

# **Pathophysiology of the skin and connective tissue**

## **Systemic diseases of the connective tissue**

# Learning objectives

- ✓ For students to learn the causes and mechanism of skin changes and types of diseases,
- ✓ For students to learn the causes and mechanism of systemic connective tissue diseases

# Lecture content

Pathophysiology of skin and connective tissue

Systemic connective tissue diseases:

- RA
- Seronegative arthropathies
- Systemic lupus erythematosus
- Antiphospholipid syndrome
- Sjogren's syndrome
- Systemic sclerosis
- Polymyositis, Dermatitis
- Systemic vasculitis

# Skin

- The skin is the largest organ, with a surface of 1.5 to 2m<sup>2</sup> , which separates the inside of the organism from the environment and protects it from external influence
- Together with accessory structures, hair, nails, sweat and sebaceous glands make up the covering system

# Epidermis

The outer layer of the skin consisting of keratinized squamous epithelium

Epidermis consists of 4 cells:

**keratinocytes**-produce keratin, porin with a protective role, tightly connected by desmosomes, originate from the basal layer, continuously divide towards the outer part and become keratinized.

**melanocytes** - synthesize melanin, the deepest layer of the epidermis

**Langerhans cells** - derived from the bone marrow, APC

**Merkel cells** - at the junction of epidermis and dermis, sensory receptors

Layers of the epidermis:

**Stratum corneum**

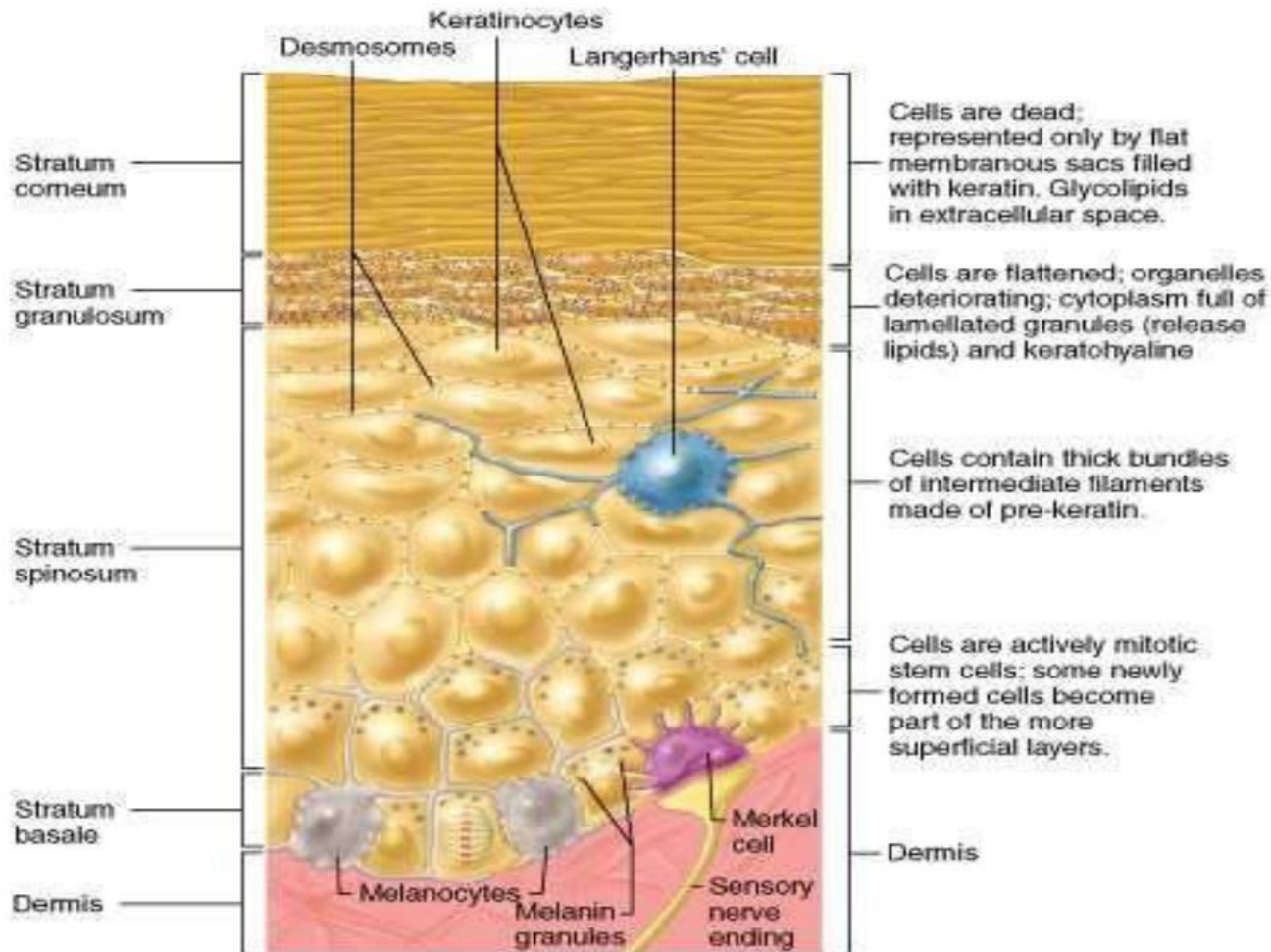
**Stratum lucidum**

**Stratum granulosum**

**Stratum spinosum**

**Stratum Basale**

# Epidermis



# Dermis

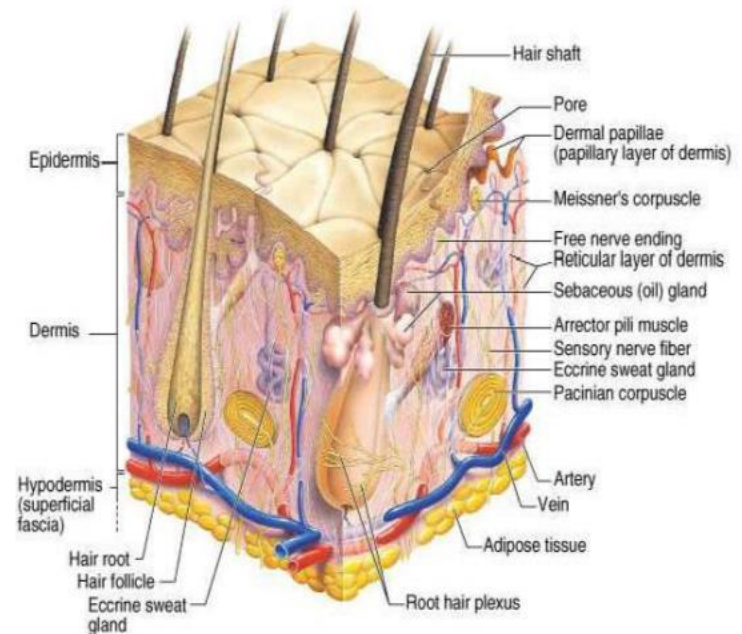
\*Dermis - richly innervated and vascularized, forms connective tissue

\*Contains hair follicles, sweat and sebaceous glands, lymph and snow receptors

\*Two layers of the dermis:

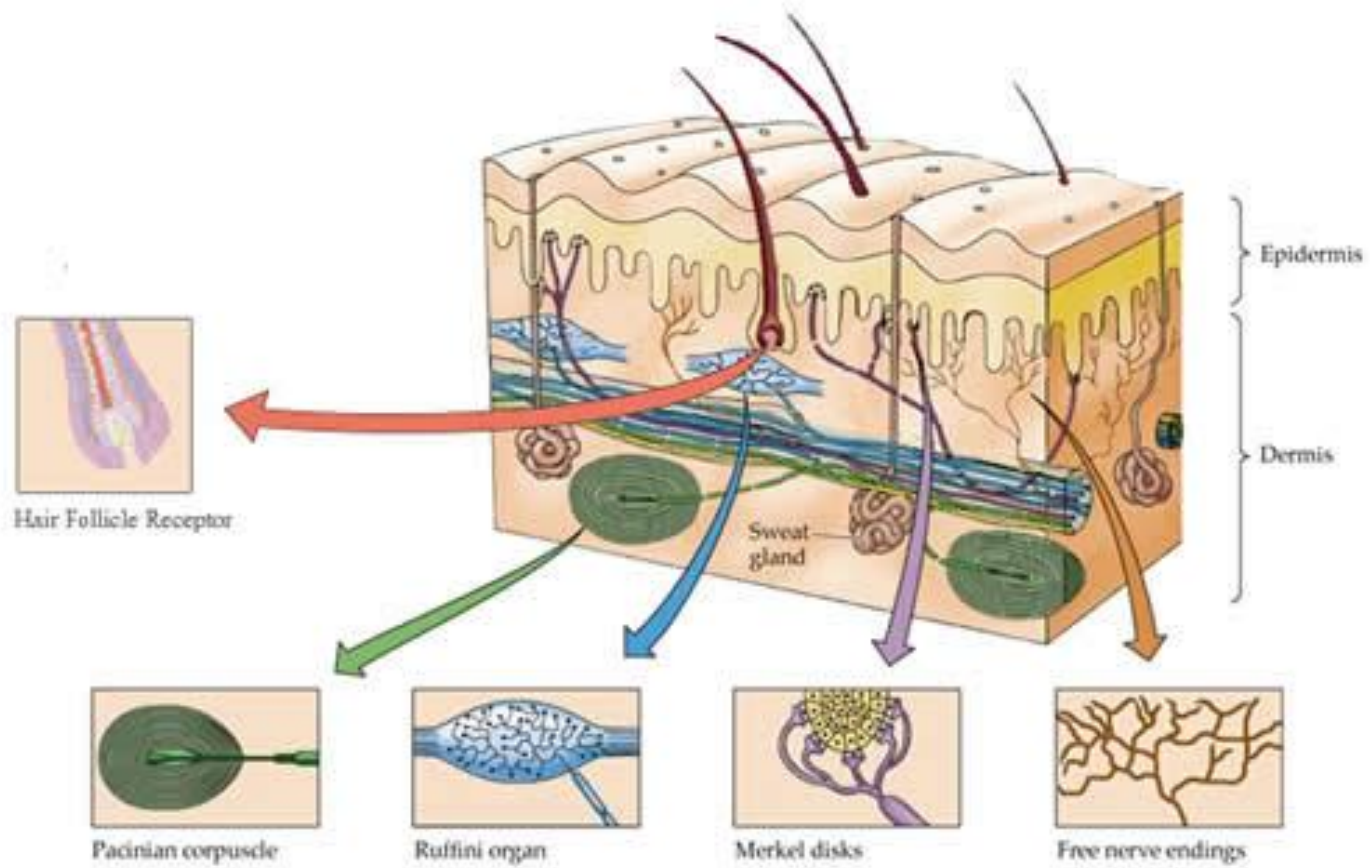
**Papillary** layer - contains dermal papillae, capillary loops and Meissner corpuscles.

**Reticular** layer - dense connective tissue



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# Skin function

- **chemical barrier** - defensins and cathelicidin
- **biological barrier** - Langerhans cells and macrophages
- **physical barrier** - some substances pass through (lipids, organic solvents, salts of heavy metal)
- **thermoregulation** - sweat glands and blood vessels
- **sensory function**
- **metabolic function**
- **blood reservoir**
- **excretory function**

# Pathophysiological mechanisms of skin changes

- **Primary and secondary skin lesions**

## **Basic characteristics of skin lesions:**

- -distribution of causative eruptions
- - type of primary or secondary lesions
- - the form of individual lesions
- - the order in which the lesions appear

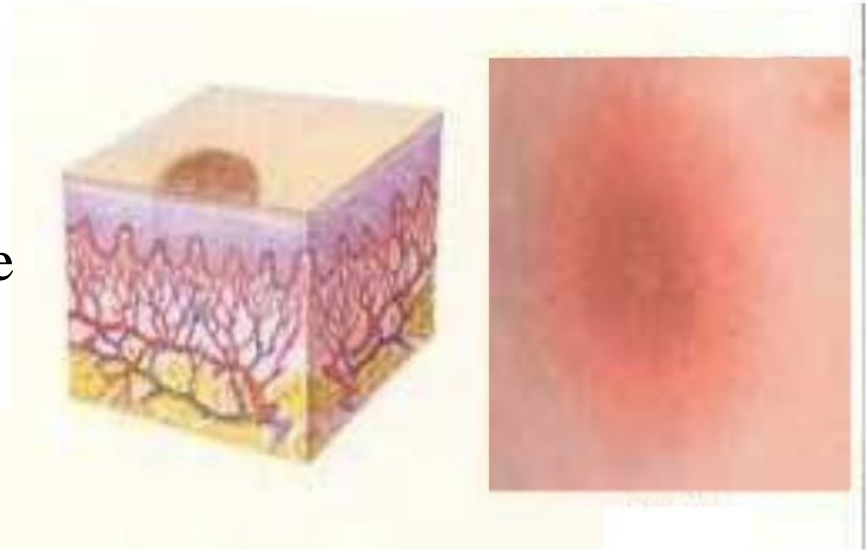
## **Recognition, analysis and correct interpretation of skin lesions**

*Conditio sine qua non* dermatological diagnoses

# Characteristics of **primary** skin lesions

## **Macule:**

a uniform change in color or consistency, diameter  $< 1\text{cm}$ , in the plane of the skin. Does not fade under pressure. The freckle is the prototype of the depigmented macula

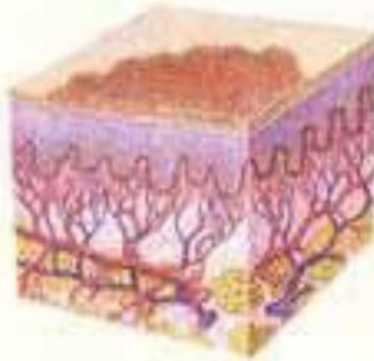


**Papule:** a small solid lesion,  $< 0.5\text{ cm}$  in diameter, raised above the surface of the surrounding skin and therefore palpable



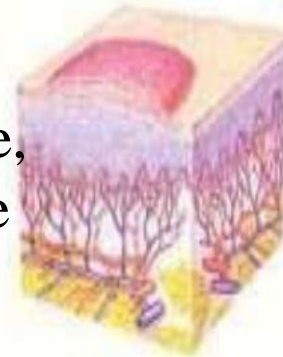
## PATCH

A large  $> 1$  cm flat lesion that differs in color from the surrounding skin. It differs from the macula only in size, Vitiligo



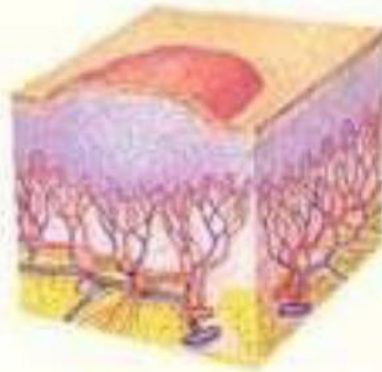
## Plaque

large  $> 1$  cm contorted lesion with a flat surface, the edges may be prominent or gradually merge with the surrounding skin. Psoriasis.



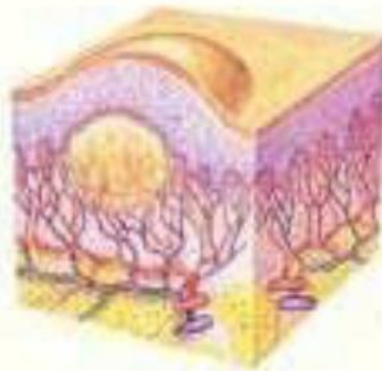
## **Blister:**

A raised, erythematous papule or plaque, resulting from short-term vasodilatation and increased permeability of blood vessels



## **Nodule**

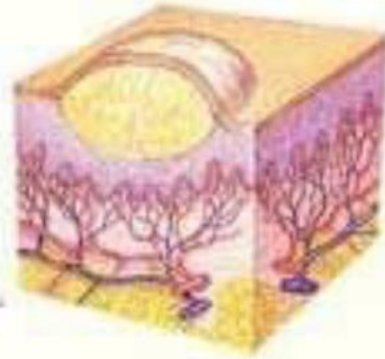
Larger 0.5-5 cm, solid lesion raised above the surface of the surrounding skin. It differs from a papule only on the basis of size





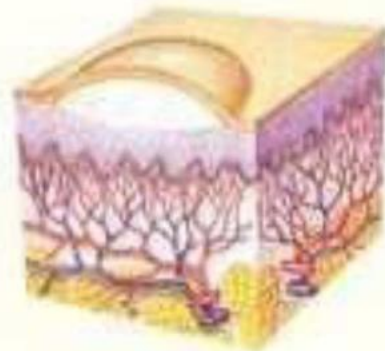
## **Tumor**

firm, raised growth with a larger diameter  $>5\text{cm}$



## **Vesicle**

small, fluid-filled lesion  $< 0.5\text{ cm}$ , raised above the plane of the surrounding skin. Fluid is often visible. Herpes infection

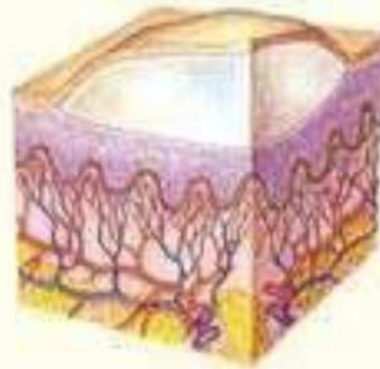




## **Bula**

A fluid-filled, raised, often translucent lesion  $> 0.5$  cm.

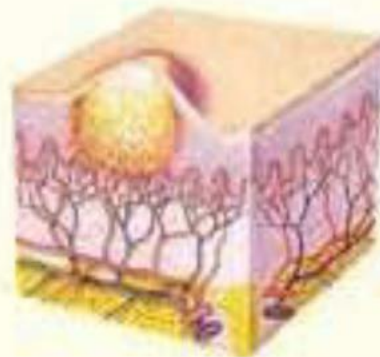
Pemphigus



## **Pustule**

Vesicle filled leukocytes.

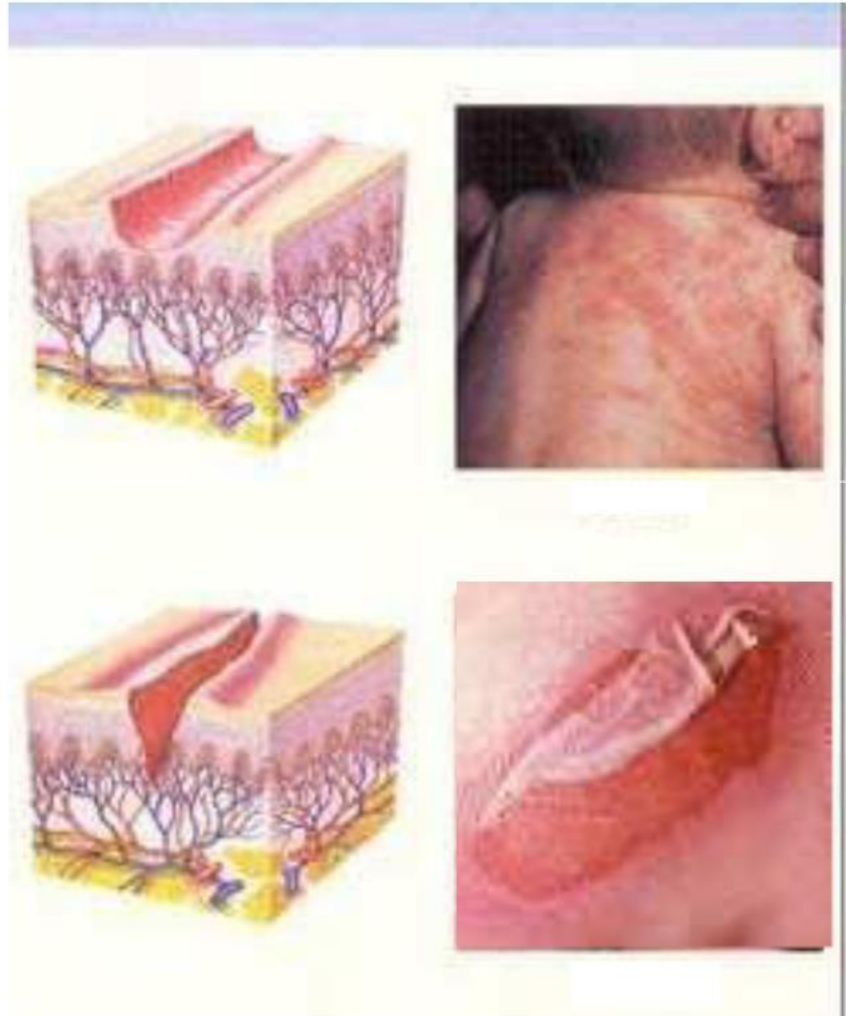
Acne



# Characteristics of **secondary** skin lesions

## **Excoriation**

Linear, spiky erosions that can be covered with a crust, often caused by scratching



## **Erosion**

Loss of the epidermis without comparative damage to the dermis

## Atrophy

Acquired loss of substance, sagging with intact epidermis (derma atrophy) and shiny wrinkled lesions (epidermal atrophy)



## Scar

Changes in the skin due to trauma or inflammation: erythematous hypopigmented, hyperpigmented



## Ulcer

loss of the epidermis and at least one part of the associated dermis

# Inflammatory skin diseases

## Inflammatory skin diseases

### Contact dermatitis

skin irritation caused by a chemical or mechanical agent



### Allergic dermatitis

Metals, cosmetics, chemicals, plants

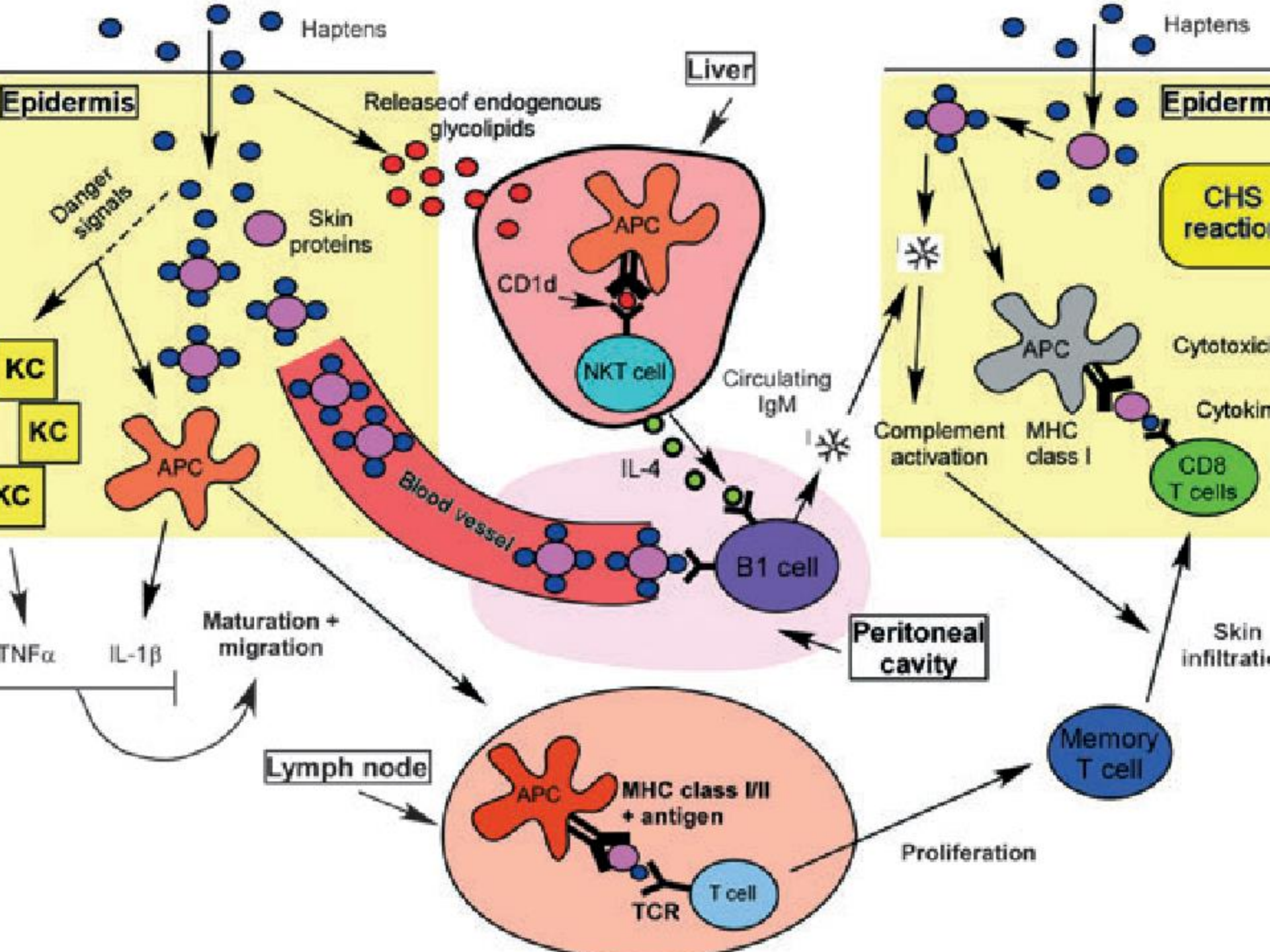
### Type IV hypersensitivity reaction

occurs at the first exposure to substances



Patch, images, redness, pruritus





# Urticaria

**Anaphylactic type hypersensitivity** -  
IgE mediated release of histamine- or  
**anaphylactoid reaction**, which can  
trigger:

Shells

Strawberries

drugs (aspirin, penicillin)

intestinal parasites

physical agent, cold or heat

\*Released histamines lead to an eruption  
of firm, raised blisters on the skin, all  
over the body, pruritus

\*Larynx - difficulty in breathing





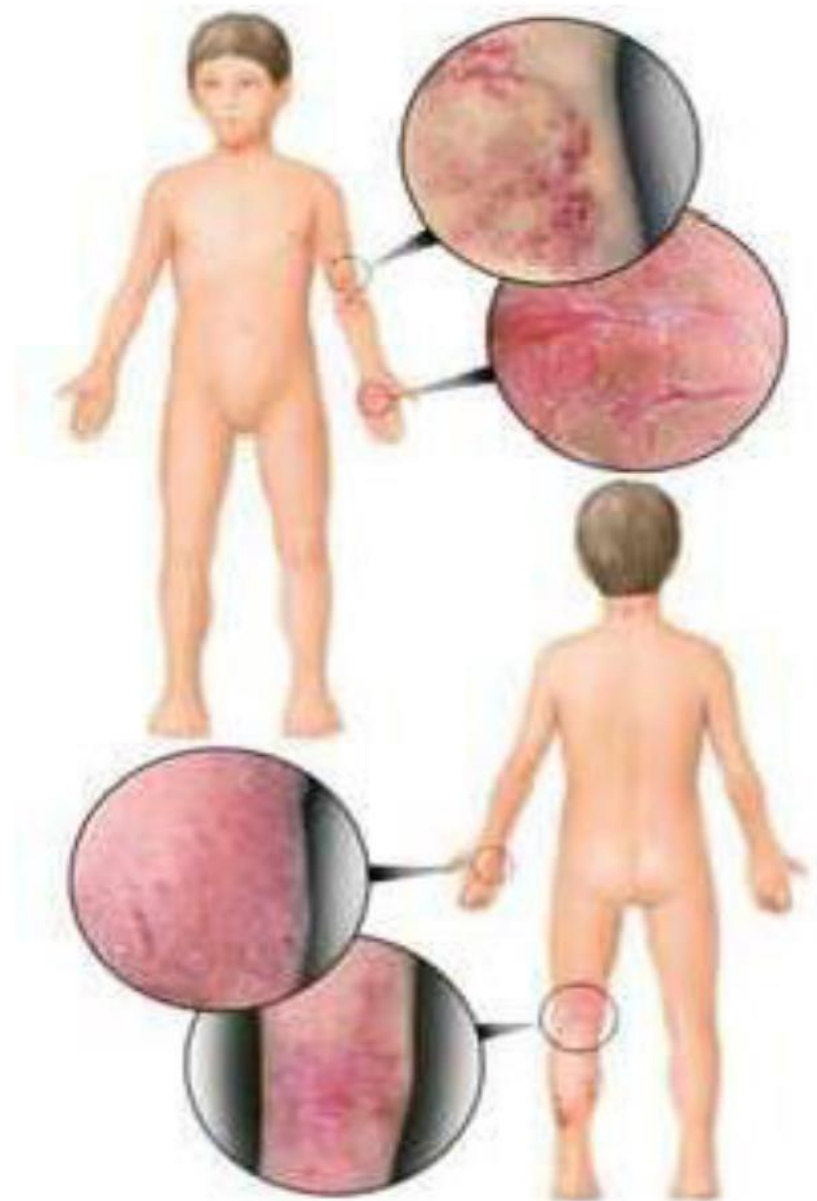
# Atopic dermatitis (Eczema)

