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Major histocompatibility complex: history of discovery, evolution, structure, significance in transplantation of allogeneic hematopoietic stem cells

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Abstract

Aim. *To reveal the significance of the major histocompatibility complex and the human leukocyte antigen evolutionary divergence in transplantation of allogeneic hematopoietic stem cells.*

The article traces the evolution of the major histocompatibility complex and discusses the reasons for its formation on the example of the recognition system of invertebrates, plants, jawed vertebrates and humans. The concepts of immunopeptidome and human leukocyte antigen evolutionary divergence have been defined; and the data on their impact on the therapy outcomes in patients with hemoblastosis have been presented. The impact of the major histocompatibility complex incompatibility on transplantation outcomes has been disclosed.

Keywords: major histocompatibility complex, human leukocyte antigen, allogeneic hematopoietic stem cell transplantation

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allo-HSCT, allogeneic hematopoietic stem cell transplantation

AML, acute myeloid leukemia

APC, antigen presenting cell(s)

CMV, cytomegalovirus

DAMP, damage-associated molecular patterns

EFS, event-free survival

GVHD, graft-versus-host disease

GVL, graft versus leukemia (effect)

HLA, human leukocyte antigen

IHW, International Histocompatibility Workshop

MHC, major histocompatibility complex

OS, overall survival

PAMP, pathogen-associated molecular patterns

PRR, pattern recognition receptor(s)

HLA and history of its discovery

HLA (Human Leukocyte Antigen) is the human version of the gene family known as the major histocompatibility complex or MHC. MHC is present in all jawed vertebrates, which include all animals from sharks onwards. The most well-studied MHCs of animals are those of rat, chicken, pig, dog, and feline.

The first descriptions of MHC were made by the British immunologist Peter Gorer in 1936. Based on his observations of agglutination of mouse erythrocytes with immune sera from rabbits, he described the major histocompatibility complex of these animals [1]. His studies were continued by George Snell, who established that a graft rejection in mice occurred due to incompatibility at the level of certain antigens. The murine MHC was named "H2" after Gorer's discovery of antigen II [2]. In 1944, Peter Medawar, while studying skin grafting in rabbits, demonstrated that rejection of a homograft (now called an allograft) was the result of a specific and systemic immune response [3].

The history of HLA research began in 1952 with an observation made by Jean Dosset [4]. He suggested that in humans, on the surface of leukocytes, there may be an antigenic system similar to that observed on mouse erythrocytes, which he demonstrated by showing massive leukoagglutination in the serum of a patient who had undergone multiple blood transfusions. However, final confirmation was received in 1958 by the results of a leukoagglutination test applied to leukocytes from a group of humans. Jean Dosset named him "MAC" based on the first letters of the names of 3 of his volunteers. It was later identified as HLA-A2 [4]. HLA was confirmed as a polymorphic system of antigens by the research of Jon van Ruda, Rose Payne, and Walter Bodmer who identified antigens 4a and

4b (Bw4 and Bw6), respectively, as well as HLA-A2 and HLA-A3 in studies on women with previous history of multiple pregnancies [5, 6]. This has given rise to mono- and oligospecific anti-HLA antibodies for detecting HLA antigens in an individual. In the 1960s, research conducted by Baroj Banacerraf [7] and Hugh McDevitt [8] proved the association of MHC genes with specific immune responses, due to which they were named immune response genes (Ir genes).

Achievements in the field of histocompatibility were marked by the award of the Nobel Prize to Peter Medawar and Frank Burnet in 1960 for pioneering research in the field of immunological tolerance and tissue transplantation. They shared the prize "for the discovery of acquired immunological tolerance."

In 1964, the first international workshop on histocompatibility was organized by Bernard Amos at Duke University, where participants compared various methods for detecting human leukocyte antigens. This marked the beginning of a productive international collaborative effort to study the HLA system. International research, with the arrangement of International Histocompatibility Workshops (IHWs), gradually led to the identification of a gene cluster on chromosome 6, including HLA-A, HLA-B and HLA-C. The complement system was mapped in the same genetic region. Further advances in molecular biology made it possible to study the HLA system directly at the level of genes, rather than of their products.

Allogeneic organ and tissue transplants began in 1954 when the first successful kidney transplant was performed by Dr. Joseph Murray in Boston, Massachusetts. Improving the results after transplantation became possible thanks to the obtained observations indicating that the HLA compatibility between the donor and recipient allows the increase in the

survival rate of allograft recipients [9].

