Academic lectures for general medicine
Summer course 3rd year
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GENERAL PATHOPHYSIOLOGY

CHRONIC INFLAMMATION

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Figures and tables in this presentation were adapted from various printed and electronic resorces and serve strictly for educational purposes.

Characteristics

Definition:

- *duration:* inflammatory disease **lasting more than 6-8 weeks**; or **recurrently for 2 consecutive y.** ; subacute inflam. (2-8 w)
  a) continuation of acute, through subacute inflammations
  b) recurrent bounces of inflammation
  c) chronic inflammation of „low intensity“ w/o acute stage
- *histology:* always lack of Neu; predominance of Mo/Mf, T-lymphocytes, maybe Ba, Eo; plasmatic cells, fibroblasts, smooth muscle cells; Non specific : gastric ulcer; Specific: granulomas - special cells (epithelioid, giant cells - Langhans, foamy cells, etc.)

Pathology vs acute inflammation:

- Less prominent vascular changes (induration instead of swelling, little redness), more visible fibrotic changes (extracellul. matrix);
- Viscous circle – destruction vs. reparation perpetuate concurrently instead of consequently → scars, Tissue alteration is prominent
- Exagerated mitotic activity - neoangiogenesis, connective tissue; cellularisation, cell transformation may occur - dysplasias, metaplasias, anaplasias ... Certain chronic inflammations lead to neoplasias.

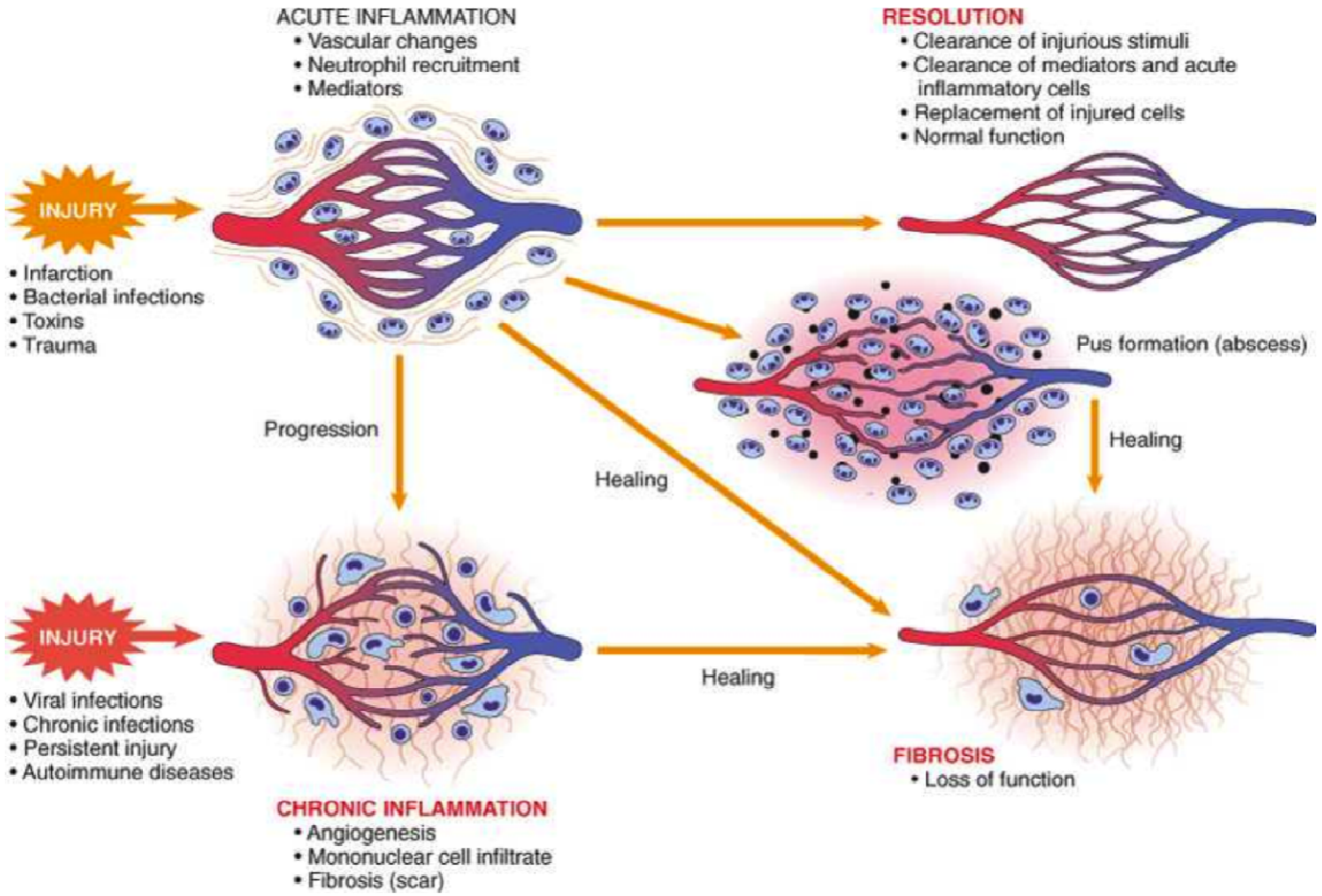
Time (2004): Chronic inflammation “The Secret Killer”

Dr. Barry Marshall, Dr. Robin Warren
H. Pylori Nobel Prize for Medicine.

Comparison of acute vs chronic inflammation

	Acute inflammation	Chronic inflammation
Causative agent	Bacterial pathogens, injured tissues	Persistent acute inflammation due to non-degradable pathogens, viral infection, persistent foreign bodies, or autoimmune reactions
Major cells involved	Neutrophils , basophils and eosinophils, mononuclears (monocytes, macrophages)	Mononuclears (monocytes, macrophages, lymphocytes, plasma cells), fibroblasts
Primary mediators	Vasoactive amines (histamin, serotonin), Eicosanoids (PTG, LT, Epoxides) Complement, coagulation sy.,	IFN-γ and other cytokines, growth factors, reactive oxygen species, hydrolytic enzymes
Onset	Immediate: minutes or hours	Delayed: days
Duration	Few days (2 weeks); subacute (2-8 weeks)	> 2 months of continuous affection, or 2 years of reccurent bursts
Outcomes	Resolution, abscess formation, chronic inflammation	Tissue destruction
Tissue injury, fibrosis	Usually mild and self-limited	Often severe and progressive
Local, systemic signs	Prominent	Less

Chronic phenotype of inflammation



- Acute inflam. may resolve perfectly, or healing gets longer through suppurative abscess or turn into viscous circuit of healing- damage resolved by fibrosis. It may cold up and turn into chronic process. Yet, some processes by nature start as chronic inflammation, never healing perfectly thus leaving scars.

