

Innate immunity and the immune system



**ASSIGN
BUSTER**

Introduction

The immune system is a complex network consisting of molecules, cells, tissues, and organs that operate in a highly interdependent manner, with the main aim of defending the body from attack by foreign organisms. The immune system in vertebrates is broadly divided into 'Innate' immune system and the 'Adaptive' immune system.

Innate immune system comprises of those elements which offer immediate host response. An important property of the innate immune system is lack of specificity towards the invading organisms. The innate immune system comprises of several key molecules, which include proteins from the complement system, Interleukins and an array of cells like Neutrophils, Macrophages, Dendritic cells, Natural Killer (NK) cells. Anatomical barriers like skin, mucus, tears, saliva etc., are also classified under the innate immune system

On the other hand, the adaptive immune system comprises of components which elicit a highly specialized response against pathogens. The adaptive immune system, when compared to innate immunity, takes a longer time to mount an attack against foreign particles. It mainly consists of a specific type of WBC's, called 'lymphocytes'. Depending on the regions of maturation, these cells are classified into B-lymphocytes (maturation site: bone marrow) and T-lymphocytes (maturation site: thymus). The B-lymphocytes mediate their immune attack via soluble glycoproteins called 'Antibodies' which are highly specific against their target. The T-lymphocytes elicit cell mediated immune responses, wherein specific cells (T-cytotoxic cells) identify and

neutralize the pathogens. The other types of T-lymphocytes, namely T-helper cells, memory and regulatory T-cells also play a vital role in launching an effective and targeted immune response. One of the striking properties of adaptive immune system is 'memory'. This enables the adaptive immune system to keep a 'record' of the pathogens which invade the body and generate an immune response in a much shorter time, in scenarios involving subsequent attacks by the same pathogen.

Antigen Presenting Cells and Major Histocompatibility Complex Proteins

Innate immunity is body's first line of defense. After recognition of the pathogen by the innate immune system, a crucial process involved in mounting an effective immune response is the activation of adaptive immunity. Antigen Presenting Cells (APC's) are a specific type of cells which play an important role in facilitating this process.

APC's are specialized cells which degrade protein antigens into peptides and display these peptides on the surface of the cells via specific membrane bound glycoproteins called Major Histocompatibility Complex (MHC) molecules. In humans, the MHC molecules are called as Human Leukocyte Antigen (HLA).

After ingestion of the pathogens (either via phagocytosis or endocytosis), the APC's digest the pathogens in lysosomal compartments resulting in the formation of antigenic peptides. The lysosomes fuse with endosomes in the cells and the antigenic peptides are loaded on to MHC II molecules. The MHC's are then transported to the surface of APC's to participate in the

process of antigenic presentation, which involves interaction with the receptors present on T-cells, called T-cell receptors (TCR). This process plays a crucial role in activating the adaptive immune system.

Classification of MHC Molecules

The MHC molecules are classified broadly into 2 classes. They are

Class I MHC Molecules:

MHC Class I molecules are composed of 2 chains, a heavy chain and a light chain. The heavy chain comprises of 3 domains - $\alpha 1$, $\alpha 2$ and $\alpha 3$, followed by a transmembrane domain, and a cytoplasmic domain. $\alpha 1$ and $\alpha 2$ domains are highly polymorphic and form a cavity which accommodates 8-11 amino acids long. The light chain, also called beta-2-microglobulin is associated with the heavy chain via non covalent interactions. The heavy and light chains are assembled in the endoplasmic reticulum (ER)

Peptides derived from cytosol, formed mainly by the action of proteasome, are transported into the lumen of the ER where they may bind to the peptide binding groove of MHC molecule. The resultant 'MHC-peptide' complex is subsequently transported, via Golgi, to the plasma membrane. On the plasma membrane, this MHC-peptide complex interacts with the T cell receptor (TCR) of CD8+ T cells. This process plays an important role in development of CD8+ T cells in thymus and their activation and proliferation in the periphery.

MHC class I molecules are expressed by all nucleated cells in the body.

Class II MHC Molecules:

MHC Class II molecules are heterodimeric glycoproteins comprised of two subunits - α subunit and the β subunit. In contrast to MHC Class I molecules, both the subunits α and β together form the peptide binding groove which accommodates antigenic peptides ranging from 9 to 40 amino acids in length. Both, α and β subunits are synthesized and directed to ER where they assemble with the invariant chain (Ii). The Ii chain occupies the MHC class II binding pocket. The MHC-Ii molecule is transferred to the golgi network where it undergoes post translational modification and later enter specialized endocytic compartments. The Ii chain prevents the binding of self peptides to MHC before it is exposed to antigens. It also prevents the association and degradation of MHC molecules.

