Hypersensitivity 1

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** EXTRA FROM THE EDITOR https://www.youtube.com/watch?v=IpHaGrYNTag

	Type	Mechanism	Examples
A	Type 1	Antigen/IgE cross linking on mast cells and basophils	Allergic rhinitis, Asthma, Anaphylaxis
C	Type 2	Cytotoxic IgG/IgM activates complement	Goodpasture Syndrome, Myasthenia Gravis, AHA, Grave's Disease
I	Type 3	Immune complex formation b/w IgG and antigen	SLE, Poststreptococcal Glomerulonephritis
D	Type 4	Delayed, cell-mediated CD8+ TH1 directly kill cells	DM, Dermatitis

Introduction

= immunologically mediated tissue injury

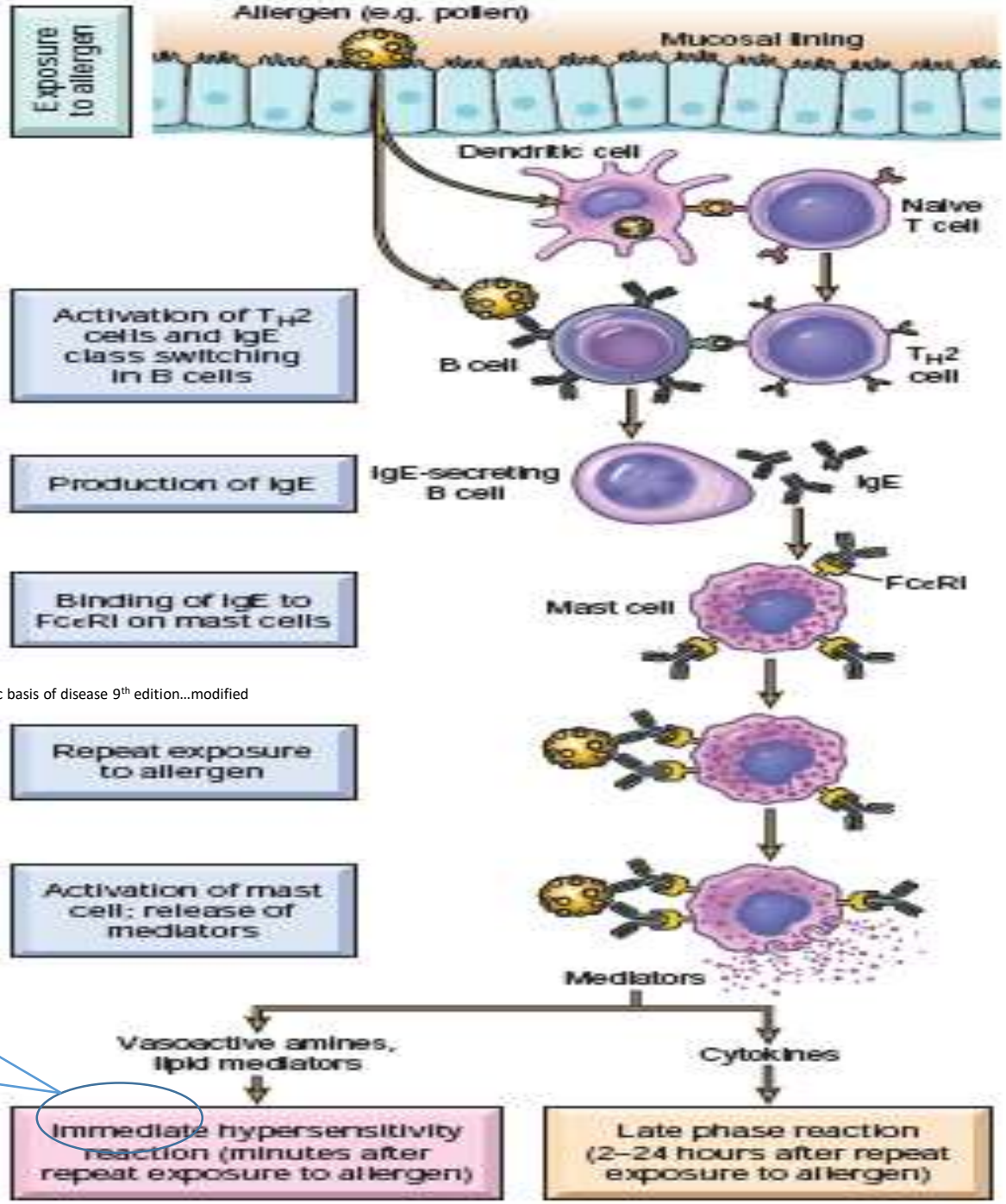
#Hypersensitivity is a general term compared to autoimmune disease

