Lung diseases

VLA 1. 12. 2015

RESPIRATORY SYSTEM

BLOOD FLOW VS. VELOCITY OF BLOOD FLOW

- Ohm´s law:
- BF=BP/R, BP=blood pressure, BF=blood flow, R= resistance of blood vessels
- BF=BP/R

- Velocity of blood flow (v):
- $\Pi \times r^2 . v =$ (constant !!!!!)
- Blood vessels „like“ their natural (physiological) diameter and they have tendency to do it by

remodelling of blood flow

BLOOD FLOW ENERGY

- Because flowing blood has mass and velocity it has **kinetic energy** (KE). This KE is proportionate to the mean velocity squared (V^2; from $KE = \frac{1}{2} mV^2$). Furthermore, as the blood flows inside a vessel, pressure is exerted laterally against the walls of the vessel; this pressure represents the **potential or pressure energy** (PE). The total energy (E) of the blood flowing within the vessel, therefore, is the sum of the kinetic and potential energies (assuming no gravitational effects) as shown below.
- $E = KE + PE$ *(where* $KE \propto V^2$*)* *Therefore,* $E \propto V^2 + PE$

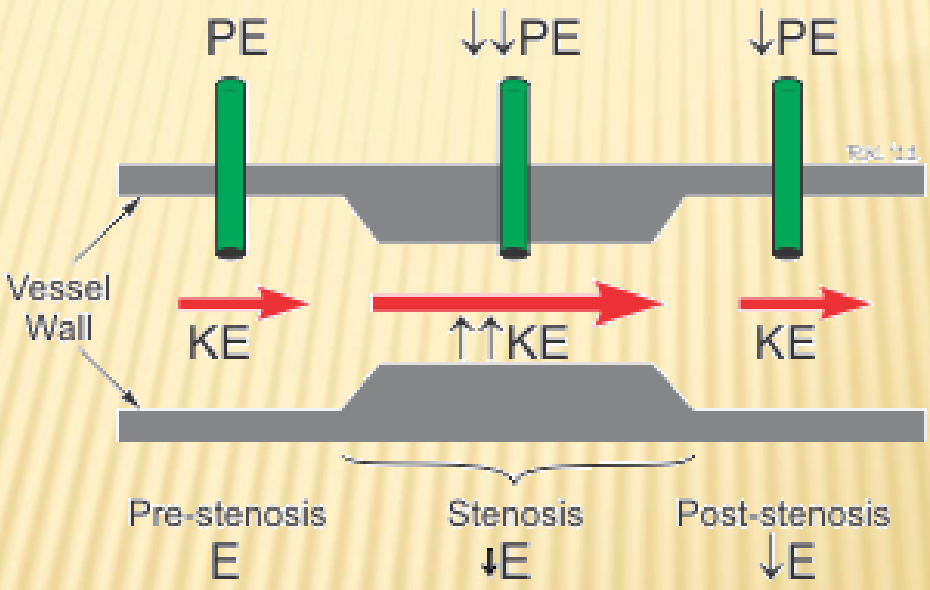
BLOOD FLOW AS HEMODYNAMIC PRIORITY!!!

- **Blood flow is driven by the difference in total energy between two points.** Although pressure is normally considered as the driving force for blood flow, in reality it is the total energy that drives flow between two points (e.g., longitudinally along a blood vessel or across a heart valve). Throughout most of the cardiovascular system, KE is relatively low, so for practical purposes, it is stated that the pressure energy (PE) difference drives flow. When KE is high, however, adding KE to the PE significantly increases the total energy, E. To illustrate this, consider the flow across the aortic valve during cardiac ejection. Late during ejection, the intraventricular pressure (PE) falls slightly below the aortic pressure (PE), nevertheless, flow continues to be ejected into the aorta. The reason for this is that the KE of the blood as it moves across the valve at a very high velocity ensures that the total energy (E) in the blood crossing the valve is higher than the total energy of the blood more distal in the aorta.

ENERGY OF BLOOD FLOW AND BERNOULLI'S PRINCIPLE

- **Kinetic energy and pressure energy can be interconverted so that total energy remains unchanged.** This is the basis of **Bernoulli's Principle**. This principle can be illustrated by a blood vessel that is suddenly narrowed then returned to its normal diameter. In the narrowed region (stenosis), the velocity increases as the diameter decreases. Quantitatively, $v \propto 1/D^2$ because flow (BF) is the product of mean velocity (v) and vessel cross-sectional area (S) ($BF = v \cdot D$), and S is directly related to diameter (D) (or radius, r) squared (from $S = \pi \cdot r^2$). If the diameter is reduced by one-half in the region of the stenosis, the velocity increases 4-fold. Because $KE \propto v^2$, the KE increases 16-fold. Assuming that the total energy is conserved within the stenosis (E actually decreases because of resistance), then the 16-fold increase in KE must result in a proportionate decrease in PE. Once past the narrowed segment, KE will revert back to its pre-stenosis value because the post-stenosis diameter is the same as the pre-stenosis diameter and flow is conserved. Because of the resistance of the stenosis, and the likelihood of turbulence, the post-stenosis PE and E will both fall.
- To summarize this concept, *blood flowing at higher velocities has a higher ratio of kinetic energy to potential (pressure) energy*.

BLOOD VESSEL WALL ENERGY AND STENOSIS



LUNG VESSELS REMODELLING

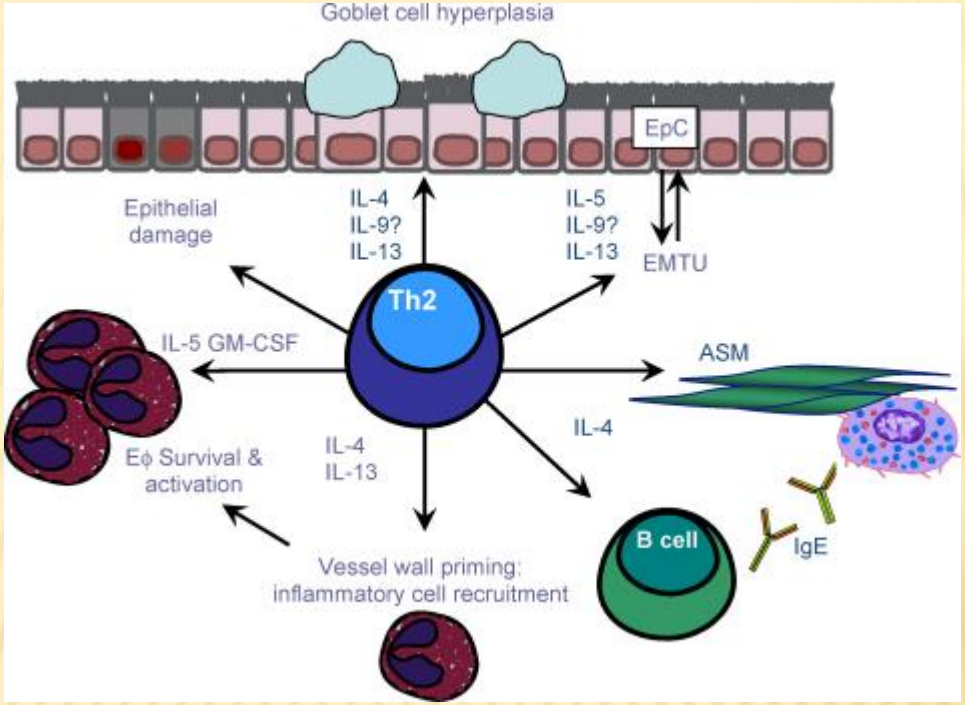
- Cooperation of actions of HIF-1 AND MiRNAs???

ASTMA

- 3 pathogenetic characteristics:
- Inflammation of airways with the wall thicking and increased permeability of capillaries
- Hypersecretion of mucus
- Contraction of smooth muscle cells in bronchi

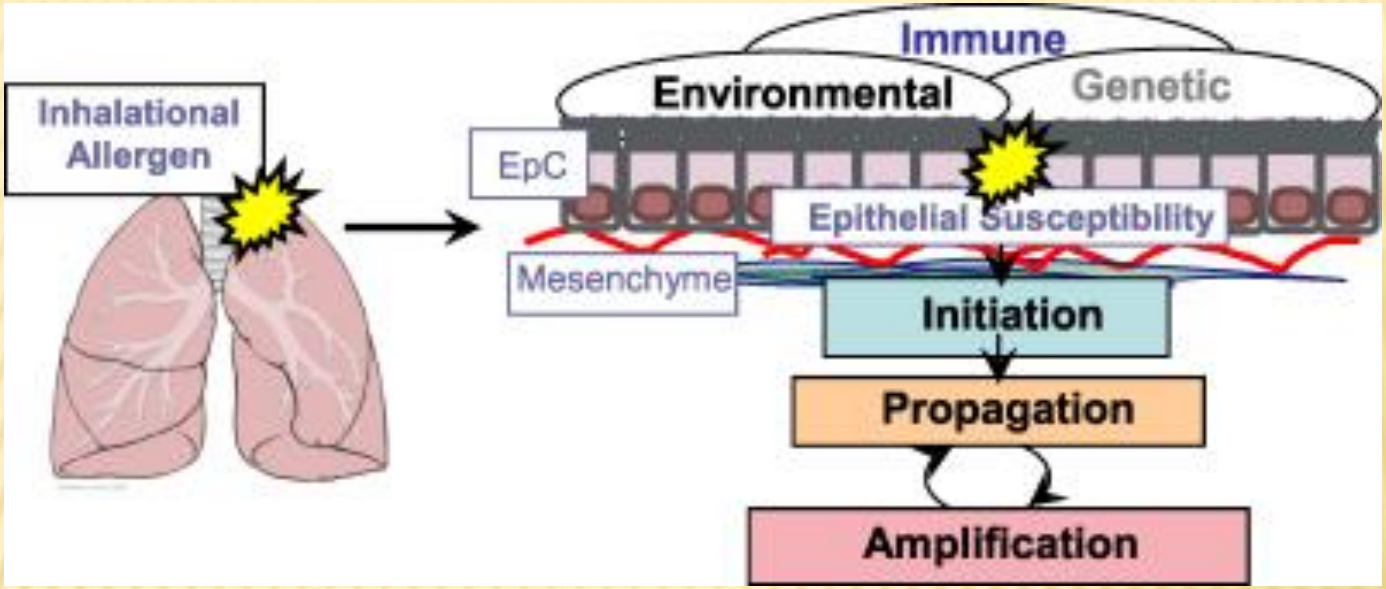
PATHOGENESIS OF ASTHMA

- Bronchiols are narrowing.
- Atelectasis is developing (microscopic, segmental and/or lobar) as a result of complete airways obstruction by mucous plug and/or as a result of edema of airways.
- Decrease of ventilation/ perfusion proportion is leading to decreased of saturation of Hb by O2.



Th2 effector cells and asthma pathogenesis. Th2 cells have a central role in orchestrating the allergen-induced inflammatory response. Th2 derived IL-4 and IL-13 stimulate B cells to synthesise IgE whilst IL-5 is necessary for eosinophilic inflammation. Th2 cytokines are also involved in mast cell proliferation and allergic airway remodelling. *Key*: Eϕ, eosinophil; EpC, epithelial cell; EMTU, epithelial to mesenchymal tropic unit; ASM, airway smooth muscle; AHR, airway hyperreactivity.

Mutat Res. 2010 August 7; 690(1-2): 24–39.
doi: 10.1016/j.mrfmmm.2009.09.005



Gene environment interactions in asthma. Asthma is an inflammatory disorder of profound heterogeneity with strong genetic and environmental components. Local airway susceptibility factors together with allergen-specific immune polarisation interact both in the induction and subsequent expression of the disease phenotype. *Key*: EpC, epithelial cell.

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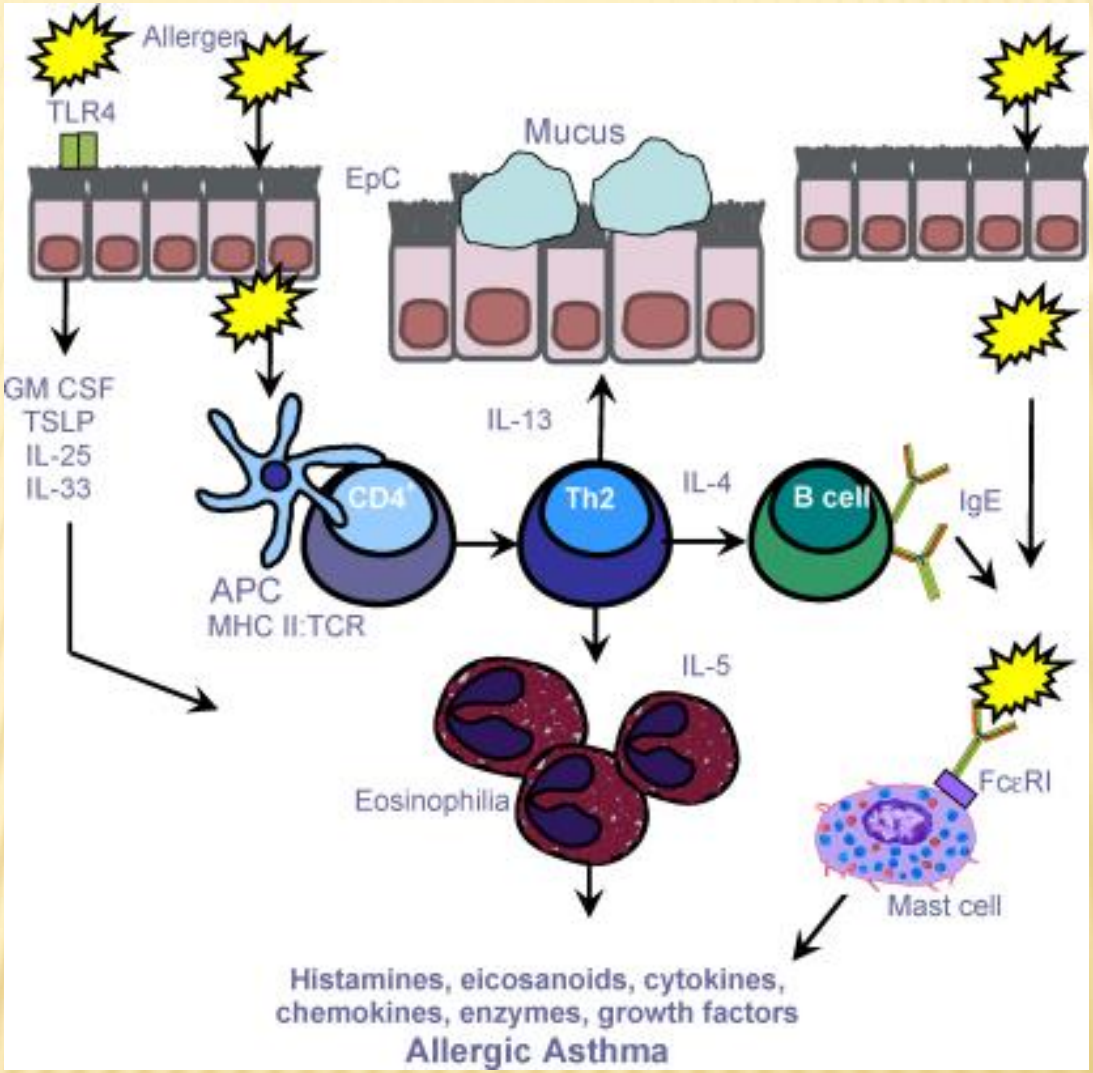

