Chronic inflammation

Outcomes of acute inflammation: progression to **chronic inflammation**

- Chronic inflammation may follow acute inflammation **if** the **offending agent** is **not removed**

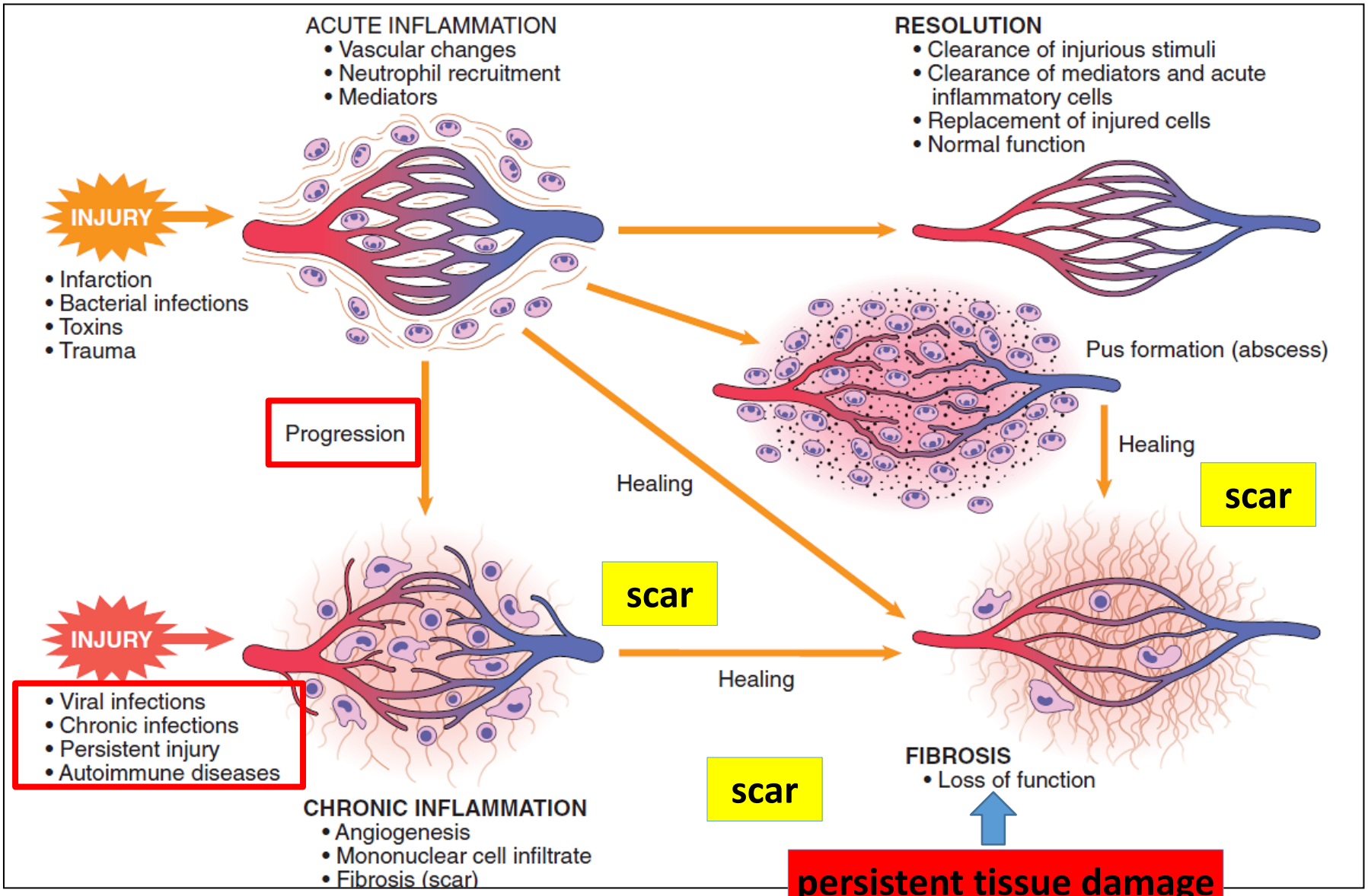
- Factors such as the **extent** of the initial and continuing tissue injury and the **capacity** of the affected tissues **to regrow**, influence the possible outcomes of chronic inflammation:

  - **restoration** of tissue **normal structure** and **function**
  - healing by **scarring**

Chronic inflammation

- Inflammation of prolonged duration (**weeks to years**) in which continuing **inflammation**, **tissue injury**, and **healing** (often accompanied by **fibrosis)** proceed **simultaneously**
- Characterized by:
  - infiltration with mononuclear cells, including **macrophages**, **lymphocytes**, and **plasma cells**
  - **tissue destruction**, largely induced by the products of the inflammatory cells
  - **repair**, involving new vessel proliferation (**angiogenesis**) and fibrosis

Outcomes of acute inflammation



Chronic inflammation

- Chronic inflammation often occurs **if the acute response fails** (progression)

- Alternatively, **some forms of injury** (e.g., immunologic reactions, some viral and bacterial infections) engender a **chronic inflammatory response from the outset** [*ab initio*], showing mild, if any, signs of acute reaction

Chronic inflammation

- **Mild forms** of chronic inflammation may underlie **the pathogenesis of many diseases** that are not conventionally thought of as inflammatory disorders. Examples of such diseases include:

  - **neurodegenerative disorders**, such as Alzheimer disease
  - **atherosclerosis**
  - metabolic syndrome and the associated **type 2 diabetes**
  - **some forms of cancer**, in which the inflammatory reaction promotes tumor development

Pathologic situations showing features of chronic inflammation (1)

1. **Persistent infections** by microbes that are **difficult to eradicate**, such as *Mycobacterium tuberculosis*, *Treponema pallidum* (the causative organism of syphilis), and certain viruses and fungi

1. These microorganisms elicit a **T lymphocyte–mediated** immune response

Pathologic situations showing features of chronic inflammation (2)

2. **Immune-mediated inflammatory diseases**, such as:

   - **hypersensitivity diseases**, including **allergic diseases**, caused by excessive activation of the immune system
   - **autoimmune diseases** (immune reactions against components of authologous tissues)

- Immune-mediated diseases may show morphologic patterns of **mixed acute and chronic inflammation**

Immune-mediated diseases will be treated later in the section «Immunopathology»

Pathologic situations showing features of chronic inflammation (3)

3. **Prolonged exposure to potentially toxic agents**, such as:

- **non degradable exogenous materials** [e.g. inhaled particulate silica, which can induce a chronic inflammatory response in the lungs (silicosis)]
- **cigarette smoke** components
- **endogenous agents** such as cholesterol crystals, which contribute to atherosclerosis

