MHC polymorphism in the immune system

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ABSTRACT

An antigen will be able to stimulate an immune response if the antigen has been presented and recognized by T-cells. Major Histocompatibility Complex (MHC) molecules are molecules that will recognize and present the peptides of the antigen. In humans, two classes of MHC are known to carry out this role, namely Class-I MHC and Class-II MHC, while Class-III MHC has a function that is not directly related to peptide binding. The genes that code for MHC molecules are so polymorphic that each individual is certain to have a different allele (heterozygous). In Class-I MHC, only the α-chain is polymorphic while in Class-II MHC both α and β-chains are polymorphic. MHC polymorphism will affect (1) the ability to create immune responses including antibody production, (2) resistance or susceptibility to infectious diseases, and (3) resistance or susceptibility to autoimmune and allergic diseases. That is why MHC is so polymorphic. The immune system has to fight many different pathogens. By having many different MHC molecules, one can present widely different antigens and can spur an effective immune response.

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INTRODUCTION

The immune system consists of tissues, cells, and molecules, and the genes involved in recognizing, reacting with them, and eliminating foreign and non-self-substances (antigens) that interfere with homeostasis in the body. The immune response to antigens can be classified into non-specific/innate immune responses (innate immunity) and specific / acquired (adaptive). Innate immunity is the oldest form of immune defense and exists in all multicellular organisms, while acquired immunity is only possessed by vertebrates. Innate immunity responds very quickly to infection but in the same way to any kind of pathogen. In contrast, acquired immunity takes several days to become active but has a memory that responds faster and better to a second pathogen exposure.[1] Innate immunity is generally in the form of physicochemical defenses such as skin, mucosal epithelium, and secretion products including sweat, mucus, and acid, immune cells such as phagocytic cells (macrophages and neutrophils), and natural killer cells (NK-cells). Inflammatory and inflammatory mediators including acute phase reactions, C-reactive protein, and complement are also innate immune responses that aim to limit and then repair damage caused by foreign body invasion or pathogens.[1] Acquired immunity is very specific and can distinguish substances even though the structure is very similar. Specific immunity will play a role together with non-specific immune responses and this is played by B-lymphocyte and T-lymphocyte cells that will produce antibodies, destroy infected cells and control the inflammatory response.[1]

The main function of T-lymphocyte cells is as a defense against intracellular microbes through T-cell receptors and activates other cells such as macrophages and B-lymphocytes. These functions require T-cells to interact with other cells that infect host cells, dendritic cells, macrophages, and B-lymphocytes. The specificity of T-lymphocyte cells is very different from that of B-lymphocyte cells and the antibodies they produce can recognize both dissolved and cell-bound antigens. The appearance of antigens bound to cells to be recognized by T-lymphocyte cells is carried out by special proteins encoded by genes at a locus known as the Major Histocompatibility Complex (MHC). The gene consists of ± 4 million base pairs found on human chromosome 6 and is known as HLA (human leukocyte antigen). There are 3 classes of MHC (class-I, class-II, and class-III), where class-I and class-II MHC play a role in binding and presenting antigens. This gene is highly polymorphic which means there are many different alleles in different individuals within a population.[1,2]

MAJOR HISTOCOMPATIBILITY COMPLEX

Major Histocompatibility Complex (MHC) is a set of genes found in all types of vertebrates that contain genes that regulate the expression of transplant antigens and genes that regulate immune responses and determine sensitivity to immunologic disorders.[3] In humans, the gene is approximately 4 million base pairs and is found on chromosome number 6, and in humans is better known as Human Leucocyte Antigen (HLA), while in mice it

is known as H-2. The function of the MHC molecule is to bind peptide fragments of pathogenic origin and present them on the cell surface for recognition by the corresponding T-cell. Consequently, there is almost always the destruction of pathogens: 1) cells infected with the virus will die, 2) macrophages will be activated to kill bacteria in intracellular vesicles, and 3) B-cells will be activated to produce antibody molecules that can eliminate and neutralize extracellular pathogens.[4] The Major Histocompatibility Complex contains at least 128 functional genes and more than 20% of them play a role in immunity. In the human genome, MHC is a dense region of genes and the region most associated with the disease. It is now known that the MHC molecule is an integral component of ligands that all T-cells can recognize because the antigen receptors of T-cells are highly specific to the foreign peptide antigen complex and the MHC molecule itself.[1]