Mutat Res. 2010 August 7; 690(1-2): 24–39.
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TO THE PREVIOUS PICTURE:

- Immune cells and the inflammatory cascade in asthma. Initial exposure(s) to allergen leads to the activation of allergen-specific Th2 cells and IgE synthesis (sensitisation). Subsequent allergen exposures cause inflammatory-cell recruitment, activation and mediator release. IgE-sensitised mast cells expressing the high affinity IgE receptor (FcRI) degranulate, releasing both pre-formed and newly synthesized mediators including histamine, leukotrienes and cytokines, which promote vascular permeability, smooth muscle contraction and mucus production. Chemokines released by inflammatory and resident cells direct recruitment of inflammatory cells characterised eosinophils and Th2 cells. Eosinophils release an array of pro-inflammatory mediators, including leukotrienes and basic proteins and mediators such as, IL-5. *Key*: APC, antigen-presenting cell; ASM, airway smooth muscle; EpC, epithelial cell; GM-CSF, granulocyte monocyte colony stimulating factor; MHC, major histocompatibility; TCR, T cell receptor; TSLP, thymic stromal lymphopoietin.

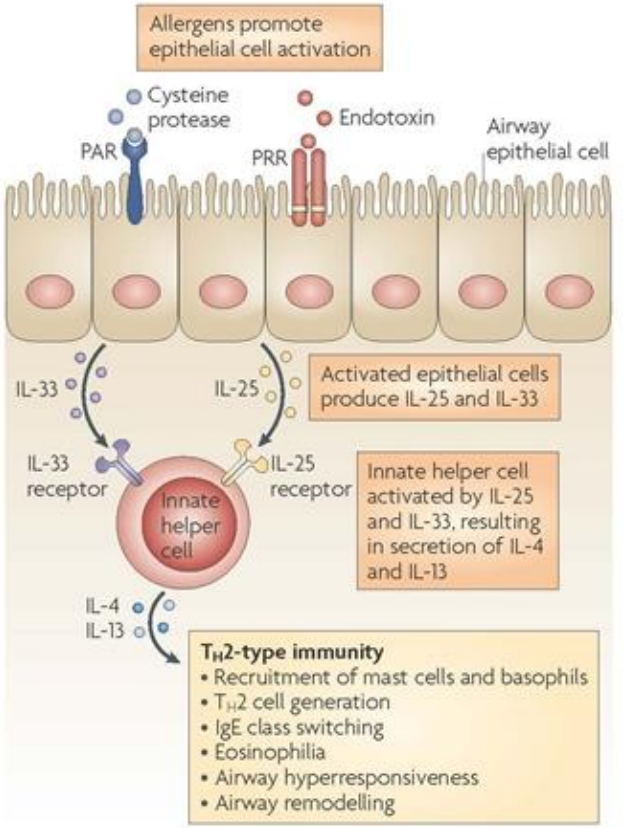


Figure 2 | **Alternative pathway to a T_H2-type response in the airways.** Cysteine protease activity and endotoxin within allergens can activate lung epithelial cells through protease-activated receptors (PARs) and pattern-recognition receptors (PRRs), such as Toll-like receptors. Recent experimental data indicate that a population of 'innate helper' cells can secrete interleukin-4 (IL-4) and IL-13 in response to epithelial cell-derived cytokines, such as IL-33 and IL-25, and promote T helper 2 (T_H2)-type immune responses. Thymic stromal lymphopoietin (TSLP) can promote T_H2-type responses in the lung, but a direct association with this cytokine and innate helper cells in the lung has not yet been found. Although these innate helper cells have been identified in a number of different tissues, including in the resting lungs, evidence for their involvement in allergic airway inflammation remains indirect. Therefore the model described here is theoretical and remains to be tested *in vivo*.

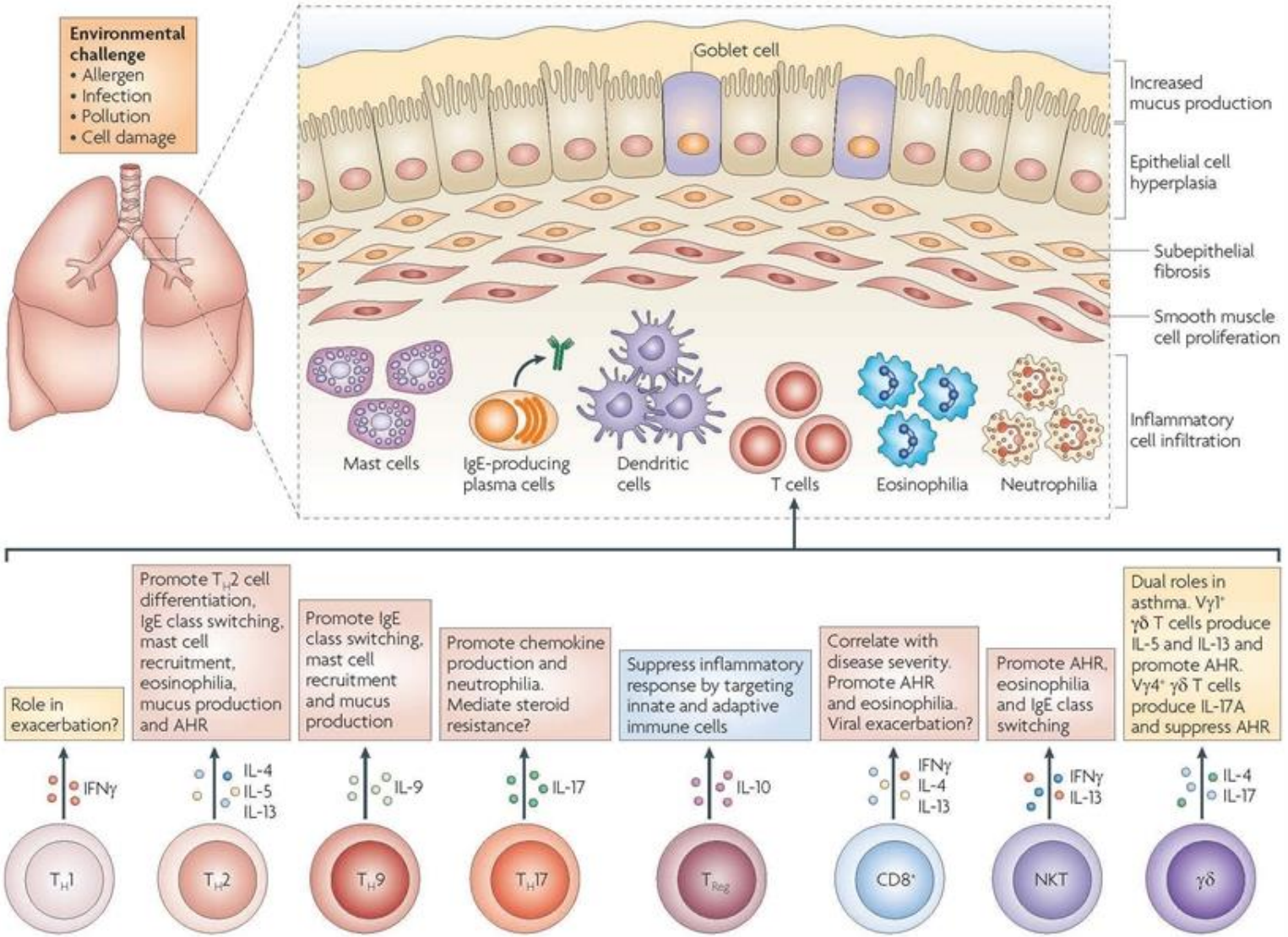
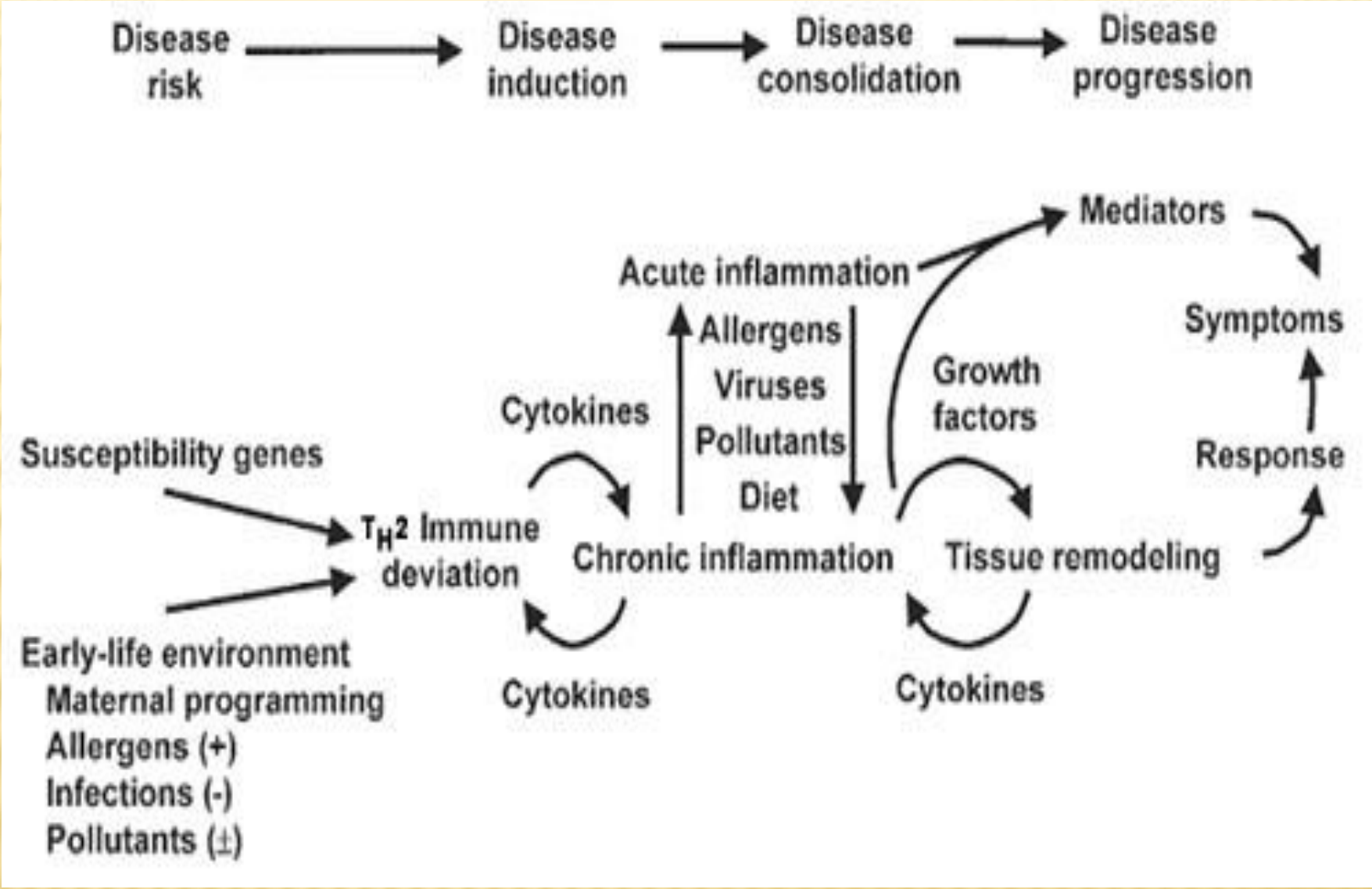
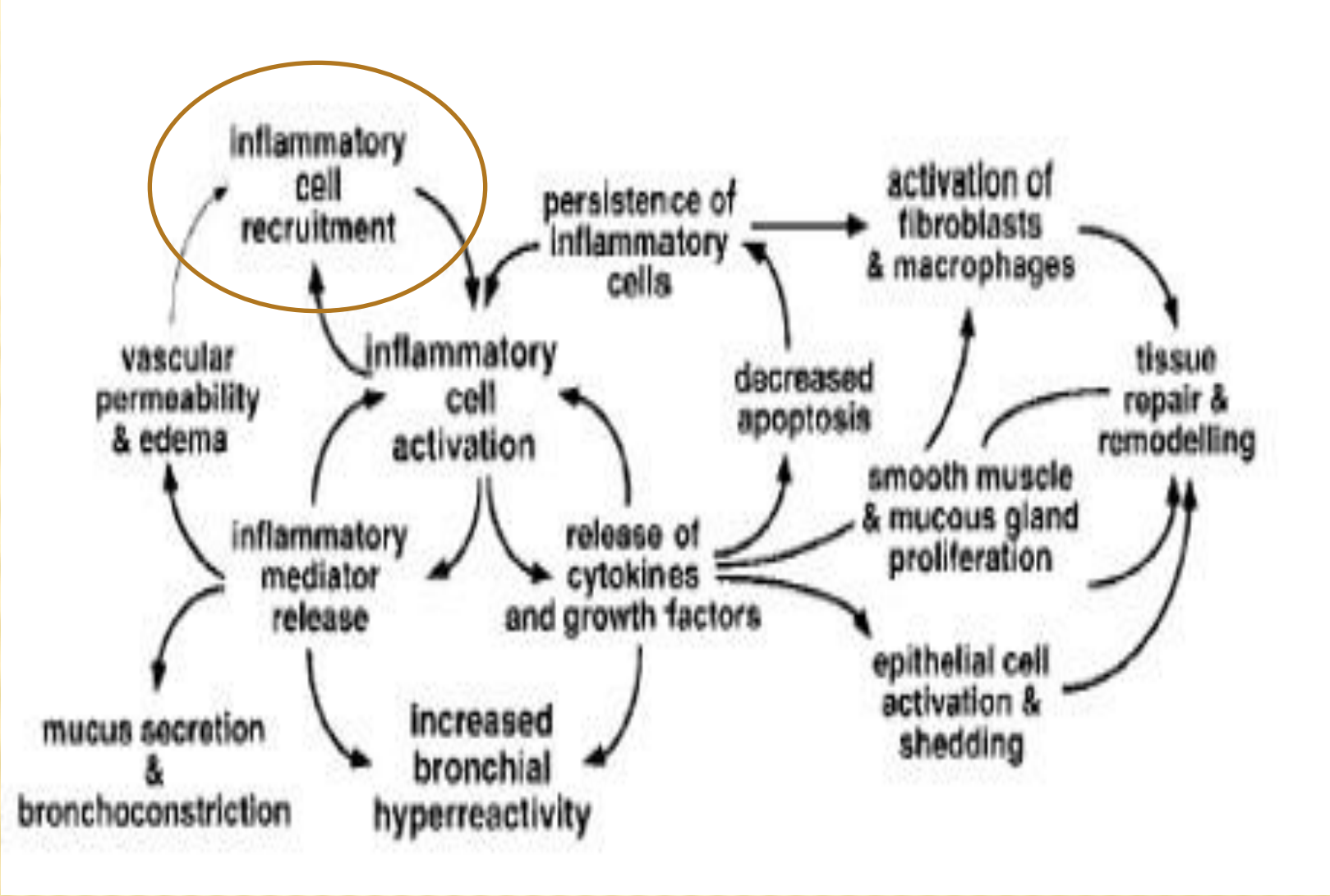