Morphological patterns of chronic inflammation

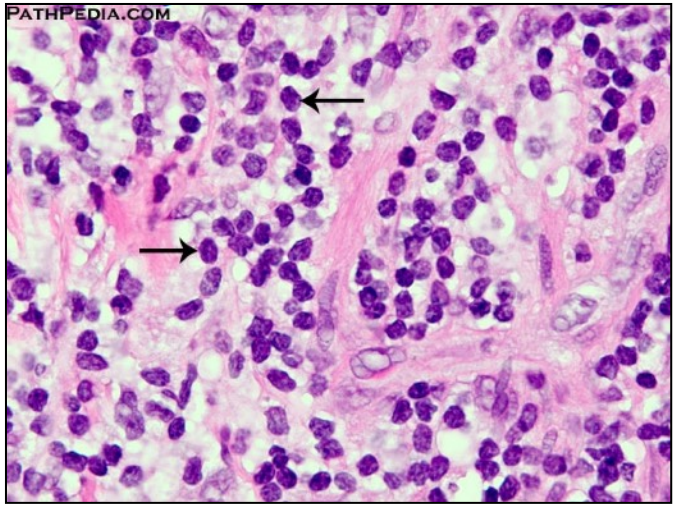
Chronic inflammation usually exhibits two main patterns:

- **diffuse**: inflammatory cells invade the tissue and disseminate (randomly)
- **granulomatous**: inflammatory cells form defined structures called **granulomas**

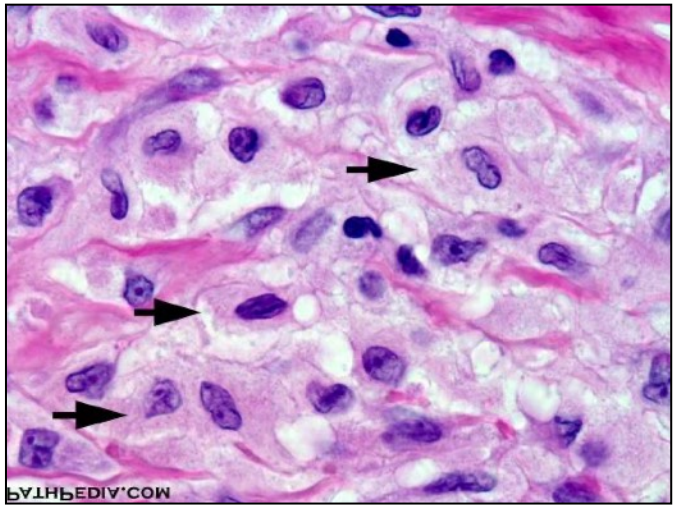
Viral hepatitis

Diffuse chronic inflammation

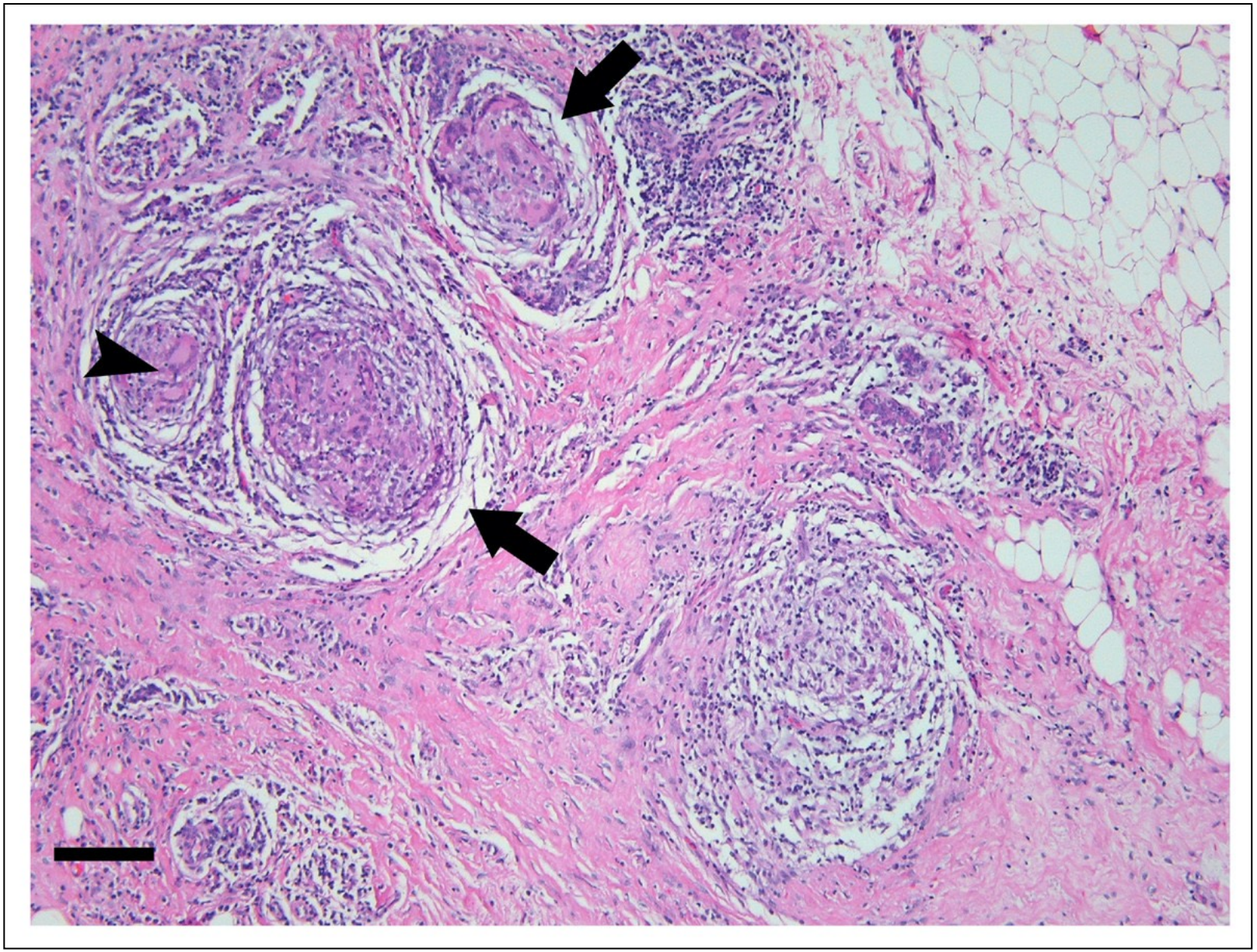
lymphocytes



macrophages



Granulomatous inflammation



Granulomatous inflammation

- Granulomatous inflammation is characterized by **aggregates** (the so called **granulomas**), of activated **macrophages** showing **different stages of differentiation** [epithelioid cells*, giant cells**]

- Depending on the noxious stimulus, **lymphocytes**, **plasma cells** and **eosinophils** can partake to granuloma structure. Older granulomas may have a **rim of fibroblasts and connective tissue**

