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, have 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. Allomorphs of HLA have emerged as important risk factors in most immune-mediated renal diseases, which, together with other genetic and environmental factors, 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 the 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.

INTRODUCTION

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 favoured 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 is the aberrant recognition of self-peptides by TCRs, leading to the development of autoimmune disease. The risk associated with such misidentification 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 class 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 be more common 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 past 10 years, 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[4,5,6] and is not discussed here.

FUNDAMENTAL APSECTS 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. The combination of the peptide and the MHC complex is recognized by the TCR. This specific recognition is a central tenet of antigen specificity, which itself is 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, HLA-B and HLA-C alleles) and the MHC class II genes (in humans, the HLA-DR, HLA-DP and HLA-DQ genes) (Figure 1a). HLA class I molecules are composed of a single α-chain that is non-covalently bound to β_2-microglobulin, with the α1 and α2 segments of the α-chain forming the peptide-binding cleft. By contrast, MHC class II molecules consist of both an α-chain and a β-chain, with the α1 and β1 segments forming the peptide-binding cleft (Figure 1b). The α-chain of HLA-DR is essentially invariant, but functionally relevant polymorphisms exist in both the α-chains and β-chains for HLA-DQ and HLA-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, HLA-DP and HLA-DQ. HLA-DM is important in the loading of peptides into MHC class II whereas HLA-DO is a negative regulator of HLA-DM. Other MHC class I genes include the largely monomorphic HLA-E, HLA-F and HLA-G genes, which interact with natural killer (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 class III region, which includes genes that encode complement components, heat shock protein 70 (HSP70), tumour necrosis factor (TNF) and receptor for advanced glycosylation end products (RAGE; also known as AGER).

These and other non-MHC class I and MHC class II genes within the MHC region have important biological functions in immune and non-immune 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, HLA-B, HLA-C, HLA-DR, HLA-DQ and HLA-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, HLA-B and HLA-C proteins and 5,355 different HLA-DR, HLA-DQ and HLA-DP proteins were known to exist, derived from polymorphisms in the HLA-A, HLA-B, HLA-C, HLA-DRA, HLA-DRB, HLA-DQA, HLA-DQB, HLA-DPA and HLA-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. Therefore, it is likely that this highly polymorphic and polygenic system evolved to favour 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 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 3D architecture, differences exist within their peptide antigen-binding clefts. Namely, the amino termini and carboxyl termini of MHC class I molecules are 'pinched off', favouring the binding of shorter-length peptides (fewer than ten 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 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 composed 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 (Figure 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 harness these mechanisms holds promise for the future, including the development of diagnostics centred on TCR repertoire usage and precision medicine approaches.

HLA typing and nomenclature

Changes to HLA nomenclature and methods for HLA typing have 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-chains 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[14] (Figure 1d). 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, HLA-B and HLA-C) and HLA class II proteins (HLA-DR, HLA-DQ and HLA-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 secretory phospholipase A2 receptor (PLA2R) and anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis) have a clear immunological basis[15] and fairly logical potential mechanisms by which different HLA types might modify disease risk. In other kidney conditions, including end-stage renal disease (ESRD) in general, linkage disequilibrium with other inflammation-related genes in the MHC class 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 disease conferred by the expression of HLA-DR15)[16,17,18], they can also differ (as reported for HLA risk alleles in the context of membranous nephropathy)[19,20,21,22]. Of note, in addition to changes in HLA nomenclature and HLA typing methods (Box 1), changes in diagnostic criteria and classification of kidney diseases have 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 naive T cells or maintain them in a quiescent state (Figure 2). Kidney disease can arise from the effects of HLA in the lymphoid organs or in the kidney. Naive $CD4^+$ 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 helper 1 (T_H1) and T helper 17 (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[23,24,25] (Figure 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 autoantigens. 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 class II and are prominent in the tubulointerstitium[26,27]. MHC class II is also present on B cells and tubular epithelial cells in the tubulointerstitium. In glomeruli, MHC class 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 class 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 that express MHC class II[31,32].

Under physiological conditions, MHC class II expression by tubular cells and perhaps intrinsic glomerular cells might help to maintain peripheral tolerance but might exert pro-inflammatory effects under certain conditions[33,34,35]. Thus, in addition to the effects of HLA in lymphoid organs, it is plausible that different 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 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 in which 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 disease, proteinase 3 ANCA-associated vasculitis (PR3-AAV), myeloperoxidase (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 to or protect against 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[3,11,37,39,40,41]. 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, affect 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 the 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 disease is a useful prototypic model for mechanistic studies of renal autoimmune disease owing to the presence of a dominant autoantigen (non-collagenous domain of the α3 chain of type IV collagen (α3(IV)NC1)) with defined T cell and B cell epitopes, high sequence homology between human and mouse α3(IV)NC1, strong positive (HLA-DR15) and dominant-negative HLA associations (HLA-DR1 and HLA-DR7) and clear diagnostic criteria[16,42]. Loss of tolerance to α3(IV)NC1 and the development of Goodpasture disease has been studied in HLA-DR transgenic mice lacking murine MHC class II, 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 HLA-DRB1*15:01 (HLA-$DR15^+$) or HLA-DRB1*01:01(HLA-$DR1^+$) or both HLA-DRB1 alleles (HLA-$DR15^+DR1^+$). Consistent with sentinel studies in humans[45], an epitope derived from α3(IV)NC1, $α3_{135–145}$(mouse $α3_{136–146}$), was established as the critical and disease-inducing epitope in disease-sensitive HLA-$DR15^+$ mice. However, in the presence of the dominantly protective HLA-DR1 allele, the $α3_{135–145}$ 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 HLA-DR15[11,44] (Figure 4a).