Causes of chronic inflammation

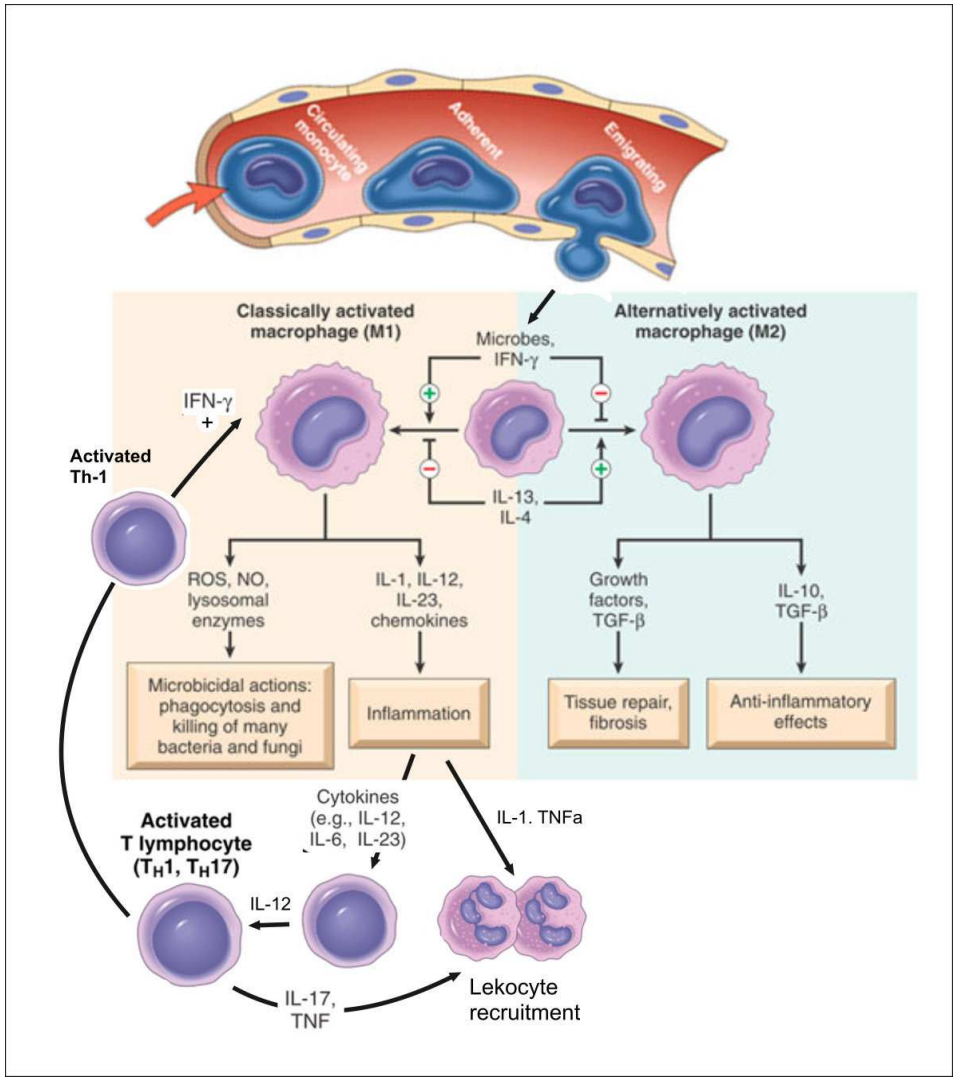
- **Persistent infection with certain microbes:** *low toxicity, resistance, granulomatous reaction*
  - *Bacteria:* Mycobacterium tuberculosis, Mycobacterium leprae, Treponema pallidum, Neisseria gonnorhoea, Listeria monocytogenenes, Legionella, Borrelia burgdorferi (Lymes disease), Helicobacter pylori
  - *Viruses:* Hepatitis v. A, C, E; Herpex simplex 2, Eppstein -Barr virus.; *Fungi:* Candidiosis, Aspergillus, Actinomyces ; *Protosoa:* Coccidiosis, a pod.
  - Parasites: Enterobius vermicularis, Trichuris trichiura, Ascaris lumbricoides, Taenia saginata, etc.

- **Long-term exposition to toxic agents:** *irritable inarganic or undegradable matter*
  - *Exogenous deposits: Skin and connective tissue :* tattoing, wooden or metal chips, talc, burns, surgery sawing (implantation wounds; *Lung:* pneumoconiosis, silicosis (silica), asbestosis beryliosis,farmers lungs, etc; *Other tissue:* implants (joints, dental), prosthesis, intrauterine bodies, etc.
  - *Endogenous deposits:* atherosclerosis (lipoperoxids), uric acid crystals (gout),

- **Immunologic disorders:**
  - *Autoimmune disorders* (reumatoid arthritis, lupus erythematodes, & other collagenoses; vasculitis, Graves dis., Diabetes type I),
  - *Hypersensitivity disorders* – asthma, delayed hypersensitivity, type IV

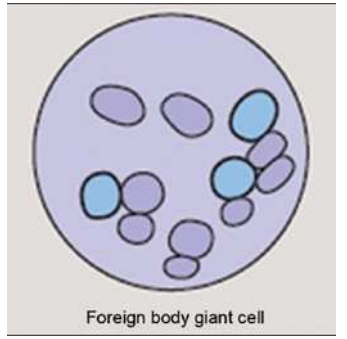
Monocyte line - main cells in chronic inflammation

