



Hypersensitivity and autoimmunity

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Outline

- Introduction to hypersensitivity reactions.
- Mechanisms and classification of HSRs.
- IgE-mediated HSR.
- Ab-mediated HSR.
- Immune complex HSR.
- Delayed type HSR.
- Autoimmune diseases.



Introduction

- **Hypersensitivity reaction (HSR):** a disorder caused by an excessive or inappropriate immune response.
- **Causes of HSRs:**
 - Immune response directed against host tissue (autoimmunity).
 - Inadequate control of immune response against pathogenic microbes.
 - Immune response against commensal microbes or environmental antigens.
- The classification of HSR is based on type of immune response and the effector mechanism resulting in tissue injury.



Mechanisms and classification of HSRs

Coombs and Gell 1963 classification of HSRs

| Type | Immune mediator of pathology | Mechanism of tissue injury | Examples |
|---|--|--|--|
| <i>Immediate (type I)</i> | IgE | Mast cells and their mediators (vasoactive amines, lipid mediators and cytokines) | Allergic reactions, anaphylaxis, asthma |
| <i>Antibody mediated (type II)</i> | IgM, IgG against cell surface or extracellular matrix antigens | Phagocytosis, Ab-dependent cell mediated cytotoxicity (ADCC), receptor blocking or complement mediated lysis | Goodpasture's syndrome, ABO incompatibility, Rh incompatibility |
| <i>Immune complex mediated (type III)</i> | Circulating immune complexes of antigens and IgM or IgG | Ag-Ab complexes activate the complement and Fc receptors resulting in activation and recruitment of leukocytes | Poststreptococcal glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis |
| <i>Cell mediated (type IV)</i> | CD4+ T cells or CD8+ cytotoxic T lymphocytes (CTLs) | Macrophage activation resulting in cytokine mediated inflammation or direct cell killing by CTLs | Contact dermatitis, tuberculosis |

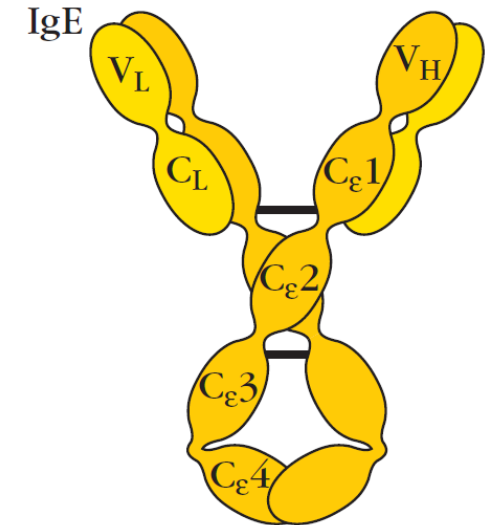


IgE-mediated HSR (Type I)

- The encounter of an antigen (Ag) that induces allergy (allergen) will result in a humoral response with plasma cells secreting IgE.
- IgE binds with high affinity to its receptors on mast cell and basophil surfaces. The receptors are Fc epsilon receptors (FcεR).
- The process of IgE coating of mast cells and basophils is called sensitization (or priming), which follows the first exposure to an allergen.
- Mast cells and basophils contain preformed mediators (e.g. histamine), and are able to synthesize new mediators upon cross linking of IgE on its surface.
- Subsequent exposure to the same allergen cross links the membrane-bound IgE on sensitized mast cells and basophils, causing degranulation of these cells with release of preformed and newly synthesized inflammatory mediators.

The effector molecule in type I HSR (IgE)

- IgE has four constant region domains with binding sites for both high- and low-affinity IgE receptors, Fc epsilon receptors I and II (FcεRI and II) respectively.
- The primary cells having FcεRI are mast cells and basophils.
- Cross linking of two FcεRI results in mast cell and basophil degranulation, however this is not the sole mechanism of degranulation.
- FcεRII (CD23) are also present on B cells.
- IgE production is dependent on T_H2 cells whereas a T_H1 response will inhibit its production.
- T_H2 cytokines promote IgE production and it includes IL-4, IL-5, IL-10 and IL-13.