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* **epithelioid cells** are **activated macrophages** with pink, granular cytoplasm and indistinct cell boundaries, resembling epithelial cells

** Frequently, multinucleate **giant cells**, showing a large mass of cytoplasm and many nuclei originating from the fusion of multiple activated macrophages, are found in granulomas

Granulomatous inflammation

- The formation of a granuloma effectively "walls off" the offending agent and is therefore a useful defense mechanism

- **Granuloma** formation **does not always lead to eradication of the causal agent**, which is frequently resistant to killing or degradation

- **Granulomatous inflammation**, with subsequent fibrosis, may even be **the major cause of organ dysfunction** in some diseases, such as tuberculosis

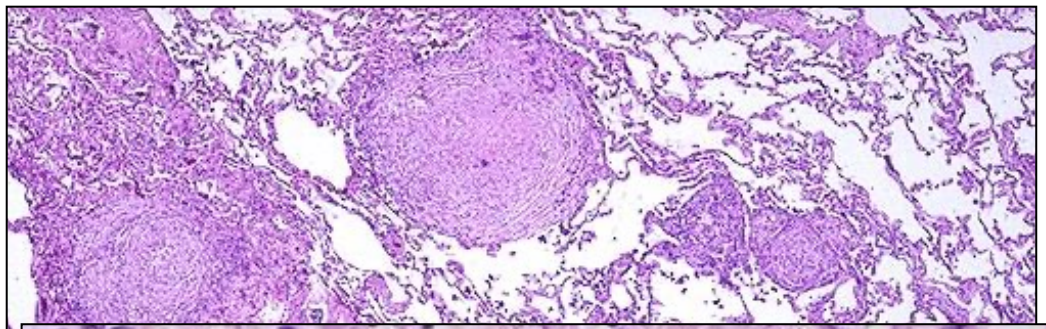
Types of granulomas

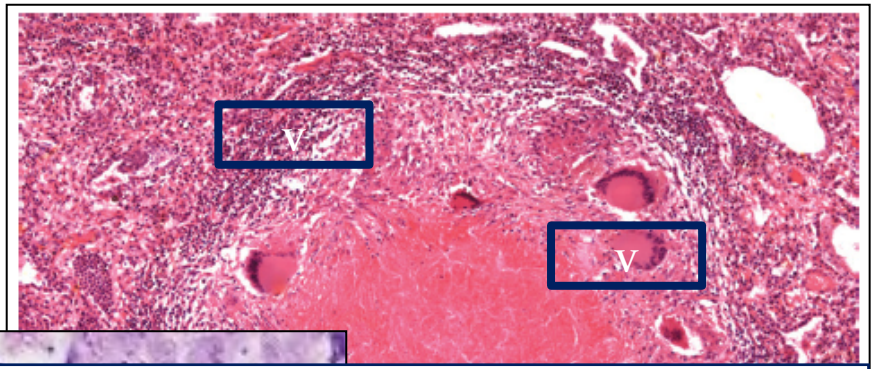
- **(1) Immune granuloma**: originates from persistent T-cell responses to certain microbes (such as *Mycobacterium tuberculosis, Treponema pallidum,* or fungi), in which **T cell–derived cytokines** (e.g. IFNγ) are responsible for **chronic macrophage activation**

- **Tuberculosis** is the prototype of a granulomatous disease caused by infection

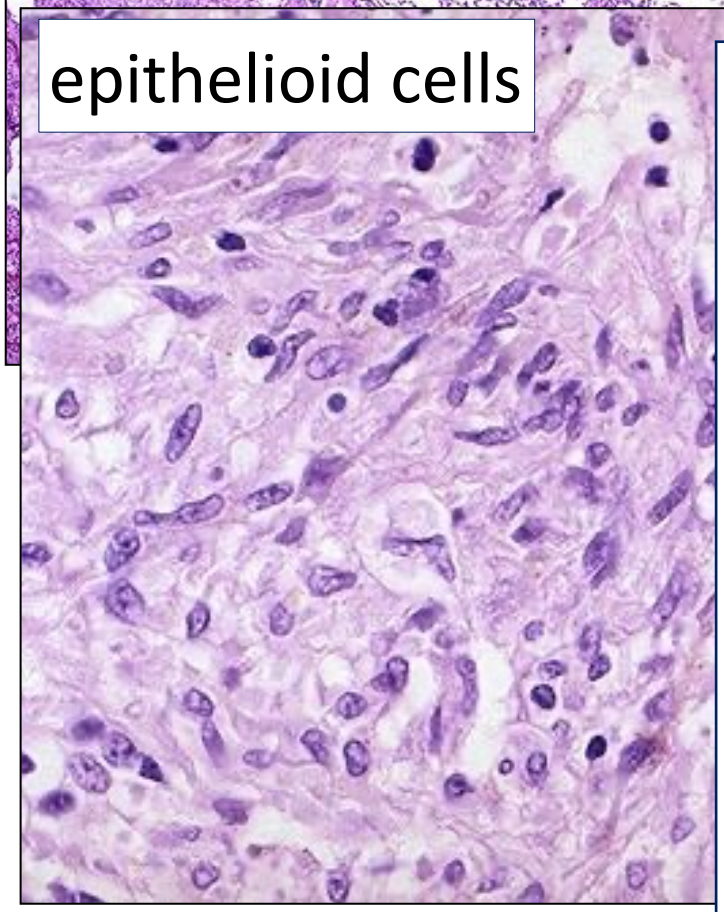
- The aggregates of epithelioid macrophages are surrounded by a collar of lymphocytes; the necrotic material at the centre of the granuloma appears as structureless, with complete loss of cellular details (***caseous necrosis***)