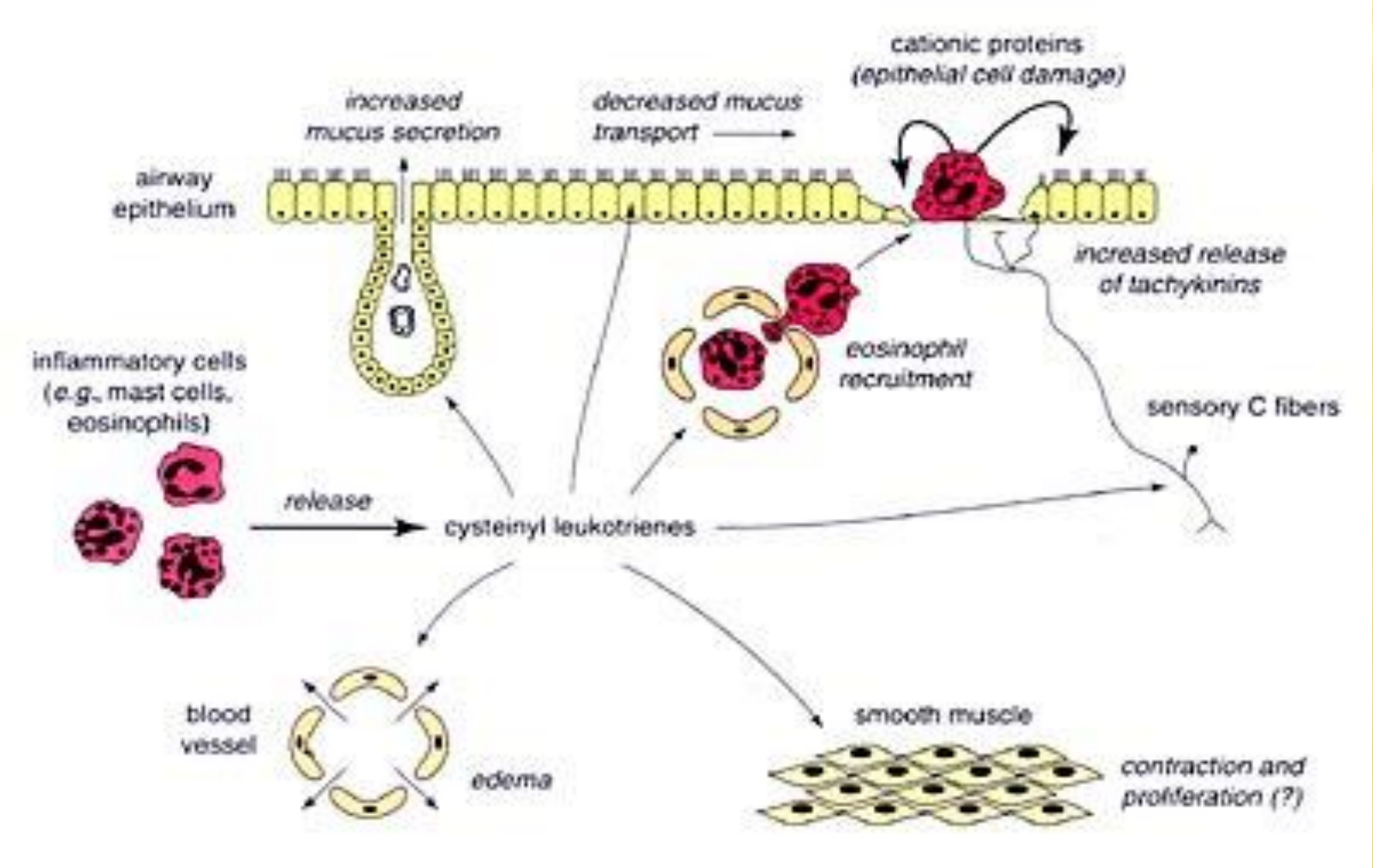
Figure 1 | **T cells involved in the induction of the allergic phenotype.** Asthma is a heterogeneous disease that is characterized by airway hyperresponsiveness (AHR), recruitment of inflammatory leukocytes to the lung and tissue remodelling, including mucus production and airway smooth muscle changes. A number of different T cell subsets are thought to influence the nature and magnitude of the allergic immune response by the cytokines that they secrete. T helper 2 (T_H2) cells are thought to promote eosinophil recruitment, in conjunction with nature killer T (NKT) cells and $CD8^+$ T cells. By contrast, T_H1 cells and T_H17 cells are thought to be associated with severe, steroid-resistant asthma, which is often marked by neutrophilic infiltrates. Regulatory T (T_{Reg}) cells and subtypes of γδ T cells are able to downregulate pulmonary immune responses and are thought to be important for maintenance of immune homeostasis in the lungs. The nature and magnitude of allergic inflammation in the lung is influenced by external environmental stimuli, such as exposure to allergens and pollution as well as infection with pathogens. IFNγ, interferon-γ; IL, interleukin.



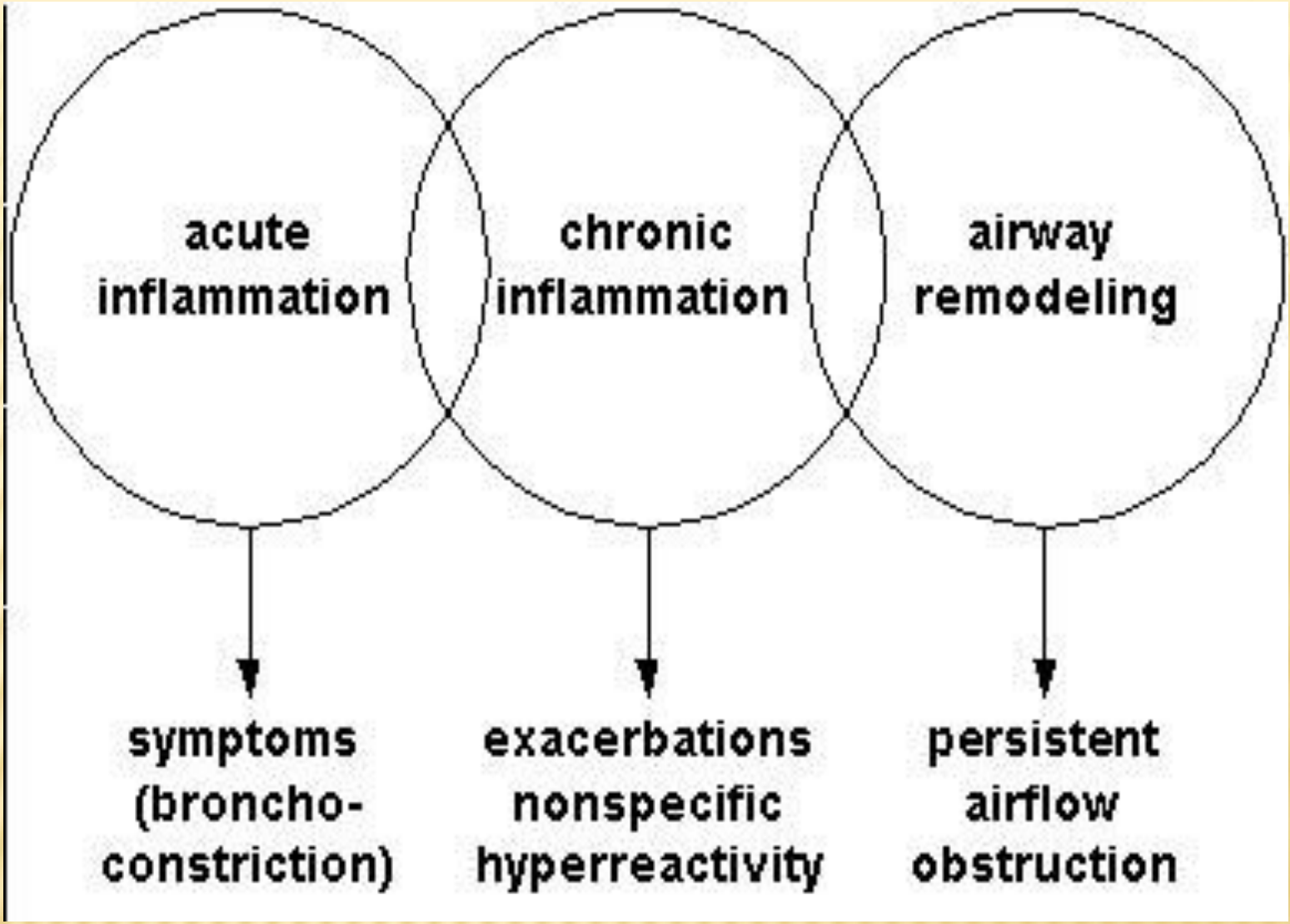
Etiopathogenesis of asthma



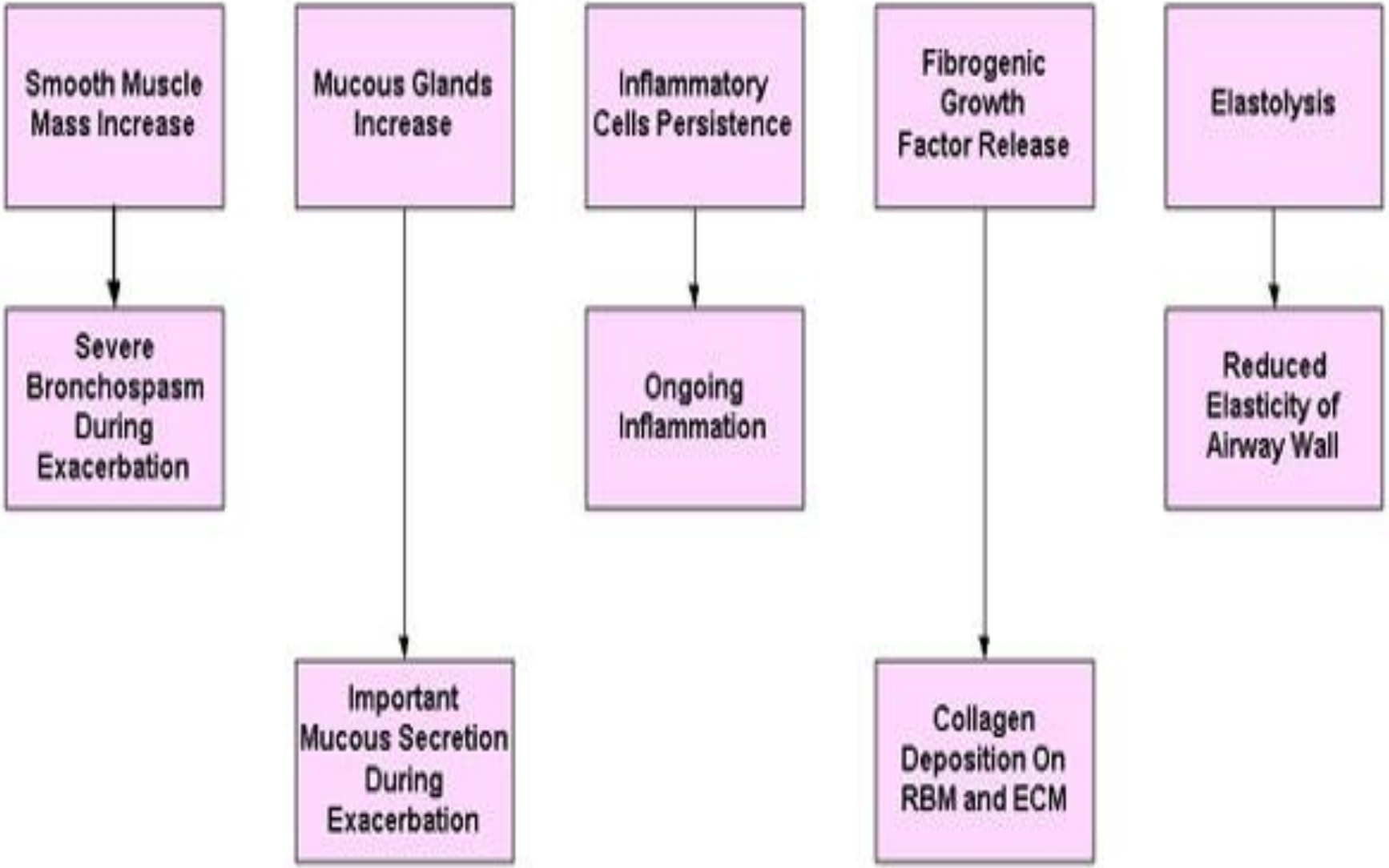
Mechanisms of acute and chronic inflammation in asthma and mechanisms of remodelling



