pathogenesis of common inflammatory disorders

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Objectives

- Definition of inflammation.
- Types of inflammation.
- Common diseases associated with inflammation.
- Pathogenesis
- Summary

Definition of inflammation

Inflammation:

Is a localized, transitory response initiated by the innate immune system to defend an organism against exterior injury, characterized by rubor (redness), tumour (swelling), calor (heat), dolor (pain), and laesa (loss of function) .

Inflammation is regarded as the primary physiological response to tissue injury that involves a cascade of events. It results from disrupted homeostatic mechanisms and is classified into acute (lasting from hours to few days) or chronic (lasting 2–6 weeks) categories.

Types of inflammation

Acute inflammation

typically consists of four distinct sub-events:

(1) vasodilatation that aids in the delivery of necessary proteins and cells (like exudation) and increases tissue temperature.

(2) fluid exudation that aids in delivering plasma proteins to sites of damage.

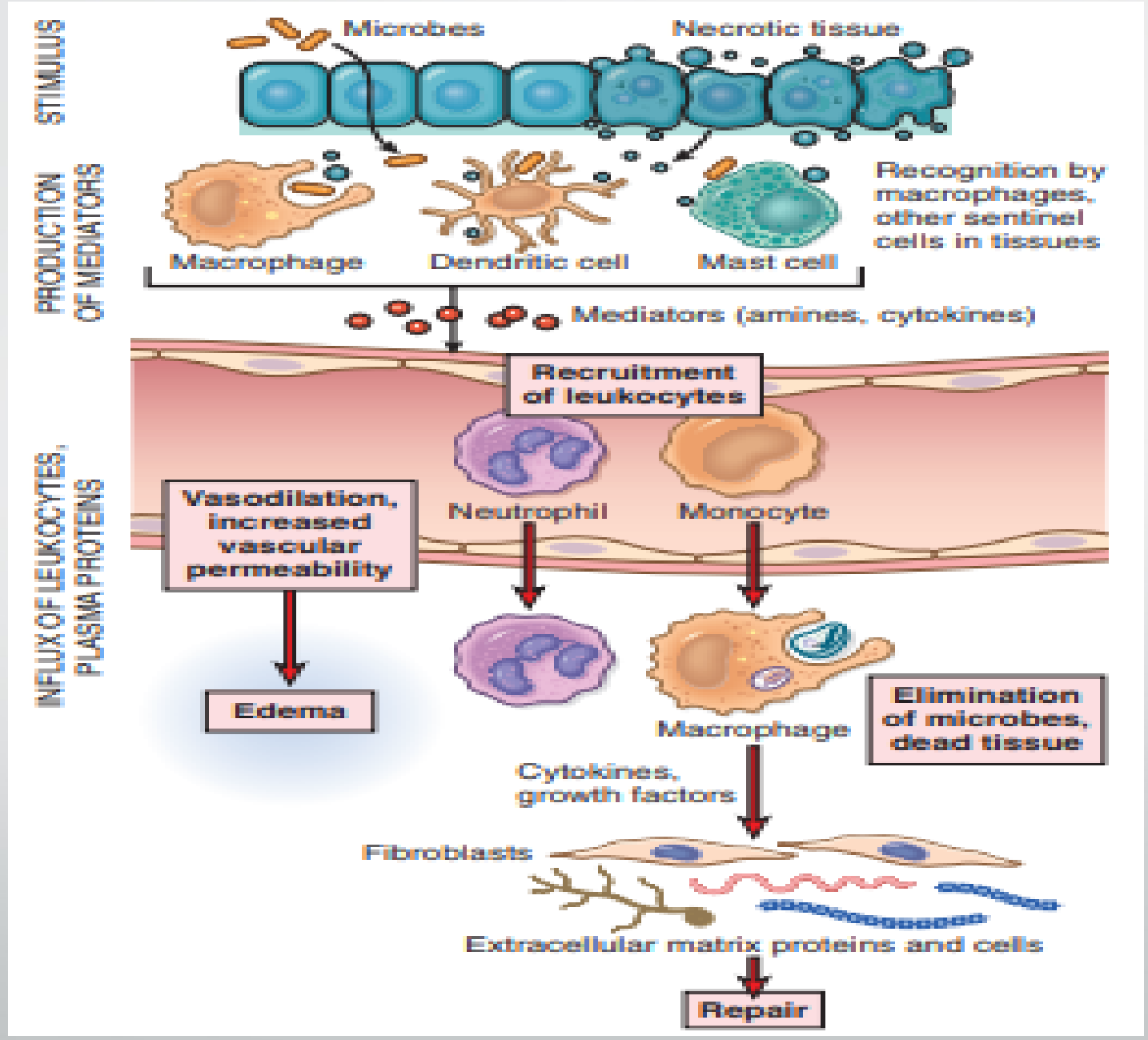
(3) neutrophil infiltration that results in the removal of pathogens and cellular fragments.

(4) pain and loss of function that encourage rest and reduces the risk of further tissue damage.

Chronic inflammation

- is slow and long-term inflammation. it is further divided into two types that is
- non-specific proliferative occurs due to the non-specific granulation tissue produced by infiltration of mononuclear cells.
- Granulomatous inflammation occurs due to the granulomas (distinct nodular lesions or produced with an aggregation of activated macrophages or its derived cells) .

