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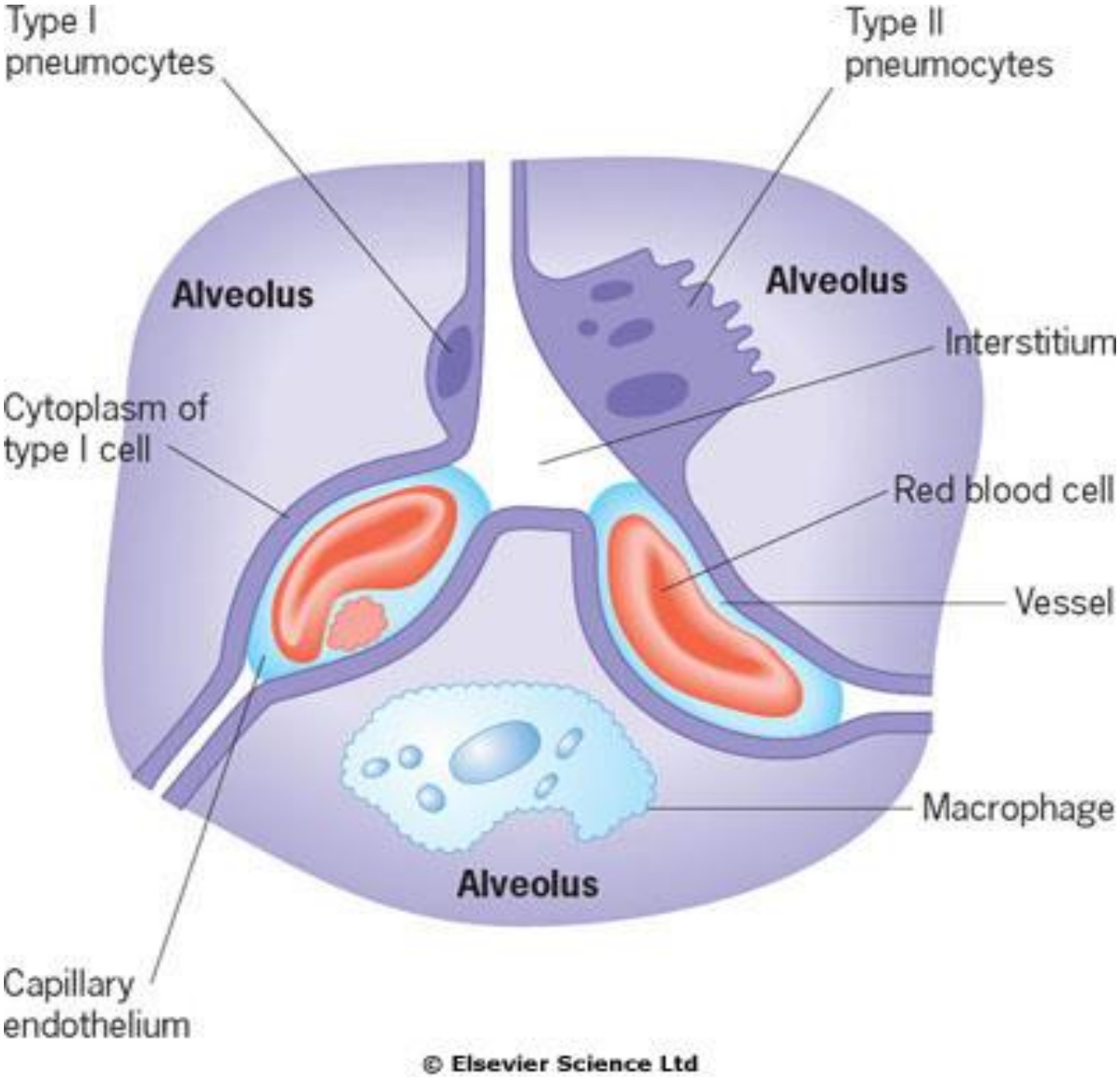
Pathophysiology of respiratory system III Obstructive disorders

General Medicine
November 24, 2020

Repetition from physiology: alveoli

- The bronchioles finally divide within the acinus into smaller *respiratory bronchioles* that have alveoli arising from the surface.
- Each respiratory bronchiole supplies approximately *200 alveoli* via alveolar ducts.
- The term 'small airways' refers to bronchioles of less than 2 mm; there are 30 000 of these in the average lung.


Type I pneumocytes
Type II pneumocytes
Alveolus
Alveolus
Interstitium
Cytoplasm of type I cell
Red blood cell
Vessel
Macrophage
Alveolus
Capillary endothelium
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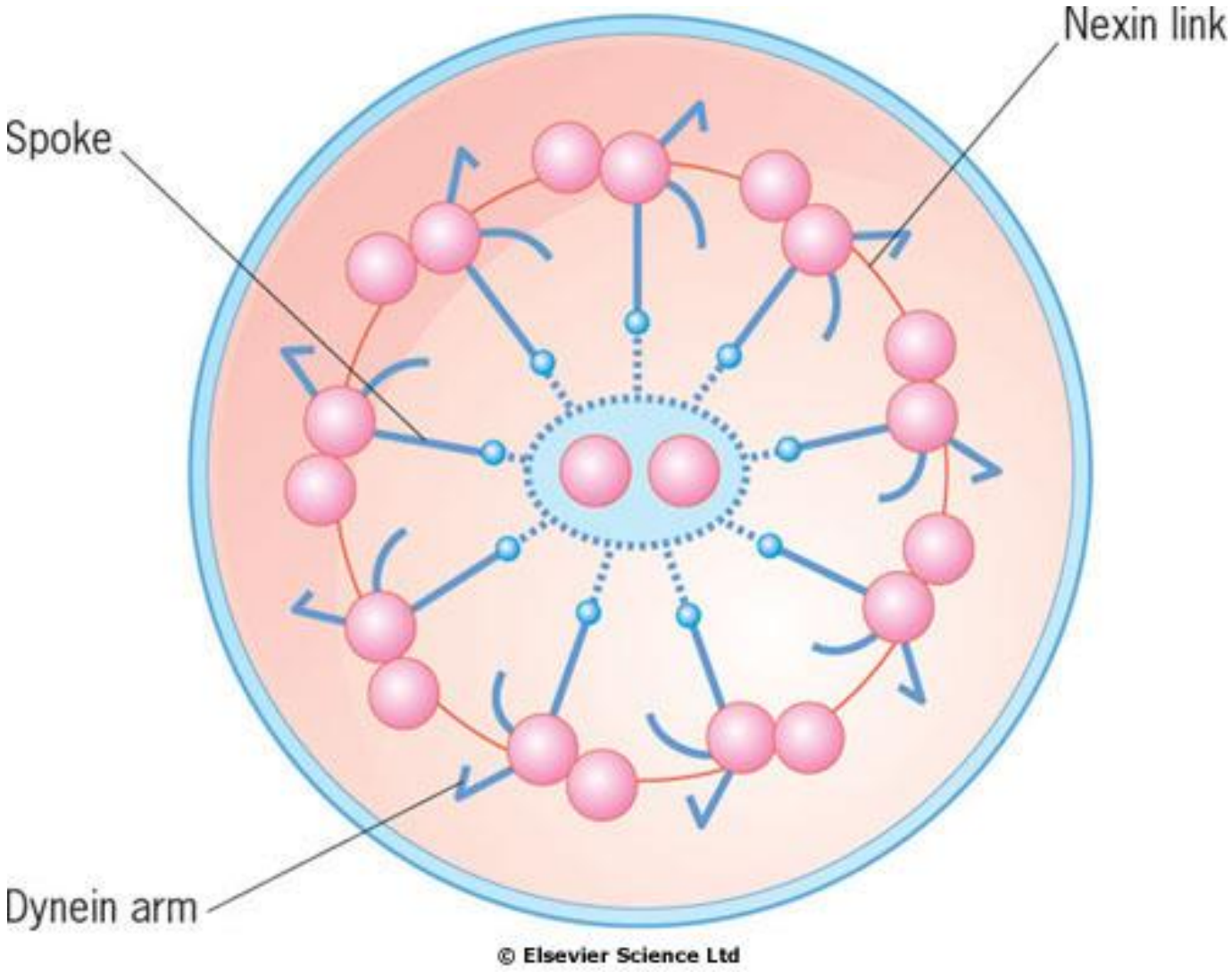
Repetition fro physiology: the ciliated epithelium

- is an important defence mechanism.
- Each cell contains approximately 200 *cilia* beating at 1000 beats per minute in organized waves of contraction.
- Each cilium consists of nine peripheral pairs and two inner longitudinal fibrils in a cytoplasmic matrix. *Nexin* links join the peripheral pairs. *Dynein arms* consisting of ATPase protein project towards the adjacent pairs.
- Bending of the cilia results from a sliding movement between adjacent fibrils powered by an ATP-dependent shearing force developed by the dynein arms. Absence of dynein arms leads to immotile cilia.
- *Mucus*, which contains macrophages, cell debris, inhaled particles and bacteria, is moved by the cilia towards the larynx at about 1.5 cm/min (the „mucociliary escalator“).

Reepetition from physiology: the ciliated epithelium



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Repetition from physiology: the mucocilial escalator

- Cooperation between ciliated epithelium and mucus production leads to removing of large dirt particles from airways.
- When ciliated epithelium is not functioning (e.g. in smokers), dirt stagnation will occur which wil activate production of mucus. This will further promote stagnation of dirt in airways and will stimulate accumulation of neutrophiles- inflammation
- This is pathophysiology of chronic bronchitis!!!

Mucociliar escalator pathophysiology

- **One of the major long-term effects of cigarette smoking is a reduction in mucociliary transport**. This contributes to *recurrent infection* and in the larger airways it *prolongs contact with carcinogens*.
- Air pollutants, local and general anaesthetics and bacterial and viral infections also reduce mucociliary clearance.
- Congenital defects in mucociliary transport occur. In the *'immotile cilia' syndrome* there is an absence of the dynein arms in the cilia themselves, and in *cystic fibrosis* an abnormal mucus composition is associated with ciliary dyskinesia.
- Both diseases are characterized by recurrent infections and eventually with the development of bronchiectasis.

