T-cells are mhc restricted essay sample

T-cells, which belong to a group of white blood cells known as lymphocytes, play a vital role in cell mediated immunity. They differ from other lymphocyte types, such as B-cells and Natural Killer NK cells by the presence of the *T-cell receptor* (TCR). T cells are called as such because their development primarily is in the thymus.

T-cells are divided into two major groups. *T-helper* CD4+ cells, the " *middlemen* " of the adaptive immune system, secrete cytokines that holds a regulatory role in the immune response. *T -cytotoxic cells* CD8+ kill virally infected cells and tumor cells and are also an important factor in transplant rejection.

T-cells are further subdivided into *Th1* and *Th2.* The distinction between CD4 and CD8 occurs during their development in the thymus. This occurs only after these cells have been activated during immune activity in the peripheral lymphoid system.

T-cells originate from *hematopoietic stem cells* in the *bone marrow* . Hematopoietic precursors derived from hematopoietic stem cells populate the *thymus* and replicate to generate a large population of immature thymocytes. Thymocytes are the T-cell precursors which develop and mature in the *thymus* (Schwarz B A, Bhandoola A. 2006).

" Double-positive" thymocytes migrate into the thymic cortex where they are presented with host " self-antigens" complexed with *Major Histocompatibility Complex* MHC molecules on the cortical epithelial surface. Only those thymocytes with affinity to the MHC complex receive a vital " *survival signal* ." The remaining thymocytes die by *apoptosis* also known as *programmed*

cell death and their remains are phagocytosed by macrophages. This process is called *positive selection* . Double-positive cells that are positively selected on corresponding MHC class II molecules become CD4+ cells, and cells positively selected on matching MHC class I molecules become CD8+ cells.

Thymocytes that survive positive selection migrate towards the area between the thymic cortex and thymic medulla. While in the medulla, they are again presented with self-antigen complexed with *Major Histocompatibility Complex* MHC molecules on *antigen-presenting cells* APCs such as *dendritic cells* and *macrophages.* Thymocytes that react with the antigen receive an apoptosis signal that causes their " suicide". A majority of all thymocytes initially produced end die during thymic selection. A small minority of the surviving cells are selected to become regulatory T-cells. The remaining cells will then exit the thymus as " naïve" T-cells. This process is called *negative selection* , an important mechanism of immune self tolerance that prevents the formation of host-reactive T-cells capable of generating autoimmune disease in the host. (Baldwin TA, 2004) Around 98% of thymocytes die during the development processes in the *thymus* by means of failing *positive selection* or *negative selection,* while the other 2% survive and leave the *thymus* to become mature T-cells, ready for their immune function.

The *Major Histocompatibility Complex* MHC is a set of molecules displayed on cell surfaces that are responsible for lymphocyte detection and " *antigen presentation* ". The MHC molecules control the immune response through recognition of " *self* " and " *non – self* " and consequently, serve as targets

during transplantation rejection. MHC molecules are called *Human Leukocyte Antigens* HLA and are encoded in the MHC genes. Class I MHC proteins are expressed on all nucleated cells. Additionally, leukocytes express the most Class I MHC, with neural cells producing the least. Class II MHC proteins are found constitutively on B-cells, dendritic cells, and thymic epithelial cells. They also can be induced on macrophages and human T-cells.

T-cell activation vary slightly between different types of T-cells, with the " *two-signal model* " in CD4+ T cells holding true for most. Activation of CD4+ T cells occurs through the interaction of both the T-cell receptor and CD28 on the T-cell by the MHC complex peptide and B7 family members on the *antigen presenting cell* APC respectively. Both are required for production of an adequate immune response, especially in the absence of CD28 co-stimulation.

The first signal is initiated by linkage of the T-cell receptor to a short peptide presented by the MHC on another cell, ensuring that only a T-cell with a *T-cell receptor* TCR specific to that peptide is activated. The " buddy" cell is oftentimes a professional APC. In the case of naïve responses, it is usually a dendritic cell, although B-cells and macrophages can be important APCs.

Since antibodes cannot enter infected cells and phagocytes are unable to detect that they are infected, cytotoxic T-cells must then be activated to identify and kill the infected cells. To be activated by endogenous antigen, CD8 T-cells use their *T-cell receptor* TCR to attach endogenous antigen peptides presented on membrane Class I MHC proteins of the target or infected cells.