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 induction of epitope-specific regulatory T (T_{reg}) cells. In HLA transgenic mice and in humans, dominant protection against autoreactivity to α3(IV)NC1 is dependent on polymorphisms that distinguish HLA-DR15 and HLA-DR1 and affect the presentation of the $α3_{135–145}$ epitope, causing a shift in the binding register[11]. The structure of the HLA-DR15 and HLA-DR1 peptide-binding pockets changes the presentation of $α3_{135–145}$ to $CD4^+$ T cells, leading to fundamental differences in their associated TCR repertoires and phenotype. Indeed, $α3_{135–145}$-specific $CD4^+$ cells in naive mice and in healthy humans show pro-inflammatory capacities in the context of HLA-DR15 but generate predominantly T_{reg} cells in the context of HLA-DR1 (Figure 4a). The power of antigen-specific T_{reg} cells in inducing tolerance was demonstrated by in vitro findings in humans and mice and by in vivo findings in mice, showing that T_{reg} cells generated in response to HLA-DR1 presentation of $α3_{135–145}$ 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 HLA-

DQ8 in T1DM, with studies in diabetes-prone non-obese diabetic mice implicating T_{reg} 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 PLA2R are epistatically linked to HLA. In addition, applying concepts explored 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, HLA-DRB1*04:04 and HLA-DRB1*01:01[47]. Citrullination of endogenous peptides promoted by cigarette smoking modifies the binding of peptides to HLA-DRB1*04:01 and HLA-DRB1*04:04 (but not the protective HLA-DRB1*04:02 allele) and stimulates autoreactive T cells[37]. In multiple sclerosis, studies have defined functional epistasis between HLA-DR15 and HLA-DR51. The HLA-DRB1*15:01 and HLA-DRB5*01:01 alleles are in almost complete linkage disequilibrium: HLA-DR51 modifies the strong pro-inflammatory effects of HLA-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 HLA-DR51 might in the past have increased survival following infection with particular life-threatening pathogens, through effective control of the infection (via HLA-DR15-mediated immunity) together with HLA-DR51–peptide interactions regulating the response to prevent lethal pro-inflammatory responses. These interactions might explain the strong linkage disequilibrium between HLA-DR15 and HLA-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], which are discussed below (Figure 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 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 (α1–6)[42]. The presence of autoantibodies to the α3 chain of collagen IV results in Goodpasture disease, which is characterized by rapidly progressive glomerulonephritis and pulmonary haemorrhage. Both antibody production and cellular immunity are important in the pathogenesis of Goodpasture 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 disease is among the strongest reported for an autoimmune disease[16].

The first association of Goodpasture 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 disease has since been demonstrated in several studies of European populations. The reported association between HLA-DQB1*06:02 and Goodpasture disease is due to linkage disequilibrium between HLA-DQB1*06:02 and HLA-DR15[52,53,54,55]. A meta-analysis in 1999 confirmed a strong association between HLA-DRB1*15:01 and Goodpasture disease (OR 8.5) and identified a weaker positive association with HLA-DRB1*04[16]. Conversely, HLA-DR1, HLA-DR7[16] and possibly HLA-DPB1*04:01[56] confer a dominantly protective effect. More recently, studies of Japanese and Chinese populations have replicated the HLA-DR15 association[17,18,57]. The most recent of these also described a protective effect of HLA-DRB1*09:01 in a Han Chinese population[57]. HLA associations reported in Goodpasture disease are described in Supplementary Table 1. The coexistence of anti-GBM antibodies and MPO-ANCA in some individuals with Goodpasture 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 HLA-DR15 and HLA-DR1 confer susceptibility to and protection against Goodpasture 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 α3(IV)NC1[16] is supported by structural and functional data using the immunodominant T cell epitope $\alpha3_{135-145}$ [44,45], which showed that polymorphic differences in HLA-DR15 and HLA-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, this disease is characterized by the presence of subepithelial 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 PLA2R, which is constitutively expressed at low levels on normal podocytes[60]. Circulating anti-PLA2R autoantibodies and PLA2R 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 protein 7A, was subsequently identified in a proportion of patients with idiopathic membranous nephropathy who are anti-PLA2R-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 HLA-DR3 association and identified HLA-DQA1 as a susceptibility factor[66]. The first genome-wide association study (GWAS) of membranous nephropathy and subsequent molecular typing studies identified HLA-DQA1 as the dominant risk locus[22,67,68,69,70], 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 (HLA-DR3) and HLA-DQA1*05:01–HLA-DQB1*02:01 (HLA-DQ2) associations represent a risk haplotype for membranous nephropathy[21]. Studies 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 disease[16]. Two studies of Chinese individuals published in 2017 identified a strong link between membranous nephropathy and HLA-DRB1*15:01[19,20], supporting earlier reports of a strong association between this disease and HLA-DR15 in Japanese populations (as HLA-DR2, the original serotype that included HLA-DR15)[71,72,73]. Ethnic differences in HLA associations in membranous nephropathy might reflect different background allele frequencies and/or indicate varying underlying disease mechanisms.

SNPs in the PLA2R locus on chromosome 2q24 have also been associated with an increased risk of developing membranous nephropathy. Interestingly, inheritance of both the HLA-DQA1 and PLA2R risk alleles synergistically increases the risk of membranous nephropathy (OR 7.3–79.4), suggesting functional epistasis between HLA class II molecules and PLA2R[21,22,67,68,69,70]. Although the mechanisms that underpin the HLA associations with membranous nephropathy remain unclear, the combination of risk variants in HLA and PLA2R 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 PLA2R 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 PLA2R, at least in the context of HLA-DR3 and HLA-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 membranous nephropathy than the leading PLA2R SNP[22].