Defence systems of airways: humoral and cellular mechanisms

Non-specific soluble factors

- a-*Antitrypsin* (a-antiprotease is present in lung secretions derived from plasma). It inhibits chymotrypsin and trypsin and neutralizes proteases and elastase.
- *Lysozyme* is an enzyme found in granulocytes that has bactericidal properties.
- *Lactoferrin* is synthesized from epithelial cells and neutrophil granulocytes and has bactericidal properties.
- *Interferon* is produced by most cells in response to viral infection. It is a potent modulator of lymphocyte function. It renders other cells resistant to infection by any other virus.
- *Complement* is present in secretions and is derived by diffusion from plasma. In association with antibodies, it plays an important cytotoxic role.
- *Surfactant protein* A (SPA) is one of four species of surfactant proteins which opsonizes bacteria/particles, enhancing phagocytosis by macrophages.
- *Defensins* are bactericidal peptides present in the azurophil granules of neutrophils.

Defence systems of airways: humoral and cellular mechanisms

Pulmonary alveolar macrophages

- These are derived from precursors in the bone marrow and migrate to the lungs via the bloodstream. They phagocytose particles, including bacteria, and are removed by the mucociliary escalator, lymphatics and bloodstream.
- They are the dominant cell in the airways at the level of the alveoli and comprise *90% of all cells obtained by bronchoalveolar lavage*. Alveolar macrophages work principally as scavengers and are not particularly good at presenting antigens to the immune system.
- *Dendritic cells* form a network throughout the airways and are thought to be the key antigen-presenting cell in the airway.

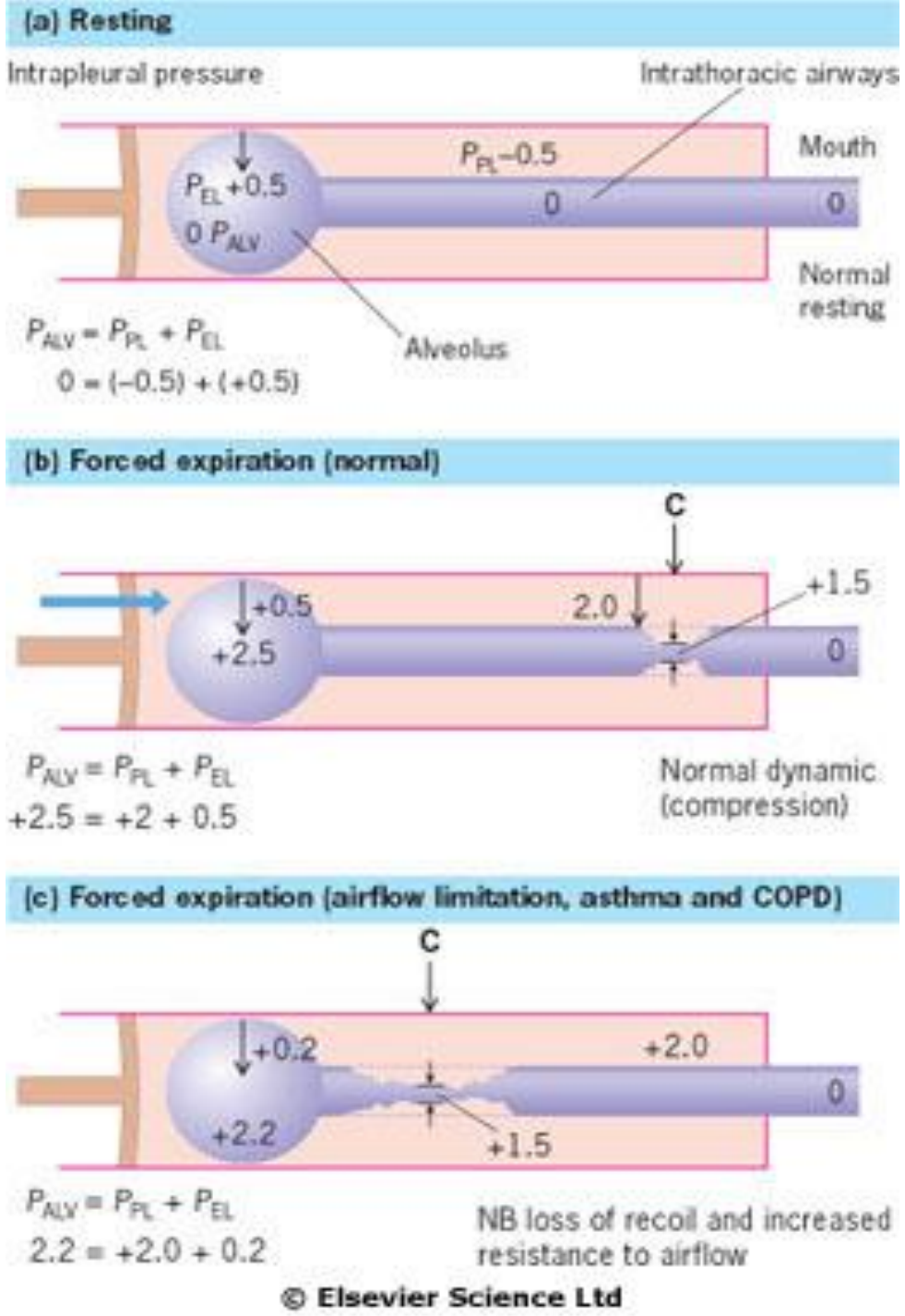
Humoral and cellular mechanisms

- **Lymphoid tissue**
- The lung contains large numbers of lymphocytes which are scattered throughout the airways. Sensitized lymphocytes contribute to local immunity through differentiation into IgA-secreting plasma cells. IgG and IgE are found in low concentrations in airway secretions from a combination of local and systemic production.
- In addition to these resident cells, the lung has the usual range of acute inflammatory responses and can mobilize neutrophils promptly in response to injury or infection and play a major part in inflammatory conditions such as asthma.

Airflow

- Movement of air through the airways results from a *difference between the pressure in the alveoli and the atmospheric pressure*; a positive alveolar pressure occurs in expiration and a negative pressure occurs in inspiration.
- During quiet breathing the sub-atmospheric pleural pressure throughout the breathing cycle slightly distends the airways. With vigorous expiratory efforts (e.g. cough), although the central airways are compressed by positive pleural pressures exceeding 10 kPa, the airways do not close completely because the driving pressure for expiratory flow (alveolar pressure) is also increased.

- *Alveolar pressure PALV is equal to the elastic recoil pressure (PEL) of the lung plus the pleural pressure (PPL).*


(a) Resting
Intrapleural pressure
Intrathoracic airways
P_{PL} −0.5
Mouth
P_{EL} +0.5
0 P_{ALV}
0
0
Normal resting
Alveolus
$P_{ALV} = P_{PL} + P_{EL}$
0 = (−0.5) + (+0.5)
(b) Forced expiration (normal)
C
+0.5
+2.5
2.0
+1.5
0
$P_{ALV} = P_{PL} + P_{EL}$
+2.5 = +2 + 0.5
Normal dynamic (compression)
(c) Forced expiration (airflow limitation, asthma and COPD)
C
+0.2
+2.2
+2.0
0
+1.5
$P_{ALV} = P_{PL} + P_{EL}$
2.2 = +2.0 + 0.2
NB loss of recoil and increased resistance to airflow
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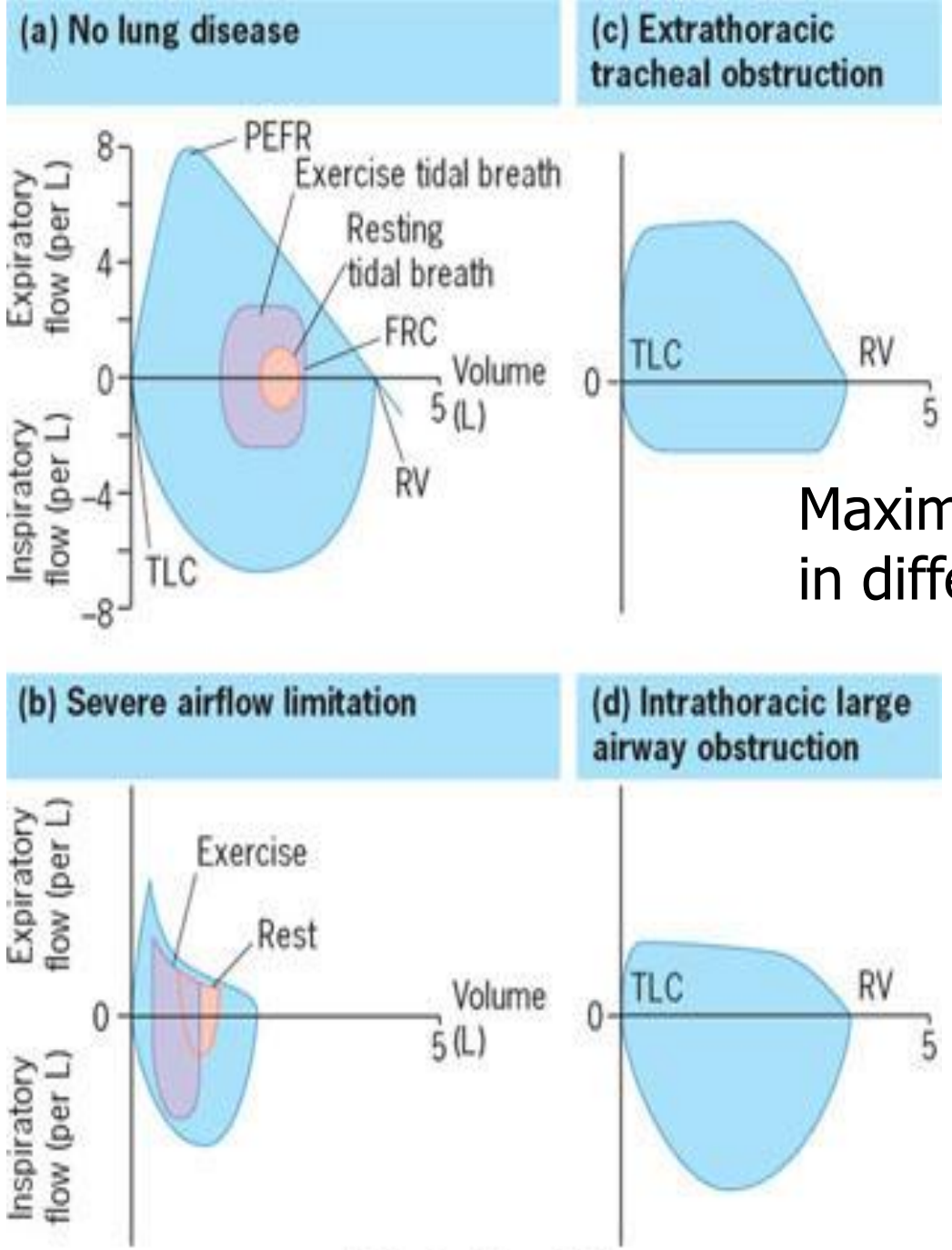
Airflow