**I type of hypersensitivity reaction  
(increased concentration of IgE in the  
blood)**

Common in children, it also occurs in  
adults

Moist lesion, redness, vesicular changes  
with crust, accompanied by itching

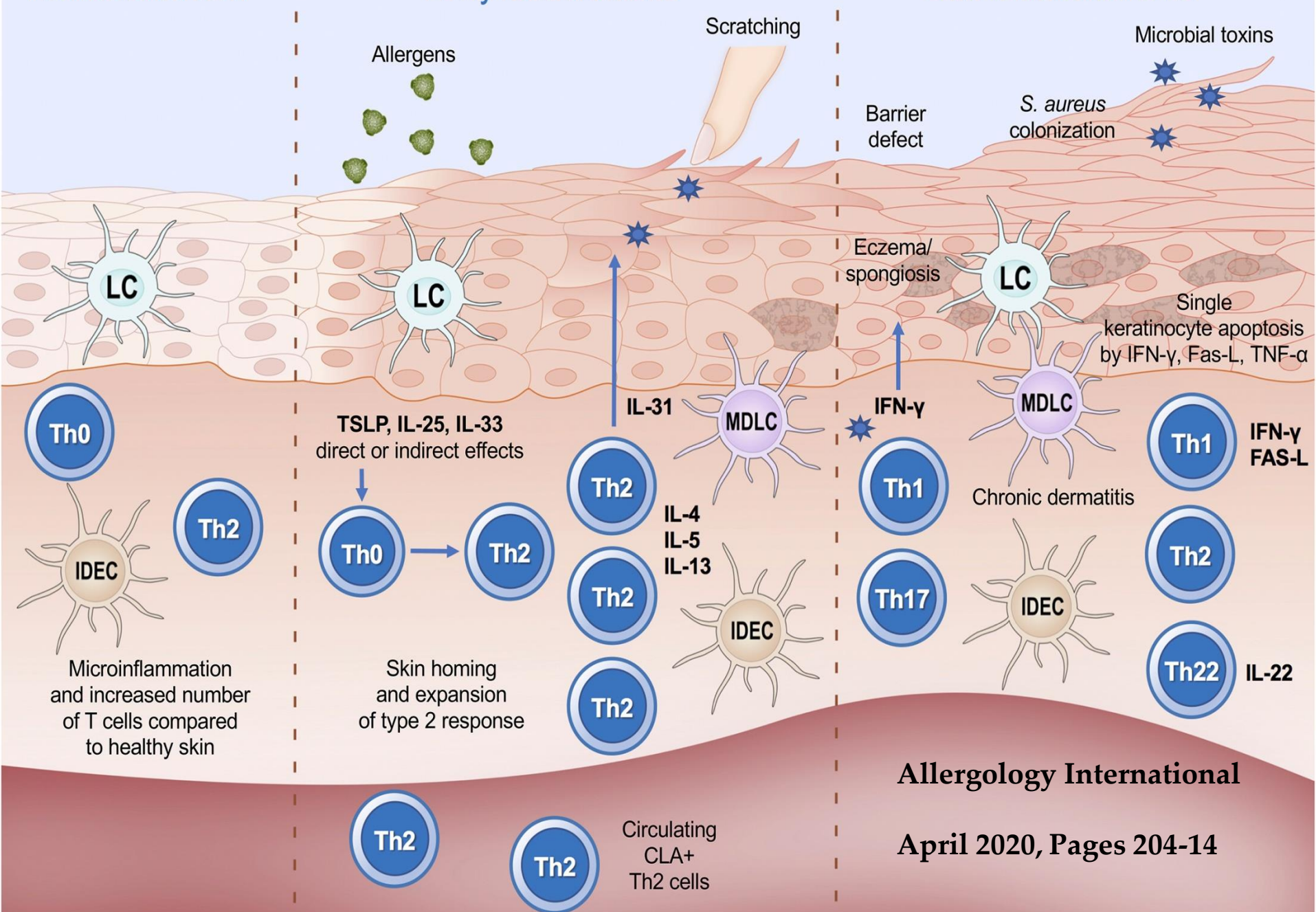
In persons with a predisposition to  
allergic conditions (asthma, allergic  
rhinitis)



## Nonlesional skin

## Early lesions/acute

## Late lesions/chronic



# Psoriasis

- \*chronic inflammatory skin disease of unknown cause? Autoimmune
- \*increased cell proliferation leads to thickening of the dermis and epidermis
- \*immune mechanisms, activation of T lymphocytes (TH 1/TH17), APC (LC), production of cytokines that indicate increased proliferation of keratinocytes
- \* papules and plaques, covered with silvery scales



# Psoriasis - pathogenesis

-The onset of psoriasis is associated with skin infections (*Candida albicans*, *HPV*). A special form of psoriasis is associated with a throat infection (*Streptococcus pyogenes*), the so-called droplet psoriasis, and it resolves spontaneously.

-Antimicrobial peptides, especially LL-37 (cathelicidin), play an important role in the pathogenesis of the disease. It is produced by monocytes, keratinocytes, and T lymphocytes. In psoriatic lesions, the amount of LL-37 is significantly increased, which is why there is no infection.



- LL-37 it can bind to its own DNA and trigger an autoimmune process. The **LL-37-self-DNA complex** activates pDCs by binding to TLR-9. Activated pDCs begin production of IFN- $\alpha$
- IFN- $\alpha$  now activates myeloid DCs to produce IL-20
- IL-20 stimulates the production of IL-23 and the consequent formation of Th17 lymphocytes. At the same time, IL-20 stimulates the proliferation of keratinocytes and the release of TNF- $\alpha$  (which stimulates the chemotaxis of neutrophils and lymphocytes, via IP-10 and IL-8)
- Th17 produce IL-22 and IL-6 which stimulate keratinocyte proliferation and IL-17 which stimulates keratinocytes to produce defensins and IL-8
- IL-1, TNF- $\alpha$  и IP-10 stimulate angiogenesis

# Skin infections

## Bacterial skin infections

### Cellulitis / Erysipelas – upper dermis

Cellulitis is an infection of the dermis and subcutaneous tissue, usually after an injury, boil or ulcer

The causative agent is most often *Staphylococcus aureus* or *Streptococcus pyogenes*

Lower extremities

Redness, swelling, pain





# Skin infections

## Viral skin infections

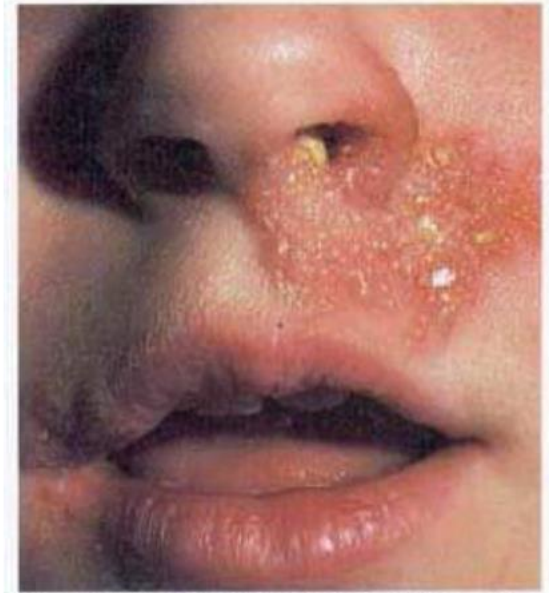
**Herpes HSV1** (*Herpes simplex virus 1*) is the most common cause of characteristic changes that appear on and around the lips (Herpes simplex labialis).

**HSV2** (genital herpes) can cause oral lesions

**Mixed infections are common**

Primary infection can be asymptomatic, the virus remains in latent form in the sensory nerve ganglions of the trigeminal nerve

The virus can reactivate when it causes skin changes in the form of hard vesicles



# Skin tumors

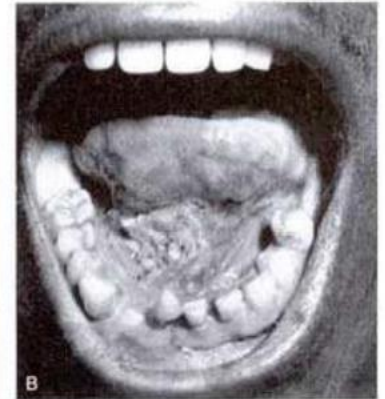
## Squamous skin cancer

Squamous skin cancer is a painless malignant tumor of the epidermis

Exposure to sunlight, the main risk factor

Lesions are found in places where the skin is most exposed, the face and neck

Smokers have a higher incidence of squamous cell carcinoma of the lower lip and oral cavity



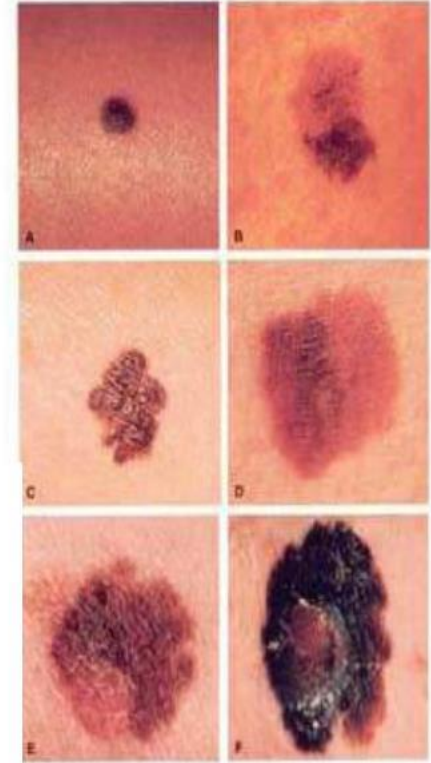
# Skin tumors

## **Malignant melanoma**

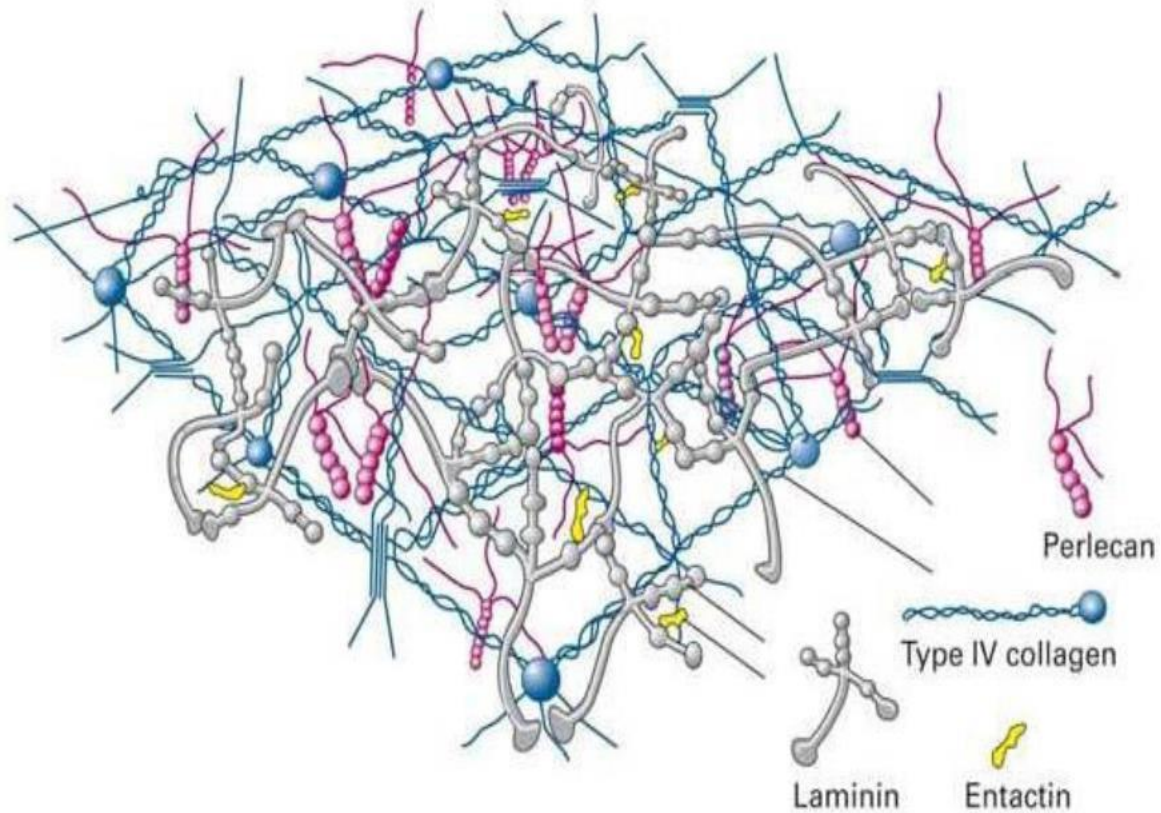
It develops from melanocytes in the basal layer of the epidermis or from an existing mole

It grows rapidly and quickly metastasizes to regional lymph nodes

Poor prognosis if not removed early



# Connective tissue



# Structure of connective tissue

- Together with bone and cartilage, it forms a group of supporting tissues
- Common stem cell

It consists of:

- ✓ cells (fixed and mobile)
  - ✓ fibers
  - ✓ intercellular substances
- Fibers and intercellular substances make up intercellular matrix

# Connective tissue-division

## 1. Dense

- **organized** (parallel bundles of collagen) in tendons, aponeuroses and ligaments
- unorganized** (densely intertwined collagen fibers in the periosteum, skin and facies)

## 2. Loose

diffusely distributed as interstitial tissue or stroma in visceral organs



# Interfibrillar matrix

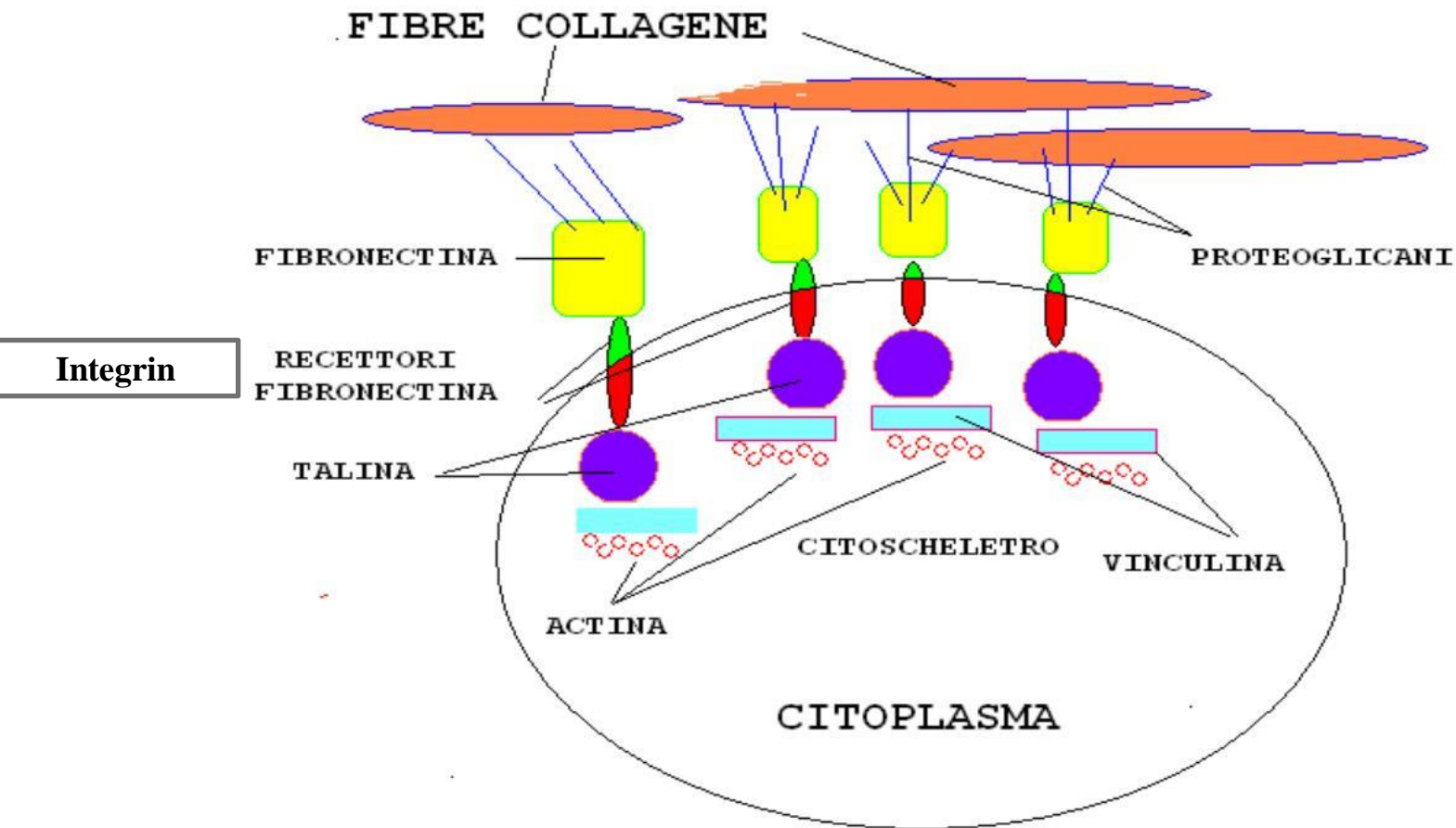
An **amorphous substance** in which fibroblasts and connective fibers are immersed

Made of:

- ✓ **interstitial fluids**
- ✓ **proteoglycan**

**Proteoglycans:** protein bound to glycosaminoglycans and at the other (N) terminus to hyaluronic acid

# The connection between the intercellular substance and the cellular cytoskeleton



# **28 types of collagen are found in the human body**

Interstitial (I, II, III)

Basement membrane collagen (IV, V)

**TYPE I** is the most widespread (90%) and is mainly found in the skin, tendons and ligaments, blood vessels, bones, but it is also present in the dentin and cementum of teeth.

**TYPE II** is found in cartilage

**TYPE III** is found in skin, ligaments, blood vessels (often together with type I) and internal organs (lymphatic system, liver, lungs...)

**TYPE IV** is found in the basement membrane of many tissues

**TYPE V** is found in the placenta, hair, dermo-epidermal junction, skeletal muscles The fastest collagen metabolism is in the uterus after childbirth, but also in the periodontium.

# Hereditary disorders in collagen metabolism

## *Osteogenesis imperfecta*

*It is inherited mainly in an autosomal dominant manner*

*Mutation of the **type I collagen gene***

*It is characterized by **osteopenia** (brittle bones with the occurrence of fractures).*

# Hereditary disorders in collagen metabolism

## *Marfan syndrome*

*It is inherited in an autosomal recessive manner*

*Mutation of the **gene FBN1** (on the long arm of chromosome 15) for the synthesis of **fibrillin I** (glycoprotein that binds calcium) associated with elastin in the skin, aorta, periosteum.*

*Visual impairment (dislocation of the eye lens)*

*Aortic aneurysm*

*Changes in the skeleton (arachnodactyly, tall stature, kyphoscoliosis, high goth palate)*



# Hereditary disorders in collagen metabolism

## *Homocystinuria*

*It is inherited in an autosomal recessive manner*

*Accumulation of **homocysteine**, which inhibits lysyl oxidase and disrupts collagen formation in the intercellular space*

*Ectopia of the eye lens*

*Arterial and venous thrombosis*

*Extremities are elongated and thin*

*Mental retardation*

# Acquired disorders in collagen metabolism

*Scurvy*

*Vitamin C deficiency*

# Systemic connective tissue diseases

Diseases characterized by **pain and inflammation of joints and connective tissue**

They are called differently:

**Systemic autoimmune diseases**

**Rheumatic diseases**

**Collagen-vascular diseases**

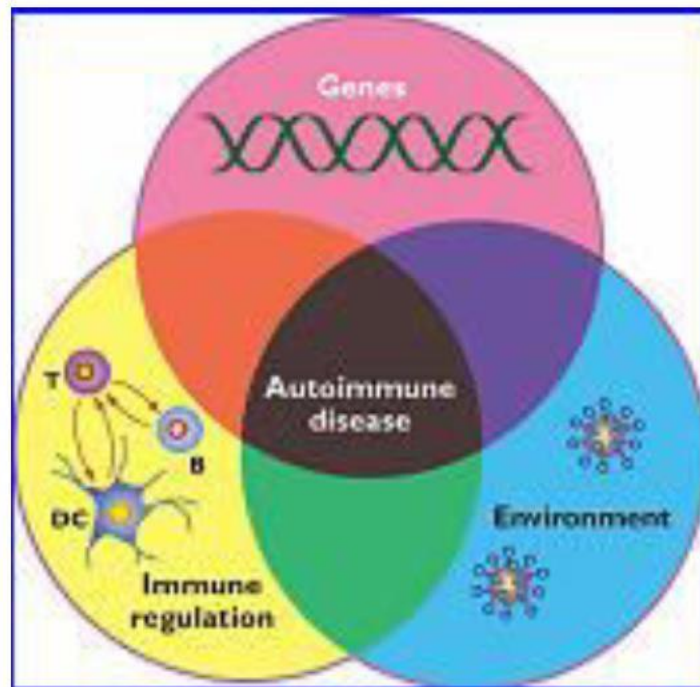
Etiopathogenesis:

- Immune system dysfunction

- Immune response directed towards tissue/organ molecules

# Etiology of systemic connective tissue diseases

Insufficiently clarified (genetic predisposition, trigger?!, disorder in the functioning of the immune system...)



# Pathogenesis of systemic connective tissue diseases

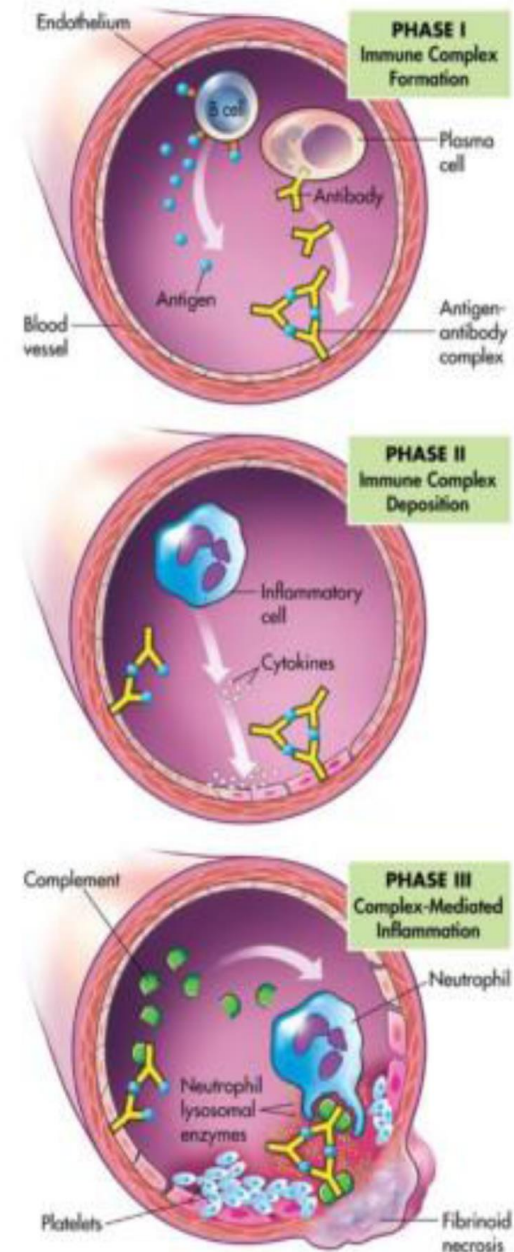
**Hypersensitivity reaction** (third type, deposition of immune complexes, inflammation...)

**Autoimmunity** (immune response directed against one's own cells and molecules...)



# III type of hypersensitivity

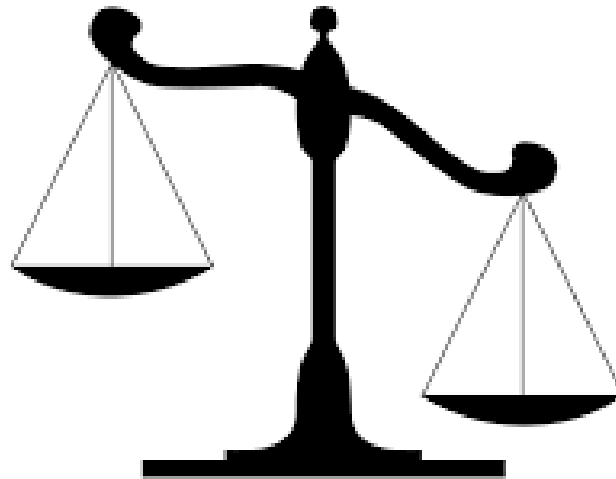
- Immune complexes (IC) contain **cationic antigens** that bind to negatively charged components of the basement membrane of blood vessels and kidney glomeruli.
- IC activate **mast cells** and **basophils**, release of vasoactive mediators, permeability of blood vessels and deposition of IC.
- IC, via Fc receptors, **activate the complement system** and **neutrophils** and **macrophages**. These cells produce pro-inflammatory cytokines and chemokines and inflammation and tissue damage occur. The release of **free oxygen radicals**, **lysosomal enzymes** and **chemotactic substances** from permanently activated cells causes damage to the walls of blood vessels, consequent **aggregation of platelets**, and tissues.
- **Mass deposition of IC** and their non-removal can cause obliteration and obstruction of the blood vessel lumen, which results in ischemia of tissues and organs.