- 4 types:

I
II
III
IV

These are the topics that we will discuss today

Immediate (Type I) hypersensitivity



Robbins and Cotran pathologic basis of disease 9th edition…modified

May include glandular secretions

Systemic or local

sheet note .1

- There is an exposure to an allergen and an abnormal response by TH2 and thus producing IgE that stay in the body waiting for another exposure (or other stimuli) so IgE accumulate in the body and bind to FcεR1 on the surfaces of mast cells and basophiles, on the second exposure the allergen causes cross-linking of the antibody IgE on the surface of these cells causing degranulation.
- In the **(second or after multiple)** re-exposure there are two types of actions:

1. Immediate in minutes after re-exposure (vasodilation, bronchoconstriction, increase mucus production).
2. Late phase in hours to 24 hours (secretion of chemokines, cytokines attracting eosinophils, chronic inflammatory cells accumulate in the tissue) and this causes a permanent change in the tissue such as asthma.

Immediate (Type I) hypersensitivity

- = allergy

#we don't know how the body exposes for the first time but the re-exposure depends on the type of the allergen.

- Routes of re-exposure:

-Injection…like bee sting #venoms

-Ingestion…like peanut allergen

-Inhalation #asthma

-Direct contact

#in the re-exposure reactions that occur might be local (asthma, allergic rhinitis, allergic\atopic dermatitis, allergic conjunctivitis) or exacerbate to systematic that ends as anaphylaxis

Immediate (Type I) hypersensitivity...late phase

- Stays for days without additional antigen exposure
- Especially in asthma and allergic rhinitis

  #in allergic rhinitis permanent inflammatory changes might occur (chronic sinusitis ,rhinosinusitis) and in asthma the remodeling, permanent changes in the wall
- Infiltration of tissues with eosinophils, neutrophils, basophils, monocytes, and CD4+ T cells #Th2 response
- Tissue destruction, typically in the form of mucosal epithelial cell damage

Some molecules and cells in type I hypersensitivity

- IL-13…IgE production
  …mucus secretion

- Mast cells are abundant around vessels and nerves and subepithelial

- Some mast cell secretagogues: -IL-8
  -codeine
  -morphine
  -adenosine
  -melittin…in bee venom
  -physical stimuli

mast cell secretagogues these agents stimulate mast cells to secrete their content and this process is called **mast cell dependent igE independent**

- Mast cell will secrete:
  -preformed (primary) mediators #already exist in the cell (vasoactive-amines histamine)
  -secondary mediators (synthesized de novo) #not exist but synthesized as a response (lipid mediator : arachodinic acid cyclooxygenase and lipoxygenase , cytokines)

- Histamine also increases mucus production in nasal, bronchial and gastric mucosae

Some molecules and cells in type I hypersensitivity, cont'd

- Mast cell enzymes: -tissue damage
  -generation of kinins # role in vasodilation and vascular permeability
  -activate complement precursors

- Mast cell proteoglycans #(the cause of positivity in toluidine blue and giemsa)…store amines

- Prostaglandin D2 #(lipid mediator) also increases mucus secretion # also plays a role in vasodilation and vascular permeability

- PAF(platelet activating factor)…a lipid mediator but not from arachidonic acid
  …vasodilation, permeability and bronchospasm
  …platelet aggregation and release of histamine