- When there is no airflow (i.e. during a pause in breathing) the tendency of the lungs to collapse (the positive recoil pressure) is exactly balanced by an equivalent negative pleural pressure. As air flows from the alveoli towards the mouth there is a gradual loss of pressure owing to flow resistance.
- In forced expiration, the driving pressure raises both the alveolar pressure and the intrapleural pressure. Between the alveolus and the mouth, a point will occur (C) where the airway pressure will equal the intrapleural pressure, and airway compression will occur. However, this compression of the airway is temporary, as the transient occlusion of the airway results in an increase in pressure behind it (i.e. upstream) and this raises the intra-airway pressure so that the airways open and flow is restored. The airways thus tend to vibrate at this point of '*dynamic compression*'.

Airflow

- The elastic recoil pressure of the lungs decreases with decreasing lung volume and the 'collapse point' moves upstream (i.e. towards the smaller airways).
- Where there is pathological loss of recoil pressure (as in chronic obstructive pulmonary disease, COPD), the 'collapse point' starts even further upstream and these patients are often seen to 'purse their lips' in order to increase airway pressure so that their peripheral airways do not collapse. The expiratory airflow limitation is the pathophysiology that underlies chronic airflow limitation. The measurement of the forced expiratory volume in the first second (FEV1) is a useful clinical index of this phenomenon. On inspiration, the intrapleural pressure is always less than the intraluminal pressure within the intrathoracic airways, so there is no limitation to airflow with increasing effort. Inspiratory flow is limited only by the power of the inspiratory muscles.



Maximal flow –volume loops in different conditions

Maximal flow-volume loops, showing the relationship between maximal flow rates on expiration and inspiration (to the previous picture)

- **(a)** In a normal subject.
- **(b)** In a patient with severe airflow limitation. Flow-volume loops during tidal breathing at rest (starting from the functional residual capacity (FRC)) and during exercise are also shown. The highest flow rates are achieved when forced expiration begins at total lung capacity (TLC) and represent the peak expiratory flow rate (PEFR). As air is blown out of the lung, so the flow rate decreases until no more air can be forced out, a point known as the residual volume (RV). Because inspiratory airflow is only dependent on effort, the shape of the maximal inspiratory flow-volume loop is quite different, and inspiratory flow remains at a high rate throughout the manoeuvre.

Maximal flow-volume loops, showing the relationship between maximal flow rates on expiration and inspiration (to the previous picture)

- (c and d) Flow-volume loops of patients with large airway (tracheal) obstruction, showing plateauing of maximal expiratory flow high in the lung volume.
- (c) Extrathoracic tracheal obstruction with a proportionally greater reduction of maximal inspiratory (as opposed to expiratory) flow rate.
- (d) Intrathoracic large airway obstruction; the expiratory plateau is more pronounced and inspiratory flow rate is less reduced than in (c). In severe airflow limitation the ventilatory demands of exercise cannot be met, greatly reducing effort tolerance.

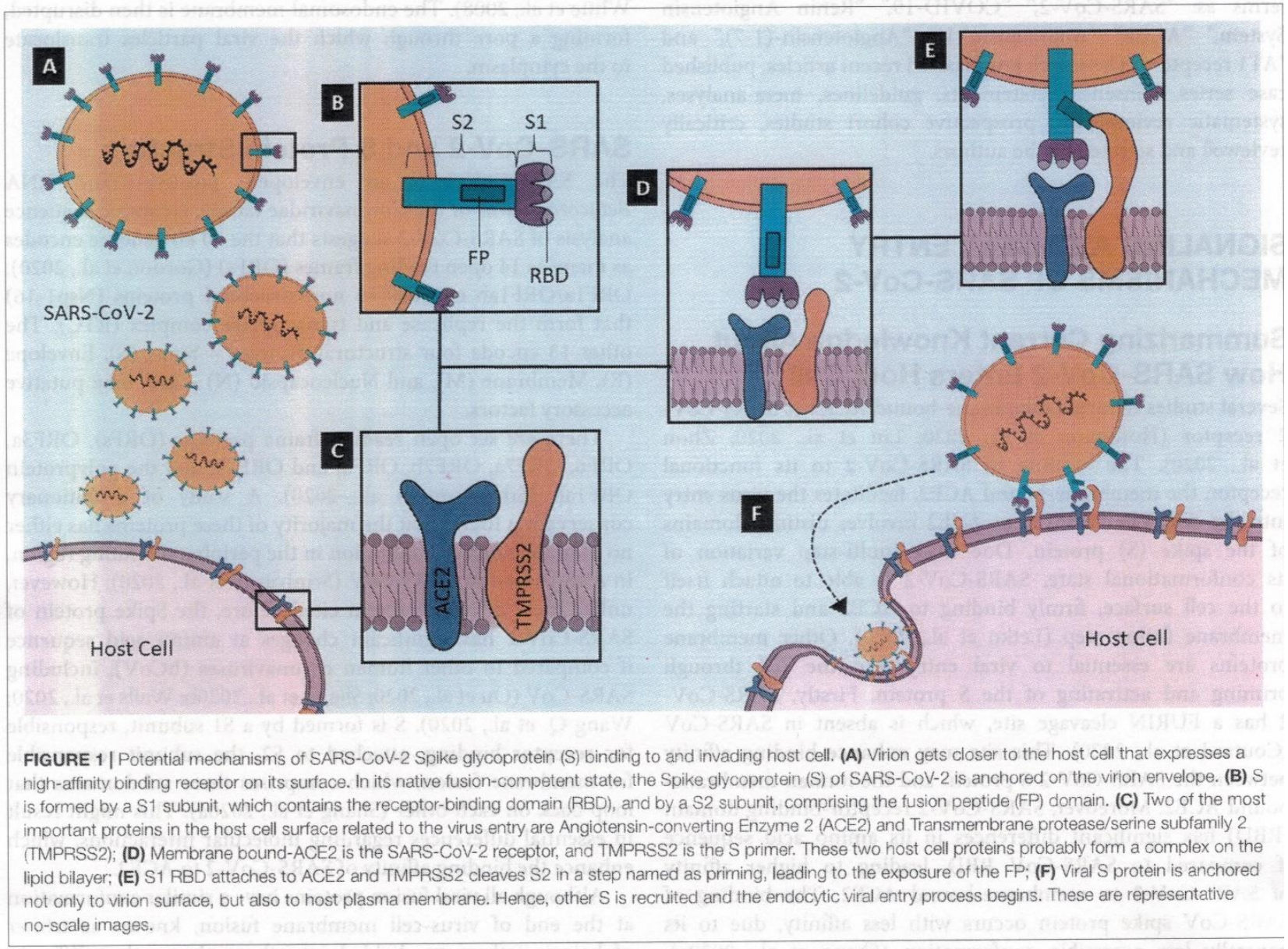


FIGURE 1 | Potential mechanisms of SARS-CoV-2 Spike glycoprotein (S) binding to and invading host cell. **(A)** Virion gets closer to the host cell that expresses a high-affinity binding receptor on its surface. In its native fusion-competent state, the Spike glycoprotein (S) of SARS-CoV-2 is anchored on the virion envelope. **(B)** S is formed by a S1 subunit, which contains the receptor-binding domain (RBD), and by a S2 subunit, comprising the fusion peptide (FP) domain. **(C)** Two of the most important proteins in the host cell surface related to the virus entry are Angiotensin-converting Enzyme 2 (ACE2) and Transmembrane protease/serine subfamily 2 (TMPRSS2); **(D)** Membrane bound-ACE2 is the SARS-CoV-2 receptor, and TMPRSS2 is the S primer. These two host cell proteins probably form a complex on the lipid bilayer; **(E)** S1 RBD attaches to ACE2 and TMPRSS2 cleaves S2 in a step named as priming, leading to the exposure of the FP; **(F)** Viral S protein is anchored not only to virion surface, but also to host plasma membrane. Hence, other S is recruited and the endocytic viral entry process begins. These are representative no-scale images.

Front Cell Dev Biol. 2020; 8: 559841.