Granuloma of **tuberculosis** in the lung

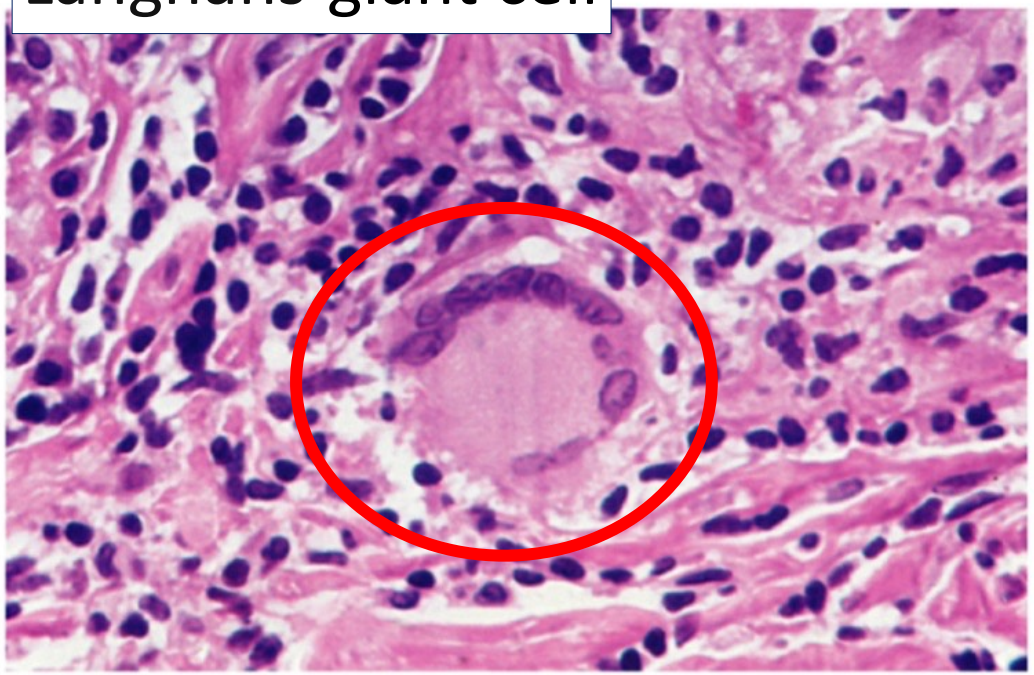




epithelioid cells



Langhans giant cell



Rubin, Patologia

Other types of granulomas

- **(2) Foreign body granulomas**: develop in response to relatively inert foreign bodies (e.g., **suture**, **splinter**, **prosthetic fragments**). Absence of necrotic area, few lymphocytes

- **(3) granulomas caused by inhaled thin dusts** [such as crystalline **silica**] can stimulate granuloma formation. **Intense fibrotic reaction** with massive collagen deposition is a typical feature of **silicosis**, a severe lung occupational pathology characterized by progressive respiratory failure

The “dark side” of inflammation: leukocyte-induced tissue injury

- Under several circumstances, the mechanisms that function to eliminate microbes and damaged tissues (the **physiologic role** of inflammation) are also capable of damaging normal tissues (the **pathologic consequences** of inflammation)

Leukocyte-induced tissue injury

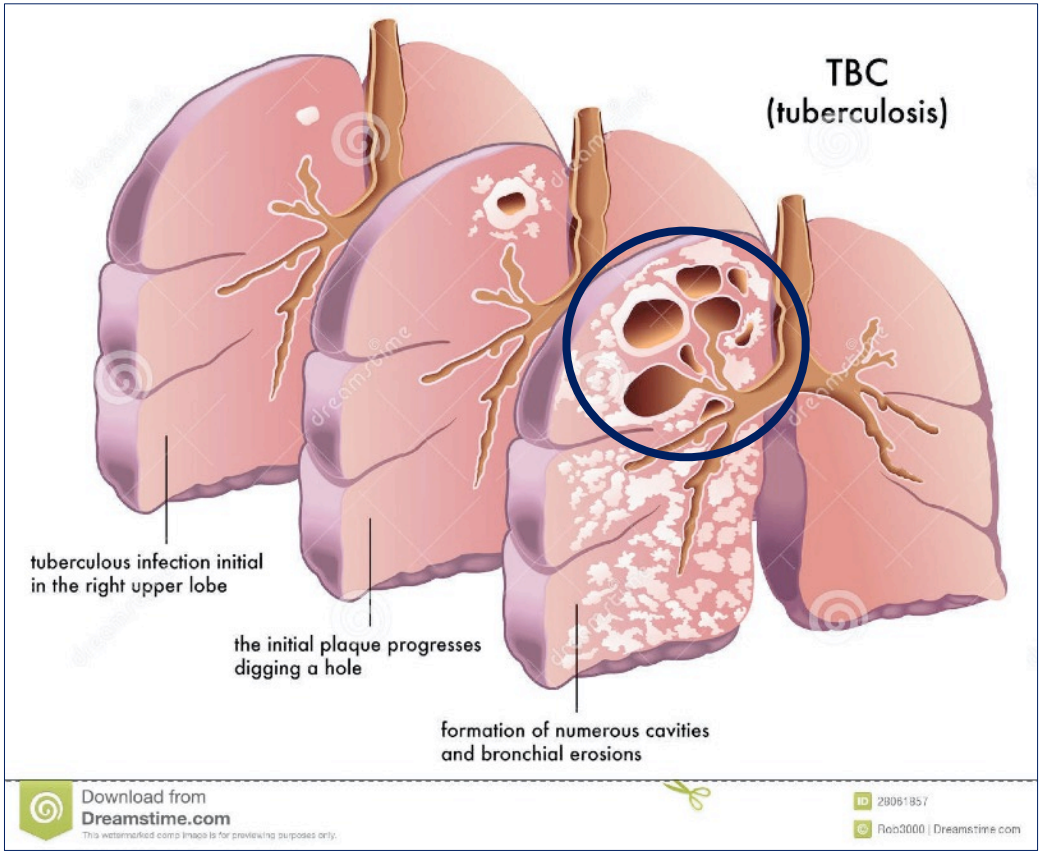
- Leukocytes - mostly polymorphonuclear cells, monocytes and macrophages - are capable of secreting potentially harmful substances such as **degradative enzymes** and **ROS**

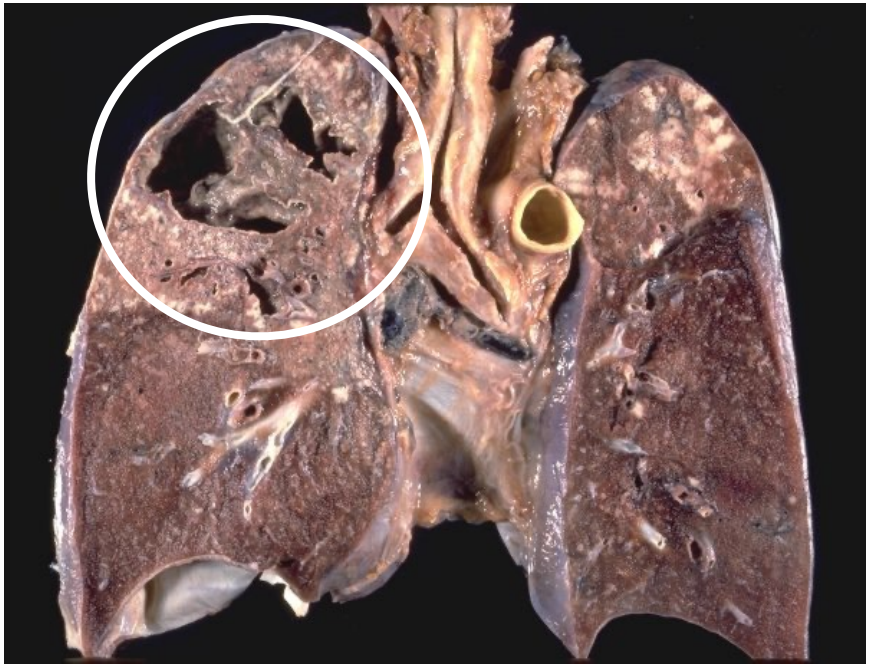
- Once the **leukocytes** are **activated**, their effector mechanisms **do not distinguish** between **offender** and **host**

