

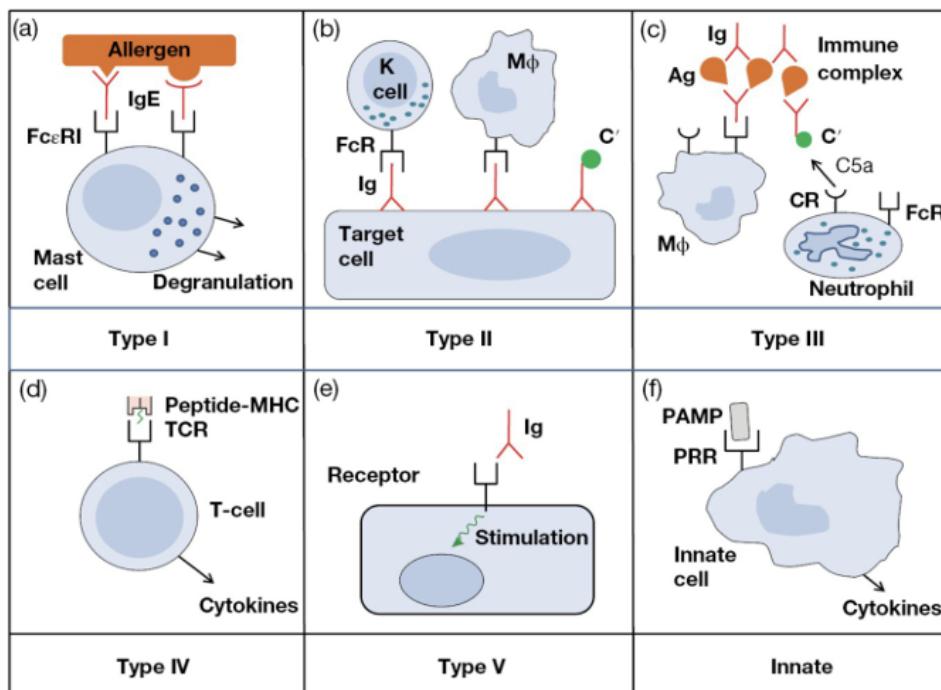
Allergy and Hypersensitivity

Course	 <u>Immunology</u>
Date	@April 12, 2024
Status	Completed
Reading	<input checked="" type="checkbox"/>

Hypersensitivity

- Overzealous immune response causing damage to the host.
 - Immune responses that cause pathology
- This can arise from responses to innocuous stimuli or environmental antigens - **Allergy**
- It can also arise as a result of autoimmunity (responses to self-tissues) or as a side effect of responses to pathogens (immunopathology)
- It is increasingly recognised that almost all diseases may involve damage caused by components of the immune system.

Types of hypersensitivity reactions



Hypersensitivity reactions, which are exaggerations of normal defence mechanisms, can be classified into 4 classical categories based on their pathology (which are rarely discrete).

- The British immunologists Philip Gell and Robin Coombs developed the Gell and Coombs classification.
- They defined **four types** of hypersensitivity of which types I – III are dependent on antibody effector mechanisms whilst type IV involves T cell effector mechanisms.
- A major virtue of this nomenclature was to distinguish between three quite different ways in which antibody could lead to pathology: namely via IgE (allergies), IgG (cytotoxicity) and antibody–antigen complexes (vascular damage).

There are two important points worth bearing in mind:

1. All hypersensitivity reactions are essentially **normal immune responses** occurring in an **inappropriate way**. The response might, for example, be excessive compared to the threat, against a harmless antigen, occurring in an inappropriate location, etc.
2. Although the mechanisms behind each type of hypersensitivity are clearly defined, in a given pathological situation there are often a **combination of different hypersensitivity reactions** occurring.