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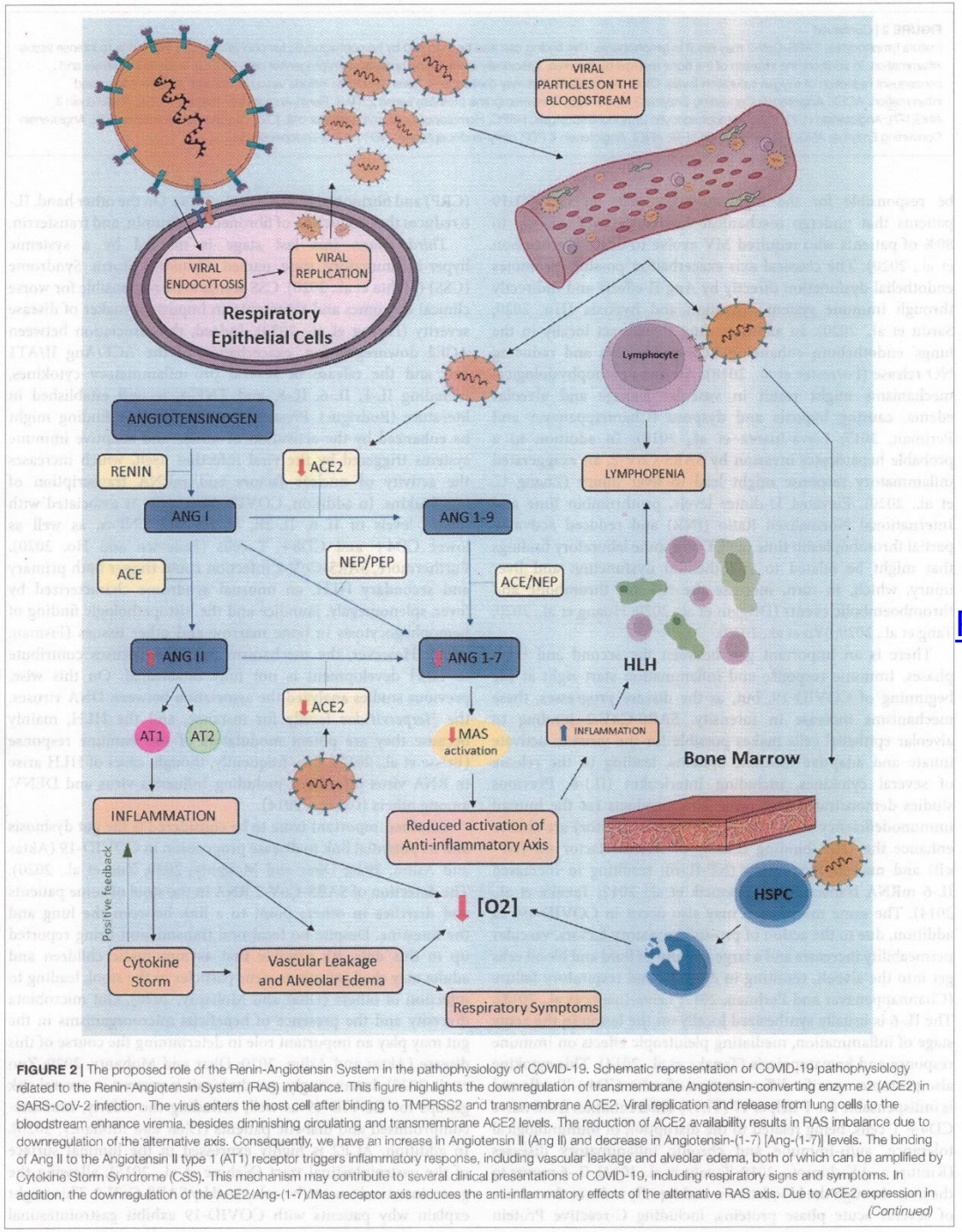

FIGURE 2 | The proposed role of the Renin-Angiotensin System in the pathophysiology of COVID-19. Schematic representation of COVID-19 pathophysiology related to the Renin-Angiotensin System (RAS) imbalance. This figure highlights the downregulation of transmembrane Angiotensin-converting enzyme 2 (ACE2) in SARS-CoV-2 infection. The virus enters the host cell after binding to TMPRSS2 and transmembrane ACE2. Viral replication and release from lung cells to the bloodstream enhance viremia, besides diminishing circulating and transmembrane ACE2 levels. The reduction of ACE2 availability results in RAS imbalance due to downregulation of the alternative axis. Consequently, we have an increase in Angiotensin II (Ang II) and decrease in Angiotensin-(1-7) [Ang-(1-7)] levels. The binding of Ang II to the Angiotensin II type 1 (AT1) receptor triggers inflammatory response, including vascular leakage and alveolar edema, both of which can be amplified by Cytokine Storm Syndrome (CSS). This mechanism may contribute to several clinical presentations of COVID-19, including respiratory signs and symptoms. In addition, the downregulation of the ACE2/Ang-(1-7)/Mas receptor axis reduces the anti-inflammatory effects of the alternative RAS axis. Due to ACE2 expression in

(Continued)

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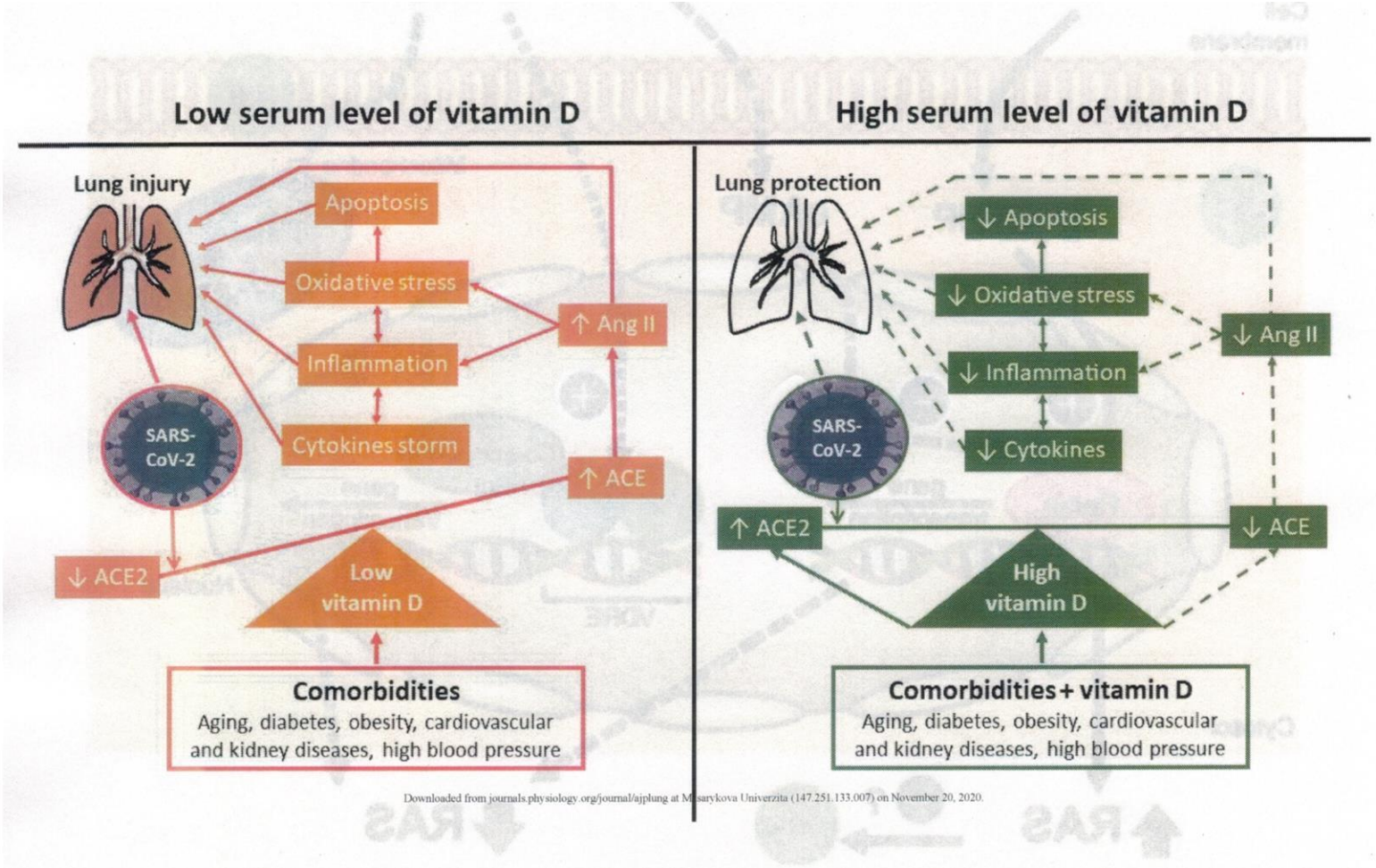

Life Sci. 2020 Aug 1; 254: 117808.

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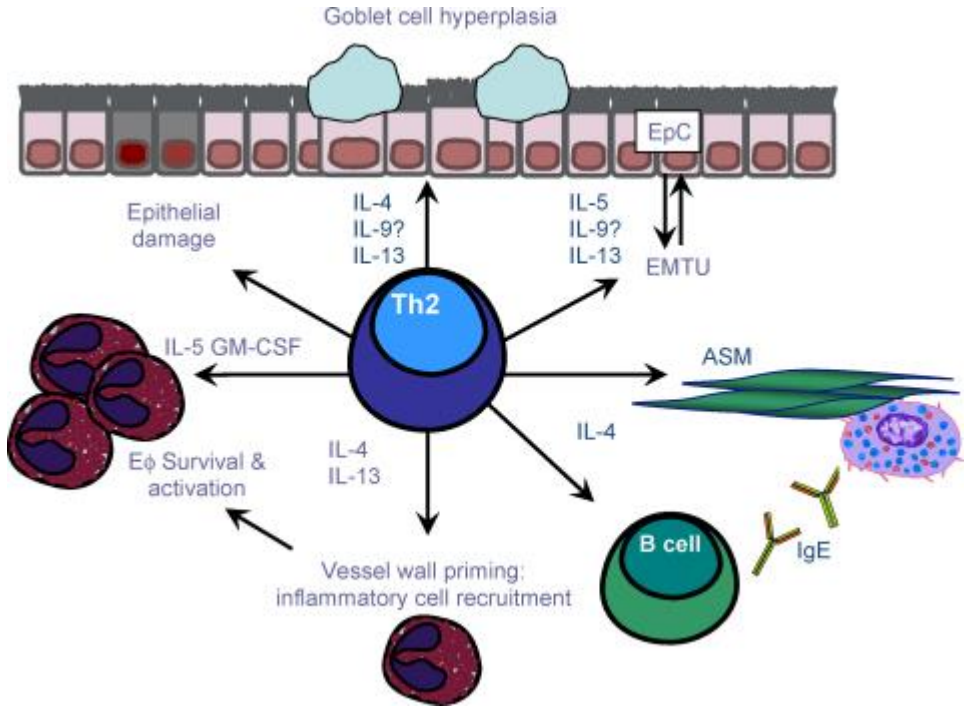
Astma

3 pathogenetic characteristics:

- Inflammation of airways with the wall thicking and increased permeability of capillaries
- Hypersecretion of mucus
- Contraction of smooth muscle cells in bronchioles

