

# IMMUNOLOGICAL TOLERANCE

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**Tolerance is a specific immunological unresponsiveness of an individual to antigen**

# INTRODUCTION

- **In 1948 Burnet and Fenner first suggested that lymphocytes would not respond to an antigen if they first met that antigen during fetal life.**
- **In 1945 Ray and Owen had observed that cows with dizygotic (not identical) twin calves had fused placental blood vessels. Therefore these animals had mixture of blood of both animals moved freely between them without inducing immune responses to self antigens. This is called a CHIMERA.**

# MECHANISMS OF IMMUNOLOGICAL TOLERANCE

- **There are several characteristics of self-tolerance in T and B lymphocyte populations and many of these are also features of tolerance to foreign antigens.**
  - 1-Tolerance results from the recognition of antigens by specific lymphocytes.**
  - 2-Self-tolerance may be induced in immature self reacted lymphocytes in generative lymphoid organs (central tolerance) or in mature lymphocytes in peripheral sites (Peripheral tolerance).**

## MECHANISMS-----

- 3-Normal individuals are tolerated of their own antigens because the lymphocytes that recognize self antigens are killed or inactivated, or change their specificity.**
  - 4-Central tolerance occurs because during their maturation in the generative lymphoid organs, all pass through a stage in which encounter with antigen leads to cell death or the expression of new antigen receptors or a change in functional capabilities.**
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## **MECHANISMS -----**

- 5-Peripheral tolerance occurs when mature lymphocytes that recognize self antigen, become incapable of responding to that antigen, or lose their viability and become short-lived cells, or are induced to die by apoptosis.**
- 6-Some self antigens may be ignored by the immune system, so that lymphocytes encounter the self antigen but failed to respond in any detectable way remain viable and functional**

# T LYMPHOCYTE TOLERANCE

- During their maturation in the thymus, many immature T cells that recognize antigens with high avidity are deleted.
- Peripheral Tolerance is the mechanism by which mature T cells that recognize self antigens in peripheral tissues become self antigens in peripheral tissues become incapable of subsequently responding to these antigens.
- Anergy (Functional unresponsiveness) results from biochemical or genetic alterations that reduce the ability of lymphocytes to respond to self antigens.

## B LYMPHOCYTE TOLERANCE

- Immature B lymphocytes that recognize self antigens in the bone marrow with high affinity either change their specificity or are deleted (Central Tolerance).
- Mature B lymphocytes that recognize self antigens in peripheral tissues in the absence of specific helper T cells may be rendered functionally unresponsive or die by apoptosis (Peripheral Tolerance).
- Clonal abortion only occurs if B cells encounter early in their development within the bone marrow.

# CLONAL ANERGY

- Because self-tolerance is essential to survival, the body cannot rely solely on negative selection within the thymus to ensure that all self reactive cells are suppressed. Some self-reactive T cells may escape from the thymus and must be suppressed by other mechanisms. This form of suppression is called clonal anergy.
- Negative selection occurs when the TCR on a thymocyte binds to epitopes on antigen presenting cells or thymic epithelial cells and triggers thymocyte apoptosis.

# CAN WE INDUCE TOLERANCE EXPERIMENTALLY

- **Historically, three types of experimental protocols for inducing tolerance have been identified.**
  - 1-Antigen that can induce immune response in adult, can induce tolerance in newborn animals.**
  - 2-Tolerance can be induced in adult animals to thymus-independent antigens such as Pneumococcus polysaccharide by administration of a dose of Ags 10 to 100-fold higher than the immunizing dose.**
  - 3-Tolerance can be induced to soluble thymus-dependent Ags in adults by the following procedures:**

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**a-The use of immunosuppressive agents together with Ags.**

**Examples:**

**X-Ray irradiation**

**Methotrexate**

**Cyclophosphomide**

**6-mercaptopurine**

**b-The use of low doses of soluble antigens such as bovine serum albumin, or the use of very high doses of Ags iv far above the immunogenic dose.**

**c-The injection of the soluble protein antigen free of aggregated or polymerized molecules. Such Ag has to be injected iv , and is believed to bypass the macrophage presenting step of immune induction.**

# PARAMETERS OF EXPERIMENTAL TOLERANCE

- 1-The immunological maturity of the animal.
- 2- The inherent immunogenicity of the antigen
- 3-The route of administration, the iv being the preferred route.
- 4-The physico-chemical state of antigen.
- 5-The dose of the antigen.