- If **unchecked**, or **inappropriately** directed **against host tissues**, leukocytes themselves become the main offenders

When may leukocytes damage host tissue? (1)

1. in **certain infections** that are **difficult to eradicate**, such as tuberculosis and some viral diseases, the inflammatory response contributes more to the pathologic process than does the microbe itself

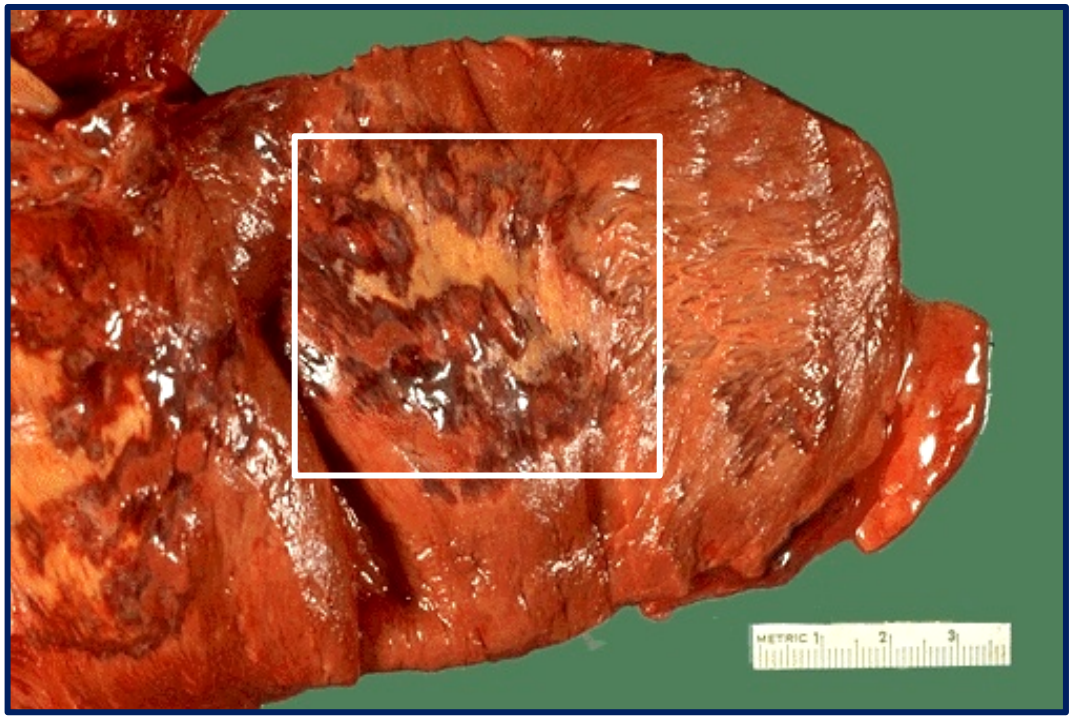




prominent **erosion** of lung parenchima in TBC

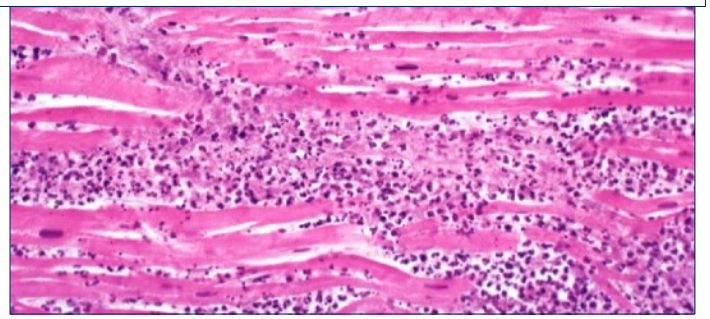
When may leukocytes damage host tissue? (2)

2. as a normal attempt to clear damaged tissues, such as **after a myocardial infarction**, inflammation may **prolong and exacerbate the injurious consequences** of the ischemia

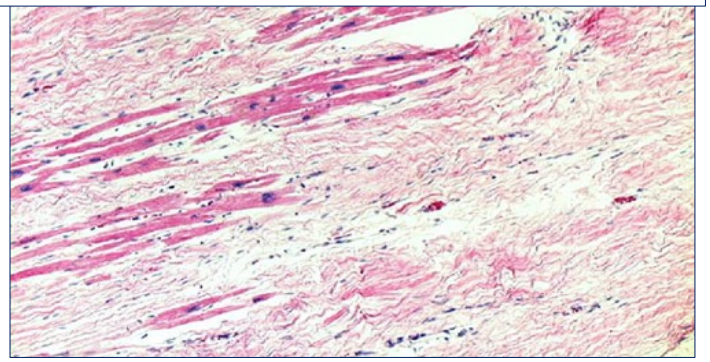


The center of the infarct contains necrotic muscle that appears **yellow-tan**. A zone of red hyperemia surrounds the necrotic area