Non-atopic immediate (Type I) hypersensitivity

- 20-30% of type I hypersensitivity reactions are not triggered by antigens.
- …but induced by temperature changes or exercise without Th2 or IgE contribution.
- …mainly an abnormality in mast cell response #mast cell dependent igE independent
- … = non-atopic allergy\hypersensitivity

#no Th2 response or igE or mast cell

#the most important example of immediate hypersensitivity reaction is atopy (disease in which a genetic exposure to an allergen such as atopic asthma)

#any inflammation in nasal mucosa can cause nasal polyps

Antibody-mediated (Type II) hypersensitivity mechanisms

#against normal tissue but not necessarily against self as autoimmune also non-self tissue (B-cell has tolerance but in some disease against non self response causes a collateral damages in normal tissue by these antibodies)

- IgG on cells ➡ opsonization #of normal cell and then phagocytosed
- IgG & IgM on cells ➡ classical pathway ➡ C3b & C4b ➡ opsonization
- IgG & IgM on cells ➡ classical pathway ➡ membrane attack complex
- Antibody-dependent cellular cytotoxicity (ADCC):

  …IgG on cells ➡ binding to Fc by ➡ phagocytes

  NK cells #the most important in this action

sheet note .2

Antibody-dependent cellular cytotoxicity (ADCC)

#antibody binds to a cell but rather than opsonize and phagocyte it by the phagocytic cell ,the phagocytic cell stimulated to secrete killing substances to kill .

#fixed tissue cannot be phagocytized like : basement membrane in glomerulus

beside the phagocytosis, the neutrophils can also secrete outside of it killing substances like acid hydrolyse which act inside the lysosome also it have neutral substance that can be secreted outside the cell such as cathepsin G

#C3b produce from the stimulation of complement by the antibody in the tissue

#immune-mediated glomerular injury we usually called it glomerulonephritis

Antibody-mediated (Type II) hypersensitivity mechanisms, cont'd

- Antibodies deposited on fixed tissues → complement activation

  → C3a & C5a (anaphylatoxins)