These discoveries later gave rise to allogeneic hematopoietic stem cell transplantation (allo-HSCT). The first allo-HSCT was performed by E. Donnall Thomas and was reported in New England Journal of Medicine September 12, 1957 [10]. In his study, 6 patients underwent radiation therapy and chemotherapy, and then received an intravenous infusion of bone marrow from a healthy donor. Acceptance occurred in only 2 patients, and all of them died 100 days after transplantation. At that time, little was known about histocompatibility antigens, and no one attempted to match donors and recipients by them. Many investigators made attempts to perform allo-HSCT, however, having received unsatisfactory results, they gave up attempts, but Thomas continued the research. In the mid to late 1960s, methods for determining and typing HLA were developed, which made it possible to match the donor and recipient by HLA. In 1969, Thomas initiated a clinical research program in Seattle in the field of allogeneic hematopoietic stem cell transplantation. In 1977, a Seattle group reported 100 chemo- and radiotherapy transplants in 54 patients with acute myeloid leukemia (AML) and 46 patients with acute lymphoblastic leukemia. Only 13 patients survived for year without a relapse of the underlying disease [11]. However, such a small cure rate only encouraged Thomas to try using allo-HSCT in the earlier stages of the treatment of acute leukemia; and in 1979 he reported as high as a 50% cure rate in patients with AML transplanted in the first remission [12]. And perhaps most importantly, what was found in this work was the ability of the immune system to destroy the tumor, the so-called "graft-versus-leukemia" response. In 1990, E. Donnall Thomas received the Nobel Prize for his discoveries in the field of cell transplantation to treat human diseases.

Another breakthrough came after the first transplant from an HLA-matched unrelated donor [13]. Hematopoietic stem cell transplantation from an unrelated donor dramatically increased the chances of finding an HLA-matched donor; for example, for European patients, these chances have increased from 25% to 75%. International collaboration was essential to establish transplant centers around the world and a global donor registry. In 1972, the International Bone Marrow Transplant Registry (IBMTR) was established to document allo-HSCT outcome data. By that time, transplants had been performed in 12 centers, making a total of about 50 procedures per year. In 1974, the European Group for Blood and Bone Marrow Transplantation (EBMT) was established for European cooperation in the field of HSCT. The first transplant from an unrelated donor inspired the creation of the National Marrow Donor Program (NMDP) in 1986, and the Bone Marrow Donors Worldwide (BMDW) Organization. This organization brings together more than 23 million registered donors in 73 countries and 600,000 cord blood units from cord blood banks in 32 countries.

Analogues of the HLA system in plants and invertebrates

It is generally accepted that the MHC multigene family is limited to vertebrates, but histocompatibility loci also occur in invertebrates. It is assumed that the system of immune recognition by histocompatibility originated in multicellular invertebrates, probably beginning with coelenterates (corals) [14]. The most studied invertebrate compatibility system is the colonial tunicate system [15, 16]. Colonial tunicates are complex marine invertebrates, protochordates. The best known species in this group is Botryllus schlosseri, and its compatibility system is called fusion/histocompatibility (Fu/HC). Allogeneic recognition in Botryllus

schlosseri is mainly controlled by a single locus with a large number of co-dominantly expressed alleles [17]. The number of alleles is estimated from 30 to 200.

Colonial tunicates in the course of intraspecific competition for food surfaces massively carry out reactions of allogeneic recognition. With the help of these reactions, colonies unite with relatives, expand dominance over the food surface, while isolating unrelated individuals. Botryllus schlosseri colony consists of many units that are embedded in a translucent gelatinous matrix, a tunic. Each hermaphroditic member of the colony has male and female gonads. After merging with non-identical relatives that share one or more Fu/HC alleles, the merged pair reproduces through an asexual budding process, further increasing food surface dominance. However, at some later point in time, multiple allogeneic recognition reactions occur between the merged relatives, leading to the destruction of all individuals of one of the genotypes and the termination of the current chimeric state [16].

In addition to preventing fusion with unrelated organisms [15, 18], Fu/HC also affects self-fertilization by developing incompatibility between male and female germ cells. Female germ cells resist fertilization by male germ cells from the colony that is represented by the same Fu/HC allele. This interaction results in selective fertilization by male germ cells carrying a different Fu/HC allele [15]. This phenomenon in hermaphroditic invertebrates is very similar to what occurs in fungi and plants.

