**IMMUNOLOGY 2**

**TOLERANCE AND AUTOIMMUNITY**

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**Learning Objectives:**

* To understand the concept of immunological tolerance
* To understand the mechanisms underlying immunological tolerance
* To understand how defects in tolerance lead to autoimmune diseases and know examples of these

**Tolerance**

The immune system mounts specific responses to proteins from microorganisms and has the capacity to retain a memory of those proteins.

How does the immune system avoid recognition of proteins from the individual itself? This is critical since such recognition could potentially lead to the destructive immune responses against one’s own tissues.

Tolerance is defined as [the](http://www.webster-dictionary.org/definition/the) [*acquired*](http://www.webster-dictionary.org/definition/acquired) [inability](http://www.webster-dictionary.org/definition/inability) [to](http://www.webster-dictionary.org/definition/to) [respond](http://www.webster-dictionary.org/definition/respond) [with](http://www.webster-dictionary.org/definition/with) [an](http://www.webster-dictionary.org/definition/an) [immune](http://www.webster-dictionary.org/definition/immune) [reaction](http://www.webster-dictionary.org/definition/reaction) [to](http://www.webster-dictionary.org/definition/to) [an](http://www.webster-dictionary.org/definition/an) [antigen](http://www.webster-dictionary.org/definition/antigen) [to](http://www.webster-dictionary.org/definition/to) [which](http://www.webster-dictionary.org/definition/which) [the](http://www.webster-dictionary.org/definition/the) [organism](http://www.webster-dictionary.org/definition/organism) [normally](http://www.webster-dictionary.org/definition/normally) [responds](http://www.webster-dictionary.org/definition/responds).

There are two major mechanisms which achieve tolerance to self proteins.

1. Central tolerance

2. Peripheral tolerance

Tolerance is required for both T-cells (which help the responses of other immune cells) and B-cells (which produce specific antibodies).

**Central tolerance**

* Central tolerance for **T**-cells
* occurs in the **T**hymus, where cells excluded or retained according to the affinity of their receptors for peptide antigen and the abundance of antigen.
* dependent on MHC: peptide: T-cell receptor interaction
* Most cells die by neglect: no or very weak recognition
* **Negative selection** occurs in ca. 5% of cells: high affinity, high abundance
* Cells die by apoptosis (possibly other mechanisms also)
* Surviving cells undergo **positive selection** on low affinity, low abundance self peptides
* Central tolerance for **B**-cells
* occurs in **B**one marrow
* crosslinking of surface Immunoglobulin by polyvalent antigens expressed on bone marrow stromal cells facilitates **deletion.**

**Peripheral Tolerance**

* Many antigens may not be expressed in the thymus or in serum and are sometimes expressed only after the immune system has matured.
* Mechanisms are required to prevent selected T-cells, which may have low Affinity for self peptide-MHC complexes becoming auto-reactive.

Tolerance in the periphery is controlled by a number of different mechanisms:

* Anergy: a refractory state resulting from antigenic stimulation under unusual conditions.
* Ignorance: expression of self antigen at immunologically privileged sites
* Suppression: negative regulation of potentially autoreactive cells by specialised factors or cells.

**Autoimmunity**

* Results from failures in central or peripheral tolerance

Failure in central tolerance can occur:

* When a particular self protein is absent or mutated. Subsequent exposure to the native form of this protein will promote an auto-immune response.
* When the mechanisms involved in the removal of autoreactive cells during   
  T- or B-cell selection are faulty.

Failure in peripheral tolerance can occur

* When mechanisms of peripheral tolerance are faulty.
* As a result of infection.

Clinical examples will be given.