implicating Treg cells in HLA-DQ6 -mediated protection[46].

The opportunity exists to apply these types of mechanistic approaches to the study of other forms of renal disease, including membranous nephropathy, in which polymorphisms in the autoantigen PLA2R1 are epistatically linked to HLA. In addition, applying concepts explored in in non-renal autoimmune diseases to renal disease might provide insights into how HLA contributes to renal disease. In rheumatoid arthritis, for example, the amino acid composition at position 13 in the base of the peptide binding groove of HLA Class II molecules, as well as the shared epitope defined by amino acids 70–74 of the HLA-DR **β** chain defines the risk alleles HLA-DRB1*04:01, *04:04 and *01:01[47]. Citrullination of endogenous peptides promoted by cigarette smoking modifies the binding of peptides to HLA-DRB1*04:01 and DRB1*04:04 (but not the protective DRB1*04:02 allele) and stimulates autoreactive T cells[37]. In multiple sclerosis, studies have defined functional epistasis between HLA-DR15 and DR51. The HLA-DRB1*15:01 and HLA-DRB5*01:01 alleles are in almost complete linkage disequilibrium: DR51 modifies the strong pro-inflammatory effects of DR15 in experimental multiple sclerosis and might also modulate the pro-inflammatory effects of one or more microbial peptides. For instance, co-inheritance of HLA-DR15 and DR51 might in the past have increased survival following infection with particular threatening pathogens, through effective control of the infection (via DR15-mediated immunity) together with DR51—peptide interactions regulating the response to prevent lethal pro-inflammatory responses. These interactions might explain the strong linkage disequilibrium between HLA-DR15 and DR51[48].Studies in multiple sclerosis have also structurally and mechanistically demonstrated the subtleties that underpin molecular mimicry in this disease, with TCR engagement and

T cell activation via HLA–peptide complexes featuring a molecular hot-spot common to different peptides that have only limited sequence homology to the autoreactive self-peptide[41].

Of note, the role of HLA in pathological inflammation is by no means confined to traditional autoimmune diseases. Alterations in HLA–peptide binding might also explain many type B adverse drug reactions (ADRs), as exemplified by the interactions of abacavir with HLA-B*57:01 [49], discussed below (Fig. 4b).

A plethora of studies have demonstrated pathogenic and protective HLA associations in autoimmune kidney diseases, including AAV, membranous nephropathy and lupus nephritis. Furthermore, HLA associations may also help define pathogenic mechanisms in other, non-autoimmune renal diseases (Table 2). These insights, together with advances in our understanding of disease pathogenesis and stratification, provide an opportunity to develop more specific treatments for kidney diseases.

HLA associations in renal diseases

Autoimmune Glomerulonephritis

Goodpasture's disease

Type IV collagen (collagen IV) is an important component of the basement membrane in the kidney and other organs, and is composed of six isomeric chains (**α**1–6) [42]. The presence of autoantibodies to the **α**3 chain of collagen IV results in Goodpasture's disease, which is characterized by rapidly progressive glomerulonephritis and pulmonary haemorrhage. Both antibody production and cellular immunity are important in the pathogenesis of Goodpasture's disease, and specific epitopes of the autoantigen that elicit B cell and T cell responses have been defined [44,45,50]. The positive association of HLA-DR15 with Goodpasture's disease is among the strongest reported for an autoimmune disease[16].

The first association of Goodpasture's disease with an HLA allele was made in 1978 following the identification of HLA-DR2 using serotyping[51]. The advent of molecular techniques enabled the subdivision of HLA-DR2 into more specific allele groups, including HLA-DRB1*15 and HLA-DRB1*16. A strong association between HLA-DRB1*15:01 and Goodpasture's disease has since been demonstrated in several studies of European populations. The reported association between DQB1*06:02 and Goodpasture disease is due to linkage disequilibrium between DQB1*06:02 and DR15[52–55]. A meta-analysis in 1999 confirmed a strong association between HLA-DRB1*15:01 and Goodpasture disease (odds ratio (OR) 8.5), and identified a weaker positive association with DRB1*04[16]. Conversely, DR1 and DR7[16] (and possibly DPB1*04:01[56]) confer a dominantly protective effect. More recently, studies of Japanese and Chinese populations have replicated the DR15 association[17,18,57]. The most recent of these also described a protective effect of DRB1*09:01 in a Han Chinese population[57]. HLA associations reported in Goodpasture's disease are described in Supplementary Table 1. The co-existence of anti-GBM antibodies and MPO-ANCA in some individuals with Goodpasture's disease is a well-recognized phenomenon[58,59]; it is feasible that HLA allomorphs contribute to the risk of "dual-positive" disease.

The mechanisms by which DR15 and DR1 confer susceptibility to and protection from Goodpasture's disease have been defined (discussed above). The hypothesis that key structural differences between the binding pockets within the peptide binding grooves of HLA-DR15 and HLA-DR1 (especially pocket 1 and pocket 4) might influence the presentation of **α**3(IV)NC1 [16], is supported by structural and functional data using the immunodominant T cell epitope $\boldsymbol{\alpha}3_{135-145}$[44,45], which showed that polymorphic differences in DR15 and DR1 result in distinct peptide-binding patterns, leading to the activation of distinct T cell repertoires. The phenotype of these T cell repertoires determines susceptibility to disease[11].

Membranous Nephropathy

Membranous nephropathy is one of the most common causes of nephrotic syndrome in adults. Histologically, it is characterised by the presence of sub-epithelial glomerular immune complex deposits and thickening of the basement membrane — a pattern of injury that is also associated with other diseases, including viral hepatitis and SLE, and with exposure to drugs and toxins such as penicillamine and gold (discussed below). In so-called primary membranous nephropathy, target autoantigens were unknown in most adults until the recognition of PLA2R1, which is constitutively expressed at low levels on normal podocytes [60]. Circulating anti-PLA2R1 autoantibodies and PLA2R1 antigen expression in glomerular deposits are present in more than 70% of cases of idiopathic membranous nephropathy [60,61]. A different autoantigen, thrombospondin type-1 domain-containing 7A was subsequently identified in a proportion of patients with idiopathic membranous nephropathy who are anti-PLA2R1-negative [62].

A summary of all HLA associations described in membranous nephropathy is provided in Supplementary Table 2. The first association was reported in 1979, with the finding of a 12-fold increased risk of membranous nephropathy associated with HLA-DR3 in an English cohort[63]; this association was subsequently corroborated in small French and German serological studies[64,65]. A study that used an early technique for DNA analysis confirmed the DR3 association and also identified HLA-DQA1 as a susceptibility factor[66]. The first GWAS of membranous nephropathy and subsequent molecular typing studies identified HLA-DQA1 as the dominant risk locus[22,67–70], with the rs2187668 risk allele conferring an increased risk of membranous nephropathy across multiple ethnic groups. It is possible that the HLA-DRB1*03:01 (DR3), DQA1*05:01/DQB1*02:01 (DQ2) associations represent a risk haplotype for MN[21]. Studies of MN in Asian populations have consistently demonstrated an additional association of membranous nephropathy with HLA-DR15 — an allomorph that has been linked to several other autoimmune diseases including Goodpasture's disease[16]. Two studies of Chinese individuals published in 2017 identified a strong link between MN and DRB1*15:01[19,20], supporting earlier reports of a strong association between membranous nephropathy and DR15 in Japanese populations (as DR2, the original serotype that included DR15)[71–73]. Ethnic differences in HLA associations in membranous nephropathy might reflect different background allele frequencies and/or indicate varying underlying disease mechanisms.