# Immune regulation and autoimmunity: question of balance

## Inhibitory signals

↓  
cytokines (IL-10)  
CD 28/CTLA  
Treg



## Activating the signal

↑  
MHC II peptide  
Cytokines (IFN gamma)  
CD40/CD40L  
T-bet TF

# Prevalence of some systemic connective tissue diseases

- RA 1-3%
- SLE 1/4000
- Sjogren's syndrome 1/20 000
- vasculitis 1/100 000

## Prevalence of autoimmune diseases

**5-10%** of the population

# Association of gender with autoimmune diseases

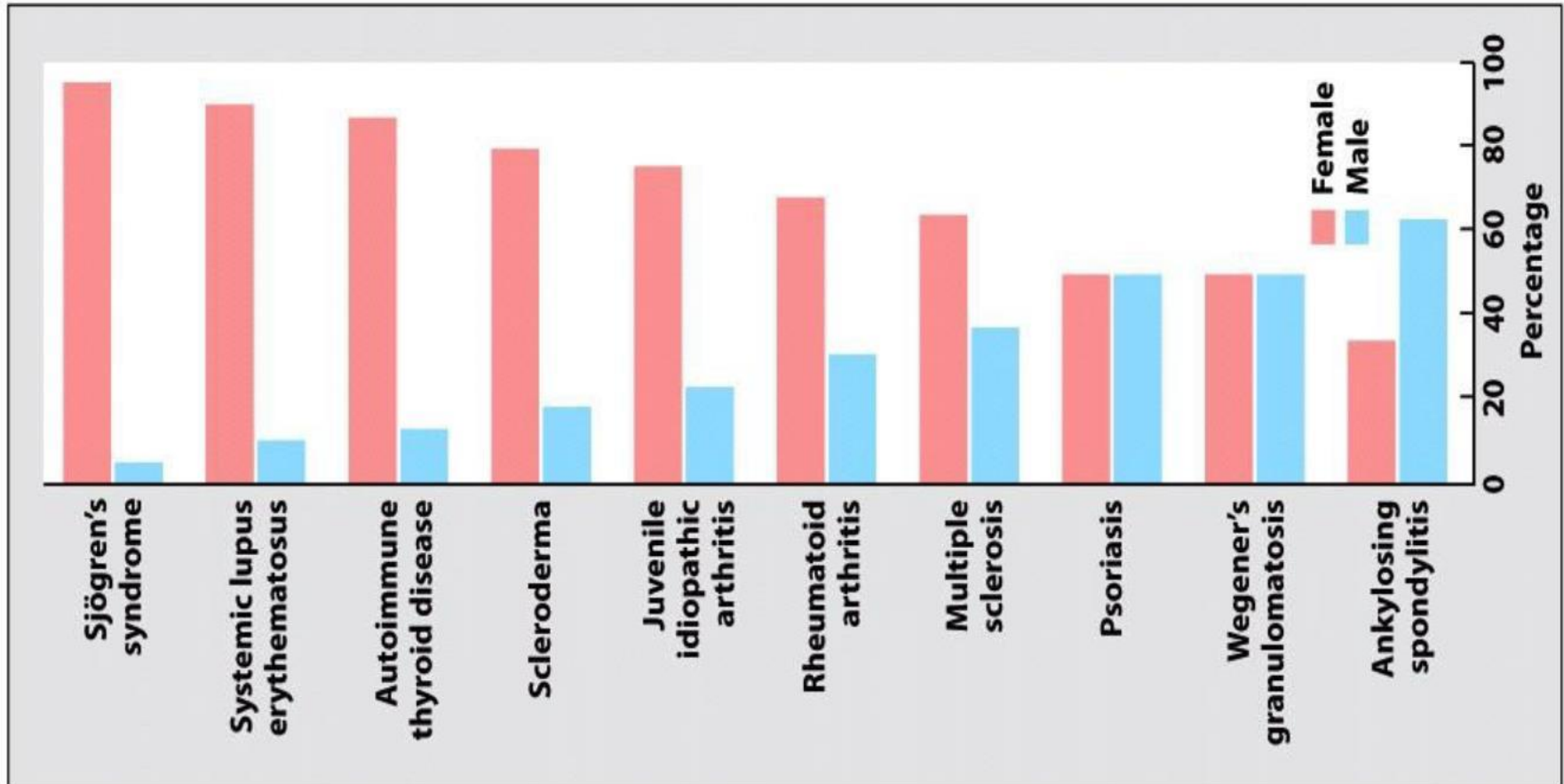


Figure 13.18 The Immune System, 3ed. (© Garland Science 2009)

# The immune response is directed against...? very diverse autoantigens

## **Rheumatoid arthritis:**

- collagen type II
- IgM (rheumatoid factor)
- Citrulline proteins (arginine residues modified)

## **Systemic lupus erythematosus:**

- nuclear antigens:
  - histones
  - ribonucleoproteins
  - dsDNA
- superficial antigens of leukocytes
- cardiolipin



# Common clinical manifestation of systemic connective tissue diseases

- Arthralgia, myalgia
- Raynaud's phenomenon
- Rash
- Serositis (pleurisy, pericarditis)
- Pulmonary fibrosis
- Pulmonary hypertension
- Pulmonary renal syndromes
- Cutaneous vasculitis
- Systemic vasculitis

# Systemic connective tissue diseases

Rheumatoid arthritis

Seronegative arthropathies

Systemic lupus erythematosus

Antiphospholipid syndrome

Sjogren's syndrome

Idiopathic inflammatory myopathy

Mixed connective tissue disease and overlap syndromes

Vasculitis syndromes

# Rheumatoid arthritis

A **systemic autoimmune disease** that predominantly affects the **joints**

- Joint inflammation:
  - begins in the synovial membrane
  - later it affects the joint cartilage, joint capsule, ligaments, tendons and bone

# Rheumatoid arthritis

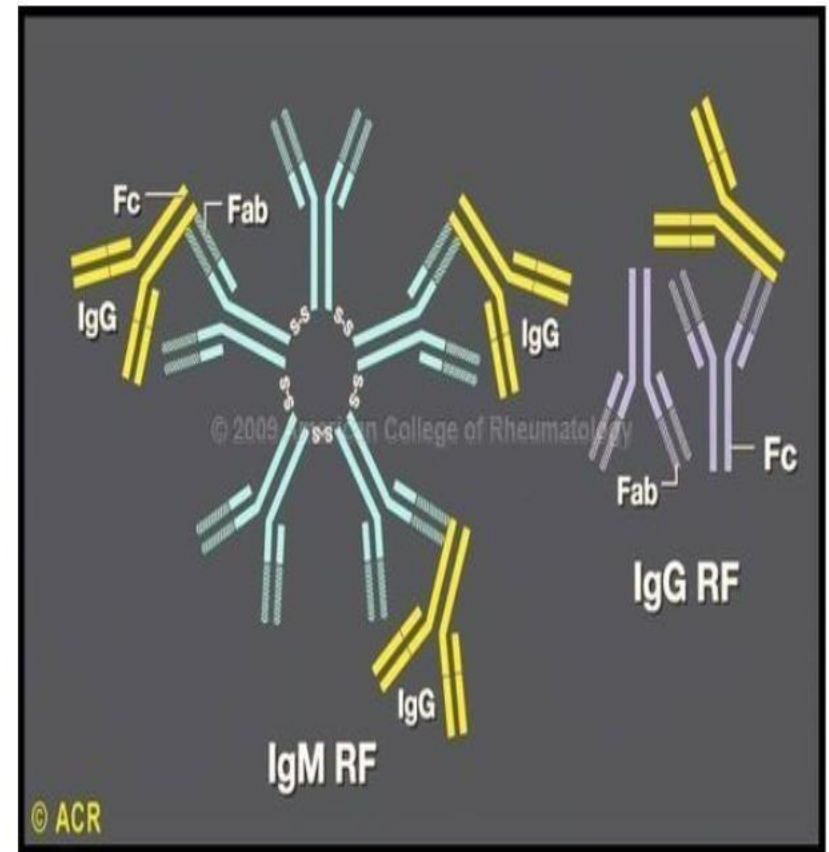
Chronic, systemic inflammatory disease with predominant changes in the joints.

**Based on the presence of rheumatoid factor** (RF: autoantibody specific for Fc region IgG ) in the serum of patients, rheumatoid arthritis is **classified** as:

- (1) seropositive rheumatoid arthritis, about 75% of patients suffering from rheumatoid arthritis:** RF can be diagnosed in the serum, has a worse prognosis, and is most often a systemic disease
- (2) seronegative rheumatoid arthritis, about 25% of patients suffering from rheumatoid arthritis:** RF cannot be diagnosed in the serum, it has a better prognosis.

# Rheumatoid factor

- Rheumatoid factor (RF) is autoantibody to Fc IgG fragment
- RF is most often determined class **IgM**, but RF can be IgG , IgE and IgA classes
- RF is present in many rheumatic and non-rheumatic diseases

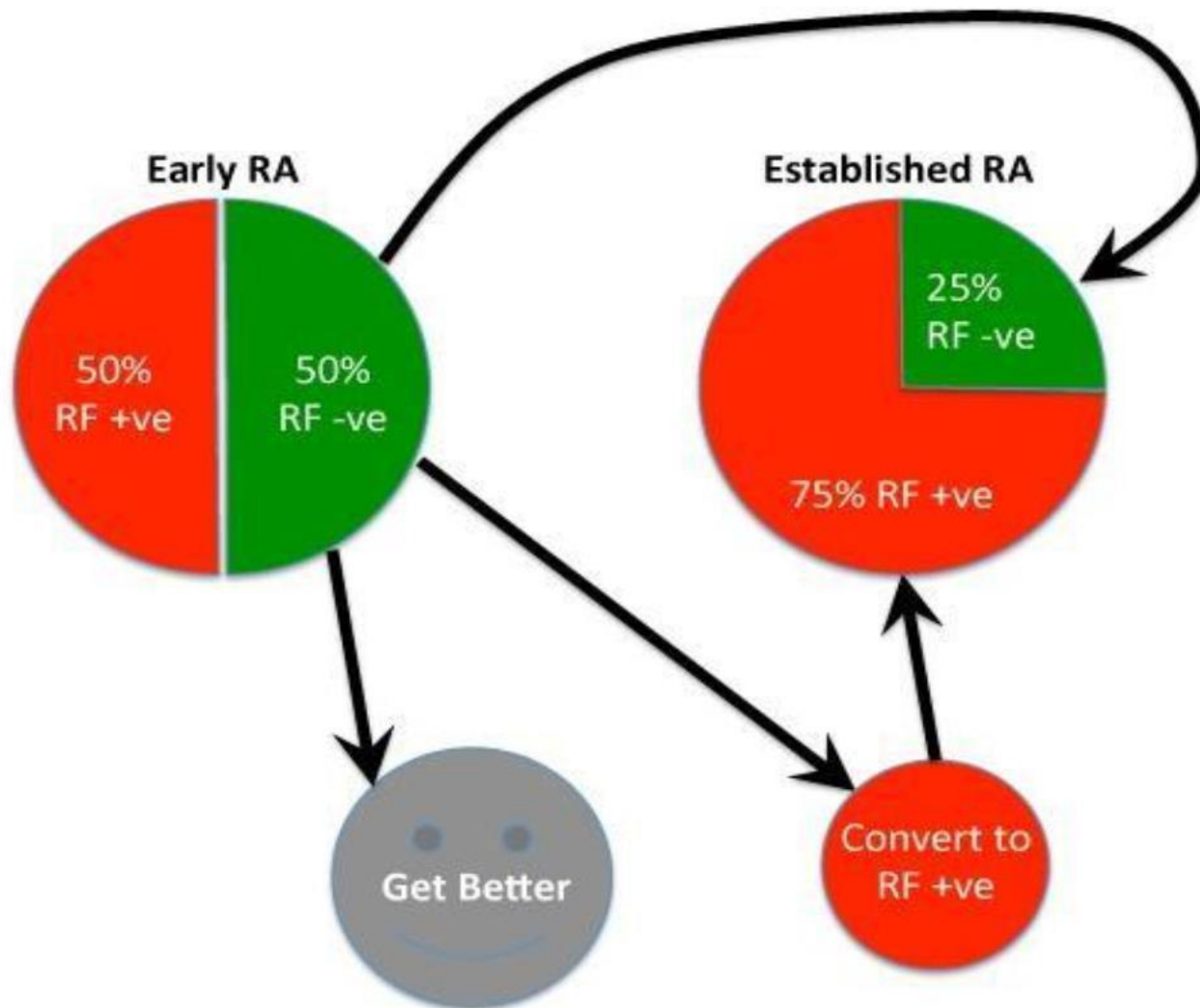




# Rheumatoid factor

- A useful test for the diagnosis of rheumatoid arthritis
  - 70-80% of patients with RA have detectable RF, while 20-25% of patients with RA are RF negative, especially in the early stages of the disease
  - 2-10% of healthy people, as well as patients with other diseases RF positive for systemic rheumatic diseases
  - Association of higher RF concentrations with heavier forms of the disease, extra-articular manifestations and poor prognosis of the disease

# Rheumatoid factor

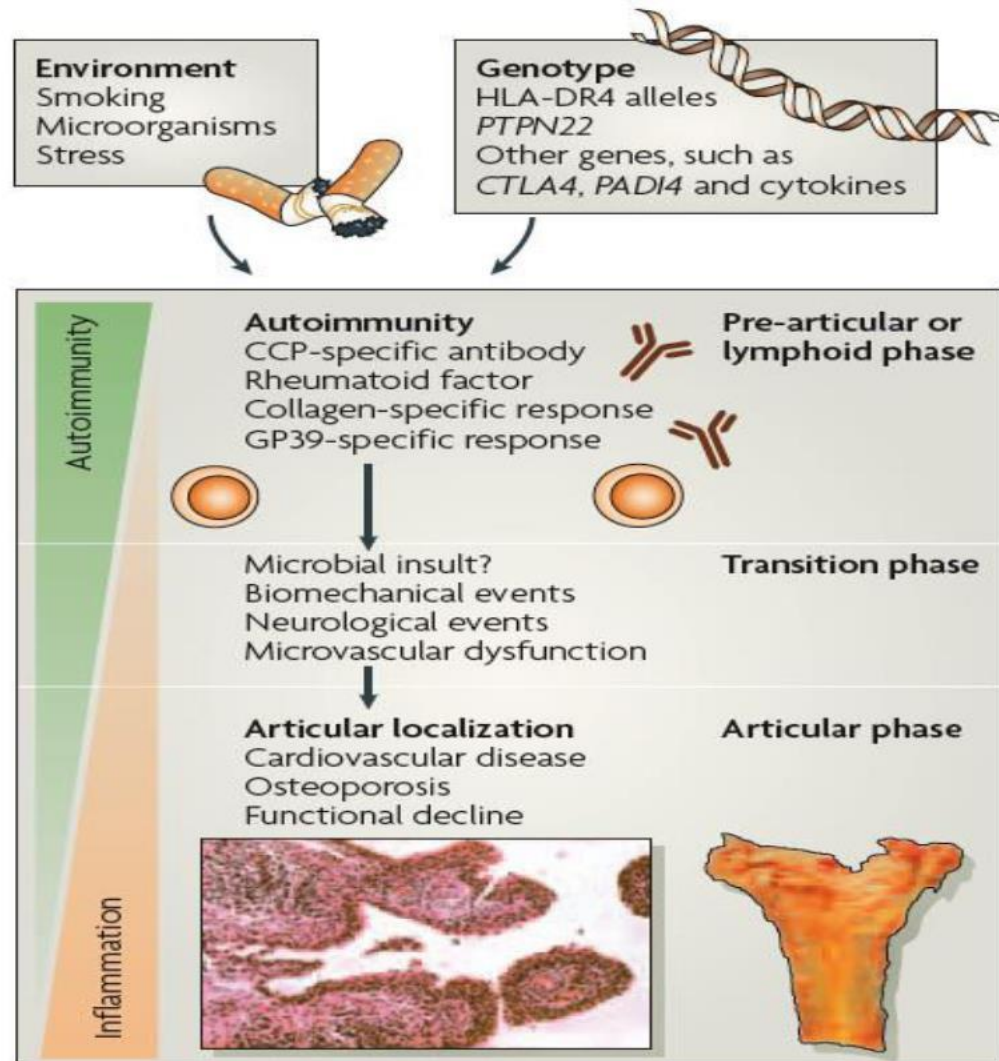


# Rheumatoid arthritis

## -Etiology-

- The disease is of **??? unknown etiology**
- **Genetic predisposition** (MHC expression) is considered to play an important role in the development of the disease class II molecules: DR1, DR4 correlate with disease symptoms in Europeans ) **and an infectious agent** (*parvovirus*, *Epstein-Barr virus*, *Prevotella spp.* *Bacteroides spp.* *Mycoplasma spp.*). Certain MHC alleles class II molecules (HLA-DRB1 \*0101, 0401, 0404), whose expression is highly correlated with the manifestation of rheumatoid arthritis, have a common sequence of 5 amino acids in the DR  $\beta$  chain, in the part responsible for peptide presentation to T lymphocytes, and this sequence is considered important in the development of arthritis.
- Although the role of estrogen in the development and progression of rheumatoid arthritis is still debatable, the fact is that this disease occurs more often in women (2:1) compared to men

# Etiology of rheumatoid arthritis



# Rheumatoid arthritis

## -immunopathogenesis-

In the immunopathogenesis of rheumatoid arthritis, the central place is occupied by **T lymphocytes**, **macrophages** and **TNF- $\alpha$** , although recently the importance of B lymphocytes for the development of this disease has been increasingly pointed out.

All these effector cells are activated by the presence of unknown autoantigen expressed in the joints. Some studies indicate the role of a whole series of potential autoantigens (**collagen type 2**, **filamin A**, **Hcgp39**, **enolases...**) important for the development of rheumatoid arthritis.

Activated macrophages produce pro-inflammatory cytokines **TNF- $\alpha$** , **IL-1**, **IL-6**, **IL-8**, **IL-12**, and chemokines that enable the influx of neutrophils and lymphocytes into the inflamed joint. **CD4<sup>+</sup>Th1** lymphocytes produce **IFN- $\gamma$**  which additionally activates macrophages.

Under the influence of **TNF -  $\alpha$**  and **IL-1**, **chondrocytes** are activated to produce **matrix metalloproteinases** that destroy tissue, and **fibroblasts** proliferate and obliterate the joint cavity.



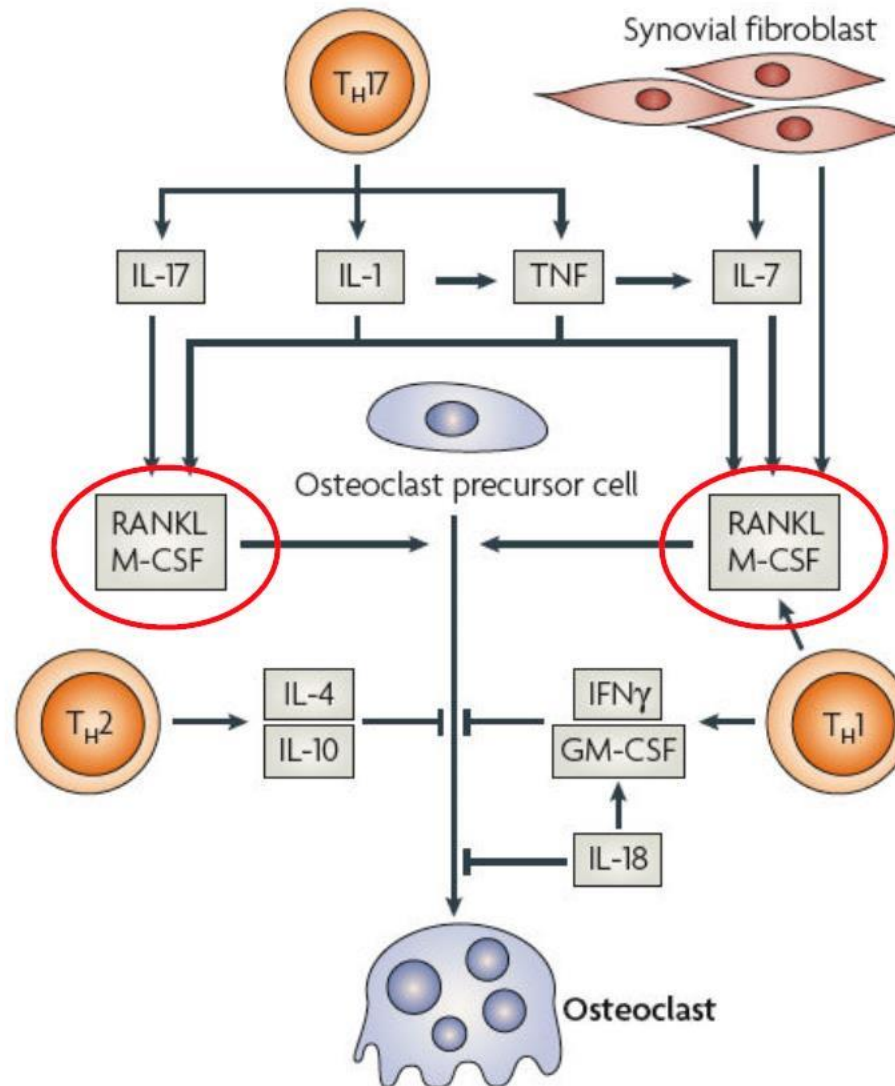
Pro-inflammatory cytokines also stimulate angiogenesis in the joint, venules with high endothelium appear, highly specialized for "accepting" lymphocytes from the circulation. Numerous adhesive molecules are expressed on these endothelial cells, which enable a massive influx of leukocytes. As a result of the resulting inflammation, in the inflamed joints of patients suffering from rheumatoid arthritis, the so-called "Soup of pro-inflammatory cytokines", activated macrophages, T and B lymphocytes, neutrophils.

Th17 lymphocytes express ligand for NF- $\kappa$ B receptor activator (RANKL) that binds to receptor (RANK) and activates osteoclasts that destroy the bone causing permanent damage

Finding of autoantibodies specific for the amino acid citrulline (***anti-CCP antibodies***) observed in high titers in patients suffering from rheumatoid arthritis (especially in patients with a progressive form of the disease), as well as the systemic disease found in seropositive (RF+) patients, indicate the importance of B lymphocyte activation for the development and progression of rheumatoid arthritis.



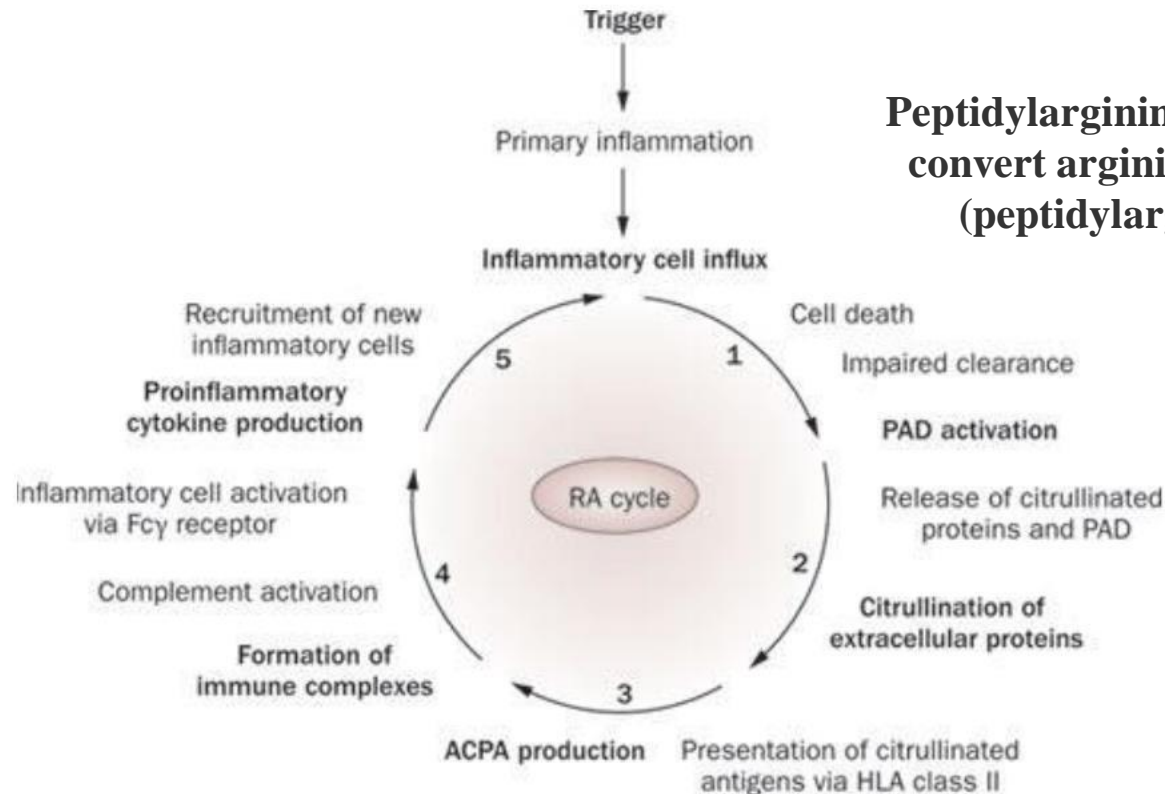
# Factors that regulate differentiation of osteoclasts in arthritis



# Anti-citrullinated protein antibodies (ACPAs)

- **ACPAs** are directed towards citrulline residues that arise in post-translational modifications of arginine (*anti-keratin antibodies* (AKA), *anti-filaggrin antibodies* (AFA), *anti-perinuclear factor* (APF)...) )...
- present in patients with rheumatoid arthritis arthritis, sensitivity 30% to 60% and specificity 95% to 98%
- high specificity and presence at an early stage of rheumatoid arthritis, when they indicate faster development of damage to the affected joints
- they can be present several years before the onset of RA
- a negative test result does not exclude the diagnosis of RA

# The role of citrullinated proteins in pathogenesis of RA



van Venrooij, WJ *et al.* (2011) Anti-CCP antibodies: the past, the present and the future *Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2011.76