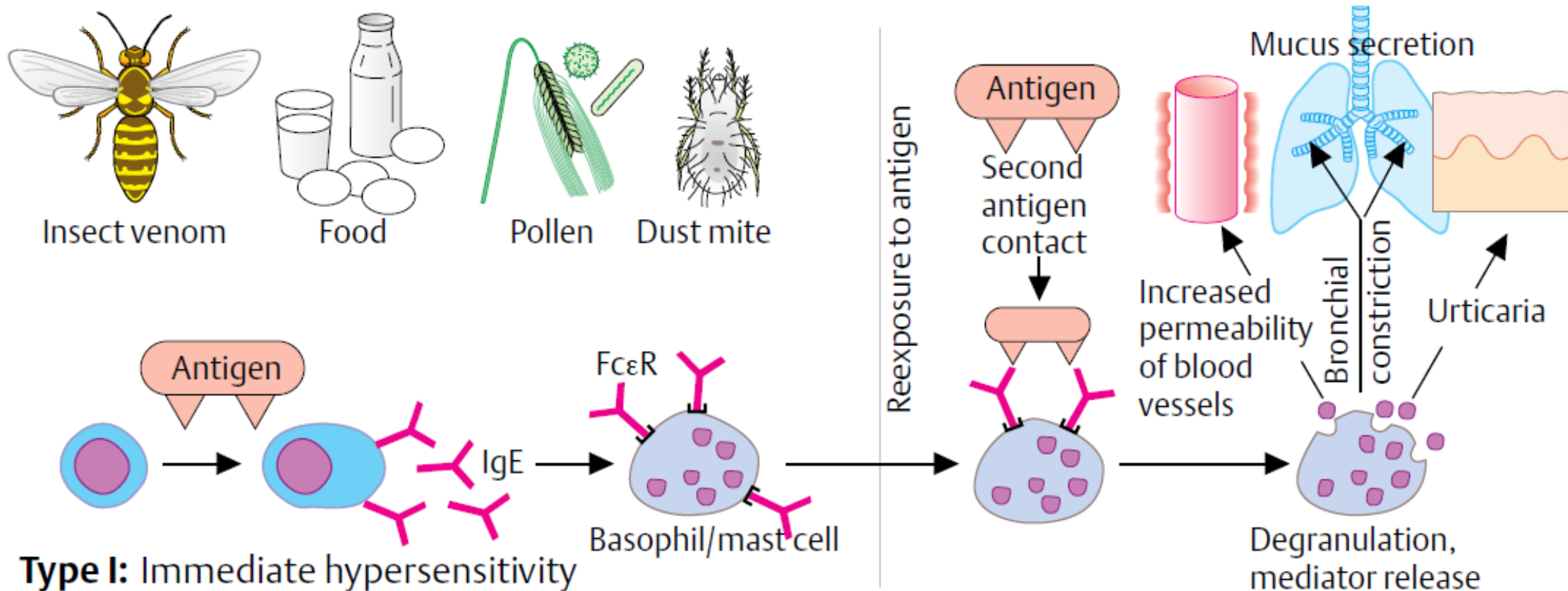




IgE-mediated HSR (Type I)

- IgE represents the Abs with the lowest concentration in serum of a normal individual likely due to the following:
 - The $t_{1/2}$ of IgE is short compared to other Abs.
 - IgE is produced only in response to a select group of Ags.
 - IgE is usually sequestered into FcεRI.
- Type I hypersensitivity responses are divided into an immediate early response and one or more late phase responses.
- The early response occurs within minutes of allergen exposure and results from the release of histamine, leukotrienes, and prostaglandins from local mast cells.
- The mediators released during the course of the immediate reaction induce localized inflammation. Cytokines released from mast cells (TNF- α and IL-1), increase the expression of CAMs on endothelial cells, facilitating the influx of neutrophils, eosinophils, and T_H2 cells that characterizes the late phase of the response.

IgE-mediated HSR (Type I)



Source: Burmester, *Color Atlas of Immunology*, 2003.



IgE-mediated HSR (Type I)

- The clinical manifestations of allergic reactions are related to the biological effects of the mediators that are released during degranulation of mast cells and basophils.
- *Allergy mediators and their effects include:*
 - **Histamine:** increased permeability of venules, contraction of intestinal, bronchial and arterial smooth muscles.
 - **Leukotrienes and prostaglandins:** bronchoconstriction, increased vascular permeability, and mucus production.
 - **Cytokines (IL-4, IL-5 and IL-13):** recruitment and activation of inflammatory cells.
- Some allergic reactions continue for a long time as a result of T_H2 mediated eosinophil migration and subsequent release of its mediators including peroxidase and major basic protein (late phase response).



Clinical conditions

- Allergy is the most common disorder of the immune system (prevalence of about 20% in developed countries).
- The cause of allergy is likely related to complex gene-environment interactions.
- The genetic tendency to develop allergy is termed “atopy”. It includes possible associations with HLA type, IgE production, FcεRI and II, several cytokines and chemokines with its receptors among others.
- The hygiene hypothesis was formulated based on the observation that disorders involving the immune system are becoming more common in the developed countries.
- The clinical manifestations of allergy depends on the tissue mostly affected.
- Localized allergies include allergic rhinoconjunctivitis, atopic dermatitis, food allergies and asthma.
- The systemic allergic reaction is termed anaphylaxis.



Suggested further reading on the hygiene hypothesis

- ❖ Bach, J.F., 2017. **The hygiene hypothesis in autoimmunity: the role of pathogens and commensals.** *Nat Rev Immunol*.
- ❖ Brown, E.M., Arrieta, M.C., Finlay, B.B., 2013. **A fresh look at the hygiene hypothesis: how intestinal microbial exposure drives immune effector responses in atopic disease.** *Semin Immunol* 25, 378-387.
- ❖ Liu, A.H., 2015. **Revisiting the hygiene hypothesis for allergy and asthma.** *J Allergy Clin Immunol* 136, 860-865.
- ❖ Stiemsma, L.T., Reynolds, L.A., Turvey, S.E., Finlay, B.B., 2015. **The hygiene hypothesis: current perspectives and future therapies.** *Immunotargets Ther* 4, 143-157.

Allergic rhinoconjunctivitis

- Also termed “hay fever”.
- One of the most common allergic conditions.
- Caused by airborne allergens.
- Characterized by seasonality.
- The symptoms include watery exudation of the conjunctivae, nasal mucosa, and upper respiratory tract, as well as sneezing and coughing.



Asthma

- “Characterized by recurrent reversible airflow obstruction and bronchial smooth muscle cell hyper-responsiveness”.
- The majority of asthmatic attacks are triggered by IgE-mediated responses to allergens such as pollens, dust, fumes or insect products; thus termed atopic asthma.
- The rest of asthmatic attacks are triggered independently of allergen stimulation and termed intrinsic asthma. The triggers include exercise, drugs or cold.
- Both atopic and intrinsic asthmata share the same pathophysiology, hence are considered together.
- The underlying airway edema, mucus secretion, and inflammation contribute to the bronchial constriction and to airway obstruction leading to the clinical manifestations such as shortness of breath and wheezing.