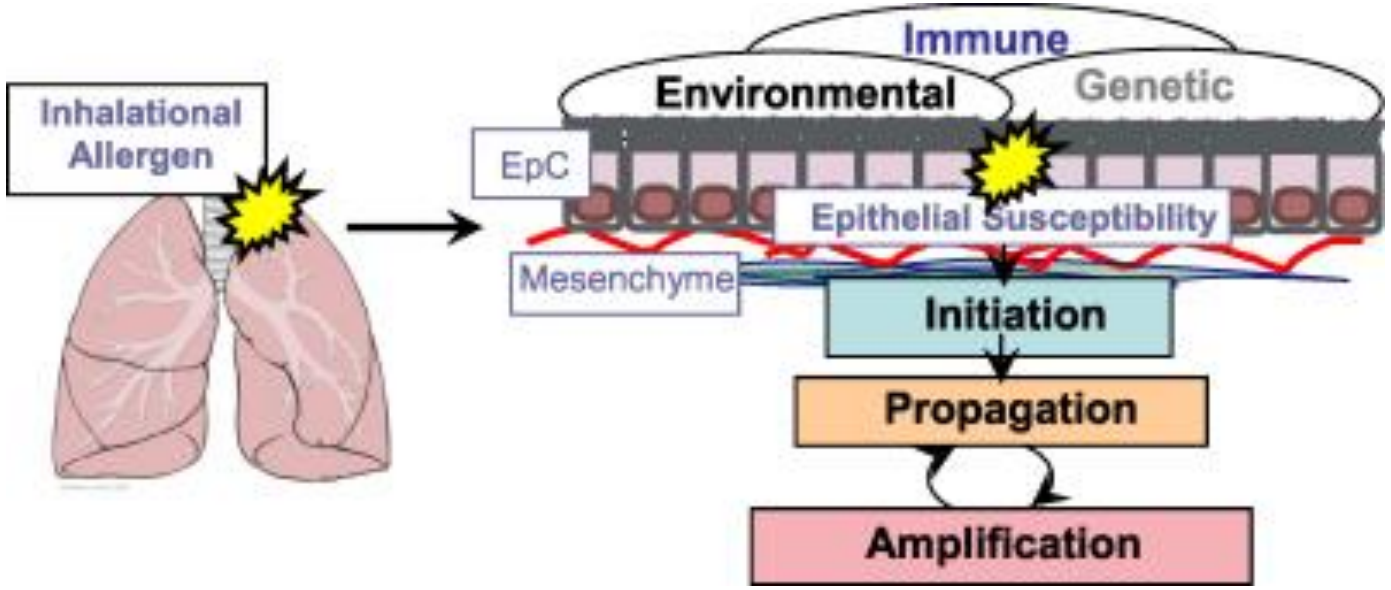
Pathogenesis of asthma

- 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 O_2.



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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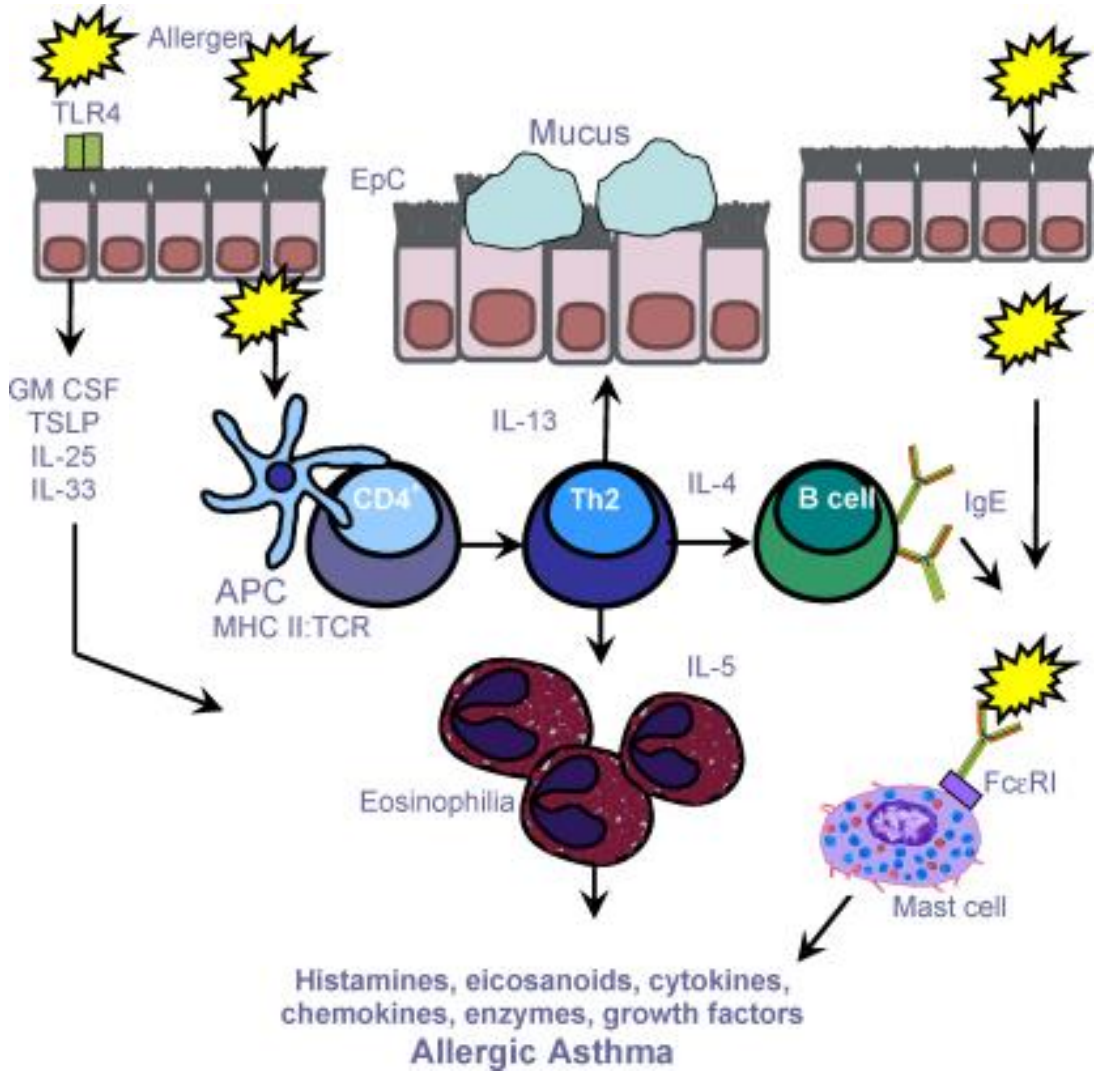

Mutat Res. 2010 August 7; 690(1-2): 24–39.
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To the previous picture:

- 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.

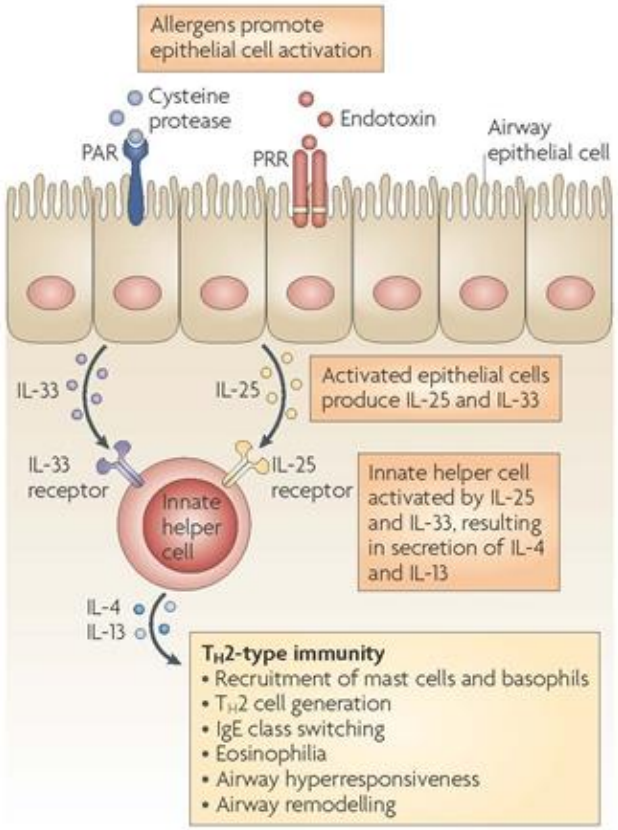


Figure 2 | **Alternative pathway to a T_H2-type response in the airways.** Cysteine protease activity and endotoxin within allergens can activate lung epithelial cells through protease-activated receptors (PARs) and pattern-recognition receptors (PRRs), such as Toll-like receptors. Recent experimental 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*.