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

ANCA-associated vasculitis

The 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 GPA (EGPA; also known as Churg–Strauss syndrome)[74,75]. The majority of people with GPA have ANCA specific for PR3 and a cytoplasmic ANCA (cANCA) pattern on imaging by indirect immunofluorescence, whereas most people with 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 to 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 HLA-DPA1–HLA-DPB1 heterodimer known as HLA-DP4, was associated with an increased risk of PR3-AAV in three European studies (OR 3.38–5.27)[79,80,81]; by contrast, HLA-DPB1*02:01 and HLA-DPB1*03:01 might be protective[79,81]. Patients with PR3-AAV who express HLA-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-AAV76, 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], whereas 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 HLA-DRB1*15 in African Americans, with HLA-DRB1*15:01 having the capacity to bind both PR3 and cPR3 peptides[85].

Compared with PR3-AAV, fewer HLA association studies have been performed for MPO-AAV, with the literature comprising several case–control studies in Asian populations (in which MPO-AAV is more common than PR3-AAV) and two GWAS in European cohorts. HLA-DRB1*09:01 is consistently and positively associated with MPO-AAV in Japanese populations[86,87,88,89], whereas HLA-DRB1*11:01 conferred risk in a Chinese population[90]. GWAS have also shown association between MPO-AAV and HLA-DQ, including variants in HLA-DQA1 and HLA-DQB1[76,83]; associations with variants in HLA-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 HLA-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 HLA-DRB4 frequency and the number of vasculitic manifestations[91]. Positive associations with EGPA were specifically reported for HLA-DRB1*04 and HLA-DRB1*07, which are alleles in strong linkage disequilibrium with HLA-DRB4[91,92], whereas a protective effect was reported for HLA-DRB1*13 and HLA-DRB3[91,92]. In light of the clear association between HLA-DP and PR3-AAV, Wieczorek et al. also examined HLA-DP alleles in EGPA but found no association[92].

Immunoglobulin A nephropathy and Henoch–Schönlein purpura

Immunoglobulin A (IgA) nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. IgAN is characterized by haematuria 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)[97,98,99] and class II HLAs (that is, in HLA-DR1, HLA-DR4 and HLA-

DQ4)[97,99,100,101,102,103,104,105]. With the exception of HLA-DR4, which has been repeatedly observed in Japanese cohorts[99,100,101,102,103,104], 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[106,107,108,109], 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 HLA-DQB1*05:01 and HLA-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 HLA-DQB1 region, with HLA-DQB1*06:02 identified as a protective allele[107]. HLA-DQ associations were also identified in two subsequent GWAS: HLA-DQB1*03:02 conferred risk of IgAN in Han Chinese patients[109], whereas in a cohort of European and Han Chinese patients, Kiryluk et al. confirmed a protective effect of HLA-DQB1*02:01[108]. The HLA-DQA1 locus has also been associated with IgAN and, similar to HLA-DQB1, seems to confer both risk (HLA-DQA1*01:01) and protective (HLA-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, HLA-DR4 has been linked with both disease progression[102] and a favourable clinical course[100]. In a 1995 study, Raguenes et al. associated HLA-DQB1*03:01 with aggressive disease[110]; 9 years later, Kiryluk et al. reported the SNP rs7763262 (in the region of HLA-DQ and HLA-DR) to be associated with the greatest risk of progression[108]. Regarding insights into the pathogenesis of IgAN, geographical variations in HLA risk allele frequency are associated with local environmental risk factors for IgAN, such as helminth diversity[108]. This observation supports a disease model in which mucosal infection and inflammation contribute to the synthesis of poorly galactosylated IgA1 and the risk of subsequent autoimmunity is modulated by the HLA repertoire.

Studies focusing on Henoch–Schönlein purpura (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 of Henoch–Schönlein purpura 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 Henoch–Schönlein purpura 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 Henoch–Schönlein purpura[113,114,115], with HLA-DRB1*01:03 identified as the specific risk allele in a Spanish population[115]. A protective effect of HLA-DRB1*07 in Henoch–Schönlein purpura has also been repeatedly reported in European cohorts[113,114,116]. The HLA-DQ associations with IgAN have not, however, been described in Henoch–Schönlein purpura, potentially related to differences in the ethnicity of the 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 HLA-DR3–HLA-DQ2, HLA-DR15(2)–HLA-DQ6(1) and HLA-DR8–HLA-DQ4 haplotypes contribute to the risk of developing SLE. These risk haplotypes are approximately twice as common among patients with SLE as in healthy controls[118]. A sequencing analysis of the HLA region in patients with lupus nephritis and healthy controls[119] identified several HLA risk variants associated with lupus nephritis, including amino acid variations in HLA-DRB1 at position 11, HLA-DQB1 at position 45, HLA-DPB1 at position 76 and HLA-A at position 156. Other studies have compared HLA associations in patients with biopsy-proven lupus nephritis to those of patients with SLE without lupus nephritis. One study showed that HLA-DQB1 alleles in linkage disequilibrium with HLA-DR15 were predictive of lupus nephritis, whereas HLA-DR4 was protective[120]. In a multiethnic US cohort, HLA-DRB1*15:03 was a risk factor for new or worse proteinuria, whereas HLA-DRB1*02:01 was protective[121,122]; by contrast, in an Italian cohort, HLA-DR3 conferred risk and HLA-DR15 and HLA-DQA1 alleles interacted in modulating risk or protection from lupus nephritis[123]. Interestingly, a study of patients with chronic kidney disease of various aetiologies found the rs2187668 SNP, which maps to HLA-DQA1 and confers a higher risk of membranous nephropathy, to also be over-represented in patients with lupus nephritis[124].