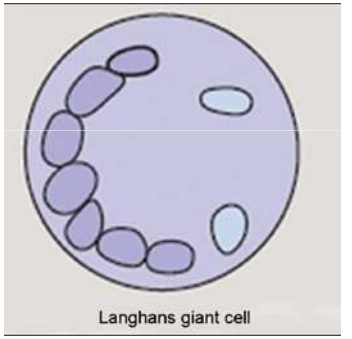
- Monocytes as undifferentiated cells are released from the bone marrow, circulate in the blood and invade areas of damage; they diapedese, differentiate into macrophages
- Massive monocyte infiltration; leukocytosis, monocytosis
- Mϕ eliminate microbes, fungi; not so effectively microbicidal as Neu; masters of phagocytosis the most important of all (scavenge microbes, debris, dead cells, inflam. cells)
- Mϕ maintain inflammation active; turn it into persistent (proinflamm. cytokines TNFa, IL-1, chemokines,) eicosanoids.
- Mϕ as antigen-presenting cells connect naive to adaptive immunity
- Mϕ have principal role is in tissue repair (angiogenesis, activate fibroblasts, stimulate collagen synthesis → scar formation, fibrosis
- **Classical macrophage activation** = microbial products (endotoxin, IFN-γ, foreign crystals and particulate matter. lysosomal enzymes, NO, and ROS,
- **Alternative macrophage activation** = cytokines IL-4, IL-13 by T – Ly, mast cells, eosinophils

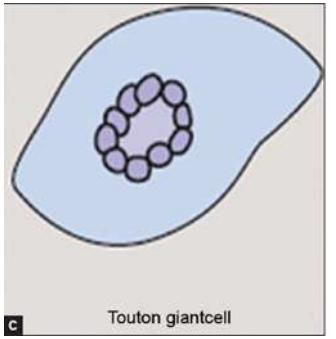


Giant cells in chronic inflammation

- **Foreign-body giant cell** have got nuclei scattered haphazardly; throughout the cytoplasm and some are present centrally in clusters frequently seen around **exogenous foreign material** (catgut, silk, talc, silica crystalls, keratine, plastic sponges).or around **endogenous debris** (cholesterol crystals, keratin, uric acid crystals in gout).
- **Langhans giant cell** (also Pirogov-Langhans cells) = large multinuclear cells (arranged in horseshoe-shaped pattern in the cell periphery) in granulomas; they are found in nearly **every form of granulomatous disease**, regardless of etiology. Typically present in *Mycobacterium* diseases as **tuberculosis or leprosy** (not specific however) **sarcoidosis**; formed by the fusion of monocytes (macrophages) as an effect of upregulation of fusion-related molecule DC-STAMP (dendritic cell-specific transmembrane protein) by the monocytes when activated by IFNγ from CD_{4+} Th1.
- **Touton giant cells** nuclei are arranged in a wreath like pattern. Its peripheral cytoplasm has a foamy or vacuolated appearance due to lipid and nuclei surrounds central area of homogeneous eosinophilic cytoplasm in center surrounded by a circle of multiple nuclei found in **xanthoma, xanthogranuloma** and **fat necrosis**.

