INTRODUCTION

MHCs are a class of molecules that influence the capability of an organism to accept or reject transplanted tissues. In contrast to the B-cell receptors and antibodies which recognize the antigen single handedly, T-cell receptor (TCR) only recognizes the antigen processed and presented by MHC molecules [1,2]. The functions of MHC molecules include its binding to a peptide fragments derived from some pathogenic microorganism. Display of these antigens happens on the cell surface for its recognition by some suitable T-cells [3]. These cause deleterious effects on the pathogen, virus-infected cells are killed, and macrophages are also induced for killing bacteria to other pathogens living in their intracellular vesicles [3]. Parallel to these happenings, B-cells are activated to generate antibodies that remove or neutralize extracellular pathogens [4]. In course of all these events, there are chances in favor of any pathogen that it has mutated in such a way so as to escape from presentation by an MHC molecule [5]. MHC molecules decide upon the response of an individual to antigenic infection. Thus, its role is implicated in the susceptibility to the disease as well as in autoimmune disease [6]. "Human leukocyte antigen" is the expanded version of "HLA" which is similar to MHC in structure and function, is a group of antigens or proteins that are found at the surface of cells and in the genetic makeup or DNA [7]. A T-cell recognizes peptide antigen which is attached by a specific kind of allelic variant of an MHC molecule. It will not recognize the same peptide bound to other MHC molecules and this quality of T-cells is called MHC restriction [8].

They are the biological tools meant to identify and prevent a foreign protein or cell in entering or its spreading in an organism's body [2]. Being one of the important components of immune system, these proteins recognize between self and nonself [2,3]. The MHC molecules are often present in vertebrates while HLA is found only in humans and in the genetic makeup or DNA [7]. A T-cell recognizes peptide antigen which is attached by a specific kind of allelic variant of an MHC molecule. It will not recognize the same peptide bound to other MHC molecules and this quality of T-cells is called MHC restriction [8].

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One of the important components of the immune system, the major histocompatibility complex (MHC) molecules allow T-lymphocytes to detect cells, such as macrophages, B-lymphocytes, and dendritic cells that ingest infectious microorganisms or the self-cells infected with microorganism. On being engulfed a microorganism, macrophage partially digests it and displays peptide fragments of the microbe on its surface, bound to MHC molecules and the T-lymphocyte recognizes the foreign fragment attached to the MHC molecule and binds to it, lead to stimulation of an immune response. The MHC molecule presents peptides from its own cell (self-peptides) in healthy self-cells to which T-cells do not normally react.

Keywords: MHC, B Cells, T Cells, Antigen Processing.

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of the endoplasmic reticulum (ER) is accomplished by the transporter associated with antigen processing (TAP) which is a member of the ABC transporter family and is a heterodimeric multimer-spanning polypeptide consisting of TAP1 and TAP2 [15,16]. The two subunit forms of TAP are peptide binding site and two ATP binding sites that face the cytosol (Fig. 3). The antigenic or nonantigenic peptides are now bonded with TAP on the cytoplasmic side and translocate them by consuming ATPs into the lumen of the ER and then, the MHC Class I molecule is in turn loaded with peptides in the lumen of the ER. This complex phenomenon of peptide loading involves several other molecules that form a large multimeric complex consisting of TAP, tapasin, calreticulin, calnexin, and Erp57 [16]. Calnexin acts to stabilize the Class I MHC α chains before β2m binding [16,17]. Following complete assembly of the MHC molecule, calnexin dissociates. The MHC molecule lacking a bound peptide is inherently unstable and requires the binding of the chaperones calreticulin and Erp57 [16]. The protein tapasin binds to the MHC molecule to link it to the TAP proteins, to facilitate enhanced peptide loading and colocalization.

On being loaded with the peptide, the MHC Class I molecule, the complex dissociates and it leaves the ER through the secretory pathway to reach the cell surface. The transport of the MHC Class I molecules through the secretory pathway involves several post translational modifications of the MHC molecule, involving change to the N-glycan regions of the protein, followed by extensive changes to the N-glycans in the Golgi apparatus. The N-glycans’ form is the completely mature form before they reach the cell surface. Fig. 1 shows the processing and presentation of the antigen by MHC Class I molecule [17].

**MHC CLASS II MOLECULES**

MHC Class II consists of two polypeptide chains, α and β, each having two domains α1 and α2 and β1 and β2. Each chain is having a transmembrane domain, α2 and β2, respectively, for attaching the MHC to the cell membrane [19]. The peptide binding groove is consisted of the heterodimer of α1 and β1. MHC Class II molecules are normally express only on professional APCs such as macrophages, B-cells, and especially dendritic cells (DCs) [20]. Although they can be conditionally expressed by all cell types. An APC takes up an antigen, performs antigen processing, and returns a molecular fraction of it termed as the epitope to the APC’s surface, coupled within an MHC Class II molecule. The process is known as antigen presentation [20] (Fig. 4). In this unique presentation, the epitopes are recognized by Th-cells [19]. The CD4 receptors as well as TCRs are present on the surfaces of helper T-cells. When a CD4 molecule of a naive helper T-cell links to an APC’s MHC Class II molecule, its TCR can meet the epitope coupled within the MHC Class II, the phenomenon similar to the coupling of T with cytotoxic cells [19]. This event primes the naive helper T-cell. The varied combination of cytokines secreted by APCs in the microenvironment causes the naive helper T-cell to polarize into either a memory Th-cell or an effector Th-cell [19].