  ↓

  chemotaxis of neutrophils & monocytes

…also WBCs binding through their Fc & C3b receptors → enzymes & ROS

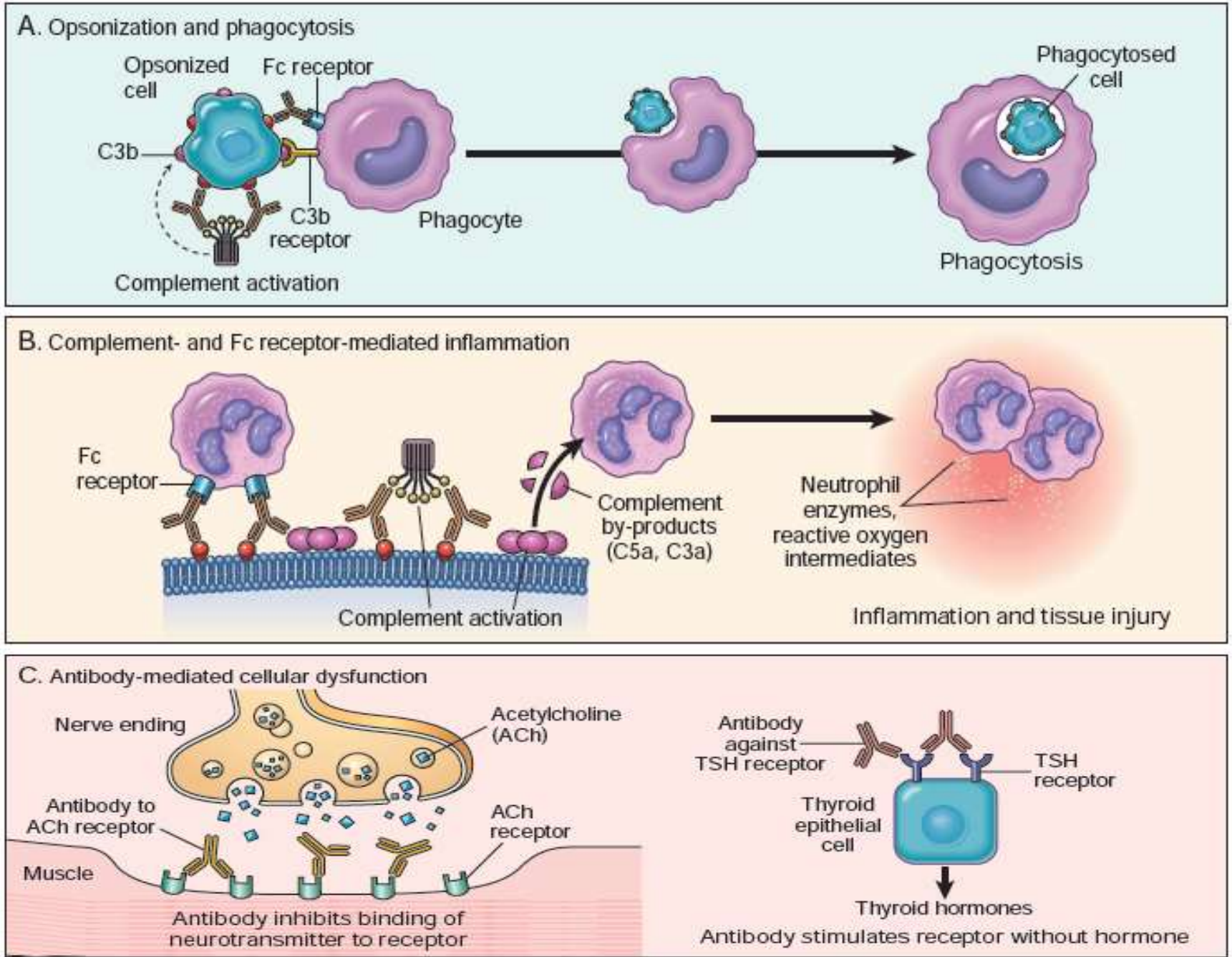
↓

Inflammation

-Some forms of glomerulonephritis
-Vascular rejection in organ grafts

Antibody-mediated (Type II) hypersensitivity mechanisms, cont'd

- Cellular dysfunction without injury or inflammation #antibody bind to a receptor causing dysfunction
  1- …Myasthenia gravis #in neuromascular junction the acetylcholine is secreted and bind to it's receptor ,the antibody bind instead with the receptor and inhibit it
  2-…Graves disease # the antibody stimulate the receptor such as thyroid stimulating immunoglobulin activate the TSH receptor (stimulatory type of type 2 hypersensitivity reaction)



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sheet note.3

A. normal cell that will bind with an antibody and this antibody causes complement activation (classical pathway) or the antibody that bound to the cell will opsonin and the phagocytic cell will come and phagocyte

B. or the antibody bind with an epitope on fixed tissue and activate on the surface via the classical pathway of complement activation producing C3a and C5a (C4 is less importantly) stimulate inflammatory cell or this activated complement produce C3b and C4b and via the complement receptor on the WBCs bind to C3b and C4b or the neutrophill via the Fc receptor binds to the antibody and releasing ROS and other enzymes

C. the antibody directly bind to a receptor and causing cellular dysfunction

Examples of type II hypersensitivity

- Transfusion reactions…preformed antibodies # mainly IgM (your blood group A you have B antibody)

- Hemolytic disease of the newborn (erythroblastosis fetalis)

  …IgG antierythrocyte antibodies from the mother cross the placenta and cause destruction of fetal red cells #RH group (D antigen) if the first child was positive for a negative RH mother he will survive but at birth he will stimulate the formation of antibodies that attack the second positve child due to the IgG that formed and cross the placenta

- Autoimmune hemolytic anemia # such as SLE, agranulocytosis # attack neutrophills and thrombocytopenia # attack platelets

- Certain drug reactions…act as haptens that bind to plasma proteins on RBCs

Immune complex-mediated (Type III) hypersensitivity

#antigen -antibody complex deposit on a fixed surface , a neutrophills bind to the Fc receptor of the antibody or complement activation (classical) .The same as type 2 hypersensitivity reaction on fixed surface (Often glomeruli , joints and vessels are affected)