Pathogenesis of inflammation


STIMULUS
Microbes
Necrotic tissue
PRODUCTION OF MEDIATORS
Macrophage
Dendritic cell
Mast cell
Recognition by macrophages, other sentinel cells in tissues
Mediators (amines, cytokines)
INFLUX OF LEUKOCYTES, PLASMA PROTEINS
Recruitment of leukocytes
Neutrophil
Monocyte
Vasodilation, increased vascular permeability
Edema
Macrophage
Elimination of microbes, dead tissue
Cytokines, growth factors
Fibroblasts
Extracellular matrix proteins and cells
Repair

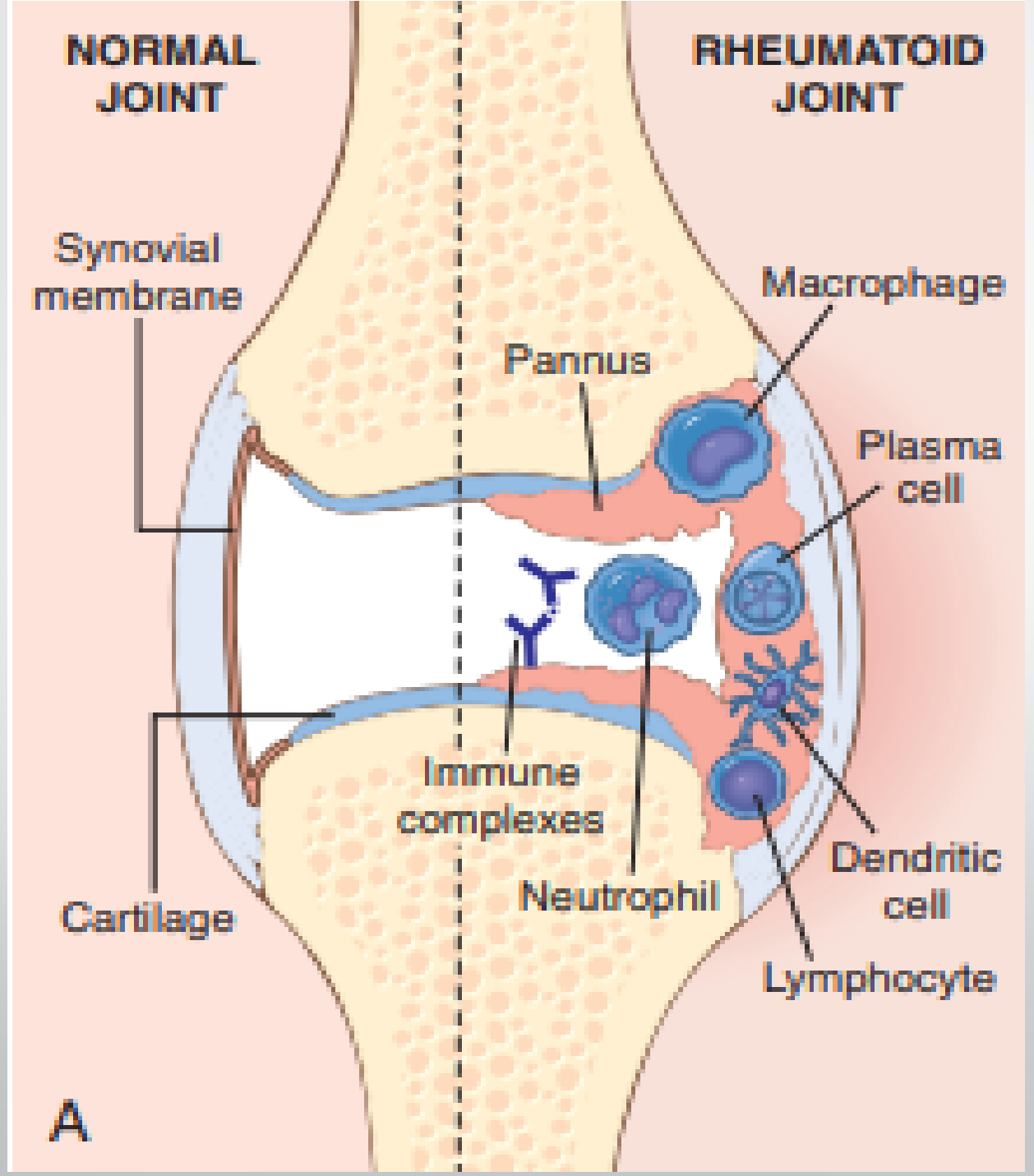
Numerous factors play a vital role in the pathogenesis of inflammations which includes infections and foreign irritants like industrial chemicals. Not only this, histamine, prostaglandins, leukotrienes, oxygen and nitrogen-derived free radicals, and serotonin are too involved in the process of inflammation. Evidences indicated that the innate immune system is the main cause of inflammation hence, immune cells like macrophages, dendritic cells, mast cells, neutrophils, and lymphocytes are too elicited to have a great impact on inflammatory responses In addition to innate immune system, non-immune cells (epithelial cells, endothelial cells, and fibroblasts) are also involved in inflammatory processes.

Diseases Which are Associated With Inflammation

Inflammation is the main cause in the progression of common diseases like rheumatoid arthritis (RA), allergic asthma, and inflammatory bowel disease (IBD) and atherosclerosis which will be discussed.

Rheumatoid arthritis

- RA is an autoimmune chronic inflammatory disease, resulting in joint damage and physical disability, principally attacks the joints, producing a nonsuppurative proliferative and inflammatory synovitis. RA often progresses to the destruction of the articular cartilage and, in some cases ankylosis (adhesion) of the joints.
- Extraarticular lesions may occur in the skin, heart, blood vessels, and lungs.