SNPs in the PLA2R1 locus on chromosome 2q24 have also been associated with an increased risk of developing membranous nephropathy. Interestingly, inheritance of both the HLA-DQA1 and PLA2R1 risk alleles synergistically increases the risk of membranous nephropathy (OR 7.3-79.4), suggesting functional epistasis between HLA Class II molecules and PLA2R1[21,22,67–70]. Although the mechanisms that underpin the HLA associations with membranous nephropathy remain unclear, the combination of risk variants in HLA and PLA2R1 might alter the interaction between HLA Class II molecules and autoantigen, enhancing antigen presentation, T cell activation and thus the production of pathogenic autoantibodies[22]. Findings from predictive software analyses (using the DNASTAR Jameson-Wolf method) suggest that the substitution His300Asp encoded by variant rs35771982 gives rise to a PLA2R1 protein with a more 'immunogenic' secondary structure that may promote antibody production[69]. However, modelling of HLA–peptide complexes suggests that amino acid changes encoded by variants of PLA2R1, at least in the context of HLA-DR3 and -DR15, have little impact on their predicted presentation by HLA, and that structural differences between HLA-DR molecules exert a greater influence[19]. Indeed, the dominant HLA-DQA1 SNP was more strongly associated with MN than the leading PLA2R1 SNP[22].

Clearly, identification of immunodominant PLA2R1 T cell epitopes and improved understanding of their interactions with HLA-DR and -DQ would further understanding of the pathogenesis of MN. Disease mechanisms in the context of PLA2R1-negative idiopathic MN require investigation, and possible differences in disease pathogenesis between ethnic groups also warrants further consideration. Interestingly, commonalities exist in some of the HLA associations in anti-PLA2R MN and some 'secondary' causes of MN (see below). Whether these commonalities are related to immune mechanisms that favour sub-epithelial immunoglobulin deposition remains to be established.

ANCA-associated vasculitis

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides are the most common cause of rapidly progressive glomerulonephritis. They can be divided into syndromically defined conditions: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA; also known as Churg-Strauss syndrome)[74,75]. The majority of people with GPA have ANCA specific for PR3 and cytoplasmic ANCA (cANCA) pattern on imaging by indirect immunofluorescence, whereas most MPA, and 40% of individuals with EGPA, have ANCA specific for MPO with a perinuclear pattern of ANCA staining (pANCA). Approximately 10% of cases of GPA and MPA are ANCA-negative. The importance of including antigen specificities (that is, PR3 or MPO) in the description of clinical syndromes in AAV is supported by clear genetic differences between PR3-AAV and MPO-AAV[76]. Early studies of HLA associations with AAV using serotyping were limited by the absence of patient stratification on the basis of ANCA specificity[77,78]. Molecular HLA typing, together with the use of antigen-specific stratification, has helped define more specific associations of HLA with AAV, a full list of which can be found in Supplementary Table 3.

The most consistent HLA association in PR3-AAV is with HLA-DP. The HLA-DPB1*04:01 allele, equating to the DPA1/DPB1 heterodimer known as DP4, was associated with an increased risk of PR3-AAV in three European studies (OR 3.38-5.27)[79–81]; by contrast, DPB1*02:01 and DPB1*03:01 might be protective[79,81]. Patients with PR3-AAV who express DPB1*04:01 — particularly homozygotes — might be at higher risk of relapse than patients with other HLA alleles[80]. Three GWAS have shown strong links between PR3-AAV and SNPs in the HLA-DP region[76,82,83]. The strongest association is with the rs3117242 SNP in European patients with PR3-AAV [76], an association that was replicated in a case control study of Chinese patients with GPA (80% of whom were cANCA-positive)[84]. A 2013 GWAS mapped the most significant SNP to HLA-DPB1*04[82], while a 2017 study identified positive associations between PR3-AAV and SNPs within the HLA-DPB1 region, including rs141530233 [83]. A comparison of HLA-DP expression levels on B cells and monocytes from healthy donors carrying the risk allele (rs141530233) or protective allele (rs1042169), demonstrated that individuals who carried the risk allele had lower expression of HLA-DP than those who carried the protective allele. Furthermore, individuals with lower expression of HLA-DP had higher proportions of complementary PR3 (cPR3) peptide-specific CD4+ T cells, suggesting that reduced HLA-DP expression results in decreased thymic deletion of these autoreactive T cells[83]. PR3-AAV has also been associated with other HLA-DR alleles (Supplementary Table 3). Of these, the most pronounced seems to be the risk effect of DRB1*15 in African-Americans, with DRB1*15:01 having the capacity to bind both PR3 and cPR3 peptides[85].

Compared to PR3-AAV, fewer HLA-association studies have been performed for MPO-AAV, with the literature comprising several case-control studies in Asian populations (where MPO-AAV is significantly more common than PR3-AAV), and two GWAS in European cohorts. DRB1*09:01 is consistently and positively associated with MPO-AAV in Japanese

populations[86–89], whereas DRB1*11:01 conferred risk in a Chinese population[90]. GWAS have also shown association between MPO-AAV and HLA-DQ, including variants in DQA1 and DQB1[76,83]; associations with variants in DQA2 have also been reported.

The HLA associations in EGPA are distinct from those associated with MPO-AAV and PR3-AAV, providing a genetic basis for classifying EGPA as a separate disease entity. The HLA-DRB4 gene (which encodes the HLA-DRB4 chain and determines the DR53 serotype) was associated with an increased risk of EGPA in both genetic association studies dedicated to this disease[91,92]. Furthermore, a correlation was reported between DRB4 frequency and the number of vasculitic manifestations[91]. Positive associations with EGPA were specifically reported for DRB1*04 and DRB1*07, which are alleles in strong linkage disequilibrium with DRB4[91,92], whereas a protective effect was reported for DRB1*13 and DRB3[91,92]. In light of the clear association between HLA-DP and PR3-AAV, Wieczorek et al. also examined DP alleles in EGPA, but found no association[92].

IgA Nephropathy and Henoch-Schönlein Purpura

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide, and is characterized by hematuria and histologically by mesangial proliferative glomerulonephritis with mesangial IgA deposition. A small proportion of patients present with acute, rapidly progressive glomerulonephritis. The pathogenesis of IgAN is thought to involve dysregulation of mucosal immunity, which facilitates the production of poorly glycosylated IgA1. The resultant galactose-deficient IgA1 acts as an autoantigen, leading to immune complex formation, deposition in the glomerular mesangium and glomerular injury[93,94].

Strong epidemiological evidence, including familial aggregation of cases and geographic variability in disease prevalence and phenotype [95,96], supports a genetic basis for IgAN, although epidemiological studies have historically been hampered by the phenotypic heterogeneity of IgAN and potential inaccuracy in case ascertainment[96]. Early (serological) HLA association studies reported a number of different risk associations in both class I HLAs (for example, HLA-B27 and HLA -B35)[97–99] and class II (that is, in HLA-DR1, -DR4, -DQ4)[97,99–105]. With the exception of DR4, which has been repeatedly observed in Japanese cohorts[99–104], there was little uniformity in the findings. Supplementary Table 4 describes all reported HLA associations in IgAN.