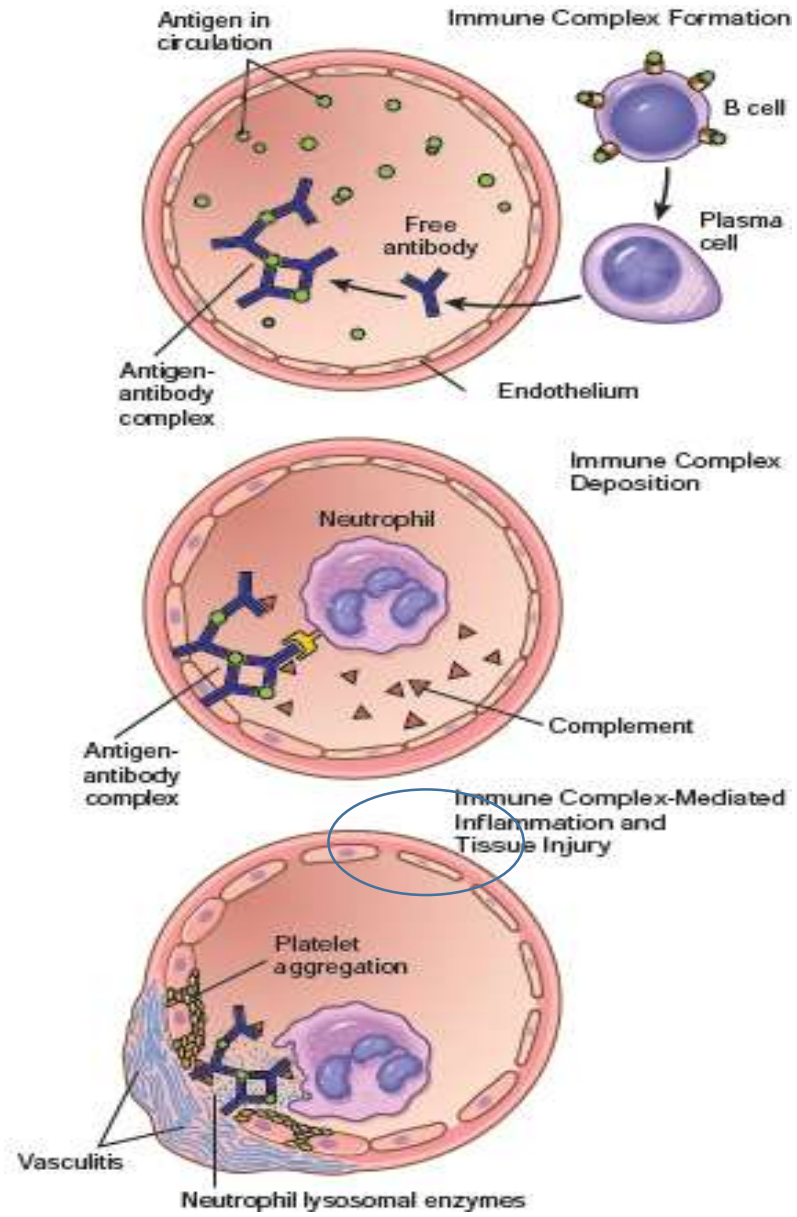
Type 3 examples

1.Systemic immune complex disease mechanisms:

-Acute serum sickness is the prototypical example

…large amounts of foreign serum (e.g., serum from immunized horses used for protection against diphtheria) #as a side effect of : horse serum contain a lot of antibodies and thus producing a lot of complexes in the body