Other localized allergic reactions

- **Food allergy**

- Causes GI symptoms, however, respiratory symptoms suggests systemic Ag exposure.
- Common food items causing food allergy include eggs, shellfish and peanut.



- **Atopic dermatitis (eczema)**

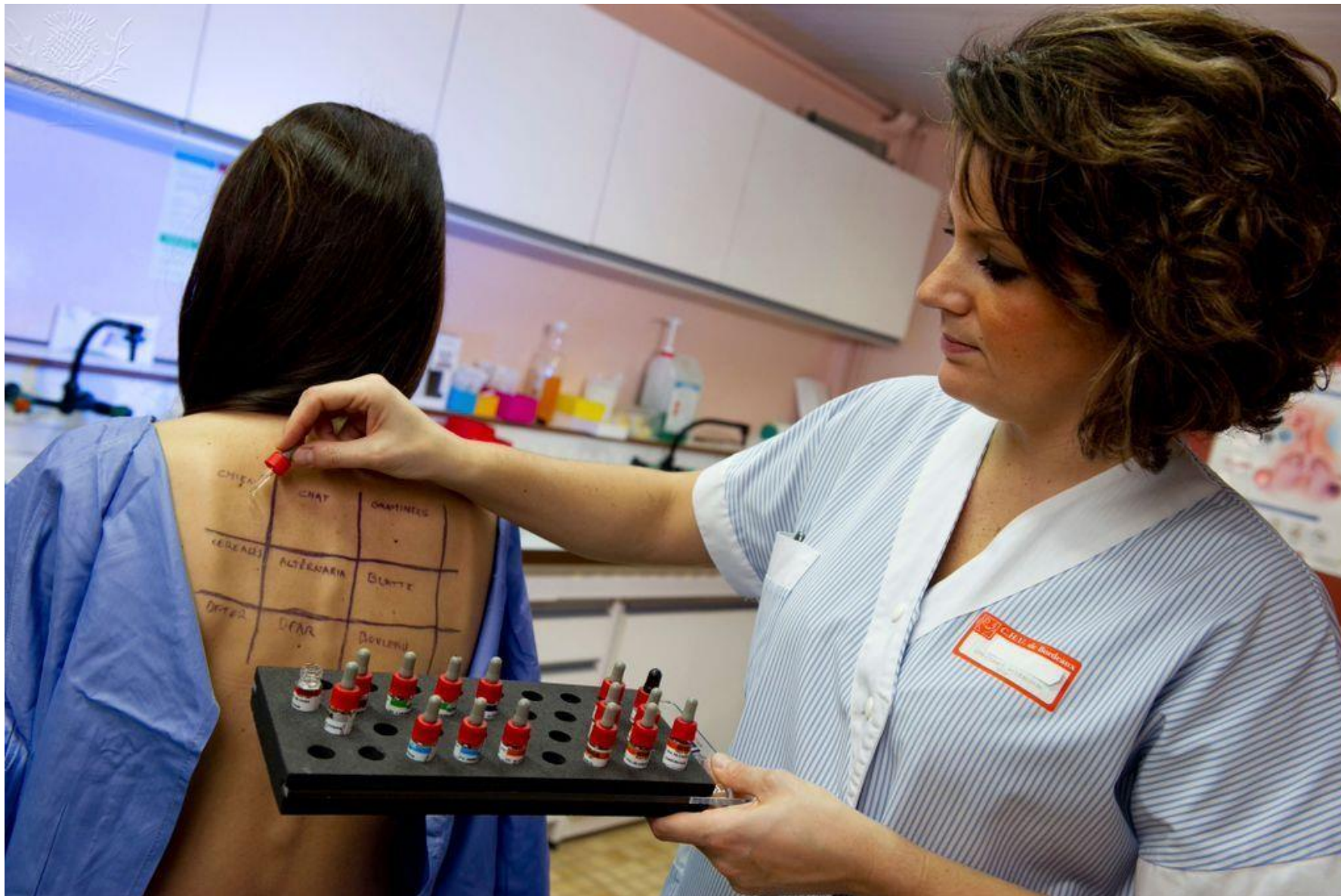
- Often associated with mutations in filaggrin leading to defective skin barrier and increased exposure to environmental Ags.



