

## Unit 10 -Immunologic tolerance

### Introduction

Our own bodies produce some 100,000 different proteins and these proteins are capable of eliciting an immune response, but our bodies can be tolerable to these proteins and this is Self-tolerance.

**Definition:** immunological tolerance occurs when an immunocompetent host fails to respond to an immunogenic challenge with a specific antigen.

### General features of Immunologic tolerance

Tolerance is antigenic specific and results from the recognition of antigens by specific lymphocytes.

Normal individuals are tolerant of their own antigens (self antigen) -----Self-tolerance.

Foreign antigens may be administered in ways that can preferentially inhibit immune response by inducing tolerance in specific lymphocytes and it is called antigen induction.

Tolerance can be referred as specific immunological non-reactivity to an antigen resulting from a previous exposure to the same antigen. While the most important form of tolerance is non-reactivity to self antigens, it is possible to induce tolerance to non-self antigens. When an antigen induces tolerance, it is termed tolerogen.

### Tolerance to self antigens

Organisms do not mount a strong immune response against its own (self) antigens, a phenomenon called self-tolerance. When the immune system recognizes a self antigen and mounts a strong response against it, autoimmune disease develops. Nonetheless, the immune system has to recognize self-MHC to mount a response against a foreign antigen. Thus, the immune system is under pressure to discriminate between self and non-self antigen to mediate the right response.

Tolerance to tissue and cell antigens can be induced by injection of hemopoietic (stem) cells in new born or severely immunocompromised animals. Also, grafting of thymus from different animal in early induce tolerance in the animal to the cells and tissue of donor animal. Such animals are known as chimeras.

### Mechanism of tolerance induction

The exact mechanism of induction and maintenance of tolerance is not fully understood, but there are several mechanism to induce tolerance. They are:-

### Clonal deletion

T and B lymphocytes during development come across self antigens and such cells undergo clonal deletion through a process known as apoptosis or programmed cell death. But sometimes these cells can escape and can trigger autoimmune disease.

### Peripheral tolerance

The clonal deletion is not a fool proof system and often T and B cells fail to undergo deletion but enter the periphery, here the regulatory T cells recognize these cells and prevent these cells from exerting autoimmunity.

### **Activation-induced cell death**

T cells upon activation not only produce cytokines or carry out their effector functions but also die through programmed cell death or apoptosis. In this process, the death receptor (Fas) and its ligand (FasL) play a crucial role. Thus, normal T cells express Fas but not FasL. Upon activation, T cells express FasL which binds to Fas and triggers apoptosis.

### **Clonal anergy**

Auto-reactive T cells when exposed to antigenic peptides on antigen presenting cells (APC) that do not possess the co-stimulatory molecules become anergic (nonresponsive) to the antigen. B cells when exposed to large amounts of soluble antigen down-regulate their surface IgM and become anergic. These cells also up-regulate the Fas molecules on their surface. An interaction of these B cells with Fas-ligand bearing T cells results in their death via apoptosis.

### **Clonal ignorance**

Sometimes T cells reactive to self-antigen mature and migrate to the periphery, but they may not come across the appropriate antigen because it may be embedded in the tissue and inaccessible to T cells. These cells may die later. Likewise, the B cells capable of autoimmunity that escape deletion, may not find the antigen or the specific T-cell help and thus not be activated and die out.

### **Anti-idiotypic antibody**

These are antibodies that are produced against the specific idiotypes of other antibodies. Anti-idiotypic antibodies are produced during the process of tolerization and have been demonstrated in tolerant animals. These antibodies may prevent the B cell receptor from interacting with the antigen.

### **Regulatory T cells (Formerly called suppressor cells)**

These regulatory T cells suppress the function of other T cells which are engaged in combating the pathogen. But the exact mechanism through which regulatory T cells suppress other T cell function is unclear.

### **Termination of tolerance**

Termination of tolerance can be induced by

- Prolonged absence of exposure to the tolerogen,
- Severely damaging the immune system (x-irradiation)

- Immunization with cross reactive antigens.