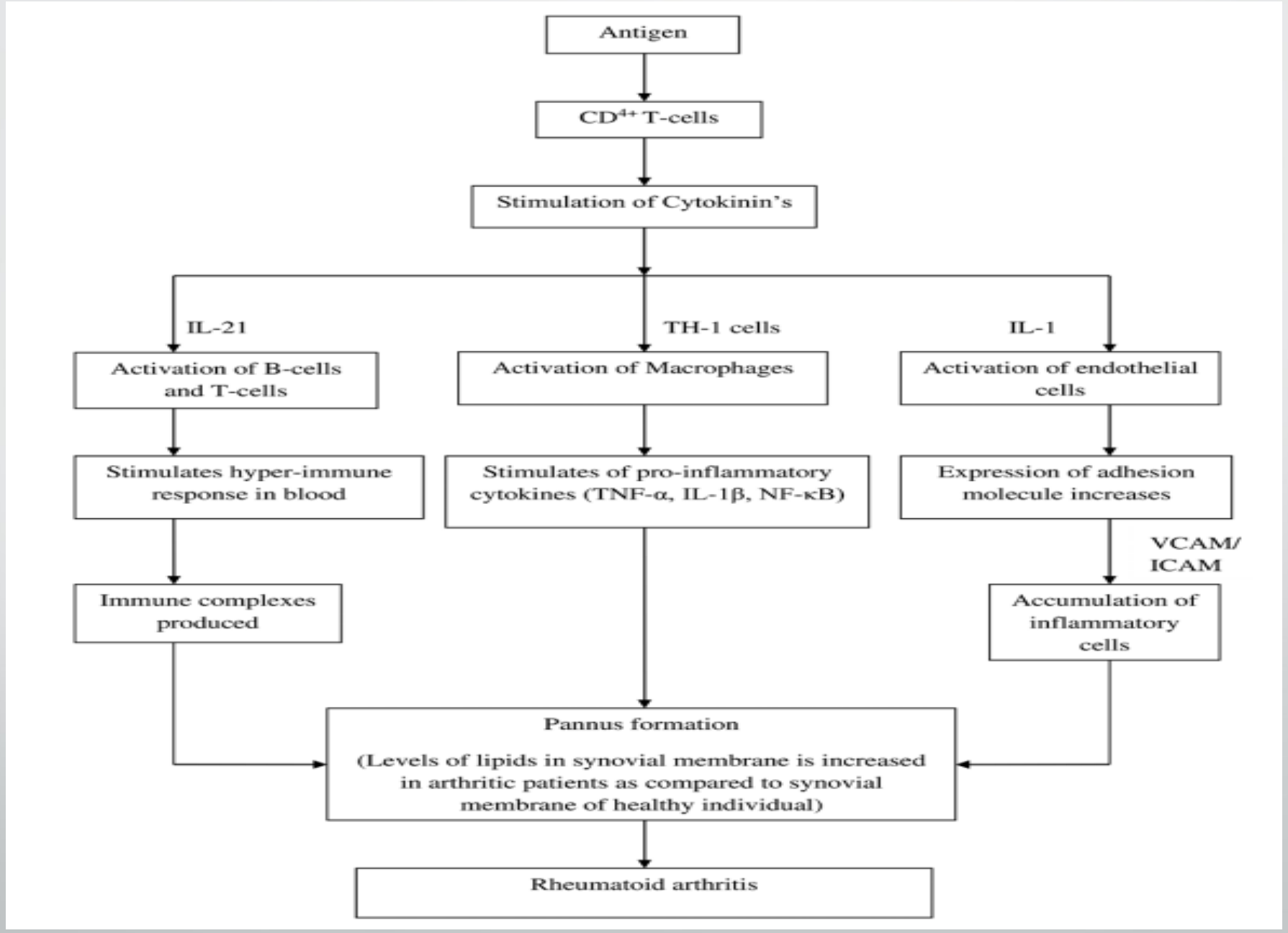

NORMAL JOINT
RHEUMATOID JOINT
Synovial membrane
Pannus
Macrophage
Plasma cell
Immune complexes
Neutrophil
Dendritic cell
Cartilage
Lymphocyte
A

PATHOGENESIS

- As in other autoimmune diseases, genetic predisposition and environmental factors contribute to the development, progression, and chronicity of the disease. The pathologic changes are mediated by antibodies against self-antigens and inflammation caused by cytokines, predominantly secreted by CD4+ T cells.
- CD4+ T helper (TH) cells may initiate the autoimmune response in RA by reacting with an arthritogen, perhaps microbial or a chemically modified self-antigen.

The T cells produce cytokines that stimulate other inflammatory cells to effect tissue injury:

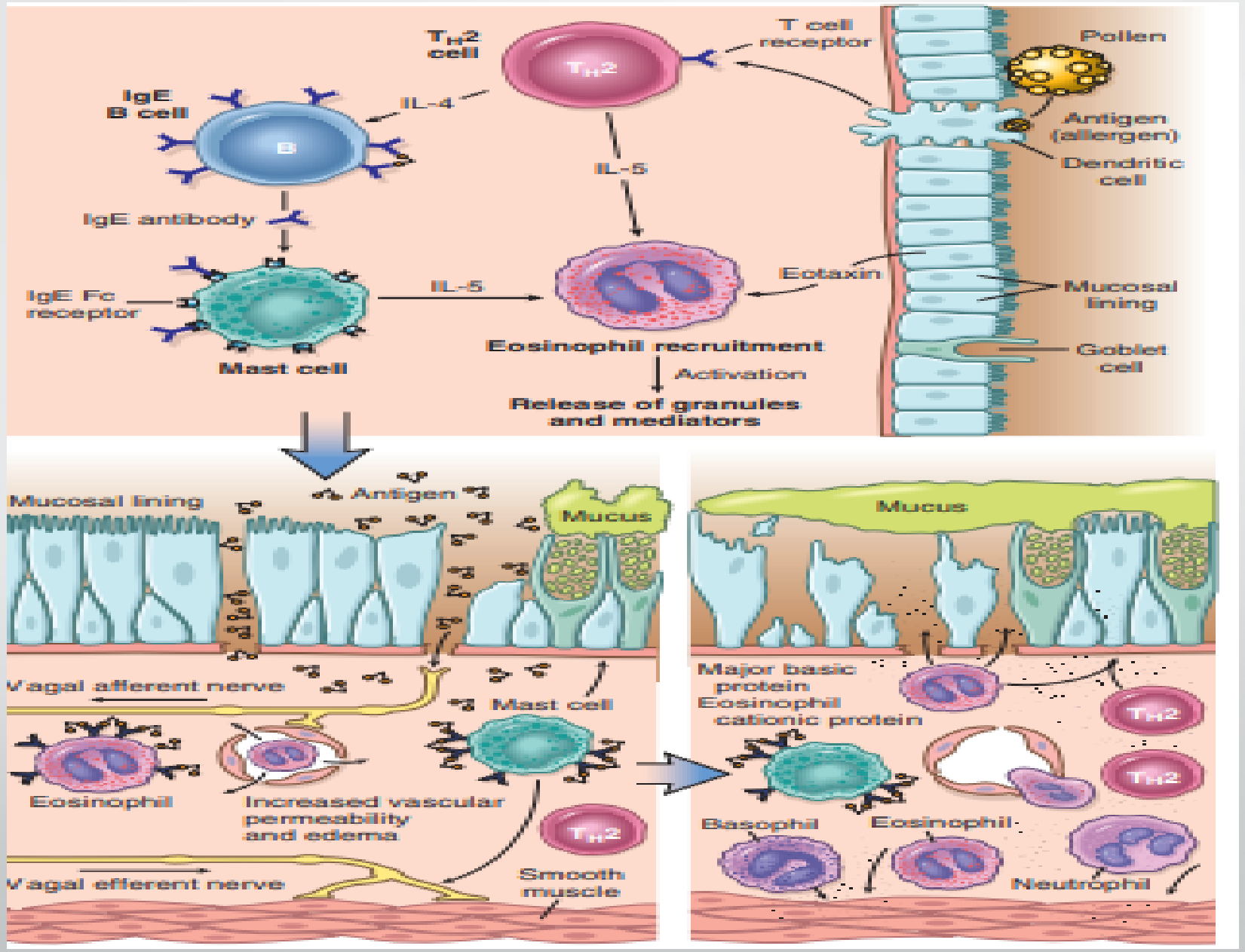
- IFN-γ from TH1 cells activates macrophages and synovial cells.
- IL-17 from TH17 cells recruits neutrophils and monocytes.
- RANKL expressed on activated T cells stimulates osteoclasts and bone resorption.
- TNF and IL-1 from macrophages stimulate resident synovial cells to secrete proteases that destroy hyaline cartilage.


Antigen
CD4+ T-cells
Stimulation of Cytokinin's
IL-21
TH-1 cells
IL-1
Activation of B-cells and T-cells
Activation of Macrophages
Activation of endothelial cells
Stimulates hyper-immune response in blood
Stimulates of pro-inflammatory cytokines (TNF-α, IL-1β, NF-κB)
Expression of adhesion molecule increases
VCAM/ ICAM
Immune complexes produced
Accumulation of inflammatory cells
Pannus formation
(Levels of lipids in synovial membrane is increased in arthritic patients as compared to synovial membrane of healthy individual)
Rheumatoid arthritis

Asthma

Asthma is a chronic inflammatory disorder of the airways that causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and/or early in the morning. The hallmarks of asthma are

1. intermittent, reversible airway obstruction.
2. chronic bronchial inflammation with eosinophils.
3. bronchial smooth muscle cell hypertrophy and hyperreactivity.
4. increased mucus secretion


T_H2 cell
T cell receptor
Pollen
IgE
B cell
IL-4
Antigen (allergen)
IL-5
Dendritic cell
IgE antibody
IgE Fc receptor
IL-5
Eotaxin
Mucosal lining
Eosinophil recruitment
Goblet cell
Activation
Mast cell
Release of granules and mediators
Mucosal lining
Antigen
Mucus
Mucus
Vagal afferent nerve
Mast cell
Major basic protein
Eosinophil cationic protein
Eosinophil
Increased vascular permeability and edema
Basophil
Eosinophil
Smooth muscle
Vagal efferent nerve
Neutrophil

Pathogenesis

Major factors contributing to the development of asthma include genetic predisposition to type I hypersensitivity (atopy), acute and chronic airway inflammation, and bronchial hyperresponsiveness to a variety of stimuli. episodes of bronchospasm may be triggered by diverse exposures, such as respiratory infections (especially viral), airborne irritants (e.g., smoke, fumes), cold air, stress, and exercise. There also are varying patterns of inflammation—eosinophilic (most common), neutrophilic, mixed inflammatory, and pauci-granulocytic—that are associated with differing etiologies, immunopathologies, and responses to treatment.

The classic atopic form is associated with excessive type 2 helper T (TH2) cell activation. Cytokines produced by TH2 cells account for most of the features of atopic asthma— IL-4 and IL-13 stimulate IgE production, IL-5 activates eosinophils, and IL-13 also stimulates mucus production. IgE coats submucosal mast cells, which on exposure to allergen release their granule contents and secrete cytokines and other mediators.

Mast cell–derived mediators produce two waves of reaction: an early (immediate) phase and a late phase.