Anaphylaxis



Allergy testing



Allergy testing-Characteristic wheal and flare





Management

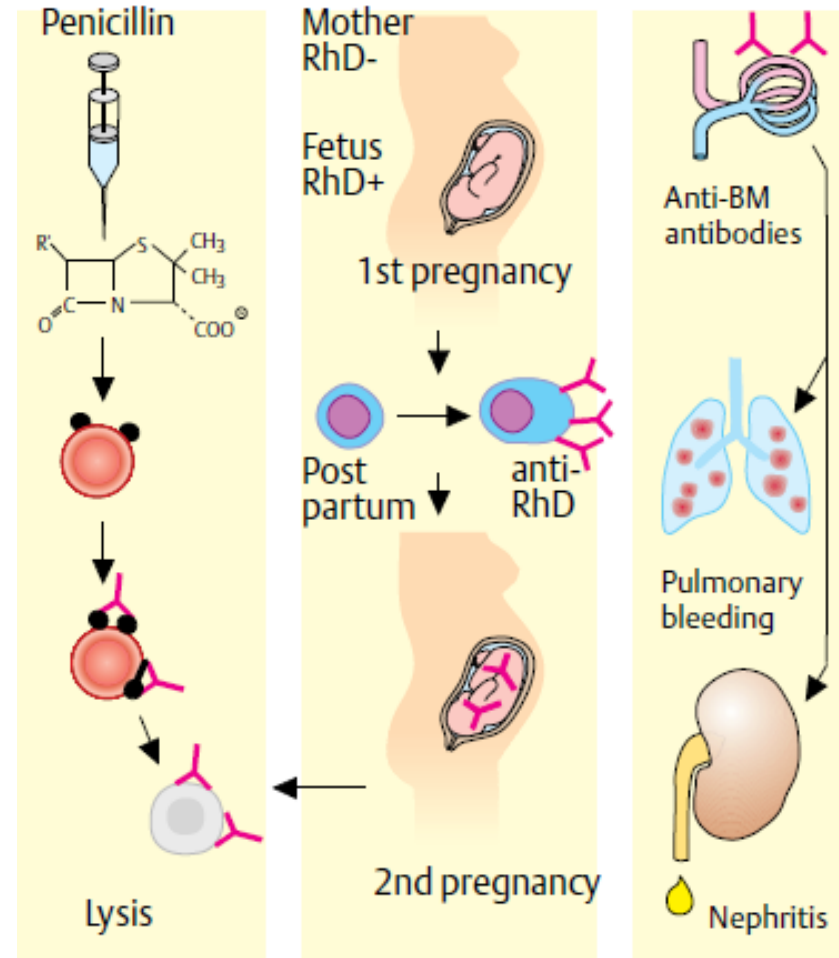
- General measures include the identification of the culprit allergen and its avoidance.
- Drug treatment aims at blocking the effect of allergy inflammatory mediators (e.g. antihistamines, β 2-adrenergic agonists, epinephrine).
- Topical steroid (anti-inflammatory).
- Sodium cromoglycate (reduces mast cell degranulation).
- Desensitization (immunotherapy). It aims to improve allergy symptoms caused by a specific allergen. Allergen is injected subcutaneously in escalating doses (possible mechanisms include induction of T_H1 response or induction of T_{reg} response that inhibits the polarized T_H2 response).



Ab-mediated HSR (Type II)

- Type II HSRs are initiated by interaction of Abs (IgG or IgM) with cell membranes or extracellular matrix (ECM) components. The Ags can be self or exogenous molecules that are adsorbed to membranes or ECM.
- Tissue damage can occur through: activation of the complement system, ADCC or phagocytosis with the Abs acting as opsonins.
- Abs against cellular or tissue Ags tend to be specific (i.e. affecting the cells or tissues where the Ag is present), whereas the immune complex disease (type III HSR) manifestations reflect the site of immune complex deposition and tend to be systemic.

Ab-mediated HSR (Type II)



Type II: Cytotoxic antibody reactions

Source: Burmester, *Color Atlas of Immunology*, 2003.

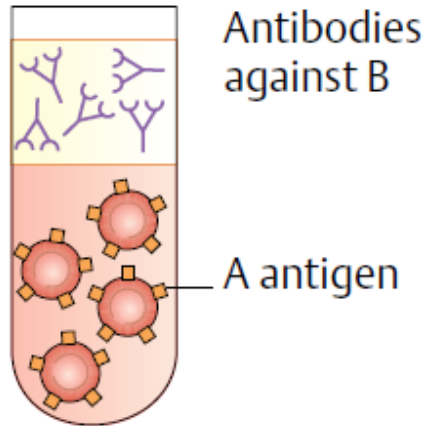


Ab-mediated HSR (Immune-mediated hemolysis)

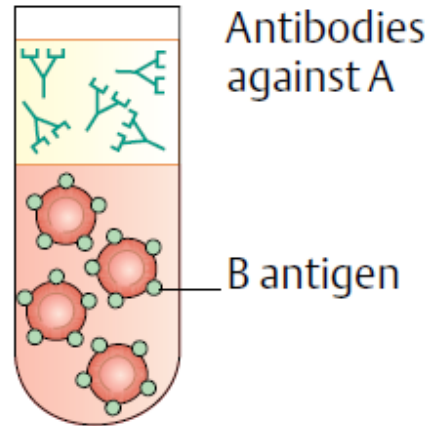
- Antigens of the ABO and Rh (C, D and E) systems are termed “alloantigens”, i.e. these Ags might differ from person to person.
- Anti-ABO Abs occur naturally in individuals lacking the A or B Ags and are of the IgM type (strong complement activator). Their natural occurrence is likely due to the ubiquitous presence of identical epitopes in a variety of microbes.
- Anti-Rh Abs arise upon exposure to Rh Ags in individuals lacking these Ags, and are of the IgG type which coat the erythrocytes and recognized by Fc receptors on the splenic and hepatic resident macrophages.

Ab-mediated HSR (Immune-mediated hemolysis)