So far, there is no evidence of a common ancestor for compatibility systems between invertebrates and MHC vertebrates [16]. This shows that the widespread distribution of these systems is not due to a common ancestor, but suggests a biological need for such a system. This assumption is supported by the evidence that the "self-incompatibility" system in plants

has arisen independently more than once. It seems that the main function of all these systems is to ensure heterozygosity, acting at the earliest stage of sexual reproduction. However, the possibility still exists that vertebrate histocompatibility genes are derived from gametic self- and non-self-recognition systems that prevent self-fertilization in hermaphroditic organisms [15].

Plants also have mechanisms for recognizing native and alien antigens. They prevent self-pollination through self-incompatibility and are critical to maintaining genetic diversity in flowering plant (angiosperm) populations. The need for these mechanisms is due to the fact that in flowering plants, male and female organs are often located in close proximity to each other on the same plant, and often on the same flower. Self-incompatibility is a genetically controlled mechanism for the rejection of one's own pollen [19, 20]. Some flowers have developed mechanical barriers to their own pollen to prevent it from reaching the female organ (pistil) in the same flower or plant. Others have temporary differences between male and female flowers. Self-incompatibility systems that create a topological barrier (due to the different morphology of their flowers) are called heteromorphic self-incompatibility systems [20]. More than half of the flowering plants have similarly shaped flowers and a homomorphic self-incompatibility type. The homomorphic type is further classified into gametophyte and sporophyte types. In the first case, the same factors (genes) controlling the synthesis of mutually recognizing substances are active in the pollen grain and pistil tissue, and effective pollination is possible if the incompatibility alleles in the pollen tube and pistil tissue are different. The incompatibility locus was marked with the letter S (self-incompatibility), and its alleles were marked with the letter S with indices: S1, S2, S3, etc.

In the more interesting sporophyte type, the two alleles of the pollen parent are recognized by the stigma, and in order to avoid self-rejection, there must be no matching combination between the two alleles of the stigma and the two alleles of the plant from which the pollen originated. These two types are not related and developed independently of each other.

Self-incompatible plants necessarily produce offspring that are heterozygous for the S locus, which in general contains 30–50 alleles [21]. The S locus alleles confer genetic identity (S haplotype specificity) to the pollen and stigma of plants that have a self-incompatibility system. The sporophyte-type S locus has two genes encoding two proteins expressed on the surface of the stigma of the pistil. It is transmembrane S receptor protein kinase (SRK) and S locus glycoprotein (SLG) with ribonuclease activity. [22]. It is the SRK gene product that determines the specificity of S haplotype stigma, but the SI response will be stronger if an SLG of the same haplotype is also expressed. When pollen reaches the stigma of the same flower or plant, a self-rejection reaction occurs. The biochemical mechanism of self-rejection involves the cytotoxic action of ribonuclease activity. The end result is the prevention of pollen tube growth. In the gametophyte type, the same is achieved with a single glycoprotein with ribonuclease activity [23].

The self-incompatibility system of plants exemplifies balancing selection in maintaining the diversity of their alleles. Any new allele will have a selective advantage, since pollen with that allele will always be accepted by the stigma until that allele reaches a noticeable frequency in the population (frequency dependent selection).

Evolution of the HLA system in vertebrates

The vertebrate immune system is divided into two subsystems, the innate immune system and the adaptive immune system. The innate immune system is the first to respond to initial infection and disease and does not retain memory of previous reactions. The components of the innate immune system are physical barriers such as skin and mucous membranes, cellular processes such as phagocytosis, and humoral factors such as soluble proteins. If the pathogen persists despite innate immune defenses, the adaptive immune system is recruited. The adaptive immune system is highly specific for a particular antigen and can provide long-term immunity [24]. The innate immune system is thought to have evolved over 600 million years ago, while the specific components of the adaptive immune system, including immunoglobulins (Igs), T cell receptors (TCRs) and MHCs, originated approximately 450 million years ago in the first jawed vertebrates (i.e. Gnathostomata) [25].

While jawless fish have an adaptive immune system based on variable lymphocyte receptors (VLRs), B-like and T-like cells, the jawless fish, being the most distant group related to mammals, have an adaptive immune system that includes immunoglobulins, T-cell receptors and major histocompatibility complex [25, 26].