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

HLA transgenic lupus-prone mice have provided mechanistic insights into HLA-mediated susceptibility and protection in lupus nephritis. A study of lupus-nephritis-prone NZM2328 mice engineered to express HLA-DR3 (HLA-DRB1*03:01) and deficient in mouse MHC class II showed they developed proteinuria at an earlier age than NZM2328 mice that expressed both HLA-DR3 and intact mouse MHC class II, with a higher proportion exhibiting renal wire loop, vasculitic and crescentic lesions[127]. Most patients with lupus nephritis have both anti-double-stranded DNA (dsDNA) and anti-Smith antigen (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 class II[127]. These findings suggest that mouse MHC class II alleles confer dominant resistance to the HLA-DR3-mediated development of anti-Sm autoantibodies in NZM2328 mice, possibly through the generation of anti-Sm-specific T_{reg} 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, although some patients present with uveitis or tubulointerstitial nephritis alone. This syndrome 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 oedema and a dense interstitial lymphocytic infiltrate, with some plasma cells and eosinophils. Documented HLA associations in TINU include the HLA-DRB1*01–HLA-DQA1*01–HLA-DQB1*05 haplotype (HLA-DR1–HLA-DQ5)[129]. Two studies in which patients underwent extended HLA-DR1 typing reported that the majority carried the HLA-DRB1*01:02 allele[129,130]. HLA typing of patients with only uveitis suggests that HLA-DRB1*01:02 is particularly associated with the uveitis component of TINU[130]. In a Finnish cohort, the associations were somewhat different, with HLA-DQA1*04:01, HLA-DQB1*04:02 (HLA-DQ4) and HLA-DRB1*08 (HLA-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 HLA-DP allomorphs[132]. Furthermore, HLA associations have been described for kidney diseases that have traditionally been considered non-immune but 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 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 HLA-DQB1*03:03 (HLA-DQ9), HLA-DQB1*06:03 (HLA-DQ6) and HLA-DRB1*15:01 alleles, probably not related to an increased risk of chronic hepatitis B infection itself[134,135,136]. Interestingly the study that implicated HLA-DRB1*15:01 in hepatitis-B-associated membranous nephropathy also found HLA-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 and hepatitis-B-related membranous nephropathy.

Hepatitis C infection results in cryoglobulinaemic vasculitis in a minority of individuals, with a membranoproliferative pattern of glomerular involvement. Although HLA-DR3 has been implicated in hepatitis C-related cryoglobulinaemic vasculitis[139], results have been inconsistent when comparing hepatitis C-infected individuals with and without cryoglobulinaemia. A GWAS found a potential association of HLA-DRB1 and/or HLA-DQA1 with hepatitis C-related cryoglobulinaemia 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 HLA-B44 and HLA-B45 groups of alleles), HLA-DRB1*03, the HLA-DRB1*13:02–HLA-DQA1*01:02–HLA-DQB1*06:04 haplotype and with alleles encoding HLA-DP5 have been described[141,142,143]. Although some of these studies were in paediatric 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 the potential to complicate these findings. Acute kidney injury (AKI) is a fairly 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 HLA-DR alleles of HLA-DRB3, HLA-DRB4 or HLA-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 paediatric 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] and with HLA-DQ2 [149], whereas HLA-DR2 (HLA-DR15–HLA-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 Cγ2, a signalling molecule that is found both in T cells[152] and in cells with high MHC class 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[154,155,156]. 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 α3, α4 or α5 chain of collagen IV disrupt the formation of α3α4α5 trimers, giving rise to Alport syndrome and thin basement membrane nephropathy[42]. Alport syndrome is characterized 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 HLA-DRB1*16[157,158]. However, the underlying mechanism for HLA associations in this essentially non-immune disease 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 HLA-DR4 allomorphs a priori, have implicated them variably as susceptibility or protective factors in overt DKD or microalbuminuria[161,162,163,164]. In a large, phenome-wide association study (PheWAS), the HLA-DRB1*04 and HLA-DQB1*03:02 alleles, found in the HLA-DR4–HLA-DQ8(3) risk haplotype, were associated with both T1DM itself and DKD[163]. However, when compared with the presence of the disease itself, the odds ratio for both HLA-DQ8 and HLA-DR4 was 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 HLA-DRB1*04:07 allele was associated with protection[167]. HLA-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 can be predicted on the basis of 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 carboxy-terminal end of the antigen-binding cleft of the HLA-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 HLA-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 class I-like molecules, including those of the CD1 and MHC class I-related gene protein (MR1) family, which present lipids and vitamin B metabolites, respectively, to other types of T cells, including innate-like NK 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 is currently unknown; however, HLA associations for type B ADRs exist for a number of drugs that induce immune-mediated kidney injury, including allopurinol, sulfonamides, nonsteroidal anti-inflammatory drugs (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-naive patients[176]. Interestingly, compared with 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. For example, penicillins and penicillamine can haptenate endogenous proteins. The association of penicillin with interstitial nephritis has been linked to HLA-A2 and HLA-DR52, whereas the association of penicillamine with membranous nephropathy and, less commonly, with AAV has been linked to HLA-B8, HLA-DR1 and HLA-DR3[170,178,179]. Gold sodium thiomalate also causes membranous nephropathy and is similarly associated with HLA-B8, HLA-DR1 and HLA-DR3 as well as with HLA-DQA1*0501[180,181]; interestingly, some of these associations have been reported in patients with ‘primary’ anti-PLA2R-mediated membranous nephropathy.