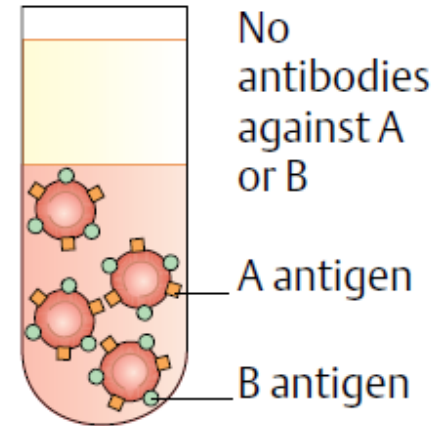
Blood group A: ~ 42%



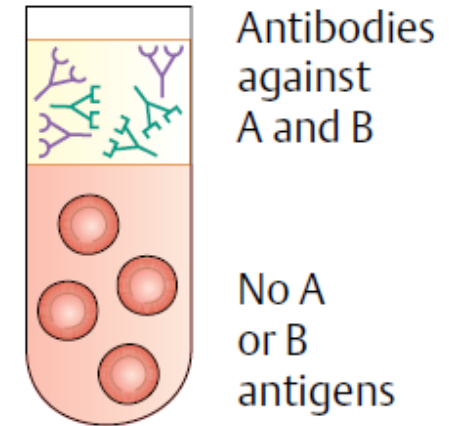
Blood group B: ~ 14%



Blood group AB: ~ 6%



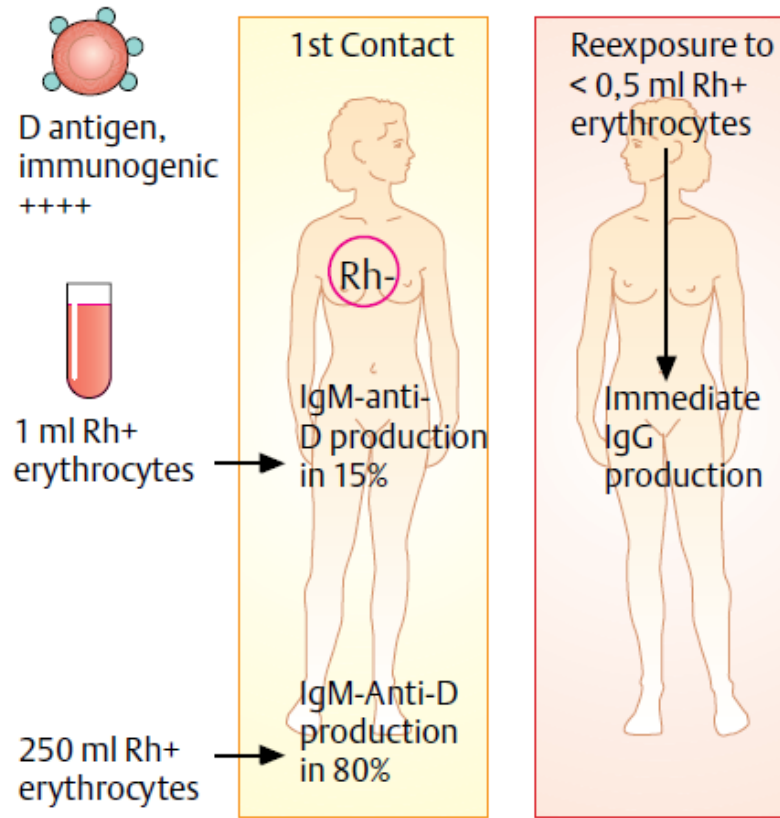
Blood group O: ~ 38%



A. The ABO blood group system

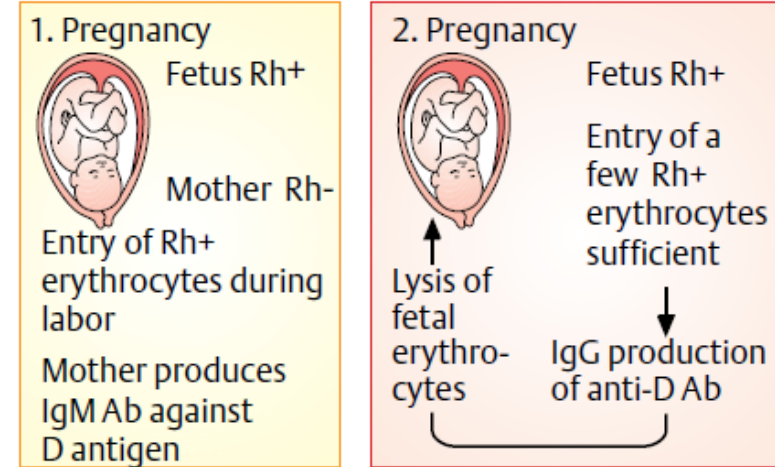
Source: Burmester, *Color Atlas of Immunology*, 2003.

Ab-mediated HSR (Immune-mediated hemolysis)

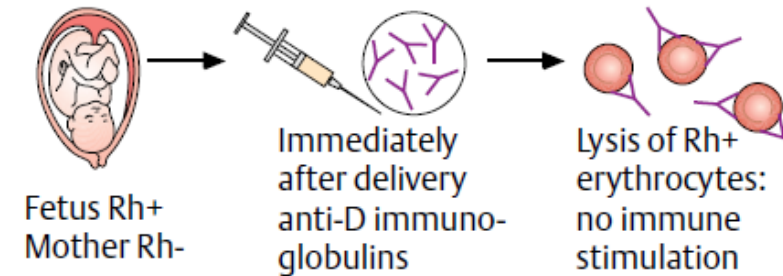


1. Anti-D immune response

B. Alloimmunization against Rh antigens



2. Hemolytic disease of the newborn



3. Prophylaxis by Rh immunization

Source: Burmester, *Color Atlas of Immunology*, 2003.



Ab-mediated HSR against solid tissue

- **Goodpasture's syndrome:**
- Auto-Abs are synthesized against type IV collagen present in the basement membranes of the kidneys and lungs. The tissue damage will be manifested clinically in hematuria, proteinuria and pulmonary hemorrhage. The diagnosis depends on detection of the Ab in the serum (indirect) or in tissue biopsy (direct immunofluorescence test).
- **Pemphigus vulgaris:**
- A skin disease characterized by bullae. The auto-Abs are directed against desmogleins of the tight junctions in the skin.
- **Myasthenia gravis:**
- An autoimmune disease that is characterised by muscle weakness and fatigue. The name was derived from Greek language and means (myo: muscle, asthenia: weakness) and the Latin language (gravis: serious). Clinically, myasthenia gravis manifests with fluctuating fatigability and weakness affecting a variety of muscle groups.