Although the structure of MHC is similar across species, the genes encoding MHC show a high degree of polymorphism in mammals, bony and cartilaginous fish, which allows the representation of different peptide repertoires [27]. In most teleosts, MHCs class I and class II are on different chromosomes, but in cartilaginous fish and all other vertebrates, the MHC I and II are on the same chromosome [28]. Interestingly, while MHC I and II are retained in most jawed vertebrates, codfish have lost the genes for MHC

II and CD4, a T-cell co-receptor that interacts with MHC. However, the Atlantic cod contains more genes associated with the MHC I component of the immune system, as well as a unique composition of the Toll-like receptor (TLR) family, compared to other vertebrates, which may help compensate for the absence of MHC II and CD4 [29].

The oldest living animal species with an ancestral MHC/T cell receptor recognition system is the cartilaginous shark [30]. Sharks and humans are at opposite ends of the jawed vertebrate evolutionary spectrum. The history of shark evolution is 450-520 million years, while the history of human evolution is probably 100-200 thousand years [31].

An important role in the development of adaptive immunity was played by transposons, i.e. DNA segments of organisms capable of movement (transposition) and reproduction within the genome. The insertion of transposons led to the evolution of the repertoire of immunoglobulin genes, T-cell receptors through transpositions mediated by the RAG1 and RAG2 recombinase enzymes, as well as to the creation of diversity in the MHC genomic region [32].

The “jawed vertebrate” hypothesis suggests that an adaptive immune recognition system and more specialized innate systems (NK cells, Bf and C2 complement factors) evolved in the gastrointestinal tract of primitive jawed vertebrates to protect against pathogens brought in due to predatory lifestyles [33]. Therefore, it is in this context that the shark is an important extant model for studying the genomic structure and gene organization of the MHC. The shark has a prototypical MHC, and assuming that little change has occurred in this region through genomic rearrangements (deletions, transpositions, insertions) over 520 million years of evolution. Previous studies of shark MHC have shown that class I and class II gene clusters are

closely related [34]. If the shark is the prototypical jawed vertebrate with the longest surviving lineage, then the prototypical structure of the MHC is likely a basic gene complex consisting only of class I and class II genes, TAP 1/TAP 2 and LMP 2/LMP 7 [30]. This prototypical structure, in one form or another, has been found in most of the studied vertebrates, even despite various genomic rearrangements, including expansion, narrowing, displacement, loss, and new insertions of genes along the evolutionary path from shark to human [30]. In this respect, the division of class I and class II regions in bony fishes is derivative rather than ancestral [35]. The loss of linkage between class II and class I genes probably occurred as a result of the translocation of class II genes to other genomic regions and different chromosomes. On the other hand, class I genes in teleosts are mixed with LMP2, LMP7, TAP2, and RING3 genes and with genes from the "extended" class II region such as KNSL2, DAXX, ZNF297, TAPBP, RXRB, and COL11A2 [36].

The advent of separate electrophoresis techniques in the 1960s led to an increase in the number of studies that examined genetic diversity across a wide taxonomic spectrum. All this led to the fact that a discussion about neutralism and selection flared up, which continues to this day [37]. Recently, the growing body of DNA sequence information has facilitated efforts to determine the effects of selection on different regions of genes and to estimate the distribution of selective effects across the genome [38]. Such data, however, do not always help clarify which processes underlie selection, since DNA sequence information cannot help determine the function of a gene.

Our understanding of how selection can act to maintain adaptive polymorphism in natural populations is still based on a small number of key

gene regions, including MHC. MHC has been characterized at the molecular level for a considerable number of years, and studies describing the diversity of MHC are extensive. The MHC remains a powerful model against which competing hypotheses about the causes and consequences of selection can be tested. MHC is central to the vertebrate immune system. This family of multigenes encodes key receptor molecules that recognize and bind foreign peptides for presentation to specialized immune cells and subsequent triggering of an immune response [39]. From an evolutionary point of view, the most important feature of MHC is the extreme diversity observed at expressed loci. The MHC contains the most variable functional genes described in vertebrates.

In the three most variable human MHC loci: HLA-A, HLA-B, and HLA-DRB1, 7644, 9097, 2221 alleles, respectively, were studied as of October 2022 [40], and the nucleotide diversity in the human MHC is two orders of magnitude higher than the average by genome [41]. As MHC genes are studied in more and more species over a wide taxonomic range, it becomes apparent that such high diversity is a characteristic feature of MHC loci.

