Autoimmunity

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Autoimmunity

- Immune recognition and injury of self tissues (autoimmunity) results from a loss of self tolerance.

Self Tolerance

- Tolerance to self is acquired by clonal deletion or inactivation of developing lymphocytes.
  - Clonal deletion by ubiquitous self antigens
  - Clonal inactivation by tissue-specific antigens presented in the absence of co-stimulatory signals
Peripheral T cell Tolerance Mechanisms

- **Immunological Ignorance**: Very few self proteins contain peptides that are presented by a given MHC molecule at a level sufficient for T cell activation. Autoreactive T cells are present but normally not activated.
- **Suppressor or regulatory T cells**: mediate active suppression of autoreactive cells

Peripheral T cell Tolerance Mechanisms

- **Immunologically privileged sites**: no lymphatic drainage or non-vascularized areas; presence of immunosuppressive factors & FasL

Peripheral B cell Tolerance Mechanisms

- **Contact with soluble antigens**:
  - downregulation of surface IgM, inhibition of signaling → anergic cells
  - Fas-mediated apoptosis of anergic B cell following secondary encounter with CD4 T cell
Peripheral B cell Tolerance Mechanisms

• Contact with soluble antigens
  – Apoptosis of autoreactive B cells generated by somatic hypermutation in germinal centers

Peripheral B cell Tolerance Mechanisms

• Lack of T helper cell signals:
  – anergy
  – inhibited migration into follicles & apoptosis in T cell areas of lymph tissue
Loss of Self Tolerance

- Most self peptides are presented at levels too low to engage effector T cells whereas those presented at high levels induce clonal deletion or anergy.
- Autoimmunity arises most frequently to tissue-specific antigens with only certain MHC molecules that present the peptide at an intermediate level recognized by T cells without inducing tolerance.

MHC Association with Autoimmune Disease

- The level of autoantigenic peptide presented is determined by polymorphic residues in MHC molecules that govern the affinity of peptide binding.
- Autoimmune diseases are associated with particular MHC genotypes.
MHC Association with Autoimmune Disease

• Only a few peptides can act as autoantigens so there are a relatively few autoimmune syndromes.
• Individuals with a particular autoimmune disease tend to recognize the same antigens with the same MHC.

Fig. 13.4
Type I Diabetes association with HLA genotype

Mechanisms for Activation of Autoreactive Lymphocytes

• **Infectious triggers**:  
  – stimulation of co-stimulatory signals, inappropriate MHC II expression, or cytokines  
  – Molecular mimicry (cross-reaction)  
  – Release of sequestered antigens  
  – T cell bypass (pathogen binding to self protein/provision of carrier T cell epitope)
Mechanisms for Activation of Autoreactive Lymphocytes

- Infectious triggers:
  - Superantigen activity/polyclonal activation
Organ-specific Autoimmune diseases

- Antigens and autoimmunity restricted to specific organs in the body
  - Type I diabetes
  - Goodpasture’s syndrome
  - Multiple sclerosis
  - Grave’s disease
  - Hashimoto’s thyroiditis
  - Myasthenia gravis

Systemic Autoimmune Disease

- Antigens and autoimmunity are distributed in many tissues (systemic)
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Scleroderma
  - Primary Sjogren’s syndrome
  - Polymyositis
Determinant spreading