HLA Epitope Matching in Kidney Transplantation: An Overview for the General Nephrologist

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Rapid changes in tissue-typing technology, including the widespread availability of highly specific molecular typing methods and solid-phase assays for the detection of allele-specific anti-HLA antibodies, make it increasingly challenging to remain up to date with developments in organ matching. Terms such as epitopes and eplets abound in the transplantation literature, but often it can be difficult to see what they might mean for the patient awaiting transplantation. In this review, we provide the historical context for current practice in tissue typing and explore the potential role of HLA epitopes in kidney transplantation. Despite impressive gains in preventing and managing T-cell–mediated rejection and the associated improvements in graft survival, the challenge of the humoral alloresponse remains largely unmet and is the major cause of late graft loss. Describing HLA antigens as a series of antibody targets, or epitopes, rather than based on broad seroreactivity patterns or precise amino acid sequences may provide a more practical and clinically relevant system to help avoid antibody-mediated rejection, reduce sensitization, and select the most appropriate organs in the setting of pre-existing alloantibodies. We explain the systems proposed to define HLA epitopes, summarize the evidence to date for their role in transplantation, and explore the potential benefits of incorporating HLA epitopes into clinical practice as this field continues to evolve toward everyday practice.

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Introduction

Recently, a number of reviews of HLA epitopes and their significance in kidney transplantation have appeared in the transplantation literature.[1-7] For the general nephrologist, keeping track of the ever-increasing complexity of transplant tissue typing, the expanding list of HLA alleles, and the significance of allele-specific anti-HLA antibodies detected by solid-phase assays has been challenging enough[8,9] without the introduction of new concepts such as epitopes. Added to this complexity are the competing priorities of organ quality matching, improving access to transplantation for sensitized individuals and disadvantaged minority populations, and addressing overall waiting times. In the modern era of highly effective immunosuppression, which has led to low rates of T-cell–mediated rejection, some have even questioned the ongoing relevance of HLA matching.

In this review, we set out to provide a brief overview of the history behind HLA typing and the theory of HLA epitopes. We explain the systems that have been proposed to define HLA epitopes and review the potential benefits of considering HLA antigen compatibility at the epitope level. We aim to assist nephrologists in navigating the increasingly complex world of HLA antigen matching and demonstrate why a shift in the paradigm of how we define tissue matching to an epitope-based system may potentially offer long-term benefits for our patients.

A Brief History of HLA Discoveries

It is just more than 100 years since it was first recognized that the growth of genetically distinct (allogenic) transplanted tumors was a heritable trait,[10] suggesting that a system for detecting phenotypically different cells exists. Major discoveries in the field of histocompatibility are highlighted in the timeline in Figure 1.[10-30]

The first human histocompatibility antigens were identified in 1958 by analyzing agglutination patterns when white blood cells were mixed with serum extracted from multiply transfused patients and multiparous women.[13-15] These were later named human leukocyte antigens (HLAs). Subsequent groups discovered a second[17] and later a third[18] set of distinct histocompatibility antigens, termed HLA-B and HLA-C, respectively. As more sophisticated serologic techniques were developed, it became possible to divide previously serologically defined HLA groups into more specific subtypes.[31] For example, HLA-A9 was first described at the 1964 workshop,[32] but later subdivided into 2 distinct groups with different reactivity patterns,[33] and in 1972, A9 was superseded by A23 and A24.[31]

Further advances were made when it was observed that mixed lymphocyte reactions could identify an additional distinct HLA antigen reactivity pattern,[34] provisionally named HLA-D. Analysis of antisera that identified antigens present on B cells, but not T cells, revealed antigens closely related to the HLA-D determinants from the mixed lymphocyte reactions. These were named D "related," or HLA-DR, antigens and subsequent analysis identified that several closely linked genetic loci (DR, DQ, and DP) encode proteins for these B-cell antigens. Thus, by the mid-1970s, the overall structure of the HLA antigen system had been mapped, and a set of serologically defined HLA types had been agreed upon though collaborative efforts.[35]

The first HLA gene sequence was reported in 1981,[21] beginning the era of molecular typing. Modern tissue typing laboratories use a number of molecular