• The early-phase reaction is dominated by bronchoconstriction, increased mucus production, and vasodilation. Bronchoconstriction is triggered by mediators released from mast cells, including histamine, prostaglandin D2, and leukotrienes LTC4, D4, and E4, and also by reflex neural pathways.

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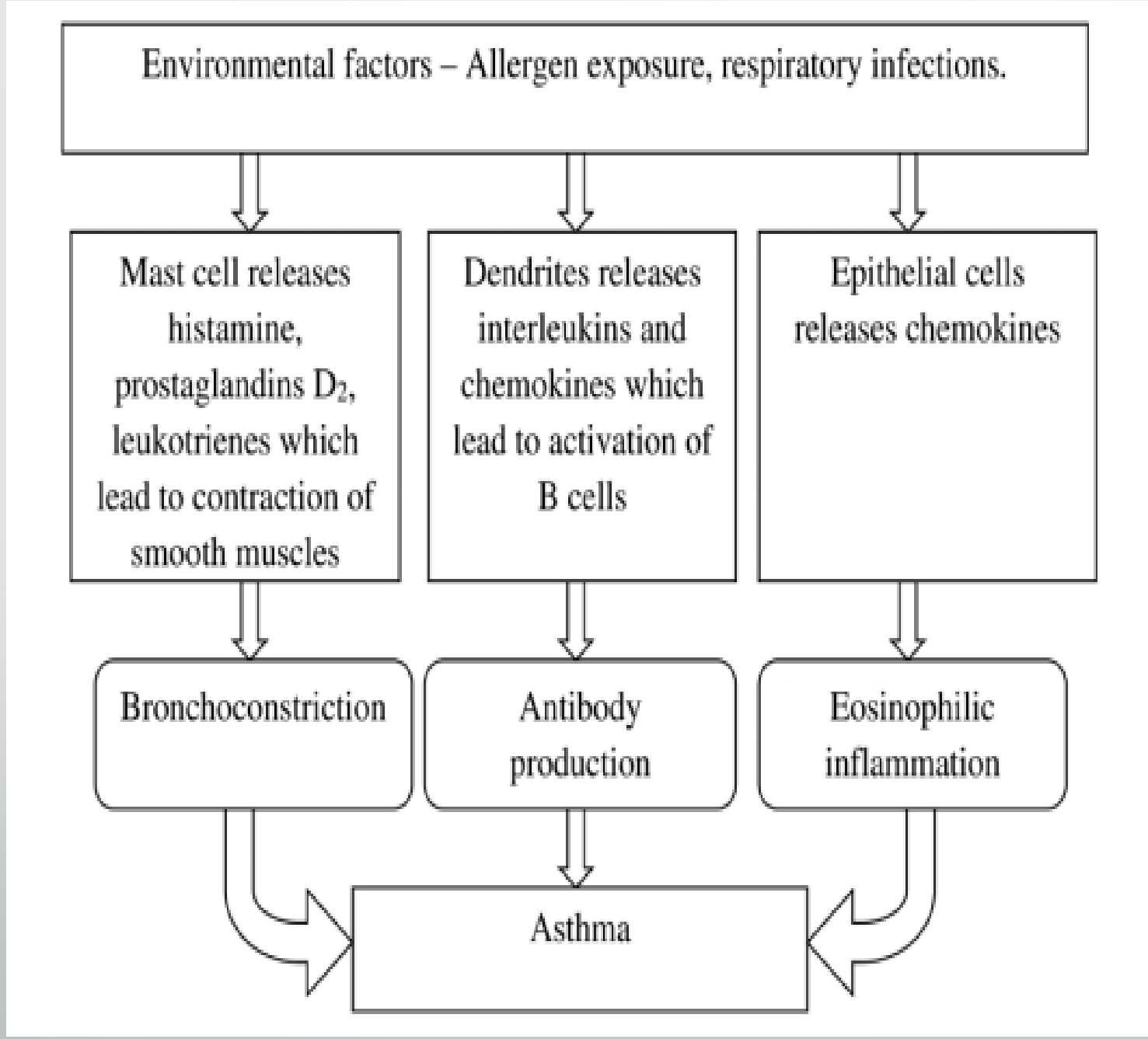
• The late-phase reaction is inflammatory in nature. Inflammatory mediators stimulate epithelial cells to produce chemokines (including eotaxin, a potent chemoattractant and activator of eosinophils) that promote the recruitment of TH2 cells, eosinophils, and other leukocytes, thus amplifying an inflammatory reaction that is initiated by resident immune cells