T-cells are MHC-restricted in their ability to see antigen. Consequently they only recognize antigen presented by *syngeneic or self* MHC on APC. CD4 T-cells bind the antigen on Class II MHC of professional APC, macrophages and B-cells. *T-cell receptor* TCR binds both the peptide and Class II MHC domains. CD8 T-cells identify antigen on infected Class I MHC cells. Unlike B-cells, T-cells fail to recognize antigens directly. They detect antigen only when associated with host surface *Major Histocomptability* MHC molecules. Since MHC molecules can only bind peptide molecules of 7-15 amino acids long, T-cells only recognize small peptides. The antigen presenting cells such as macrophages and B-cells consume antigen and partially degrade it into smaller peptides which then occupy the antigen-presenting groove in MHC-I and MHC-II molecules (Decker, 2006).

T-cells are unable to recognize intact antigens or non-protein antigens such as carbohydrates. The two classes of MHC molecule are MHC class I, which present intracellular antigens such as viruses, and MHC class II, which present extra cellular antigens such as bacteria . CD8+ T-cells can only detect antigen when associated with MHC I. The role of the CD8 molecule would be to bind MHC I and thus reinforce this association. Thus, without interaction with CD8, T-cells are not activated. CD4+ T-cells can only bind antigen in association with MHC II as they only bind to MHC II. Consequently, without interaction with CD4, T-cells will not be activated.

Activated T-cells kill the cells to which they bind, i. e. infected tissue cells. On the other hand, T-cells do not kill the cell that activates it, namely APC’s.

During their development, T-cells are selected in the thymus to recognize self *Major Histocompatibility Complex* MHC. Up to 5% of T-cells are able to respond to cells bearing *allogeneic* MHC, compared to a much lower frequency of T-cells which respond to a particular foreign peptide-self MHC complex. *Alloreactivity* of T-cells is responsible for rejection of grafts between individuals mismatched at their MHC loci. CD8 T-cells react to foreign Class I MHC while CD4 T-cells respond to foreign Class II MHC.

A disease called *bare lymphocyte syndrome* is characterized by a partial or complete deficiency in Class I or Class II MHC proteins in afflicted people. Victims of bare lymphocyte syndrome are especially vulnerable to viral and opportunistic infections. Symptoms range from none to *severe combined immune deficiency* (SCID). SCID is known for lack of both the humoral and cellular adaptive immune responses, dependent on the number of MHC loci that can be expressed.

In addition to Class I and Class II MHC, there are *minor histocompatibility antigens* that induce weaker graft rejection reactions. These are tissue-specific or sex-specific. Some are proteins encoded by viral DNA integrated with host cell DNA, while others are foreign peptides bound to Class I and Class II MHC. Occasionally, these trigger graft rejection episodes between identical twins (Decker, 2006).

A genetic association exists between *Human Leukocyte Antigens* HLA type and several diseases. These include insulin-dependent diabetes mellitus (IDDM), which occurs four times as often in people with HLA-DR4 as in people without the DR4 allele, idiopathic hemochromatosis, for which HLA-A3 allele

carriers have a sevenfold increased risk and with concommittant ankylosing spondylitis arthritis of spinal vertebrae. Thymic conditioning in people with certain alleles may fail to delete T-cells that cause autoimmunity (Decker, 2006).

In a study by Zhang (1993) *,* patients with multiple sclerosis were inoculated with irradiated *myelin basic protein* -reactive T-cells. T-cell responses to inoculated subjects were induced to deplete circulating MBP-reactive T-cells. Regulatory T-cell lines gathered from the recipients' repressed T-cells were used for vaccination. The cytotoxic action of the CD8+ T-cell lines was limited by major histocompatibility MHC antigens. It was then concluded that clonotypic interactions regulating auto reactive T-cells in humans can be induced by T-cell vaccination (Zhang J et al 1993).

Another study on *MHC-restricted and -unrestricted CD8 T cells* was done by Rau L, Cohen N, Robert J in 2001. According to Rau et al(2001):

CD8 function has been investigated in the frog Xenopus by antibody depletion, skin allografting, and tumor transplantation. Injection of adult frogs with anti-Xenopus CD8 monoclonal antibody effects transient CD8 T-cell depletion in vivo that correlates with delayed rejection of MHC-disparate skin allografts and an impaired immune response against transplanted syngeneic MHC class I-negative tumors.

It was then concluded that CD8 T-cells were involved in acute skin allograft rejection in ectothermic vertebrates. Their data also suggested that T-cells which express CD8 epitopes may be effectors in MHC-uninhibited anti-tumour reactions (Rau et al, 2001).

Positive selection pertains to those T-cells that react with MHC-self antigen. Negative selection rids the body of those that react strongly with MHC-self antigen. Consequently, effective T-cell differentiation selects for MHC restricted TCR's with low attraction or reactivity with self antigens, and cells that do not conform to this function die via apoptosis. A T-cell that binds inadequately to self MHC or self Antigen will not be activated but will be activated by a stronger linkage to self MHC oraforeignAntigen complex.

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