The need to maintain high allelic diversity at the MHC loci may seem intuitive given that individuals or populations with higher sequence variability at the MHC loci can identify and process more pathogenic antigens and thus combat a wider range of pathogenic antigens. However, we are still far from a correct understanding of what evolutionary, ecological, and ethological processes generate and, more importantly, maintain MHC diversity in natural populations [42].

The structure of human HLA

The human MHC gene is divided into three regions. Each region contains many gene loci, including expressed genes and pseudogenes [43].

There are at least 18 HLA class I gene loci, where three classical genes (HLA-A, HLA-B and HLA-C), three non-classical genes (HLA-E, HLA-F and HLA-G) and 12 non-coding genes or pseudogenes (HLA -S/17, HLA-X, HLA-N/30, HLA-L/92, HLA-J/59, HLA-80, HLA-21, HLA-K/70, HLA-16, HLA-H/54 , HLA-90 and HLA-75) clustered within three separate duplication blocks, designated as alpha, beta and kappa blocks [44].

There are also seven MIC genes that are HLA I-like genes. They are distributed over three duplication blocks, two are expressed in the beta block, while the rest are non-expressed or pseudogenes within the kappa and alpha blocks [45]. These duplication blocks have been found in most mammalian species studied (with the exception of pigs), and they are separated from each other by a large set of non-HLA genes (97 loci in humans) with diverse functions [31].

Class I antigens are expressed on virtually every cell in the body except erythrocytes and trophoblasts. Class I antigens consist of a heavy chain (alpha chain) that is non-covalently coupled to a light chain (beta chain) to form the final dimerized molecule. Class I alpha chains are encoded by genes in the MHC (e.g., HLA-A, HLA-B), while the beta chain (beta-2 microglobulin) is encoded on chromosome 15 rather than in the MHC.

The class III region, located between the class I and class II region, contains 62 loci of 58 expressed genes and two pseudogenes. This is an area with high gene density. The class III region contains genes for complement factors C2, C4 and Bf, the genes for tumor necrosis factor cytokines,

lymphotoxin-alpha and lymphotoxin-beta, and many genes with no apparent association with immune function or inflammation [46].

The class II region contains the classic class II α- and β-chain genes HLA-DP, HLA-DQ, and HLA-DR, which are expressed on the surface of antigen-presenting cells (e.g., dendritic cells, macrophages, or B cells) to present peptides to T-helper cells. Thirty four loci have been identified in class II region from HLA-DRA to HLA-DPA3 with 16 expressed genes, three candidate genes, and 15 pseudogenes. Nineteen loci are HLA class II-like sequences comprising 15 classical HLA class II loci and four non-classical HLA class II loci (HLA-DM and HLA-DO). HLA-DRB loci vary in number and depend on the MHC haplotype [46].

Presentation of the antigen in the HLA molecule

It is through the HLA system that a foreign antigen is presented to T cells with the participation of antigen-presenting cells (APCs) for the subsequent implementation of an antitumor and anti-infective immune response [47, 48]. T cells can develop into memory cells or effector cells. The two main types of effector T cells that make up the adaptive immune system are T helper cells (Th) and cytotoxic T cells (TCs). In addition, T-regulatory cells are also distinguished, which regulate the immune response, preventing autoimmune reactions, but promoting the survival of tumor cells [49].

Th cells are distinguished by CD4 expression, subset-specific expression of transcription factors (T-bet, GATA3, and RORγt), and the release of cytokines that influence the activation and differentiation of other immune cells. There are 5 main varieties of Th cells (Th1, Th2 and Th17, Th22, Tfh), each of which is specialized in defense against certain

infections. Th1 cells primarily secrete interferon-γ (IFN-γ) that is associated with protection against intracellular microbes (mainly viruses) and initiation of anti- or pro-tumor effects; Th2 cells fight parasitic infections by secreting specific interleukin (IL) proteins, including IL-4, IL-5, and IL-13; and Th17 cells fight microbial pathogens by secreting cytokines such as IL-17A, IL-17F, and IL-22 [50 , 51]. Th 22 protect against extracellular bacteria by secreting IL-22 localizing in the skin and colon; and T-follicular helpers (Tfh) form germinal centers in the follicles of peripheral lymphoid organs and stimulate events that occur in these formations: switching isotypes of immunoglobulins, maturation of antibody affinity, formation of memory B cells and long-lived plasma cells [51]. Cytotoxic T cells are characterized by CD8 expression and the ability to directly contact and kill transformed and infected cells. T cells act in concert with B cells, resulting in the formation of an immunological memory for specific pathogens, including cancer cells. An adaptive immune response against a particular antigen may take several days to fully develop, but its implementation upon repeated exposure to that antigen is extremely rapid.