GWAS over the past 8 years have identified several susceptibility loci, of which the HLA region has emerged as the strongest signal[106–109], with HLA-DQ being particularly important. Other non-HLA genes within the MHC region are also associated with IgAN, including interferon-regulated genes involved in antigen degradation and processing[107]. In one study of patients of European ancestry with biopsy-proven IgAN, the strongest SNP associations were localized to HLA-DQ, with the imputed alleles DQB1*05:01 and DQB1*02:01 exerting risk and protective effects respectively[106]. A combined GWAS of Han Chinese and European populations similarly localized the most significant SNPs to the DQB1 region, with DQB1*06:02 identified as a protective allele[107]. HLA-DQ associations were also identified in two subsequent GWAS: DQB1*03:02 conferred risk of IgAN in Han Chinese[109] whereas in a cohort of European and Han Chinese patients, Kiryluk et al. confirmed a protective effect of DQB1*02:01[108]. The DQA1 locus has also been associated with IgAN, and like DQB1 seems to confer both risk (DQA1*01:01) and protective (DQA1*01:02) influences[108,109].

In light of the phenotypic heterogeneity of IgAN, HLA correlations have been examined in the context of stable and progressive disease, with varying results. In Japanese cohorts, DR4 has been linked with both disease progression[102], and with a favorable clinical course[100]. In a 1995 study, Raguenes et al. associated DQB1*03:01 with aggressive disease[110]; 9 years later, Kiryluk et al. reported the SNP rs7763262 (in the region of HLA-DQ and DR) to be

associated with the greatest risk of progression[108]. The geographical patterns of genetic risk and the association of environmental risk factors for IgAN, such as helminth diversity with the frequency of HLA and other risk alleles [108] supports a pathogenic model of IgAN in which mucosal infection and inflammation contribute to the synthesis of poorly-galactosylated IgA1, with the risk of subsequent autoimmunity being modulated by the HLA repertoire.

Studies focusing on Henoch–Schönlein purpura (HSP; also known as IgA vasculitis) have uncovered a range of HLA associations, some of which overlap with those linked to IgAN. HLA-B35 was reported as conferring risk for HSP in Turkish[111] and Han Chinese populations[112], and has also been associated with IgAN in both European and Asian patients[98,99]. HLA-A11, a risk allele for HSP in Turkish and Mongolian cohorts, has also been linked to IgAN[109]. HLA-DRB1*01 is the most commonly reported class II HLA associated with HSP[113–115], with DRB1*01:03 identified as the specific risk allele in a Spanish population[115]. A protective effect of DRB1*07 in HSP has also been repeatedly reported in European cohorts[113,114,116]. The HLA-DQ associations with IgAN have not, however, been described in HSP, potentially related to differences in the ethnicity of different cohorts studied.

Lupus nephritis

SLE is the prototypic multisystem autoimmune disease; it is characterized by a strong female predominance, complement activation and the presence of circulating and tissue deposited immune complexes. The kidney is a major target in SLE with lupus nephritis being a leading cause of morbidity and mortality. Considerable evidence supports a genetic component in SLE: although the majority of SLE heritability is attributed to non-HLA genes, important HLA associations have been identified[117]. For example, the DR3–DQ2, DR15(2)–DQ6(1) and DR8–DQ4 haplotypes contribute to the risk of developing SLE. These risk haplotypes are approximately twice as common among patients with SLE as compared with healthy controls[118]. A sequencing analysis of the HLA region in patients with LN and healthy controls[119] identified several HLA risk variants associated with LN, including amino acid variations in HLA-DRB1 at position 11, DQB1 at position 45, DPB1 at position 76 and HLA-A at position 156. Other studies have compared HLA associations in patients with biopsy-proven LN to those of SLE patients without LN. One study showed that HLA-DQB1 alleles in linkage disequilibrium with DR15 were predictive of LN, whereas DR4 was protective[120]. In a multiethnic US cohort, DRB1*15:03 was a risk factor for new or worse proteinuria, whereas DRB1*02:01 was protective[121,122]; by contrast, in an Italian cohort, HLA-DR3 conferred risk and DR15 and DQA1 alleles interacted in modulating risk or protection from LN[123]. Interestingly, a study of patients with chronic kidney disease of various etiologies found the rs2187668 SNP, which maps to DQA1 and confers a higher risk of membranous nephropathy, to be also over-represented in patients with LN[124].

Meta-analyses have also examined HLA determinants in LN susceptibility. One meta-analysis[125] of three GWAS that compared HLA associations in European women with SLE with and without LN, found an association of HLA-DR3 with LN, with links to DR15 falling short of statistical significance. Another meta-analysis of case-controlled studies focussed on HLA-DR in LN[126]. The researchers identified a number of HLA-DR alleles associated with the risk of and protection from SLE and LN, with the greatest magnitude of effects identified for DR3 and DR15 (as risk allomorphs) and DR4 and DR11 (as protective allomorphs).

HLA transgenic lupus prone mice have provided mechanistic insights into HLA-mediated susceptibility and protection in LN. A study of LN-prone NZM2328 mice engineered to express HLA-DR3 (DRB1*03:01) and deficient in mouse MHC II, showed they developed proteinuria at an earlier age than NZM2328 mice that expressed both HLA-DR3 and intact mouse MHC II, with a higher proportion exhibiting renal wire loop, vasculitic and crescentic

lesions[127]. Most patients with LN have both anti-dsDNA and anti-Sm antibodies[128]; in this study, NZM2328.DR3-transgenic mice spontaneously developed both anti-dsDNA and anti-Sm antibodies only when deficient in murine MHC II[127]. These findings suggest that mouse MHC II alleles confer dominant resistance to the HLA-DR3-mediated development of anti-Sm auto-antibodies in NZM2328 mice, possibly through the generation of anti-Sm specific Treg cells, in a manner similar to that mediated by HLA-DR1 in anti-GBM disease[11].

Tubulointerstitial nephritis and uveitis

Tubulointerstitial nephritis and uveitis (TINU) is a rare syndrome characterized by the presence of both tubulointerstitial nephritis and uveitis, though some patients present with uveitis or tubulointerstitial nephritis alone. It is most commonly diagnosed in adolescents, and patients can present with impaired kidney function; the development of chronic kidney disease is not unknown. TINU is probably an autoimmune disease and tends to respond to corticosteroids. Histologically, it is characterized by tubulointerstitial edema and a dense interstitial lymphocytic infiltrate, with some plasma cells and eosinophils. Documented HLA associations in TINU include the HLA-DRB1*01–DQA1*01–DQB1*05– haplotype (DR1–DQ5)[129]. Two studies in which patients underwent extended HLA-DR1 typing reported that the majority carried the DRB1*01:02 allele[129,130]. HLA typing of patients with only uveitis suggests that DRB1*01:02 is particularly associated with the uveitis component of TINU[130]. In a Finnish cohort, the associations were somewhat different, with DQA1*04:01, DQB1*04:02 (DQ4) and DRB1*08 (DR8) being implicated[131].