quick response: myriad neutrophils invade necrotic myocardium

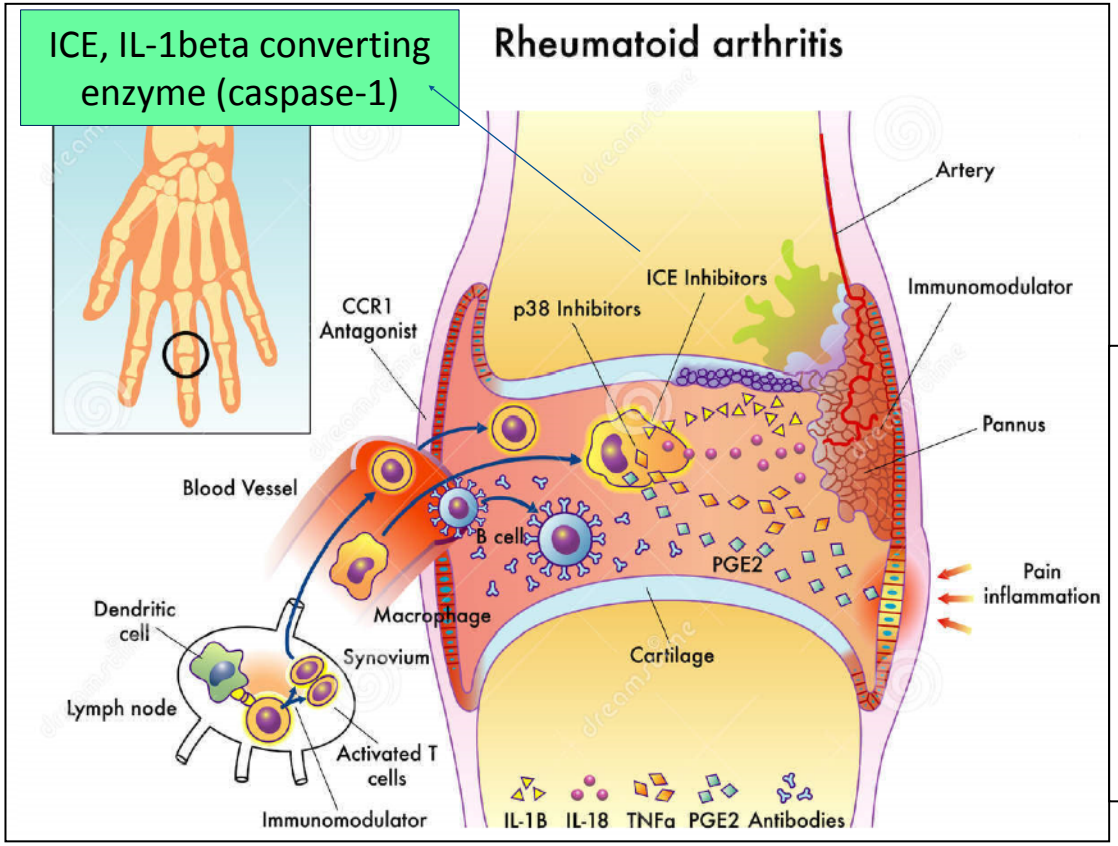


15 days later: collagen fibers substitute dead myocardiocytes



When may leukocytes damage host tissue? (3)

3. when the inflammatory response is **inappropriately directed against host tissues**, as in certain **autoimmune diseases** (such as **rheumatoid arthritis**) or when the host **reacts excessively** against nontoxic environmental substances, as in **hypersensitivity reactions**



Rheumatoid arthritis is a **chronic** inflammatory disorder that affects joints. As an **autoimmune** disorder, RA occurs when the immune system mistakenly attacks body's tissues

Inflammed synovial tissue (synovitis)

- Inflammatory cell infiltration: T cells, B cells, neutrophils, macrophages and plasma cells

- Production of:

ROS, cytokines and proteases

Examples of diseases with significant leukocyte-induced injury

ACUTE

- Asthma
- Septic shock
- Vasculitis

CHRONIC

- Arthritis
- Atherosclerosis
- Chronic lung diseases (**Cystic Fibrosis**)
- Inflammatory bowel disease (**Crohn's d.**)

Anti-inflammatory therapies

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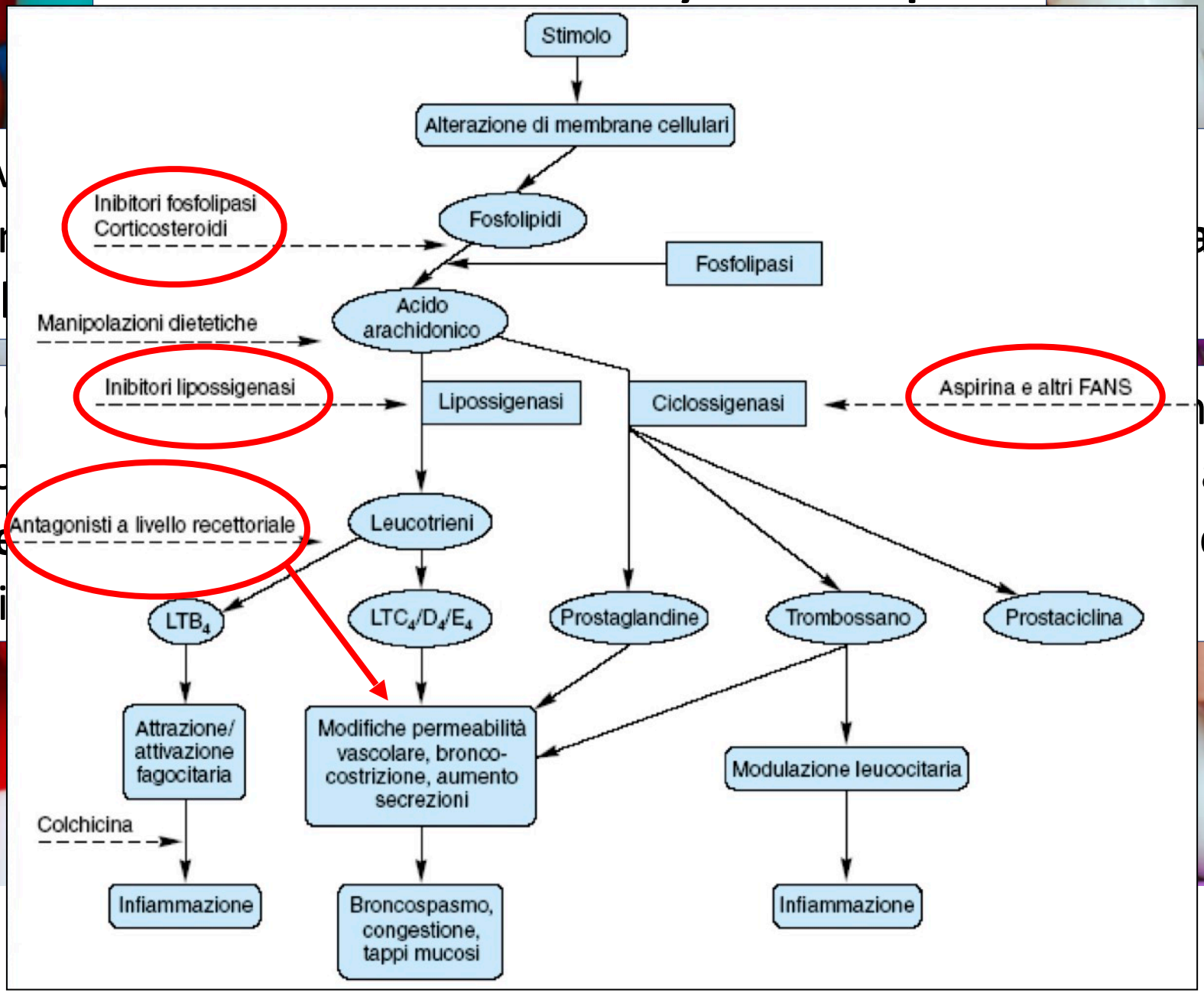
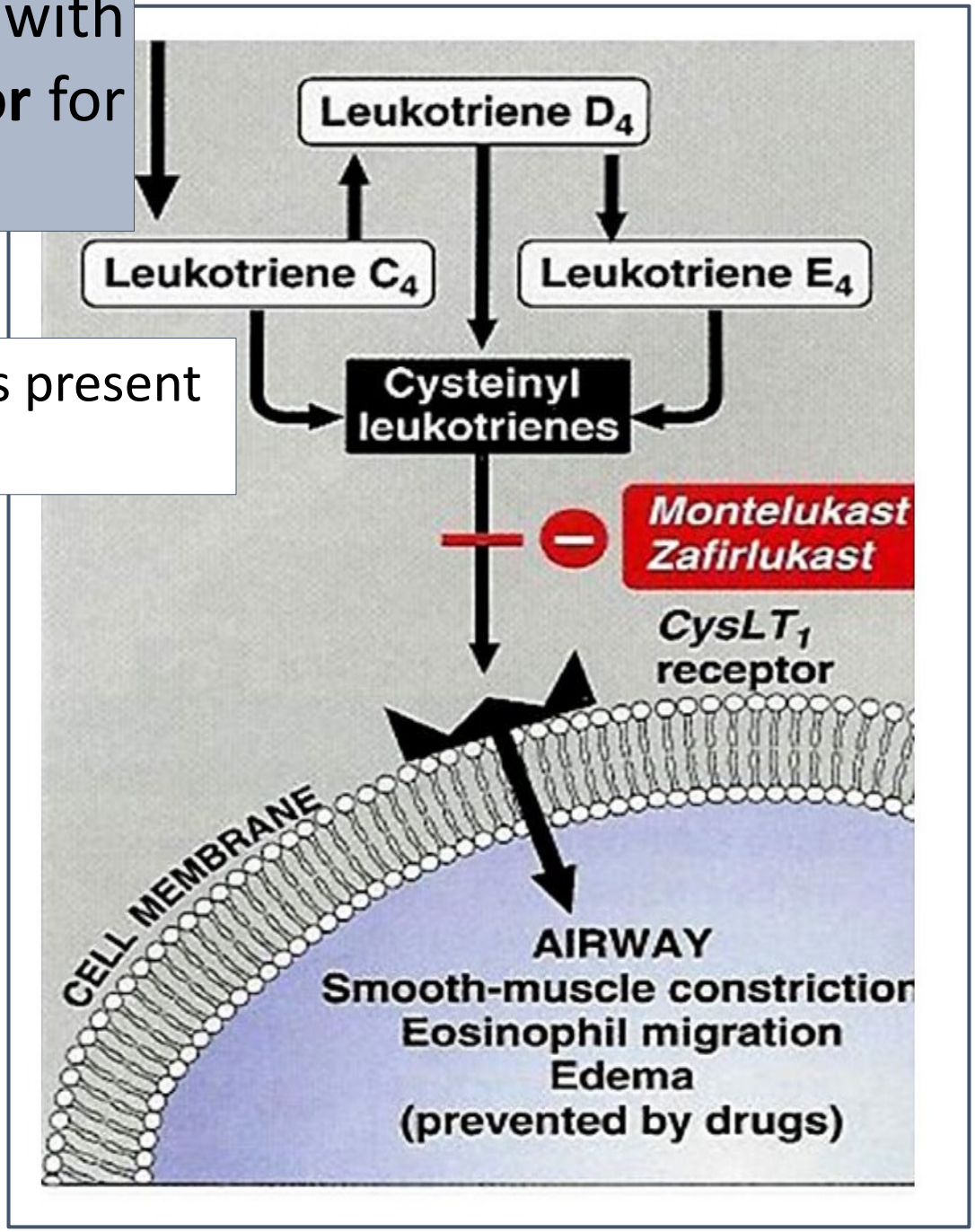


