

# Mhc class i deficiency treatment



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The biological process which protects against disease by identifying and killing pathogens is known as Immune system which is divided into innate and adaptive immune system. The innate or natural non specific immune system that provides first line of immune system whereas adaptive immune system is very specific with immunological memory and consists functions such as recognition of antigen, generation of responses and resulting immunological memory cells and lymphocytes which produced in bone marrow, are responsible for this action and they are of two types; the B cell and T cell. During immune response the B and T cells activates specific receptors against antigens.

T cells do not secrete antibodies but identify antigens and mature in thymus and develop in either T helper cells or Killer T cells. T cells have two subsets CD4 and CD8 T cells. CD4 cells express major histocompatibility complex class I (MHC class I) molecule on the cell surface while CD8 T cells express MHC class II molecule on its surface. These MHC molecules are classified as Human leukocyte Antigen (HLA) in human and they function as antigen presenting cells. Class I MHC molecules consist of a large glycoprotein chain and  $\beta$ 2-microglobulin and protein with a single domain. They are expressed on most nucleated cells. MHC genes are tightly linked and generally inherited as a unit from parents. MHC alleles influence immune responsiveness and the ability to represent antigen and has a susceptibility to a number of disease. In general class I molecule represent processed endogenous antigen to CD8+ T cells. When virus infect the host cell, the protein of the virus degraded in cytosol and newly derived MHC class I molecule bind to it and travel to the cell surface and now this cell is

presenting antigen peptides on its surface and this is known as antigen presenting cell. By cell's biosynthetic mechanism the antigen peptide which bind MHC class I molecule is derived from the virus.

In the case of Tatiana and Alexander, no MHC class I molecules were found in their cells when typed for HLA antigens. However, a very few amount of MHC class I molecules were expressed when a more sensitive FACS technique was used. In the case study, HLA typing also revealed that the mother and father shared the MHC haplotype (HLA-A3, -B63, HLA-DR4, -DQ3) [3].

During antigen presentation various intracellular, viruses can evolve the ways to inhibit MHC Class I presentation, and there are three processing pathways which are cleavage, transport and MHC binding. The function of T cells is to kill the cells which have been infected by virus. This process is known as cytotoxicity and CD8 cells are responsible for the immune response cascade as CD8 T cells bind the foreign peptide on MHC class I molecule on Antigen Presenting Cell with high affinity. The peptide chains responsible for the binding of the antigen which consists of MHC I and II molecules are translocated during its production into the ER lumen.

In endoplasmic reticulum the peptide chains has to be folded in the correct manner before it is transported to the surface of the cell for it to function correctly.

From the case study Tatiana and Alexander were diagnosed by MHC class I deficiency with the help of HLA typing. The MHC deficiency is further observed by the inability of T cells to bind to the antigen presenting cells which caused repeated viral infections in Tatiana and Alexander [11].

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Moreover, low levels of CD8 cells found from the blood test stated that there were less epitopes binding to the antigen presenting cells for its destruction. The low level of these cells suggests that lack of CD8 is caused by the defect in the gene that codes for MHC class I molecule. The proteins those are associated with the transfection of the mutant cells that present the peptides by MHC class I molecule are known as Transporters associated with Antigen Processing-1 and -2 (TAP1 and TAP2).

A heterodimer and mutation of both TAP-1 and TAP-2 proteins are formed which can prevent antigen presentation by MHC class I molecules. The interferons are induced by TAP genes which are developed depending on the infection caused by virus.

Proteins are internalized by microsomal vesicles that act as the endoplasmic reticulum, which later attaches to MHC class I molecule in the lumen of microsome. Peptides are not transferred by mutant TAP genes by vesicles.

The MHC molecules are held in ER until they bind to a peptide. The MHC class I molecule has to bind to the peptide for it to become stable. MHC class I molecules are existed only in a partially folded state in the ER if the peptide supply to the ER is disrupted. This is the main reason why TAP genes fail to express MHC class I molecules on the surface of the cell.

The assembly and folding of the MHC class I is associated with  $\beta_2$  chain with  $\beta_2$ -microglobulin and then with peptide. The MHC molecule is only released from the ER after the peptide has been bound to the MHC molecule [09].

Transportation of MHC molecule:

\*Partially folded MHC class I  $\alpha\beta$  chains bind to calnexin until  $\beta_2$ -microglobulin binds

MHC class I  $\alpha\beta$ :  $\beta_2$  m complex is released from calnexin; binds a complex of chaperone proteins (Erp57) and binds to TAP via tapasin

\*Cytosolic proteins are degraded to peptide fragments by the proteasome, a large multicatalytic protease

TAP delivers a peptide that binds to the MHC class I molecule and completes its folding. The fully folded MHC class I molecule is released from the TAP complex and exported. MHC class I  $\alpha\beta$  chains bind to the chaperone protein and calnexin in ER. Assembly of folded T-cell receptors and immunoglobulins are also associated with calnexin. The heterodimer is dissociated from calnexin when  $\alpha\beta$  chains are bound to the  $\beta_2$ -microglobulin which later binds to a protein complex called calreticulin.

Tapasin; another TAP associated component develops the bridge between MHC class I molecules and TAP genes making the folded heterodimer wait for cytosol. Chaperone molecule; Erp57 is the third component of the complex that function in breaking and reforming MHC class I  $\alpha\beta$  bond. Finally, the attachment of the peptide TAP: tapasin: calreticulin: Erp57 complex releases the partially folded heterodimer when the peptide binds to it. The MHC molecule which is fully folded is able to leave the ER to the cell surface. MHC class I molecules are translocated back to cytosol when they become unstable in TAP mutated gene cells. The MHC molecules are then degraded [15].

