Monday, October 29, 2018

IMM2022 - Immunology in Health and Disease

Lecture objectives - Week 1 (Hypersensitivities)

1. Name the different types of immune hypersensitivities

Hypersensitivity are classified based on their *immunological mechanism* that causes pathology (tissue injury and disease).

There are 4 types of hypersensitivities:

1. Immediate (Type 1) - Allergies
2. Antibody mediated (Type 2)
3. Immune complex mediated (Type 3)
4. T-cell mediated (delayed) (Type 4)

- Allergies (type 1)
- Autoimmune diseases/contact sensitivity (Type 2 - 3)

2. Describe the key mechanisms of pathology associated with each type of hypersensitivity and give some examples of these pathologies associated.

Hypersensitivity	Mechanism of tissue injury and disease	Pathologic immune mechanisms
Type 1 (Allergies)	Th2 cells, IgE antibody , mast cells, eosinophils • Rapid reaction - vascular leakage, mucosal secretions, inflammation • Atopy - Predisposition to allergy • Allergy - generation of immune reaction	Mast cell-derived mediators (vasoactive amines, lipid mediators, cytokines).

Priming Period
- IgE binds strongly to the IgE Fc receptors found on inflammatory cells such as mast cells
- Repeat exposure to allergen cross links the IgE on mast cell.
- Cross linking causes activation of inflammatory mediators

Immediate (reaction)
- IgE and mast cell
- First 5-10 mins

Late phase (reaction)
- Infiltration of leukocytes causing swelling
- 2-4 hours max 24 hours.
- Much more exaggerated

*~ **Antibodies** are the ones that are being made and being sensitive to the allergen ~*

This activation can lead to:
- Vascular dilation, smooth muscle contraction (bronchi)
- Tissue damage
- Vascular dilation (decreased blood pressure)
- Smooth muscle contraction
- Inflammation (leukocyte recruitment)

Examples - **Nut, Food allergies, anaphylaxis (nuts, shellfish, penicillin, bee stings), bronchial asthma**

Hypersensitivity	Mechanism of tissue injury and disease	Pathologic immune mechanisms
Type 2 (Autoimmune Disease) • Antibody mediated	IgM, IgG antibodies against cell surface or extracellular matrix antigens.	Complement - and Fc receptor-mediated recruitment and activation of leukocytes (neutrophils, macrophages). Opsonization and phagocytosis of cells. Abnormalities in cellular function (e.g., hormone or neurotransmitter receptor signaling)

- Immunoglobulins/antibodies can cause disease by binding to it's target antigen on cells or tissues.
- Targets are most often self-antigens.
- Outcomes of this binding may vary and may include:
    - Destruction of the cell or tissue damage.
    - Blockage of function (stops activity).
    - Activation of function (over/hyper activity).

Destruction

- Antibody binds to self antigen on cell and then leads to complement activation.
- Results in recruitment of inflammatory immune cells and tissue injury.
- Tissue damage occurs due to all the other mediators being present.
- Opsonization can also occur:
    - Can make certain cells for recycling as they are thought to be dead (i.e., RBC's and platelets; leads to anaemia).

Activation

- Mimics the natural agonist.
- The binding stimulates the receptor but there is no feedback control (normal process).
    - Other areas of the body can be impacted, as the hormone might have more than one target.
- Causes constant stimulation via receptor. (i.e., Grave's Disease)
    - Antibodies bind TSH receptors and an excess production of thyroid hormones are produced.
    - Antibodies can cross the placenta as IgG antibodies are made - these can break down or disappear with time.
    - Inflammation occurs behind the eyes to cause bulging.

Inhibition

- Antibodies generated binds to target structure such as receptor and blocks the binding of the natural agonist.
- Example: Myasthenia Gravis
    - Blocks *ACh* receptor (muscarinic) and this no binding occurs.
    - Weakness of muscle, droopy eyes, fatigue and muscles controlling speaking, swallowing and chewing.

Other Examples:

- Autoimmune hemolytic anemia
- Autoimmune thrombocytopenic purpura.
- Goodpasture syndrome
- Pemphigus vulgaris.
- Pernicious anamia.
- Rheumatic fever

Hypersensitivity	Mechanism of tissue injury and disease	Pathological immune mechanism
Type 3 (Immune complex mediated diseases)	Immune complexes of circulating antigens and IgM or IgG antibodies deposited in vascular basement membranes.	Complement - and Fc receptor-mediated recruitment and activation of leukocytes and tissue damage secondary to impaired blood flow.

- In this autoimmune disease, the antigen is plentiful and so antibodies and antigen can form large immune complexes - chronic pathology.
- Inflammation occurs in the small blood vessels - can lead to pathology of certain organs.
- Systemic Lupus Erythematosus (SLE)
    - Cells die via necrosis and large amounts of the cell contents are released.
    - DNA is part of this and is combined with the other proteins molecules such as histones and ribonucleic proteins.
    - Autoantibodies bind to the protein (histone , ribonucleic proteins) and form a complex.
    - dsDNA (hapten) combined with a carrier protein (histone) creates a complex that causes an immune response.
- There is no particular class of antibody that does this.
- No known cure for autoimmune diseases.
- There are treatments though
    - Corticosteroids
    - Other approaches more focused and specific on the mechanisms behind the pathology.

Hypersensitivity	Mechanism of tissue injury and disease	Pathological immune mechanism
Type 4 (T-cell mediated diseases)	1. CD4+ T cells (cytokine-mediated inflammation). 2. CD8+ CTLs (T cell-mediated cytolysis)	1. Macrophage activation, cytokine-mediated inflammation. 2. Direct target cell lysis, cytokine-mediated inflammation

- Exaggerated or persistent responses to environmental antigens or chronic infections.
- Usually localized to a single organ or section in or on the body.
- Response is to auto antigen directly.
    - i.e., Type 1 diabetes, multiple sclerosis, Hashimoto's thyroiditis.
    - CD8+ T cell cause destruction of insulin producing beta cells in the pancreatic islets.
    - There is a T and B cell response, but the T cells cause the pathology.
    - T1D is a slow process attack individual islets in the pancreas until glucose levels are no longer able to be controlled.
- Response to environmental agents (contact sensitivity)
- Response to chronic inflections.
- Cytokines - too many cytokines in localization can cause tissue injury (Bystander injury as it is not directly on the tissue itself)
    - Usually are infiltrated due to CD4+ T cells.
    - Fibrin can mold the cells and cause scarring.
- T-cell mediated killing of host cells - CD8+ directly killing the host cell (specific and direct injury)

Contact sensitivities

- Caused by inflammatory response triggered by T cells to self-antigens that are modified by coming in contact with a mother substance.