Immunological Tolerance

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Introduction

• Definition: Unresponsiveness to an antigen that is induced by exposure to that antigen

• Tolerogen = tolerogenic antigen = antigen that induces tolerance
Important for several reasons

• Self-tolerance

• May be used for: - autoimmune diseases
  - allergic diseases
  - transplantation
  - gene therapy
Experiments

- Peter Medawar et al. ...1950s
Self-tolerance

• Central

• Peripheral
Central tolerance

• Immature self-reactive T or B cells

• In generative lymphoid organs

• It is not known why high-affinity binding to self antigens induces apoptosis rather than activation/proliferation
Peripheral tolerance

• Not all self antigens may be present in the thymus, and hence T and B cells bearing receptors for such autoantigens escape into the periphery

- Anergy
- Suppression by Tregs
- Deletion by apoptosis

• These mechanisms are best defined for T cells, especially CD4+
Anergy

= functional unresponsiveness

• Activation of antigen-specific T cells requires two signals: recognition of peptide antigen in association with self MHC molecules on the surface of APCs and a set of costimulatory signals ("second signals") from APCs

By binding of molecules on T cells to their ligands (the costimulators B7-1 and B7-2) on APCs
Anergy, cont’d

• On resting dendritic cells in normal tissues...costimulatory molecules are weakly expressed

This encounter with autoreactive T cells induces anergy

These resting APCs present self antigens of that tissue by this way (little or no costimulation and absent innate response)
Anergy, cont’d

• CTLA-4 binds to B7 with high affinity
  ...so when APCs present self antigens (low levels of B7)...CTLA-4 is preferentially engaged

  ...microbial products elicit innate immune reactions ➔ B7 levels on APCs increase and low-affinity receptors on T cells are engaged more

• Polymorphisms in the *CTLA4* gene are associated with some autoimmune endocrine diseases in humans
Anergy, cont’d

• Regulatory T cells may also use CTLA-4 to suppress immune responses

• Some tumors and viruses may use the same pathways of immune regulation to evade immune attack

  antibodies are developed that block CTLA-4 and PD-1 for tumor immunotherapy
Suppression by regulatory T cells

- They develop mainly in the thymus, as a result of recognition of self antigens
- They may also be induced in peripheral lymphoid tissues
- The best-defined regulatory T cells:
  - CD4+ & expressing high levels of CD25 (the α chain of the IL-2 receptor)
  - FOXP3...a transcription factor of the forkhead family
Suppression by regulatory T cells

• IL-2 and FOXP3 are required for the development and maintenance of functional CD4+ regulatory T cells

*IPEX* (an acronym for immune dysregulation, polyendocrinopathy, enteropathy, X-linked) is a severe systemic autoimmune disorder

*Recent studies: polymorphisms in the *CD25* gene are associated with multiple sclerosis*
Suppression by regulatory T cells, cont’d

• Of Treg inhibitory activity: release of **immunosuppressive cytokines**

  ...Tregs also express CTLA-4

  IL-10, TGF-beta, etc.
Deletion by apoptosis

• 2 mechanisms of inducing death in mature self-reactive T cells...based on animal studies:

  -Expression of pro-apoptotic member of the Bcl family without anti-apoptotic members

  -Fas (CD95)-Fas ligand system
  ...for deleting B or T cells
  ...in mice, mutation in Fas or Fas ligand: autoimmune disease resembling SLE
  ...in human, mutations in Fas gene cause ALPS (autoimmune lymphoproliferative syndrome)
Ignorance

• Some antigens in certain tissues are hidden (sequestered) from the immune system ...no communication with the blood and lymph

...self antigens in these tissues are ignored by the immune system

...like the testis, eye and brain

“Immune-privileged sites” because it is difficult to induce Immune responses to antigens introduced into these sites

...post-traumatic orchitis and uveitis
Mechanisms of autoimmunity: General principles
Role of Susceptibility Genes

• Most autoimmune diseases are complex multigenic disorders

• Among the genes known to be associated with autoimmunity, the greatest contribution is that of HLA genes

• Ankylosing spondylitis and \textit{HLA-B27}

• The mechanisms underlying these disease associations remain poorly understood

• Different HLA alleles may contribute to a disease but their presence is not, by itself, the cause of any disease
Role of Susceptibility Genes, cont’d

• Association of Non-MHC Genes with Autoimmune Diseases

-PTPN22 association with rheumatoid arthritis, type 1 diabetes, and several other autoimmune diseases

-NOD2 and Crohn disease
• Polymorphisms in the genes encoding the *IL-2 receptor (CD25)* and *IL-7 receptor α* chains are associated with multiple sclerosis and other autoimmune diseases.

...These cytokines may control the maintenance of regulatory T cells.
Association of Non-MHC Genes with Autoimmune Diseases, cont’d

• Remember: AIRE, CTLA4, PD1, FAS, FASL, and IL2 and its receptor CD25

• B cells express an Fc receptor that recognizes IgG antibodies bound to antigens and switches off further antibody production (a normal negative-feedback mechanism)

  ...Knockout of this receptor results in autoimmunity, presumably because the B cells can no longer be controlled
Role of Infections

A. Induction of costimulators on APCs

1. Microbe
2. Self-antigen
3. APC expresses costimulatory molecules
4. Self-reactive T cell
5. Self tissue
6. Autoimmunity

B. Molecular mimicry

1. Microbe
2. Microbial antigen
3. Self-reactive T cell that also recognizes microbial peptide
4. APC presents microbial peptide that resembles self antigen
Thank You