MHC class I molecules which are retained in the endoplasmic reticulum for some time exposed to excess of peptide. This is very important for the function of MHC class I molecules because they must be immediately available to transport viral peptides to the cell surface if the cell becomes infected. When a cell is infected by a virus, the presence of excess MHC class I molecules in the endoplasmic reticulum allows the rapid appearance of pathogen-derived peptides at the cell surface.

Because the presentation of viral peptides by MHC class I molecules, cytokines signals CD8 T cells to kill the infected cell, some viruses have evolved ways of evading recognition by preventing the appearance of peptide on MHC class I complexes at the cell surface. The herpes virus prevents the transport of viral peptides into the endoplasmic reticulum by producing a protein that binds to and inhibits TAP. Adenoviruses, also encode a protein that binds to MHC class I molecules and retains them in the endoplasmic reticulum. Cytomegalovirus accelerates the retrograde translocation of MHC class I molecules back into the cytosol of the cell, where they are degraded. The advantage to a virus of blocking the recognition of infected cells is so great that it would not be surprising if other steps in the formation of MHC-peptide complexes, for example, the association of the MHC class I: chaperone complex with TAP, were found to be inhibited by some viruses.

If the individual is suffering from chronic respiratory bacterial infections and skin ulceration with vasculitis, it has been observed in small number of patients that they have almost no cell surface MHC class I molecule; and this condition known as MHC class I deficiency. Here, individuals have normal

levels of mRNA responsible for the encoding MHC class I molecules and normal production of MHC class I proteins, but not all of them could reach to the cell surface. This defect is similar to that in the TAP mutant cells mentioned previously, and mutations in either TAP1 or TAP2, which encode the subunits of the peptide transporter, have been found in patients with MHC class I deficiency [4].

If the individual have MHC class II deficiency where, CD4 T cells are low in number, due to the less secretion of stimulatory cytokines (IL 2 and INF gamma), less number of MHC class I molecules get activated and as they are already low in number due to the immunodeficiency, only few number of the infected cell get phagocytosis. People with MHC class I deficiency are not abnormally susceptible to viral infections, which is surprising given the key role of MHC class I presentation and of cytotoxic CD8  $\hat{\pm}$ :  $\hat{2}$  T cells in combating viral infections. There is, however, evidence for TAP-independent pathways for the presentation of certain peptides by MHC class I molecules, and the clinical phenotype of TAP1 - and TAP2-deficient patients indicates that these pathways may be sufficient to allow viruses to be controlled [8].

## **TREATMENT**

There are two types of treatment for this condition as listed below:

- Gene Therapy
- Bone marrow transplant

### **Gene therapy**

Gene therapy was first discovered in 1980s in which method of treatment, the cells are removed from the patient and in the laboratory; a virus is

altered so it cannot reproduce. A gene is inserted into the virus and the altered virus is mixed with cell from removed from patient. In the last step, the altered cells are injected into the patient where the genetically altered cells produce the desired protein or hormone. There are some approaches of gene therapy under study including: substitution of a mutated gene, inactivating or knocking out, and introduction of a new gene [03].

Even though this method seems to be useful for treatment of some disorders, but it is still under study and it has its own disadvantages

Some of the disadvantages are included in the table below:-

## **DISADVANTAGES**

Short lived nature of gene therapy

- DESCRIPTION: The rapid speed of division many cells may prevent the long term benefit

Expression problems

- DESCRIPTION: Gene might not express itself or the virus might not produce the desired response

Immune response

- DESCRIPTION: Non-self immune response

Viral vectors

- DESCRIPTION: Toxicity, immune, inflammatory response, and recovery of viral vectors to cause disease

Multigene disorder

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- DESCRIPTION: The gene inserted might mutate and cause disease

#### Insertional mutagenesis

- DESCRIPTION: If DNA integrated placed in the wrong genome i. e. tumour suppressor gene, might cause tumour

#### Ethical and legal problems

- DESCRIPTION: Some believe that this is an invasion of the privacy

#### Religious concerns

- DESCRIPTION: Some religions believe that this is an interference in God's work

#### Regulation

- DESCRIPTION: i. e insurance problems, terms and conditions, what should include or exclude.

However gene therapy works on some disorders, it is still experimental and has many disadvantages some of which is mentioned in the above table. Therefore the second type of therapy is considered as known as bone marrow transplant [16].

### **Bone marrow transplant**

The first successful Bone marrow transplant was performed in 1968 between two siblings. This technique involves the extraction; purification and transferring of stem cells found in bone marrow which is later placed where the unhealthy stem cells are to treat the patient. Bone marrow is also known as blood factory (fig1) and if it ever has any malfunction in its role, could even lead to death.

There are two type of Bone Marrow transplant:-

- Autologous - The donor and the recipient is the same person.
- Allogenic - The donor is a genetically different person from the recipient but their tissue is compatible. The best donors for this method are known to be the patient's siblings because of the inherited tissues; however 25 to 30% of the allogenic cases happen to be a sibling with compatible tissue [9].

There are genetic elements in human body known as human leukocyte antigens (HLA), which an immune response is dependent upon. The HLA typing is performed in Allogenic Bone marrow transplantation to determine whether the genotypes of the sibling donors are identical to the one that the patient has or not. There two drugs accustomed to remove the bone marrow of the patient. These drugs are " Busulfan" and " Cyclophosphamide".