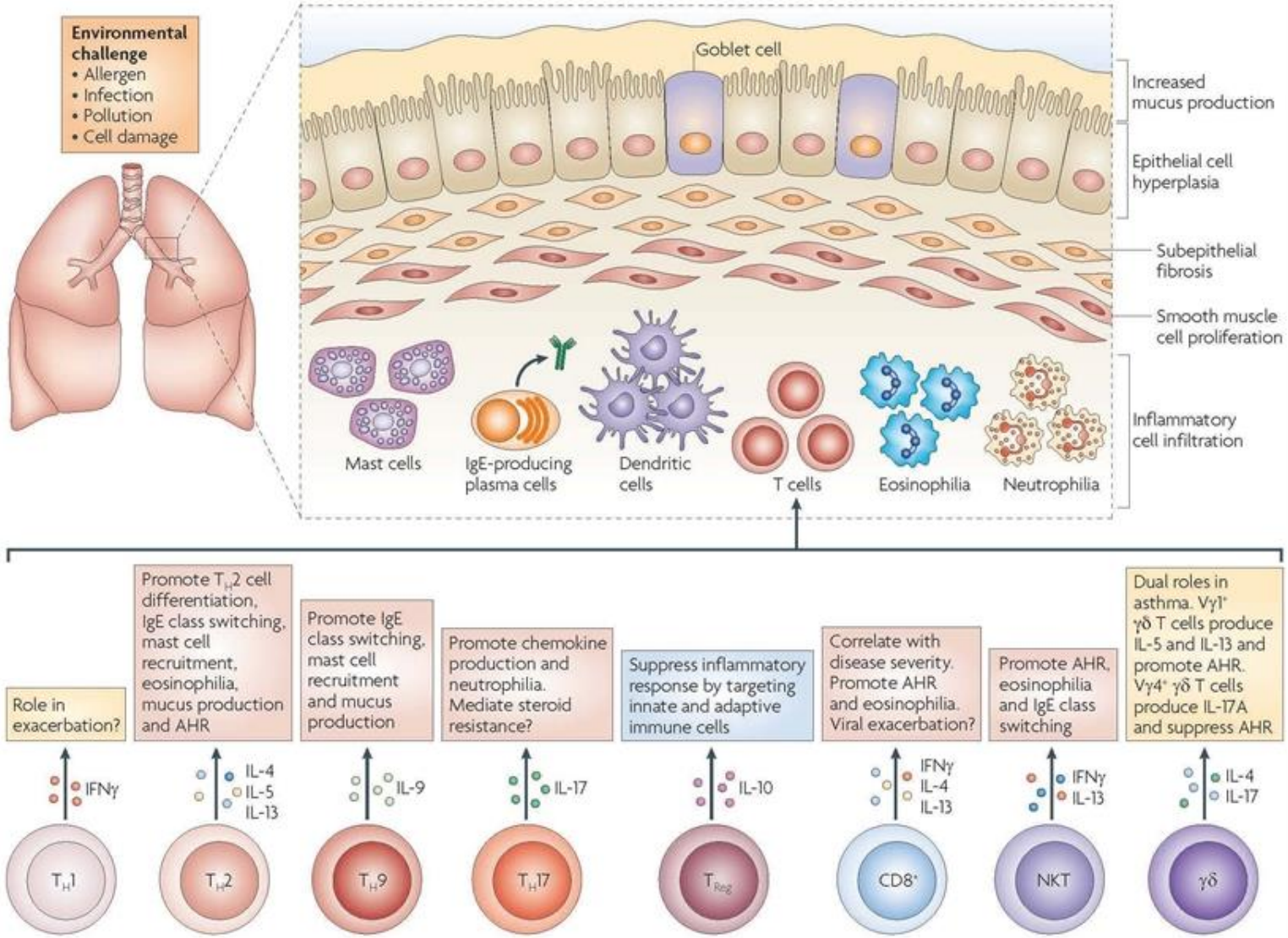
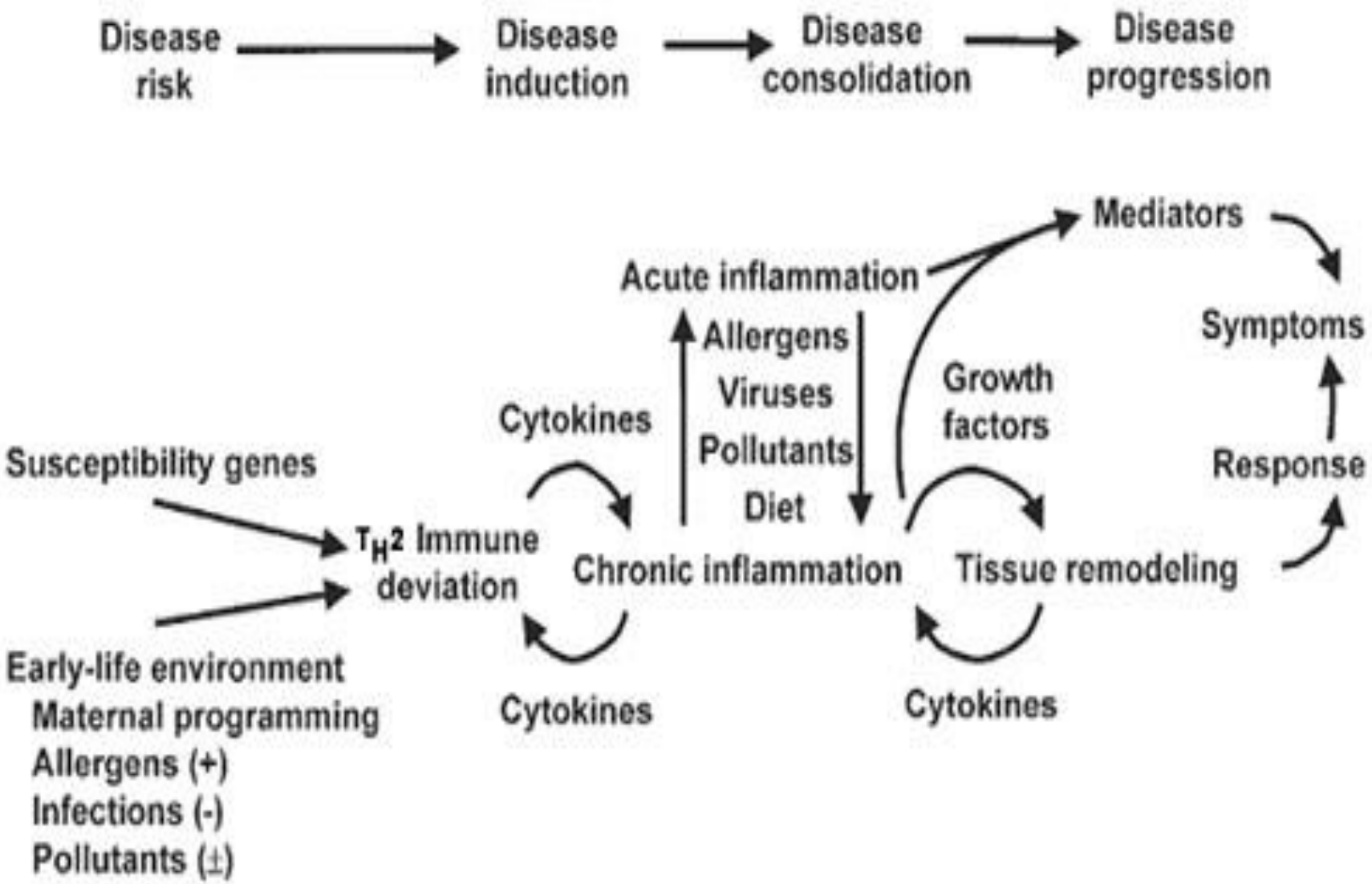
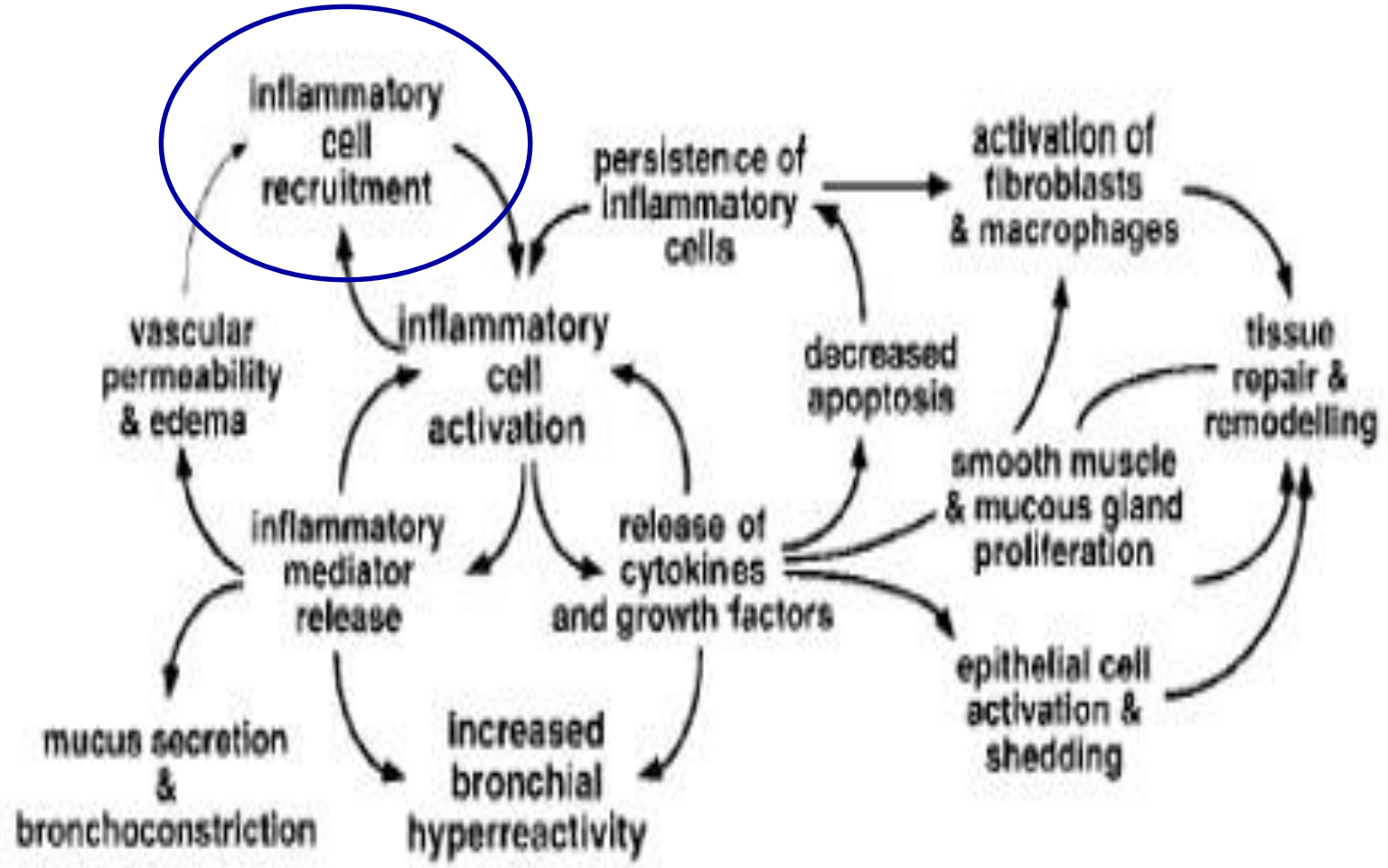