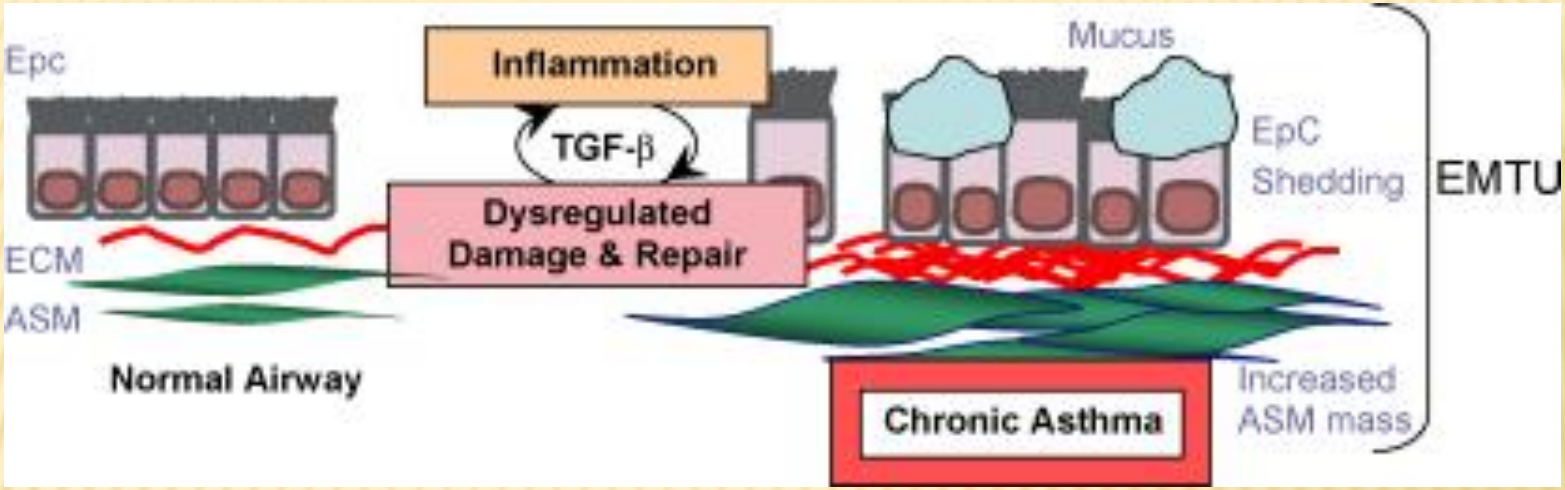
Leukotriens in asthma



Relations between pathophysiological mechanisms and clinical state



Clinical relations of airway remodelling in asthma (RBM- basal membrane, ECM - extracellular matrix)



Airway remodelling in asthma. Activation of airway epithelium by aeroallergens and pollutants leads to downstream effects including inflammation, dysregulated repair, activated EMTU and tissue remodelling. *Key*: ASM, airway smooth muscle; ECM, extracellular matrix; EMTU, epithelial to mesenchymal trophic unit; Epc, EpC, epithelial cell; TGF-β, transforming growth factor-β.

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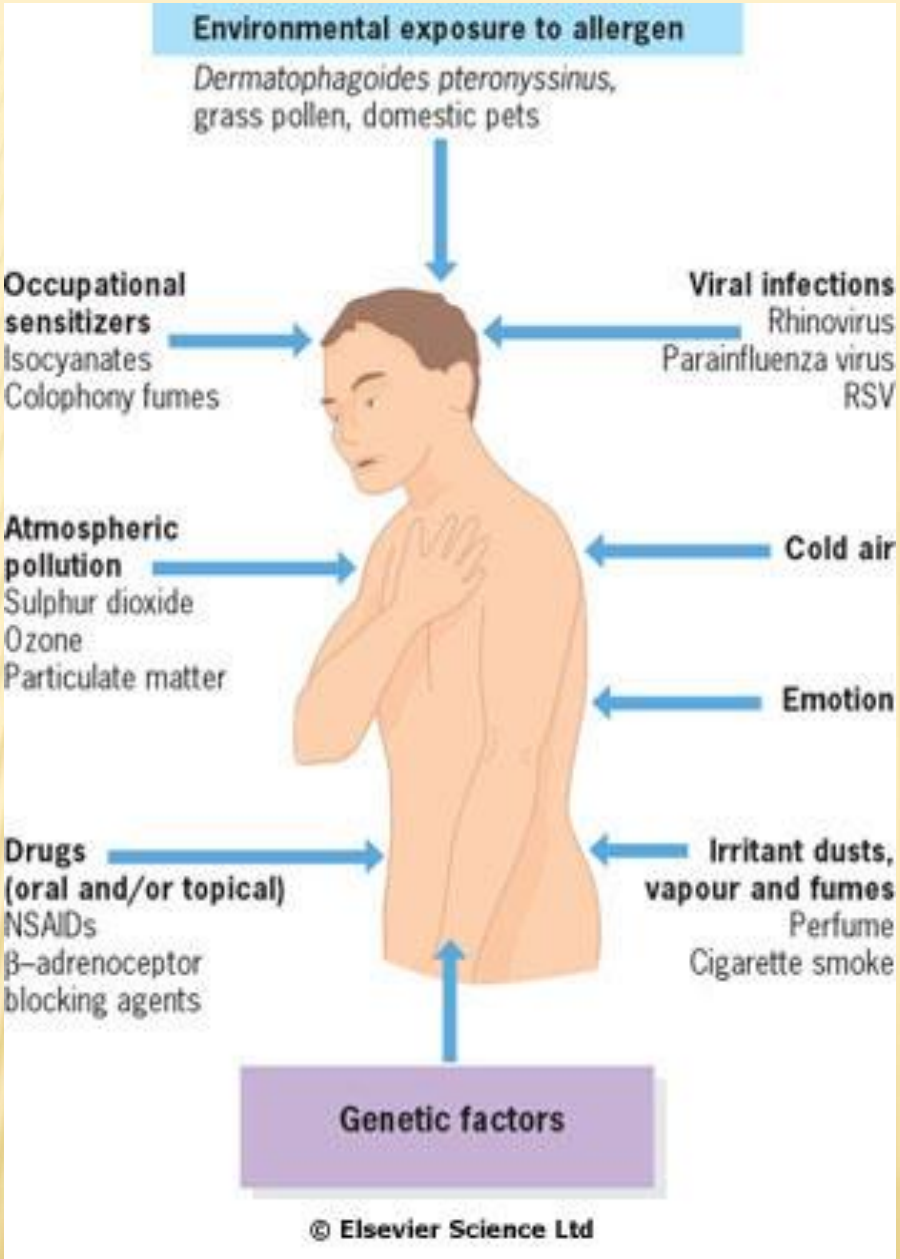
TYPES OF ASTHMA

- *Extrinsic* – clear external cause
- *Intrinsic (cryptogenic)* – it is nit possible to identify cause.
- *Extrinsic asthma* in atopic persons with positive skin prick tests for inhalation allergens (90% of children with persitent asthma, only 50% of adulat patients).
- *Intrinsic asthma* starts in middle age („late onset“).


Environmental exposure to allergen
Dermatophagoides pteronyssinus, grass pollen, domestic pets
Occupational sensitizers
Isocyanates
Colophony fumes
Viral infections
Rhinovirus
Parainfluenza virus
RSV
Atmospheric pollution
Sulphur dioxide
Ozone
Particulate matter
Cold air
Emotion
Drugs (oral and/or topical)
NSAIDs
β–adrenoceptor blocking agents
Irritant dusts, vapour and fumes
Perfume
Cigarette smoke
Genetic factors
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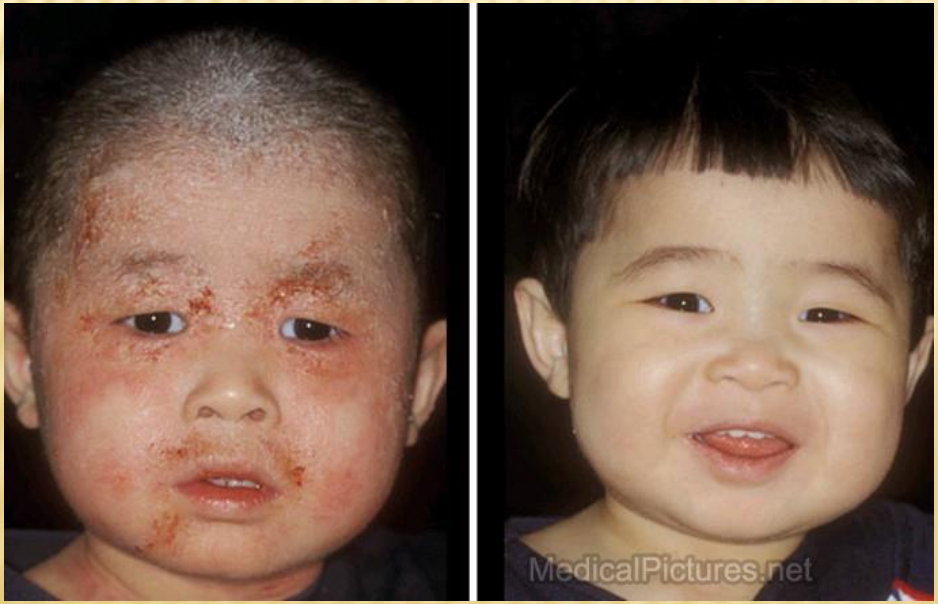
ALLERGY AND ATOPY

- Atopy:
- Familial occurrence
- Characteristic reaction to environmental allergens prostředí
- Circulationg antibodies
- IgE antibodies in 30-40% of population
- Correlation between IgE levels and hyperreactivity of airways
- Genetic factors and environmental factors influence IgE levels.
- Candidate genes for IL-3, IL-4, IL-5, IL-9, IL-13 a GM-CSF – cluster on 5q31-33.
- Hygienic theory of asthma dvelopment

ATOPIC DISEASES

- Atopic rhinitis
- Atopic dermatitis
- Atopic astma
- Combinations (4)

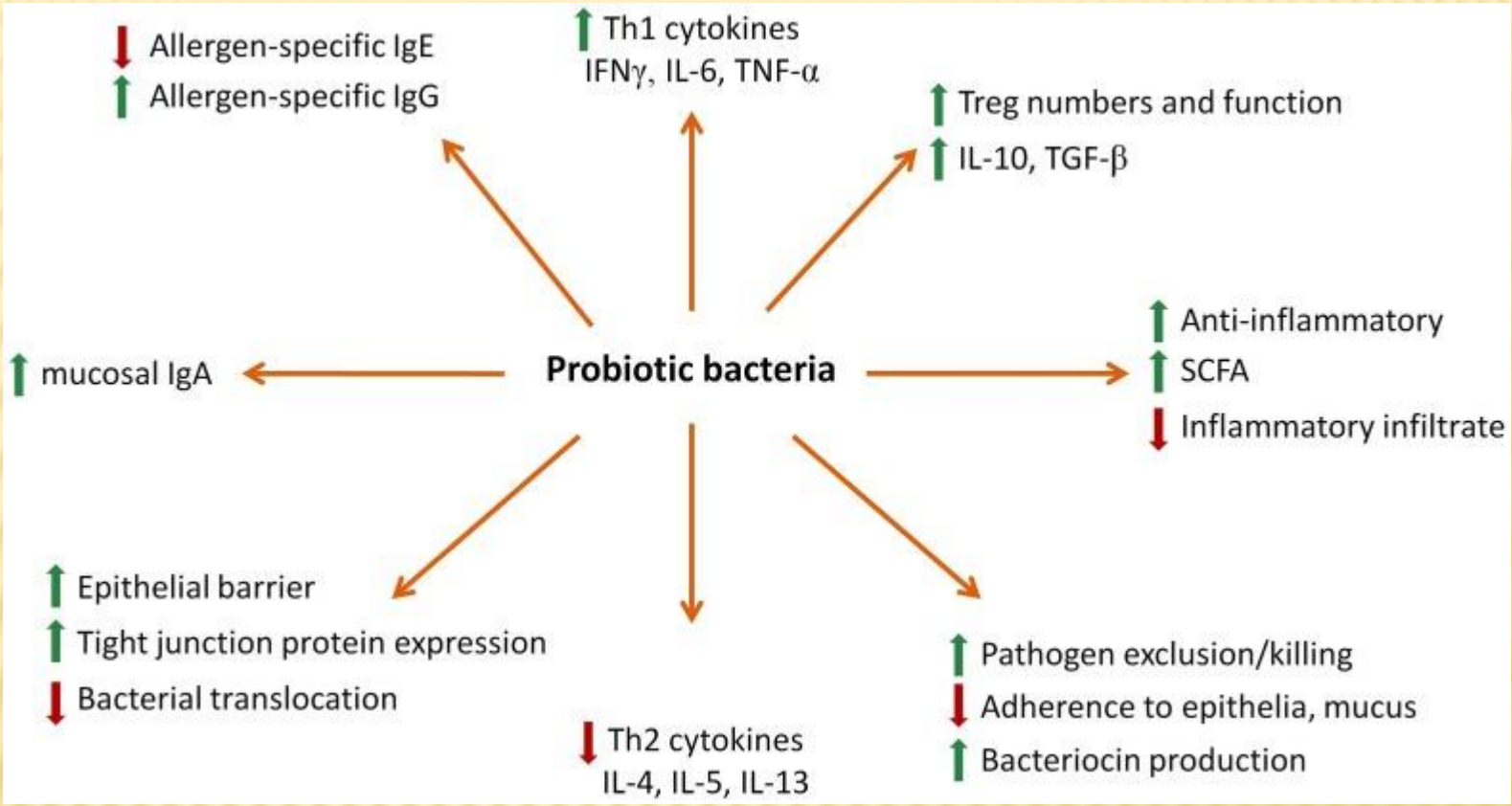


ATOPIC DERMATITIS

- complex interaction between defects in skin barrier function, immune abnormalities, and environmental and infectious agents.
- Skin barrier abnormalities appear to be associated with mutations within the filaggrin gene, which encodes a structural protein essential for skin barrier formation. The skin of individuals with AD has also been shown to be deficient in ceramides (lipid molecules) as well as antimicrobial peptides such as cathelicidins, which represent the first-line of defense against many infectious agents. These skin barrier abnormalities lead to transepidermal water loss (passage of water from inside the body through the epidermal layer of the skin to the surrounding atmosphere) and increased penetration of allergens and microbes into the skin. The infectious agent most often involved in AD is *Staphylococcus aureus* (*S. aureus*), which colonizes in approximately 90% of AD patients.

