MOLECULAR IMMUNOLOGY – Manipulation of immune response

Autoimmune diseases & the pathogenic mechanism

SCHMAIEL SHIRDEL
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- Classification
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Autoimmune diseases & pathogenic mechanisms

- Systemic lupus erythematosus
- Type 1 diabetes
- Multiple sclerosis
- Rheumatoid arthritis

Summary
INTRODUCTION
Autoimmune diseases (AD)

- Autoimmunity adaptive immunity specific for self antigens
  → potential antigen on tissues, against immune response usually not made, except in autoimmunity

- AD in which pathology caused by adaptive immune response to self antigen

- In the west ~5% have an AD

- Cause is generally unknown

- Some are hereditary, some may be triggered by infections or other environmental factors
Classification

- Autoimmune diseases can be classified into clusters

- Organ-specific
  → expression of autoimmunity restricted to specific organs of body

- Systemic
  → many tissues of body affected

- Both chronic because autoantigens never cleared from the body

- Some AD's dominated by pathogenic effects of particular immune effector pathway
  → either autoantibodies or activated T cells

Organ specific autoimmune diseases

- Type 1 diabetes mellitus
- Goodpasture’s syndrome
- Multiple sclerosis
- Psoriasis
- Crohn’s disease
- Graves’ disease
- Hashimoto thyroiditis
- Autoimmune hemolytic anemia
- Autoimmune Addison’s disease
- Vitiligo
- Myasthenia gravis

Systemic autoimmune diseases

- Rheumatoid arthritis
- Scleroderma
- Systemic lupus erythematosus
- Primary Sjögren’s syndrome
- Polymyositis
Involved components

- **Autoantibodies:**
  - antibody specific for self antigens
  - recognize: acetylcholine receptors

- **Antibodies as immune complexes**
  - complement activation and ligation of Fc receptors
  - damage: inflammation of tissue

- **Effector T cells**
  - recognize: self peptides of self-MHC
  - damage: local inflammation or direct tissue damage
## Involved components

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- T cell can have multiple roles:
  - helping B cells make antibody & directly promoting tissue damage

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Autoimmune diseases & pathogenic mechanisms
Systemic Lupus Erythematosus
Pathology of systemic lupus erythematosus (SLE)

- Lupus is a rare chronic disease that causes systemic inflammation affecting multiple organs: skin, joints, kidneys
- Symptoms: fatigue, weight loss, fever
- Usual on set: 15-45 year old
- Frequency: 2-7 per 10.000 (2006)
- Woman affected nine times more than men (2014)

Malar rash after sun exposure, source: wikipedia
Deposition of immune complexes in renal glomerulus causes renal failure in SLE

- Deposition of immune complex → thickening of glomerular basement membrane (a)

- Electron microscope: immune complex as dense deposits between glomerular basement membrane and renal epithelial cells (c)

- Polymorphonuclear neutrophilic leukocytes present, attracted by deposit immune complex

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Pathogenesis of systemic lupus erythematosus (SLE)

- Immune system attacks tissue they normally protect
- Dead and dying cells release nuclear parts from injured tissues
- Because of defect → immune cells recognize nuclear parts as foreign
- If not cleared B cells produce antibodies, which bind antigens
  → continuously immune complex
  → deposited in walls of small blood vessels (joints, other organs) causing inflammation
Defective clearance of nucleic acid-containing immune complexes activates overproduction of BAFF and type I interferons that can cause SLE

- Nucleus → apoptosis, release of nucleic acid immune complexes containing ssRNA / dsDNA from dead cells bound by FcγRIIa on plasmacytoid dc’s

- The Fc receptor-bound ssRNA & dsRNA delivered to endosomes
  → activate TLR-7 and TLR-9, release of cytokines
  → induce IFN-α production

- In addition nucleosomes (DNA/histone) also recognized by TLR receptor

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Defective clearance of nucleic acid-containing immune complexes activates overproduction of BAFF and type I interferons that can cause SLE

- IFN-α increases BAFF production by monocytes & dendritic cells

- BAFF interacts with receptors on B cells

- Excess BAFF can increase autoreactive B-cell survival
  → increased autoantibody production
Type I Diabetes
Pathology of type 1 diabetes

- Form of diabetes mellitus, not enough insulin produced → high blood sugar

- Symptoms: frequent urination, increased hunger, weight loss
  Long term: kidney failure, heart disease, stroke

- Treatment: insulin, diabetic diet for survival

Source: Diabetes.co.uk
T cell specific for self antigen can cause direct tissue injury and sustain autoantibody responses

- In diabetes glucose not in cells, stays in blood → high glucose level

- Insulin → decrease blood glucose

- Glucagon → increase blood glucose

- Insulin-producing β-cells of pancreatic islet of Langerhans in disease selectively destroyed by specific cytotoxic T cells (CD8 T cells) → loss of self tolerance

- Rare cases: patients with diabetes were transplanted with half a pancreas from identical twin donor → β-cells in grafted tissue were rapidly and selectivly destroyed by recipients T cells → can be prevented by immunosuppresive drug cyclosporin A, which inhibits T cell activation
Selective destruction of pancreatic β-cells in type 1 diabetes indicates that autoantigen is produced in β-cells and recognized on their surface

- Destruction of insulin producing β-cells in pancreatic islet of Langerhans

- Other islet cell types (α and δ) spared

The islets of Langerhans contain several cell types secreting distinct hormones. Each cell expresses different tissue-specific proteins.