Type I - IgE-mediated mast cell degranulation

- Occurs within minutes of exposure to antigen

Examples:

- Upper respiratory tract; rhinitis, hayfever
- Lower respiratory tract; atopic asthma
 - Asthma is the most common chronic disease of children in Western countries (2,000 deaths/year in UK)
 - Many are allergy-related
- Skin: allergic eczema
- Mouth, throat, gut: food (e.g. fish).
- Systemic: peanuts
 - Leads to anaphylaxis
- Infections: worms
 - IgE MC degranulation normally respond to parasitic infections

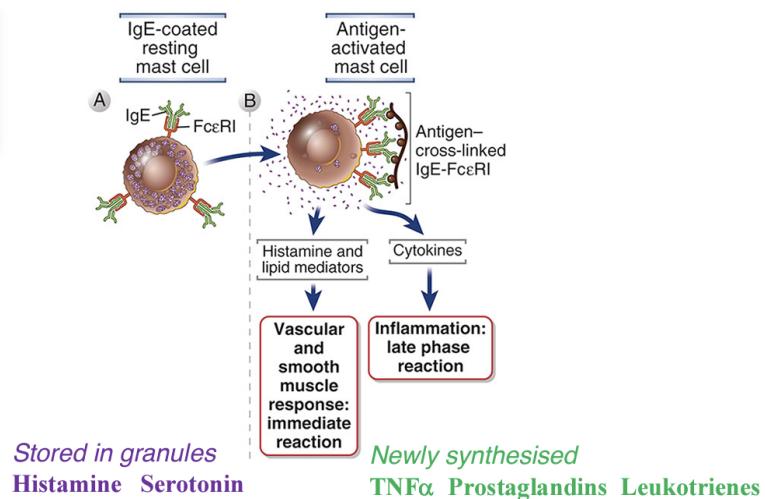
IgE

- Serum concentration: 100 ng - low thus normally not allergic
 - Vs. IgG 15mg/ml
- Half life: 2.5 days in serum, 12 weeks if bound to MC
 - Most of the IgE bound to Fc R on MC
- Elevated in:
 - Certain parasitic diseases
 - e.g. schistosomiasis
 - Hyper-IgE syndrome
 - A very rare primary immunodeficiency with defective IFNgamma production, therefore elevate IL-4
 - IL-4 and IFNgamma cross regulate each other
 - High IL-4 promote production of IgE

- Allergy
- Class switching to IgE promoted by IL-4 and IL-13, inhibited by IFNgamma

Interaction of antigen with **mast cells** pre-sensitised with **IgE** induces the release of preformed mediators such as **histamine** & newly formed mediators such as **prostaglandins** & **leukotrienes**.

- IgE bound to FcεRI on MC, which turns the signalling of the MC antigen-specific rather pathogen specific (PRR)
- Activation of the Fc R requires crosslinking, thus a high level of IgE is required for Type I hypersensitivity

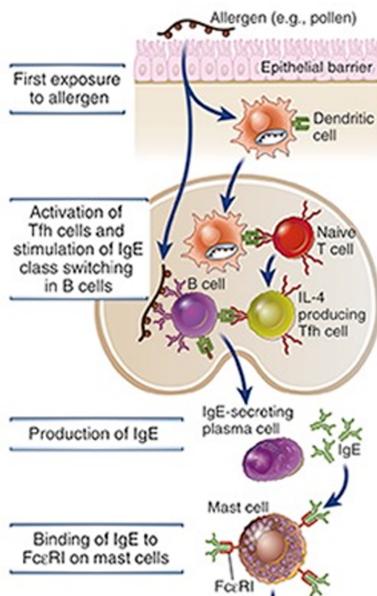


- The immediate IgE-mediated response, which is over in 1 hour, is frequently followed by a **late phase response** occurring 5-12 hours later associated with infiltration by **CD4+ helper T-cells, monocytes and eosinophils**.
- MC are in all mucosal surfaces with preformed granules

Skin prick - allergy testing

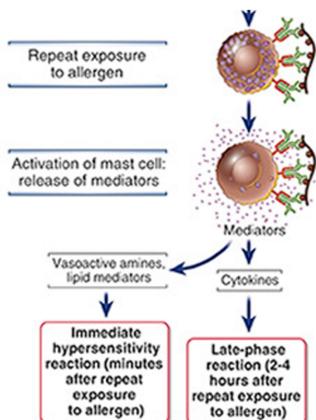
- Wheel and flare response
 - Wheel: swelling - increased vascular permeability
 - Flare: redness - vasodilation
- Common allergen: dust mite faces

Mechanism - Sensitisation



Upon the first exposure to allergen, the APC picks up the allergen

- B cells
- DCs present to naive T cells, which develop into IL-4 producing T follicular helper cell
 - Th2/Tfh cells: IL4, IL5, IL13 production
- IL4 promotes class switching of the B cells to produce IgE that will recognise the allergen
- IgE bound to MC FcR
 - Mast cells and eosinophils
 - Eosinophils are important to parasites with granules full of cytotoxic materials



- Upon re-exposure, antigen (allergen) is bound by the IgE, the result can be cross-linking of the receptors leading to the release of granules from the mast cell.
- The granules contain inflammatory mediators such as histamine.
 - Vasodilators
 - Endothelial or epithelial cells
 - The mediators also cause changes in gut musculature to cause cramping and expel parasites (IgE response)

Why are some people more allergic than others?