# Rheumatoid arthritis -immunopathogenesis-

**Inflammation**



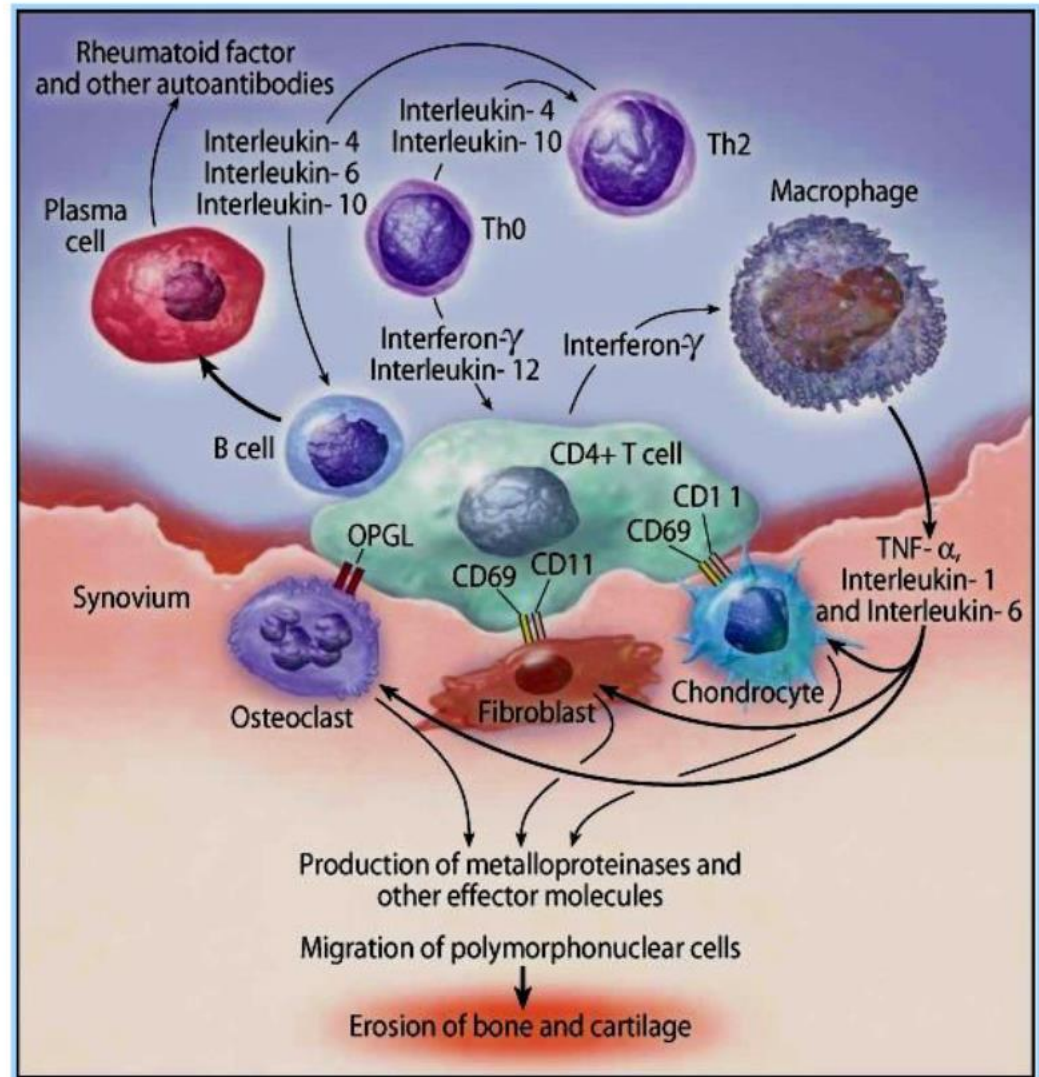
**Sinovial  
proliferation**



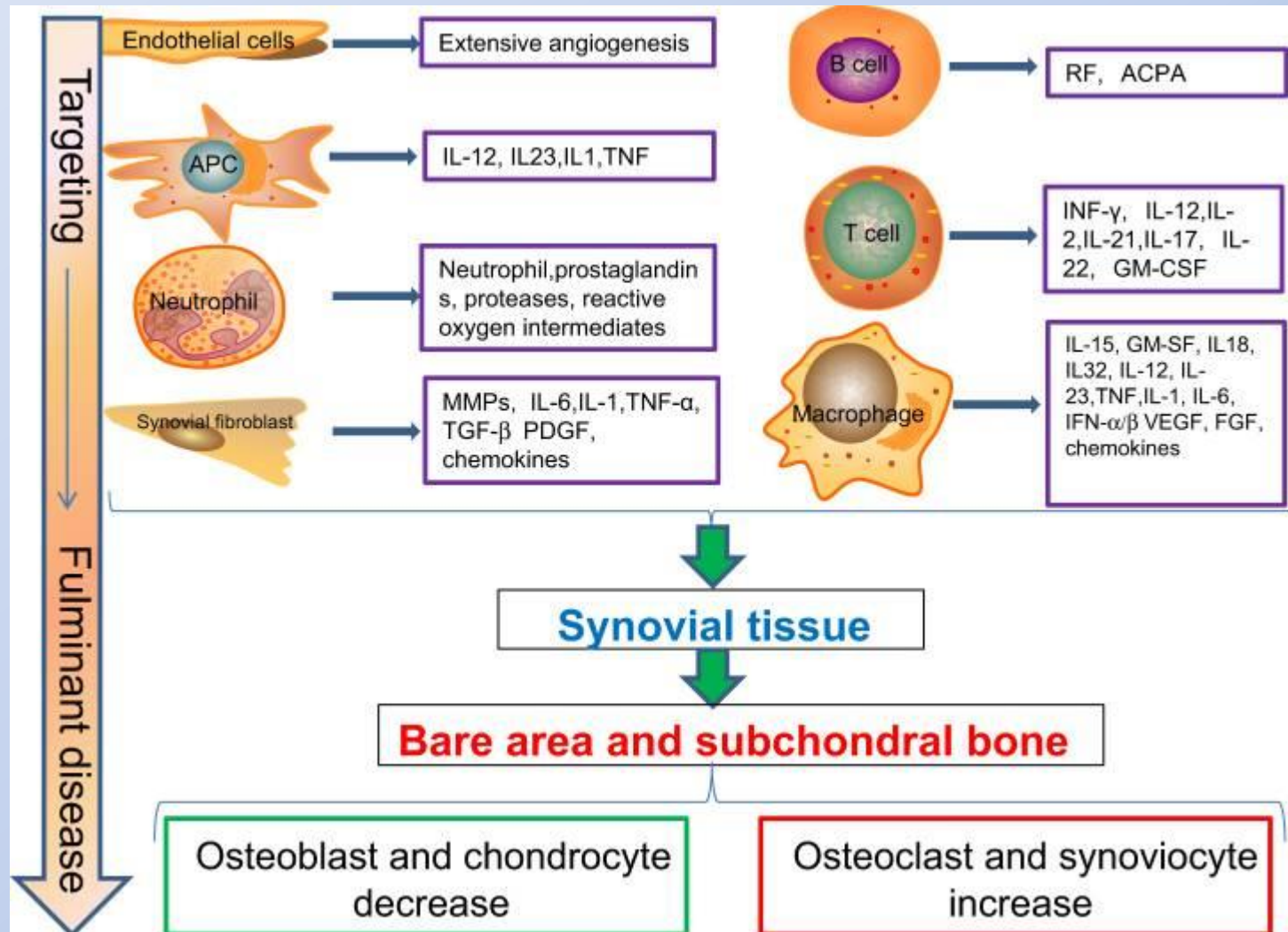
**Articular  
destruction and  
deformation**



**Function  
impairment**



# Rheumatoid arthritis -immunopathogenesis-

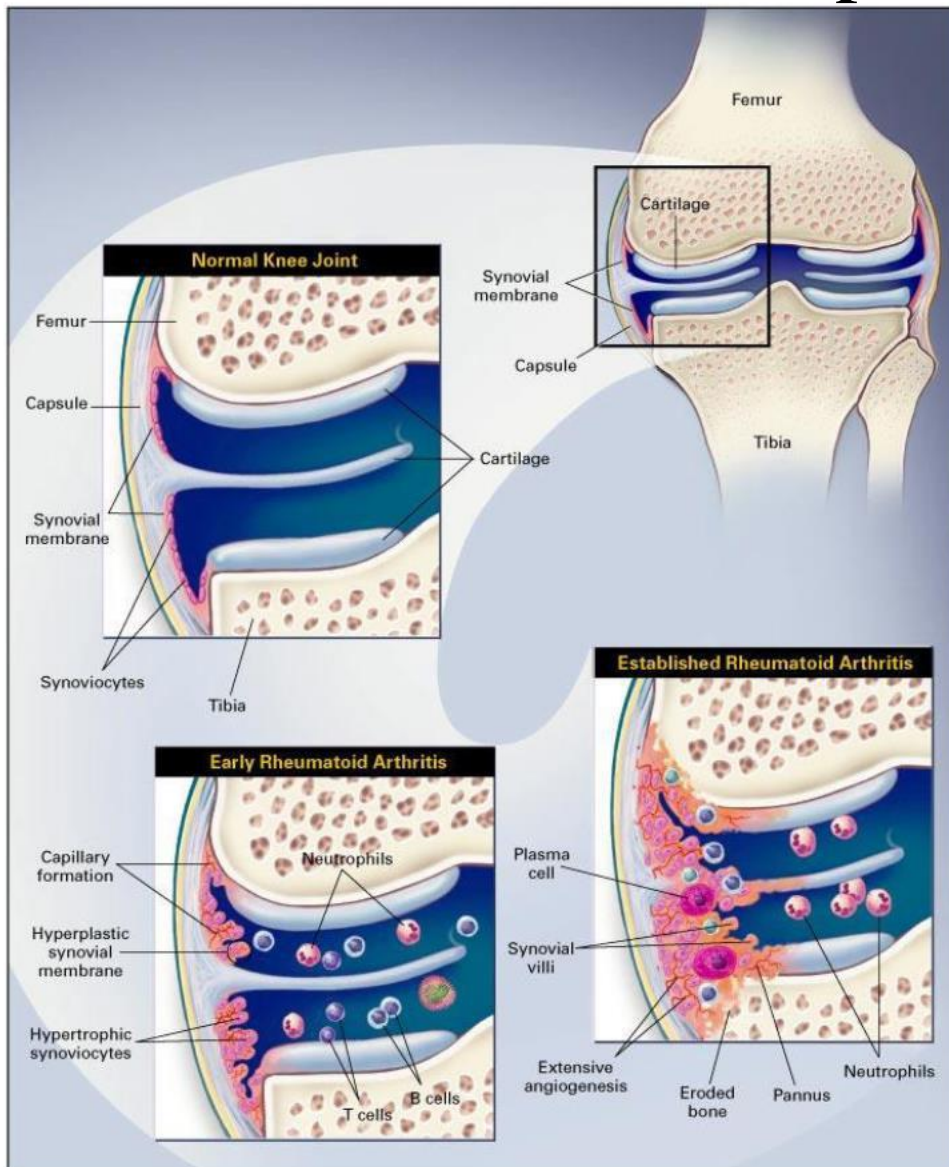




# Rheumatoid arthritis -immunopathogenesis-

## Inflammation of synovial tissues (synovitis)

- Proliferation of synoviocytes and villous hyperplasia
- Accumulation of inflammatory cells  
T lymphocytes, B lymphocytes, macrophages, plasmacytes
- Release of cytokines
- Higher vascularization
- Self-strengthening process





# Clinical picture of rheumatoid arthritis

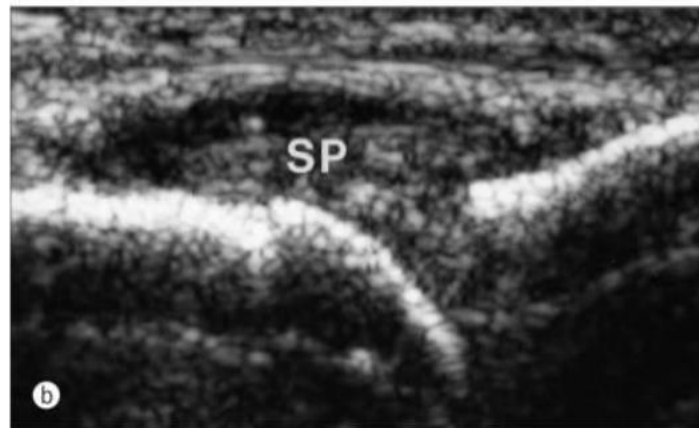
The disease most often begins with inflammation of the small joints of the hands and feet and morning stiffness. The skin above the joints is red, inflamed, there is swelling around the joints, limited mobility, pain and loss of function.

## In the beginning:

- pain, morning stiffness, swelling of joints of hands and feet
- polyarticular symmetric arthritis
- general symptoms: tiredness, subfertility, body weight loss

# Clinical picture of rheumatoid arthritis

## In the beginning



# Clinical picture of rheumatoid arthritis

The progression of the disease is characterized by the involvement of a large number of joints (even larger joints: knee, shoulder joint, ...) as well as the destruction of joint surfaces with the appearance of deformities.

## Later:

- shoulders, cervical spine, hips, knees, elbows
- deformities and subluxations of joints, ankylose, contractures, invalidity

# Clinical picture of rheumatoid arthritis

Later:



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# Extraarticular (systemic) manifestations of rheumatoid arthritis

- **Rheumatoid nodules** in the **skin**  
(usually localized around the olecranon and in the region metacarpophalangeal joint)



Rheumatoid nodules

- Extra-articular manifestations (in seropositive arthritis)
  - ✓ serositis (pleuritis, endocarditis, pericarditis)
  - ✓ amyloidosis
  - ✓ fibrosis in the lungs



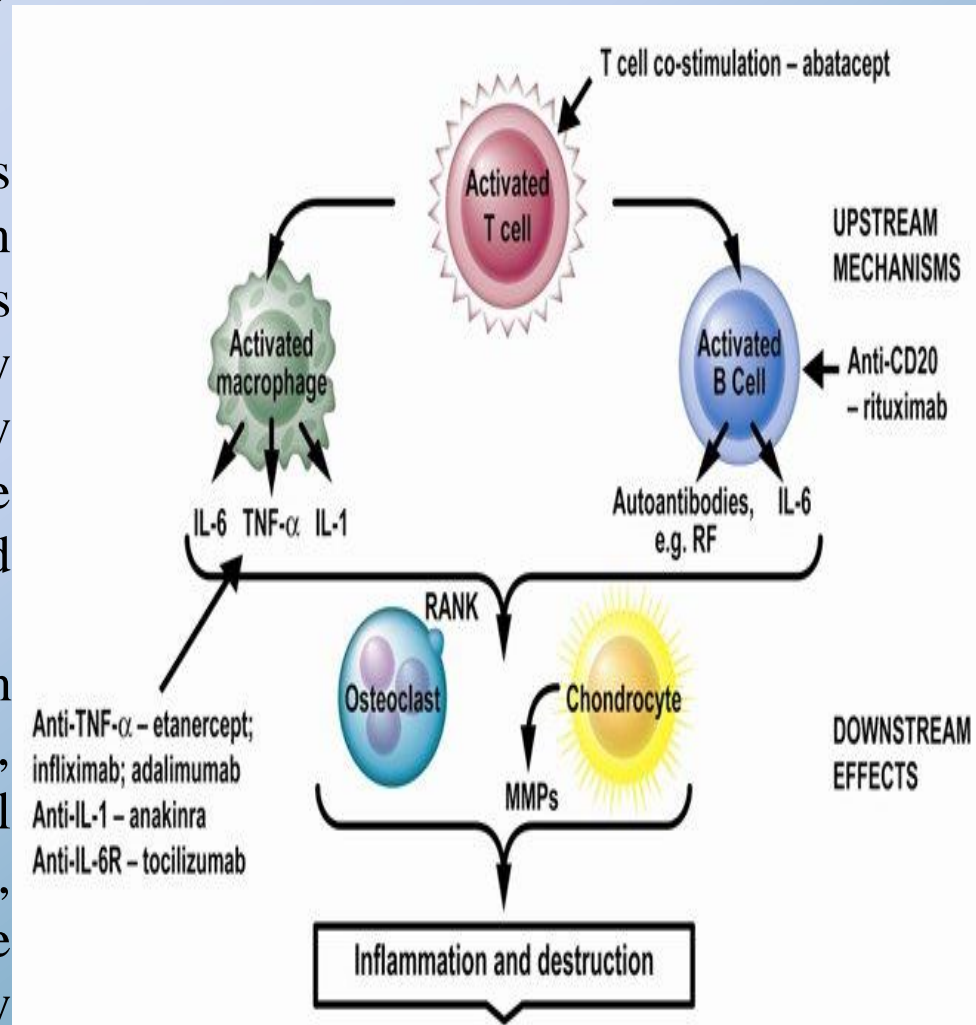
Domain	Weighted Score
<b>Joint Involvement (0–5)</b>	
1 medium to large joint	0
2–10 medium to large joints	1
1–3 small joints	2
4–10 small joints	3
>10 joints (with at least one small joint)	5
<b>Serology (0–3)</b>	
Neither RF- or ACPAs-positive ( $\leq$ ULN)	0
At least one test, low positive titer ( $>1 \leq 3 \times$ ULN)	2
At least one test, high positive titer ( $>3 \times$ ULN)	3
<b>Duration of Synovitis (0–1)</b>	
<6 weeks	0
$\geq 6$ weeks	1
<b>Acute-Phase Reactants (0–1)</b>	
Neither ESR nor CRP abnormal	0
Abnormal ESR or CRP	1
<b>TOTAL (<math>\geq 6</math> indicates <i>definite</i> RA):</b>	



# Rheumatoid arthritis - therapy

- **Standard therapy:** MTX (Methotrexate)
- , Prednisone , NSAID
- Physical therapy
- Recently, experimentally, as well as clinically, "**biological therapy**" has been applied which implies the use of antibodies directed against pro-inflammatory cytokines or molecules selectively expressed on effector cells important in the immunopathogenesis of rheumatoid arthritis.

Although the first results of the application of "biological therapy" are encouraging, this therapeutic approach requires special caution in the selection of the drug, dose, side effects, and because of the possible effect of sudden termination of therapy (rebound effect) .



# Rheumatoid arthritis - therapy

**Adalimumab** is humane a monoclonal antibody that specifically binds a cytokine  $\text{TNF-}\alpha$  and is used in the treatment of rheumatoid arthritis

For the treatment of RA, its use was approved in 2001

# Juvenile idiopathic arthritis

It occurs in children under 16 years of age

Like rheumatoid arthritis, juvenile arthritis can be seronegative (RF-) and seropositive (RF+), depending on the presence of RF in the serum.

Genetic predisposition (HLA-DR4 , HLA-DR5 , HLA-DR8 , HLA-B27) and an infectious agent (unknown) are considered to play an important role.

A special form of the disease is the so-called Still's disease (a systemic disease that manifests itself in elderly patients)

The immunopathogenesis is similar to the immunopathogenesis of rheumatoid arthritis

There are oligoarticular and polyarticular forms of the disease:

**(1) Oligoarticular form of juvenile arthritis**

- Up to 4 joints affected by inflammation
- The most common inflammation of the wrist or knee joint
- Iritis and uveitis

**(2) Polyarticular form of juvenile arthritis**

- More than 5 inflamed joints
- The most common inflammation of the small joints of the hands and feet
- Neck stiffness

# Seronegative arthropathies

Chronic diseases of unknown etiology characterized by: inflammation in the **spine** (muscle attachments, most often paravertebral), inflammation of peripheral joints (more often unilaterally affected large **joints** ) and **the absence of rheumatoid factor** in the serum.

## Common characteristics:

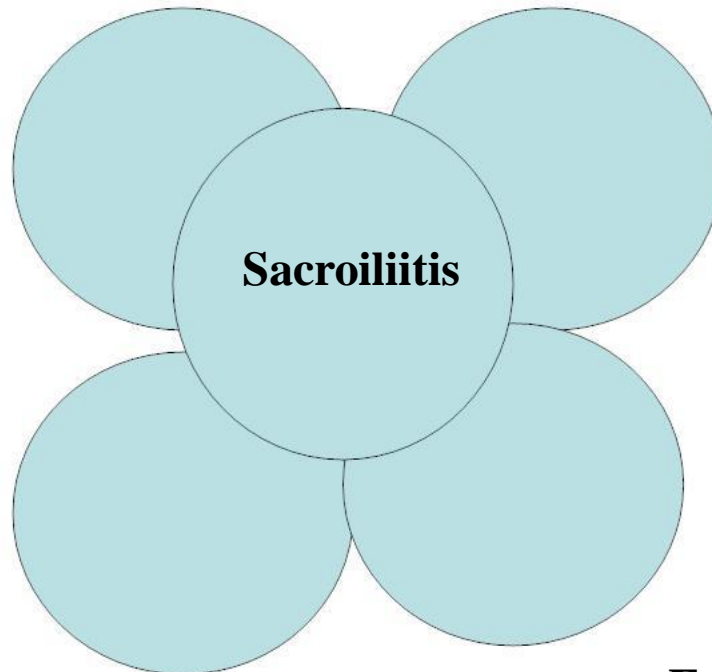
- **lack of IgM RF** in serum (negative Waaler-Rose test)
- clinical and radiological **changes on sacroiliac joints and spine**
- **genetic predisposition** (HLA B27 and family character)
- inflammation **of peripheral joints**
- **mucocutaneous changes**
- **lack of rheumatoid nodules**

# **Seronegative arthropathies**

## **Seronegative spondyloarthritis**

**Ankylosing spondylitis**

**Psoriatic arthritis**



**Reactive arthritis  
(Reiter syndrome)**

**Enteropathic arthritis  
(ulcerous colitis, Crohn's disease)**



# Ankylosing spondylitis

## Bechterew's disease

- **Chronic progressive disease** of unknown origin in younger men (15-30 years)
- **Axial bones:**
  - **Sacroiliac joint**
  - joints and connective tissues of the **spine**
  - **surrounding connective tissues** (mostly tissues connected to bones)
- **Metaplasia** occurs (change of connective tissue by bones) and characteristic **ankylose** of joints

# Ankylosing spondylitis

Unknown etiology, not yet confirmed

- ✓ Because of the similarities with reactive arthritis (bowel infections), **enterobacteria** are considered to have an initial role in the disease. Some studies suggest the possibility of infection as initiator for onset of new disease, close look at bacteria *Bacteroides*
- ✓ In the serum of patients with ankylosing spondylitis **IgA** is elevated (they have an important role in mucose immunity) and **proteins of acute inflammation phase**
- ✓ APC mucous origin are important in pathogenesis

# Ankylosing spondylitis

- ✓ Some of best examples of the connection of disease and HLA genes (HLA B27)
- ✓ More than **90%** of patients with ankylosing spondylitis have **HLA B27**, but less than 5% B27+ will have ankylosing spondylitis
- ✓ Complex disease, **genetic predisposition consists of more than one gene**



# Pathogenesis of ankylosing spondylitis

Not completely understood

-interaction between **HLA B27** and **T lymphocytes**

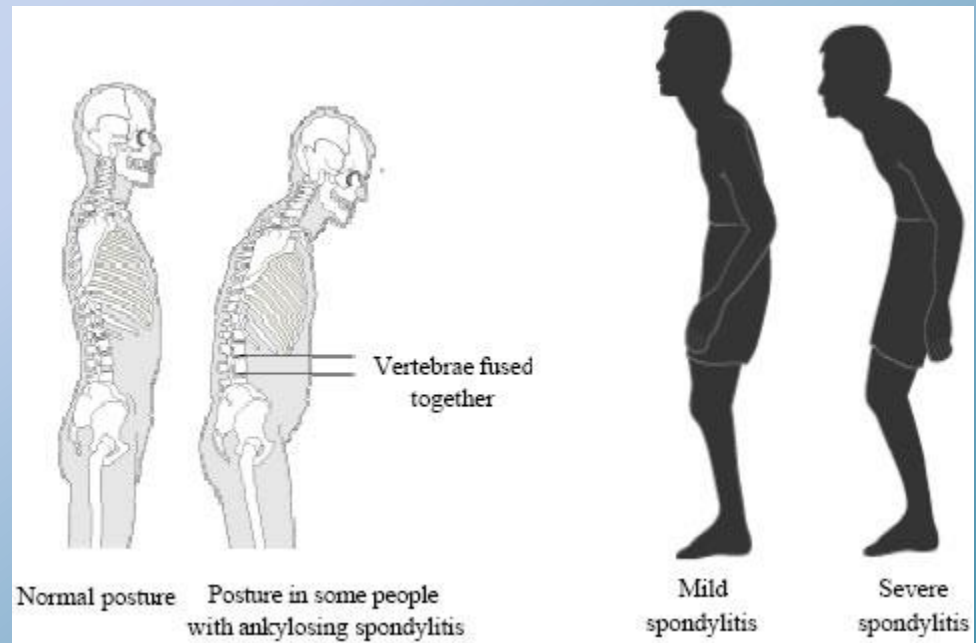
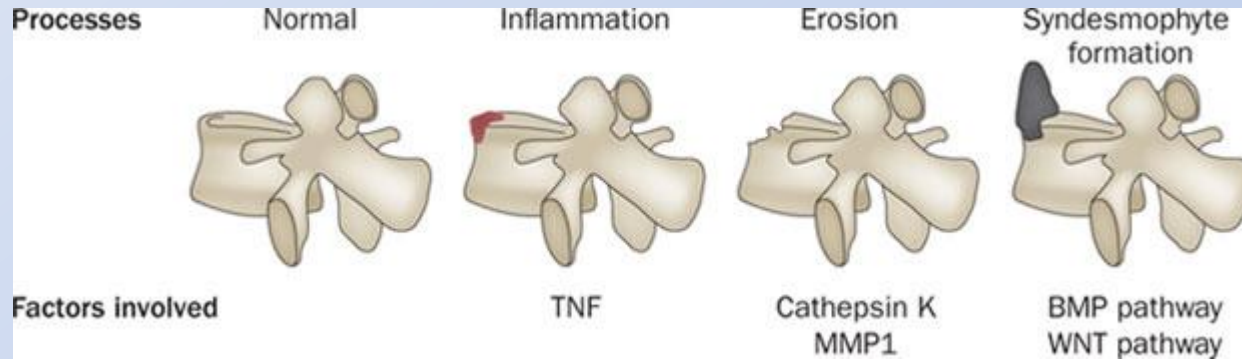
Larger concentration of T lymphocytes (Th17), macrophages, DC (CD14-CD16+), and inflammatory cytokines (IL-6)

## **Role of TNF- $\alpha$ :**

Among cytokines, the central place in the pathogenesis of this disease is occupied by **TNF- $\alpha$** , responsible for local paravertebral inflammation.

After inflammation under the action of matrix metalloproteinases and cathepsins, bone erosion occurs, formation of syndesmophytes and "ossification" of the spinal column (dominantly in the lumbo-sacral part), which causes limited mobility and pain.

# Ankylosing spondylitis



- Radiographically, the spinal column has a "bamboo spine" appearance.

# Therapy ankylosing spondylitis

**Secukinumab ( Cosentyx )** is a human IgG1  $\kappa$  antibody that binds IL-17A and it is used in the therapy of ankylosing spondylitis

Use approved 2015 . year (for AS therapy since 2016)

**Ixekizumab (Taltz)** humanized IgG 4 monoclonal antibody that specifically binds to IL-17A and it is used in the therapy of ankylosing spondylitis.

Use approved in 2016. (for AS therapy from 2019)

1. Taltz gives fewer side effects compared to Cosentyx .
2. Cosentyx has a faster onset of action, but Taltz shows longer effectiveness



# Reactive arthritis

It occurs during the **infection of anatomically far** joint cavity

From the beginning of the infection until the onset of arthritis **1-3 weeks**

From synovial liquid **causative factor can be isolated**, that doesn't react to antibiotics

**Reactive arthritis** consists of:

- Reiter syndrome
- Arthritis in rheumatoid fever
- Arthritis in brucellosis infection
- Arthritis in lime disease

# Reactive arthritis

Reactive arthritis (mostly sacroiliitis) can be caused by:  
*Chlamidiae, Mycoplasmae, Yersinia, Shigellae, Salmonellae and Helicobacter*

-Characterised by the ability to survive in infected cells:

-People who develop reactive arthritis have:

- Less digestive symptoms
- Lower IgM response
- Stronger and long-lasting IgA and IgG response
- Higher concentration of secretory IgA antibodies and
- Weaker T lymphocyte response to causing factors
- There is unusual persistence of humoral immune response to infection, with weaker cellular immune response (weak antibacterial response with a lot of regulatory T cells and IL-10)

# Reiter's syndrome

- It occurs more often in men (3:1) compared to women. It is more common in men under the age of 40.
- It is characterized by : **arthritis** (often unilateral, most often knee joint), **non-infectious urethritis and conjunctivitis** . Bursitis and tendinitis in the area of the Achilles tendon, ulceration in the oral cavity and changes in the genitals can also occur.
- Mostly occurs **after urogenital and bowel infections** (*Chlamydia trachomatis*, *Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*) in persons that have HLA B27 gene, around 75% of ill people
- Although there are no viable bacteria in the inflamed tissue of patients with Reiter's syndrome, antigens and DNA of these bacteria have been observed in the inflamed joints, as well as cytotoxic T lymphocytes specific for these antigens. The T cell response is important in disease pathogenesis.