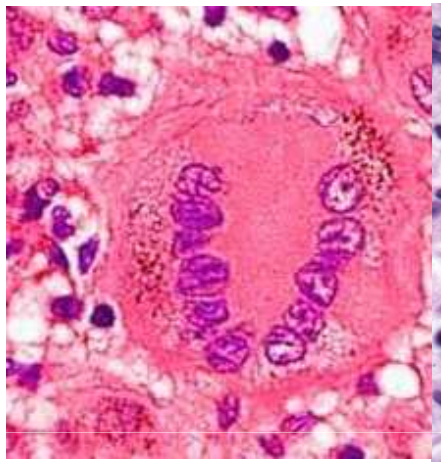

Foreign body giant cell

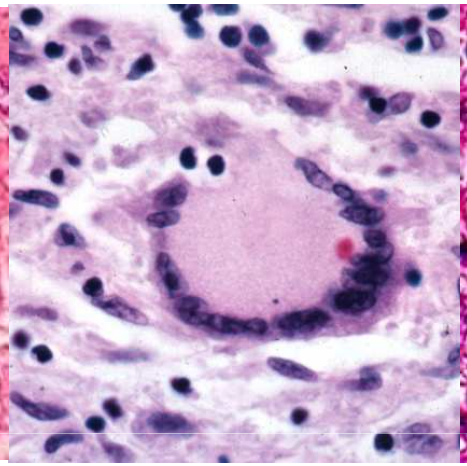

Langhans giant cell


Touton giantcell

Various forms of giant cells in chronic inflammation

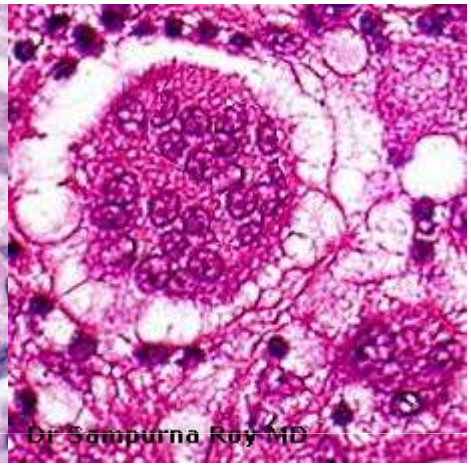
Langhans giant cell



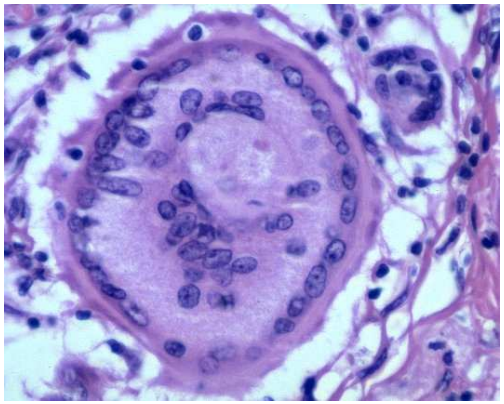


Tuberculosis Classic Langerhans Giant Cell: *Micro high mag H&E*

Foreign-body giant cell



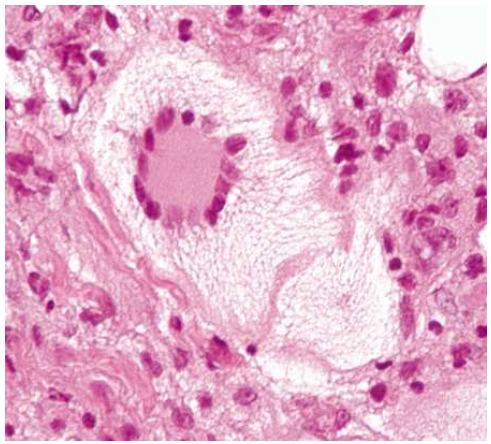
Atypical giant cell

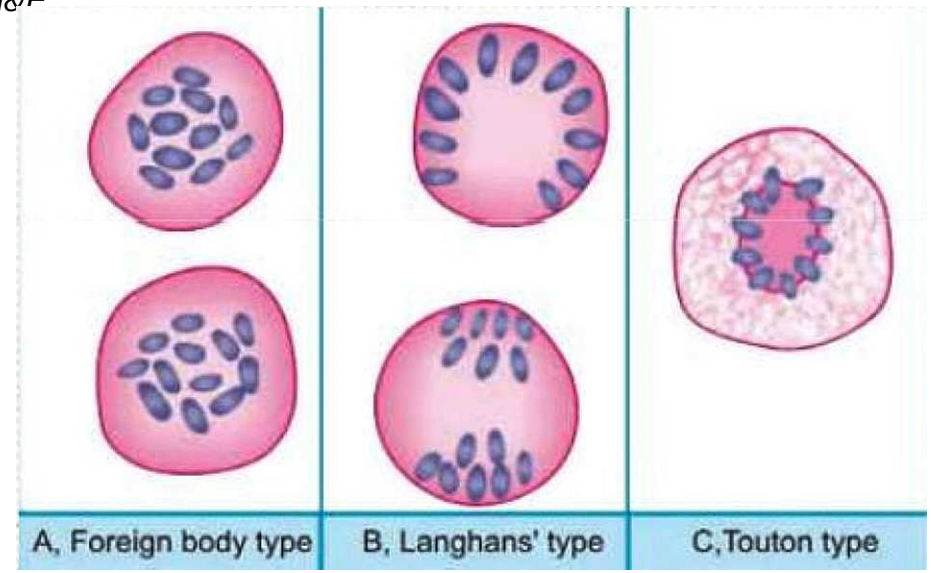


Giant cell with features of both Langhans and foreign body types

Touton giant cell

Xantelasma *Micro high mag H&E*





http://www.pathopedia-india.com/giant_cells.htm *http://www.oculist.net/downaton502/prof/ebook/duanes/pages/v9/v9c007.html*
http://peir.path.uab.edu/library/picture.php?/8316

1. Chronic inflammatory stress response (CISR)

- constant low-level response (small camp fire → out of control forest fire).
- inability to turn off the inflammatory response →damaging healthy tissue

- **Atherosclerosis** (chronic coronary syndrome, anginose state, stroke (ischemic brain attack)
- **Cancer**
- **Autoimmune diseases (**Rheumatoid arthritis, Psoriasis. Lupus erythematoides,
- Vasculilis (Wegener granulomatosis), Sarcoidosis, Ulcerative colitis, Crohn's disease, Multiple sclerosis
- **Neurological:** Alzeheimer dis., Parkinson dis., Alergies (asthma), urticaria
- Metabolic X syndrome, Typ 2 DM,
- **Obesity** - Steatosis
- **Hypertension**

Sy:

- *Ongoing, irritating pain in the body (like the joints or muscles)*
- *Allergies or asthma (especially when they keep getting worse)*
- *High blood pressure or blood sugar problems*
- *Ulcers and Irritable bowel syndrome (constipation or diarrhea)*
- *Constant fatigue or lethargy*
- *Skin problems or red, bloodshot eyes*

La:

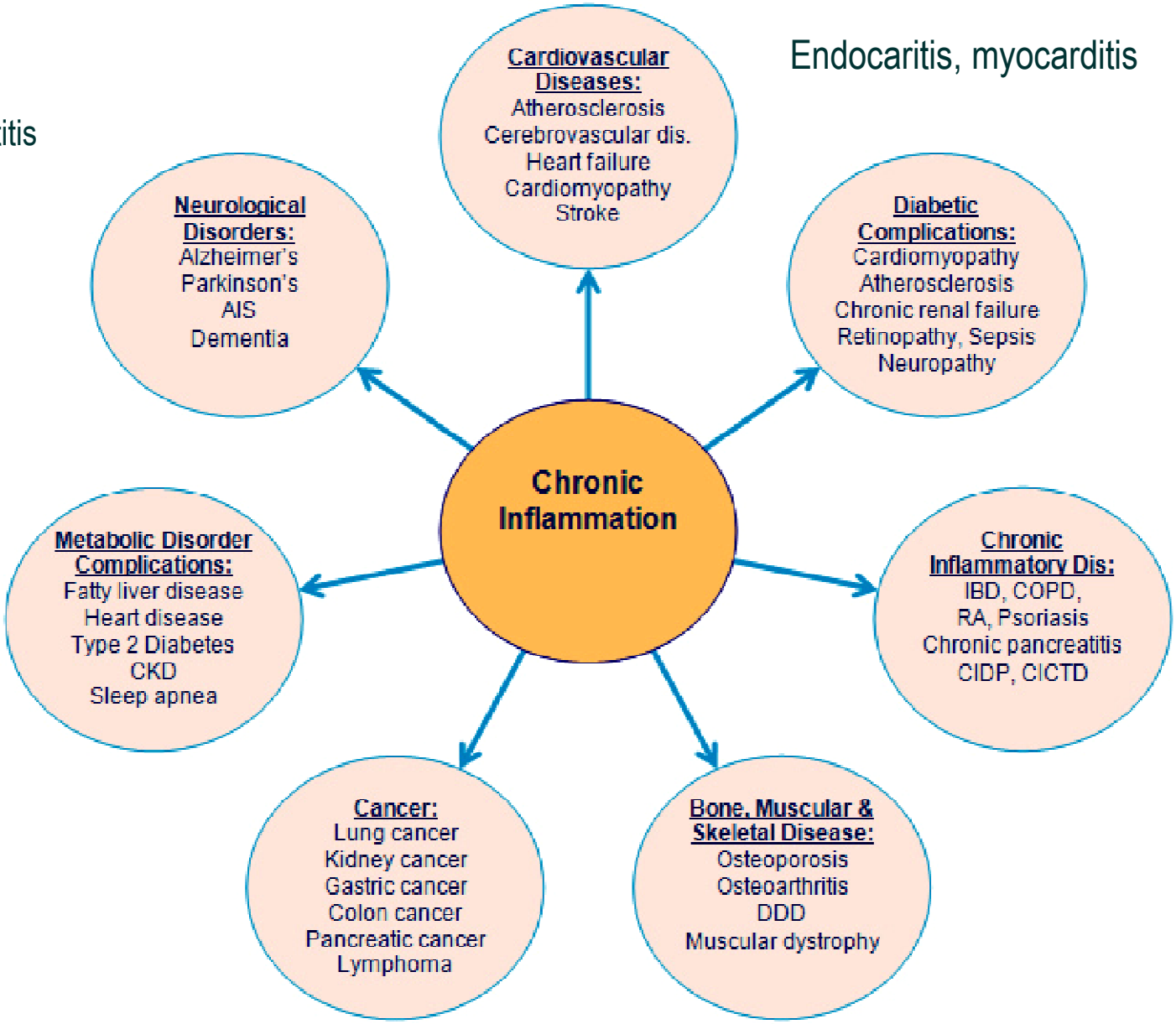
- ↑ High Sensitivity C-Reactive Protein (HS-CRP) > 10x (norma < 10 mg/l).
- ↑ ESR (FW, Fahræus Westergren) ♂ (mm/h) ≤ age / 2; ♀ (mm/h) ≤ (age +10) / 2.
- ↑ Homocysteine, Ferritin
- ↑ LDL, cholesterol
- ↑ Monocytes Hyperglycaemia (leading indicator of inflammation) >150 mg/dl
- Hypertension 130/85 mmHg