HLA and other renal diseases

In addition to autoimmune diseases, HLA types are also associated with susceptibility to various infectious diseases, probably by influencing the strength and direction of immune responses. For example, chronic Hepatitis B infection, an ongoing major global health problem, is associated with HLA-DQ and -DP allomorphs[132]. Furthermore, HLA associations have been described for kidney diseases that have traditionally been considered non-immune, but that are now recognized as having marked inflammatory components. The mechanisms that might underpin these HLA associations are unclear, assuming that the associations are not confounded by non-HLA genetic polymorphisms within the MHC region.

Infection-related glomerulonephritis and sepsis-induced acute kidney injury

Various infections can cause glomerulonephritis, either through the formation of in situ immune complexes in response to planted (or potentially endogenous) glomerular antigens, through T cell reactivity to these antigens and/or through the deposition of circulating immune complexes. Classical experimental studies suggest that the intensity and direction of the immune response helps determine the nature and severity of glomerular injury[133]. Cohorts of patients with biopsy-proven hepatitis B-associated membranous nephropathy suggest an increased frequency of DQB1*03:03 (DQ9), DQB1*06:03 (DQ6) and DRB1*15:01 alleles, probably not related to an increased risk of chronic hepatitis B infection itself[134–136]. Interestingly the study that implicated DRB1*15:01 in hepatitis B-associated membranous nephropathy also found DRB1*15:02 to be associated with hepatitis B-associated membranoproliferative glomerulonephritis[137], consistent with subtle differences in HLA influencing immunity and thus the pattern of injury. With one possible exception[138], studies have not shown an association between HLA class I molecules with hepatitis B-related membranous nephropathy.

Hepatitis C infection results in cryoglobulinemic vasculitis in a minority of individuals, with a membranoproliferative pattern of glomerular involvement. Although HLA-DR3 has been implicated in hepatitis C-related cryoglobulinemic vasculitis[139], results have been inconsistent when comparing hepatitis C infected individuals with and without cryoglobulinemia. A

GWAS found a potential association of HLA-DRB1 and/or DQA1 with hepatitis C-related cryoglobulinemia, but noted that the SNP was located in an intronic region of the MHC Class III gene *NOTCH4*[140], potentially implicating this non-HLA gene in this complication of hepatitis C.

Findings from studies of HLA associations with post-streptococcal glomerulonephritis (PSGN) have also been inconsistent. Associations with HLA-B12 (the serotype of the B44 and B45 groups of alleles), DRB1*03, the DRBl*13:02–DQA1*01:02–DQB1*06:04 haplotype, and with alleles encoding HLA-DP5 have been described[141–143]. Although some of these studies were in pediatric populations, in whom PSGN is more likely to be a sole contributor to the glomerular lesion, the now recognized overlap between PSGN and C3 glomerulopathy has potential to complicate these findings. Acute kidney injury (AKI) is relatively common complication of systemic sepsis, resulting from effects of the pathogen itself or to the body's response to infection. One study that examined the relationship between HLA-DR and AKI found no association in early AKI, but reported that individuals with four HLA-DR alleles (that is, those individuals expressing two further DR alleles of DRB3, DRB4 or DRB5) had a higher risk of receiving early renal replacement therapy than those who expressed fewer than four HLA-DR alleles[144].

Minimal change disease and primary focal and segmental glomerulosclerosis

Minimal change disease (MCD) and primary focal and segmental glomerulosclerosis (FSGS) are characterized by heavy proteinuria, with evidence of both immune dysfunction and podocyte vulnerability. Most cases of adult disease are biopsy-proven, whereas in children the conditions are defined syndromically according to their responsiveness to corticosteroids. Studies of HLA in pediatric patients with steroid sensitive nephrotic syndrome (SSNS) date back to 1980, with the identification of HLA-DR7 as a risk factor[145,146] — a finding that was supported by further studies[147]. Other studies of SSNS have identified an association with HLA-DQ[148], with DQ2[149], whereas DR2 (DR15–DR51) might be protective[147]. The largest GWAS of childhood SSNS[150] identified a significant association at the HLA-DQA1 locus; the strongest associations involved missense variants that resulted in impaired or aberrant HLA-DQ assembly, leading to the hypothesis that antigen presentation might in some way be impaired[151]. Another potentially important finding in that study was the presence of rare variants in *PLCG2* which encodes phospholipase C**γ**2, a signaling molecule that is found both in T cells[152] and in cells with high MHC II expression, including dendritic cells and B cells[153,154]. Of interest, abnormal *PLCG2* function is associated with immune abnormalities in both humans and mice[154–156]. Defining the functional relationship between HLA-DQ and *PLCG2* may help elucidate the mechanisms that underpin immune dysregulation in SSNS.

Alport Syndrome

Mutations in genes encoding the **α**3, **α**4 or **α**5 chains of type IV collagen disrupt the formation of **α**3**α**4**α**5 trimers, giving rise to Alport syndrome and thin basement membrane nephropathy[42]. Alport syndrome is characterised by haematuria, proteinuria, progressive renal impairment, sensorineural deafness and ocular abnormalities. Most cases of Alport syndrome arise from X-linked inheritance of *COL4A5* mutations, with other cases resulting from autosomal inheritance of mutations in *COL4A3* and *COL4A4* on chromosome 2[42]. Two groups have evaluated HLA in Alport syndrome, and found associations with HLA-DR2 and DRB1*16[157,158]. The underlying mechanism for HLA associations in this essentially non-immune disease, however, remains unexplained.

Diabetic kidney disease

Diabetic kidney disease (DKD) is associated with the autoimmune disease T1DM or the metabolic disease type 2 diabetes mellitus (T2DM), and is one of the most common causes of

renal disease worldwide. T1DM has clear HLA associations[38], and in comparisons with healthy populations, HLA risk alleles for T1DM are likely to also be present in patients with T1DM-associated DKD. Some studies have found no relationship between HLA and the risk of diabetic complications[159,160]. Other reports, some of which controlled for disease duration and focusing on the HLA-DR3 and DR4 allomorphs a priori, have implicated them variably as susceptibility or protective factors in overt DKD or microalbuminuria[161–164]. In a large, phenome-wide association study (PheWAS) the HLA-DRB1*04 and DQB1*03:02 alleles, found in the DR4–DQ8(3) risk haplotype, were associated with both TIDM itself and DKD[163]. However, when compared with the presence of the disease itself, the odds ratio for both DQ8 and DR4 were substantially higher for both acute and chronic complications of T1DM, suggesting that disease severity, age of onset or disease duration contribute to the association of these HLAs with DKD. HLA-A2 has been associated with the development of microalbuminuria in T1DM[165]. HLA associations have been variably reported with DKD in patients with T2DM. Indigenous Canadians with T2DM who carry HLA-A2 with either HLA-DR4 or HLA-DR8 develop ESRD at a younger age than those who carry other HLA types, possibly reflecting differences in the severity or age of onset of T2DM[166]. In a Mexican population with T2DM, HLA-DRB1*15:02 was associated with DKD, and in an American Indigenous population with T2DM, the DRB1*04:07 allele was associated with protection[167]. DQB1*05:01 may be protective in Han Chinese with T2DM[168]. These findings highlight some of the complexity in assessing the potential role of HLA in DKD, with contributions from ethnicity and in the case of T1DM the autoimmune basis of the underlying disease. Further complicating analyses of HLA in DKD is the role of proteins that exist in linkage disequilibrium with HLA. Many of these proteins, including RAGE and TNF are also associated with complications of diabetes mellitus, including DKD[169].