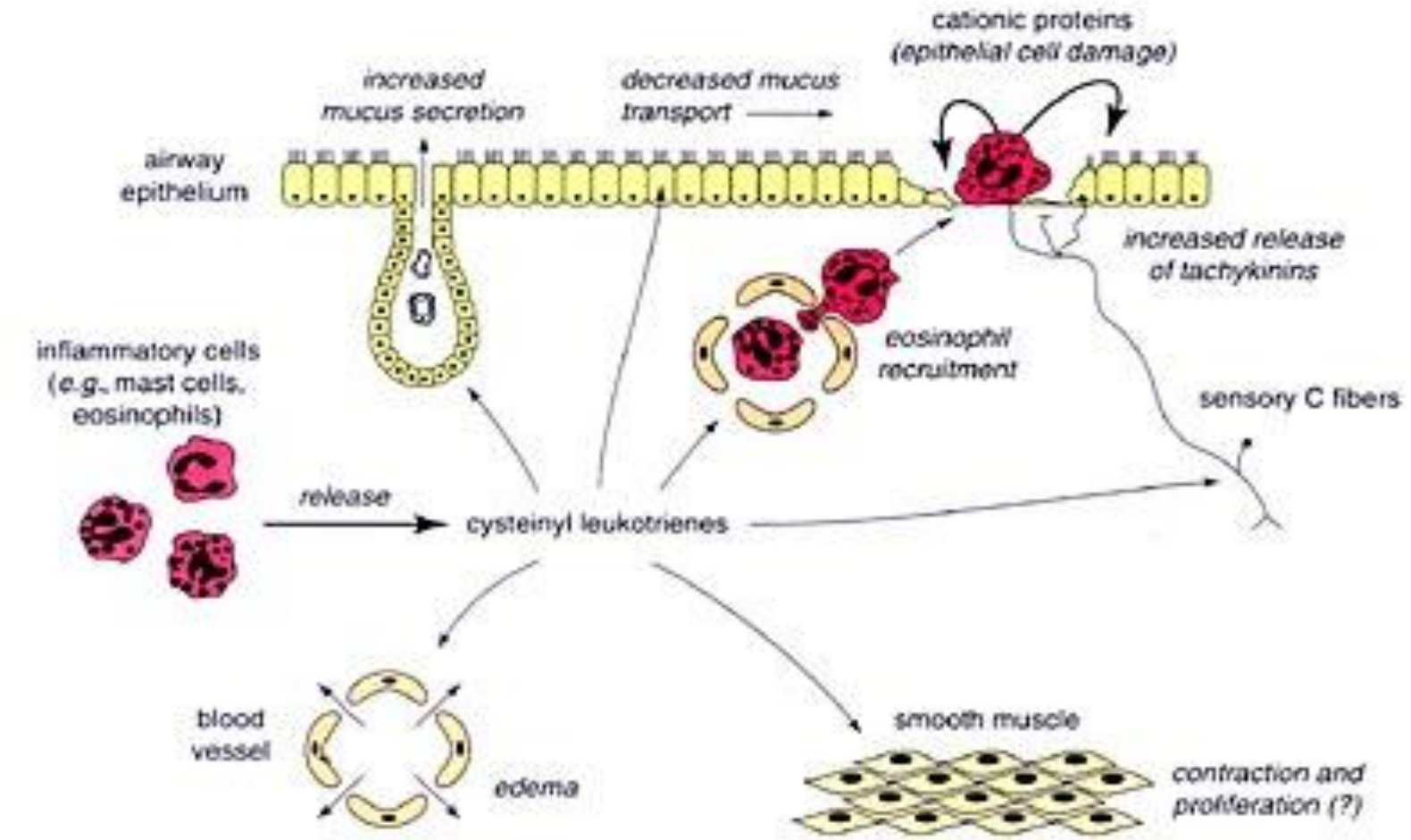
Figure 1 | **T cells involved in the induction of the allergic phenotype.** Asthma is a heterogeneous disease that is characterized by airway hyperresponsiveness (AHR), recruitment of inflammatory leukocytes to the lung and tissue remodelling, including mucus production and airway smooth muscle changes. 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.



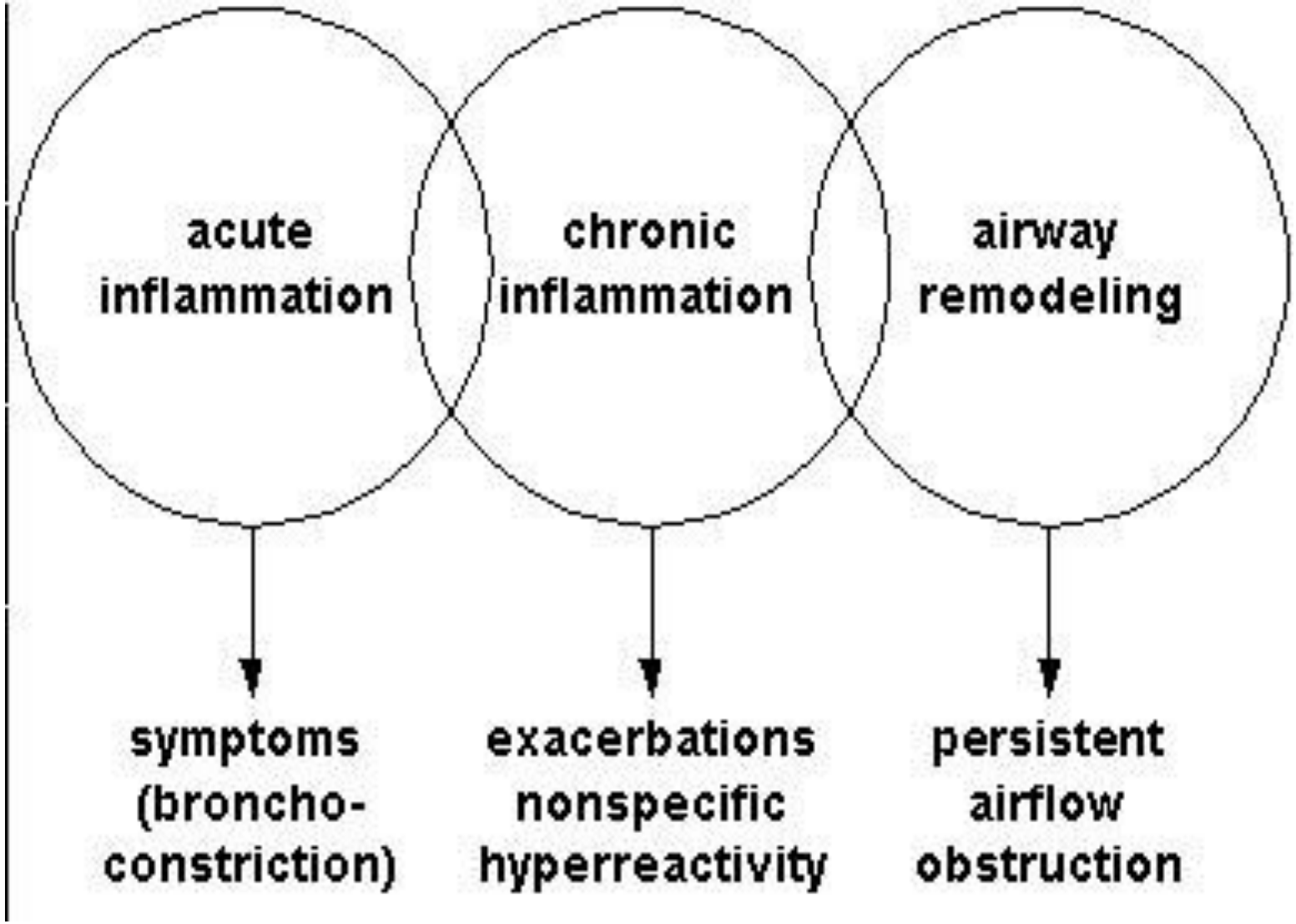
Etiopathogenesis of asthma



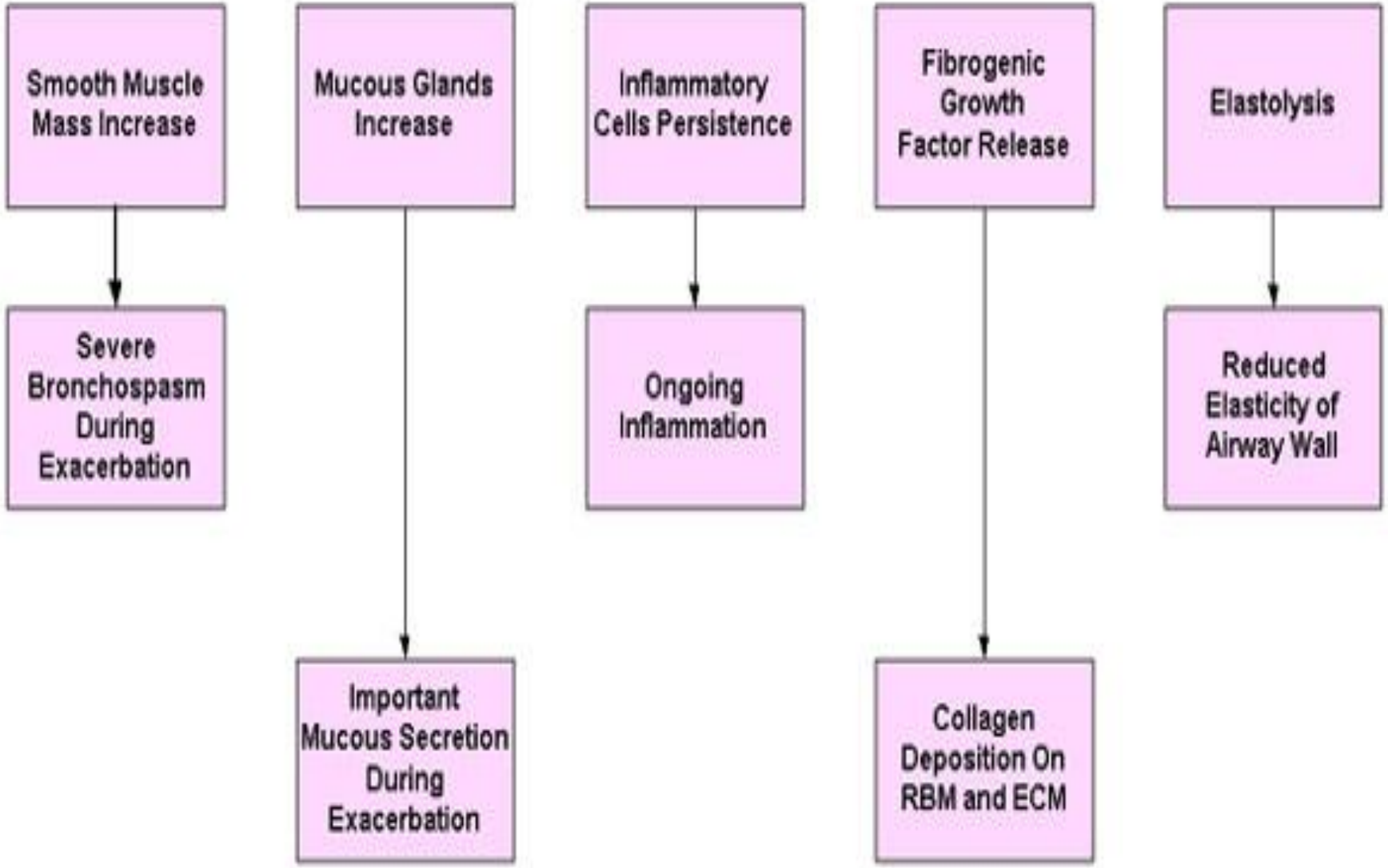
Mechanisms of acute and chronic inflammation in asthma and mechanisms of remodelling