Diseases based on the chronic inflammation

Lupoid (autoimune) hepatitis
Chronic active hepatitis
Chronic pancreatitis, cholecystitis
Chronic gastritis,
Chronic peptic ulcer

Multiple sclerosis

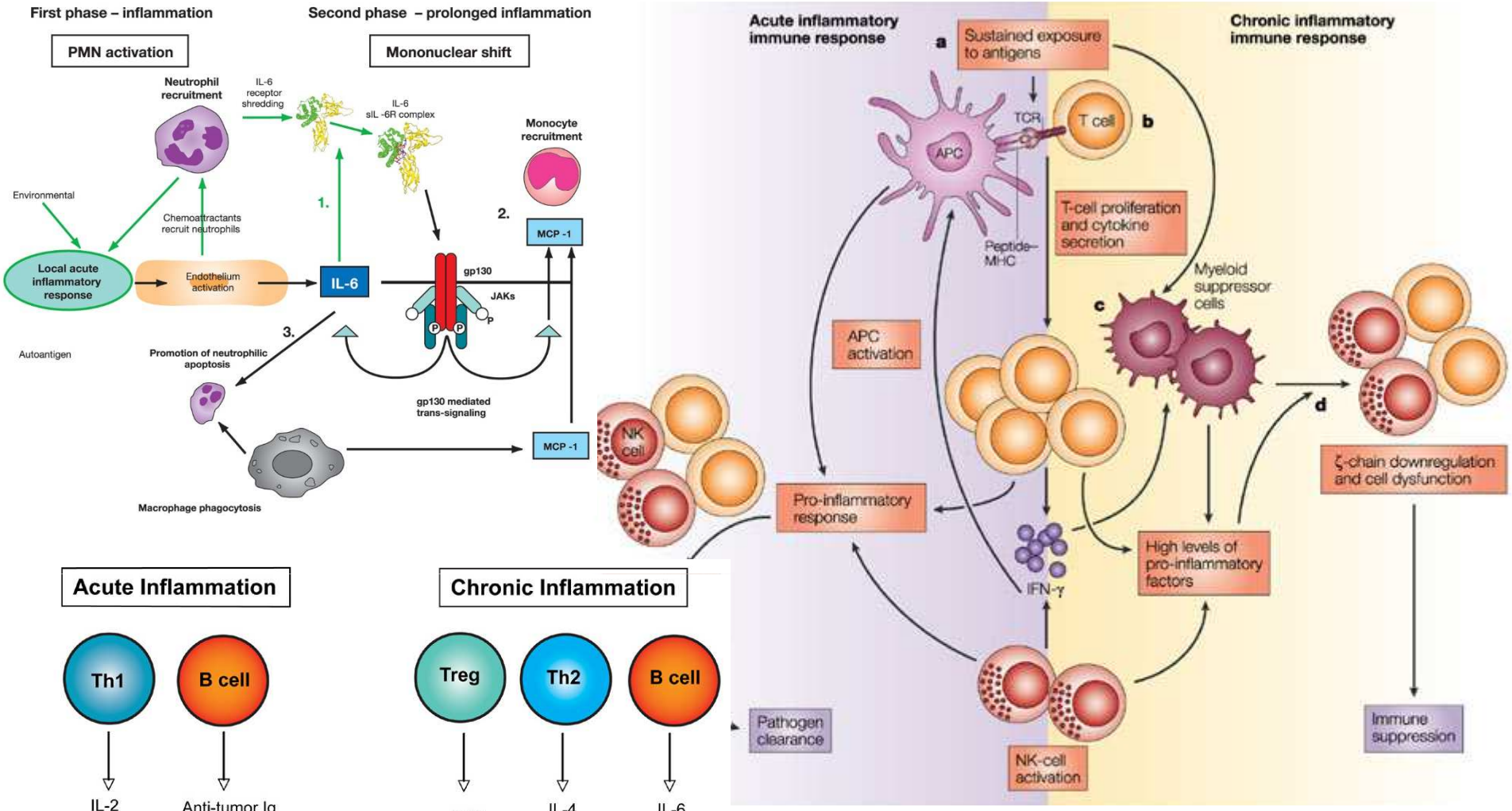
Chronic nasosinusitis,
Chronic pharyngitis

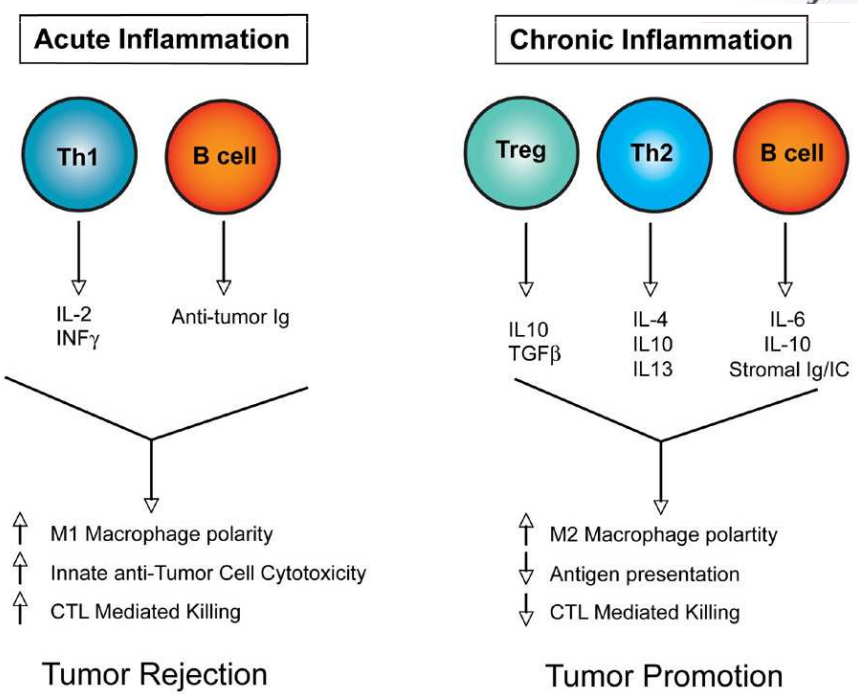


1. Granulomatous inflammation

- distinctive pattern of chronic inflammation characterized by **aggregates of activated macrophages** with scattered lymphocytes

