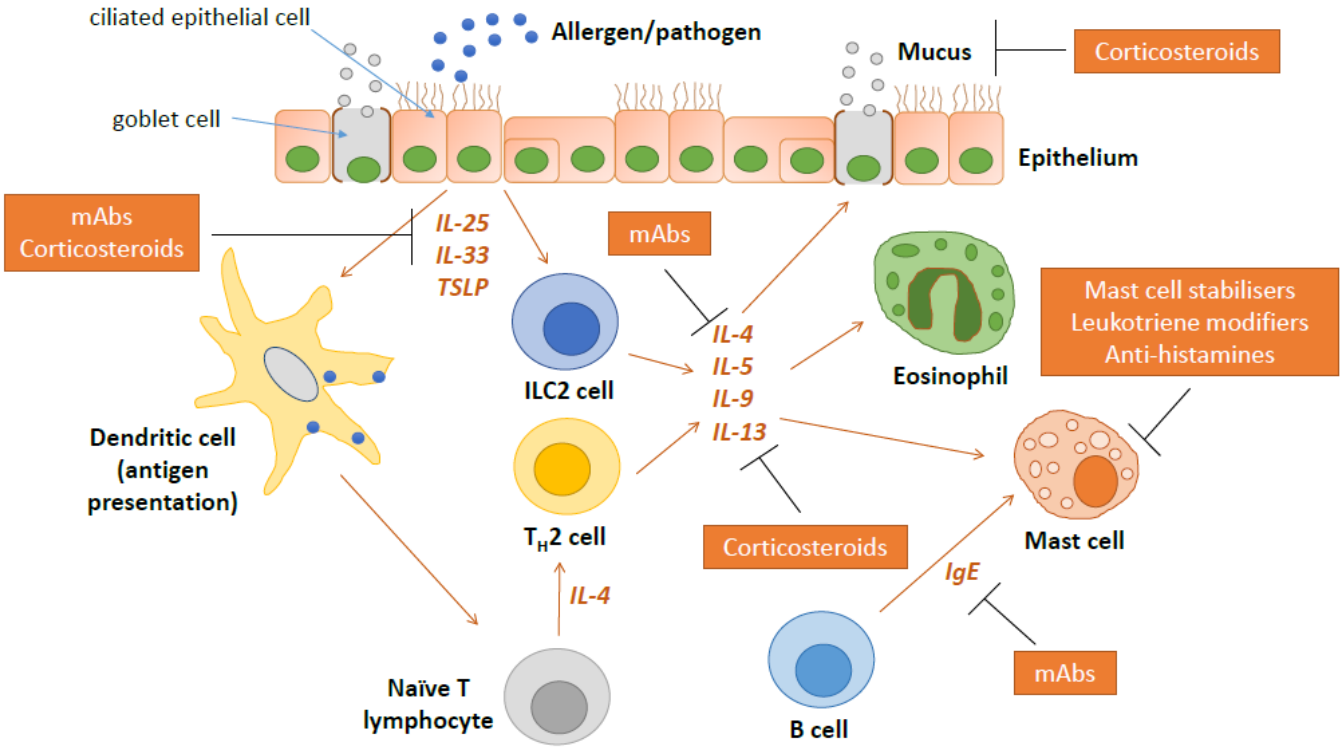
Understanding Allergy and Asthma

Allergy and atopy;

- Allergic reaction → hypersensitive reaction of the immune system in response to harmless 'environmental' factors – antigen. (Inappropriate immune response).
- Allergen → innocuous antigen; causes reaction (food or inhaled)
- Atopy → a genetic predisposition to develop allergy (atopic status)

Type 2 immunity & allergic inflammatory disease;



Eosinophils; release mediators that cause cell damage → bronchial obstruction/constriction.

Mast cell; degranulate and release histamines → increases capillary permeability, allows movement of WBCs into the tissues.

B-cells; make IgE antibodies → bind to antigen, get allergic response → airway narrowing & inflammation.

APCs → present the antigen to the naïve T-cell, proliferates into Th2 cells → initiate response. Release cytokines.

Respiratory epithelium → respond to allergen/antigen, produce cytokines → mediates the whole response.

IL-4, IL-5, IL-13, IL-9 → act on goblet cells to increase secretion of mucous → obstruction.

Types of hypersensitivity;

Type 1;

- Immediate, contact mediated
- Systemic → anaphylactic reaction, can be life threatening.
- Local → food/nasal allergy or asthma.
- IgE binds to receptor on mast cell → intracellular signalling → degranulation of mast cells causing release of histamine and other immune mediators.

Type II;

- Humoral antibodies (IgG) → injure cells by predisposing them for lysis or phagocytosis.
  - Antibody-dependent cell-mediated cytotoxicity
  - Complement activation → targets cells
  - Can get into synapses and block receptors
  - Can get in the way of normal cell binding
  - Recruit neutrophils for phagocytosis.
- Eg; blood transfusion.