HLA and disease-independent risk of ESRD

Several reports have examined possible associations between HLA types and ESRD[182,183,184]. Most of these studies have studied waitlisted candidates for renal transplantation in fairly homogeneous ethnic populations. Although underpowered, most of these studies have not defined significant associations and 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 HLA-DQB1*03:02 alleles and DKD, the large PheWAS discussed earlier also reported an association between HLA-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 in which pathogenesis remains uncertain (for example, MCD), 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 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 in the development of new tolerogenic therapies, including peptide immunotherapies, peptide complexed nanoparticles and cell therapy using antigen and peptide-specific T_{reg} 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 also of its relationship with antigenic peptide and, more crucially, the responses via the TCR of the responding T cells

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.

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 pro-inflammatory 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 T_{reg} 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 owing to common ancestral descent inherited in linkage disequilibrium.

Clonotypic
In the context of the TCR, 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 TCR 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 TCRs.

T cell cross reactivity
The capacity of a T cell, via its TCR, 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 TCR repertoire, there is preferential use of a limited number of TCRs 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 not only to the initial focused epitope but also to 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 a similar peptide.

Shared epitope
Refers to a sequence motif at amino acids 70–74 of the HLA-DR 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 affect 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 A 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 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.

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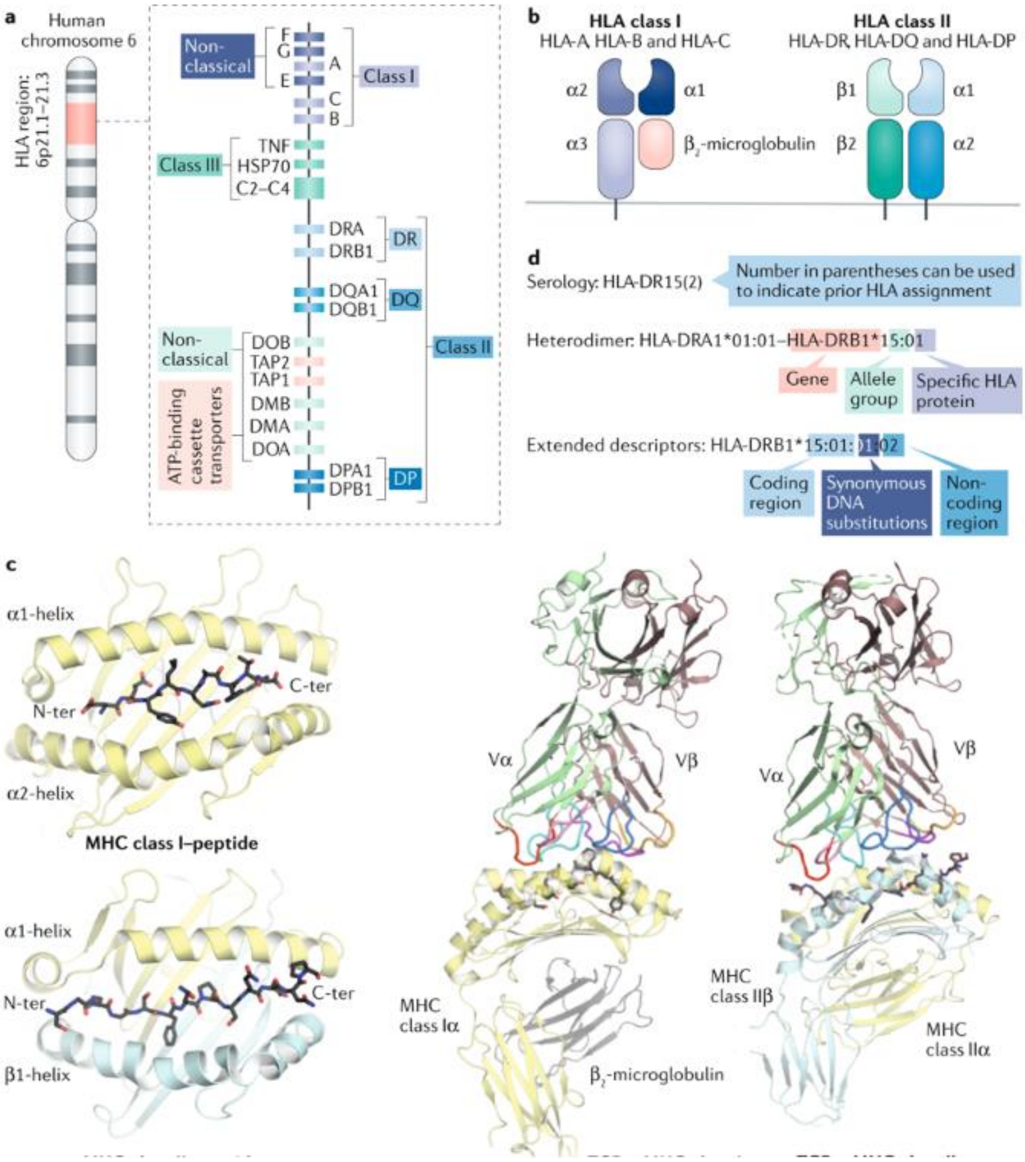
Figure 1



a | A simplified diagram of the human major histocompatibility complex (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.