Ab-mediated HSR affecting cellular function

- **Graves disease:**
 - Auto-Abs specific for TSH receptor mimicking the stimulating effect of the hormone can cause the disease without tissue damage.
- **Wegener's granulomatosis (granulomatosis with polyangiitis):**
 - Vasculitis caused by auto-Abs against proteinase 3 that is present in PMNs (the Abs are termed cytoplasmic anti neutrophil cytoplasmic Abs [c-ANCA]). c-ANCA activates PMNs and cause degranulation with subsequent damage of endothelial cells.

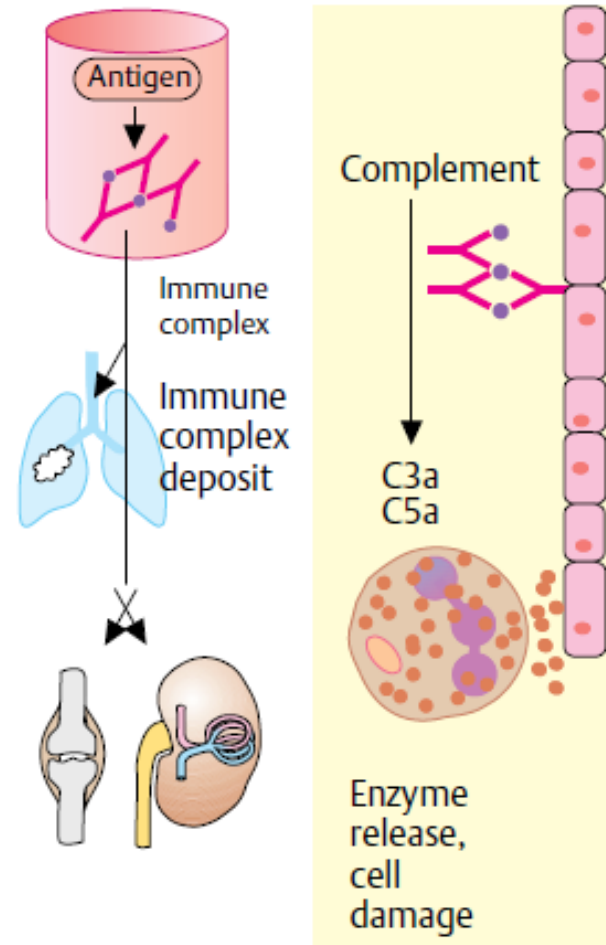




Immune complex HSR (Type III)

- Immune complexes are lattices of Abs and with its cognate Ags. The physiologic function of immune complex formation is to facilitate the clearance of Ags by phagocytes. However, the presence of large numbers and networks of immune complexes can lead to tissue damage.
- Failure of the immune mechanisms to clear immune complexes due to ongoing excessive production (e.g. chronic antigenemia), will end up in activating the complement system and recruiting leukocytes with ensuing inflammation and tissue damage.
- Immune complex deposition is most likely where there is high blood pressure and turbulence (e.g. glomerular capillaries).
- Deposited immune complexes can be visualized using immunofluorescence which aids in diagnosis.

Immune complex HSR (Type III)



Type III: Immune complex reaction

Source: Burmester, *Color Atlas of Immunology*, 2003.



Immune complex HSR (Type III)

- **Systemic lupus erythematosus (SLE):**
 - The prototypic autoimmune disease characterized by the production of Abs to components of the cell nucleus in association with a diverse array of systemic clinical manifestations.
- **Poststreptococcal glomerulonephritis:**
 - Glomerulonephritis streptococcal Ags with biochemical affinity for glomerular basement membrane, circulating immune complexes, and activation of complement.



Delayed type HSR (Type IV)

- An exaggerated interaction between Ag and the normal T cell mediated immune responses.
- It is characterized by T cell response driving an inflammatory reaction involving macrophages.
- The immune response might be directed against microorganisms (*Mycobacterium tuberculosis*, *Leishmania* spp.) or against contact Ags (nickel salts, poison ivy).
- The effector T cell response in type IV HSR is an adaptive response that is considered an essential line of defence against intracellular pathogens, however, if the response is excessive it can cause tissue damage.
- Typically, T cells are sensitized through the dendritic cell presentation during infection or contact with the triggering chemical.
- Subsequent exposure to the same Ag will result in recruitment of Ag-specific T cells to the site with the development of an immune response within 48-72 hours.



Delayed type HSR (Type IV)