Non-Atopic Asthma

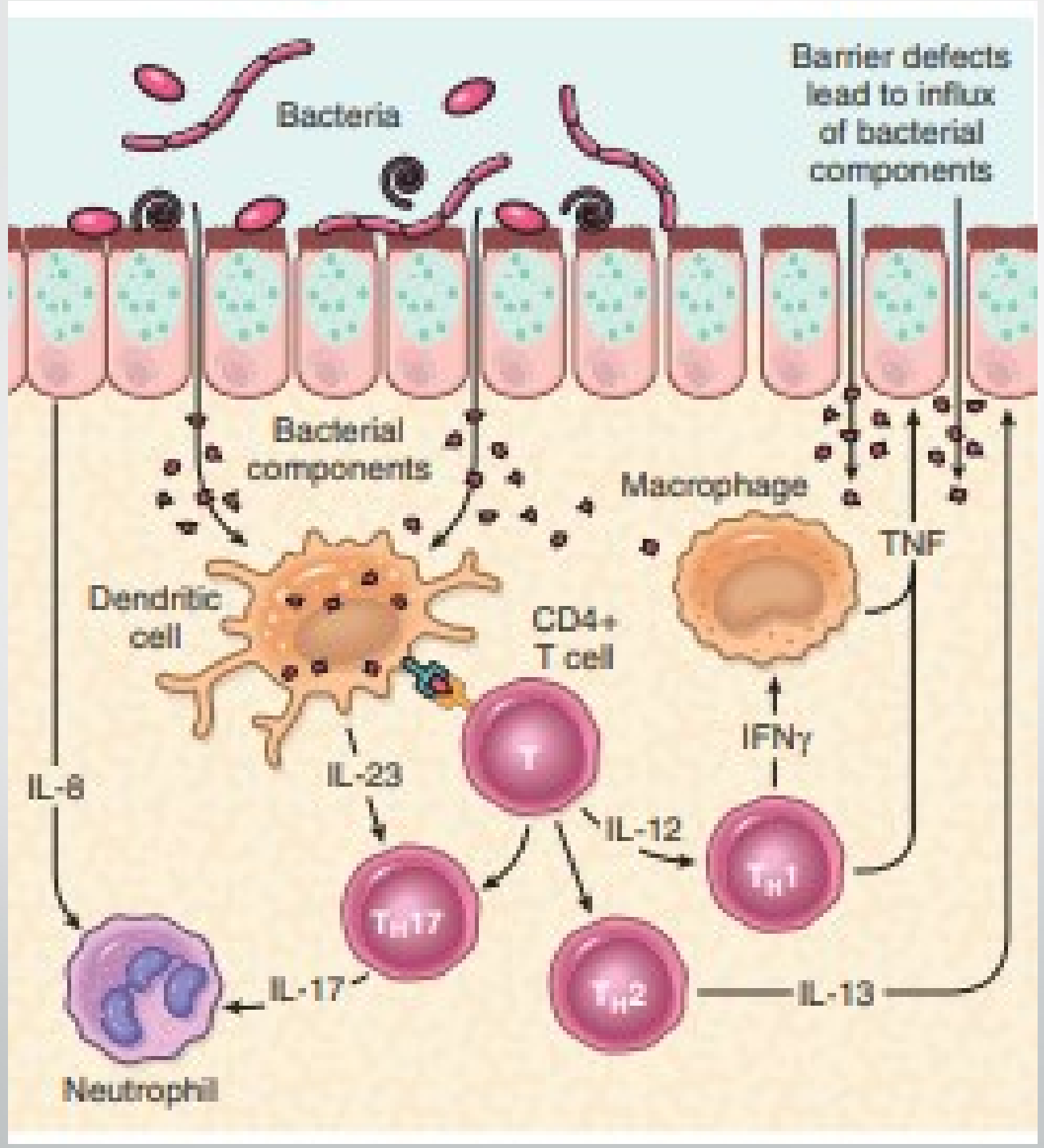
Patients with nonatopic forms of asthma do not have evidence of allergen sensitization, and skin test results usually are negative. A positive family history of asthma is less common. Respiratory infections due to viruses (e.g., rhinovirus, parainfluenza virus) and inhaled air pollutants (e.g., sulfur dioxide, ozone, nitrogen dioxide) are common triggers.


Environmental factors – Allergen exposure, respiratory infections.
Mast cell releases histamine, prostaglandins D_2, leukotrienes which lead to contraction of smooth muscles
Dendrites releases interleukins and chemokines which lead to activation of B cells
Epithelial cells releases chemokines
Bronchoconstriction
Antibody production
Eosinophilic inflammation
Asthma

Inflammatory bowel diseases

Is a chronic condition resulting from complex interactions between intestinal microbiota and host immunity in genetically predisposed individuals resulting an inappropriate mucosal immune activation.

IBD encompasses two entities, Crohn disease and ulcerative colitis.


Bacteria
Barrier defects lead to influx of bacterial components
Bacterial components
Macrophage
TNF
Dendritic cell
CD4+ T cell
IFNγ
IL-8
IL-23
IL-12
IL-17
IL-13
Neutrophil

Pathogenesis

Although precise causes are not yet defined, most investigators believe that IBD results from the combined effects of

1. alterations in host interactions with intestinal microbiota.
2. intestinal epithelial dysfunction,
3. aberrant mucosal immune responses,
4. altered composition of the gut microbiome.

1. The role of genetics in IBD

Risk for disease is increased when there is an affected family member, and in Crohn disease, the concordance rate for monozygotic twins is approximately 50%.and for ulcerative colitis is only 16%.

2. Mucosal immune responses., immunosuppressive and immunomodulatory agents remain mainstays of IBD therapy.

Polarization of helper T cells to the TH1 type is well recognized in Crohn disease, and some data suggest that TH17 T cells also contribute to disease pathogenesis. ALSO certain polymorphisms of the IL-23 receptor confer protection from Crohn disease and ulcerative colitis.

3. Epithelial defects. A variety of epithelial defects have been described in Crohn disease, ulcerative colitis, or both.

a. defects in intestinal epithelial tight junction barrier function occur in patients with Crohn disease.

b. the Paneth cell granules, which contain anti-microbial peptides that can affect composition of the luminal microbiota, are abnormal in patients with Crohn disease.