Classically, MHC genes are divided into 3 classes, namely class-I and II which encode MHC molecules that represent antigens, and class-III MHC which is a mixed collection of genes that encode molecules with important immune functions such as complement components and TNF and other molecules whose immune function is unknown. The gene that codes for MHC in humans is located on chromosome number 6 and is divided into 2 classes, namely MHC class I and MHC class II. The difference between the two main types of MHC gene products, namely MHC class I molecules and MHC class II molecules, is determined by the location of the antigen protein, whether cytoplasmic/intracellular antigen (class-I MHC) or extracellular antigen endocytosed into vesicles (class-II MHC). Class-I MHC molecules are found on the surface of all nucleated cells and present peptide antigens to CD8+ cytotoxic T-cells (CTLs) that directly destroy cells containing those antigens. While class-II MHC molecules are present on the surface of B cells, macrophages, dendritic cells, and some special antigen-presenting cells (APCs) and present peptide antigens to CD4+ T-helper cells.[4]

MHC CLASS I MOLECULES

Class-I MHC proteins consist of two polypeptide chains, namely the α-chain and the 2-microglobulin β-chain. The α-chain will fold and form a large groove between the A1 and A2 domains where the MHC molecule attaches to the protein antigen. The groove is closed at both ends and the bound peptide consists of 8-10 amino acids. MHC class I also has two helical α that spread across the β-chain so that it can bind to T-cell receptors. The sequence motif in class-I MHC makes it possible to identify which peptides on the protein will bind to the corresponding MHC molecule. So, this feature is important in designing peptide vaccines.[5]

3 genes code for the class-I MHC α-chain, so it is said to be polygenic. Each individual inherits 6 α-chains (3 α-chains from the father and 3 from the mother). Each α-chain gene has about 90-500 different variations or alleles so the chances of each inheriting an identical copy of all three class-I MHC genes from both parents are very low. The cells of most people will express 6 different class-I MHC molecules or in other words, no two people may have the same six class-I MHC molecules. This feature often causes problems in organ or tissue transplants. The group of genes belonging to class-I MHC is organized into several loci and the most important are 3 major loci called HLA-A, HLA-B, and HLA-C as well as some minor loci that are not yet known. Each major locus encodes one particular polypeptide.[2,6]

Class-I MHC plays a role in expressing peptides on the surface of cells infected by viruses so that they can be recognized by cytotoxic T-cells. The figure below describes schematically the process of breakdown of foreign proteins in cells and their expression on the cell surface by MHC-I molecules.[1]

Foreign antigens in the cell cytoplasm (cytosolic peptides) can be products of viruses or other intracellular microbes that infect the host cell. In addition, peptides presented by class-I MHC molecules can come from microbes or other proteins that undergo internalization in phagosomes.

Some types of microbes can damage phagosomal membranes and cause pores that can be passed by microbes and proteins to enter the cytoplasm.[1] When these microbes are already in the cytoplasm, they will undergo a degradation process just like other cytosolic peptides. The main mechanism in the process of peptide formation from cytosolic antigen proteins is proteolysis by the proteasome. The proteasome is a complex multiprotein enzyme that has extensive proteolytic activity and is found in the cytoplasm of almost all cell types. The peptides resulting from proteolysis by the proteasome are then carried by special transport molecules called Transporter Associated with Antigen Processing (TAP) into the endoplasmic reticulum. In the lumen of the endoplasmic reticulum, the TAP protein binds non-covalently to the MHC-I molecule via a connective protein called tapas. The MHC-I molecular complex with peptides is a stable molecule that will be carried to the Golgi complex and will then be expressed on the cell surface through exotic vesicles. When expressed on the cell surface, this MHC-I complex and peptide will be recognized by specific CD8+ T-lymphocyte cells (cytotoxic T-cells).[1]

MHC CLASS II MOLECULES

In contrast to class I MHCs, the genes for class II MHCs are organized in α and β loci that express α and β polypeptides. Both have almost the same molecular weight (polypeptide α with a molecular weight of 32-34 kD and β with a molecular weight of 29-32 kD) and combine to form a heterodimer with a tertiary structure similar to MHC class I.[1,2] There are 3 pairs of α and β (polygenic) chain genes known in humans as HLA-D (DP, DQ, and DR). Both chains contribute to peptide binding gaps and both are polymorphic. DR is somewhat different in that it has an extra chain where the alpha chain is not polymorphic at all but can be paired with an extra β chain encoded by one of four different genes, DRB1, DRB3, DRB4, and DRB5 so that from three sets of MHC class II genes produce 4 MHC class II molecules.

