Allergy:
IgE and IgE-mediated diseases
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Allergy in general

- Allergy = hypersensitivity reaction of the adaptive immune system to harmless environmental antigens

- Allergens = (glyco-)proteins from e.g. different fruits, vegetables, grass and tree pollen, house dust mite, animal hair and urine, insect bites which bind IgE

- Almost half of the population of North America and Europe is sensitized

https://jamaicahospital.org/newsletter/wp-content/uploads/2016/05/Food-Allergy.jpg
Allergen

- Most allergens are relatively small, highly soluble proteins

- E.g. airborne allergens are carried on particles like pollen grains or mite feces

- After contact with the mucus-covered epithelia these proteins are eluted and diffused into the mucosa

- Allergens are typically presented to the immune system in low concentrations

Murphy, Kenneth M.; Janeway's Immunobiology, 8th Edition; chapter 14
Allergy classification

- Hypersensitivity reactions of the immune system are classified into four groups.

- IgE-mediated allergies and Type IV-reactions are the most common.

Murphy, Kenneth M.; Janeway's Immunobiology, 8th Edition; chapter 14
Type I Hypersensitivity reaction

- IgE-mediated allergic reactions against innocuous antigens
- IgE normally defenses against parasites
- 2 steps are necessary for a allergic reaction
  - First: sensitization
  - Second: a second (repeated) contact with the allergen
Sensitization

- Sensitization is driven by IgE production against a specific antigen
- Can be developed at any time of life
- The immune response for IgE production is divided in 2 parts
  - First: antigen recognition and processing, stimulation of T-cells and differentiation of naive T cells to $T_H^2$ cells
  - Second: cytokines and co-stimulatory signals initiate B cells to the class switch and the production of IgE antibodies (development of B cells to plasma cells)
Allergen example Der p 1

- Der p 1 = allergen from *(Dermatophagoides pteronyssimus)*
- Protease that cleaves occludin (= component of tight junctions)
- Parasites often cleave tight junctions to invade the host

Sensitization example house dust mite I

- Antigen enters the mucosa
- Allergen is captured by dendritic cells which migrates to lymph nodes => naive T cells become specific $T_{H2}$ cells

Murphy, Kenneth M.; Janeway's Immunobiology, 8th Edition; capter 14
Sensitization example: house dust mite II

- $T_H^2$ cells secrete cytokines like IL-4, IL-5, IL-9 and IL-13
- $T_H^2$ cells cause the switch of B cells to IgE production
- IgE producing plasma cell travels back to the mucosa and releases specific IgE
Sensitization example house dust mite III

- IgE is trapped by specific FcεRI receptor on the surface of mast cells
- Mast cells amplify the IgE response by degranulation (e.g. histamine release)
Amplification of IgE production by mast cells and basophils

- Surface-bound IgE gets cross-linked by antigen => mast cells express CD40L (Ligand) and secrete IL-4

- IL-4 binds to IL-4R and CD40L to CD40 at the surface of B cells => class switch to IgE production
Why do some people develop allergic diseases?
Genetic factors I

- Atopy = individual shows a tendency to respond with IgE production to a wide variety of environmental allergens
- Strong familial basis
- Influenced by multiple genetic loci
- Higher level of total IgE and eosinophils

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Genetic factors II

- Atopy individuals have a higher chance to get allergic asthma, rhinoconjunctivitis or atopic eczema

- Gen loci for asthma overlap with inflammatory diseases like psoriasis

- Mutations lead to stronger IgE response

- Some people are predisposed for getting allergies

Murphy, Kenneth M.; Janeway’s Immunobiology, 8th Edition; capter 14
Environmental factors

- Big problem in economically advanced regions of the world (Western life-style)

- Hygiene hypothesis first published in 1989

- Less hygienic environment in early childhood (with microbial diversity) = helps to protect against atopy and allergic asthma by skewed response to $T_{H1}$ instead of $T_{H2}$ (drawback: hookworm infection)