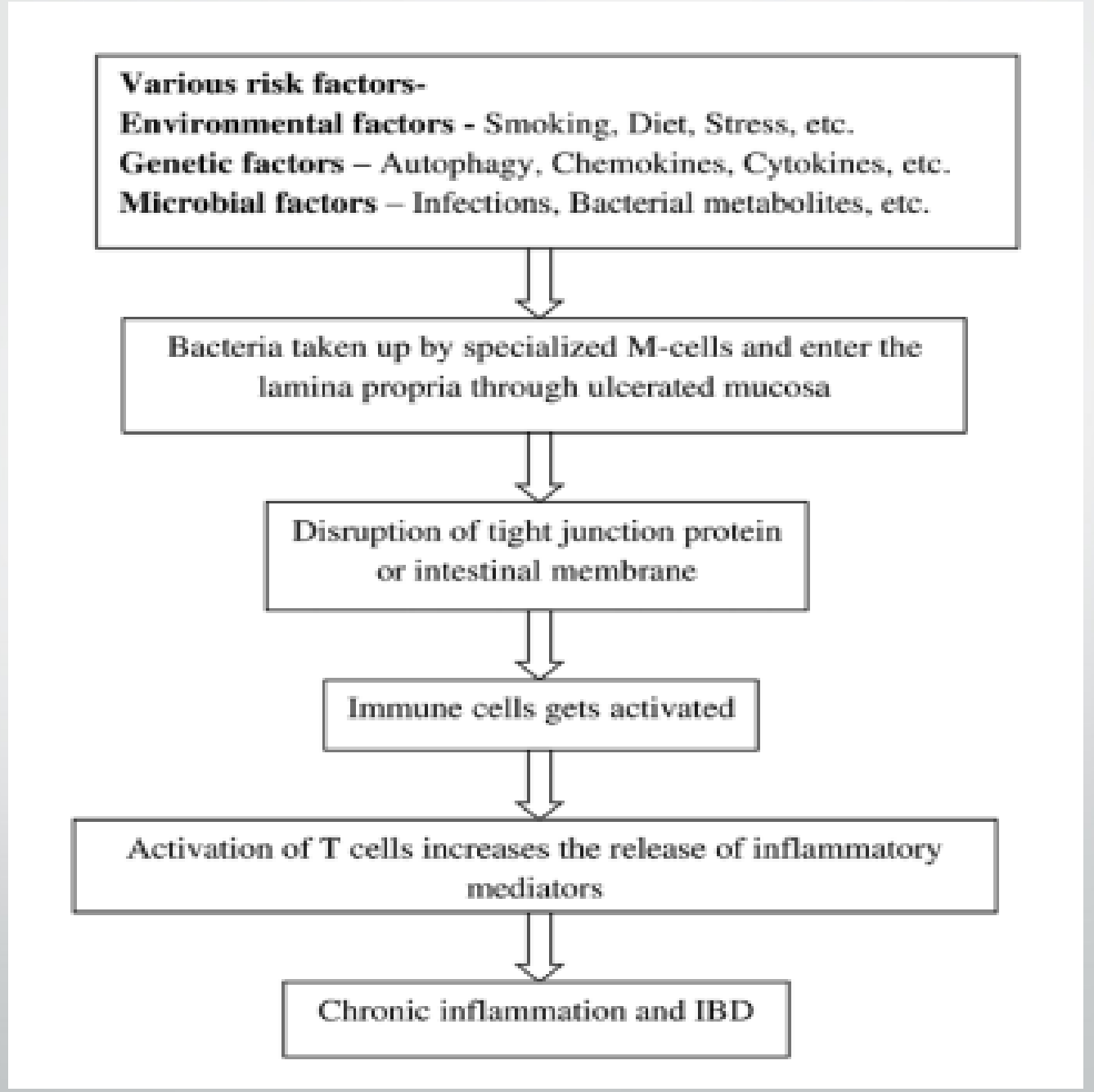

Various risk factors-
Environmental factors - Smoking, Diet, Stress, etc.
Genetic factors – Autophagy, Chemokines, Cytokines, etc.
Microbial factors – Infections, Bacterial metabolites, etc.
Bacteria taken up by specialized M-cells and enter the lamina propria through ulcerated mucosa
Disruption of tight junction protein or intestinal membrane
Immune cells gets activated
Activation of T cells increases the release of inflammatory mediators
Chronic inflammation and IBD