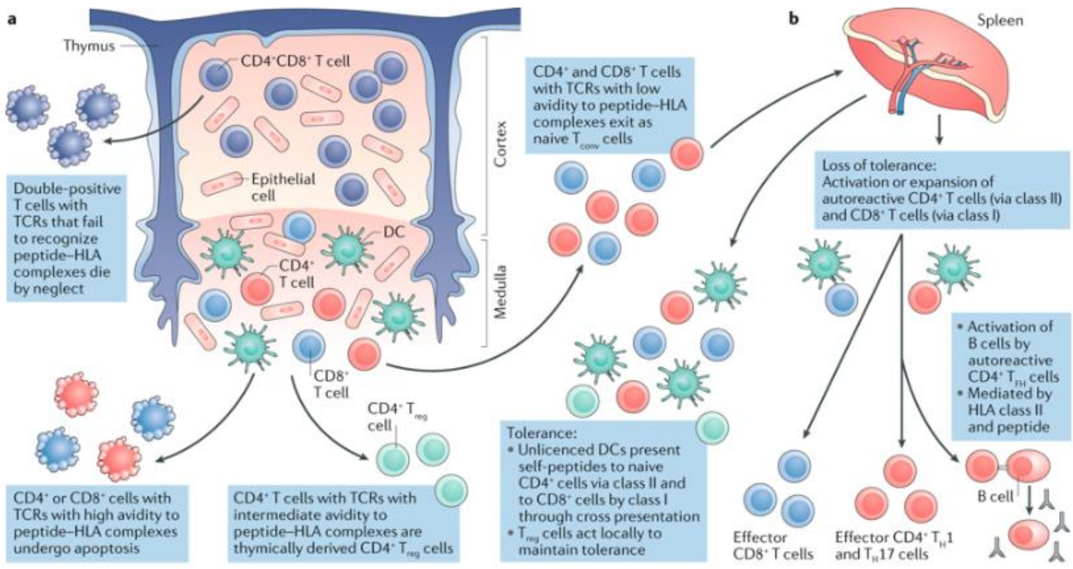
b | Basic format of HLA class I and class II complexes. The class I HLA-A, HLA-B and HLA-C molecules consist of three α-chains encoded by one allele and complexed with β_2-microglobulin. The peptide-binding groove is formed by the α1 and α2 chains, and the molecule is anchored to the cell membrane by the α3 chain. The class II HLA-DR, HLA-DQ and HLA-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 α1 and β1 chains.

c | Examples of the structures of complexes comprising the MHC class I and peptide; MHC class II and peptide; $CD8^+$ T cell receptor (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 α1 and α2 chains (class I) and α1 and β1 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 TCRα and TCRβ chains. Structures for HLA class I molecules were defined by MacDonald et al.[187] and for HLA class II by Broughton et al.[188].

d | 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. C-ter, carboxyl terminus; HSP70, heat shock protein 70; N-ter, amino terminus; pMHC, peptide MHC; TNF, tumour necrosis factor.

Part **c** courtesy of J. Petersen, Monash University, Australia.

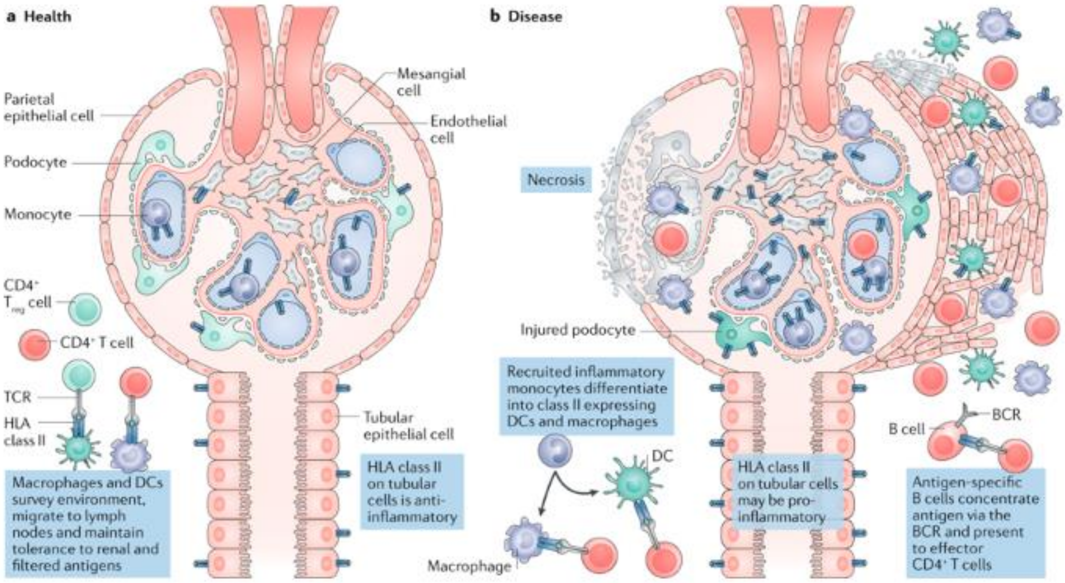
Figure 2



a | Interactions between peptide–HLA complexes on thymic epithelial cells and dendritic cells (DCs) and T cell receptors (TCRs) define the T cell repertoire via positive and negative selection of T cells in the thymus.

b | HLAs within secondary lymphoid organs, such as the spleen (shown as an example) and lymph nodes, maintain tolerance but also induce autoreactive T cell responses. In addition to mediating the generation of effector CD4$^+$ T cells, HLA class II molecules are critical for autoantibody formation by generating T follicular helper (T_{FH}) cells. These T cells promote the activation of antigen-specific autoreactive B cells. T_{conv} cell, conventional T cell; T_H1 cell, T helper 1 cell; T_H17 cell, T helper 17 cell; T_{reg}cell, regulatory T cell