- Counter-regulation hypothesis = all types of infection might protect against atopy by down-regulating $T_{H1}$ and $T_{H2}$ response
Summary of factors for atopy

- Not all infections helps the individual to get protected
  - E.g. respiratory infections with the respiratory syncytial virus (RSV) 
  - => higher chance for asthma

- The tendency of IgE overproduction is influenced by genetic and environmental factors

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Effector mechanisms involved in IgE-mediated allergic reactions

- Recontact with an allergen after sensitization can trigger allergic reactions
- Allergens crosslink IgE bound to high affinity receptor FcεRI on mast cells
- Activated mast cells secrete by granulation histamine, prostaglandins, leukotrienes and other pharmacological mediators
- Leads to inflammation of the surrounding tissue

<table>
<thead>
<tr>
<th>Class of product</th>
<th>Examples</th>
<th>Biological effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme</td>
<td>Typtase, chymase, carboxypeptidase</td>
<td>Remodel connective tissue matrix</td>
</tr>
<tr>
<td>Toxic mediator</td>
<td>Histamine, heparin</td>
<td>Toxic to parasites, increase vascular permeability, cause smooth muscle contraction, antiaggregation</td>
</tr>
<tr>
<td>Cytokine</td>
<td>IL-4, IL-13, IL-3, IL-5, GM-CSF</td>
<td>Stimulate and amplify T&lt;sub&gt;H&lt;/sub&gt;2-cell response</td>
</tr>
<tr>
<td></td>
<td>TNF-α (some stored preformed in granules)</td>
<td>Promotes inflammation, stimulates cytokine production by many cell types, activates endothelium</td>
</tr>
<tr>
<td>Chemokine</td>
<td>CCL3</td>
<td>Attracts monocytes, macrophages, and neutrophils</td>
</tr>
<tr>
<td>Lipid mediator</td>
<td>Prostaglandins D&lt;sub&gt;1&lt;/sub&gt;, E&lt;sub&gt;2&lt;/sub&gt;, Leukotrienes C4, D4, E4</td>
<td>Smooth muscle contraction, chemotaxis of eosinophils, basophils, and T&lt;sub&gt;H&lt;/sub&gt;2 cells, increase vascular permeability, stimulate mucus secretion, bronchoconstriction</td>
</tr>
<tr>
<td></td>
<td>Platelet-activating factor</td>
<td>Attracts leukocytes, amplifies production of lipid mediators, activates neutrophils, eosinophils, and platelets</td>
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Mast cell activation and effects

- Mast cell activation effect depends on the allergen and the presenting way to the body

- Symptoms from swollen eyes to life threatening circulatory collapse

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Eosinophils I

- Eosinophils are granulocytic leukocytes that originate in bone marrow
- Usually only a very small number of eosinophils are in the circulation
- Normally in tissue (under the epithelium)
- Defense role against invading organisms
- Express receptors for IL-5 and can be activated through it
Eosinophils II

- Eosinophils release highly toxic granule proteins and free radicals
- Normally to kill microorganisms or parasites
- Activation leads to synthesis of prostaglandins and other mediators
- Amplification of inflammatory response
- Normally strictly regulated

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<td>Toxic to targets by catalyzing halogenation</td>
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<td>Triggers histamine release from mast cells</td>
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<tr>
<td></td>
<td>Eosinophil collagenase</td>
<td>Remodels connective tissue matrix</td>
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<td></td>
<td>Matrix metalloproteinase-9</td>
<td>Matrix protein degradation</td>
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<tr>
<td>Toxic protein</td>
<td>Major basic protein</td>
<td>Toxic to parasites and mammalian cells</td>
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<td>Eosinophil cationic protein</td>
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<td>Eosinophil-derived neurotoxin</td>
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<td>IL-3, IL-5, GM-CSF</td>
<td>Amplify eosinophil production by bone marrow</td>
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<td>Eosinophil activation</td>
</tr>
<tr>
<td></td>
<td>TGF-α, TGF-β</td>
<td>Epithelial proliferation, myofibroblast formation</td>
</tr>
<tr>
<td>Chemokine</td>
<td>CXCL8 (IL-8)</td>
<td>Promotes influx of leukocytes</td>
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<td>Lipid mediator</td>
<td>Leukotrienes C4, D4, E4</td>
<td>Smooth muscle contraction, increase vascular permeability</td>
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Basophils