# Psoriatic arthritis

**Arthritis** in patients with:

- psoriasis
- expression of HLA B27, HLA B7

**Pathological changes** in skin and joints:

- inflammation
- with signs of activation of the complement system

**Antinuclear antibodies** and present and **antibodies to keratin and cytokeratin 18**

# Enteropathic arthritis

- In IBD (Chron's and ulcerous colitis)
- Expression of HLA B27, peripheral arthritis
- Digestive symptoms not in correlation to joint changes
- Most joint changes are spondyloarthropathies
- Exact pathogenesis of joint changes not known, considered to be is:
  - infection can ease the entrance of foreign antibodies in interstitial tract
  - circulatory immune complexes are formed during the immune response for adsorbed antigens, they can be in joints and induce the onset of arthritis

# **Systemic lupus erythematosus**



# **Systemic lupus erythematosus (prototype of systemic autoimmune disease)**

- Systemic autoimmune disease of unknown origin that takes more organ systems
- Potentially can get to all tissues and organs (big imitator)
- Immunoserologic findings of numerous antibodies (antinuclear and others)
- Pathogenetic mechanisms:
  - autoimmune lead inflammation
  - organ specific destruction
  - organ non specific immune complexes
  - vascular destructions

# Epidemiology of systemic lupus erythematosus

- Women to men 9:1
- Mostly disease of younger women, aged 15-40
- Onset of disease in younger life time:
  - worse clinical picture
  - progressive
- Disease can occur in two or more family members, which implies genetic predisposition
- In ill people and family members another autoimmune disease can occur

# Genetic predisposition

- HLA-DR2, HLA-DR3, HLA-DR25, C4 A locus (.,null alleles)-HLA III region
- gene mutations for molecules responsible for conducting signals from receptors to the nucleus, i.e. for intracellular signaling: IRF5, STAT4, BLK kinase
- C1q, C2, C4 deficiency ( disorder removal immune complex )
- FcγRIIb deficiency (activation of V lymph., macrophages, dendritic cells)
- CTLA-4 deficiency (impaired function of Tregs )
- Estrogen - B proliferation and antibody secretion. Shown in experimental models that estrogen blockade causes improvement, and estrogen application causes disease exacerbation↑

# Factors of the external environment

- UV rays (DNA damage and apoptosis of keratinocytes and expression of autoantigens, so-called Ro, La antigens)
- Viruses - Epstein-Barr virus (EBV ) ???
- Bacteria ???
- Medicine induced SLE ( procainamide , hydrazine , phenytoin ....)

# Hypotheses that indicate a possible cause of systemic lupus

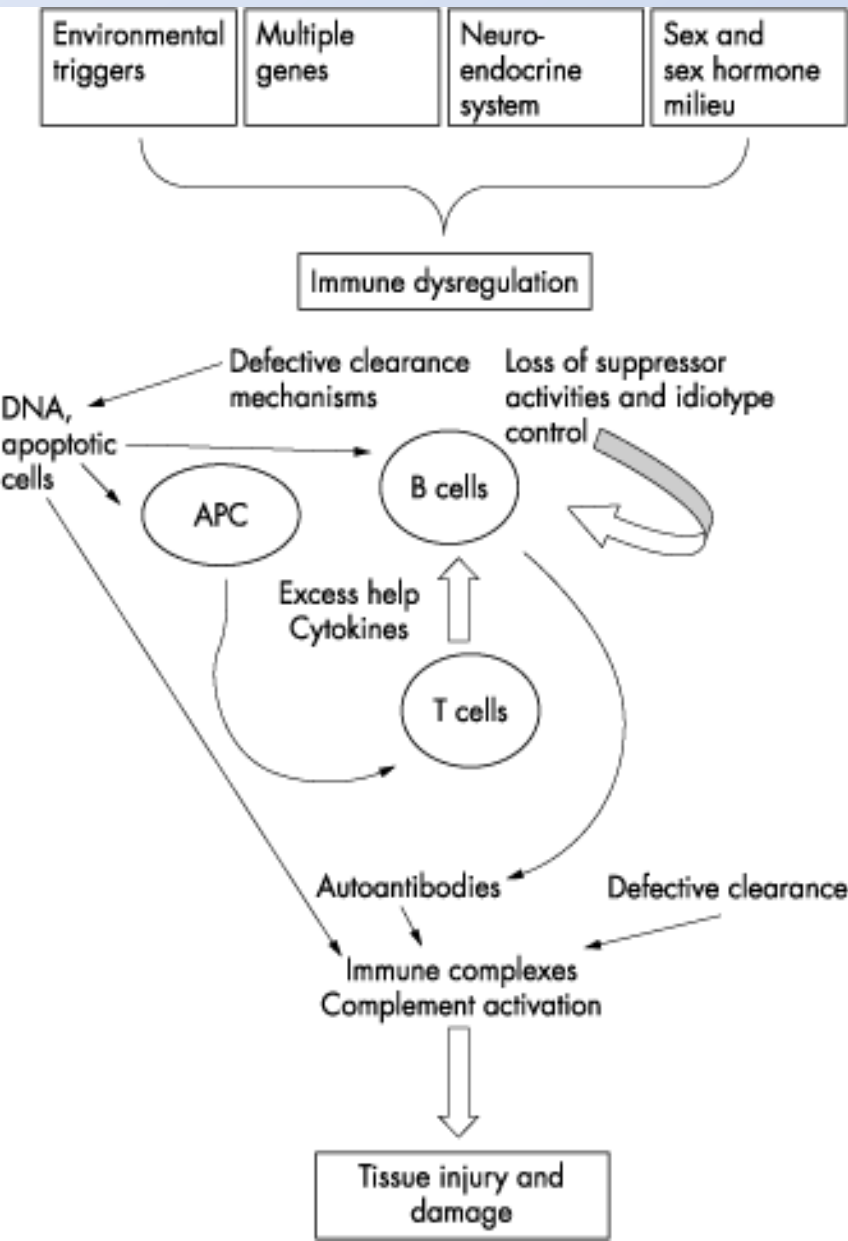
There are two hypotheses that indicate the possible cause of systemic lupus:

- (1) Impaired removal of apoptotic cells as an important mechanism in the development of systemic lupus, "**the cleansing hypothesis**"

**Hereditary or acquired deficiency of C1q and C4 proteins**, which bind to apoptotic cells and are important in the process of their removal, causes systemic lupus. In addition, **deficiency of pentaxins** (C reactive protein and serum amyloid P protein), which bind to DNA fragments or other nucleosome components, also causes symptoms characteristic of systemic lupus.

Unsuccessful removal of apoptotic cells (due to pentaxin and complement system protein deficiency) enables the presentation of autoantigens from apoptotic cells to autoreactive B and T lymphocytes. Otherwise, these autoantigens are normally degraded within the cell. But, during the development of lupus, they appear on the surface of apoptotic bodies and become visible to autoreactive B and T lymphocytes as well as cells of non-specific immunity.

# Defect in removal of apoptotic cells



Apoptotic cells are an excellent source of autoantigens, they provide signals for the activation of dendritic cells, they are an excellent source of antigens for cross-presentation to CD8+ T lymphocytes.

Unremoved apoptotic cells are present in the germinal centers, which is why the autoimmune disease develops.

1. Autoantigens activate the complement system
2. FDC (present autoantigens to B lymphocytes)
3. Disorder of T lymphocyte tolerance, due to phagocytosis disorder

■ Imbalance ↓ IL-12 / IL-10 ↑

IL-10 autoantibodies ↑

IL-12 autoantibodies ↓



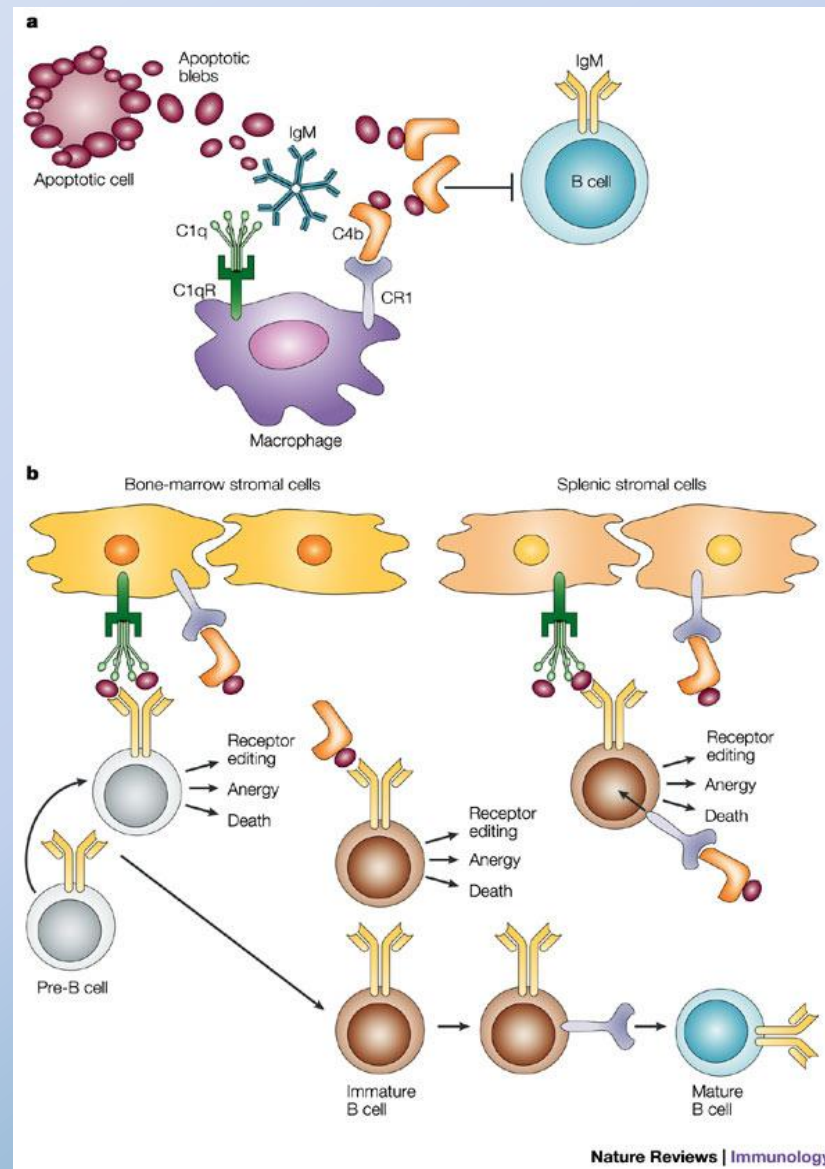
# Hypotheses that indicate a possible cause of systemic lupus

- (2) Disturbance in the maturation process of B lymphocytes , the "tolerance hypothesis"

During B lymphocyte maturation, bone marrow stromal cells present autoantigens via C1q and S4 proteins. Immature B lymphocytes that recognize their own antigens with strong affinity change the receptor ("receptor *editing*"), so if they recognize autoantigens with strong affinity again, they die by apoptosis. In conditions of C1q and S4 protein deficiency, the mechanism of autoantigen presentation is disrupted, which prevents the deletion of clones of autoreactive B lymphocytes.

The same mechanism may be responsible for the disturbance in the process of peripheral tolerance of B lymphocytes (disabled presentation of autoantigens on the stromal cells of the spleen due to the deficiency of C1q and S4 proteins).

# Hypotheses a) "cleaning" and b) "tolerance"



# The importance of viral infection in the development of systemic lupus

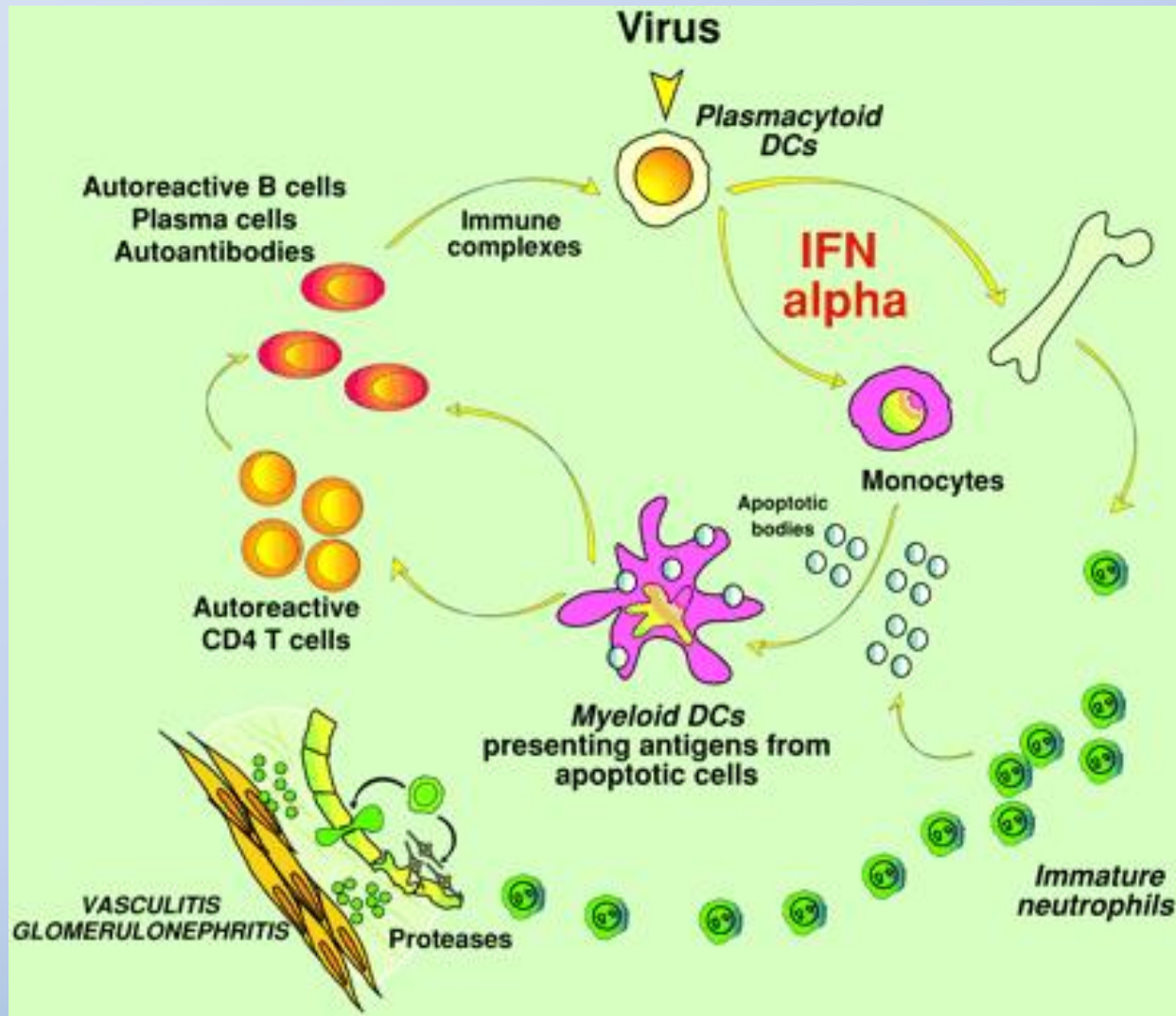
There is a hypothesis that indicates the importance of (so far unknown) viral infection in the development of systemic lupus.

The virus is recognized by **plasmacytoid dendritic cells**, these cells are activated and produce IFN -  $\alpha$  under the influence of which polymorphonuclear cells are rapidly synthesized in the bone marrow and immature forms of neutrophils are mobilized.

In addition, **myeloid dendritic cells** recognize autoantigens from apoptotic bodies, process them, and present them to autoreactive B and T lymphocytes. Autoreactive B lymphocytes produce autoantibodies that bind to autoantigens forming immune complexes.

Chemokines attract leukocytes "mobilized" from the bone marrow to the site of inflammation.

# The importance of viral infection in the development of systemic lupus





# Systemic lupus erythematosus immunopathogenesis

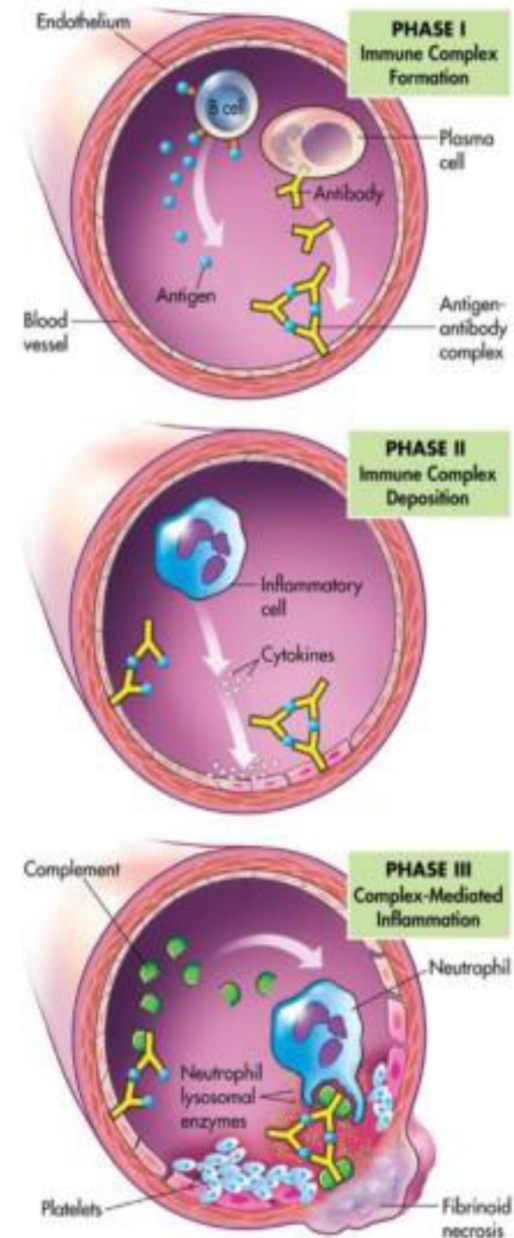
In the immunopathogenesis of systemic lupus, the central place is occupied by **the presence of anti-nuclear antibodies, the formation and deposition of immune complexes** .

**Mechanisms of the second and third type of hypersensitivity are the most responsible for pathological changes in systemic lupus** . Autoantigens are recognized by autoreactive B lymphocytes, they present antigens to T lymphocytes, they proliferate, "change classes" of antibodies. Autoantibodies recognize autoantigens and form immune complexes. Immune complexes are deposited in the wall of small and medium-sized blood vessels, as well as in filtration sites (kidney, joint synovium), the complement system is activated , and via Fc receptors mast cells, neutrophils, macrophages.

The presence of numerous anti-nuclear antibodies indicates **non-specific polyclonal activation of B lymphocytes**. Autoantibodies are directed mainly against molecules responsible for transcription and translation and show increasing affinity as the disease progresses, indicating a persistent presence of the antigen. Certain studies indicate that **the nucleosome**, which contains DNA and histones, is the first and "main" target of auto-antibodies, which, according to numerous authors, are created several years before the first symptoms appear.

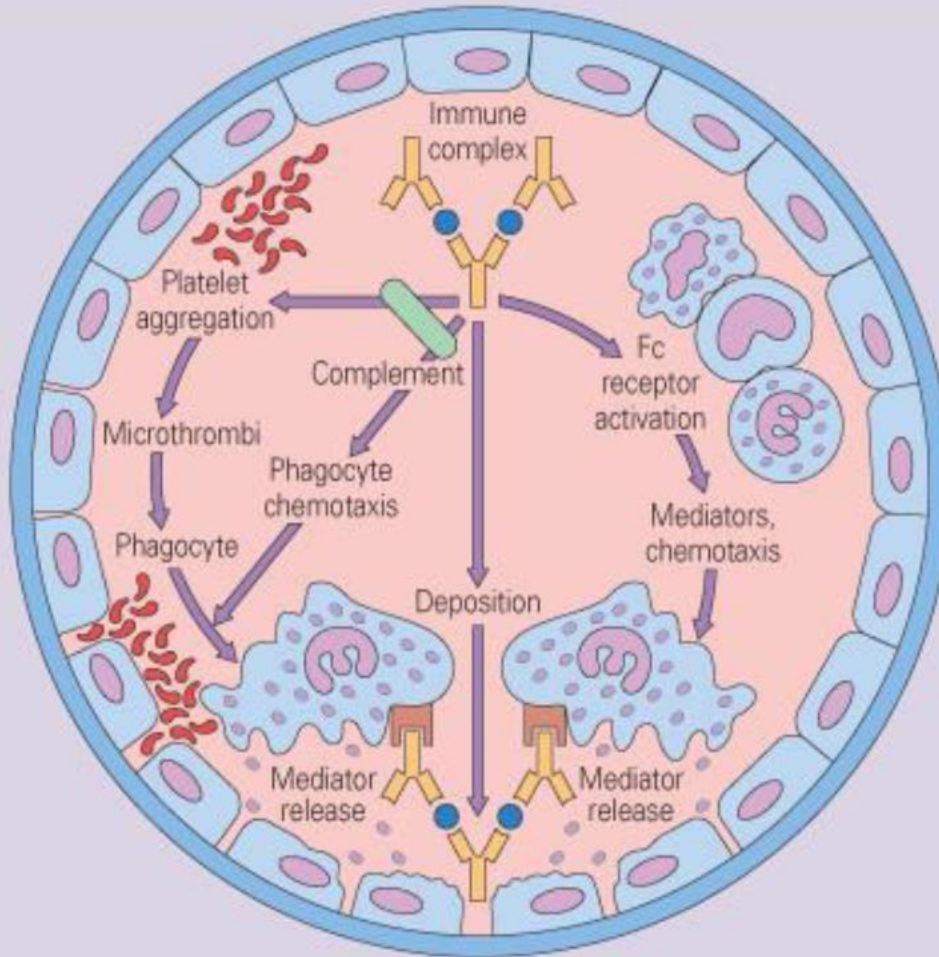
# III type hypersensitivity

- Immune complexes ( IC ) contain **cationic antigens** that bind to negatively charged components of the basal membrane of blood vessels and kidney glomeruli.
- IC activate **mast cells and basophils** , release of vasoactive mediators, permeability of blood vessels and deposition of IC .
- IC , via Fc receptors, **activate the complement system and neutrophils and macrophages** . These cells produce pro-inflammatory cytokines and chemokines and inflammation and tissue damage occur. The release of **free oxygen radicals, lysosomal enzymes and chemotactic substances** from permanently activated cells causes damage to the walls of blood vessels, the subsequent aggregation of platelets, and tissues.
- Mass deposition of IC** and their non-removal can cause obliteration and obstruction of the blood vessel lumen, which results in ischemia of tissues and organs.





### IMMUNE COMPLEX ACTIVATION OF INFLAMMATION



Immune mechanisms activate complement. *C3a, C5a fragments are released.*

Complement fragments attract *inflammatory cells*. Inflammatory mediators and enzymes are released from inflammatory cells (*frustrated phagocytosis*).

Endothelial cells in the blood vessel wall are damaged, inflammation increases and platelet aggregation occurs.

# The beginning of the disease

## *monosystemic*

capture of one system

- pleurisy/pericarditis
- thrombocytopenia
- autoimmune hemolytic anemia
- nephritis

## *multisystemic*

capturing multiple systems simultaneously

- joints, skin, serosis, nephritis, hematological signs, CNS

# Autoantibodies in patients with SLE

✓ *Antinuclear antibodies (ANA) are not specific for SLE*

Anti-dsDNA – specific for renal nephritis

*Antibodies to extractable nuclear antigens (ENA)*

Anti-Sm (Smith)

Anti-RNP (ribonucleoprotein)

Anti-SSA; Anti-SSB (also found in Sjogren's Sy)

Anti-Jo1 (also found in polymyositis)

Anti-Scl70 (also found in Scleroderma/diffuse)

Anti-centromeric (also found in Scleroderma/limited)

✓ *Antierythrocyte and antiplatelet antibodies*

✓ *Antiphospholipid antibodies*

✓ *Anticytoplasmic antibodies*

Anti-mitochondrial

Anti-ribosomal

Anti-lysosomal

# Clinical picture of SLE

## Skin changes

**Acute:** *Erythematous rash ("butterfly")* - no scar  
frequent occurrence of *systemic manifestations of the disease*



## Chronic:

Discoid lesions - scar formation 5% of the  
occurrence of systemic manifestations of the disease



Alopecia  
ulcerations



Mucocutaneous  
(oral and genital mucosa)





# Clinical picture of SLE

## *Vasculitis*

Often inflammation in the area a. centralis retinae which can cause blindness in that eye.