Drug-induced renal disease

ADRs are relevant to the kidney in terms of being a target of drug-induced damage and in mediating the toxic effects of drugs such as allopurinol. Although type A ADRs **[G]** can be predicted based on the drug's mechanism of action, type B ADRs are idiosyncratic. Type B ADRs are often immune-mediated, often in a CD8+ or CD4+ cell-mediated, delayed type hypersensitivity-like manner. An increasing body of evidence indicates that HLA molecules are not only associated with Type B ADRs, but are also involved mechanistically[170].

Indeed, HLA allotypes have been directly implicated in a number of ADRs. A broad array of HLA–drug associations exist across HLA Class I and HLA Class II molecules, involving many commonly prescribed drugs and antibiotics. A number of theories have been postulated to explain the mechanisms underlying these HLA–drug associations, including direct haptenation of the drug to the peptide–HLA complex, as well as the 'p-i concept' in which the drug bridges the interface between the TCR and peptide–MHC complex, thereby activating T cells bearing TCRs that would ordinarily be non-reactive[170]. Arguably, the best understood example of HLA involvement in ADRs is the association of HLA-B*57:01 with hypersensitivity reactions in patients taking the anti-retroviral drug, abacavir. Abacavir sits deep within the C-terminal end of the antigen-binding cleft of the B*57:01 molecule, thereby altering the repertoire of self-peptides that this HLA molecule presents[49]. The co-binding of abacavir, with the consequent altered self-peptide repertoire presented by HLA-B*57:01 in essence creates an 'altered self', resulting in the ensuing peptide–drug–HLA complex being identified as foreign and inducing an ADR. This association was very specific for HLA-B*57:01, as very closely related HLA allomorphs, including B*57:03 (which differ only by a few residues) were incapable of binding abacavir[49]. Accordingly, tissue typing for HLA-B*57:01 is now recommended for individuals with HIV infection being considered for abacavir therapy. However, more work is required to understand the mechanistic bases underpinning other HLA–drug associations.

Beyond abacavir, reports from the past couple of years have implicated other drugs (such as doxofylline)[171], drug-like molecules (such as 3-formylsalicylic acid and 2-hydroxy-1-naphthaldehyde)[171] and contact sensitizers (such as urushiol and house dust mite-derived phospholipase)[172,173] in association with MHC I-like molecules, including those of the CD1 and MR1 family, which present lipids and vitamin B metabolites, respectively, to other types of T cells, including innate-like natural killer T cells and mucosal-associated invariant T cells. However, this area of research is very germinal and requires further investigation.

The mechanism of HLA associations with drug-induced kidney disease are currently unknown; however, HLA associations for Type B ADRs exist for a number of drugs that induce immune-mediated kidney injury, including allopurinol, sulphonamides, NSAIDs, penicillins, penicillamine and gold sodium thiomalate[170]. The association between allopurinol hypersensitivity and HLA-B*58:01 was initially identified in a Han Chinese population[174] and subsequently confirmed as having a gene dosage effect in other ethnicities [175]. Interestingly the risk of severe reactions is increased in individuals with renal impairment. $CD8^+$ T cells from HLA-B*58:01 positive individuals respond to allopurinol in vitro, regardless of whether the T cells were derived from individuals with allopurinol hypersensitivity or allopurinol naïve patients[176]. Interestingly, compared to allopurinol, T cell responses were stronger to oxypurinol, which is the major allopurinol metabolite[176,177] that accumulates in patients with renal impairment, suggesting a mechanistic link between kidney disease itself and HLA-mediated drug toxicity.

HLAs are also associated with the development of drug-induced kidney injury. Penicillins and penicillamine, for example, can haptenate endogenous proteins. The association of penicillin with interstitial nephritis has been linked to HLA-A2 and -DR52, whereas the association of penicillamine with membranous nephropathy and less commonly, with ANCA-associated vasculitis, has been linked to HLA-B8, -DR1 and -DR3[170,178,179]. Gold sodium thiomalate also causes membranous nephropathy and is similarly associated with HLA-B8, -DR1 and -DR3, as well as DQA1*0501[180,181]; interestingly, some of these associations have been reported in patients with ‘primary’ anti-PLA2R1-mediated membranous nephropathy.

HLA and disease-independent risk of ESRD

Several reports have examined possible associations between HLA types and ESRD[182–184]. Most of these studies have studied waitlisted candidates for renal transplantation, in relatively homogeneous ethnic populations. Although underpowered, most of these studies have not defined significant associations to date no consistent HLA associations with ESRD itself have been identified. Of note, studies of the association of HLA types with ESRD might be confounded by the presence of HLA associations with individual diseases. In addition to describing associations between the HLA-DRB1*04 and DQB1*03:02 alleles and DKD, the large PheWAS discussed earlier also reported an association between DQB1*03:02 and kidney transplantation (OR 1.4), which was potentially related to the increased risk of T1DM, and DKD (OR 7.1) observed for this allele[163]. Some reports suggest that some HLA types can affect the severity of kidney disease or risk of progression independent of disease aetiology. Although this hypothesis remains to be adequately tested, our current understanding of the mechanisms of HLA and of disease progression suggest that it is the influence of HLA on the individual underlying conditions causing kidney disease that mediates its involvement in progressive renal disease. Nonetheless, particular HLA types could promote, for example, a more generalized pro-fibrogenic T cell phenotype, which might contribute to disease onset or disease progression.

Conclusions

The development and evolution of genetic and molecular typing technologies and better case ascertainment has enabled detailed examination, and in many cases definition of HLA associations in a variety of kidney diseases. The field continues to evolve, both with the recognition of epistasis between variants of autoantigens and HLA, and with growing understanding of the mechanisms that underpin the associations between HLA and disease. These findings have several implications that are highly relevant to disease. Some autoimmune renal diseases have characteristics that render them suitable archetypal autoimmune diseases for the study of HLA, having the potential to define fundamental disease biology with wide applicability. In diseases where pathogenesis remains uncertain, for example, minimal change disease, discoveries in the HLA field might help define disease mechanisms. Insights from HLA studies can also aid disease diagnosis and classification, for example by strengthening the notion that PR3-AAV and MPO-AAV are distinct entities on the basis of their different HLA associations. HLA-based identification of subgroups of individuals at risk of disease progression might therefore in the future form part of risk stratification algorithms.

Arguably the most important area of disease management that would be affected by greater mechanistic understanding of the relationships between susceptibility and protective HLA allomorphs is in the development of new and more targeted therapies. Current treatments for immune kidney disease are not only of limited efficacy, but also lack specificity, being associated with substantial adverse immune and metabolic adverse effects. Improved understanding of the relationships between the TCR, HLA and the process of antigen presentation and recognition at a peptide and structural level will aid the development of new tolerogenic therapies, including peptide immunotherapies, peptide complexed nanoparticles and cell therapy using antigen and peptide specific Treg cells. Such treatments, especially when combined judiciously with conventional or new anti-inflammatory agents, have the potential to restore tolerance and perhaps even effect a cure. The field of HLA biology in kidney disease progressed substantially from the first description of the association of HLA allomorphs with renal disease. The future promises much, with the evolution of understanding not only of HLA itself, but its relationship with antigenic peptide, and more critically, the responses via the TCR, of the responding T cells.

