Lecture 1

Sem - IV
CC10
Unit - V - 5.5

1

Immunological disorders and MHC

MHC linked immune response

The major histocompatibility complex (MHC) is a group of genes that encode proteins on the cell surface that have an important role in immune response. Their main role is in antigen presentation where MHC molecules display peptide fragments for recognition by appropriate T cells. This is an important process in the immune system response for destroying invading pathogens.

The MHC complex on the cell surface is necessary for cell self recognition and the prevention of the immune system targeting its own cells. Certain MHC alleles are associated with an increased risk of autoimmune disease such as Hodgkins lymphoma and multiple sclerosis.

Another function of the major histocompatibility complex is tissue allorecognition an important factor in the prevention of successful organ transplantation.

The MHC controls how the immune system detects and responds to specific antigens. Antigen specificity of T cell recognition is controlled by MHC molecule with different antigen presentation between MHC class I and class II molecules.

The two classes of MHC molecules have a similar function involving the delivery of short peptides to the cell surface for recognition by CD_8 and CD_4+ T cells respectively. MHC class I molecules present antigens that are intracellular and or endogenous, whilst MHC class II molecules present antigens

that are extracellular or exogenous. The MHC class I complex at the surface of the cell disconnects over time, leading to internalization into the endosome and entrance into the MHC class II Pathway.

Cross presentation also occurs where MHC class I molecules present extracellular antigens to CD8 + T cells. Degradation through autophagy can cause endogenous antigens to be presented By MHC class II molecules.

Role of MHC Molecules in ~~Acute~~ Antigen Recognition and Immune responses - The MHC mol are Polygenic every individual has its own set of MHC molecules. The Antigen presenting cells like phagocytic cells, B lymphocytes engulf the antigen by endocytosis followed by the fusion of the endosome with a lysosome where antigen is degraded into short peptides. fragments of these peptides are then displayed at the surface of the cell nested with a class II molecules.

Antigens that are generated within a cell are also degraded into short antigen peptide fragments within the cell and displayed at the surface of cell. Most CD8 cells are cytotoxic cells. They have the machinery to destroy the infected cell by MHC class I and class II pathway -

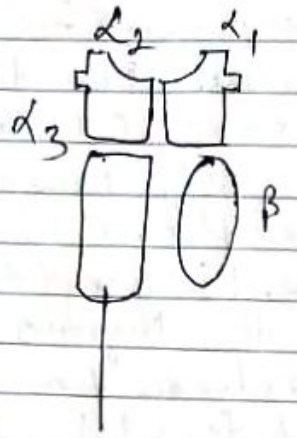
(1) Class I Pathway - Class I histocompatibility molecules are made up of two subunits 1) the transmembrane polypeptide called as alpha α heavy chain and 2) β (β-2) microglobulin. The assembly of these two chains are done by molecules of Calnexin, calreticulin and toposin in lumen of RER.

class I MHC Proteins are present in cytotoxic T lymphocytes (CTLs) Most CTL's possess both T cell receptors (TCR) and CD8 molecules on their surfaces. These TCR's are able to recognise peptides when they are expressed in complexed with MHC class I molecules. Due to genetic recombination events each CTL expresses a unique TCR which only binds a specific MHC Peptide complex. CTL's which recognise self peptides (i.e peptides of host body) are removed in the thymus or to be fixed after their release from the thymus. So if a CTL can bind to a MHC peptide complex on the cell surface, that cell is producing a peptide which is not native to the host.

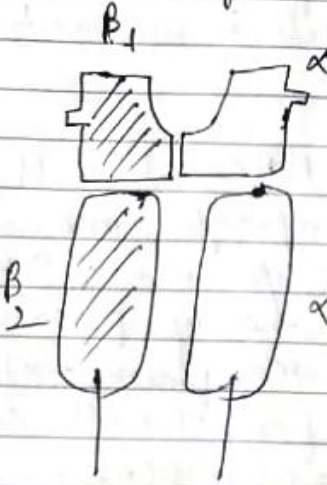
Class II Pathway —The MHC class II Proteins (found only in B lymphocytes, macrophages and other cells that present antigens to T cells) which Primarily present peptides which have been digested from external sources are needed for T cell communication with B cells and macrophages.

Class II MHC molecules consists of two transmembrane molecules consisting of polypeptides and a third molecules nestled in the groove they form. Foreign antigenic material is engulfed by endocytosis forming endosomes which fuses with lysosomes. The antigen is then digested into small antigen fragments. The vesicles then move to the plasma membrane and the complex is displayed on the peptide groove of MHC class II mol at the cell surface. The complex can bind to TCR a protein called invariant chain is located in the groove.

and bind the peptide and flanking portions of histocompatibility molecule and CD4 molecules ~~bound~~ that bind the CD4 receptor found on all class II molecules.



Schematic representation of MHC class I



MHC class II ℰ

The MHC complex is located on chromosome 6 in humans containing more than 200 genes of at least 7×10^6 bP encoding α and β chains of MHC class and class II molecules the genes for β_2 microglobulin and invariant chain are of chromosome 15, 5 respectively)

Functions of MHC — The function of MHC molecules is to bind peptide fragments derived from pathogens and display them on cell surface for recognition by the appropriate T cells. They are deleterious to the pathogens virus infected cells are killed, macrophages are activated to kill bacteria and B cells are activated to produce antibodies that eliminate or neutralize extracellular pathogens. The MHC are highly polymorphic and can kill mutating pathogens.