Treatment of **ASTHMA** with drugs **blocking the receptor** for **cysteinyl leukotrienes**

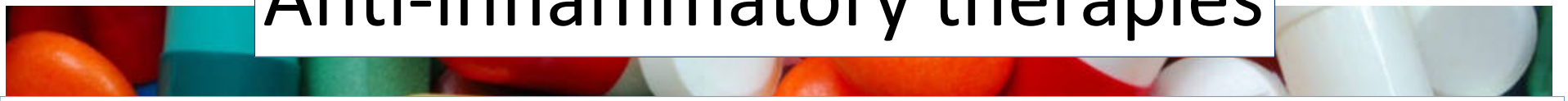
amino acid cystein is present in their structure



Anti-inflammatory therapies

- Several dozens of anti-inflammatory drugs are available as to dampen the deleterious effects of **prolonged** and **overactive** inflammation
- The **vast majority** of them act by **interfering** with the biochemical **pathways** that generate **cell-derived inflammatory mediators**, such as some powerful metabolites of arachidonic acid (e. g. **steroidal and non steroidal drugs**)
- By exploiting the continous improvements in pharmaceutical biotechnologies, **new-generation of anti-inflammatory therapies** are designed and many are already applied in clinical trials

Anti-inflammatory therapies



- Several **novel drugs** showed potent clinical effects in **chronic inflammatory diseases**. They include:
  - small molecules interfering with intracellular signaling pathways (e. g., inhibitors of **kinase-dependent synthesis of proinflammatory citokines,** such as **JNK, p38**)
  - **therapeutic antibodies** that are **directed against** extracellular targets, such as **leukocyte adhesive molecules** and **pro-inflammatory cytokines and/or their receptors**.
  - recently, an orally administered **antisense nucleotide against SMAD7**, an endogenous **inhibitor of** the immunosuppressive, anti-inflammatory cytokine **TGF-β1**, was successfully used in active chronic inflammations

Transforming growth factor-β (TGF- β)

- **Anti-inflammatory cytokine** produced by and affecting many different cell types
- Homeostatic role in **regulation of inflammation** and wound healing following infection or injury
- **Inhibits** activity of many immune cell types