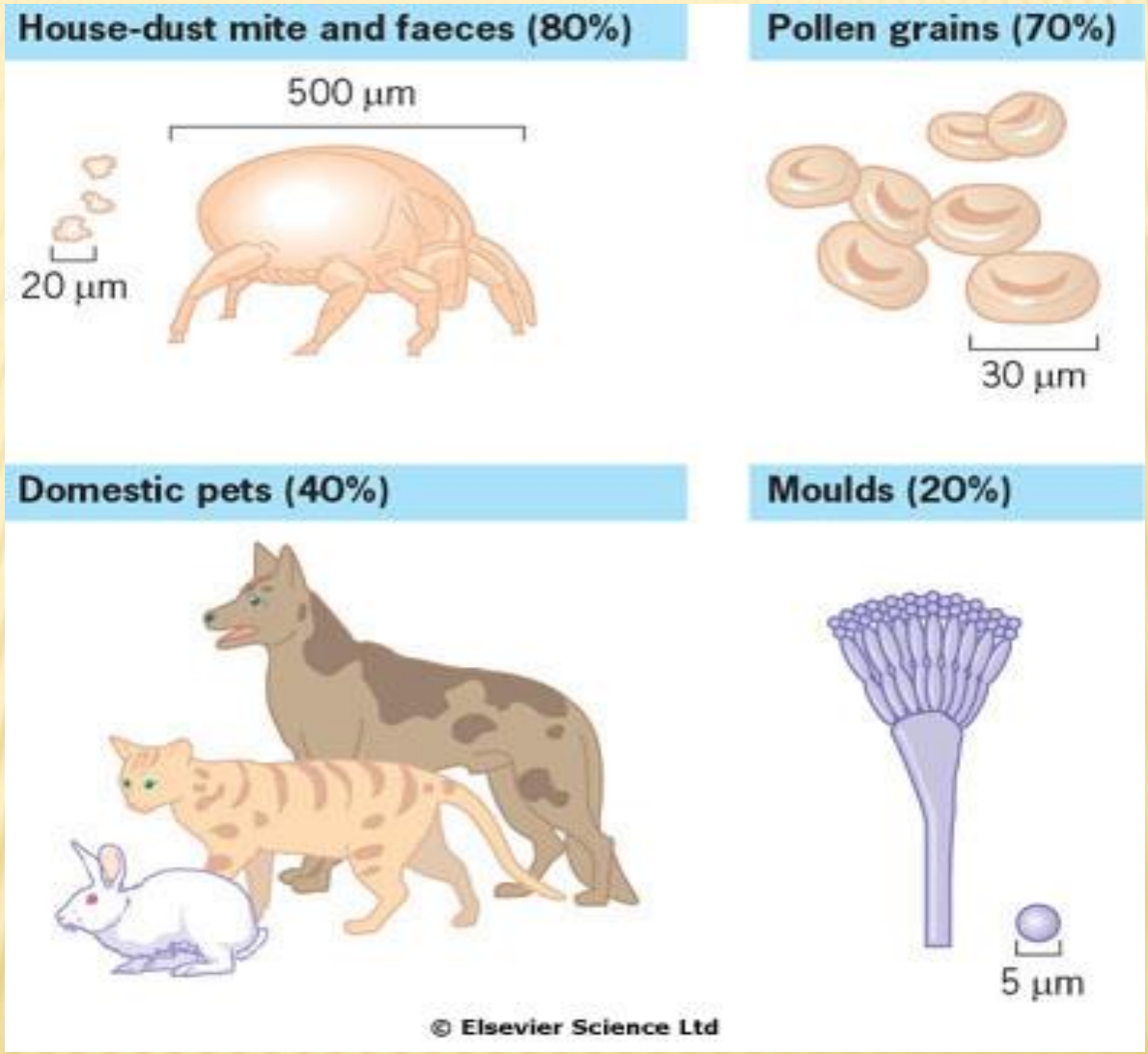
ATOPIC DERMATITIS

- Defective innate immune responses also appear to contribute to increased bacterial and viral infections in patients with AD. This interplay of factors leads to T-cell responses in the skin (initially a predominantly T helper-2 [Th2] response and later a predominantly Th1 response) with resultant release of chemokines and proinflammatory cytokines (e.g., interleukin [IL]-4, 5 and tumour necrosis factor) that promote immunoglobulin E (IgE) production and systemic inflammatory responses, leading to pruritic inflammation of the skin.


↓ Allergen-specific IgE
↑ Allergen-specific IgG
↑ Th1 cytokines
IFNγ, IL-6, TNF-α
↑ Treg numbers and function
↑ IL-10, TGF-β
↑ mucosal IgA
Probiotic bacteria
↑ Anti-inflammatory
↑ SCFA
↓ Inflammatory infiltrate
↑ Epithelial barrier
↑ Tight junction protein expression
↓ Bacterial translocation
↓ Th2 cytokines
IL-4, IL-5, IL-13
↑ Pathogen exclusion/killing
↓ Adherence to epithelia, mucus
↑ Bacteriocin production

Probiotics demonstrating a beneficial effect in clinical studies of eczema.

Type of clinical study	Probiotic
Treatment	*Lactobacillus rhamnosus GG*
	Lactobacillus rhamnosus HN001
	Lactobacillus sakei KCTC
	Lactobacillus acidophilus La-5
	Lactobacillus acidophilus[*]
	Lactobacillus salivarius LS01
	Lactobacillus fermentum VR1
	Bifidobacterium lactis Bb12
	Bifidobacterium lactis UABLA-12[**]
	Bifidobacterium bifidum
Prevention	*Lactobacillus rhamnosus GG*
	Lactobacillus rhamnosus LC705
	Lactobacillus paracasei F19
	Bifidobacterium breve Bb99
	Propionibacterium freudenreichii[***]

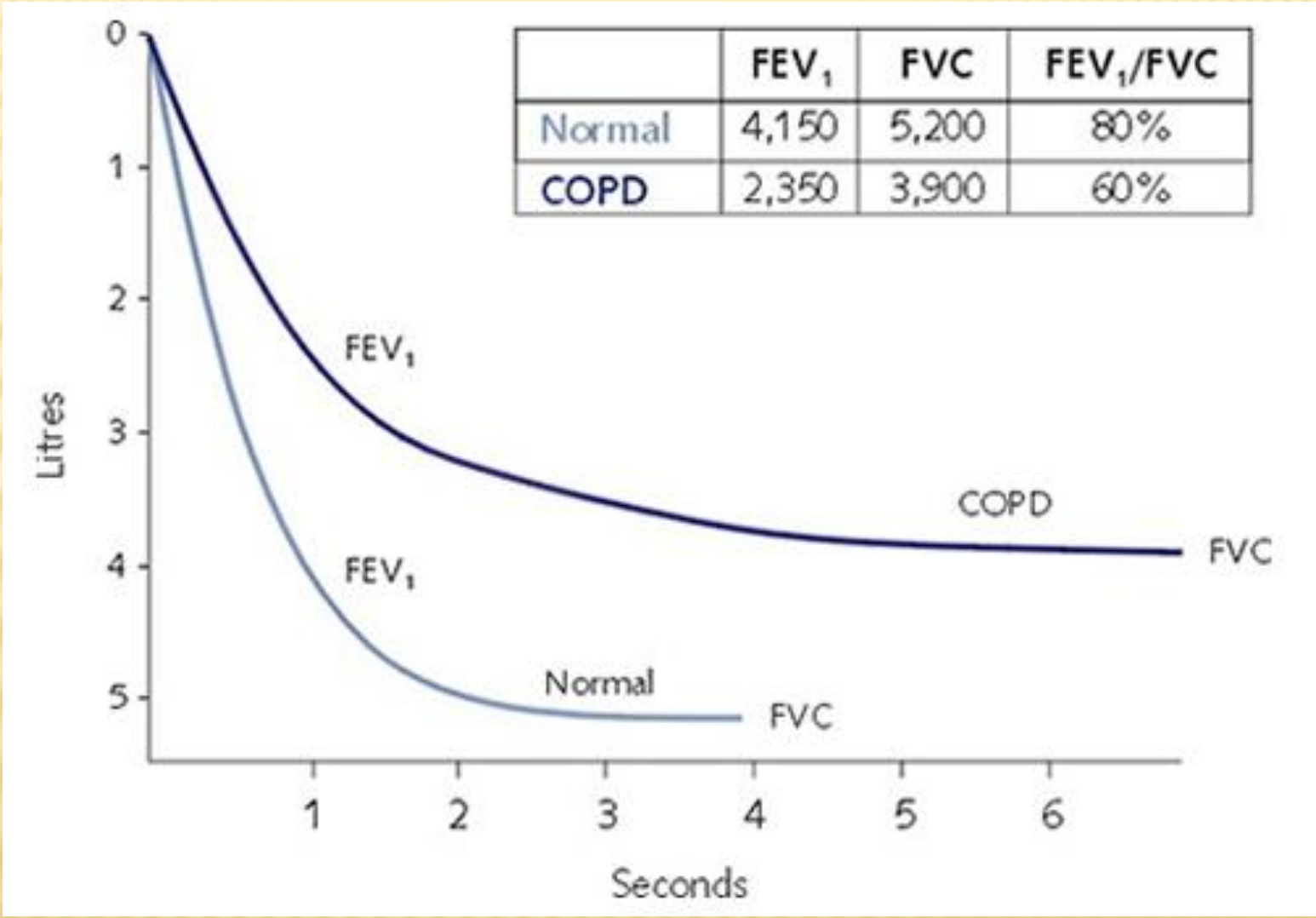


Antigens causing allergic rhinitis and asthma

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

- ***Symptoms***

- Chronic (long-lasting) cough
- A cough that produces mucus
- An increase in respiratory infections (such as flu and colds)
- Shortness of breath, especially during physical activity
- A tight feeling in the chest
- Wheezing