The classic APCs are dendritic cells (DCs) and B cells. To elicit an immune response, APCs must first recognize and bind their target. To do this, APCs express antigen-specific surface receptors, including pattern recognition receptors (PRRs). PRRs recognize pathogen-associated molecular patterns (PAMPs), which are produced by microbes, and damage -associated molecular patterns (DAMPs), which are produced by damaged or mutated host cells [52]. Depending on the receptor, PRR expression can be either constitutive or inducible. PRRs include Toll-like receptors (TLRs). TLRs are usually expressed on the cell surface or in endosomes and are type I transmembrane proteins whose extracellular domains contain leucine-rich

repeats used to recognize and bind to specific PAMPs. Once the extracellular domain binds its target, TLR activates a cytosolic signaling cascade that is triggered by an adapter protein that interacts with the TLR intracellular domain.

Another group of PRRs are the nucleotide-binding oligomerization domains (NOD)-like receptors (NLRs). NLRs are present in the cytoplasm and, like TLRs, initiate signaling cascades upon binding to microbial PAMPs. [53, 54].

After binding to the appropriate PAMP or DAMP, APCs initiate target phagocytosis, pinocytosis, or clathrin-mediated endocytosis. The pathway by which molecules are endocytosed determines how they will be degraded and then displayed by the major histocompatibility complex (MHC) for recognition by T cells [47, 48]. Class I MHC receptors are present on all nucleated cells and serve to present endogenous antigens to activate CD8+ T cells.

MHCs Class II have only APCs; they serve to present exogenous antigens and activate CD4+ T helpers. Some APCs, including dendritic cells, can also present exogenous antigens to the MHC class I receptor to activate CD8+ T cells in a process called cross-presentation. Presentation of antigens by receptors of MHC I or MHC II also depends on the composition of the antigen (corpuscular or soluble antigens), the mode of endocytosis and degradation by lysosomal proteases [48]. Cytotoxic T lymphocytes and T helpers use membrane-bound T cell receptors (TCRs) to bind MHC receptors [55]. TCRs are composed of two polypeptide chains (alpha and beta) linked by disulfide bonds.

The HLA system, playing an important role in the implementation of the mechanisms of anti-infective and antitumor immune response, can

determine the predisposition to the development of some autoimmune and viral diseases. Thus, it has been shown that the most common HLA haplotypes are less susceptible to many infectious diseases, including cytomegalovirus (CMV), due to their evolutionary advantage [56]. Allogeneic kidney recipients with HLA-B*44 have been shown to be more susceptible to CMV infection compared to patients without this allele; on the contrary, kidney transplant recipients with HLA-DRB1*01 were more susceptible to CMV infection than patients without this allele [57]. HLA-B*27 is known to be associated with ankylosing spondylitis. The association of HLA with the development of celiac disease, Sjogren's disease, type I diabetes mellitus, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus is being studied.

The impact of immunopeptidome on the "graft versus leukemia" reaction

The discovery and determination of the HLA function made it possible to establish fitness between donors and recipients in terms of HLA gene variants, as well as to identify peptide antigens that can be represented by these molecules on the cell surface. In recent years, in-depth analysis of the immunopeptidome of tumors, including the blood system tumors, has allowed the identification and characterization of targets for the T-cell response and has paved the way for the understanding, optimization and development of T-cell therapy. An immunopeptide is a set of peptides presented by the basic MHC molecules to T cells.

Individuals carrying different alleles at HLA loci (heterozygotes) produce both molecules, thus the number of potentially presented peptidomes increases. Thus, heterozygotes have more "extended immunity".