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Author Contributions

K.J.R and A.R.K conducted literature searches, researched data and selected relevant articles; K.J.R., J.D.O and A.R.K. planned the format of the article; K.J.R., J.D.O., S.R.H., J.R. and A.R.K. wrote the article; and K.J.R and A.R.K reviewed, edited and finalized the article for submission.

Competing Interests

The authors declare no competing interests.

Databases

IPD-IMGT/HLA database (https://www.ebi.ac.uk/ipd/imgt/hla/)

HLA alleles, proteins and nomenclature (http://hla.alleles.org)

GWAS catalogue (https://www.ebi.ac.uk/gwas/)

pheWAS resources (https://phewascatalog.org/)

Immune Epitope Database (http://www.iedb.org/)

The Systemic Atlas (https://systemhcatlas.org)

Key Points

The HLA, which is the most polymorphic region of the human genome, is associated with various kidney diseases; some of these diseases are immune-mediated whereas in others the pathogenesis is uncertain, or the relevance of HLA is less clear

Advances in molecular techniques and the use of model systems have helped define the mechanistic basis of HLA associations, and in some instances have epistatically linked HLA to other genes

The characteristics of some renal diseases potentially enable them to serve as archetypes for the study of HLA associations in other conditions.

Exactly how HLA facilitates the development of immune kidney diseases at the level of HLA–peptide–T cell receptor interactions is a fundamental research question; mechanistic insights will have. clear translational implications for the development of more targeted therapies.

Box 1: HLA typing methods and nomenclature

Understanding HLA nomenclature and typing methods is important in interpreting studies of the association between HLA and kidney disease, particularly given that HLA typing methods have evolved substantially over the past few years. Progress has in part been driven by the transplantation field. Here, the potential antigenicity of polymorphisms throughout the HLA molecule is relevant as the HLA allomorphs themselves serve as alloantigens. This contrasts with autoimmunity, where HLA polymorphisms in the peptide-binding groove and in potential T cell receptor contacts are most relevant. Information on HLA nomenclature, alleles and proteins can be accessed via the IPD-IMGT/HLA database (https://www.ebi.ac.uk/ipd/imgt/hla/) and at HLA alleles, proteins and nomenclature (http://hla.alleles.org)[185]. A brief description of the main HLA typing methodologies are outlined as follows:

HLA serotyping

Serotyping was the first method of HLA typing, and uses antibodies that recognize HLA complexes on the cell surface. Improvements in serotype definitions over time resulted in nomenclature changes. For example, DQ1 was "split" into two serotypes, DQ5 and DQ6.

HLA haplotypes.

Linkage disequilibrium within the HLA region (excluding DP) results in the generation of haplotypes that are commonly among populations. An example of this is the so-called 8.1 ancestral haplotype, which includes HLA-A1, HLA-Cw7, HLA-B8, HLA-DR17(3), HLA-DR52, HLA-DQ2. This strong linkage disequilibrium in the HLA region can complicate analyses of disease susceptibility, for example in defining associations between HLA-DR and -DQ.

PCR based identification.

A variety of PCR-based methods have been developed using probes that can identify specific HLA types with varying resolution. With the advent of the molecular characterization of HLA alleles, the nomenclature evolved to reflect the individual **α** chains for HLA Class I molecules (and both **α** and **β** chains for HLA Class II molecules), and the increasing number of alleles that were being defined.

Genome-wide association studies (GWAS)

Single nucleotide polymorphism (SNP) array data spanning the whole genome are used to impute individual HLA types (or regions) via SNPs situated close to HLA allelic regions. Some studies have confirmed HLA associations by targeted PCR-based HLA based typing. GWAS databases exist that can be interrogated for HLA alleles and disease, for example, the GWAS catalogue (https://www.ebi.ac.uk/gwas/)

Phenome-wide association studies (PheWAS)

This technique uses similar SNP and imputation techniques to GWAS but examines the effects of one or a limited number of variants in multiple phenotypes (see for example, pheWAS resources https://phewascatalog.org/)

Next generation sequencing (NGS), including whole exome (WES) or whole genome sequencing (WGS)

NGS, involving parallel sequencing of millions of small DNA fragments, enables rapid HLA Class I and Class II typing, including the identification of rare variants. These techniques, often performed as part of WES (which involves sequencing of all the coding regions of DNA) or WGS (involving sequencing of the complete genome) are becoming established approaches to determine the HLA allelic makeup of an individual.

Box 2: Methodologies for dissecting mechanisms of HLA's involvement in disease

Peptide display

Intracellular processing of antigens generates a limited number of peptide sequences. Given that an individual HLA allomorph does not bind every peptide that is generated, it is important to identify HLA–peptide pairings to investigate association with disease. Although predictive algorithms such as those used by the Immune Epitope Database (http://www.iedb.org/) are useful, it is now possible to identify and quantify the peptidome presented by different HLA types, for example using unbiased assessment of HLA-bound peptides by mass spectrometry[186] as described in the Systemic Atlas (https://systemhcatlas.org).

HLA-peptide tetramers/multimers

Although critically important in immune responses, antigen-specific T cells exist at low frequencies and can be difficult to identify. Conventional flow cytometry reagents will not identify antigen-specific T cells; however, multimeric clusters of HLA–peptide complexes generated using fluorochrome-labelled HLA have increased binding avidity to T cell receptors meaning that T cells as rare as 1–5 per million can be identified, phenotyped and isolated. HLA class I–peptide multimers are readily available; HLA Class II–peptide multimers are more difficult to synthesize and are not as widely available.

Structural Biology

If immunodominant T cell epitopes are known or suspected, modelling can be used to suggest peptide–MHC structures. However, crystallography is needed to accurately and definitively determine the structure of HLA–peptide–TCR complexes.

HLA transgenic humanized mice

These humanized mice carry HLA molecules (Class II or Class I), usually of a single type and replacing the binding component of the corresponding mouse MHC molecules at a minimum. The selection of CD4+ or CD8+ T cells and activation of the corresponding T cell repertoire is therefore determined by interactions between HLA and mouse peptides. If mouse and human antigens are homologous (for example, in the case of **α**3(IV)NC1) the system can be used to discover immunodominant epitopes and to define mechanisms of autoimmune disease. If the target mouse antigen is very different to the human antigen, human transgenes can be introduced, although care must be taken to preserve fidelity of expression.

Figure **1. Basic biology of the HLA. a** A simplified diagram of the human MHC locus, focusing on HLA loci known to be directly involved in antigen presentation, with examples of non-classical HLA gene loci and Class III genes. **b** Basic format of HLA Class I and Class II complexes. The Class I HLA-A, B and C molecules consist of three **α** chains encoded by one allele, complexed with **β**2-microglobulin. The peptide binding groove is formed by the **α**1 and **α**2 chains and the molecule is anchored to the cell membrane by the **α**3 chain. The class II HLA-DR, DQ and DP molecules are heterodimers of two **α** chains encoded by one allele and two **β** chains by another. The peptide binding groove is formed by the **α**1 and **β**1 chains. **c** Simplified basic HLA nomenclature, using HLA-DR15 as an example. The simplest terminology describes HLA types determined by serology. Molecular typing allows the allele group and particular protein to be specified and extended descriptors indicate synonymous variants (that is, variants that do not result in a change in the amino acid sequence) and documentation of changes in non-coding regions. The letters at the end of the final field that indicate changes in expression are not depicted. **d** Examples of the structures of complexes comprising the MHC class I and peptide; MHC class II and peptide; CD8+ TCR, peptide and MHC class I; and CD4+ TCR, peptide and MHC class II. The view from above shows the peptide binding in the peptide binding pockets in the groove formed by the **α**1 and **α**2 chains (Class I) and **α**1 and **β**1 chains (Class II). The side views depict HLA–peptide complexes with TCRs contacting the landscape formed by the composite of HLA surface residues and outwardly oriented regions of the peptide. The TCR contacts are formed by hypervariable complementarity-determining regions with the variable domains of the TCR **α** and TCR **β** chains. Structures for HLA Class I molecules were defined by MacDonald et al.[187] and for HLA Class II by Broughton et al.[188]. Jan Petersen, Monash University, is thanked for contributing the graphic shown in Fig. 1c.