Genes

- Many weak associations have been reported, some immune related some are not
 - FcRepsilon, HLA-DQ, IL-2Rbeta, IL4R, fillagrin, etc.

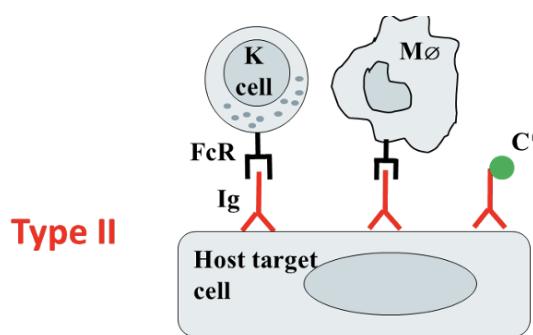
Environment

- Why has the prevalence of atopy increased over the past decades?
 - The hygiene hypothesis - clean environment thus less infection exposure, skewing immune system to a type II response
 - Pollution
- Dietary conundrums

Treatment

- Allergen avoidance
- Pharmacotherapy
 - Corticosteroids: suppress transcription of proinflammatory genes
 - Sodium chromoglycate: blocks mediator release from MC
 - Antihistamines
 - Montelukast (leukotriene receptor antagonist)
 - Leukotriene: lipid mediators
- Immunotherapy
 - Omalizumab (anti-IgE mAb, down-regulate IgE & FcεRI)
 - Repeated low dose allergen injection or sublingual (SLIT)
 - Tolerance to allergen

Type II - Antibody mediated killing (IgM, IgG)



Antibodies act as opsonins or activate complement leading to killing.

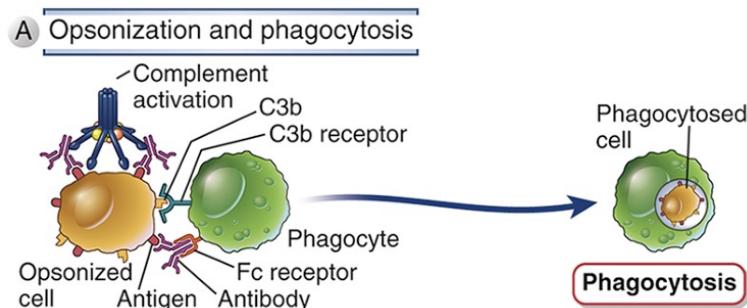
- **Phagocytosis**, this being enhanced in the presence of complement.

- **Antibody-dependent cellular cytotoxicity (ADCC)** reactions (NK cells) activate killing of the cell.
- **Complement** fixation also leads to the generation of the membrane attack complex (MAC) ending in cell death.

Examples:

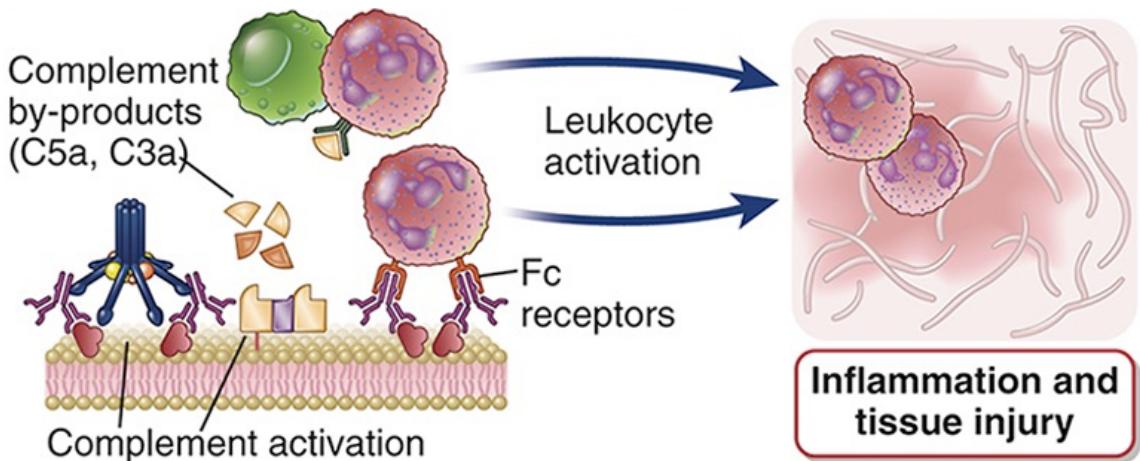
- Transplantation: transfusion reactions, hyperacute transplant rejection (kill transplanted organ)
- Haemolytic disease of the newborn
- Many autoimmune diseases (e.g. Goodpastures syndrome, Myasthenia gravis)
- Autoimmune cytopenias (destroy own neutrophils and platelets)
- Drug reactions (penicillin allergy)
 - Penecillin or its breakdown product binds to own cells, creating a new antigen

Opsonisation or phagocytosis



- Autoimmune cytopenias (neutrophils, erythrocytes)
- Hyperacute transplant rejection
- Transfusion reaction

Complement recruiting leukocytes



- Antibodies bind in tissues or activation of complement recruit immune cells such as neutrophils, macrophages, causing inflammation

Goodpastures syndrome

- Antibodies against both lung parenchyma & kidney basement membrane because these organs share common antigens - collagen

Myasthenia gravis

- Antibodies act as antagonists and block acetylcholine receptors
 - Inhibit binding of neurotransmitter to receptor

Haemolytic disease of the newborn (HDN)

- A Rhesus D negative mother bears a Rhesus D positive foetus because her partner is Rhesus D positive.
- During the first pregnancy foetal red cells enter the maternal circulation at the time of birth and can induce production of anti-Rhesus D antibodies in the mother.
- This is not the problem during the first pregnancy but in subsequent pregnancies with a RhD+ baby, IgG anti-Rhesus D antibodies can cross the placenta and cause HDN.
- This is preventable by giving the mother anti-Rhesus D at 28 weeks of pregnancy and immediately following birth.
- The antibody mops up free RhD antigen and hence prevents an antibody response from developing.

Immune pathology of infection

- Type II hypersensitivities can also contribute to immune pathology of infection, for example in streptococcal endocarditis.

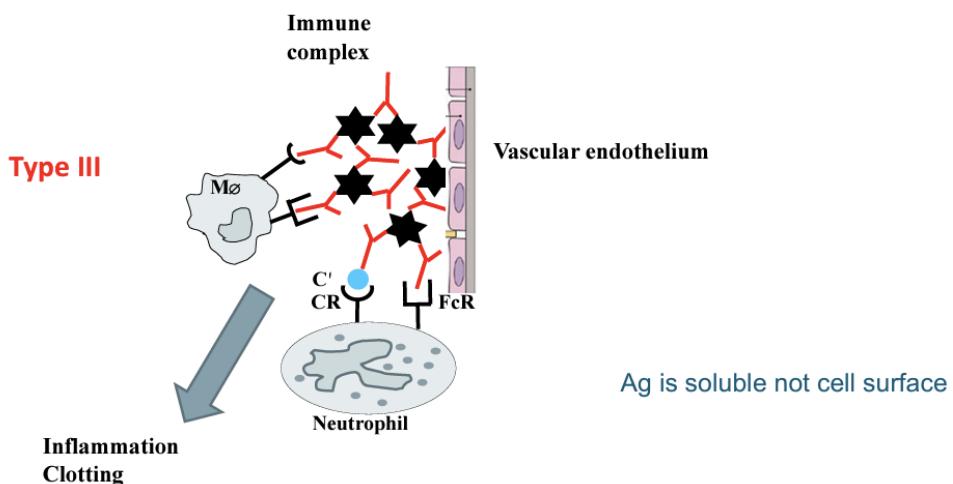
Graves' disease

- Autoantibodies are produced which actually stimulate thyroid function by binding agonistically to the TSH receptor.
- Continuous signals to the TSH receptors to produce high level of thyroid hormone

Type V hypersensitivity: Autoantibodies act as agonists

- This paradoxical type of hypersensitivity, which stimulates the target tissue rather than destroying it, is more recently been classified as **Type V hypersensitivity**.
- Vs Type II: cytotoxic effect, inflammation, tissue damage, prevention of binding or stimulation

Type III - Immune complex mediated



Immune complexes which fail to be cleared in the normal way lead to type III hypersensitivity.