The antigenic proteins acquired via phagocytosis, pinocytosis or endocytosis, eventually reach lysosomes where they are digested into smaller peptides. These lysosomes fuse with endocytic vesicles carrying the MHC-Ii molecules. The Ii chain of MHC molecules is digested in these lyso-endosomal compartments leaving a small peptide in the MHC binding pocket which is referred to as CLIP (Class II associated invariant chain peptide). CLIP is released and exchanged for an antigenic peptide fragment through a mechanism which involves a catalytic protein, HLA-DM. HLA-DM is a non-polymorphic heterodimer and its structure is similar to the general fold of a conventional class II MHC molecule. HLA-DM catalyses the exchange of CLIP with antigenic peptides. The formed MHC-antigenic peptide complex is transported to the cell surface where it is presented to CD4+ T-cells. The

interaction of class II MHC-antigenic peptide complex and the TCR, along with other co-stimulatory signals induces a helper T-cell immune response.

Association of peptides to MHC Class II molecules

Over — crystal structures of different human and murine class II MHC molecules in complex with different antigenic peptides have been determined over the past 10 years. The overall structure of all the MHC molecules determined so far are similar. Describe the structure of MHC II briefly from Chu. Analysis of the existing MHC structures revealed that the antigenic peptides adopt an elongated polyproline II (PPII) helical structure in the binding pocket. Multiple hydrogen bonds are found between conserved residues in the class II MHC protein and the peptide main chain carbonyl and amide groups. Get some figures to explain the PPII structure. Peptides associated with MHC class II proteins are usually 9 to 20 amino acids long. Occasionally peptides greater than 35 amino acids are found associated with MHC II molecules. A stretch of 9 amino acids of the antigenic peptides are specifically recognized. Within this region strong side chain preferences are found in certain positions. The pattern of this side chain specificity is called the peptide binding motif which reveals the presence of pockets in the peptide binding site. These pockets accommodate the side chains of peptide residues at the P1, P4, P6 and P9 positions with smaller pockets at the P3 position. These pockets correspond to positions where strong side chain preferences are observed in the studies of MHC peptide interaction.

The kinetics of peptide binding to class II MHC molecules has been extensively studied by different research groups (). The kinetic model

includes an initial bimolecular binding step followed by a slow unimolecular conformational change that produces a stable MHC-peptide complex. In addition, a reversible inactivation of the empty MHC protein that competes with productive binding is observed.

The MHC Class II - peptide- TCR complex

Detailed structural information on the MHC-TCR interaction is available for — MHC-pep-TCR molecules. The important interactions responsible for the ternary complex have been investigated by mutagenesis studies, mapping experiments and truncation studies.

In the MHC-peptide-TCR interaction, the complementarity determining regions from V α and V β domains of TCR are lying across the MHC-peptide complex, with CDR3 loops of both domains extending down over the center of the peptide and the CDR1 and CDR2 loops contacting the alpha helices in the peptide binding site of MHC protein. TCR's contact from 6 to 7 residues of a span of 9 residues of the class II MHC bound peptides. Single amino acid substitutions in peptides, even in residues not directly in contact with TCR can transform a strong agonist MHC peptide ligand into a weak agonist or an antagonist.

II. Significance of Secondary Structure of MHCII Binding Antigenic Peptides - Importance of Polyproline II (PPII) Structure

Introduction:

Peptides ranging from 9 to 40 amino acids in length are presented by MHC II molecules for antigen presentation. Extensive research was carried out on <https://assignbuster.com/innate-immunity-and-the-immune-system/>

the importance of sequence and length of these antigenic peptides, and their role in forming a complex with MHC II molecules. Detailed studies were performed on binding affinity of various sequences of peptides derived from islet antigens, to HLA-DR molecules by Annemieke et al. Similarly, studies were carried out by Wang Qiao et al, to evaluate the impact of variations in sequence and length of gliadin peptides, in forming a complex with HLA-DQ2. In contrast to this, limited data is available to understand the role played by the structure of these peptides in associating with the MHC II molecules.

Previously, spectroscopic techniques were adopted to investigate the association between structure of MHC ligand peptides and their antigenicity (3-5 from sette's paper). Simulation studies suggested that ordered regions such as amphipathic or α - helices (6-7sette) and β -sheet structures (8 sette) are frequently found within T cell epitopes. Based on structural data obtained from X-ray crystallography, Jardetzky et al (reference) proposed that antigenic peptides adopt polyproline II (PPII) like conformation in the binding pocket of HLA-II molecule. The antigenic peptides were also found to adopt a similar structure in the