This advantage means that, other things being equal, natural selection will favor heterozygosity for the HLA loci. In addition, when evolving pathogens infect HLA-heterogeneous populations, they are forced to re-adapt with each transmission. This makes it difficult for these pathogens to adapt to the host population as a whole, and also contributes to the emergence of many rare HLA alleles in hosts [58]. Further, diversity according to the HLA system is “fixed” through reproductive mechanisms. Data from animal and human studies indicate some bias in mate selection. Thus, the choice is made in favor of partners carrying the major histocompatibility complex (MHC) or HLA alleles that are rare and/or different from native ones. There is also evidence that couples that are more discordant for HLA alleles are more fertile [59]. Such behavioral and reproductive phenomena increase the HLA diversity of offspring and the population as a whole.

HLA evolutionary divergence is a quantitative measure of amino acid sequence divergence between HLA molecules, which may ultimately reflect the diversity of immunopeptidomes.

High evolutionary HLA divergence (HED) between homologous HLA alleles has been shown to be associated with a more diverse immunopeptide. This, in turn, may directly determine the ability to present tumor-associated antigens, which is a necessary condition for an antitumor immune response, including such effects as the graft-versus-leukemia (GVL) reaction [60]. The Grantham distance makes it possible to quantify the evolutionary divergence between HLA (HED) alleles, taking into account the physicochemical differences in the corresponding peptide sequences of the binding domains [61]. The Grantham distance between each pair of amino acids is calculated based on the Grantham formula, which takes into account the structure, polarity, molecular volume of the corresponding amino acids:

$$D_{ij} = [\ \alpha\ (c_i - c_j)^2 + \beta\ (p - p_j)^2 + \gamma\ (v_i - v_j)^2\ ]$$ [62].

It has been shown that patients with a higher Grantham distance, and thus more diverse immunopeptide, respond better to checkpoint inhibitor therapy [60]. Checkpoint inhibitor therapy can block the inhibitory checkpoints CTLA4, PD-1, and PD-L1, restoring normal immune system function. However, in different people, the effectiveness of the antitumor response of the immune system may differ due to different immunopeptides. There is evidence that a low Grantham distance is associated with worse overall survival in patients with AML after allo-HSCT from a fully matched donor [61], which is probably due to less diverse immunopeptide HLA molecules.

It is the differences in immunopeptidomes that underlie the allowable and inadmissible differences in HLA-DPB1.

Unlike HLA-compatible donors, where minor histocompatibility antigens are almost exclusively targets of T-cell alloreactivity, most HLA-compatible unrelated donors additionally have mismatches for HLA-DP antigens, causing direct alloreactive T-cell responses with subsequent influence on the development of the graft versus host disease (GVHD) and GVL effect. A growing body of evidence suggests that HLA-DPB 1 differences between donors and recipients may be of clinical significance [63]. HLA-DPB 1 mismatch has been reported to elicit a wide range of alloreactive T-cell responses associated not only with an increased risk of acute GVHD, but also with a reduced risk of leukemia recurrence as a result of GVL [64]. Since HLA-DPB 1 mismatch occurs in >80% of pairs with an unrelated donor, the definition of acceptable HLA-DPB 1 mismatches, i.e. combinations of HLA - DPB 1 that cause limited T-cell alloreactivity with a reduced risk of GVHD, but retain the clinical efficacy of GVHD, poses an

important challenge for improving the results of allo-HSCT from HLA-compatible unrelated donors. Differentiation into valid and non-permissible was achieved by functional selection of groups of T-cell epitopes (TCEs) demonstrating cross-recognition between different HLA-DPB 1 alleles [65]. The study performed in 2012 showed that an acceptable HLA-DPB1 mismatch was associated with a lower risk of mortality and recurrence after allo-HSCT [66]. In another study, the presence of graft-versus-host HLA-DRB1 antigen mismatch was associated with a reduced risk of recurrence and improved survival. The National Research Center for Hematology also analyzed the effect of incompatibility for the HLA-DPB1 gene on the results of allo-HSCT from HLA-ABC–DRB1-DQB1-compatible unrelated donors. Mismatch between the donor and the patient for DPB1 alleles did not have a statistically significant effect on overall survival (OS), event-free survival (EFS), and an increase in the likelihood of developing aGVHD after allo-HSCT; however, in patients with allo-HSCT from a donor with an unacceptable mismatch for DPB1 alleles, there was a tendency to increase ESF [67]. Thus, the effect of the mismatch between the epitopes of donor and recipient T cells on the results of allo-HSCT requires further study.