- If Ag has multiple binding site, lots of Ab binding lots of antigens
 - Lots of interface, develop into large complex that is insoluble
 - Note that antigen is soluble rather than on the cell surface
- Immune complexes forming are always cleared by macrophages and neutrophils when it is small

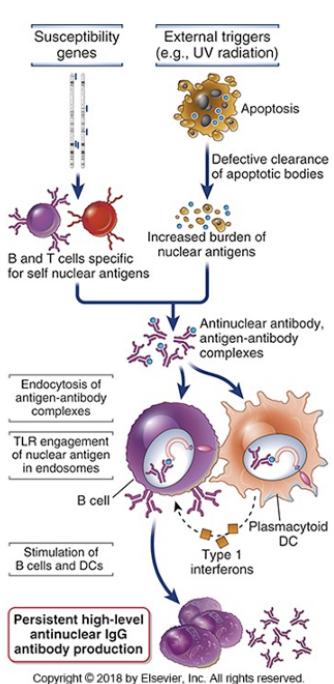
- Thus only occur when the [Ag] and [Ab] are high
- Because it is blocking the vessels, it will cause inflammation

Examples

- Some allergies are also due to Type III hypersensitivity, rather than the more usual Type I.
 - Farmer's lung
 - Pigeon fancier's disease
- Infection: post-streptococcal glomerular nephritis
 - Antigen remnants create antibody against it, which can deposit in kidneys
- Some autoimmune diseases: **systemic lupus erythematosus**
 - Complexes are deposited in many sites, particularly the kidney and skin

SLE

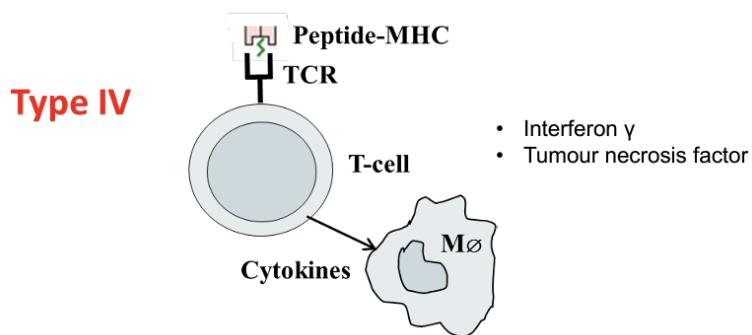
- Approximately 0.1% of the worldwide population
- Can affect all major organs - brain, heart, lung, kidneys, gut, joints, etc.
- Treatments include steroids (anti-inflammatory), immunosuppressants and biological therapies



- Driver of SLE is cell death and nuclear proteins released
- Increase apoptosis or poor clearance of apoptotic bodies due to variations in complement genes
 - Increased burden of nuclear antigens (e.g. nucleosomes, histones, DNA)
- Antinuclear antibody, antigen-antibody complexes
- Endocytosis of Ag-Ab complexes and recognised by nuclear antigens in endosomes (usually recognise viral nuclear components)

- DC release type I interferons and stimulate B cells
- Creating persistent high-level of antinuclear IgG antibody
- Positive feedback loop: more damage, more antibody, which then cause more damage

Type IV - Delayed type hypersensitivity (DTH), T cell mediated



- The interaction of antigen with T cells induces proliferation and cytokine release.
 - Inflammatory cytokines: Interferon gamma and TNF and recruited macrophages
 - May involve direct cytotoxicity by CD8 T cells
- This form of hypersensitivity **does not involve antibodies**.