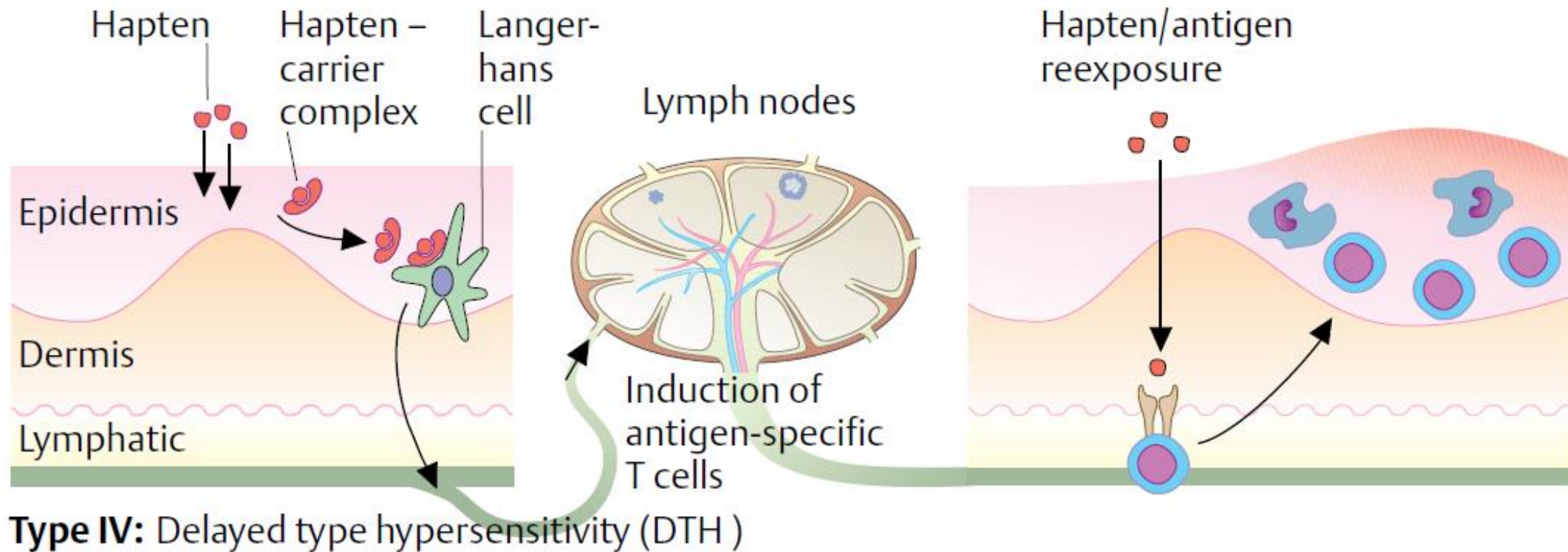
- Type IV HSR can be divided into the following variants: contact HSR, tuberculin-type HSR and granulomatous HSR.
- The granulomatous HSR develops over a period of 3-4 week in contrast to 48-72 hours for the first two variants.
- Granulomas are formed by aggregation of macrophages and lymphocytes.
- Contact HSR is often seen following contact with immunologically active components (haptens) of sensitizing agents such as nickel or pentadecacatechol (the sensitizing agent in poison ivy).
- Haptens are too small to be antigenic by themselves hence they conjugate to proteins to form neo-Ags
- Langerhans cells (the skin APC) play a key role in contact HSR IV, by uptaking the hapten-modified proteins followed by migration to regional LNs and presentation of Ags to T cells.



Delayed type HSR (Type IV)

- Tuberculin type IV HSR is induced by soluble Ags from variety of microorganisms.
- Reaction to these Ags demonstrates a past infection with the pathogen (tuberculin skin test).
- The same test can be used as a measure of cell-mediated immunity.
- Granulomatous HSR usually stems from persistence of intracellular organisms or particles within macrophages.
- This leads to chronic stimulation of T cells which ends up in the formation of granulomas that contain epithelioid cells, lymphocytes and macrophages.
- IFN- γ is essential for granuloma formation.
- Chronic diseases that manifest in type IV granulomatous HSR include: leprosy, TB, schistosomiasis and sarcoidosis.

Delayed type HSR (Type IV)



Source: Burmester, *Color Atlas of Immunology*, 2003.



Autoimmune disease (AID)

- Autoimmunity can be defined as adaptive immune responses directed against self Ags. It underlies many diseases, some of which are organ-specific and others are systemic in nature. AIDs arise as a result of loss of self-tolerance.
- The autoimmune responses can involve Abs (auto-Abs) or self reactive T cells, which can cause tissue damage through HSRs II to IV.
- Auto-Abs can be found in some healthy individuals, however, their very low levels and low affinities for self Ags hinder the occurrence of subsequent AID.
- Genetic factors play a role in the development of AID including factors such as HLA type, CTLA-4 SNP.
- The auto-Ags are almost impossible to be eradicated from self, hence, AIDs tend to be active for a long time (chronicity).
- In general, women are more susceptible than men to autoimmunity (overall more than 75%).



HLA association with AID

Some HLA associated autoimmune diseases

| Disease | HLA | Pts ^a | Ctrls ^a | RR ^b |
|--------------------------------|------------|------------------|--------------------|-----------------|
| Ankylosing spondylitis | B27 | > 95 | 9 | > 150 |
| Subacute thyroiditis | B35 | 70 | 14 | 14 |
| Psoriasis vulgaris | Cw6 | 87 | 33 | 7 |
| Graves disease | DR3 | 65 | 27 | 4 |
| Myasthenia gravis | DR3 | 50 | 27 | 2 |
| Addisons disease | DR3 | 69 | 27 | 5 |
| Rheumatoid arthritis | DR4(some) | 81 | 33 | 9 |
| Juvenile idiopathic arthiritis | DR8 | 38 | 7 | 8 |
| Celiac disease | DQ2 (+DQ8) | 92 | 28 | 30 |
| Narcolepsy | DQ6(02) | > 95 | 33 | > 40 |
| Multiple sclerosis | DQ6(02) | 86 | 33 | 12 |
| Type 1 diabetes | DQ8(+) | 81 | 23 | 14 |
| Type 1 diabetes | DQ6(02) | < 0.01 | 33 | 0.02 |

^a The figures show antigen frequencies in a Norwegian population.

^b RR: relative risk; i.e. how many times more frequent the disease is in those having the corresponding HLA molecule compared to those lacking it.

Source: Thorsby E, Lie BA. HLA associated genetic predisposition to autoimmune diseases: Genes involved and possible mechanisms. *Transpl Immunol* 2005;**14**:175-182.