MHC Class II thus mediates immunization to APCs, differentiate the T-cell into memory, and effector cells so that in future if the same antigen invades the organism, the memory cells get activated and trigger the immune response [20]. The polarization during primary exposure to an antigen is key in determining a number of chronic diseases, including inflammatory bowel diseases and asthma, by inducing the immune response that is memory Th-cells coordinate when their memory recall is triggered upon secondary exposure to similar antigens [21].

In the phase of processing and presentation of the antigen, the phagocytes such as macrophages and immature dendritic cells take up antigenic entities by phagocytosis into phagosomes [22]. B-cells exhibit the more general endocytosis into endosome [23]. These phagosomes or endosomes fuse with lysosomes [22]. Its acidic enzymes cleave the uptaken protein into many different peptides. Out of these, a particular peptide exhibits immunodominance and loads onto MHC Class II molecules. APCs express both kind of MHC I & II molecules (Fig. 2). However, in the cell, there is highly advanced system exists to prevent Class II molecules from binding to same set of antigenic peptides as the Class I molecules [24]. In course of synthesis of MHC II in the ER, three pairs of Class II α β chains associate with a preassembled protein (trimeric) called invariant chain which interacts with peptide binding cleft of the MHC Class II molecules block the attachment of any endogenous peptide to the cleft [20]. The invariant chain complex with Class II molecule is now transported from the RER through golgi complex to endosome-lysosome assembly. During the journey from RER to the endosome-lysosome assembly, the invariant chain gets degraded under the influence of proteolytic enzymes and a small fragment CLIP (Class II-associated invariant chain peptide) remains attached to the Class II cleft [25]. For exchange of CLIP with antigenic
peptide, there is requirement of nonclassical Class II molecule which is called HLA-DM. It is a heterodimer but not polymorphic and is not expressed at the cell membrane. HLA-DM is found predominantly in the endosomal compartment. The reaction between HLA-DM and Class II CLIP complex facilitates the exchange of CLIP for another peptide. Now, the MHC Class II molecule uploaded with the antigenic peptide is trafficked to and externalized on the cell surface [26].

**MHC MULTIMERS**

The tailor-made various oligomeric forms of MHC molecules have been designed to identify and isolate T-cells with high affinity to specific antigens amid a large group of unrelated T-cells are known as MHC multimers. TCRs have a low affinity for their MHC counterparts. Initially, it was problematic to label T-cells effectively using single MHC-T-cell interactions. In 1996, John Altman used a complex of multiple MHC molecules to form a more stable bond between corresponding T-cells and this gave birth to the MHC multimers [27].

These multimeric molecules may range in size from dimers to octamers. Currently, few companies are using even higher quantities of MHC per multimer to increase their specificity. These molecules are used to display Class 1 MHC, CLASS 2 MHC, or nonclassical molecules such as CD1d from species such as monkeys, mice, and humans [27]. The most commonly used MHC multimers are tetramers which are typically produced by biotinylating soluble MHC monomers. Soluble MHC monomers are typically produced recombinantly in eukaryotic or bacterial cells and they then bind to a backbone, such as streptavidin or avidin, creating a tetravalent structure [28]. These backbones are conjugated with fluorochromes to isolate bound T-cells through flow cytometry technique. MHC multimers are of use in antigen-specific T-cell detection and isolation and their ability gives rise to several clinical applications. MHC multimers have broadened the strategy for ex vivo selection and proliferation of T-cells specific to viral or tumor-related antigens. These T-cells can then be reintroduced to augment the immune system. Beside its vast scope in T-cell selection and proliferation, MHC multimers can also be used to eliminate graft-originating T-cells on transplant organs, ex vivo and in vivo; these MHC multimers may also be used to eliminate harmful or unwanted T-cells, such as those that target self-cells and lead to autoimmune disease. We can do desirable modifications in cancer immunotherapy and vaccine development by involving MHC multimers [29].

**CONCLUSION**

The two major classes of MHC protein molecules are Class I and Class II. Class I MHC molecules span the membrane of almost every nucleated cell in an organism. On the other hand, class II molecules are concerned with cells of the immune system known as macrophages, dendritic cells, and lymphocytes. In human beings, these molecules are encoded by several genes which are clustered in the same region on chromosome 6 and each gene has an unusually large number of alleles which are actually alternate forms of a gene producing alternate forms of the proteins. Hence, rarely any two individual have the same type of set of MHC molecules, which are jointly known as tissue type. The MHC class III genes are so diverse and they encode for other proteins such as complement proteins, cytokines (chemical messengers), and enzymes. Besides multimer, MHC molecules have diverse scope in the field of clinical medicine and research. They can also be used to remove or arrest graft-originating T-cells due to organ transplant, ex vivo. In vivo, these MHC multimers may also be used to eliminate harmful or unwanted T-cells that lead to autoimmune disease.
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