Figure 3

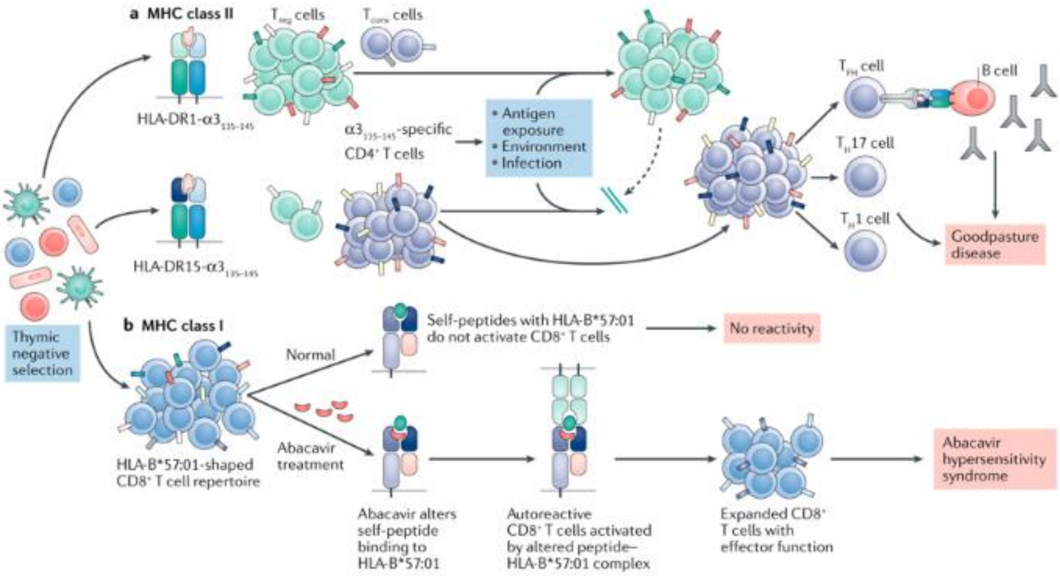


The expression of HLA class II is complex and varies between the glomerulus and the tubulointerstitium and in normal and inflammatory states.

a | In health, a network of HLA class II-expressing interstitial dendritic cells (DCs) and macrophages survey the environment and have a number of roles, including presentation of filtered self-peptides to help maintain tolerance. In the glomerulus, HLA 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). DCs are rare in normal glomeruli.

b | In severe glomerular disease, HLA class II is upregulated on intrinsic renal cells and infiltrating mononuclear phagocytes, with HLA class II expressed on intravascular monocytes mediating antigen-specific effector $CD4^+$ cell activation. In the diseased interstitium, a variety of HLA class II-expressing cells may be important. Recruited monocytes differentiate into HLA class II-expressing inflammatory DCs and macrophages, B cells form aggregates and present their own antigen effectively to $CD4^+$ T cells and tubular cells may acquire a pro-inflammatory phenotype. HLA class I is ubiquitously expressed by nucleated cells and mediates the local cytotoxic and pro-inflammatory effects of $CD8^+$ T cells (not shown). BCR, B cell receptor; TCR, T cell receptor; T_{reg} cell, regulatory T cell.

Figure 4



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 (TCRs).

a | The immunodominant CD4$^+$ T cell epitope in Goodpasture disease, $\alpha 3_{135-145}$, binds to the risk HLA-DR15 and dominantly protective HLA-DR1 allomorphs in different registers, resulting in the preferential generation of conventional T (T_{conv}) cells in the context of HLA-DR15 and regulatory T (T_{reg}) cells by HLA-DR1. In the context of the other genetic and environmental factors that cause Goodpasture disease, HLA-DR15$^+$ humans and transgenic mice are at risk of activation, expansion and differentiation of $\alpha 3_{135-145}$-specific T_{conv} cells into T follicular helper (T_{FH}) cells and T helper 1 (T_H1) and 17 (T_H17) cells, which are essential for autoantibody production and serve to effect injury locally in the kidney. In humans and mice expressing HLA-DR1, antigen-specific T_{reg} cells react with HLA-DR1 $\alpha 3_{135-145}$ and dominantly protect those with HLA-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 ‘autoreactive’ TCRs. CD8$^+$ T cells acquire effector functions and mediate abacavir hypersensitivity syndrome. MHC, major histocompatibility complex.

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: β_2-microglobulin with highly polymorphic α-chain; the α-chain encompasses the peptide-binding cleft and potential T cell receptor 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 the highly polymorphic β-chain	Serology largely, but not always, follows β-chain nomenclature (in the case of the HLA-DRB1 chain that is always present); HLA-DRB3, HLA-DRB4 and HLA-DRB5 are represented by serologically defined HLA-DR52, HLA-DR53 and HLA-DR51, respectively	Some haplotypes include a further HLA-DR type encoded by an HLA-DRB3, HLA-DRB4 or HLA-DRB5 chain, often expressed at lower levels
HLA-DQ	Heterodimer: formed by polymorphic α-chains 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 (for example, HLA-DQ2.2, HLA-DQ2.3 and HLA-DQ2.5)	Strong linkage disequilibrium between HLA-DR and HLA-DQ regions
HLA-DP	Heterodimer: formed by polymorphic α-chains and β-chains	Serological nomenclature usually references the β-chain	Less strong linkage disequilibrium with other HLA components owing to position nearer the centromere and recombination hot spot between HLA-DQ and HLA-DP