Mechanisms of loss of self-tolerance

- **Molecular mimicry:**
 - The process in which a microbial infection will result in subsequent development of AID as a result of enough similarity between some self Ags and microbial Ags.
 - *Examples:*
 - **Rheumatic fever:** Abs against the M protein of *Streptococcus pyogenes* cross reacts with the cardiac myosin
 - **Ankylosing spondylitis:** possible association with *Klebsiella* sp.
 - **Reactive arthritis:** Possible association with *Chlamydia trachomatis*.



Mechanisms of loss of self-tolerance

- **Epitope spreading:** Microbial antigens can initiate an immune response with tissue damage that exposes self epitopes triggering an AID.
- Examples (suspected):
 - Systemic lupus erythematosus
 - Inflammatory bowel disease
 - Multiple sclerosis
 - Pemphigus vulgaris
 - Insulin dependent DM



Mechanisms of loss of self-tolerance

- **Sequestered antigens:** The presence of self molecules that are normally isolated and never exposed to the immune system. The sites of these self molecules are called immunologically privileged sites. (e.g. Lumen of the testicular tubules, the cornea, anterior chamber of the eye).
- Other form of sequestered antigens is due to the 3D protein structure which might shelter epitopes in the interior of the molecule (cryptic antigens). If the molecule is denatured or cleaved, these epitopes become exposed and recognized by self reactive immune response. (e.g. rheumatoid factor).
- **Failure of T_{reg} cells inhibition:** Potential role in SLE.



Classical systemic autoimmune diseases

- **Rheumatoid arthritis:**
- Systemic chronic inflammatory disease that is manifested in destructive polyarthrititis with extra-articular manifestations.
- Diagnosis depends on the clinical features with serologic testing for rheumatoid factor (neither highly sensitive nor specific) and for antibodies against cyclic citrullinated peptides (anti-CCP).
- Other conditions include systemic sclerosis, Sjögren syndrome and mixed connective tissue disease (MCTD).



Endocrine autoimmune diseases

- **Graves disease:** discussed earlier
- **Hashimoto's thyroiditis:** Abs are formed to a number of thyroid proteins, including thyroglobulin and thyroid peroxidase, both of which are involved in the uptake of iodine. Binding of the auto-Abs to these proteins interferes with iodine uptake, leading to decreased thyroid function and hypothyroidism. The resulting type IV HSR is characterized by an intense infiltration of the thyroid gland by lymphocytes and macrophages.
- **Insulin dependent DM:** Caused by an autoimmune attack against insulin-producing β -cells of the pancreas. The immune attack is considered type IV HSR.



Gastrointestinal autoimmune diseases

- **Inflammatory Bowel Diseases (IBDs):** a group of inflammatory disorders affecting the GI tract. The major types are Crohn's disease and ulcerative colitis, both of which are debilitating conditions.
- **Celiac disease (gluten sensitive enteropathy):** a chronic condition that is characterized by the presence of circulating auto-Abs in addition to an enteropathy, triggered by exposure to the gliadin fraction of gluten, a family of proteins found in wheat, barley, and rye.
- Exposure to gliadin, causes recognition by specific T cells in the setting of specific HLA alleles. Once the enzyme tissue transglutaminase modifies the glutamine into glutamic acid, the gliadin molecule can tightly adhere with the HLA of lymphocytes.
- The gliadin peptides, bound to dendritic cells, activate a proinflammatory response in which CD4+ cells participate in upregulation of IFN- γ , TNF- α , and IL-21. The end results are the observed villus blunting and atrophy.



Neurologic autoimmune diseases

- **Multiple sclerosis**
- It is characterized by lesions termed “plaques” in the white matter of the brain and spinal cord, resulting in the progressive destruction of the myelin sheath of axons (with several myelin proteins as the auto-Ags).
- Autoreactive T cells and activated macrophages is thought to be stimulated by a preceding viral infection.
- Intrathecal oligoclonal bands (bands of IgG in the CSF) are present in the majority of patients.



Neurologic autoimmune diseases

- **Guillain-Barré Syndrome:**
- The disease follows a variety of infections including upper respiratory tract infections, EBV, CMV mononucleosis, and *Campylobacter jejuni* gastroenteritis.
- Auto-Abs against myelin proteins are produced resulting in demyelinating polyneuropathy.
- The main symptom of the disease is rapidly progressive ascending paralysis.



Nephrologic autoimmune diseases

- **IgA nephropathy:**
- One of the most common types of glomerulonephritis globally.
- It is an immune complex-mediated disease defined by the presence of diffuse mesangial IgA deposits in the kidneys.
- Clinically, it is characterized by hematuria, but proteinuria can occur with progression to end-stage renal disease.



Hematologic autoimmune diseases

- Various forms of the hematologic autoimmune diseases (autoimmune hemolytic anemia, thrombocytopenia, granulocytopenia) can be attributed to auto-Abs attaching to blood cells with subsequent cellular destruction.
- Several drugs can get attached to the platelet cell membrane forming a neoantigen that induces the production of antibodies resulting in platelet destruction (e.g. some β -lactams, tetracyclins, INH).
- Pernicious anemia is caused by auto-Abs to intrinsic factor, a membrane protein on gastric parietal cells. Intrinsic factor facilitates uptake of vitamin B12 from the small intestine. Binding of the auto-antibody to intrinsic factor blocks absorption of vitamin B12, which is necessary for hematopoiesis, thus, the number of functional mature erythrocytes decreases below normal causing megaloblastic anemia.

Thank you for listening