Type III;

- Humoral antibodies (IgG) form complexes with components of the blood → accumulate in the circulation (insoluble)
- Activate complement pathways → cell damage in blood vessels and tissues where the complexes are deposited eg; lung, skin, kidneys.

Type IV;

- Cell-mediated delayed response (not antibody-mediated)
- Mediated by T-lymphocytes (CD8+ or CD4+) → cell death and tissue injury
- Response to large insoluble antigens eg; viral clearance, autoimmune disease.
- Two forms;
  - Delayed-type → 1st exposure to antigen → CD4+ and MHCII → differentiation of naïve T-cells into Th1 cells → release of cytokines.
  - T-cell mediated → by cytotoxic CD8+, kill antigen bearing target cells by two mechanisms.

Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity: Type I	IgE antibody	Mast cells and their mediators (vasoactive amines, lipid mediators, cytokines)
Antibody mediated: Type II	IgM, IgG antibodies against cell surface or extracellular matrix antigens	Opsonization and phagocytosis of cells Complement- and Fc receptor–mediated recruitment and activation of leukocytes (neutrophils, macrophages) Abnormalities in cellular functions, e.g., hormone receptor signaling
Immune complex mediated: Type III	Immune complexes of circulating antigens and IgM or IgG antibodies	Complement- and Fc receptor–mediated recruitment and activation of leukocytes
T cell mediated: Type IV	1. $CD4^+$ T cells (delayed-type hypersensitivity) 2. $CD8^+$ CTLs (T cell–mediated cytolysis)	1. Macrophage activation, cytokine-mediated inflammation 2. Direct target cell killing, cytokine-mediated inflammation

Immunology of asthma;

- Hygiene hypothesis; being too clean increases the susceptibility of children to allergic diseases → suppresses the natural development of the immune system.
- Sensitisation → begins with dendritic cells (APCs) binding and presenting allergens to naïve T cells → become Th2 cells. Trigger B-cell production of allergen specific antibodies (IgE). Allergen is usually an otherwise harmful agent from the environment.
- Memory → re-exposure → binding of allergen to IgE → immune response (more aggressive & rapid)

- Manifestation → 2 phases;
  - Immediate → within 15 minutes (mast cell-IgE mediated)

    - Late → 4-6 hours later, Th2 cell driven
- Driven by Th2 cytokines (IL-4, IL-5, IL-13)

Allergy and asthma;

- Early life allergic sensitisation increases the risk of asthma development eg; food allergies
- Asthma; chronic inflammatory airway disease (reversible airway obstruction)
    - Features;
        - Inflammation of the airways → infiltration of WBCs and oedema
        - Airway obstruction (mucous)
        - Enhanced bronchial responsiveness → hyperreactivity, enhanced smooth muscle contraction.
        - Remodelling of the airway → thickening of underlying tissues → further restriction.
- Bronchoconstriction → causes airway narrowing and reduces airflow, gas exchange. Symptoms eg; chest tightening, dyspnoea, cough, wheezing.
- Clinical presentation → wheezing, limited airflow, persistent cough (trying to clear mucous)
- Heterogenous disease → group of conditions characterised by a common set of clinical features → caused by different mechanisms
    - Young people allergically sensitised early in life
- Process;
    - Airway epithelium responds to exposure to the Ag → releases mediators for Th2 response.
    - Th2 cells produce cytokines → activating mast cells, B cells, innate lymphoid cells → cause airway narrowing, IgE and mucous production by goblet cells.

Treatment;

- If already have asthma, try and avoid triggers. Children with allergic asthma should avoid this as its possible to train the immune system to react correctly to allergens.
- β2- agonists; bronchodilators → short or long acting
- Oral/inhaled corticosteroids → anti-inflammatory effect (suppress cytokines that cause inflammation) → are slightly immunosuppressive.
- 10-15% of asthmatics don't respond very well → severe asthma

Anaphylaxis → adrenaline administration → reduces throat swelling, opens the airways, maintains heart function and blood pressure.

Antihistamines → target the H1-receptor for histamines in mast cells, smooth muscles and endothelium → treat allergic reactions in the nose. Target H2 receptor for in the gastrointestinal tract.

Mast cell stabilisers → stop the degranulation of mast cells by inhibiting calcium channels (without calcium, the vesicles can't fuse to the membrane and degranulate → stop release of histamine, inhalers, nasal sprays, eye drops.

Steroid based anti-inflammatories → bind to glucocorticoid receptor and suppress the expression of genes that cause inflammation → reduce swelling and tightening in the airways. Target pretty much everything.

Leukotriene modifiers → prevent the action of leukotrienes (chemicals the body release during Th2 response)

Monoclonal Abs (emerging) → have actions downstream of the allergic cascade.