In type 1 diabetes an effector T cell recognizes peptides from a β-cell specific protein and kills the β cell.

Glucagon and somatostatin are still produced by the α and δ cells, but no insulin can be made.

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Selective destruction of pancreatic β-cells in type 1 diabetes indicates that autoantigen is produced in β-cells and recognized on their surface

- Islets from normal & diabetic mice stained
  - insulin (brown) → β-cells
  - glucagon (black) → α-cells.

- Lymphocytes infiltrating islet in diabetic mouse & selective loss of β-cells, α-cells spared

- Characteristic morphology of islet disrupted with loss of β-cells

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Multiple Sclerosis
Pathology of multiple sclerosis (MS)

- Demyelinating disease, myelin is damaged
- Patients develop neurological symptoms: muscle weakness, ataxia, blindness, paralysis of limbs
- Usual on set: 20-50 years old
- 5-10 year shorter life expectancy
- Frequency: 2 Million (2015)
Pathogenesis of multiple sclerosis (MS)

Videosource:
https://www.youtube.com/watch?v=yzH8ul5PSZ8
Pathogenesis of multiple sclerosis

- T cell-mediated chronic neurological disease

- Caused by destructive immune response against brain antigens:
  Myelin basic protein (MBP), proteolipid protein (PLP), myelin oligodendrocyte glycoprotein (MOG)

Images:
- MBP: Jawahar Swaminathan et al., EMBL-EBI
- MOG: McMahon et al., (2011)
- PLP: Craig S. Clements et al. PNAS 2003
Pathogenesis of multiple sclerosis

- Name derived from hard (sclerotic) lesions/plaques
  → develop in white matter of central nervous system (CNS)

- Lesions show dissolution of myelin
  → sheathes nerve cell axons, inflammatory infiltrates of lymphocytes & macrophages along blood vessels

- Normally blood cells do not cross blood brain barrier (BBB)

- If brain & blood vessels become inflamed
  → BBB breaks down
Pathogenesis of multiple sclerosis

- Activated CD4 T cells bind VCAM* on activated venule endothelium surface → T cells migrate to blood vessel

- Reencounter specific autoantigen presented by MHC class II molecules on microglia cells → macrophage like cells of innate system in CNS

- Inflammation causes increased vascular permeability → sites infiltrated by $T_{H17}$ & $T_{H1}$ cells → produce of IL-17 & IFN-γ

* vascular cell adhesion molecules
Pathogenesis of multiple sclerosis

- Cyto- & chemokines produced by infiltrating effector T cells recruit & activate myeloid cells ↑ inflammation
  → further recruitment of B cells, T cells, innate immune cells

- Autoreactive B cells produce autoantibodies against myelin AG with help from T cells

- Combined activity
  → demyelination & interference with neuronal function
Pathogenesis of multiple sclerosis

1. **Unknown trigger sets up initial focus of inflammation in brain, and blood–brain barrier becomes locally permeable to leukocytes and blood proteins**

2. **T cells specific for CNS antigen and activated in peripheral lymphoid tissues reencounter antigen presented on microglia or dendritic cells in brain**

3. **Inflammatory reaction occurs in the brain due to mast-cell activation, complement activation, antibodies, and cytokines**

4. **Demyelination of neurons occurs**

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Pathogenesis of multiple sclerosis

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Rheumatoid arthritis
Rheumatoid arthritis (RA)

- RA is a systemic disease → affect the whole body
- 0.8% of adult population, woman 3 times more affected than men
- Characterized by inflammation of synovium around the joints
- As disease progresses → inflamed synovium invades & damages cartilage → followed by erosion of bone
- Chronic pain, loss of function, disability

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Pathogenesis of rheumatoid arthritis

- First considered an AD driven mainly by B cells producing anti-IgG autoantibodies
  → **rheumatoid factor**

- Factor in some healthy patients, absent in some affected
  → more complex mechanism

- Discovery: RA associated with particular class II HLA-DR genes of MHC
  → T cells involved in pathogenesis

- Autoreactive CD4 T cells activated by dc’s & by inflammatory cytokines
  → T cells help B cells to differentiate into plasma cells producing arthrogogenic ABs
Pathogenesis of rheumatoid arthritis

- Type II collagen, proteoglycans, aggregan proposed as potential antigens
  → induce arthritis in mice, in human ascertain

- Activated T cells produce cytokines, stimulate monocytes/macrophages, endothelial cells, fibroblasts to produce more pro inflammatory cytokines: TNF-α, IL-1, IFN-γ or chemokines (CXCL8, CCL2) and finally MMps*
  → responsible for tissue destruction

*matrix metalloproteinases
Pathogenesis of rheumatoid arthritis

Unknown trigger sets up initial focus of inflammation in synovial membrane, attracting leukocytes into the tissue.

Autoreactive CD4 T cells activate macrophages, resulting in production of pro-inflammatory cytokines and sustained inflammation.

Cytokines induce production of MMP and RANK ligand by fibroblasts.

MMPs attack tissues. Activation of bone-destroying osteoclasts by RANK ligand results in joint destruction.

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Summary

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- Autoimmune diseases classified into two clusters:
  - Organ-specific
  - Systemic
- Induce of autoimmune diseases unknown
- Involved components:
  - autoantibodies, antibodies as immune complexes, effector Tcells
References


THANK YOU FOR YOUR ATTENTION!