Table 2: Key HLA associations with kidney disease

Locus and/or allele	Serological equivalent	Previous equivalents	Disease	Nature of association	Refs
HLA class I					
HLA-A2	HLA-A2	NA	Diabetic nephropathy	Risk (+)	165, 166
			Penicillin-associated AIN	Risk (++)	170
HLA-A*11:01	HLA-A11	NA	IgAN	Risk (+)	109
HLA-B8	HLA-B8	NA	Penicillamine and/or gold-associated membranous nephropathy[b]	Risk (++)	181, 189
HLA-B35	HLA-B35	NA	IgAN and Henoch–Schönlein purpura	Risk (+)	99
HLA-DR					
HLA-DRB1*01:01	HLA-DR1	HLA-DRw1	Goodpasture disease	Dominant protection	16, 52
HLA-DRB1*01:02	HLA-DR1	HLA-DRw1	TINU	Risk (+)	129, 130
HLA-DR3	HLA-DR3	HLA-DRw3	Penicillamine or gold-associated membranous nephropathy	Risk (++)	180, 181, 189
HLA-DRB1*03:01	HLA-DR17(3)	HLA-DR3	Lupus nephritis	Risk (++)	119
			Membranous nephropathy	Risk (+++)	19, 21, 190, 191
HLA-DRB1*04	HLA-DR4	HLA-DRw4	Diabetic nephropathy	Risk (++)	163, 166, 167
			IgAN	Risk (++)	99, 100, 101, 102, 103,– 104, 192
			Goodpasture disease	Risk (+)	16, 18, 54
HLA-DR7	HLA-DR7	HLA-DRw6	Steroid-sensitive nephrotic syndrome	Risk (+)	139, 140,– 141
HLA-DRB1*07:01	HLA-DR7	HLA-DRw6	Goodpasture disease	Dominant protection	16, 52, 53

Locus and/or allele	Serological equivalent	Previous equivalents	Disease	Nature of association	Refs
HLA-DRB1*09:01	HLA-DR9	HLA-DRw9	MPO-AAV	Risk (+)	86,87,88,– 89
		HLA-DRw9	Goodpasture disease	Protection	55
HLA-DRB1*11:01	HLA-DR11(5)	HLA-DR5	MPO-AAV	Risk (+)	89, 90
HLA-DRB1*15	HLA-DR15(2)	HLA-DR2b and HLA-Dw2	Lupus nephritis	Risk (+)	122
HLA-DRB1*15	HLA-DR15(2)	HLA-DR2b and HLA-Dw2	PR3-AAV	Risk (++)	85
HLA-DRB1*15:01	HLA-DR15(2)	HLA-DR2b and HLA-Dw2	Goodpasture disease	Risk (+++)	16,17,– 18, 52,53,54,– 55, 57, 193
			Membranous nephropathy (including hepatitis-B-associated)	Risk (++)	19, 20, 137, 194
HLA-DQ					
HLA-DQA1	NA	NA	Lupus nephritis	Risk (+)	123
			MCD or FSGS	Risk (+)	148, 150
HLA-DQA1*05:01[c]	HLA-DQ5(1)	HLA-DQ1	Membranous nephropathy	Risk (++)	21, 22, 67,68,69,– 70,190
			Penicillamine or gold-associated membranous nephropathy	Risk (++)	180
HLA-DQA2[d]	NA	NA	MPO-AAV	Risk (+)	76, 83
HLA-DQB1	NA	NA	MPO-AAV	Risk (+)	83, 88
HLA-DQB1*02:01	HLA-DQ2	HLA-DQB2	Membranous nephropathy	Risk (++)	21, 190
HLA-DQB1*03:01	HLA-DQ7(3)	HLA-DQw7 and HLA-DQ3	IgAN	Risk (++)	108, 195, 196
HLA-DQB1*03:02	HLA-DQ8(3)	HLA-DQ3	Diabetic nephropathy	Risk (++)	163

Locus and/or allele	**Serological equivalent**	**Previous equivalents**	**Disease**	**Nature of association**	**Refs**
HLA-DP					
HLA-DPA1	NA	NA	IgAN	Protection	107
HLA-DPB1*04:01[e]	HLA-DPw4	HLA-DPB4.1 and HLA-DPw4a	Goodpasture disease	Protection	56
			PR3-AAV	Risk (+++)	79,80–81,83,84

1. AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; AIN, allergic interstitial nephritis; FSGS, focal and segmental glomerulosclerosis; IgAN, immunoglobulin A nephropathy; MCD, minimal change disease; MPO, myeloperoxidase; NA, not applicable; PR3, proteinase 3; TINU, tubulointerstitial nephritis and uveitis.

2. [a]Risk effects categorized as + to +++ estimated on the basis of number and size of studies, consistency of association, odds ratio and mechanistic explanation. [b]Membranous nephropathy is ‘primary’ anti-PLA2R (secretory phospholipase A2 receptor)-antibody-positive membranous nephropathy unless otherwise stated.

3. [c]Studies denoting specific association with HLA-DQA1*05:01 are[21,180,190]; other studies quoted localize only to HLA-DQA1.

4. [d]Merkel et al. 2017[83] localizes to HLA-DQA2 and Lyons et al. 2012[76] only to HLA-DQ.

5. [e]Studies denoting specific association with HLA-DPB1*04:01 are[56,79,80,81]; Merkel et al. 2017[83] and Wu et al. 2017[84] localize only to HLA-DPB.

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, in which 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 and at HLA alleles, proteins and nomenclature[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, HLA-DQ1 was 'split' into two serotypes, HLA-DQ5 and HLA-DQ6.

HLA haplotypes
Linkage disequilibrium within the HLA region (excluding HLA-DP) results in the generation of haplotypes that are common 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 and 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 HLA-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-chains 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).

Phenome-wide association studies (PheWAS)
PheWAS use similar SNP and imputation techniques to GWAS but examine the effects of one or a limited number of variants in multiple phenotypes (see, for example, PheWAS resources).

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 (involving 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 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 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.

HLA–peptide tetramers and 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 (TCRs), 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–major histocompatibility complex (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 α3 chain of type IV collagen), the system can be used to discover immunodominant epitopes and to define mechanisms of autoimmune disease. If the target mouse antigen is very different from the human antigen, human transgenes can be introduced, although care must be taken to preserve fidelity of expression.

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