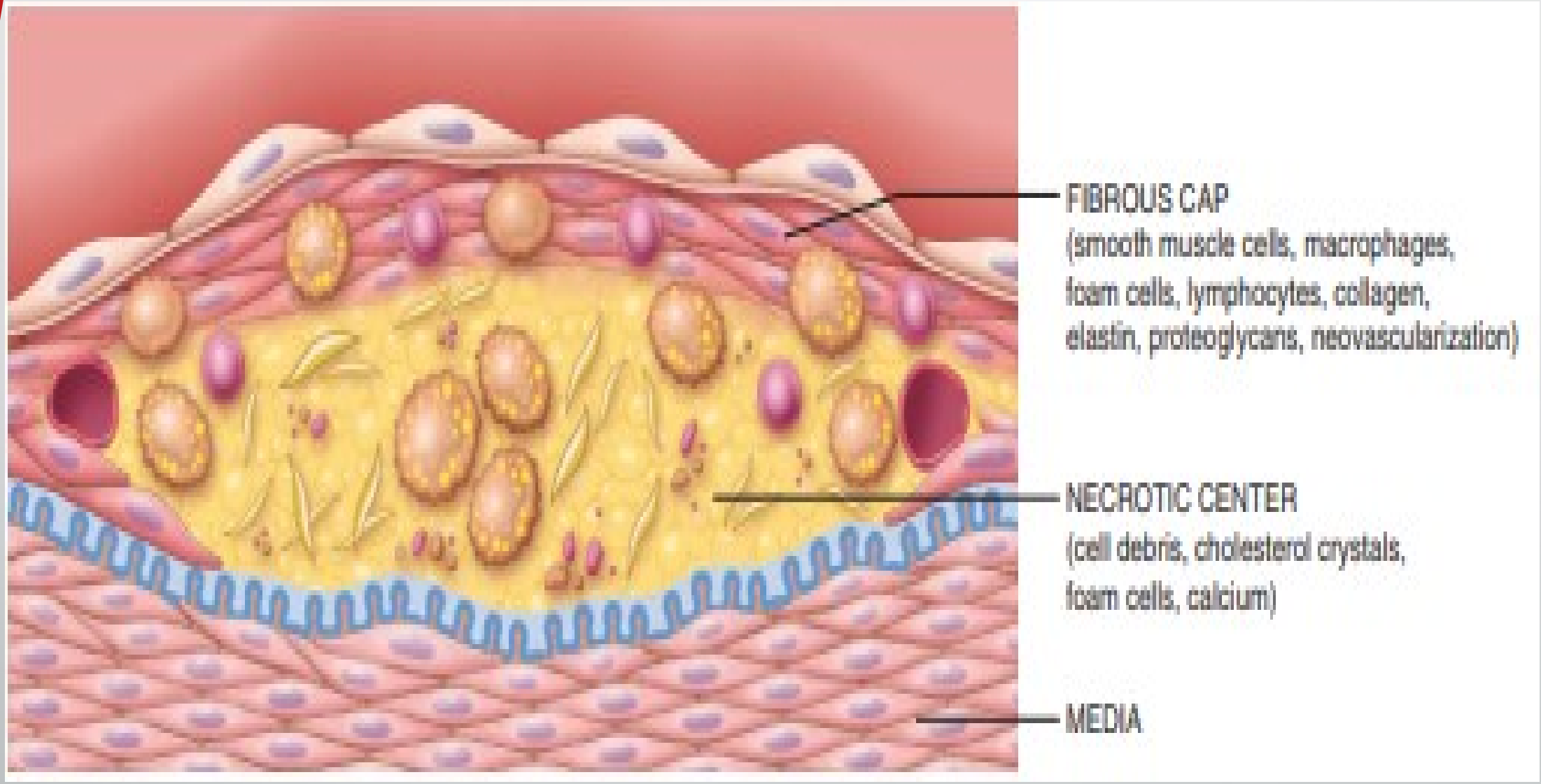
Table 15.5 Features of Crohn Disease and Ulcerative Colitis

Feature	Crohn Disease	Ulcerative Colitis
Macroscopic		
Bowel region affected	Ileum ± colon	Colon only
Rectal involvement	Sometimes	Always
Distribution	Skip lesions	Diffuse
Stricture	Yes	Rare
Bowel wall appearance	Thick	Thin
Inflammation	Transmural	Limited to mucosa and submucosa
Pseudopolyps	Moderate	Marked
Ulcers	Deep, knifelike	Superficial, broad-based
Lymphoid reaction	Marked	Moderate
Fibrosis	Marked	Mild to none
Serositis	Marked	No
Granulomas	Yes (~35%)	No
Fistulas/sinuses	Yes	No
Clinical		
Perianal fistula	Yes (in colonic disease)	No
Fat/vitamin malabsorption	Yes	No
Malignant potential	With colonic involvement	Yes
Recurrence after surgery	Common	No
Toxic megacolon	No	Yes

NOTE: Not all features may be present in a single case.

ARTERIOSCLEROSIS

- Arteriosclerosis literally means “hardening of the arteries”; it is a generic term reflecting arterial wall thickening and loss of elasticity.
- Atherosclerosis is characterized by intimal lesions called atheromas (or atheromatous or atherosclerotic plaques) that impinge on the vascular lumen and can rupture to cause sudden occlusion.



The basic structure of an atheromatous plaque.

Pathogenesis

Atherosclerosis is a chronic inflammatory response of the arterial wall to endothelial injury. Lesion progression involves interaction of modified lipoproteins, monocyte derived macrophages, T lymphocytes, and the cellular constituents of the arterial wall .According to this model, atherosclerosis results from the following pathogenic events:

- EC injury—and resultant endothelial dysfunction—leading to increased permeability, leukocyte adhesion, and thrombosis.
- Accumulation of lipoproteins (mainly oxidized LDL and cholesterol crystals) in the vessel wall.

- Accumulation and activation of macrophages in the intima.
- Platelet adhesion.
- Factor release from activated platelets ,macrophages and vascular wall.
- Lipid accumulation both extracellularly and within macrophages.
- SMC proliferation and ECM production.

summary

- Inflammation is a beneficial host response to foreign invaders and necrotic tissue, but it may also cause tissue damage.
- The main components of inflammation are a vascular reaction and a cellular response, both are activated by mediators that are derived from plasma proteins and various cells.
- The causes of inflammation include infections, tissue necrosis, foreign body, trauma and immune responses.
- The outcome of acute inflammation is either elimination of the noxious stimulus followed by decline of the reaction and repair of the damaged tissue, or persistent injury resulting in chronic inflammation.

Reference

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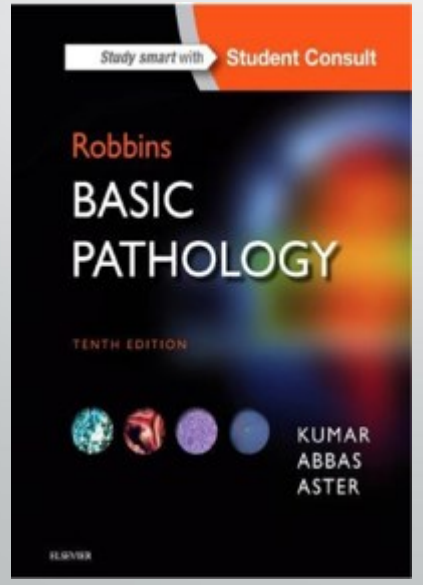


THANK YOU!