Cerebro-vascular disorders

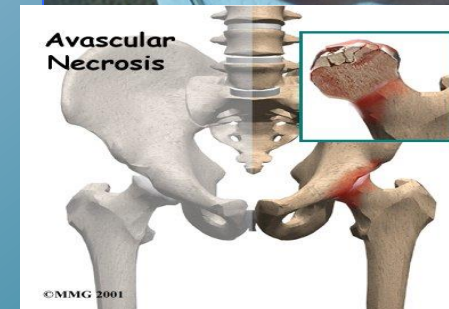
*Secondary Raynaud's phenomenon: due to disorders of peripheral vascularization*



*Changes in the nails*



*Avascular bone necrosis*



# Clinical picture of SLE

## *Locomotive system*

### *Arthralgias and Arthritis*

- Pain is mostly present
- the small joints of the hands are mostly affected
- symmetrical
- deformities rarely develop



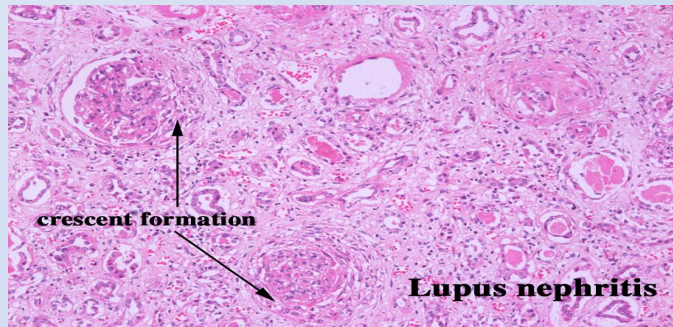
### *Myalgias and myositis*

- generalized

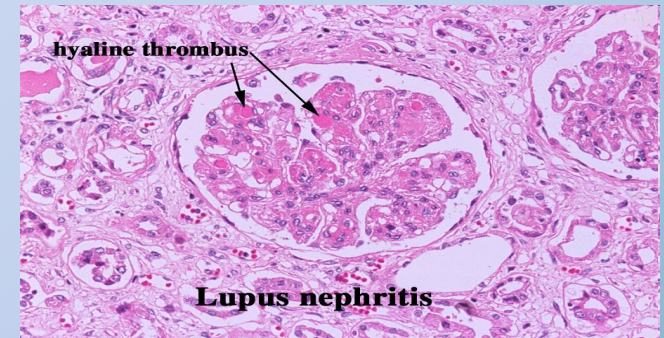


# *Lupus nephritis*

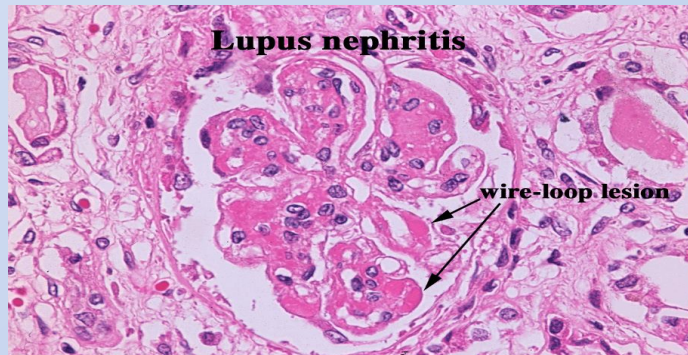
## 1. *Mesangial glomerulonephritis*



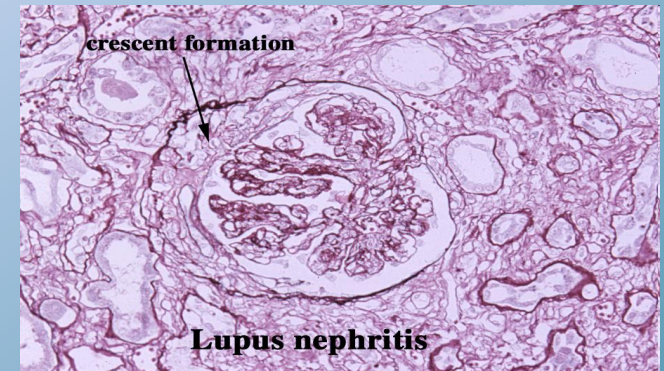
## 2. *Focal glomerulonephritis*



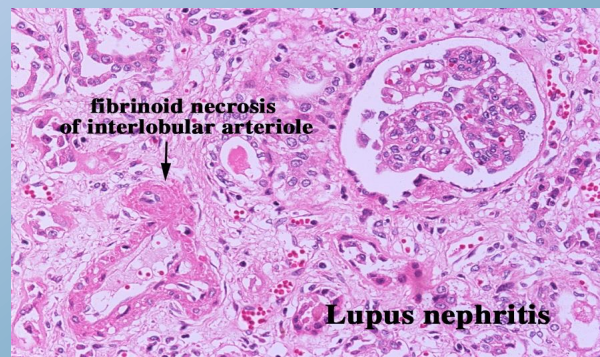
## 3. *Diffuse proliferative glomerulonephritis*



## 4. *Membranous glomerulonephritis*



## 5. *Sclerosing glomerulonephritis*





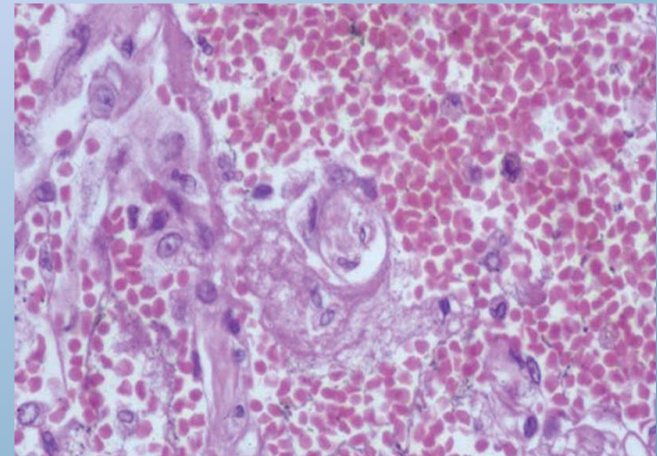
# Clinical picture of SLE

## *Nervous system*

Behavioral changes  
Depression  
Convulsions  
Headaches Peripheral neuritis

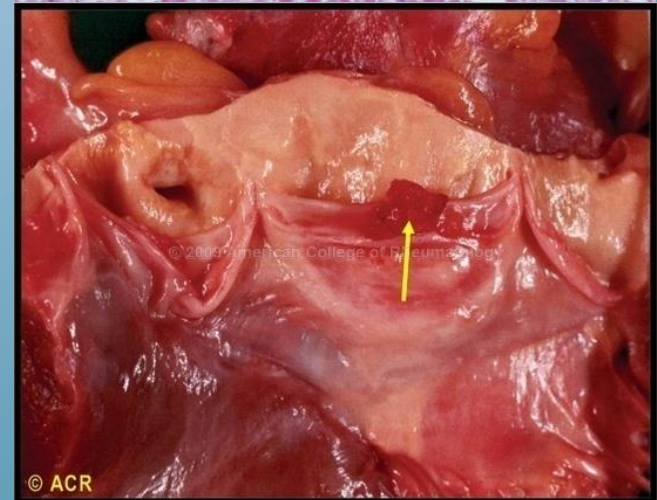
## *Respiratory system*

Pleurisy  
Alveolar hemorrhages



## *Cardiovascular system*

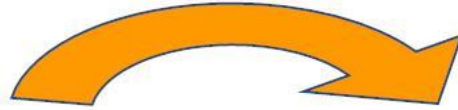
Myocarditis Libman-Sacks endocarditis (valvular verrucae) Arrhythmia  
Heart attack - atherosclerosis



## *Gastrointestinal system*

Due to vasculitis: Dysphagia, abdominal pain, diarrhea, hemorrhages

# Clinical spectrum of SLE



## ***LIGHTER FORMS***

- SKIN, JOINTS,  
SEROS

## ***HEAVIER FORMS***

- NEPHRITIS,  
CNS,  
SERIOUS  
HEMATOLOGICAL  
DISORDERS

# DIAGNOSIS OF SLE

## ■ Clinical picture

To establish a diagnosis of SLE, a patient must have four or more of these criteria:

- Malar rash,
- Discoid rash on the skin,
- Photosensitivity,
- Ulcerations in the oral cavity,
- Non-erosive arthritis,
- Serositis (pleuritis/ pericarditis),
- Renal disease (persistent proteinuria/urinary casts),
- CNS dysfunction,
- Hemolytic anemia/ leukopenia/ lymphopenia/ thrombocytopenia,
- Antinuclear/ anti-dsDNA/ anti-Sm (ENA)/ antiphospholipid antibodies

# DIAGNOSIS OF SLE

## ■ *Laboratory findings:*

- Antinuclear antibodies (ANA) – 98% of patients  
IgG/IgM ratio 0.8 nephritis; 0.8 skin damage.
- LBT (lupus band test) - dermoepidermal junction.
- Normocytic, normochromic anemia.
- Leukopenia  $<4.0 \times 10^9/l$ .
- Thrombocytopenia  $<100 \times 10^9/l$ .

# Antinuclear Antibodies (ANA)

- Antinuclear antibodies (ANA) were administered according to different nuclear antigens that can be detect in the serum of patients with rheumatic i non-rheumatic diseases, as well as in healthy people.
- Detection and characterization of ANA - indirect immunofluorescence (IIF), enzyme immunoassay (ELISA), immunoblot
- Immunofluorescence microscopy on human epithelial cell line (HEP-2) is used for initial screening
- Test results - positive or negative, titer



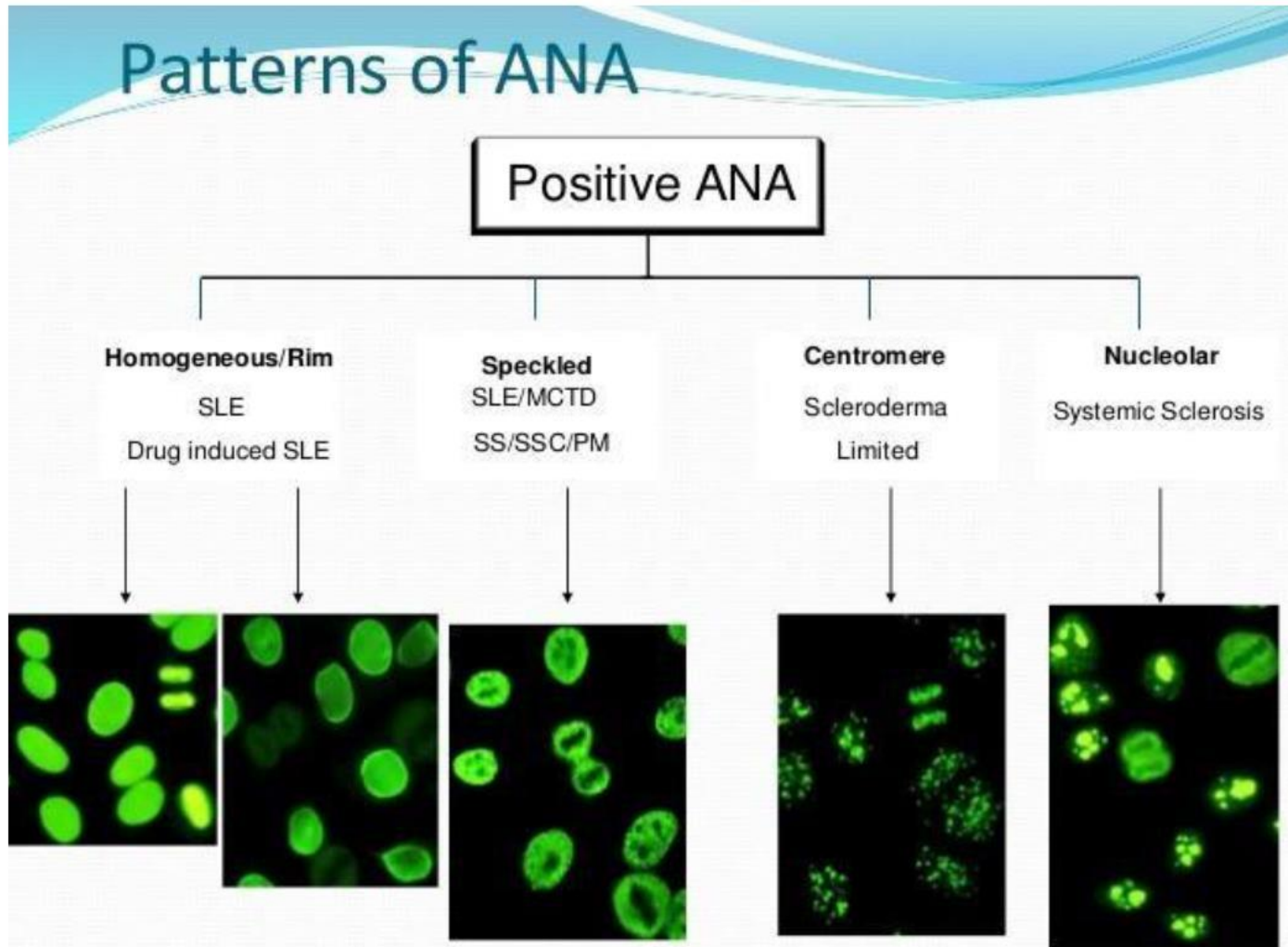
# ANA Types of nuclear immunofluorescence

Fluorescence type	The antigen responsible for the type of Fluorescence
Homogeneous	DNP histones, DNA
Rim	dsDNA
Speckled	Sm (Smith), U1, RNP, SS-a, Jo-1, SCL70
Nucleolar	PM-Scl, Fibrillarin, U3RNP, RNA polimerasa, NOR-90

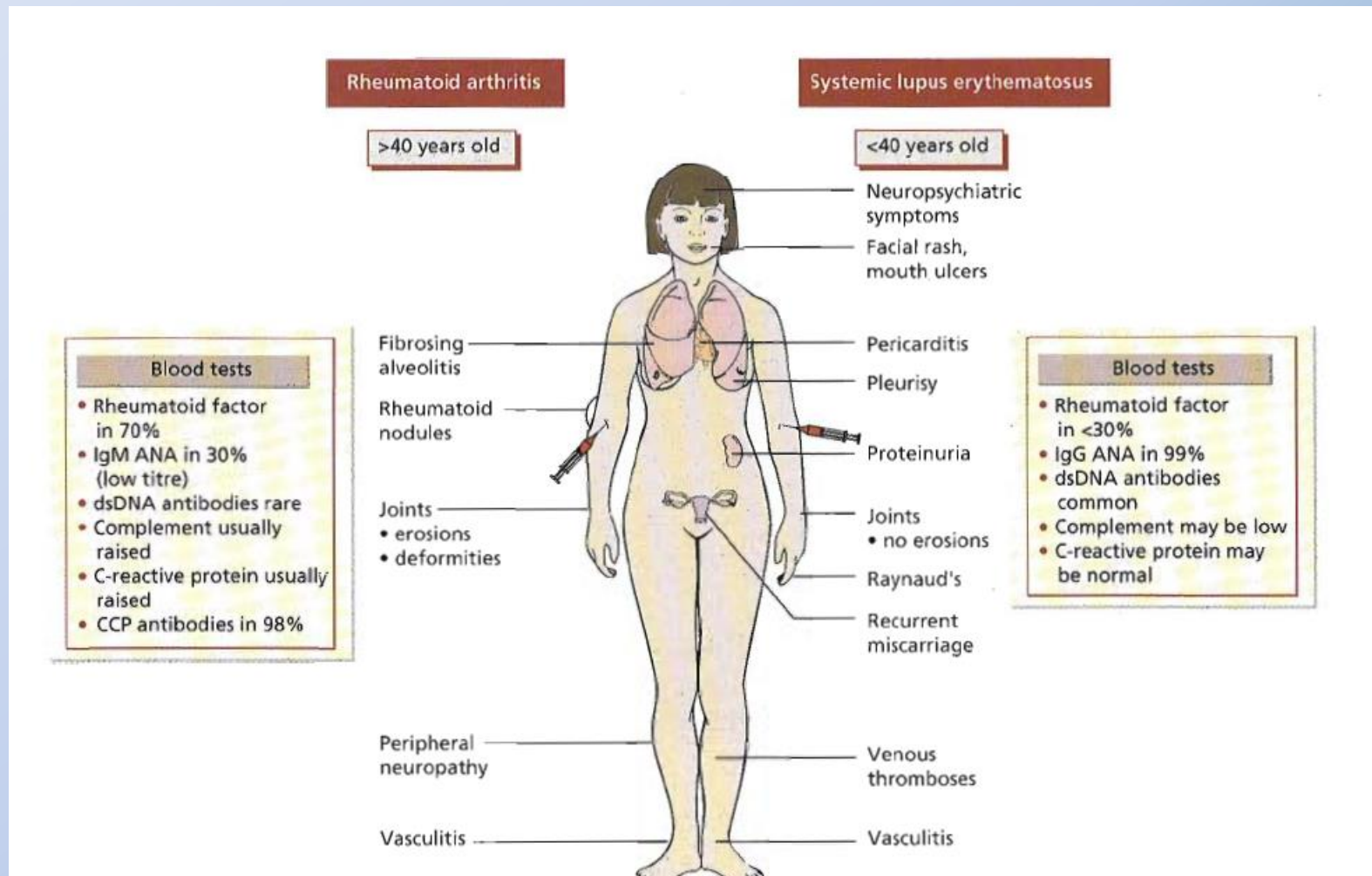
antigen/type of immunofluorescence	Diseases
<b>HOMOGENEOUS</b>	
histones	SLE (50-80%) Drug induced SLE (95%) PA (15-50%)
<b>RIM</b>	
dsDNA	SLE (60-90%)
<b>SPECKLED</b>	
U1-nRNP	MBVT(95-100%), SLE(15-40%)
Scl-70	Systemic sclerosis diffuse form (25%-75%)
Sm (Smith)	SLE (5%-40%)
SS-A (Ro)	Sjogrens sy (40%-95%) SLE (20%-60%), neonatal lupus (100%)
SS-B (La)	Sjogrens sy (40%-95%) SLE(10-20%)
<b>NUCLEOLAR</b>	
NUCLEOLAR RNA, RNA polymerase1	Systemic sclerosis diffuse form (4%)
PM-Scl (PM1)	POLY/DERMATOMYOSITIS(50-70%)
<b>CENTROMERE</b>	
CENP	SYSTEMIC SCLEROSIS LIMITED FORM (80-95%)

# ANA

## Types of nuclear immunofluorescence



# Significant differences for the diagnosis of rheumatoid arthritis and systemic lupus erythematosus



# SLE therapy

- Anti-malarials (Chloroquine, Hydrochloroquine)  
Skin and muscle changes.
- NSAIDs (arthritis)  
Skin and musculoskeletal changes.
- Corticosteroids:
  - > 0.5 mg/kg/d renal and hematological changes, CNS, vasculitis
  - < 0.5 mg/kg/d hematological, skin and musculoskeletal changes.
- Immunosuppressants  
(Cyclophosphamide, Methotrexate (MTX), Azathioprine)  
renal changes, CNS, vasculitis.



# SLE therapy

*Belimumab* is a human monoclonal antibody that specifically binds B-cell activating factor (BAFF) and is used in the treatment of systemic lupus erythematosus.

It was approved for the treatment of SLE in 2011.

# Sjogren's syndrome

Chronic autoimmune disease characterized by inflammation of the epithelial tissue with pronounced disorders of the secretion of lacrimal and salivary glands due to lymphocytic infiltration and destruction of their parenchyma (*autoimmune exocrinopathy*).

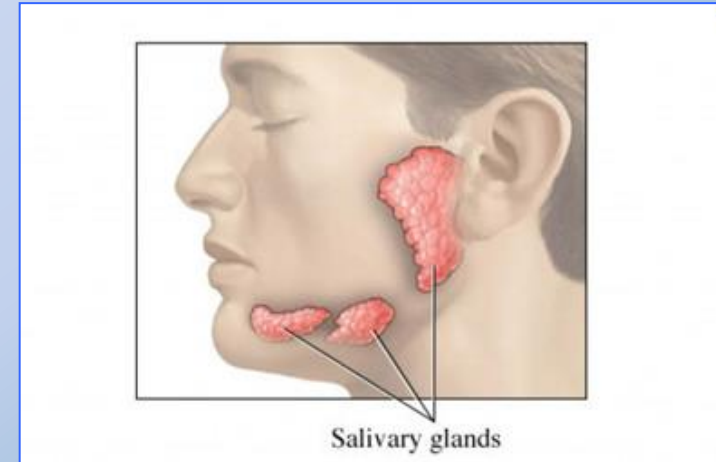
■ women : man - 9:1

Women 30-50 years

- 30% with RA (secondary Sjogren's syndrome)
- 15% with SLE, PSS (progressive systemic sclerosis) and PBH (primary biliary cholangitis (secondary Sjogren's syndrome).

■ Primary Sjogren's syndrome  
(*sicca syndrome*, *kertoconjunctivitis sicca*)

■ **Secondary Sjogren's syndrome** ( associated with other autoimmune diseases or systemic connectivetissue diseases) .



# Genetic predisposition and environmental factors

- Genes for: HLA-DR3, HLA-DQ2, IRF5

- Viruses :

  - Herpes virus

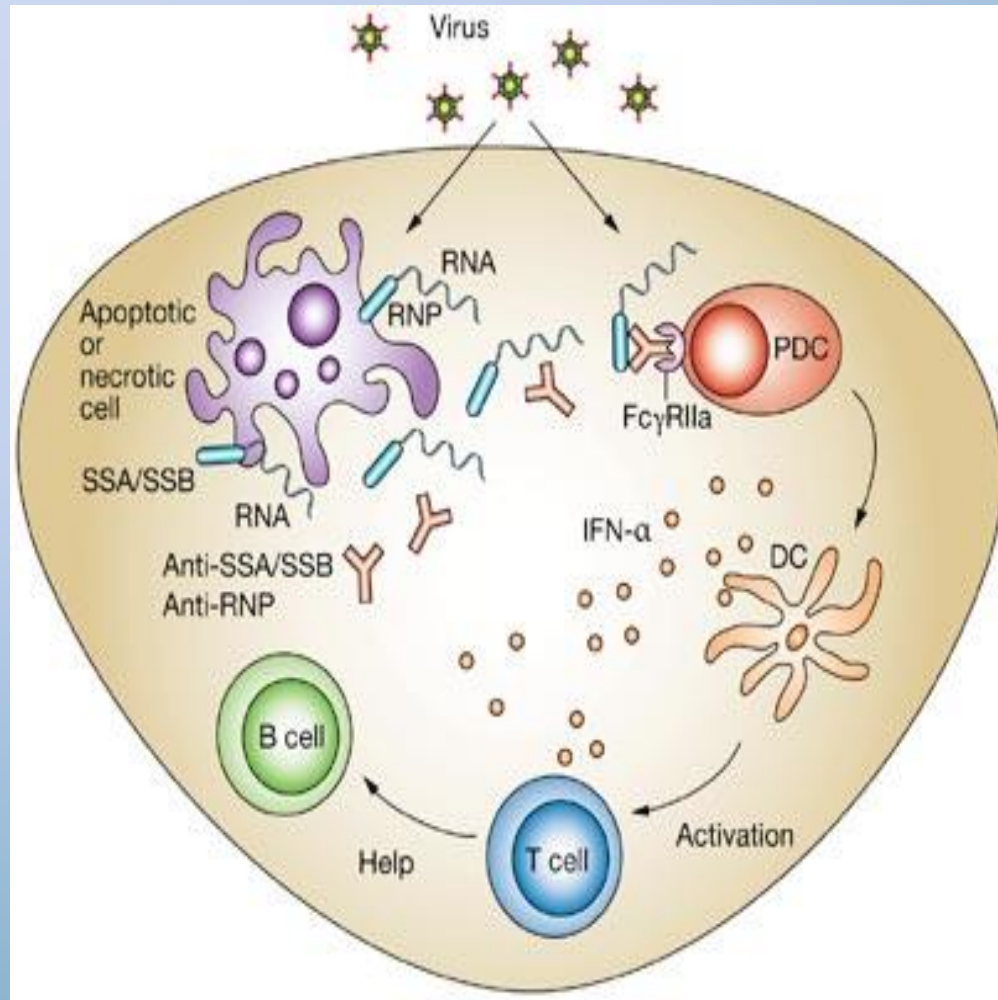
  - Coxsackie virus

- Bacteria :

  - H. pylori* ???

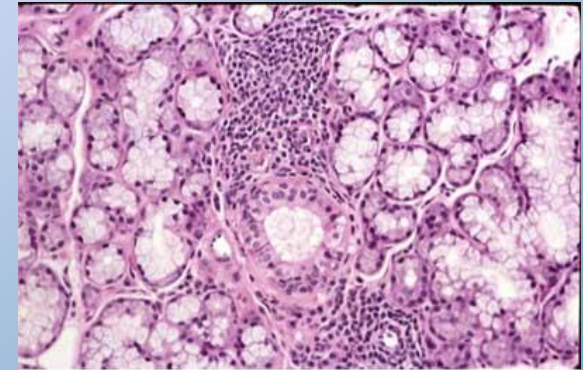
# Pathogenesis

The virus recognizes plasmacytoid dendritic cells, they are activated and produce IFN- $\alpha$ , which causes apoptosis of the epithelial cells of the lacrimal and salivary glands. Ro/SSA, La/SSB antigens and ribonucleoprotein were expressed on apoptotic bodies. Dendritic cells take up apoptotic cells and activate CD4+Th1 lymphocytes which activate V lymphocytes specific for SS/A, SS/B antigens and ribonucleoprotein and produce autoantibodies against these antigens. Autoantibodies bind to antigens, form immune complexes that are recognized by Fc $\gamma$ RIIa receptors on plasmacytoid dendritic cells and in response additionally produce IFN- $\alpha$ , which forms a "vicious circle".



# Pathogenesis

- Lymphocytic infiltration (dominantly T lymphocytes) of exocrine and epithelial tissue (reduced apoptosis of T lymphocytes)



The slide shows a classic focal lymphocytic infiltration in a minor salivary gland section stained with hematoxylin and eosin. These findings are typical of Sjogren's syndrome.

Courtesy of NIH/NIDCR.

- Increased proliferation, differentiation and hyperactivity of V lymphocytes
  - anti-SSA antibodies
  - anti-SSB antibodies
  - anti-M3R antibodies
  - blocking the secretion of exocrine tissue products



# Clinical picture

## ■ Xerostomia

Dryness of the oral cavity, difficulty swallowing, dry and furrowed tongue, caries



## ■ Keratoconjunctivitis sicca

Photophobia, eye burning Schirmer's test (< 5mm in 5 min.)

■ Enlargement of salivary glands (parotid or submandibular)



■ Peripheral neuropathy, occasional epistaxis, dysphonia, tracheobronchitis, pneumonia

# Systemic manifestations of Sjogren's syndrome

- Arthralgias/arthritis
- Subfebrile temperature
- Raynaud phenomenon
- Vasculitis: skin, lungs (interstitial pneumonitis), kidneys (interstitial nephritis), GIT, CNS
- Depression
- Mononeuritis multiplex
- Recurrent urticaria, erythema nodosum, skin ulceration

# Autoantibodies in Sjogren's syndrome

- ANA
- RF (90%)
- Antibodies specific for two antigens that can be extracted from the nucleus( extractable nuclear antigens):
  - anti Ro/SSA (50-90%)
  - anti La/SSB (50-90%)
- Organ specific antibodies

# Diagnostic criteria for Sjogren's syndrome

1. Symptoms of dry eyes
2. Symptoms of dry mouth
3. Positive Schimer or Rose Bengal test
4. Pathological finding of scintigraphy or sialography
5. Pathohistology of salivary gland biopsy
6. Positive anti Ro/SSA or anti LA/SSB antibodies

Criteria of the European Study Group 1993.

# Therapy

- Oral hygiene maintenance
- Use of artificial tears NSAIDs
- In advanced disease:
  - Corticosteroids
  - Immunosuppressants - Azathioprine - MTX
- IFN- $\alpha$  ( $\downarrow$ xerostomia)





# **Systemic sclerosis (scleroderma)**

# Systemic sclerosis (scleroderma)

Chronic multisystem inflammatory (autoimmune) disease of unclear etiology, characterized by *progressive fibrosis of the skin and visceral organs and functional and structural disorders of small blood vessels.*

Woman : man - 4:1

Genetic predisposition and the influence of external factors contribute to the loss of self-tolerance.

# Genetic predisposition and environmental factors

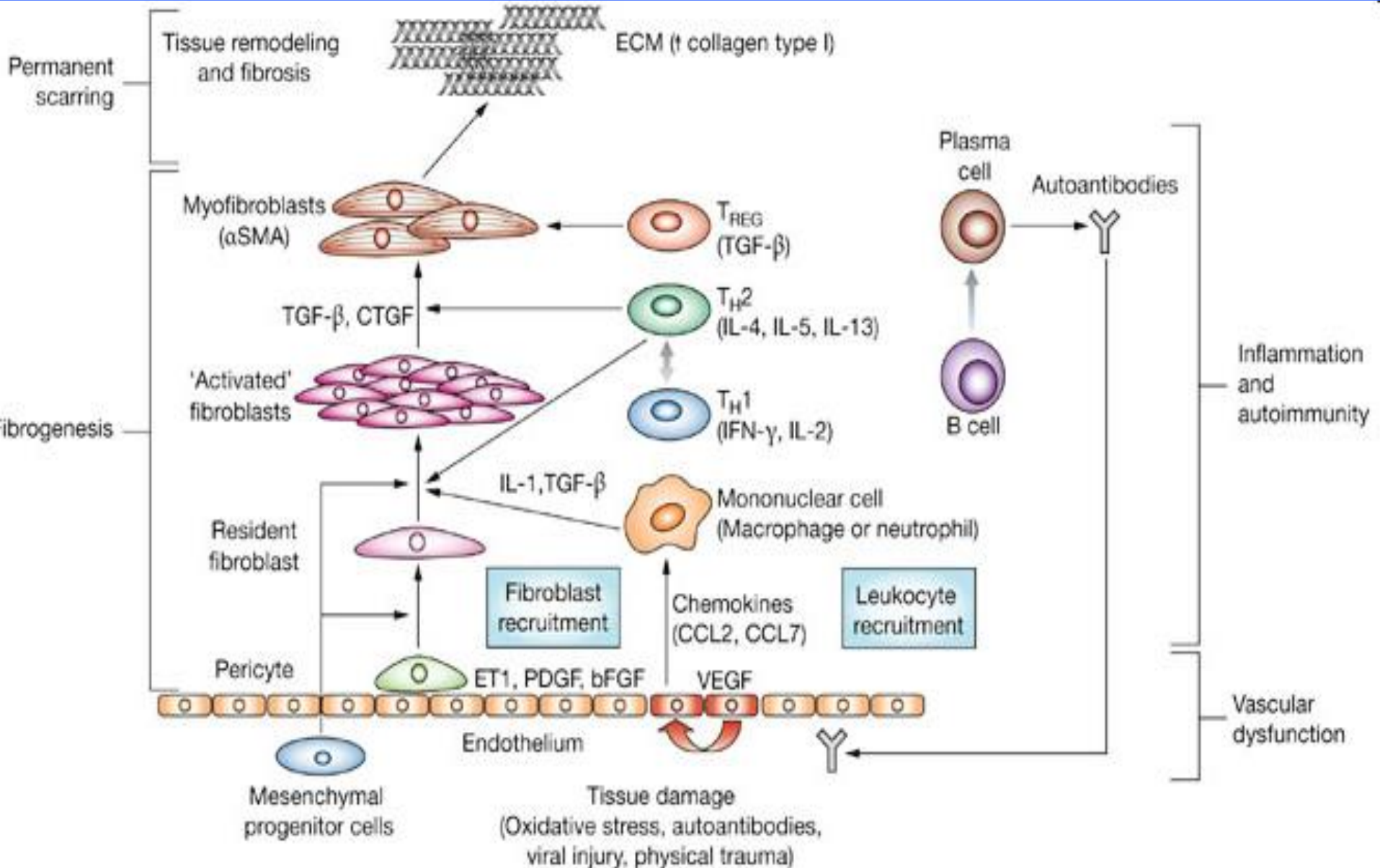
- No clear connection has yet been confirmed certain HLA genes and systemic sclerosis
- Genes for: IRF5, IL-23R...
- Viruses
  - (CMV)???
  - parvovirus B19 ???
- Organic solvents, nutrition (oils), silicon (implants), drugs (bleomycin...)