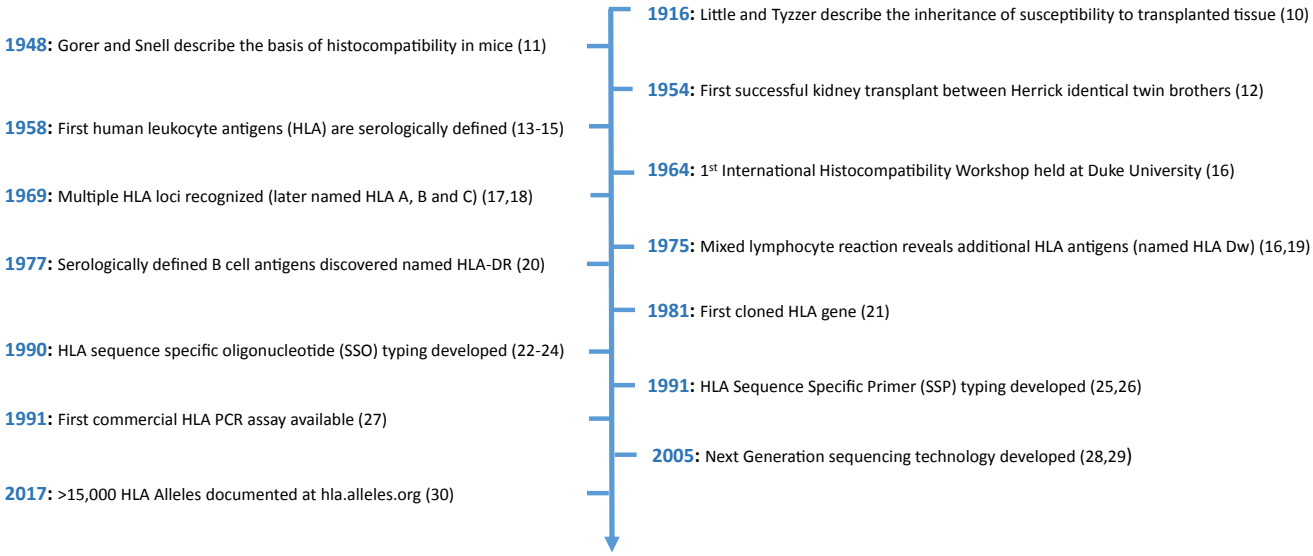

Figure 1. Timeline of key discoveries relating to HLAs. Abbreviation: PCR, polymerase chain reaction.

technologies to perform HLA typing, which are based on determining the sequences of HLA genes rather than on patterns of serologic reactivity to leukocytes.[2,27] As techniques of molecular typing have developed, HLA antigen naming conventions have had to be adapted to accommodate proteins that are within the same serologic class but differ in their amino acid sequence or genetic coding. The current system of HLA allele classification is denoted by a letter representing the HLA locus followed by an asterisk to indicate that molecular typing has been performed, and up to 4 sets of digits represented by separated colons (Fig 2).

Basic Structure and Genetics of HLA Molecules

Class I HLA molecules consist of a polymorphic α chain encoded within the major histocompatibility complex region on chromosome 6 and a nonpolymorphic β_2-microglobulin protein encoded on chromosome 15.[37] In contrast, class II HLA molecules are heterodimers formed by α and β glycoprotein chains, both of which can be polymorphic and are encoded within the major histocompatibility complex region.[37,38] The HLA-DQ and HLA-DP regions both contain 1 functional gene for each of their α and β chains (*HLA-DQA1* and *-DQB1*, *-DPA1*, and *-DPB1*, respectively). However, the HLA-DR region encodes 1 highly conserved DR α chain that is essentially invariant and either 1 or 2 DR β chains. Each haplotype contains 1 DRB1 gene and may also include an *HLA-DRB3*, *-DRB4*, or *-DRB5* paralogue (a distinct gene that derives from the same ancestral gene) that is coexpressed with *HLA-DRB1*.[38,39] Thus, molecular typing across the key class I and class II HLA loci in kidney transplantation includes sequence information on the following genes: *HLA-A*, *-B*, *-C*, *-DRB1*, *-DRB3*, *-DRB4*, *-DRB5*, *-DQA1*, *-DQB1*, *-DPA1*, and *-DPB1*.

The resolution of molecular typing methods (ie, their ability to distinguish minor differences in allele sequences) varies according to the technology used and number of alleles at a particular locus. Low-resolution or 2-digit typing distinguishes allele groups and is about equivalent to serologic typing, whereas high-resolution or 4-digit typing is able to distinguish alleles to the protein level

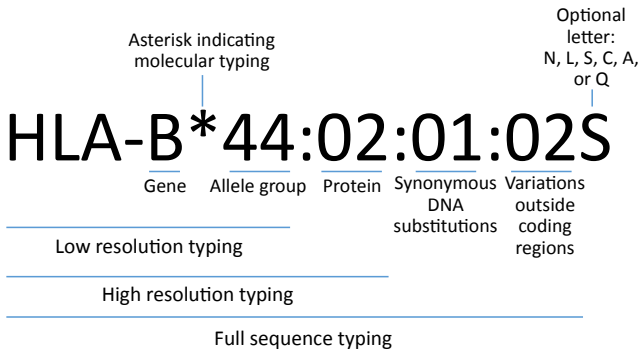

Figure 2. When molecular HLA typing has been performed, the gene is denoted by a letter or alphanumeric combination (eg, -B or -DQB1) followed by an asterisk. The first set of digits denotes the allele type, which usually (but not always) corresponds to the serologic antigen. The next set of digits refers to different alleles within the group that differ by at least 1 amino acid in the encoded protein. The third set of digits denotes synonymous substitution alleles (ie, there is no change in amino acid sequence of the protein), and the fourth set of digits denotes alleles with sequence variations in noncoding regions. These numbers are sometimes followed by a letter that indicates expression status (N = null allele, S = secreted molecule not present on cell surface, C = cytoplasmic protein not present on cell surface, A = aberrant expression, Q = questionable expression). Based on nomenclature specified in[36].