TGF-β1 signaling pathway

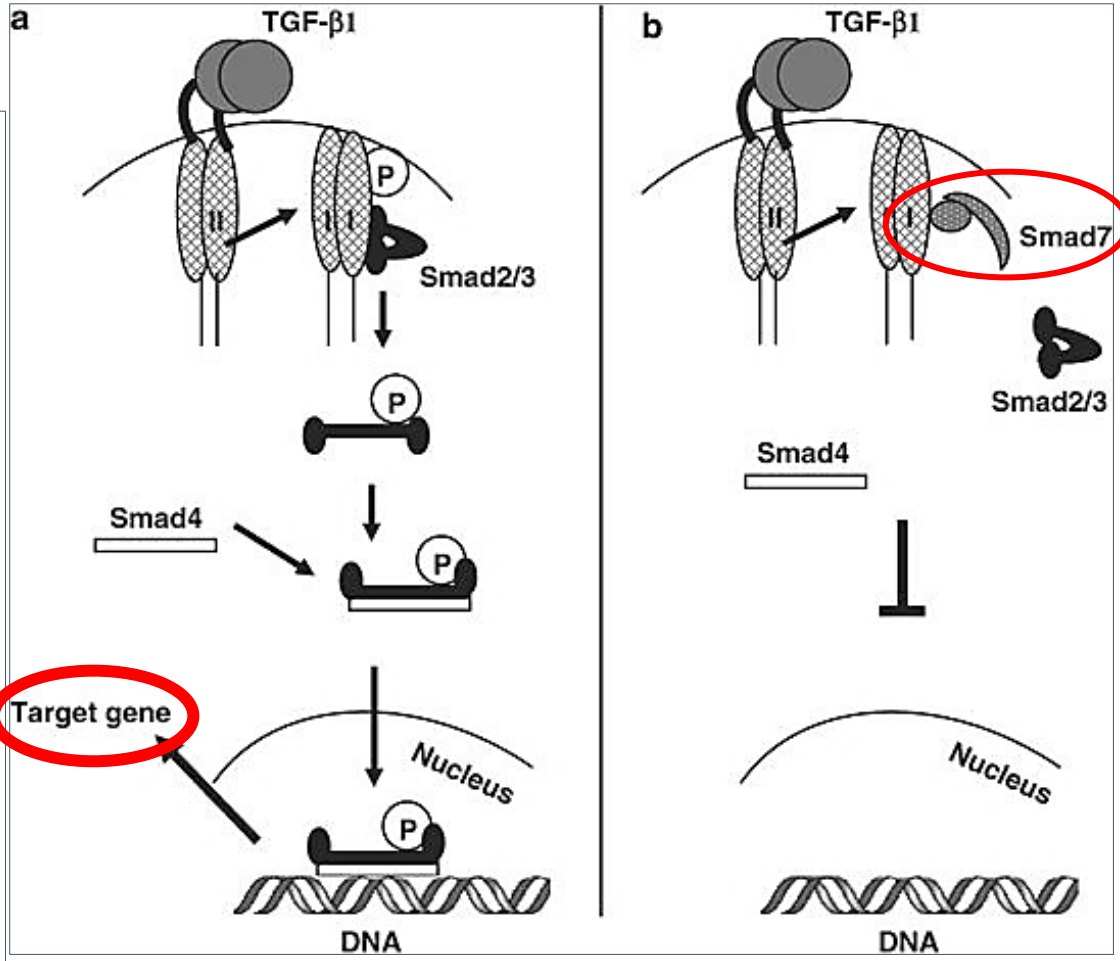
(a)

- Binding of TGF-β1 to the type II receptor causes the activation of the type I receptor which phosphorylates Smad2/3.

- **Smad2/3** interact with **Smad4**

- The complex **Smad2/3/Smad4** migrates into the nucleus and binds to DNA

- Trascription of genes coding for anti-inflammatory mediators

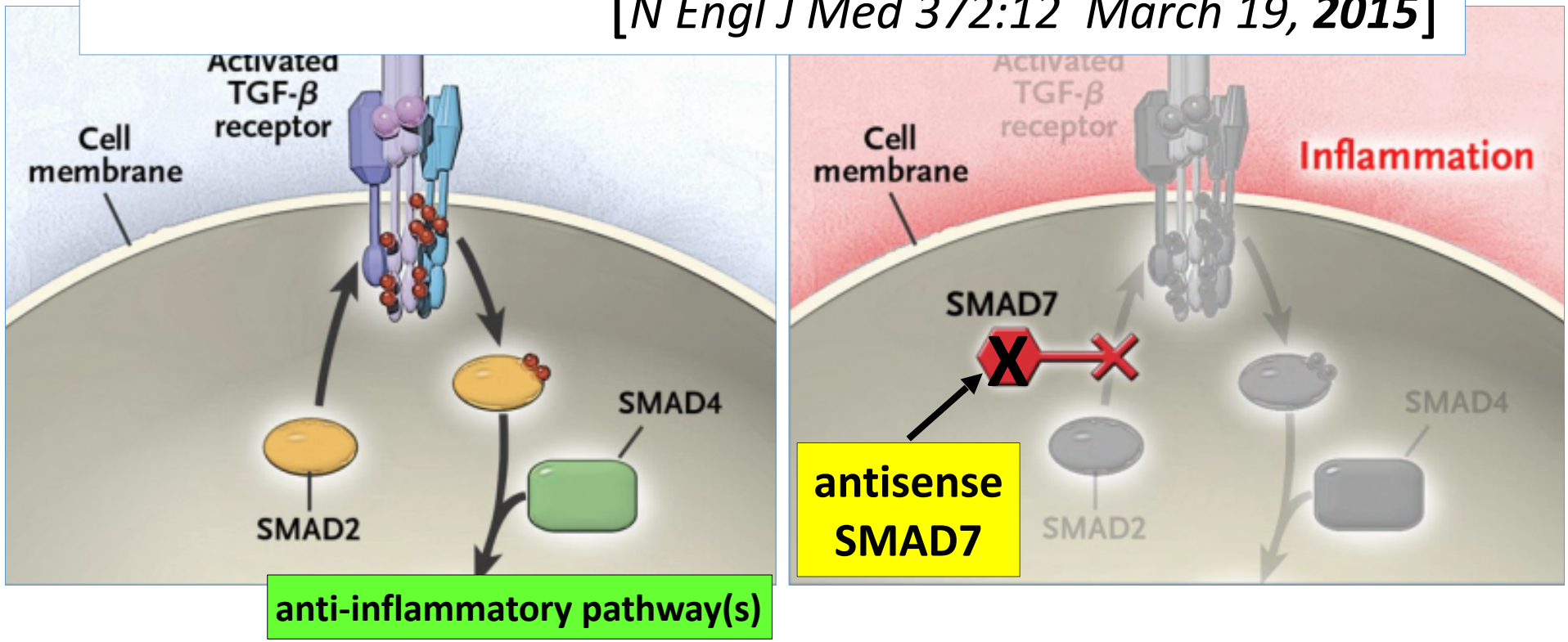


(b)

- The **inhibitor Smad7** interacts with the type I receptor of TGF-β1 and prevents Smad2/3 phosphorylation
- Block of the TGF-β1-associated Smad signaling pathway illustrated in (**a**)

Dall'Università di Tor Vergata una nuova prospettiva nella lotta alla malattia di Crohn

[*N Engl J Med 372:12 March 19,* ***2015***]



«La soppressione di Smad7, un inibitore dell'attività del Transforming Growth Factor-beta, **il più potente immunosoppressore intestinale dotato di attività anti-infiammatoria**, consente di ripristinare nell'intestino dei pazienti con malattia di Crohn i normali e fisiologici meccanismi antinfiammatori operanti nei soggetti sani».