# Pathogenesis of systemic sclerosis

- ✓ CD4+Th2 lymphocytes, macrophages and fibroblasts play an important role in the immunopathogenesis of scleroderma. Vascular damage (viruses, mechanical damage, drugs) triggers the development of SS. After endothelium damage, leukocytes and cells participating in reparation (mesenchymal lineage cells: pericytes and resident fibroblasts) are present at the site of injury.
- ✓ **Activation and proliferation of fibroblasts** is triggered due to cytokines (IL-1, TGF- $\beta$ ) produced by macrophages, CD4+Th2 lymphocytes. In addition, autoreactive V lymphocytes are also activated and produce autoantibodies (antinuclear antibodies, anti-centromere antibodies (localized form), topoisomerase antibodies, anti Scl70 antibodies (systemic disease)).
- ✓ Activated fibroblasts differentiate into **myofibroblasts** under the influence of TGF- $\beta$  and CTGF. A large amount of collagen type 1 and 3 is produced, which is deposited in the tissue, causing fibrosis.

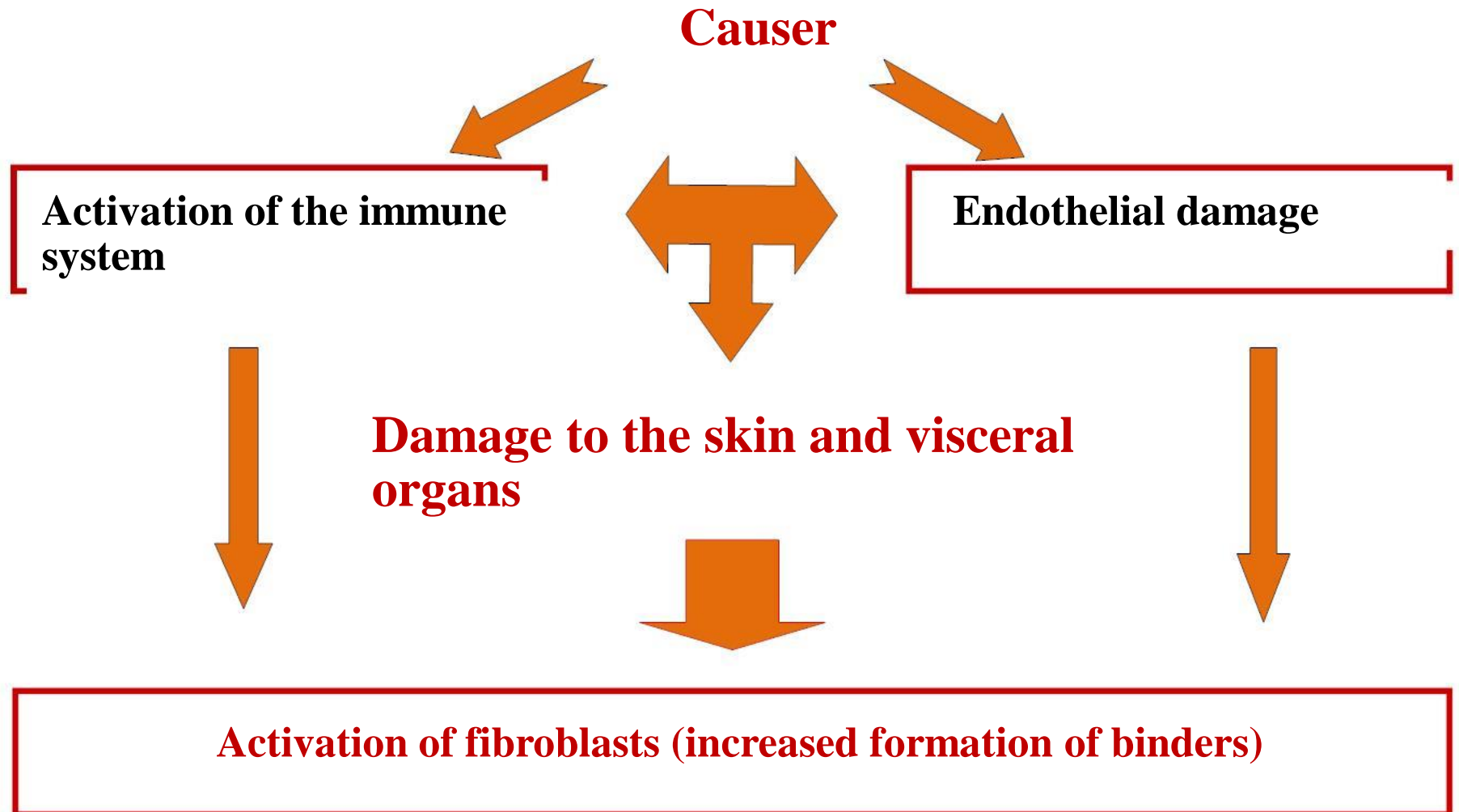
There are infiltrates of memory CD4+ T lymphocytes in the **skin** (Th1, Th2, Th17)

# Pathogenesis

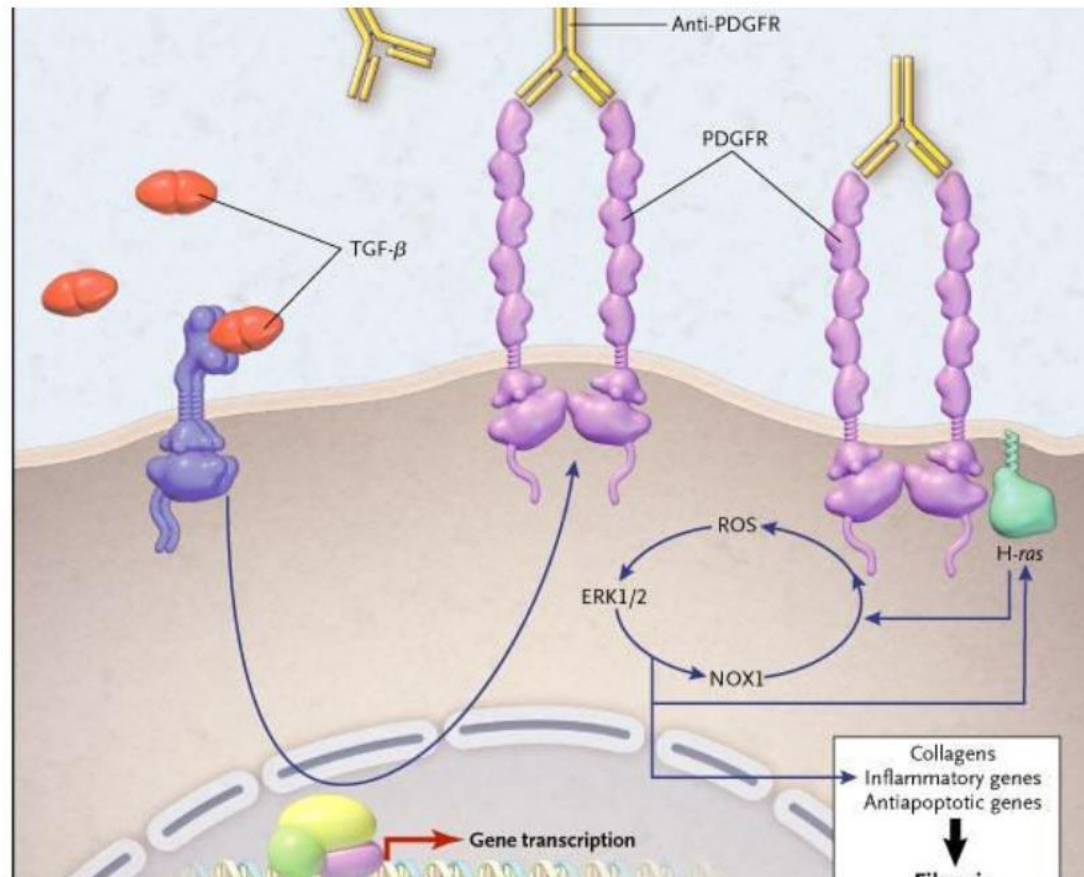




# Pathogenesis of systemic sclerosis



# Pathogenesis of systemic sclerosis



Selective regulation (**up-regulation**) receptors for PDGF (PDGFR) on fibroblasts in systemic sclerosis

# Classification of systemic sclerosis

*Diffuse cutaneous scleroderma* – changes in both the skin (body, face, extremities) and visceral organs.

*Limited cutaneous scleroderma* - changes both on the skin (distal from the elbow and knee, less often on the face) and on the visceral organs.

*CREST syndrome.*

*"Sine" scleroderma* - affects visceral organs without changes in the skin.

*"Overlap" syndrome* - at the same time there is lupus erythematosus, polymyositis...

*Early disease* - secondary Raynaud phenomenon + SS

# Diffuse cutaneous scleroderma

## **Changes on skin :**

- Raynaud's phenomenon is registered first, and swelling on the fingers, hands, and face is registered soon after.
- later the stage of fibrosis occurs with skin atrophy, hair loss, skin ulceration.

## **Changes in visceral organs:**

### ***-Lungs:***

- interstitial lung fibrosis, pulmonary hypertension.

### ***-Gastrointestinal system:***

- loss of appetite and weight, dysphagia, malabsorption, intestinal hypomotility, persistent diarrhea.

### ***-Kidneys:***

- renal crisis (anti-RNA polymerase III antibodies): progressive kidney damage, malignant hypertension.

### ***- Heart:***

- arrhythmia, myocardial fibrosis.

### ***- Locomotor system:***

- flexion contractures (knees, hands, shoulders).

# Limited cutaneous scleroderma

## **Changes on skin :**

- Raynaud's phenomenon is registered first, and only after a few years, fibrosis of the skin (distal from the elbow and knees, and rarely on the face) and telangiectasias on the fingers, lips and face are registered.

## **Changes in visceral organs:**

- **Gastrointestinal system:** dysphagia, gastroesophageal reflux.
- **Lungs:** pulmonary hypertension (rare).
- **Severe Raynaud's phenomenon** with the development of gangrene of the fingers.



# CREST SY

The prognosis is generally good

Anti-centromere antibodies

- Calcinosis (subcutaneous)
- Raynaud phenomenon
- Esophageal dysmotility
- Sclerodactylia
- Telangiectasias

# Raynaud phenomenon (pallor, cyanosis, hyperemia)



- diffuse painless swelling of the hands



# Scleroderma



# Clinical picture of systemic sclerosis

## TELEANGIECTASIS



# Clinical picture of systemic sclerosis

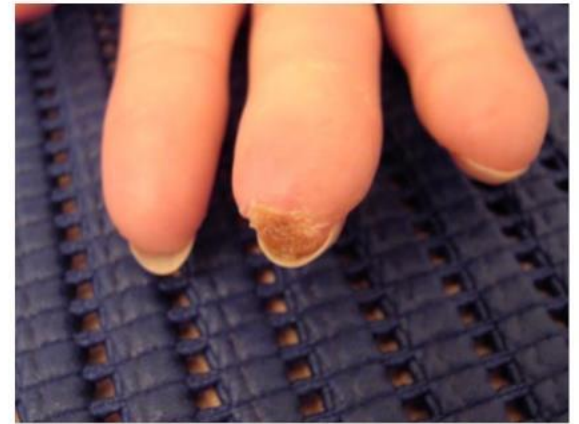
1. Shortened frenulum of the tongue
2. Tooth loss
3. Furrows around the lips
4. Atrophy of the skin around the lips and tip of the nose (bird's face)
5. Narrowed mouth opening





# Clinical picture of systemic sclerosis

Sores and scars





# Scleroderma - laboratory

- Diffuse cutaneous scleroderma - anti-ScL-70
- Limited cutaneous scleroderma and **CREST SY-**  
anticentromere antibodies
- Increased sedimentation, anemia, ANA,
- Hypergammaglobulinemia, RF

# Therapy

Therapy depends on the degree of activity and the clinical phenotype of the disease.

## *Raynaud phenomenon:*

Ca<sup>2+</sup> channel blockers, Angiotensin II receptor antagonists.

## *Limited Cutaneous Scleroderma:*

Proton pump inhibitors, treatment of Raynaud's phenomenon.

## *Diffuse cutaneous scleroderma:*

NSAIDs, corticosteroids, antifibrotics, immunosuppressants (Cyclophosphamide), IFN- $\gamma$

**Idiopathic inflammatory**

**Dermatomyositis and poliomyositis**

# Polymyositis and dermatomyositis

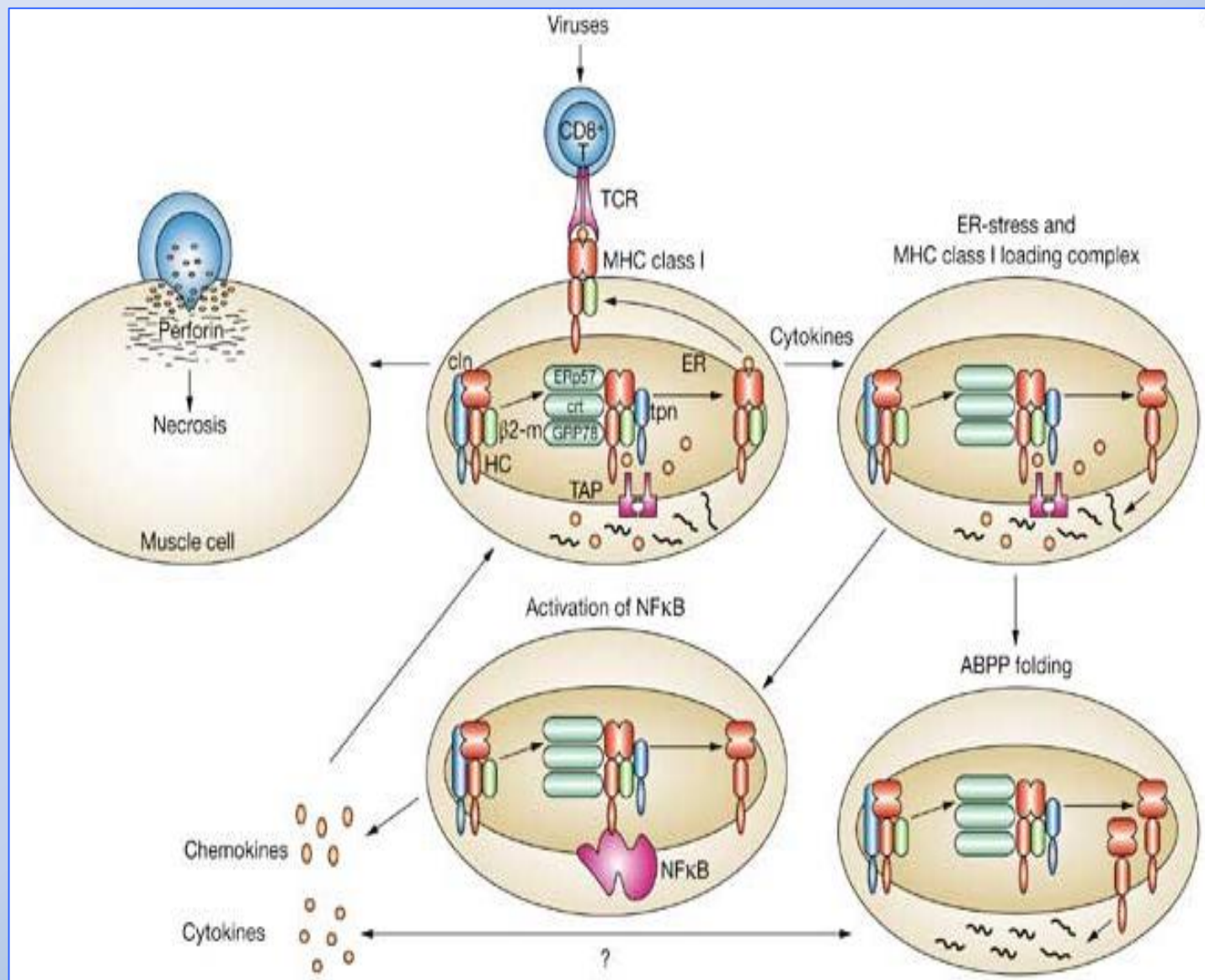
- Chronic inflammatory (autoimmune) muscle disease (polymyositis) with possible involvement of the skin (dermatomyositis)
- More often in women
- Genetic predisposition and the importance of infection for the development of polymyositis and dermatomyositis
  - HLA-DQA1, HLA-DRB1
- During 2020, a new autoantigen (eng - eukaryotic initiation factor 3 (eIF3)) was discovered

# Immunopathogenesis

- Autoreactive **cytotoxic CD8+ T lymphocytes** are responsible for muscle damage in polymyositis, which recognize (so far unknown) autoantigen expressed on muscle cells by MHC class I molecules and perforins and granzymes damage muscle cells. Due to the activation of CD8+ T lymphocytes, as well as under the influence of IFN- $\alpha$  produced by plasmacytoid dendritic cells activated by the virus, intracellular signaling pathways in myocytes are activated, resulting in the activation of the transcription factor NF $\kappa$ B. Many new MHC class I molecules representing new autoantigens are expressed on the myocyte membrane, which enables "de novo" activation of cytotoxic CD8+ T lymphocytes and disease progression.
- Activation and perivascular infiltration of **CD4+Th1 lymphocytes and B lymphocytes** are important in the immunopathogenesis of dermatomyositis. Formed immune complexes (autoantibodies/autoantigens) are deposited in the microvasculature and cause inflammation.



# Pathogenesis of polymyositis



# Systemic changes in idiopathic inflammatory myopathies

## System "target"

- **Skin** (dermatomyositis)
- **Joints** (arthritis)
- **Lungs** (shortness of breath, fibrosis, serum autoantibodies)
- **Gastrointestinal tract** (swallowing difficulties, ulcerations)

# Idiopathic inflammatory myopathy

*myo* = muscle; *-itis* = inflammation

- **Inflammatory myopathy** is the more commonly used name
- **Heterogeneous group** of autoimmune syndromes
- 
- **They are characterized by:**
  - inflammation of muscle tissue
  - accompanied by muscle weakness
- **Systemic complications**
- **Cause unknown** (idiopathic inflammatory myopathies)

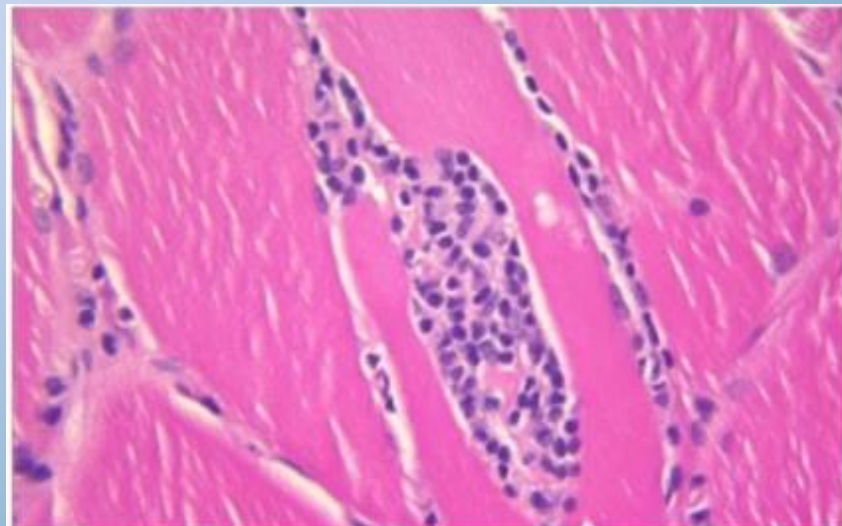
# Idiopathic inflammatory myopathy

## Clinical symptoms:

- **Progressive weakness of the proximal musculature**
  - ✓ neck muscle weakness
  - ✓ difficulty speaking nasal
  - ✓ regurgitation dysphagia
  - ✓ aspiration pneumonia
- **Skin changes** (heliotropic measles, Gottron's papules)

# Idiopathic inflammatory myopathy

- **Increased concentration of muscle enzymes in serum** (CK, ALT, AST, LDH, aldolase)
- **Myopathic changes on electromyography**
- **Pathohistological findings during muscle biopsy** (inflammation in muscle tissue)





# Clinical manifestation inflammatory myopathies

- **Many different forms**, which develop more quickly or more slowly
- **Weakness** - difficulty walking/climbing, combing, lifting objects
- **Severe fatigue that interferes** with normal activity
- **Skin rash or sores**
- **Joint pain or swelling**
- **Problems swallowing**
- **Shortness of breath or cough**
- **Fever**, sweating or weight loss

# Clinical manifestation inflammatory myopathies

## They can manifest themselves:

- in many ways affecting different
- parts of the body imitating man
- other diseases
- that is why they are difficult to diagnose

# Clinical manifestation dermatomyositis

**Gottron's papules:** erythematous, scaly changes on the extensive sides of the metacarpophalangeal joints and fingers

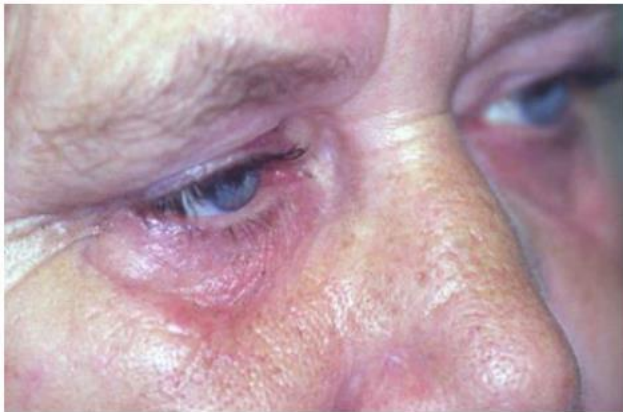
**Gottron's sign:** a rash at the skin level on the extensor sides of the elbow and knee, the outer part of the ankle joint



# Clinical manifestation dermatomyositis

1/3 of patients with dermatomyositis develop malignancy  
(within 5 years)

## Heliotrope rash



## Redness in the form of a scarf



## Periungual erythema



# Therapy

## ■ Corticosteroids

- Prednisone

## ■ Immunosuppressants

- Azathioprine
- MTX
- Cyclosporine



# Diagnostic criteria for idiopathic inflammatory myopathy

1. Progressive weakness of the proximal musculature
2. Increased muscle enzymes (CK, ALT, AST, LDH)
3. Myopathic changes on EMNG
4. Skin changes (heliotropic measles, Gautron's sign)
5. Pathohistology of muscle biopsy findings

## Bohan and Peter 1975.

- Certain diagnosis - 4 out of 5 criteria met
- Possible diagnosis - 2 out of 5

# Systemic diseases of connective tissues which **do not belong to defined entities**

20% the patient

undifferentiated  
SDCT

overlap  
syndrome  
SDCT

mixed connective  
tissue disease

# Undifferentiated SDCT

old name: collagenage, mesenchymopathy

- **A set of symptoms and signs and laboratory indicators**
  - located at SDCT
    - but they are not sufficient for the diagnosis of a clearly defined SDCT
    - or are located at multiple SDCT

# Overlapping syndrome of the SDCT

**Co-occurrence** of the main symptoms and/or signs of more than one SDCT

**Basic clinical features:**

**The most common clinical means:**

Raynaud's phenomenon, arthritis and scleroderodactyly

**The most common severe manifestations of the disease:**

Poliomyositis and fibrillizing arthritis

# Overlapping syndrome of the SDCT

- Sjogren's syndrome/SLE
- Systemic sclerosis/polymyositis
- Rhupus: RA/SLE

It means SLE + erosive polyarthritis, rheumatoid nodules



# Mixed connective tissue disease

## Special syndrome:

- features more SDCT
- with clearly defined serological specificity (detection of antibodies specific for ribonucleoproteins U1RNP)
- **Molecular homology** of the retroviral antigen or antigens of the influenza B virus and the protein that is part of the U1RNP molecule

# Vasculitis syndromes

## Definition

Inflammation and fibrinoid necrosis of blood vessels

- **Idiopathic** (unknown cause, primary autoimmune vasculitides)
- **Secondary** (infectious agents, drugs, hypersensitivity reactions, tumors...)