Figure **2. Sites of actions of HLA class I and II within the immune system in autoimmune and renal disease. a** Interactions between peptide–HLA complexes on thymic epithelial cells and dendritic cells and T cell receptors (TCR) define the T cell repertoire via positive and negative selection of T cells in the thymus. **b** HLA within secondary lymphoid organs, such as the spleen (shown as an example) and lymph nodes, maintain tolerance but also induce autoreactive T cell responses. Not only does HLA Class II mediate the generation of effector CD4+ T cells, HLA Class II molecules are critical for autoantibody formation by generating T follicular helper cells (TFHs). These T cells promote the activation of antigen specific autoreactive B cells. Tconv, conventional T cell; TCR, T cell receptor; Th1, T helper 1 cell; Th17, T helper 17 cell; Treg cell, regulatory T cell.

Figure **3. Sites of actions of HLA II within the kidney.** The expression of Class II is complex and varies between the glomerulus and the tubulointerstitium, and in normal and in inflammatory states. **a** In health, a network of Class II expressing interstitial dendritic cells and macrophages survey the environment and have a number of roles, including presentation of filtered self-peptides to help maintain tolerance. In the glomerulus, Class II expression is less prominent with some expression on intrinsic glomerular cells, and on patrolling monocytes, as well as intravascular B cells (not shown). Dendritic cells are rare in normal glomeruli. **b**. In severe glomerular disease, Class II is upregulated on intrinsic renal cells, and infiltrating mononuclear phagocytes, with Class II expressed on intravascular monocyte mediating antigen specific effector $CD4^+$ cell activation. In the diseased interstitium, a variety of Class II expressing cells may be important. Recruited monocytes differentiate into Class II expressing inflammatory dendritic cells and macrophages, B cells form aggregates and present their own antigen effectively to $CD4^+$ T cells and tubular cells may acquire a proinflammatory phenotype. HLA Class I is ubiquitously expressed by nucleated cells and mediates the local cytotoxic and proinflammatory effects of CD8+ cells (not shown). BCR, B cell receptor; DC, dendritic cell, Treg, regulatory T cell.

Figure 4. Mechanisms of HLA-mediated risk and protection. Positive and negative selection in the thymus, mediated by thymic epithelial cells and dendritic cells results in T cell repertoires that are shaped by interactions between HLA–self-peptide complexes and T cell receptors (TCR). **a** The immunodominant CD4+ T cell epitope in Goodpasture's disease, $\boldsymbol{\alpha}3_{135–145}$, binds to the risk HLA-DR15 and dominantly protective HLA-DR1 allomorphs in different registers, resulting in the preferential generation of conventional T cells (Tconv cells) in the context of DR15 and regulatory T cells (Treg cells) by DR1. In the context of the other genetic and environmental factors that cause Goodpasture's disease, HLA-DR15+ humans and transgenic mice are at risk of activation, expansion and differentiation of $\boldsymbol{\alpha}3_{135–145}$-specific Tconv cells into T follicular helper (TFH) cells, T helper (Th1) cells and T_H17 cells, which are essential for autoantibody production and that serve to effect injury locally in the kidney. In humans and mice expressing HLA-DR1, antigen specific Treg cells react with DR1-$\boldsymbol{\alpha}3_{135–145}$ and dominantly protect those with DR15 from developing disease. **b** In abacavir-induced hypersensitivity syndrome, abacavir binds specifically to the peptide binding groove of HLA-B*57:01, altering how self-peptides are presented by HLA-B*57:01 and converting some non-self-reactive CD8+ T cells to cells with 'auto-reactive' TCRs. CD8+ cells acquire effector functions and mediate abacavir hypersensitivity syndrome.

Table 1. Conventional HLA types and their characteristics

HLA type	Structure	Serological nomenclature	Other features
HLA Class I: HLA–peptide complexes that bind to CD8+ T cells			
HLA-A	Heterodimer: β2 microglobulin with highly polymorphic α chain. The α chain encompasses the peptide binding cleft and potential TCR contacts	In most cases serological numbering tends to equate to allelic nomenclature	None
HLA-B	As for HLA-A	In most cases serological numbering tends to equate to allelic nomenclature	Some HLA-B serotypes are listed as "Bw", referring to shared motifs (eplets) that are recognized by alloantibodies
HLA-C	As for HLA-A	Listed as Cw, to avoid confusion with complement components and other proteins	None
HLA Class II: HLA–/peptide complexes that bind to CD4+ T cells			
HLA-DR	Invariant α chain that forms the peptide binding cleft with highly polymorphic β chain	Serology largely, but not always follows β chain nomenclature (in the case of the DRB1 chain that is always present). DRB3, DRB4 and DRB5 are represented by serologically defined DR52, DR53 and DR51, respectively	Some haplotypes include a further DR type encoded by a DRB3, DRB4 or DRB5 chain, often expressed at lower levels
HLA-DQ	Heterodimer: formed by polymorphic α and β chains	Serological nomenclature usually references the β chain. Some β chains form functional HLA proteins with more than one different α chain, resulting in serological subtypes (eg DQ2.2, 2.3, 2.5)	Strong linkage disequilibrium between HLA-DR and -DQ regions
HLA-DP	Heterodimer: formed by polymorphic α and β chains	Serological nomenclature usually references the β chain.	Less strong linkage disequilibrium with other HLA components due to position nearer the centromere and recombination hotspot between HLA-DQ and -DP