Disease	Cause	Tissue Reaction
Tuberculosis	*Mycobacterium tuberculosis*	Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli
Leprosy	*Mycobacterium leprae*	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	*Treponema pallidum*	Gumma: microscopic to grossly visible lesion, enclosing wall of histiocytes; plasma cell infiltrate; central cells are necrotic without loss of cellular outline
Cat-scratch disease	Gram-negative bacillus	Rounded or stellate granuloma containing central granular debris and neutrophils; giant cells uncommon
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease	Immune reaction against intestinal bacteria, self antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate



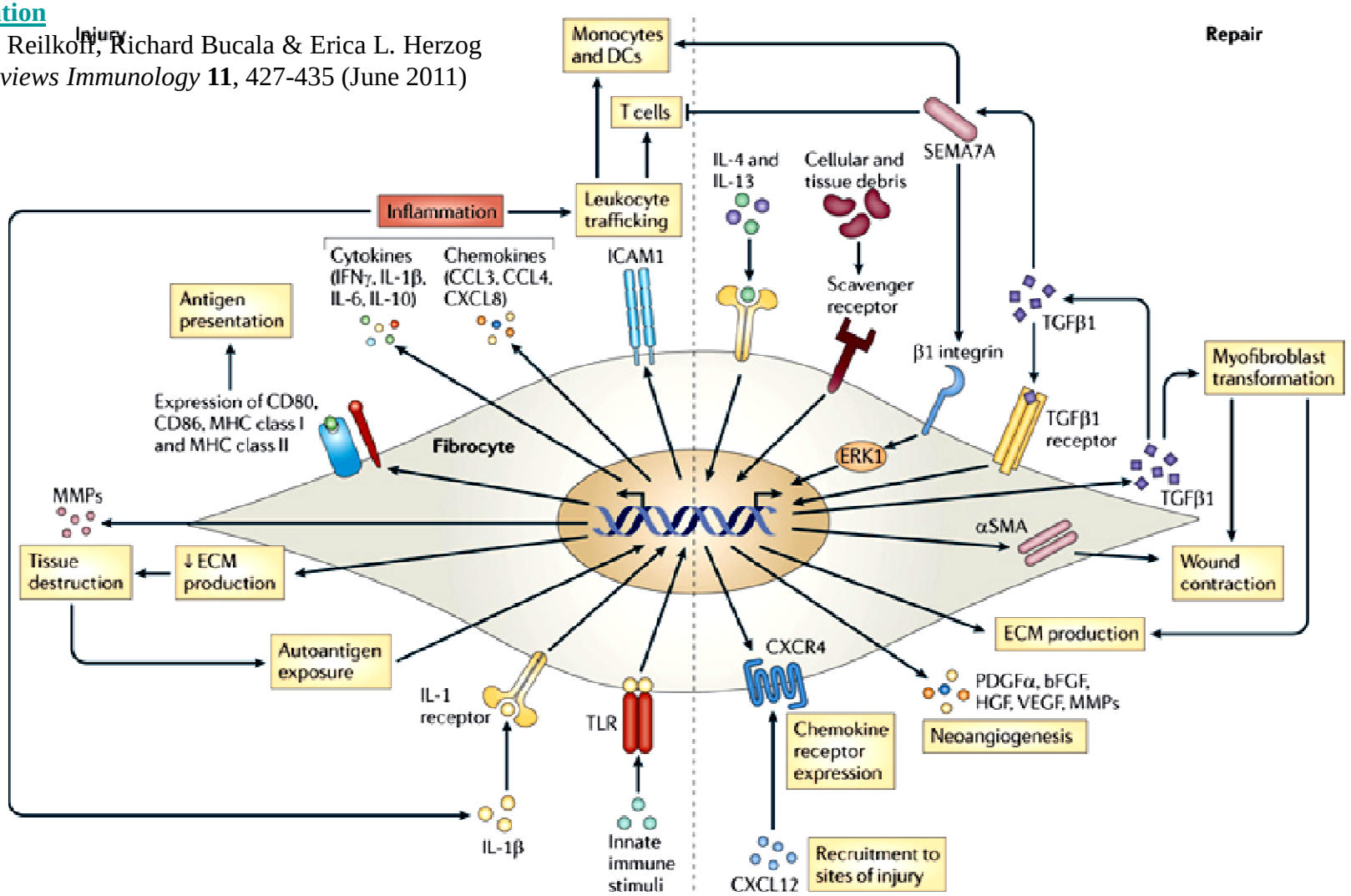


TH1 response ; antigen-presenting cells (APCs), Antigen-špecifické TH1 cytokines, their proliferation, and the activation of APCs and natural killer (NK) cells. Activation of various immune cells could also be mediated through the interaction of Toll-like receptors with pathogen-associated molecular patterns. In all of these situations, activated cells (T cells, APCs and NK cells) produce pro-inflammatory factors (including nitric oxide, hydrogen peroxide and prostaglandins) and cytokines (such as interferon- , IFN-) and tumour-necrosis factor