HLA-incompatible transplantations of allogeneic hematopoietic stem cells

Historically, the best allo-HSCT results have been obtained when the stem cell donor was an HLA-matched sibling. Given the small size of families in developed countries and the 25% chance that a sibling is fully HLA-compatible with the patient, only 30% of patients have an HLA-compatible sibling donor. For patients who do not have an HLA-matched sibling, alternative HSC sources include stem cells obtained from an HLA-

matched or partially matched unrelated donor, or an HLA-haploidentical, related donor. Over the past decade, there has been a significant improvement in the results of haploidentical transplantations. The decision on which donor to choose depends, to a large extent, on the clinical situation and the approaches used in a particular transplant center.

The main problem with allo-HSCT from a haploidentical donor is intense bidirectional alloreactivity leading to either a high incidence of graft failure or GVHD. However, advances in the field of GVHD prevention have significantly reduced the risk of developing these post-transplant complications.

Potential HLA-haploidentical donors include biological parents, biological children, full or half siblings, and even donors from distant relatives such as aunts, uncles, nephews, nieces, cousins, or grandchildren.

For patients with high-risk acute leukemia, the efficacy of allo-HSCT from a haploidentical donor may be associated with a more pronounced graft versus leukemia effect compared with transplantation from an HLA-matched donor, resulting in a decrease in the cumulative recurrence rate and an improvement in overall survival [68]. However, the first experience of allo-HSCT from a haploidentical donor was associated with the leveling of this advantage by a large number of GVHD and high graft mortality. Subsequently, a number of advances in graft engineering and pharmacological modulation of alloreactivity have reduced the incidence of GVHD and non-relapse mortality, improved overall and disease-free survival, and made this type of donor an acceptable alternative for patients without an HLA-matched donor. There are 3 most common approaches to the prevention of GVHD in patients with allo-HSCT from a haplo-donor: 1) post-transplant cyclophosphamide (PT-CP); 2) “GIAC ” strategy, involving

stimulation of the donor by using granulocytic colony-stimulating factor, conditioning with antithymocyte globulin, intensive post-transplantation immunosuppression, and allografts of peripheral blood and bone marrow stem cells; 3) T cell depletion with a "megadose" of CD34+ cells or selective depletion of α/β T cells and B cells.

It is the use of PT-CP that has been associated with results comparable to those of HLA-matched HSCT [69]. All this led to the rapid spread of allo-HSCT from a haplo-donor. For example, among the centers of the European Society of BMT and HSC, the use of haploidentical donors increased by 291% from 2005 to 2015 [70].

Currently post-transplant cyclophosphamide is widely used to overcome the immunological incompatibility of the donor-recipient pair. It has been shown that its use leads to the deletion of alloreactive T-effector cells, and also T-regulatory cells, leading to the predominant restoration of Treg in the post-transplant period due to cells of the donor genotype [71].

With haplo-HSCT, it is possible to use myeloablative, non-myeloablative conditioning and conditioning in a reduced intensity mode. Different conditioning regimens and GVHD prevention regimens may have different effects on the subsequent recovery of T-cell subpopulations, thereby determining the development of GVHD [72]. The proportion of granzyme B+ T- reg cells may also influence the development of GVHD [73].

In the development of GVHD in allo-HSCT from haploidentical siblings, the issue of whether the common haplotype for the donor and recipient is inherited from the mother or father can be significant in clarifying. In utero fetal exposure to maternal cells can cause immunological hyporeactivity to non-inherited maternal HLA antigens (NIMA), which can

lead to reduced alloreactivity for NIMA-mismatched, HLA-haploidentical siblings after HCT. Other things being equal, mismatch of maternal rather than paternal antigens is better tolerated in allo-HSCT from a haploidentical sibling [74]. NIMA-based selection requires HLA typing of at least one parent to determine the lineage of inherited and non-inherited HLA haplotypes.

Studies have been conducted regarding the gender of the parent for the development of GVHD. In patients who received grafts from a haploidentical parent, the five-year EFS was significantly higher in those who received a transplant from the mother rather than from the father (51% vs. 11%, respectively). The protective effect of the maternal haploidentical donor was observed in both male and female recipients, suggesting that maternal exposure to the child's alloantigens inherited from the father may have affected these results [75].

Conclusion

HLA system is a leading component of the immune system, and its role in the immune recognition of alien antigens can hardly be overestimated. However, it is important to know that this system itself has become an evolutionary response to the aggressiveness of the external biome, and it is precisely the features of its structure and functionality that determine situations when two systems collide in one organism - the “donor” and the “host” ones.

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