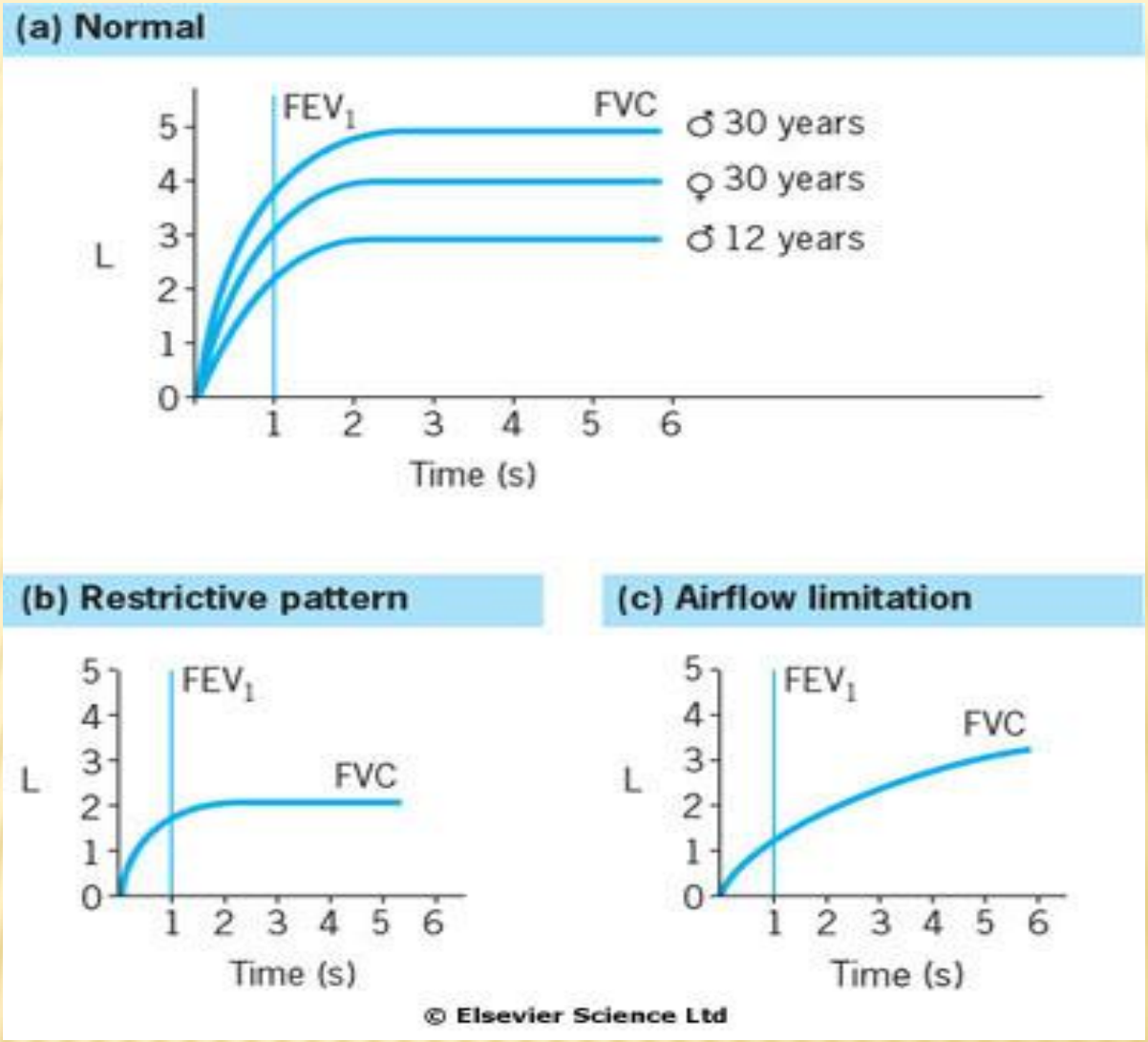


	FEV_1	FVC	FEV_1/FVC
Normal	4,150	5,200	80%
COPD	2,350	3,900	60%

Chronic obstructive pulmonary diseases: diagnostic criteria

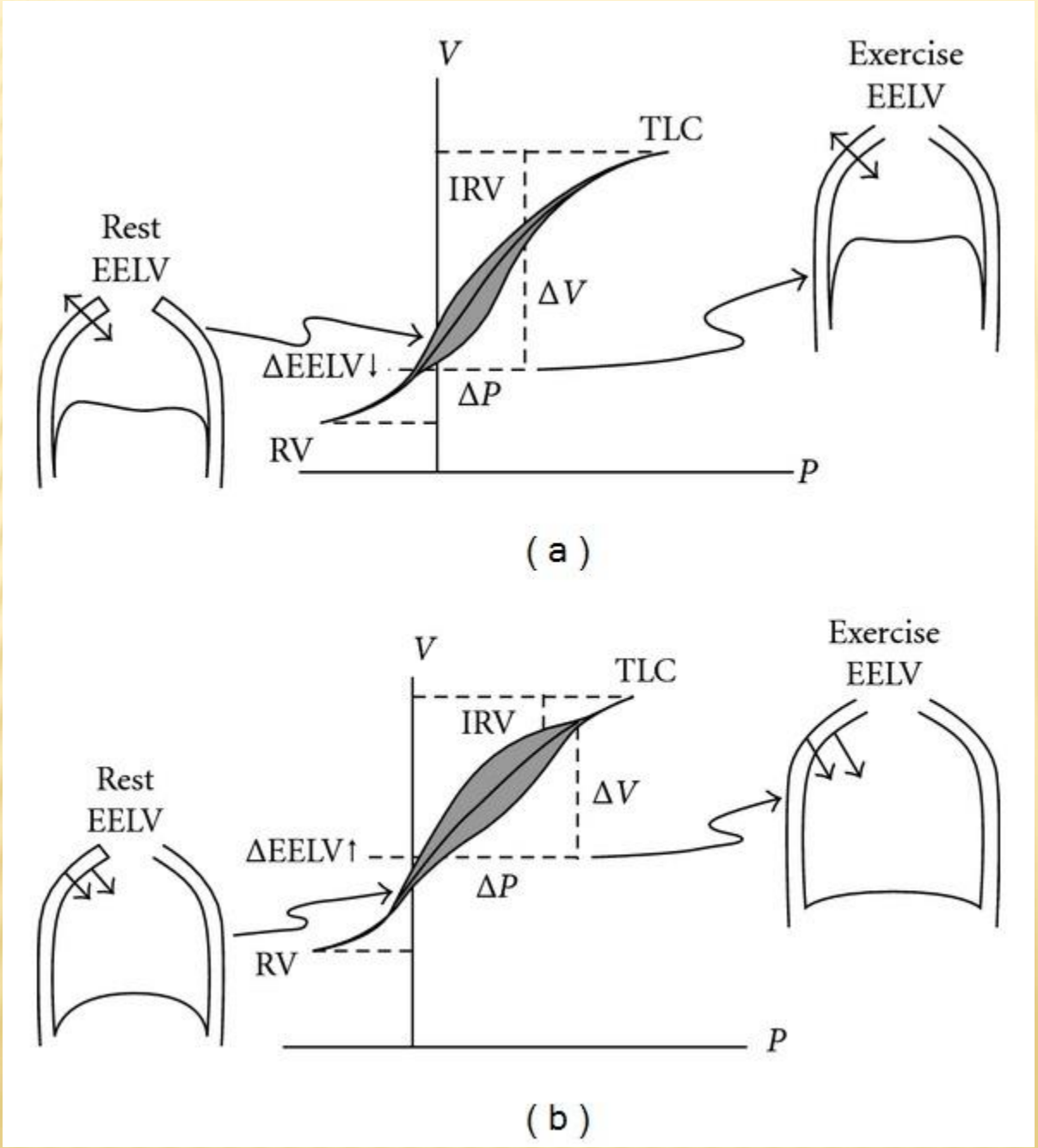
FEV1 VALUES

- FEV1 greater 80% of predicted= normal
- FEV1 60% to 79% of predicted = Mild obstruction
- FEV1 40% to 59% of predicted = Moderate obstruction
- FEV1 less than 40% of predicted = Severe obstruction

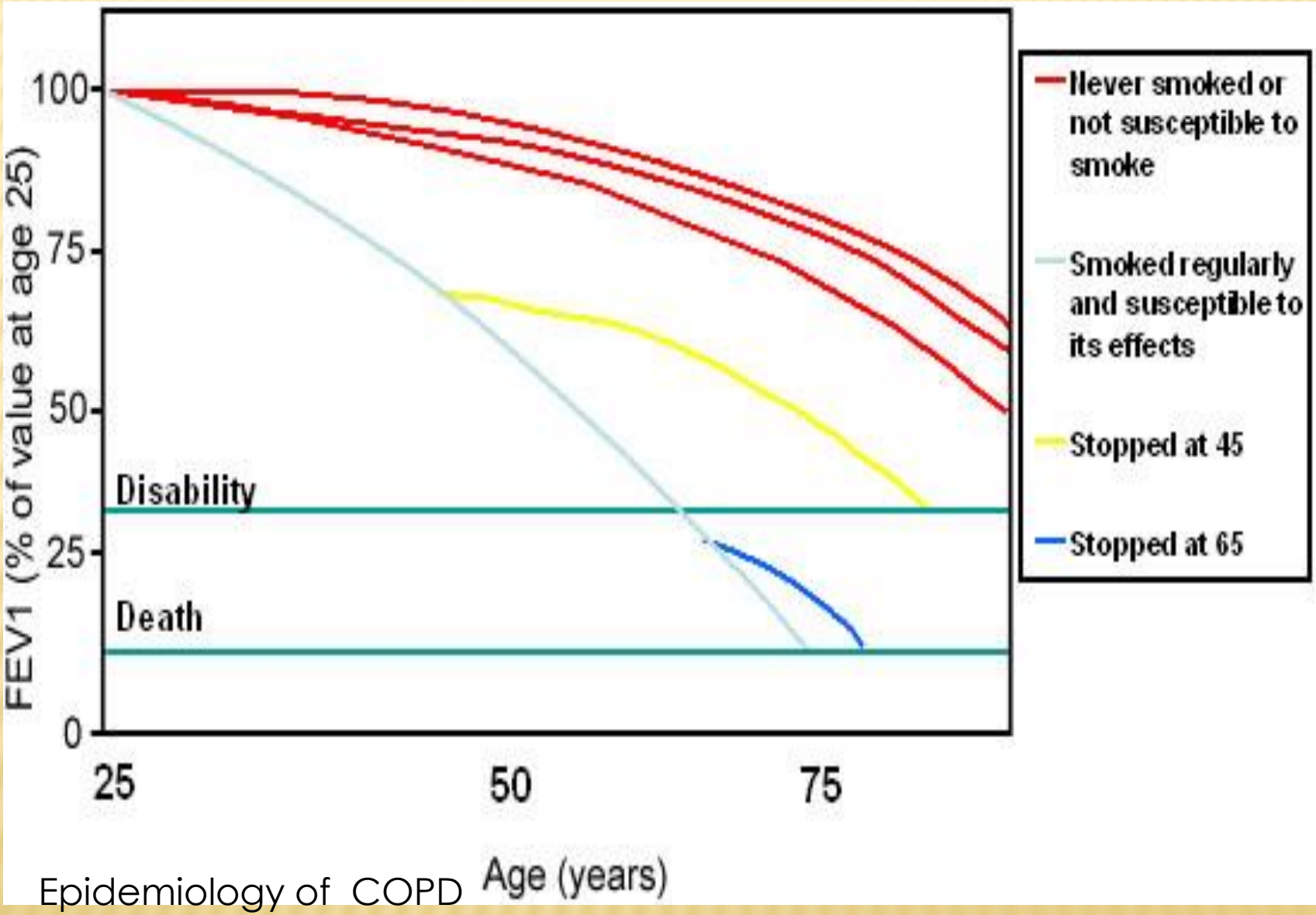


FEV1- expiratory volume exhaled in the first second of forsed expiration.

FVC - forced expiratory vital capacity



Volume- pressure loops in a/ healthy persons, b/ patients woth COPD



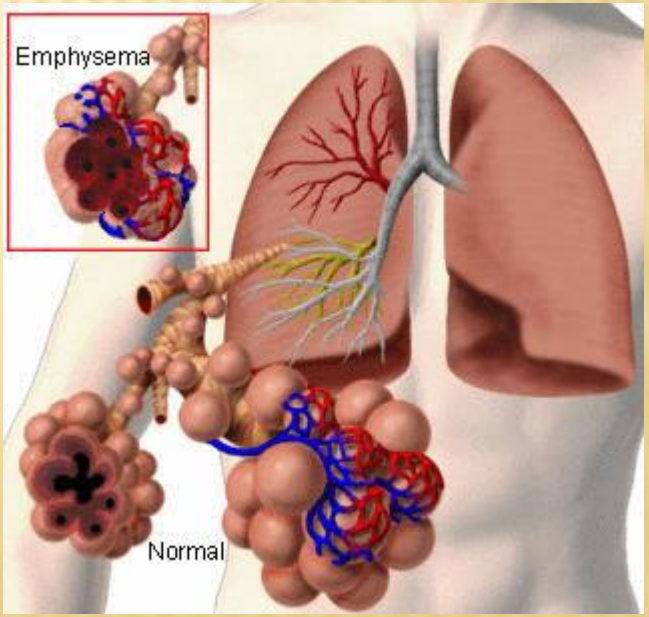
Epidemiology of COPD

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

- ***Two main forms***
- Chronic bronchitis is an ongoing inflammation of the airways.
- **Pathophysiology**: chronic irritation of airways by smoking (including second-hand smoke), air pollution, chemical fumes, gases, vapors, or mists, dust) leading to damage of mucociliar escalator.
- **Pathology:** hyperplasia of mucus glands
- **Pneumology**: bronchial irritation, increased secretions and a productive cough lasting at least three months, two years in a row.

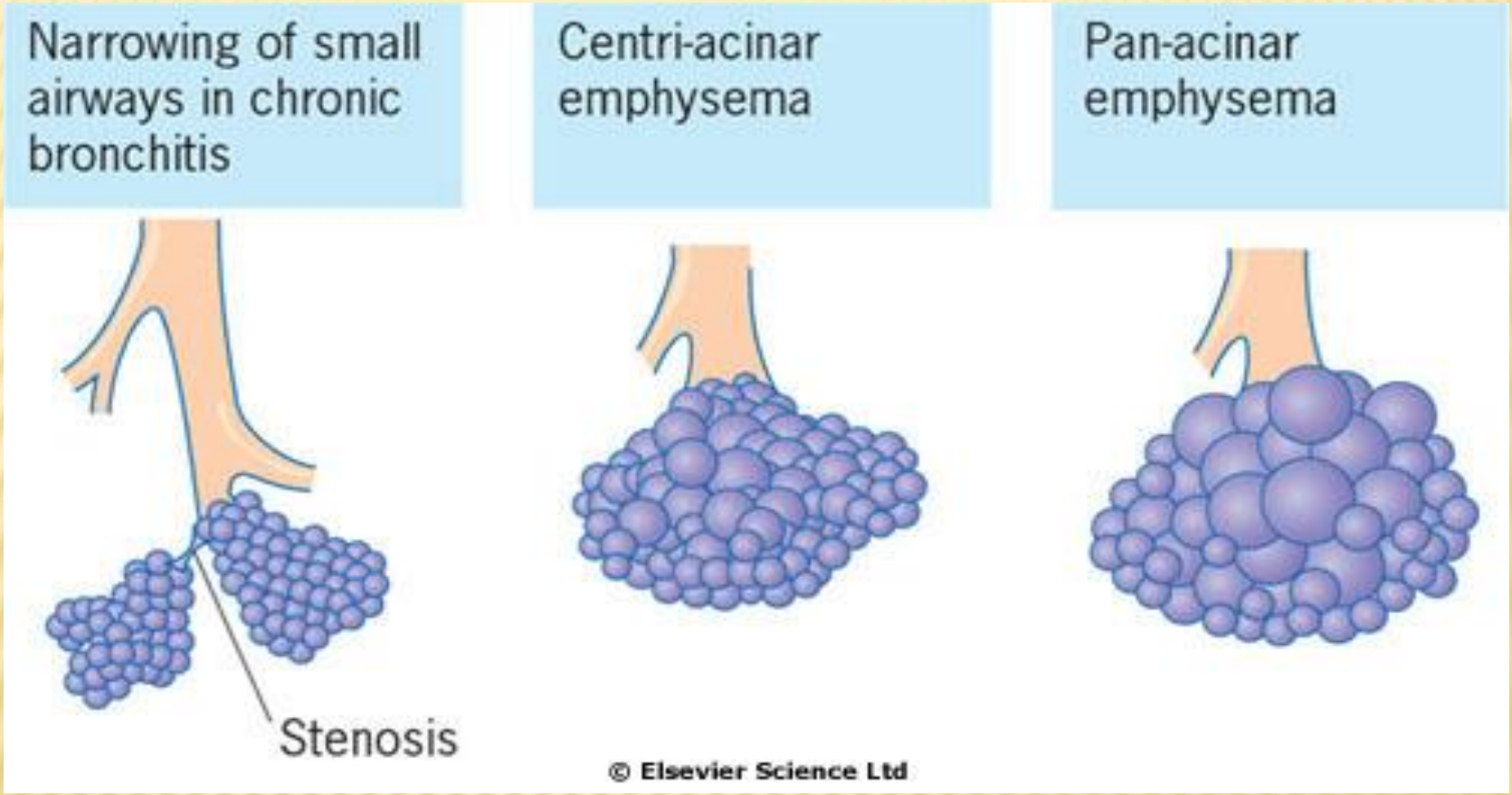
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

- Emphysema
  - Is the permanent widening of the structure of pulmonary gas exchange that is distal to the terminal bronchioles, accompanied by destruction of alveolar walls.
  - Inhalation of cigarette smoke or pollutants stimulate cells in the lung macrophages and neutrophils to produce elastase and collagenases. These enzymes are able to damage the fibers of elastin and collagen, which form the framework of the alveoli and acini in order not to collapse.