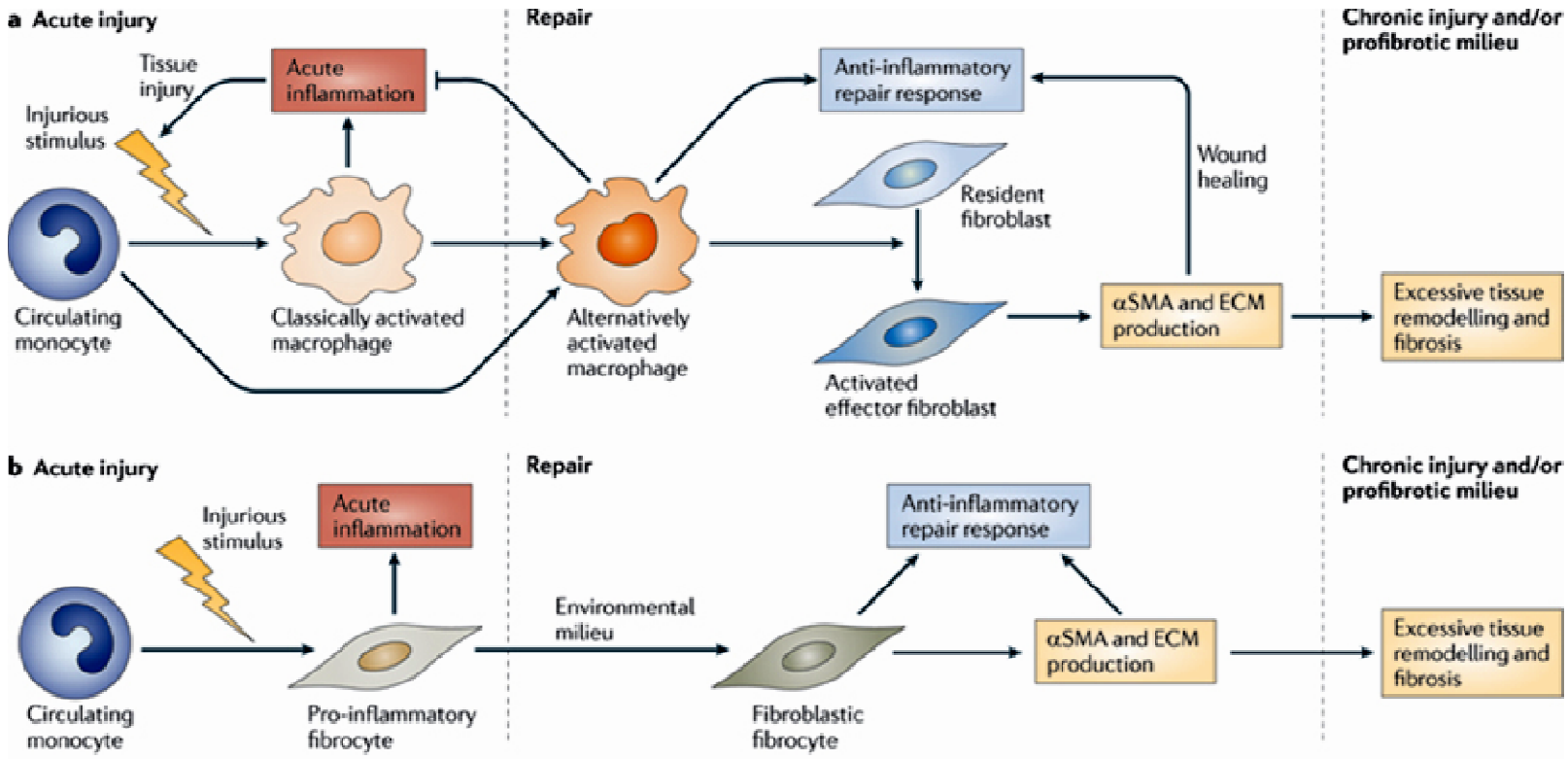
Activation of fibrocytes

Fibrocytes: emerging effector cells in chronic inflammation

Ronald A. Reilkoff, Richard Bucala & Erica L. Herzog
Nature Reviews Immunology **11**, 427-435 (June 2011)