A normal copy of chromosome 6 contains the DRB1 gene present in more than 300 alleles, as well as 3 other DRB genes. This model of variation in certain genes found in one person but not in others is known as *presence-absence polymorphism*.[1,2,7]

In addition to differences in the length and organization of polypeptide chains, the overall three-dimensional structure of MHC class II molecules is very similar to MHC class I.[1,8] The gap formed in MHC class II is more open so that it can bind longer peptides and it is more flexible in peptide binding. This makes it harder to predict which peptides will bind to class II MHC molecules. In contrast to MHC class I where the peptide bound is derived from proteins synthesized within the cell, peptides bound to MHC class II are usually derived from proteins that have been internalized by the cell and then degraded. Such peptides usually have different sizes and can be cut when binding to MHC class II molecules. Class II MHC molecules bind peptide molecules that have been processed by APC cells into complexes which are then transported to the cell surface so that they can be recognized by CD4+ T cells. The presentation of antigens that stimulate the CD4+ T set is the beginning of an immune response that determines the type of response that will occur.[1,8]

MHC CLASS III MOLECULES

The formation of components of several cytokines and other molecules such as complement components (C2, C4), tumor necrosis factor (TNF), heat shock proteins, enzymes, and some molecules involved in antigen processing is determined by MHC which belongs to MHC class III molecules. Unlike MHC I and MHC II whose structure and function are very similar, there is no similarity in structure or function between genes in MHC II.[1,8]

MHC MOLECULAR POLYMORPHISM

Many proteins are expressed with more than one genetic variation in the human population. The difference between these proteins is known as polymorphism, and almost all polymorphic proteins are found in 2 or 3 forms/variants. MHC molecular polymorphisms were originally thought to result from rejection reactions in tissue or organ transplants. The fact that transplantation does not occur naturally means that MHC polymorphisms do not develop in response to reactions to refuse the transplantation of organs or foreign tissue. The discovery of a limited immune response to a particular MHC and the role of MHC molecules presenting antigens explains the polymorphism of MHC molecules.[8] MHC loci in humans, mice, and certain mammals are known to be highly polymorphic with heterozygosities of up to 80-90%. 4 hypotheses explain why the degree of polymorphism is so high, namely (1) high mutation rates, especially *point mutations*, (2) gene conversion or interlocus genetic changes, (3) over-dominant selection, and (4) frequency-dependent selection.[5]

The diversity of MHC molecules is so great, at some loci, hundreds of alleles have been identified. Due to the great diversity of MHC molecules, each individual has a specific immune response to a different subset of peptides of a particular pathogen. Pathogens that can evade presentation by one host's MHC molecule may not be able to evade the presentation of another host's MHC molecule.[2] The MHC model polymorphism is not found in other proteins and is believed to be an attempt by the immune system to defend against disease due to exposure to pathogens that have very high mutation rates. The evolution of this peptide binding diversity is driven by the diversity and mutational ability of infectious agents that threaten human life.[5]

The existence of these 2 classes of MHC makes it difficult for pathogens to evade the immune response of this MHC pathway. This is because MHC is polygenic: there are many MHC class I and class II genes, encoding proteins with different peptide-binding specificities. In addition, MHC is highly polymorphic: there are many alleles for each gene. MHC genes are known to be the most polymorphic of all genes. MHC polymorphism determines which peptides will bind and be presented to T cells. Most of these differences are localized to exposed surfaces and to peptide binding gaps. In cases (rare) where the protein does not have a peptide corresponding to one of the MHC molecules expressed on the cell surface, the person will fail to respond to antigens called Immune Response (Ir) gene defects.[6]

There are two important pieces of evidence supporting that MHC molecular polymorphisms are driven by the need to maximize peptide binding diversity. First, polymorphisms are concentrated in amino acids that form peptide binding gaps. Second, when the bound peptide is extracted from the MHC molecule it is seen that although each variant of the MHC molecule binds to a different peptide in a very wide variation, the bond is formed by a different set of variants. It is suspected that the polymorphism of the MHC molecule is made possible by the presence of clusters of genes encoding the MHC molecule through recombination that produces new variants.[6]

In terms of disease resistance, an important effect of MHC molecular polymorphism is to maintain a high probability that each individual will inherit different alleles from each parent, or it can be said that each individual's MHC molecule is heterozygous. Since not all potential immunogenic peptides can bind to one MHC gene product, having two MHC gene products doubles an individual's chance to form a functional MHC peptide. Research in mice has also shown that MHC polymorphisms can produce new T cell specificity in the thymus that can improve their survival.[5]

CONCLUSION

Major Histocompatibility Complex (MHC) molecules are molecules that will recognize and present the peptides of the antigen. In humans, two classes of MHC are known to carry out this role. MHC polymorphism will affect the ability to create immune responses including antibody production, resistance or susceptibility to infectious diseases, and resistance or susceptibility to autoimmune and allergic diseases.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared.

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ETHICAL STATEMENT

Not applicable.

AUTHOR CONTRIBUTION

All authors contributed equally to this study.

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