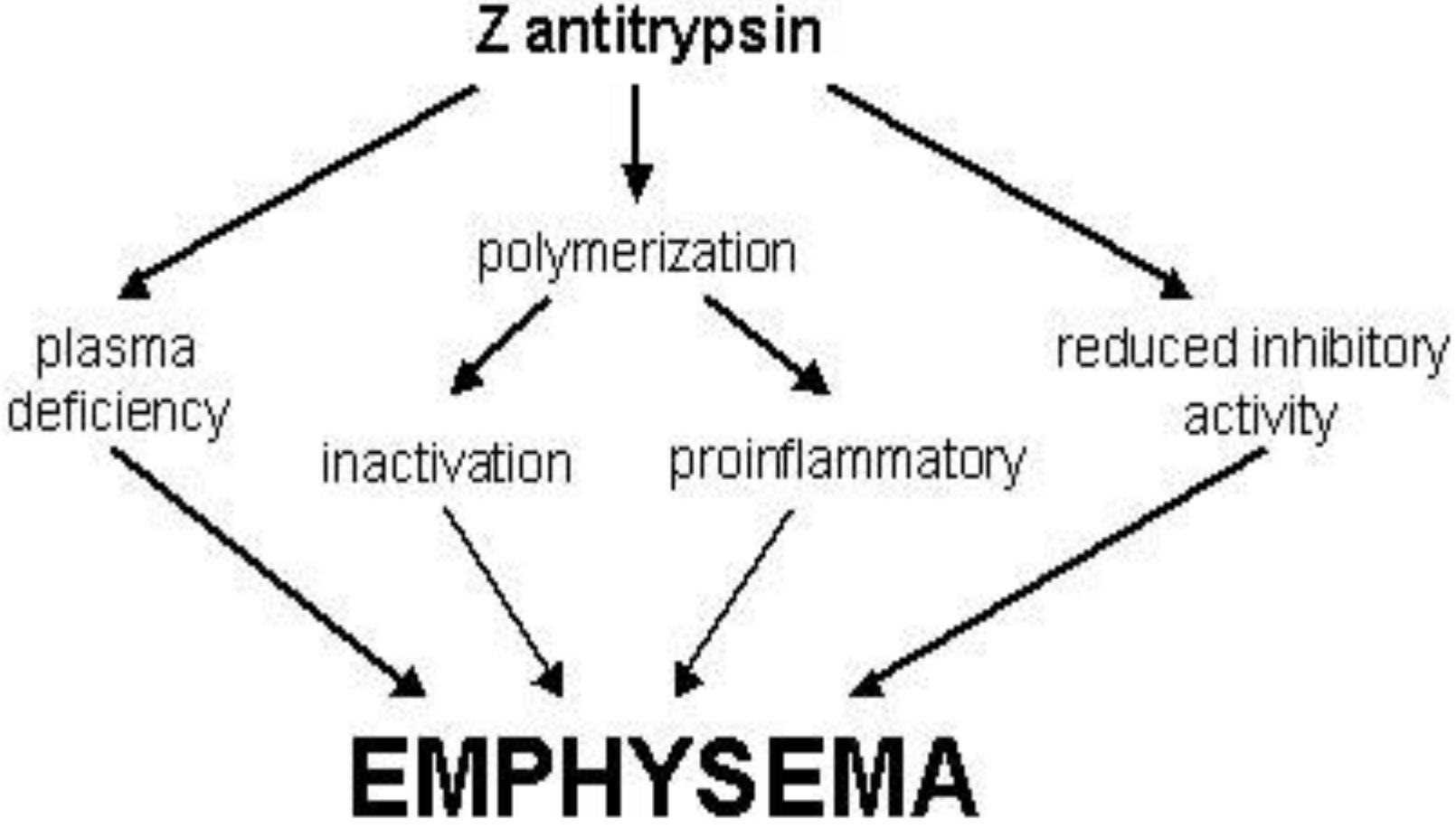


EMPHYSEMA: TYPES

- **Centriacinar Emphysema:** The abnormal permanent enlargement of air spaces distal to the terminal bronchioles, accompanied by the destruction of the walls and without obvious fibrosis. It begins in the respiratory bronchioles and spreads peripherally.
- **Panacinar Emphysema:** Panacinary (or panlobular) emphysema is related to the destruction of alveoli, because of an inflammation or deficiency of alpha 1-antitrypsin.
- **Paraseptal Emphysema:** Paraseptal emphysema is a type of emphysema(as abnormal permanent enlargement of air spaces distal to the terminal bronchioles) which involves the alveolar ducts and sacs at the lung periphery.

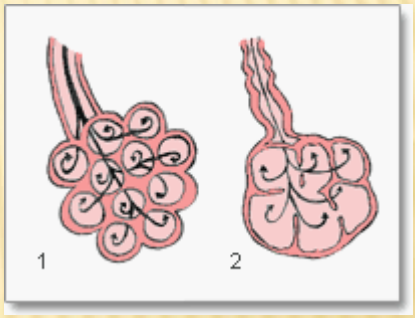


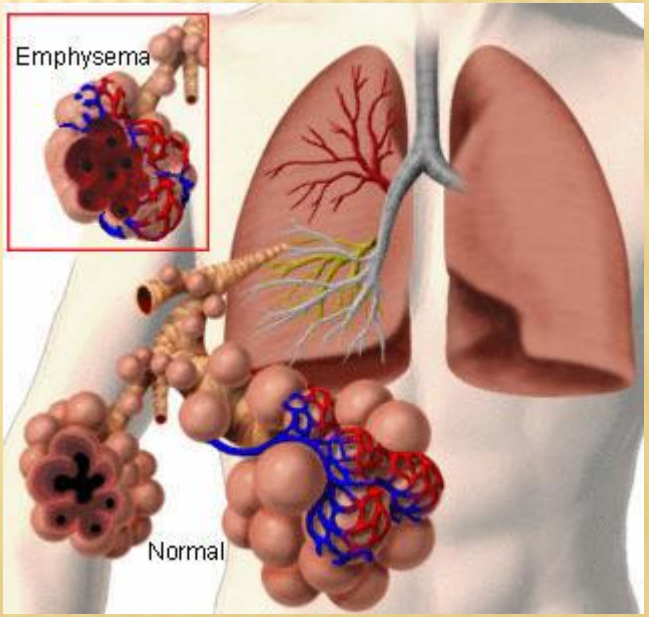
Pathological signs of chronic bronchitis and emphysema


Z antitrypsin
polymerization
plasma deficiency
inactivation
proinflammatory
reduced inhibitory activity
EMPHYSEMA

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

- Emphysema
- Smoking also inhibit the action of alpha-1-antitrypsin, an enzyme that protects elastin fibers against proteases.
  In the lung there is a balance between destroying enzyme (protease) and protective enzymes (alpha-1-antitrypsin).
  Due to destruction of fibers of the lung elastin & collagen elastic recoil loss will occur.





- Respiration. 2012;84(2):89-97. doi: 10.1159/000341382. Epub 2012 Aug 6.
- **Pathophysiology of the small airways in chronic obstructive pulmonary disease.**
- Baraldo S, Turato G, Saetta M.

INFLAMMATION

- One of the earliest histological abnormalities that can be detected in cigarette smokers is the presence of an inflammatory reaction in the peripheral airways.
- This inflammatory reaction consisted predominantly of the infiltration of mononuclear cells in the airway wall and clusters of macrophages into the airway lumen. It is conceivable that this early inflammatory infiltrate which has been observed in smokers' airways, probably represents a nonspecific response to the insult from cigarette smoke.

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	Smokers with COPD	Smokers without COPD
Luminal occlusion*	+++	+
Goblet-cell metaplasia	++	+
Squamous-cell metaplasia	++	+
Muscle hypertrophy and hyperplasia	++	
Fibrosis	++	
Total wall thickening	+++	+
Loss of alveolar attachments	+++	+

From references [23, 24, 31, 35, 39, 44, 45].
* Mainly in patients with bronchitis.

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	Smokers with COPD	Smokers without COPD
CD8+ T lymphocytes	+++	+
CD4+ T lymphocytes	++	+
B lymphocytes	+++	+
Macrophages	++	+
Neutrophils*	++	+
Mast cells**	++	+
Eosinophils	+	+
Lymphoid follicles***	++	

From references [24, 30–32, 34, 35, 38, 41].
* Mainly in the airway lumen and during exacerbations.
** Particularly in patients with centrilobular emphysema.
*** Mainly in patients with severe disease.

Respiration. 2012;84(2):89-97. doi: 10.1159/000341382. Epub 2012 Aug 6.
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SMOKING EFFECTS

- Each puff of a cigarette contains more than 2,000 xenobiotic compounds and 10^{15} free radicals, which increases the oxidant burden in the lung. This burden, associated with the decrease in endogenous antioxidant defenses which occurs with aging, will result in reduced protection against oxidative stress and increased damage to lung epithelial cells and connective tissue proteins. The products released during this process may possibly activate the immune system. The tissue damage that is associated with the infection that will alert the immune system to respond, rather than the microbial antigens themselves. Tissue damage with the resulting cellular stress will cause the release of endogenous damage-associated molecular pattern (DAMP) molecules, such as alarmins, which alert the host to danger by triggering immune responses and activating repair mechanisms through their interaction with pattern recognition receptors. Among these danger signals, high-mobility group box 1 (HMGB1) and the receptor for advanced glycation end products (RAGE) are upregulated in the lungs of smokers and have the potential to activate an immune response by interacting with Toll-like receptors.

Respiration. 2012;84(2):89-97. doi: 10.1159/000341382. Epub 2012 Aug 6.
Pathophysiology of the small airways in chronic obstructive pulmonary disease.
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INCREASE IN SMOOTH MUSCLE

- Increase in smooth muscle correlates with the degree of airflow limitation; the greater the amount of smooth muscle, the lower the FEV_1 and the more severe the airway obstruction. So, increased smooth-muscle mass is an important component of airway wall thickening, which can be due to several mechanisms including hypertrophy and hyperplasia, possibly due to the activity of inflammatory mediators, cytokines and growth factors.
- The airways of smokers can react to nonspecific stimuli by constricting, and this results in increased resistance and decreased FEV_1.
- The major functional consequence of the increase in smooth-muscle mass is that, in airways with thickened walls, the same degree of smooth-muscle shortening may cause considerably greater lumenal narrowing than in the normal airways.

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PERIPHERAL WALL FIBROSIS

- Another important component of remodeling is fibrosis of the airway wall. The cigarette smoke induces oxidative stress in human lung fibroblasts, which may then initiate a process of repair and collagen deposition. Furthermore, the interaction between fibroblasts and inflammatory cells may also play a role in fibrotic remodeling. Along with this is the observation that mast cells, which have important profibrotic and prorepair properties, are increased in the airways of smokers with COPD, particularly in those with centrilobular emphysema.

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PERIPHERAL WALL FIBROSIS

- Fibrosis, along with an increased airway smooth muscle and other inflammatory components, ought to increase the airway wall thickness and change the mechanical characteristics of the airway to decrease the luminal diameter.
- The total thickness of the airway wall was the parameter found to correlate best with airflow limitation in smokers across the different stages of severity.

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THICKNESS OF THE AIRWAY WALL

- Inflammation, fibrosis and smooth-muscle hypertrophy, by increasing the thickness of the airway wall, may facilitate uncoupling between airways and parenchyma, therefore promoting airway closure. In addition, airway wall inflammation could contribute to the destruction of alveolar attachments (i.e. the alveolar walls directly attached to the airway wall), further reducing the tethering effect of lung parenchyma, thus allowing the airway wall to deform and narrow. This hypothesis is supported by the observation that, in smokers, the destruction of alveolar attachments is correlated with the degree of inflammation in the peripheral airways. This finding suggests a pathogenetic role for airway inflammation in inducing the destruction of alveolar attachments. It is possible that mediators released by inflammatory cells may weaken the alveolar tissue and facilitate its rupture, particularly at the point where the attachments join the airway wall and the mechanical stress is maximal.