-Often glomeruli and joints are affected



Immune complex-mediated (Type III) hypersensitivity

2. Local immune complex disease mechanisms:

= Arthus reaction

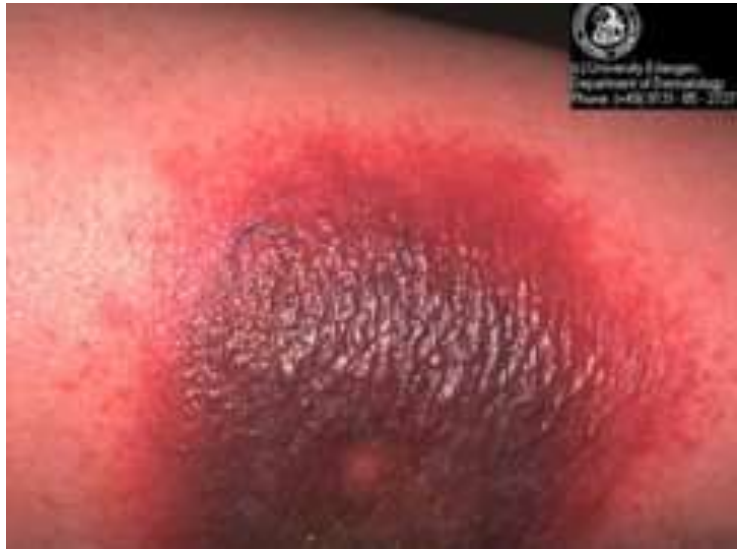
-acute & local

-usually in the skin

-mainly experimentally induced

-injection of antigen (sensitization) ➡ dermal injection of that antigen ➡ the antigen gains access to local blood vessels ➡ complexes are formed causing vasculitis with fibrinoid necrosis of that vessel followed by ischemia and tissue necrosis **locally**

#occur in some Vaccines as a side effect especially multiple-dose
#sensitization : antibody is formed



T cell–mediated (Type IV) hypersensitivity

- CD4+ T cells…cytokines

  -induced by environmental and self antigens
  -the cause of many chronic inflammatory diseases, including autoimmune diseases

  Delayed-type hypersensitivity reaction is the prototype

  #mainly Th1 such as TB and allergic contact dermatitis

  Th1 & Th17

  # T cell–mediated with Th2 is possible such as systemic sclerosis but mainly Th1 .

  # mainly T-cell mediated :
  rheumatoid arthritis mainly Th1 and Th17,
  psoriasis ,
  multiple sclerosis,
  inflammatory bowel disease
  DM type 1

  or

- CD8+ T cells…killing

  -DM type 1
  -important in graft rejection

CD4+ T Cell–Mediated Inflammation, sensitization

- Dendritic cell + antigen + CD4+ T cell ➡ IL-2 ➡ more CD4 activation

  #sources of IL-2 : CD4+ ALSO CD8+

- Cytokines from APCs ➡ differentiation to Th1 and Th17

  by IFN-gamma & IL-12

  by IL-1, IL-6 and IL-23

Now we have memory pool of T cells

sheet note.4

#dendritic cell present an antigen to CD4+ and thus secreting IL-2 from CD4+ and CD8+ will increase the differentiation toward CD4+

#IL-2 mainly secreted by T-cell and stimulate the differntion of t-cell to CD4+

CD4+ T Cell–Mediated Inflammation, repeated exposure

- IFN-gamma by Th1 ➡ classical activation of macrophages #and inflammation

- In addition to the actions of these macrophages, they augment Th1 responses by IL-12 and by expressing more MHC II

- Th17 secrete: -IL-17
  -IL-22
  -chemokines
  ➡ recruitment of neutrophils and monocytes #and inflammation
  -IL-21…amplifies Th17 responses

CD4+ T Cell–Mediated Inflammation, repeated exposure

- Tuberculin test is the prototypical example
- Granuloma and perivascular cuffing by mononuclear cells (CD4+ cells and macrophages) are typical histological patterns here

#not all types mainly tuberculin and TB such as allergic contact dermatitis Granuloma does not occur alot

- Contact dermatitis is also an example

Skin rashes in most drug reactions

Visit https://www.medicinenet.com/poison_ivy_oak_and_sumac/article.htm for references

Similar mechanisms

sheet note.5

#β-lactam cause allergy type 1 such as penicillin but can cause type 4

#remember that alot of drugs cause rash most of them are type 4 hypersensitivity reactions

#poison ivy casues allergic contact dermatitis also a prototypical example of delayed type hypersensitivity reaction

#delayed ⟶ mostly Th1

Thank You