Examples

- Allergies: allergic contact dermatitis (nickel, poison ivy, hair dye)
 - Hamptons: small molecules that are not proper antigens
 - Antigen: hamptons-attached own cells
 - CD8+ T cells may respond and kill keratinocytes

Patches test: investigating allergic contact dermatitis

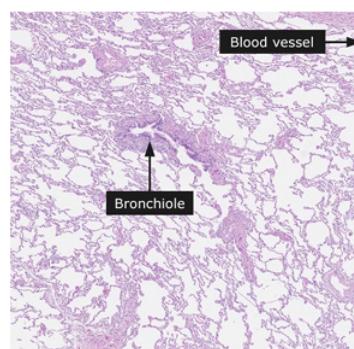
- Tuberculin skin reaction to mycobacterial antigens
 - The **tuberculin** skin reaction is a good example of this phenomenon.

- This occurs following intradermal injection with mycobacterial cell wall proteins in an individual who has previously been exposed to *M. tuberculosis* antigens.
- Cellular infiltration is maximal at 48 hours gradually disappearing over the course of days

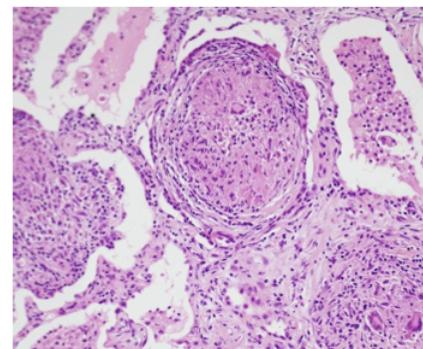
Mantoux test

- A test to see if the person is exposed to the antigen, infection, or a disease such as TB, vaccine
 - Must have pre-disposed T cells
- Infections: Tuberculosis and the granuloma
 - Continuous response because unable to clear the antigen

Chronic local DTH reaction - granuloma

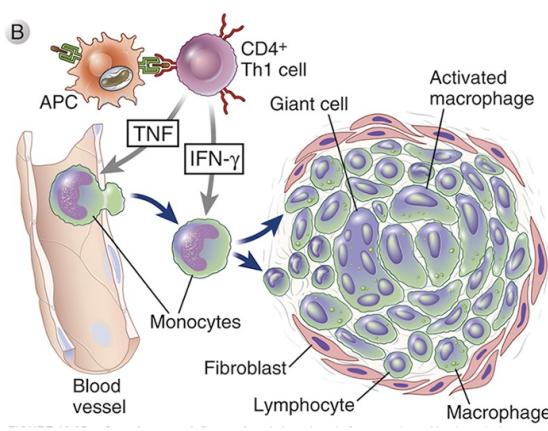


Normal lung



Lung granuloma

- Continuous activation of T cells - makes lots of interferons (key in Type IV) and recruit macrophages
 - In comparisons to other type IV, this is continuous
- Accumulation of large number of macrophages unable to clear the antigen
- Epitheloid cells or giant cells



- Granuloma formation
 - Giant cells: macrophages continuously trying to phagocytose but cannot thus join together to create multinuclear cells
 - Protective mechanism to localise disease and prevent spreading

Innate hypersensitivity reactions

The reactions described above are all components of the **adaptive** immune response.

However, overzealous **innate** responses can also lead to pathology.

Acute inflammation

- Sepsis
- Toxic shock syndrome
 - Massive activation of macrophages and thus high [TNF]
- Some infections, e.g. with *Streptococcus pyogenes* and *Meningococcus*, can sometimes provoke a fatal inflammatory response involving excessive release of TNF, IL-1 and IL-6.
- Another example of innate hypersensitivity is the **acute respiratory distress syndrome** which is associated with Gram-negative bacteria and primarily due to the lipopolysaccharide (LPS) endotoxin provoking a massive invasion of the lung by neutrophils.

Overactivation of the macrophages has been associated with many of the **major chronic diseases**

- Chronic activation of innate immunity, especially macrophages is now believed to drive the pathology of many of the common chronic diseases associated with ageing, including Alzheimer's, Type II diabetes and atherosclerosis.
- Indeed a generalized increase in inflammation may be a key component of the ageing process.

- Atherosclerosis
- Alzheimer's
- Type II diabetes
- Inflammaging
 - To predict poor health and higher level of inflammation

Summary

- Immune responses often cause damage to host tissues
- Damage can be caused by several distinct mechanisms, which are classified as hypersensitivities
 - In actual disease: caused by multiple mechanisms instead of just one, but focus on the key contributors
- When the damaging immune response is caused by a non-pathogenic environmental antigen (e.g. food) it is called allergy