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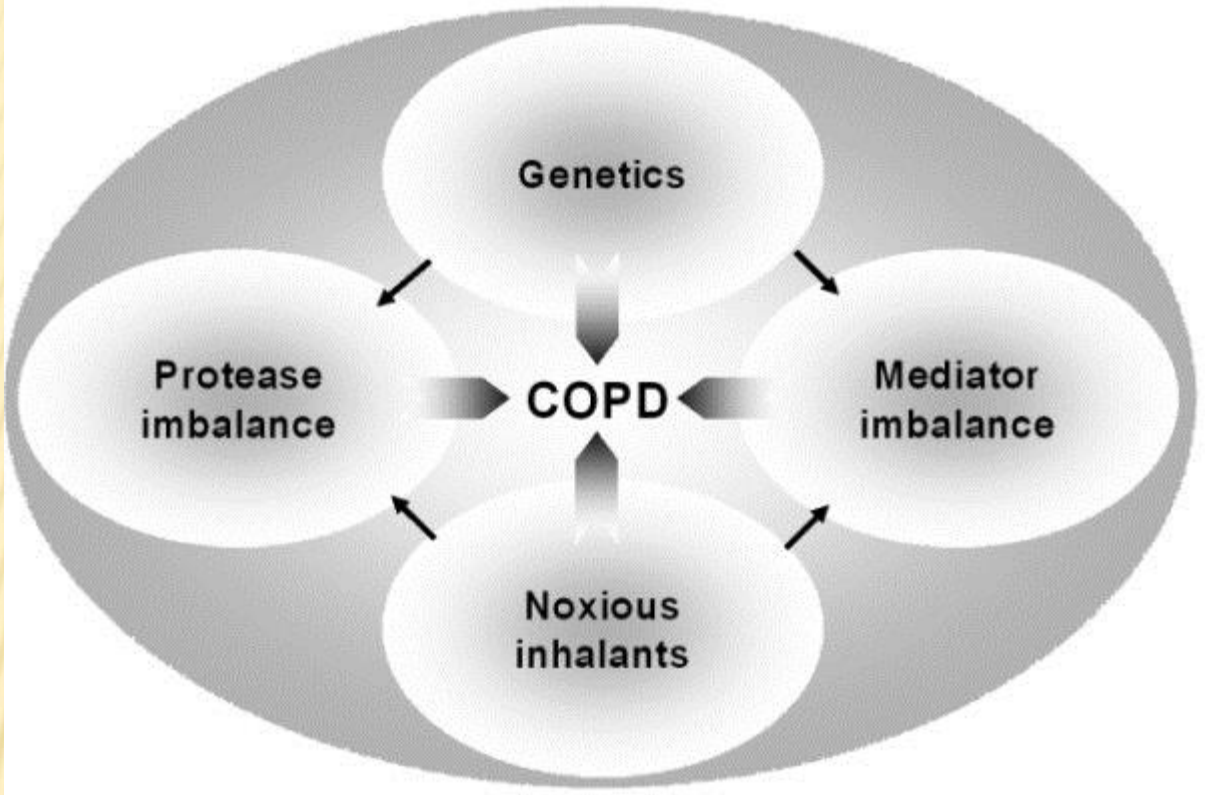


Potential pathogenetic mechanisms involved in COPD Exogenous inhaled noxious stimuli such as tobacco smoke, noxious gases or indoor air pollution and genetic factors are proposed to be the major factors related to the pathogenesis of COPD. These factors may influence protease activity and may also lead to an imbalance between pro-inflammatory and anti-inflammatory mediators.
Groneberg and Chung *Respiratory Research* 2004 **5**:18 doi:10.1186/1465-9921-5-18

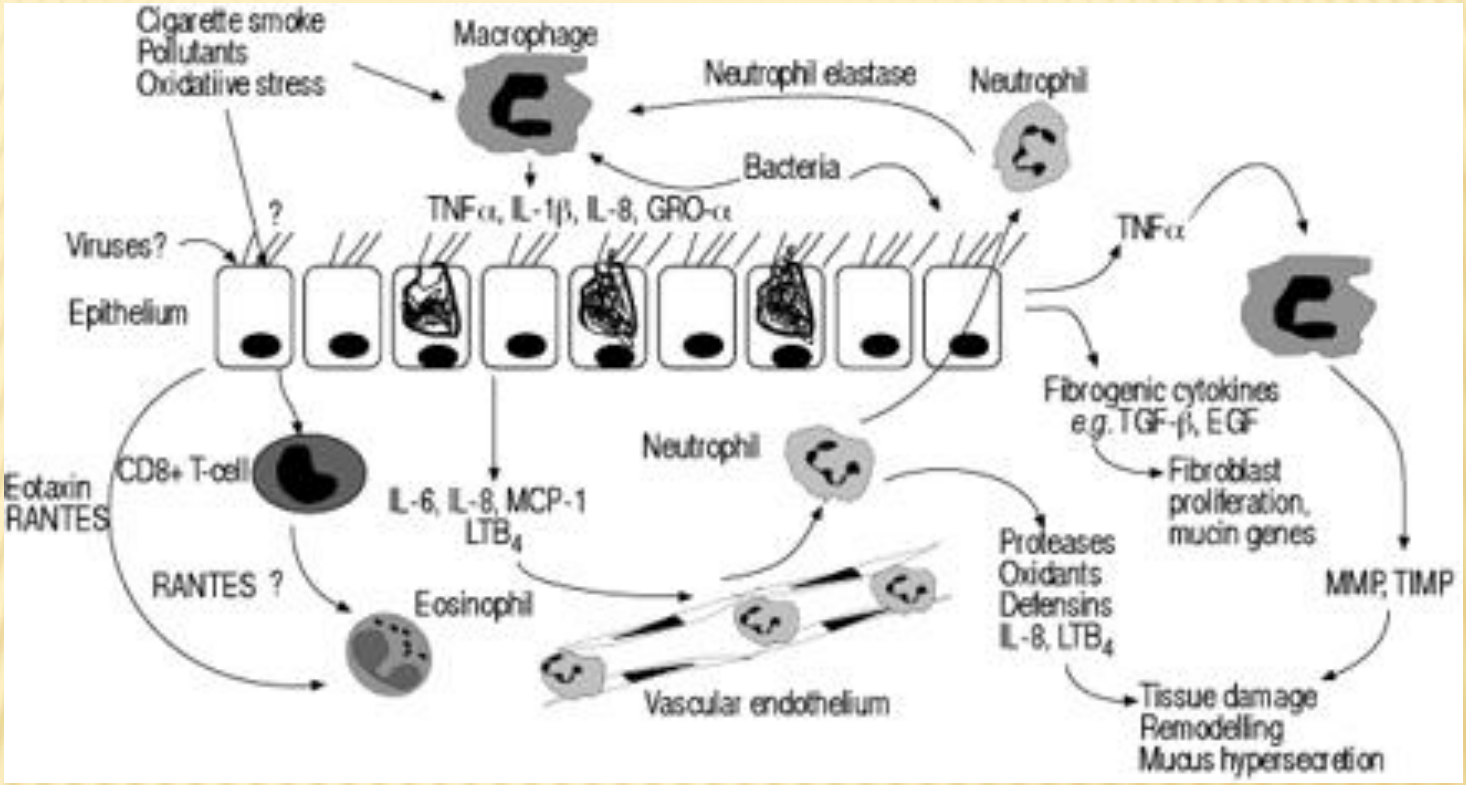
TYPES OF RESPIRATORY INSUFFICIENCY

- *Type A* is „*pink puffer*“. Symtoms:

1. Severe exspiratory dyspnoe (PaO2 and PaCO2 in blood near to normal values
2. Cor pulmonale -no
3. Higher proportion of emphysema Partial respiratory insufficience

- *Type B is „blue bloater*“. Symtoms:

1. Small or none dyspnoe
2. Arterial hypoxia and hypercapnia
3. Secondary polycytemia
4. Cor pulmonale.
5. Higher proportion of chronic bronchitis
6. Global respiratory insufficiency (no pure O2!!!)



Interaction of cells and cytokines in the airway inflammation of chronic obstructive pulmonary disease.

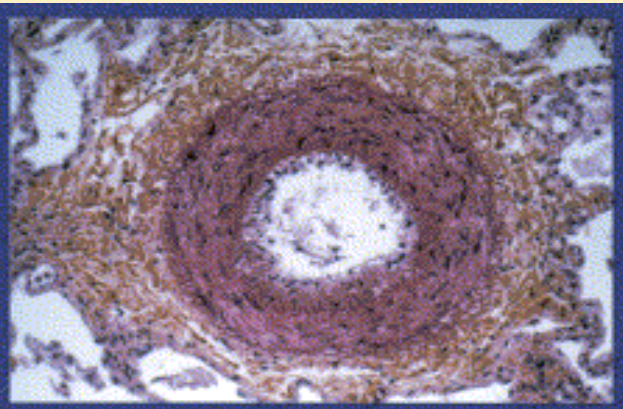
PULMONARY VASCULAR DISEASE

is an important risk factor for disease progression and exacerbation risk. Relative pulmonary artery enlargement on computed tomography scan, defined by a pulmonary artery to aortic (PA:A) ratio >1, has been evaluated as a marker of pulmonary vascular disease.

In healthy patients a PA:A ratio >0.9 is considered to be abnormal. The PA:A ratio has been compared with invasive hemodynamic parameters, primarily mean pulmonary artery pressure in various disease conditions and is more strongly correlated with mean pulmonary artery pressure in obstructive as compared with interstitial lung disease.

In patients without known cardiac or pulmonary disease, the PA:A ratio is predictive of mortality, while in COPD, an elevated PA:A ratio is correlated with increased exacerbation risk, outperforming other well established predictors of these events.

Factors influencing the state of pulmonary circulation



Pre-pro-endothelin→ pro-endothelin

Endothelin-1

ET_A ET_B

vasoconstriction
proliferation

L-arginine→ L-citrulline

Nitric Oxide

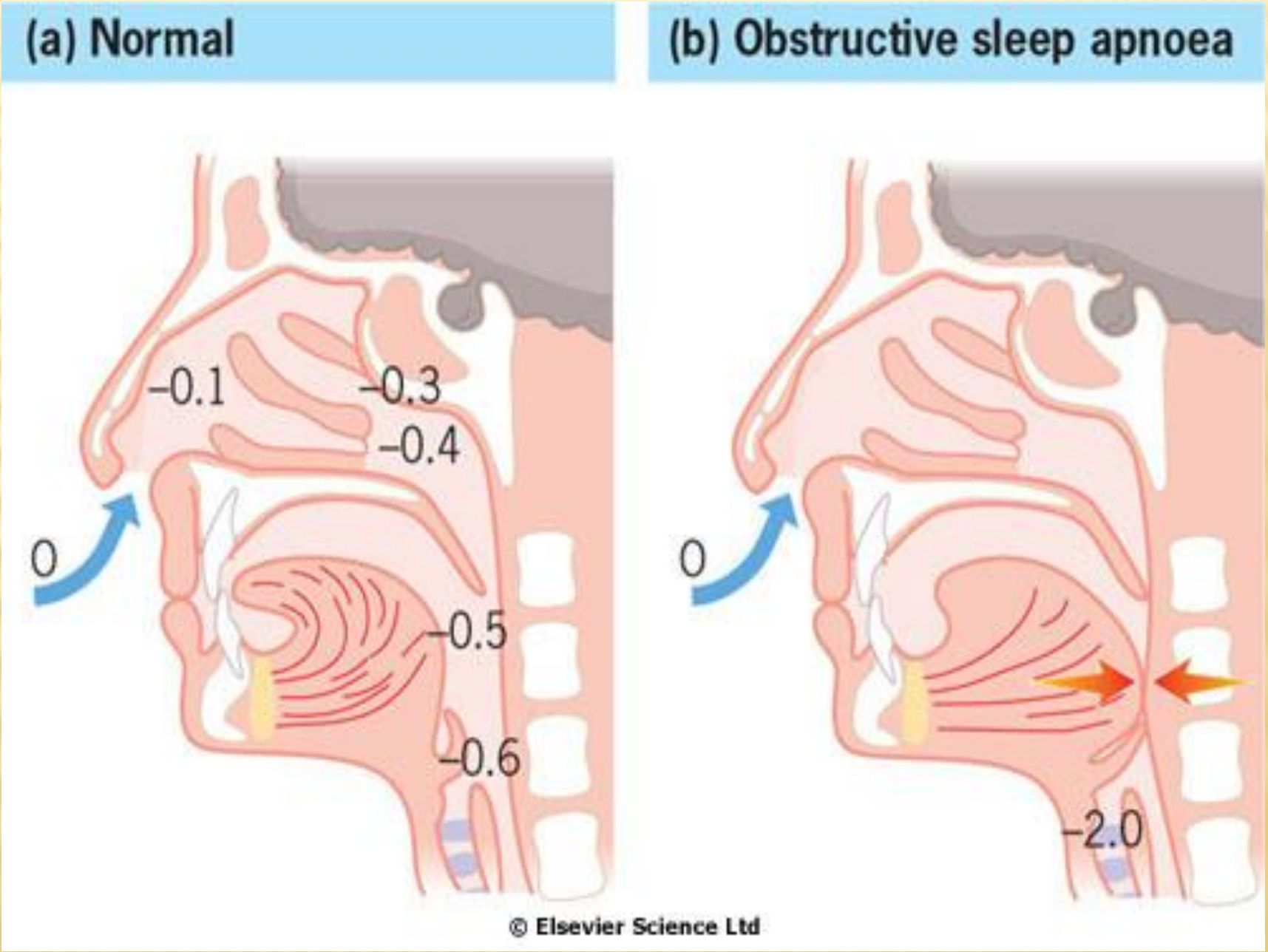
cGMP vasodilatation
anti-proliferation

PDE5

Arachidonic Acid

Prostacyclin

cAMP vasodilatation
anti-proliferation


(a) Normal
(b) Obstructive sleep apnoea
–0.1
–0.3
–0.4
0
–0.5
–0.6
0
–2.0
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Thank you for your attention