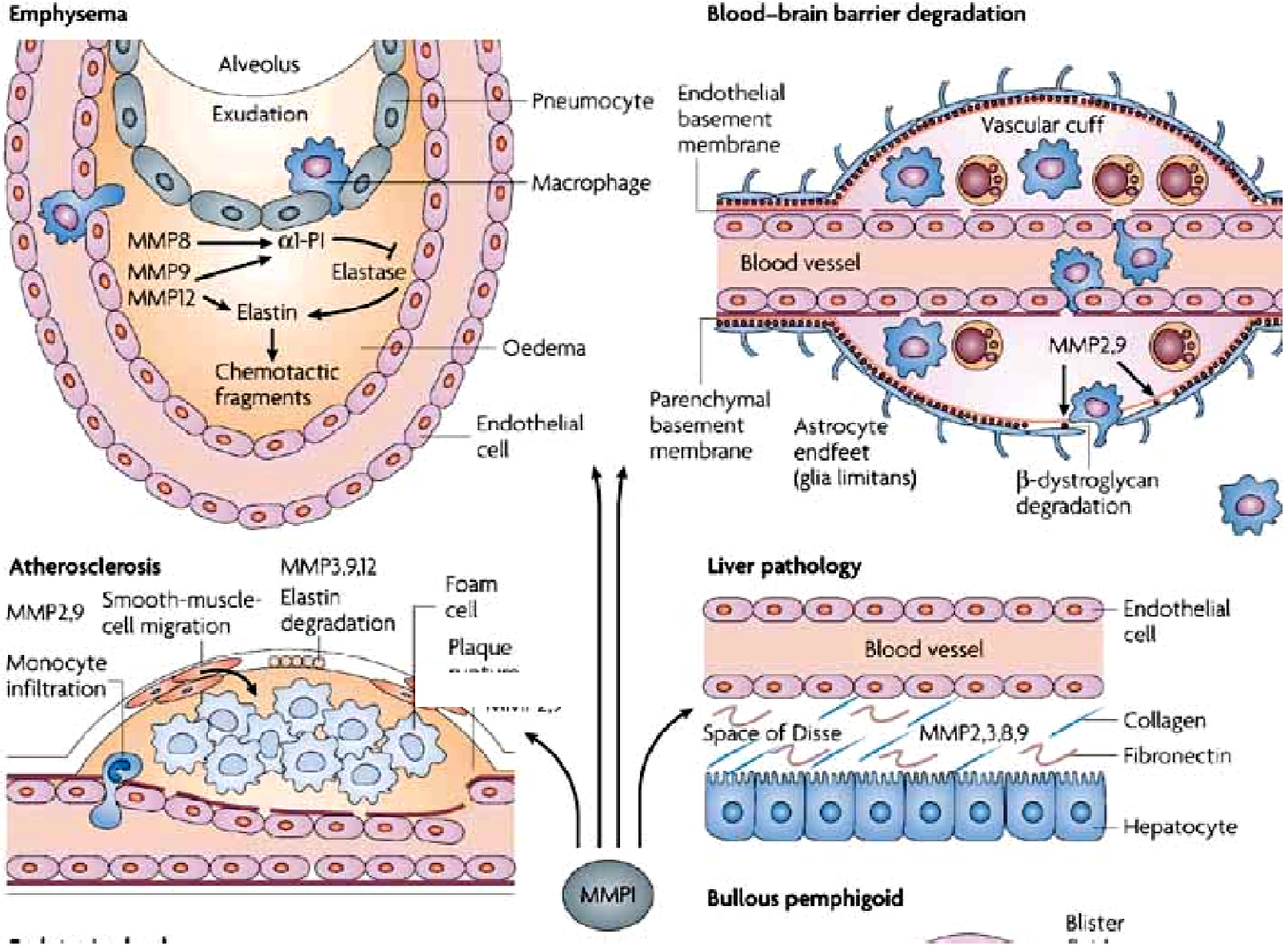


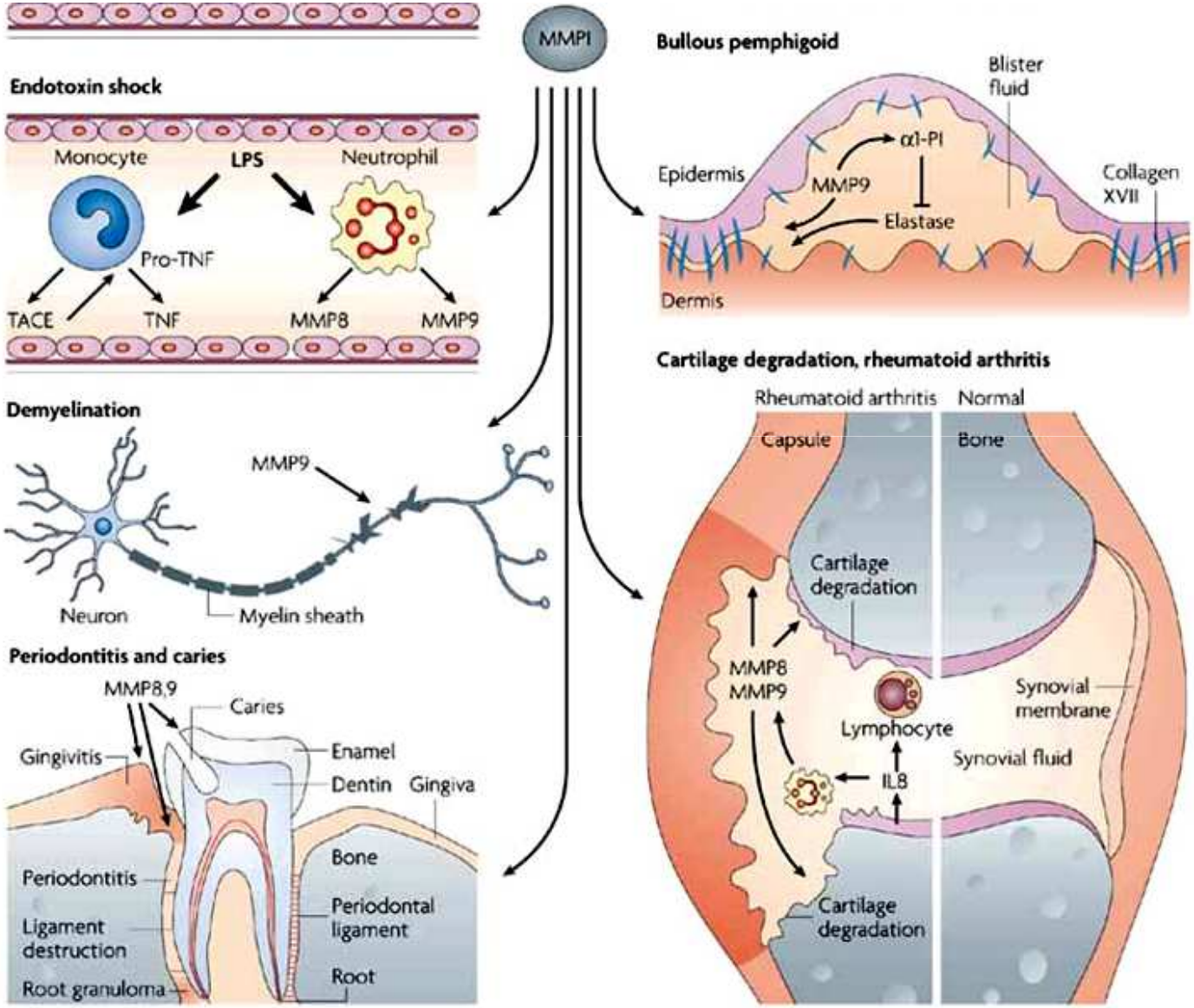
Cellular transactivation – changes in phenotypes



Activated macrophages infiltrate diseased organs. **Macrophage phenotype shifts**: stimulate resident fibroblasts to expression of α-smooth muscle actin (αSMA) and enhanced extracellular matrix (ECM) production. In the setting of severe or persistent injury, or a **profibrotic milieu,** this fibrosis. **Proinflammatory fibrocytes** have properties of both macrophages and fibroblasts. As damage subsides, fibrocytes respond to local cues to downregulate their inflammatory responses and adopt a fibroblastic phenotype to promote repair and, in some pathological conditions, remodelling and fibrosis.

Chronic inflammation – tissue alteration




MMP1
Endotoxin shock
Monocyte
LPS
Neutrophil
Pro-TNF
TACE
TNF
MMP8
MMP9
Bullous pemphigoid
Blister fluid
Epidermis
α1-PI
MMP9
Elastase
Collagen XVII
Dermis
Demyelination
MMP9
Neuron
Myelin sheath
Cartilage degradation, rheumatoid arthritis
Rheumatoid arthritis
Normal
Capsule
Bone
Cartilage degradation
MMP8
MMP9
Lymphocyte
Synovial membrane
Synovial fluid
IL8
Cartilage degradation
Periodontitis and caries
MMP8,9
Caries
Gingivitis
Enamel
Dentin
Gingiva
Bone
Periodontitis
Periodontal ligament
Ligament destruction
Root granuloma
Root