- Normally present in very low numbers in the circulation
- Seems to have a similar role in the immune system like eosinophils
- They are recruited by IgE-mediated allergic reactions
- Express FcεRI receptor
- Release histamine on a similar pathway like mast cells
Kinetics of IgE-mediated allergic reactions I

- The immune response can be divided into immediate reaction and late-phase reaction
- Immediate reaction starts within seconds
- Result of actions of histamine, prostaglandins and other mediators released by mast cells
Kinetics of IgE-mediated allergic reactions II

- Result: visible edema, reddening of the skin
- For airborne allergens narrowing of the airway (edema)
- Histamine acts on H1 receptor on local nerve endings leading to vasodilatation => so-called wheal-and-flare reaction
Kinetics of IgE-mediated allergic reactions III

- Late-phase reaction depends on allergen dose
- Peaks between 3 and 9 hours
- Caused by the continued synthesis of vasoactive mediators and leads to vasodilatation and large edema
Anaphylaxis I

- Occurs mostly when allergens introduced directly into the bloodstream (bee sting) or absorbed rapidly (gut)

- The severity can range from mild urticaria to fatal anaphylactic shock

- Acute urticaria caused through massive histamine release from mast cells

- Red swelling and large itch all over the body
Anaphylaxis II

- Anaphylactic shock
- Histamine release leads to massive loss of blood pressure
- Airway constriction causing difficulties in breathing
- Mostly caused by food (peanuts) or bee/wasp stings
- Drugs (e.g. penicillin) could act as haptens and interact with host proteins
- Help: immediate epinephrine injection reverses histamine H$_1$ receptor interaction.
Allergic rhinitis and conjunctivitis

- IgE-mediated allergic reaction to airborne allergens (pollen)
- Results by activation of mucosal mast cells in the nasal epithelium
- Characterized by intense itching and sneezing, local edema (block of nasal passage)
- Conjunctivitis allergic reaction of the eye
- Both typically seasonal (e.g. by pollen) or perennially by e.g. dust mites or furry animals

https://swamiramdevherbalproducts.files.wordpress.com/2015/06/treatment-for-allergic-rhinitis.jpg
Allergic asthma

- More serious respiratory disease
- Results by activation of submucosal mast cells in the lower airways
- Leads to bronchial constriction, secretion of fluid and mucus
- Making breathing difficult
- Can be life-threatening

http://www.allergyclinic.co.za/images/inhaler02.jpg

Murphy, Kenneth M.; Janeway's Immunobiology, 8th Edition; chapter 14
Allergic asthma chronic response

- Chronic inflammation of the airways
- Characterized by continuous increased number of $T_H^2$ lymphocytes, eosinophils and other leukocytes
- General hyperreactivity of the airways to nonimmunological stimuli is developed often
- Airways remoddeling takes place

Murphy, Kenneth M.; Janeway's Immunobiology, 8th Edition; capter 14
Take home message

- IgE-mediated allergies are very common and can developed at any time of life

- 2 steps are necessary to get an allergic reaction: Sensitization and renewed contact with the allergen

- Allergic reaction and effects mainly driven by IgE, T<sub>H</sub>2 cells, mast cells, basophils, eosinophils and their mediators histamine and cytokines

- IgE-mediated allergic reaction can differ in their severity; e.g. rhinitis versus anaphylaxis
Thank you for your attention!

http://www.praxisvita.de/sites/default/files/allergie-wenn-unser-korper-harmlose-stoffe-bekampft.jpg