Table 2: Key HLA associations with kidney disease

Locus/Allele	Serological equivalent	Previous equivalents	Disease	Nature of association[a]	Refs
HLA Class I					
A2	A2	NA	Diabetic Nephropathy	Risk (+)	165,166
			Penicillin-associated AIN	Risk (++)	170
A*11:01	A11	NA	IgAN	Risk (+)	109
B8	B8	NA	Penicillamine/Gold-associated MN	Risk (++)	181,189
B35	B35	NA	IgAN, HSP	Risk (+)	99
HLA-DR					
DRB1*01:01	DR1	DRw1	Goodpasture's Disease	Dominant protection	16,52
DRB1*01:02	DR1	DRw1	TINU	Risk (+)	129,130
DR3	DR3	DRw3	Penicillamine/Gold-associated MN	Risk (++)	180,181,189
DRB1*03:01	DR17(3)	DR3	Lupus Nephritis	Risk (++)	119
			MN	Risk (+++)	19,21,190,191
DRB1*04	DR4	DRw4	Diabetic Nephropathy	Risk (++)	163,166,167
			IgAN	Risk (++)	99–104,192
			Goodpasture's Disease	Risk (+)	16,18,54
DR7	DR7	DRw6	Steroid sensitive nephrotic syndrome	Risk (+)	139–141
DRB1*07:01	DR7	DRw6	Goodpasture's Disease	Dominant protection	16,52,53
DRB1*09:01	DR9	DRw9	MPO-AAV	Risk (+)	86–89
		DRw9	Goodpasture's Disease	Protection	55
DRB1*11:01	DR11(5)	DR5	MPO-AAV	Risk (+)	89,90
DRB1*15	DR15(2)	DR2b, Dw2	Lupus Nephritis	Risk (+)	122
DRB1*15	DR15(2)	DR2b, Dw2	PR3-AAV	Risk (++)	193
DRB1*15:01	DR15(2)	DR2b, Dw2	Goodpasture's Disease	Risk (+++)	16–18,52–55,57,194
			MN (incl. Hepatitis B-associated)	Risk (++)	19,20,137,195
HLA-DQ					
DQA1	NA	NA	Lupus Nephritis	Risk (+)	123
			MCD/FSGS	Risk (+)	148,150
DQA1*05:01[b]	DQ5(1)	DQ1	MN	Risk (++)	21,22,67–70,190
			Penicillamine/Gold-associated MN	Risk (++)	180

DQA2[c]	NA	NA	MPO-AAV	Risk (+)	76,83
DQB1	NA	NA	MPO-AAV	Risk (+)	83,88
DQB1*02:01	DQ2	DQB2	MN	Risk (++)	21,190
DQB1*03:01	DQ7(3)	DQw7, DQ3	IgAN	Risk (++)	108,196,197
DQB1*03:02	DQ8(3)	DQ3	Diabetic Nephropathy	Risk (++)	163
HLA-DP					
DPA1	NA	NA	IgAN	Protection	107
DPB1*04:01[d]	DPw4	DPB4.1, DPw4a	Goodpasture's Disease	Protection	56
			PR3-AAV	Risk (+++)	79–81,83,84

[a]Risk effects categorized as + to +++ estimated on the basis of number and size of studies, consistency of association and odds ratio. AAV: ANCA-associated vasculitis; AIN: Allergic interstitial nephritis; FSGS: Focal and segmental glomerulosclerosis; HSP: Henoch-Schönlein Purpura; IgAN: IgA nephropathy; MCD: Minimal change disease; MN: Membranous nephropathy ('primary'/anti-PLA2R antibody positive MN unless otherwise stated); NA, not applicable; TINU: Tubulointerstitial nephritis & uveitis. [b] Studies denoting specific association with DQA1*05:01 are refs 21,180,190; other studies quoted localize only to DQA1. [c] Merkel et al. 2017 (ref. 83) localizes to DQA2, Lyons et al. 2012 (ref. 76) only to DQ. [d] Studies denoting specific association with DPB1*04:01 are refs 56,79–81; Merkel et al. 2017 (ref. 83) and Wu et al. 2017 (ref. 84) localize only to DPB.

Glossary:

Self-peptides

Peptides derived from endogenous (host) proteins that are often displayed on HLA Class I and II.

CD8+ T cells

T cells that recognize peptide/HLA class I complexes. When activated they can induce target cell death and produce proinflammatory cytokines.

CD4+ T cells

T Cells that recognize peptide/HLA class II complexes. They direct immune responses as T helper cells or maintain tolerance and regulate responses as regulatory T cells.

Non-self peptides

Peptides derived from foreign proteins, such as microbial pathogens that are often displayed on HLA Class I and II.

Polymorphisms

A polymorphism is a DNA sequence variation within an allele that can result in a different gene product.

Haplotype

A group of alleles on the same chromosome that are commonly inherited as a unit.

Linkage disequilibrium

The non-random association of alleles at two different loci, such that the observed population frequency of the allele combination exceeds that expected by chance.

8.1 ancestral haplotype: Also known as the HLA-A1-B8-DR3-DQ2 haplotype, the 8.1 ancestral haplotype is common in European populations, most likely due to common ancestral descent inherited in linkage disequilibrium.

Clonotypic

In the context of the T cell receptor, a clonotype describes the unique combination of nucleotide sequences that exists after gene rearrangement.

Allomorph

The unique HLA molecule arising from one (Class I) or two (Class II) particular alleles.

Variable domain

The **αβ** T cell receptor is made up of **α** and **β** chains each with constant and variable domains. With genetic recombination, the variable domain is highly diverse, ensuring a very broad repertoire of different T cell receptors.

T cell cross-reactivity

The capacity of a T cell, via its T cell receptor, to recognize more than one peptide-MHC complex.

Alloreactivity

Cellular or humoral reactivity to antigens, for example HLA, not present in the particular individual but expressed by other individuals of the species.

Biased TCR usage

A phenomenon whereby, despite the diversity of the T cell receptor repertoire, there is preferential use of a limited number of T cell receptors in an immune response.

Dominantly protective allele

An HLA allele that confers protection from the specified disease even in the presence of a co-inherited risk allele.

Epitope spreading

The broadening of an immune response involving reactivity to not only the initial focused epitope but other epitopes on the same or a different protein.

Peptide binding register

The particular amino acid sequence of a peptide that binds to the peptide-binding groove of the MHC.

Immunodominant peptide epitopes

T cell responses are usually specific for one or only a few epitopes within a particular antigen, referred to as immunodominant.

Epitope capture

A process whereby a high-affinity peptide that binds to one HLA molecule preferentially, effectively limits the binding to another HLA allomorph with a lower affinity for the same or similar peptide.

Shared epitope

Refers to a sequence motif at amino acids 70–74 of the HLA-DR **β** chain that is shared by HLA alleles implicated in rheumatoid arthritis and found in the majority of individuals with this disease.

Citrullination

The post-translational modification of proteins via the conversion of arginine to citrulline. Reactivity to these altered self proteins is common in rheumatoid arthritis.

Epistasis

Interactions between different genetic loci that potentially impact on phenotype in health or disease.

Molecular mimicry

A phenomenon whereby a pathogen-derived peptide sufficiently similar to a self-peptide can induce loss of tolerance.

Type B adverse drug reactions (ADRs)

Type B ADRs are less common than Type ADRs, tend to be idiosyncratic and unpredictable, and are often immune-mediated.

DNASTAR Jameson-Wolf method

A computer algorithm that uses a primary amino acid sequence to predict the structural features of a protein and its potential antigenic determinants.

Phenome-wide association study (PheWAS)

A study that examines the effects of one or a limited number of genetic variants in multiple phenotypes.

Type A ADRs

Type A adverse drug reactions (ADRs) can be predicted on the basis of the drug's pharmacological properties and mechanism of action.

Delayed type hypersensitivity

A cell-mediated effector immune response, occurring 24 hours to several days after antigen re-exposure.

Haptenation

The process whereby a small molecule (hapten) such as a drug or drug metabolite binds covalently to an endogenous peptide or protein that is itself not usually antigenic. The resultant complex can elicit an immune response.

P-i concept

The p-i (or ‘pharmacological interaction with immune receptors) concept describes a non-covalent, reversible interaction between a drug and the MHC at the surface of an immune cell.