## Etiology/pathogenesis

- Cell damage or humoral immune response
- Inflammation leads to:  
narrowing or occlusion of the vascular lumen with  
ischemia, local aneurysm and possible rupture

## Epidemiology

Rarely occurs

# Which blood vessels can be affected?

Variations are great, any blood vessel can be affected:

- arteries
- arterioles
- capillaries
- venules
- veins


Vasculitis can cause damage to any organ or tissue

# Classification of vasculitis

dominant blood vessel	primary	secondary
Large arteries	giant cell arteritis Takayasu arteritis	Aortitis in RA Infectious (syphilis, TBC)
Middle arteries	Polyarteritis nodosa PAN M. Kawasaki	HVB Ubiquitous antigen Candida
Small blood vessel (ANCA +)	Wegener-ova granulomatosis Churg-Strauss-ov sy microscopic polyangitis	Vasculitis in RA, SLE, Sjogren's sy Drugs consumption HIV infection
Small blood vessel leukocytoclastic	Henoch-Schonlein's purple,	Drugs, HVC
vasculitis(hypersensitivity allergic vasculitis)	Cryoglobulinemia	

# Classification of vasculitis

Primary (autoimmune) and secondary (much more common)

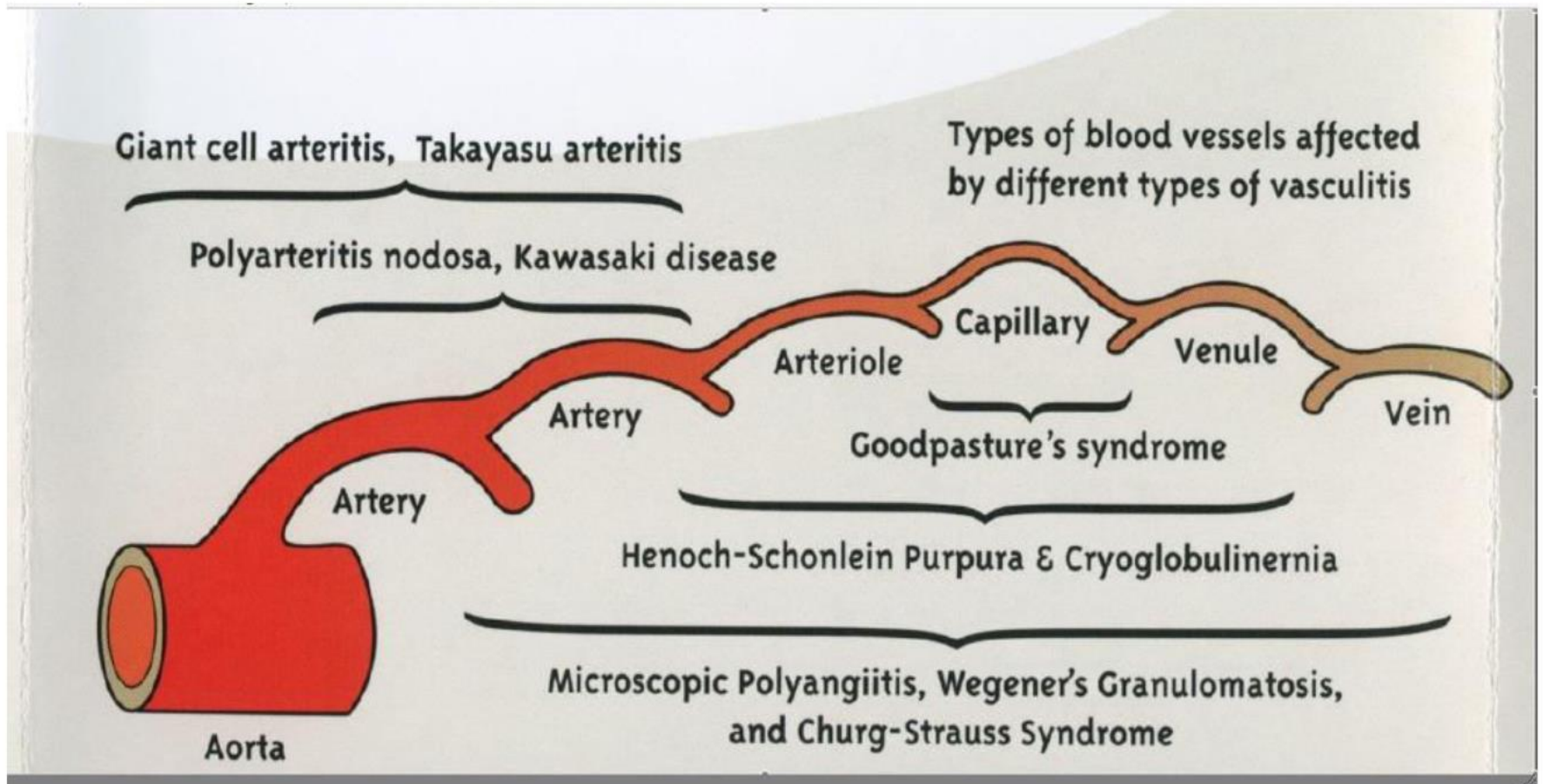
	<b>primary</b>	<b>secondary</b>
	<b>category</b>	RA, SLE, MCTD,
	<b>rheumatic diseases</b>	DM, RF, SS
	<b>inflammatory diseases</b>	HBV, HCV, SBE
	<b>cryoglobulinemia</b>	<b>secondary in myeloma, in lymphoma</b>

# Primary autoimmune vasculitis (according to the size of the blood vessel)

Blood vessel size	Disease
1-large blood vessels (aorta and aortic branches)	*Giant cell arteritis (GCA- PMR) *Takayasu's arteritis
2-Medium blood vessels (main visceral arteries)	*Polyarteritis nodosa (PAN) *Kawasaki disease
3-small blood vessels (venules, capillaries, arterioles and small arteries)	*Wegener's granulomatosis (WG) *Henoch-Schönlein purpura (HSP)



# Primary autoimmune vasculitis (according to the size of the blood vessel)



# Primary (autoimmune) vasculitis

- They can develop at any age
- They can be local or systemic
- Systemic can affect many organs and tissues
- Untreated local can progress to systemic forms.

# Clinical manifestation vasculitis syndrome

- The clinical manifestation of vasculitis is very diverse
- Two people with the same form may have different manifestations of the disease (symptoms).

# Clinical manifestation vasculitis syndrome

- skin rash
- fatigue
- fever muscle weakness
- headache unexpected
- weight loss muscle and joint pain
- chronic cough
- blood in the urine
- bleeding eyes
- changes in the ear
- changes in memory and movement coordination
- vision problems
- and other...

# Primary autoimmune vasculitis

- Polyarteritis nodosa
- Henoch-Schönlein purple
- Churg-Strauss syndrome
- Wegener-granulomatosis
- Thrombangitis obliterans (M.Burger)

# Polyarteritis nodosa (PAN)

- Vasculitis of medium and small blood vessels of unclear etiology and without confirmed genetic predisposition
- It has been proven that in 30% of patients, vasculitis is caused by the deposition of immune complexes (IC) containing antigens of the hepatitis V virus.



# PATHOGENESIS

- Immune complexes (IC) contain cationic antigens that bind to negatively charged components of the basement membrane of blood vessels and kidney glomeruli. IC is deposited in the subendothelium of blood vessels.
- ICs activate mast cells and basophils, which release vasoactive mediators that increase blood vessel permeability and IC deposition.
- IC, via Fc receptors, activate the complement system and neutrophils and macrophages. The release of free oxygen radicals, lysosomal enzymes and chemotactic substances from permanently activated cells causes damage to the walls of blood vessels and tissues.

# Clinical picture

- Temperature, malaise, weight loss
- Skin:
  - livedo reticularis, subcutaneous nodules, leg ulcers.
- Peripheral nerves: primarily sensory disorders develop.
  - mononeuritis multiplex – peroneus, tibialis, medianus...
- Gastrointestinal system: periumbilical pain (30 min. after eating).
- Kidneys: renin-mediated hypertension, hematuria.
- Heart: pericardial effusion, infarction.
- Cutaneous PAN without systemic disease manifestations

# Diagnosis

- Clinical picture

- Laboratory findings

anemia

high sedimentation

- Histology

vasculitis

absence of granuloma

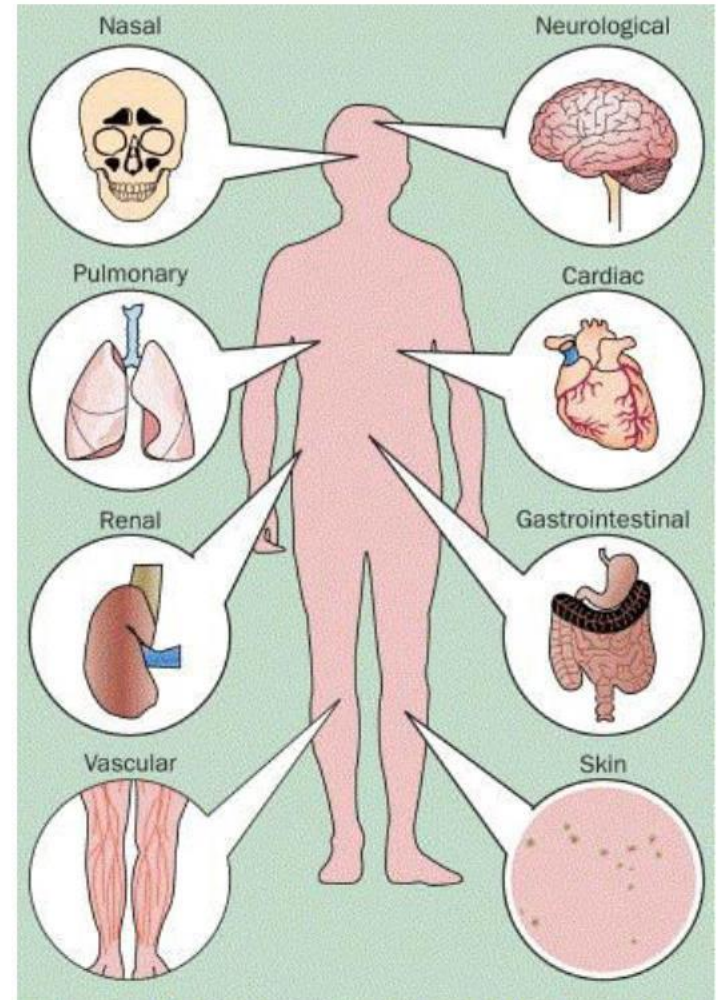
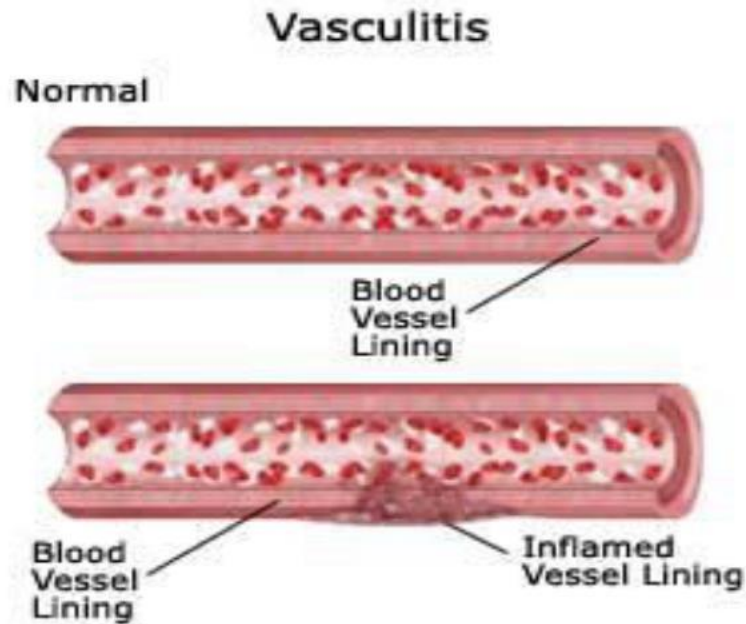
- Angiography

microaneurysms in the spleen and kidneys

# Therapy

- Simultaneous application:
- immunosuppressive drugs and high doses of corticosteroids
- Cyclophosphamide 3-6 months. Pronison
- then Azathioprine for another 12 months. 6-12 months.
  
- When using Cyclophosphamide every 15 days, a mandatory WBC check ( $<4000/\text{ml}$ )
  
- Antiviral therapy
- lamivudine
  
- Pegylated interferon-alpha 2b
  
- Plasmapheresis

# Henoch-Schönlein purple (HSP)



# Pathogenesis Henoch-Schönlein purple

- Consequence of type II and III hypersensitivity caused by drugs (penicillin, aspirin...) and infectious agents ( $\beta$  hemolytic streptococcus). The most common are upper respiratory tract infections

- IgA1 antiendothelial antibodies

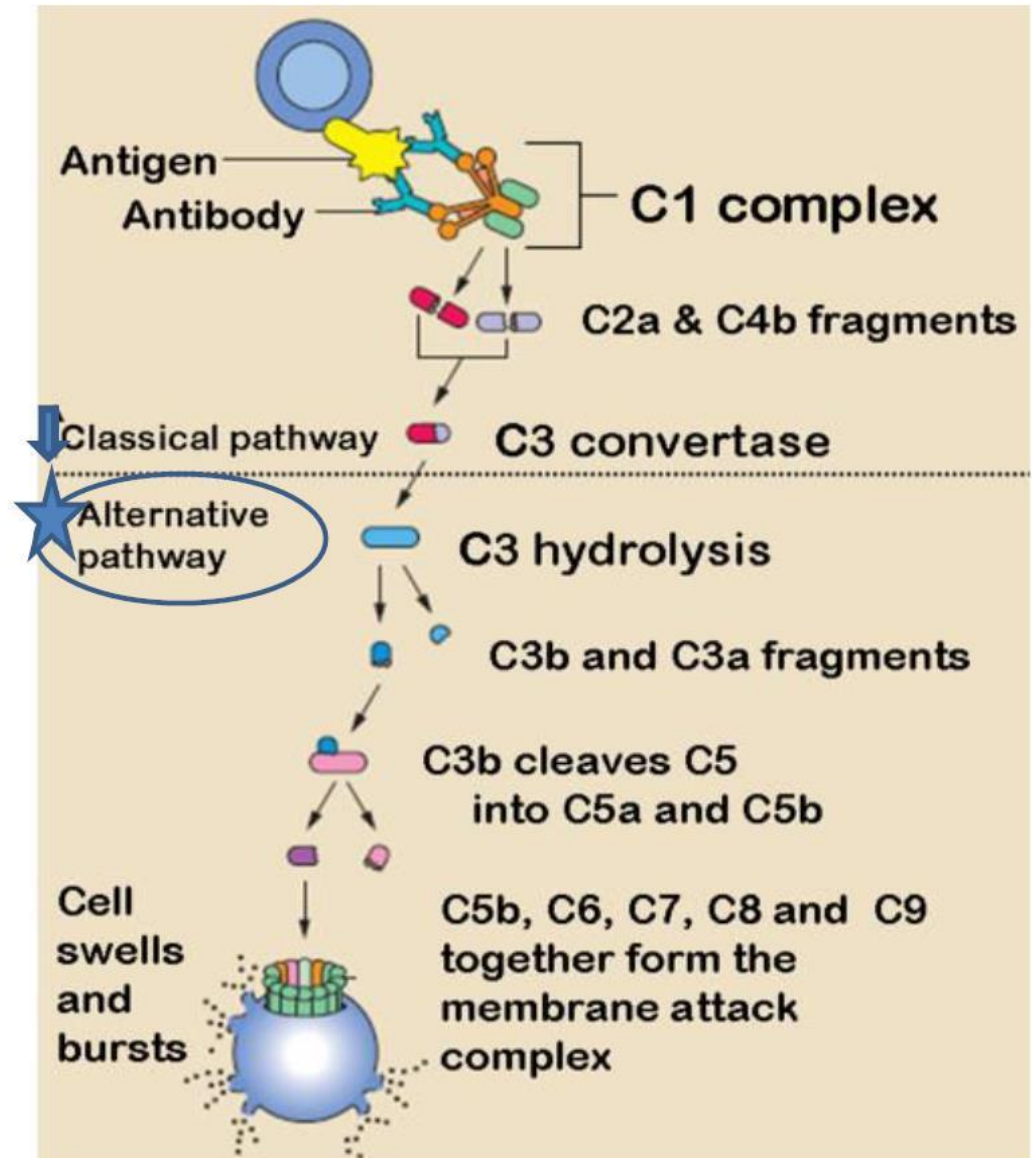
Polymeric - pIgA1 immune complexes in IgA vasculitis with nephritis and IgA nephropathy

- (skin, GIT, glomerular capillaries)



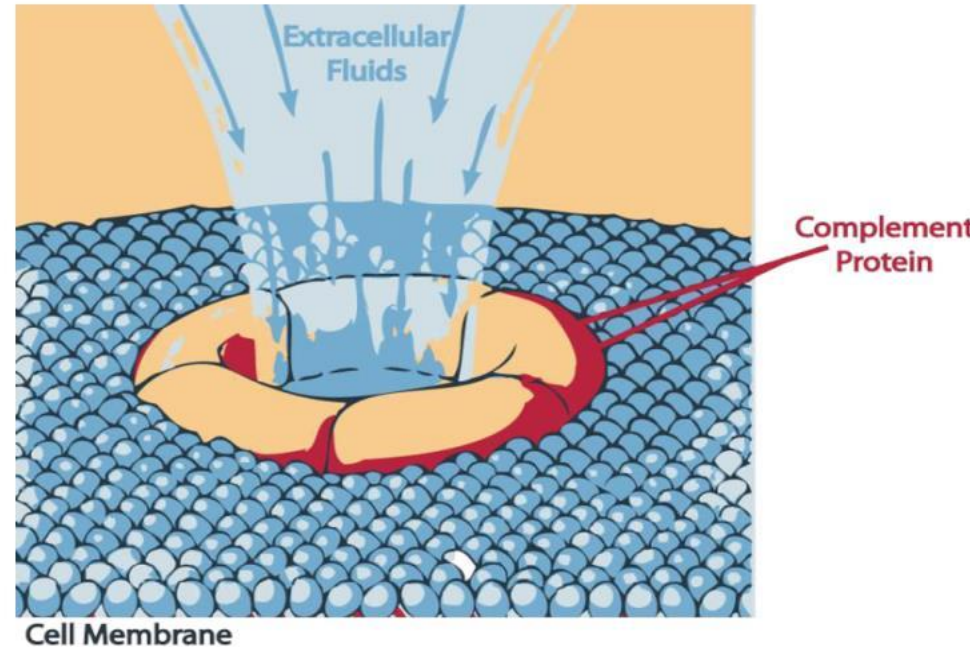
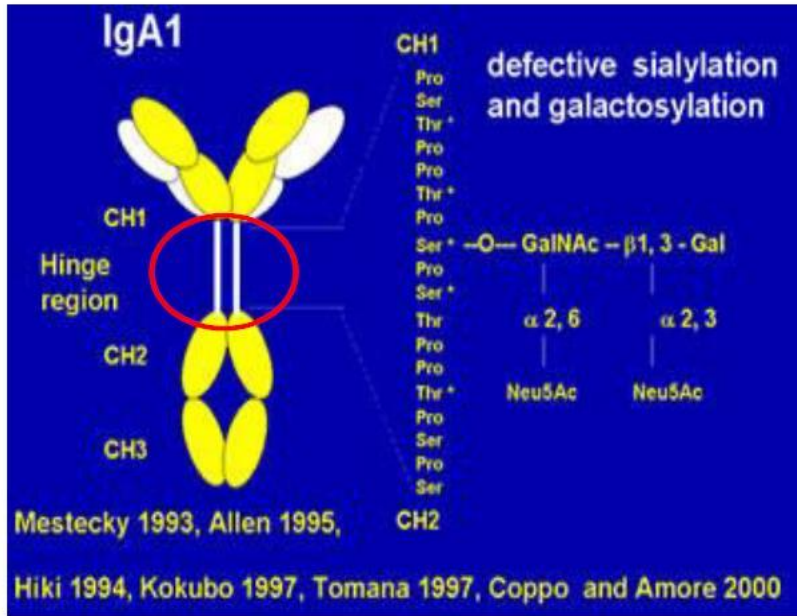


# Pathogenesis Henoch-Schönlein purple



# Pathogenesis

## Henoch-Schönlein purple



↑IgA synthesis  
↓ IgA elimination

Repeated exposure to antigens and mucosal immunity defect results in the aggregation of abnormally glycosylated **IgA1 - pIgA1**



↑CIC production and ↑ IgA R and C deposition in capillaries and mesangium – cell destruction and inflammation



# Clinical manifestation

## Henoch-Schönlein purple

- Palpable purpura
- Arthralgias
- Gastrointestinal symptoms (abdominal pain)
- glomerulonephritis



A



B

# Churg-Strauss syndrome

- Systemic necrotizing vasculitis **granulomas**
- Can affect small and large blood vessels  
(**vasculitis**)
- often affects the lungs
- It is associated with **asthma** and eosinophilia
- Symptoms; fatigue, night sweats, fever, myalgia

# Wegener's granulomatosis

- ANCA (antineutrophil cytoplasmic antibodies) associated vasculitis (AVV) of small blood vessels
- Systemic necrotizing vasculitis
- Genetic predisposition and the influence of external factors contribute to the loss of self-tolerance



# Genetic predisposition and environmental factors

- Genes for: Fc $\gamma$ RIIB, CTLA-4,  $\alpha$ 1-antitrypsin (ATT)..
- Microorganisms???
- Silicon



# PATHOGENESIS

- c-ANCA (antineutrophil cytoplasmic antibodies) – anti serum proteinase 3 antibodies (PR3) mainly of the IgG class. The enzyme is present in neutrophils and macrophages
- ↑ of activated CD4+ Th1, monocytes and V lymphocytes
- production of Th1 cytokines: IFN- $\gamma$ , TNF
- production of M1 cytokines: TNF, IL-12
- ANCA secretion, antigen presentation
- TNF ↑ translocation and expression of PR3 on the membrane of neutrophils; interaction with extracellular ANCA
- ANCA ↑ activation and neutrophil degranulation
- The release of free oxygen radicals, lysosomal enzymes and chemotactic substances from permanently activated neutrophils cause damage to the endothelium of blood vessels.
- PR3 and chemotactic substances → endothelial cells to produce IL-8
- PR3 ↑ expression of VCAM-1 on endothelial cells which promotes ↑ the adhesion of neutrophils and monocytes to the endothelium.

# PATHOGENESIS

- Necrotizing granulomas in the respiratory system
- Necrotizing vasculitis of arteries and veins
- Segmental glomerulonephritis

# Clinical manifestations

- Nasal manifestations: >90% of patients
  - bleeding, obstruction, perforation of the septum,

saddle nose



- Destructive changes in sinus bones
- Subepiglottic stenosis (stridor)
- Hearing impairment:
  - conduction disorder (otitis media);
  - facial paralysis
- Arthritis and arthralgia (large joints)

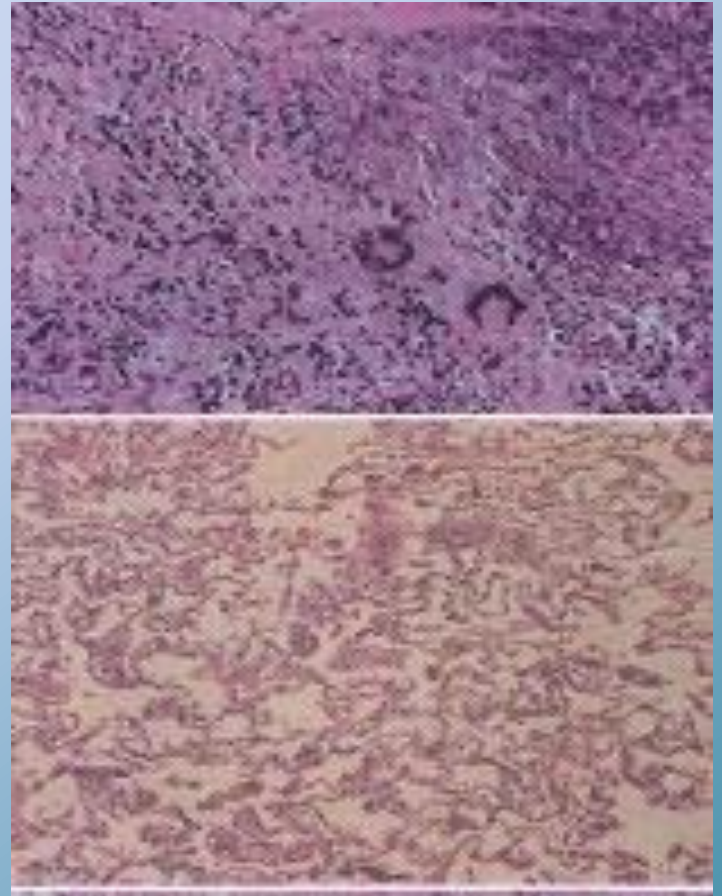
## ■ Ocular lesions

- ptosis (retrobulbar mass)
- vision loss (optic nerve ischemia)
- necrotizing scleritis, ulcerative keratitis, uveitis



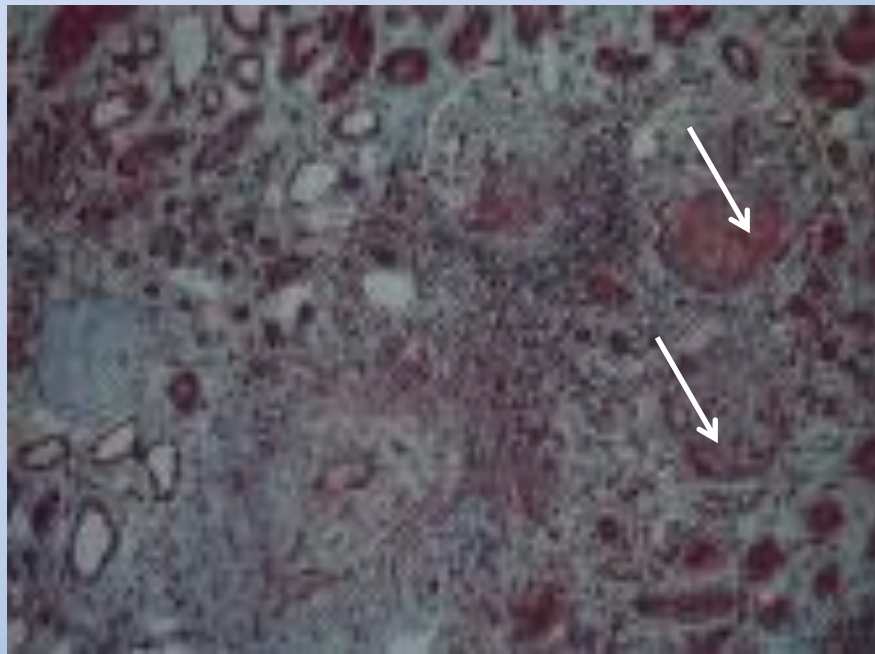
## ■ Damage to the respiratory tract

- from the presence of asymptomatic nodules to severe pulmonary hemorrhages





# ■ **Kidney damage** - proteinuria, hematuria, renal insufficiency





# Diagnosis

- Clinical manifestations
- First, IF, and then in the case of a positive finding, confirmation with an ELISA test
  - Anti-neutrophil cytoplasmic antibodies - ANCA
    - present C-ANCA (serine proteinase 3 PR3) in 80-90% of patients
- Definitive diagnosis is made by biopsy

# Therapy

- Simultaneous application:
  - immunosuppressive drugs and high doses of corticosteroids
  - Cyclophosphamide 3-6 months. Prednisone
  - then Azathioprine for another 18 months.
- When using Cyclophosphamide every 15 days, a mandatory WBC check ( $<4000/\text{ml}$ )
- Tests:
  - - IVIG
  - - Soluble TNF inhibitor
  - - Plasmapheresis

# Arteritis giant cell

- Another name: temporal arteritis
- Chronic inflammation of large blood vessels, especially the carotid artery and its branches
- The disease affects arteries rich in elastic fibers
- Granulomatous inflammation most represented in the media
- Lymphocytes, epithelioid and giant cells dominate

# *Thrombangitis obliterans* (M.Burger)

- **Definition:** Inflammatory, occlusive disease of small and medium-sized arteries and veins of the extremities
- The **etiology** is unknown, there are several theories:
  - allergic reaction to nicotine in genetically predisposed (HLAA9 and B6)
  - autoimmune reaction to collagen type I and III in blood vessels

# *Thrombangitis obliterans*

## **Pathophysiology:**

- segmental arteritis without calcifications and thrombophlebitis of superficial veins, which histologically correspond to panarethritis or panphlebitis (infiltration by lymphocytes, fibroblasts and giant cells)
- inflammatory processes spread perivascularly and affect the artery, vein and nerve
- thrombosis of the affected blood vessels occurs

# *Thrombangitis obliterans*

- Thrombangiitis obliterans

Diminished blood supply causes damage and death of tissue