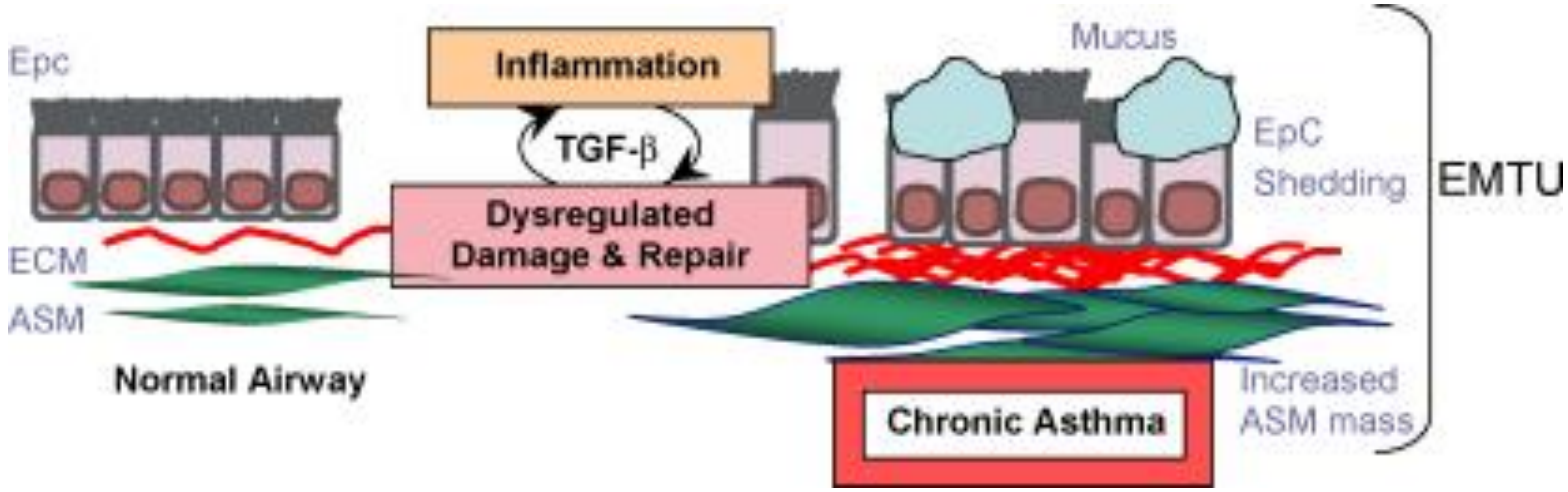
Leukotriens in asthma



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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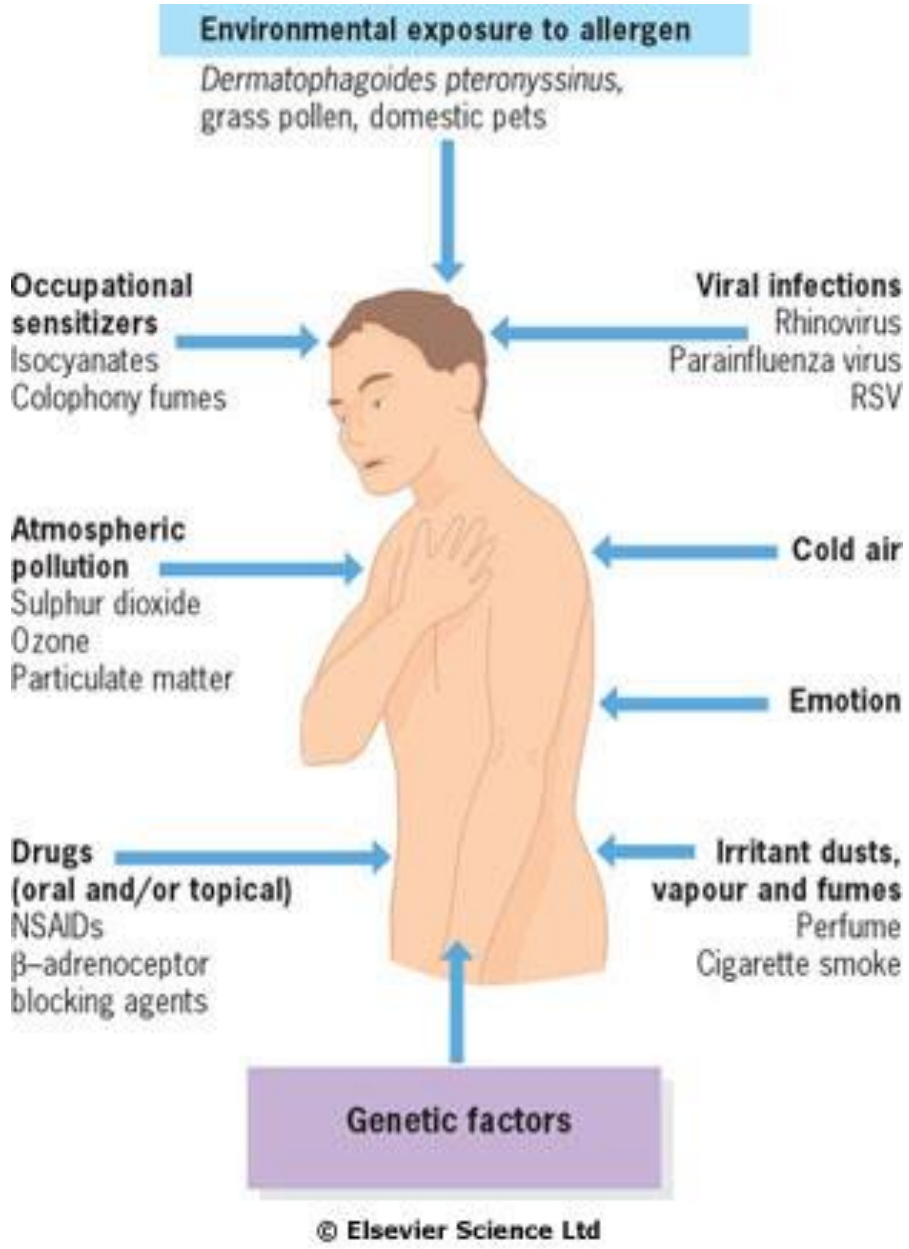
doi: 10.1016/j.mrfmmm.2009.09.005

Types of asthma

- *Extrinsic* – clear external cause
- *Intrinsic (cryptogenic)* – it is not 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 adult 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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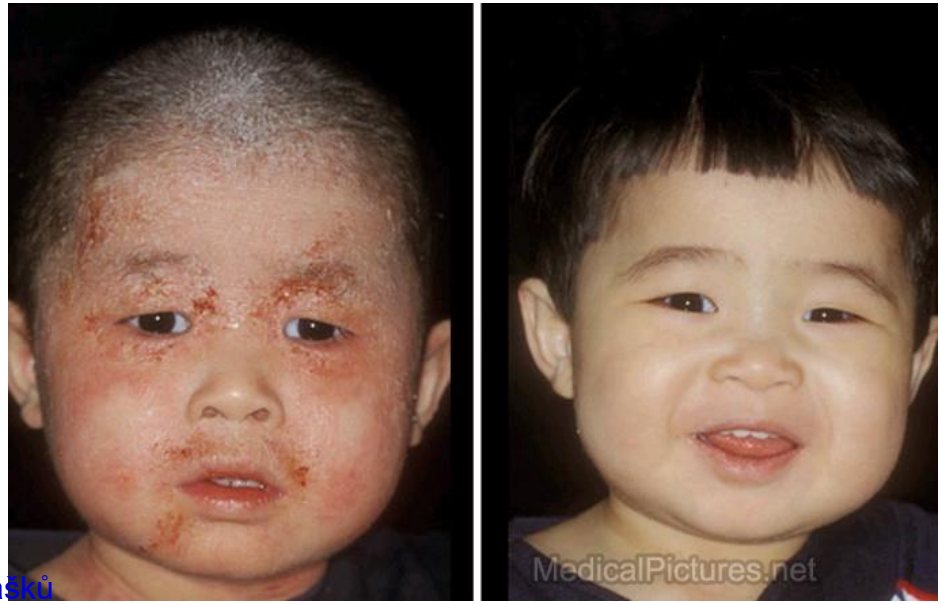
Allergy and atopy

+Atopy:

- Familial occurrence
- Characteristic reaction to environmental allergens
- Circulating antibodies
- IgE antibodies in 30-40% of population
- Correlation between IgE levels and hyperreactivity of airways
- Genetic factors and environmental factors influencing 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 development

Atopic diseases

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



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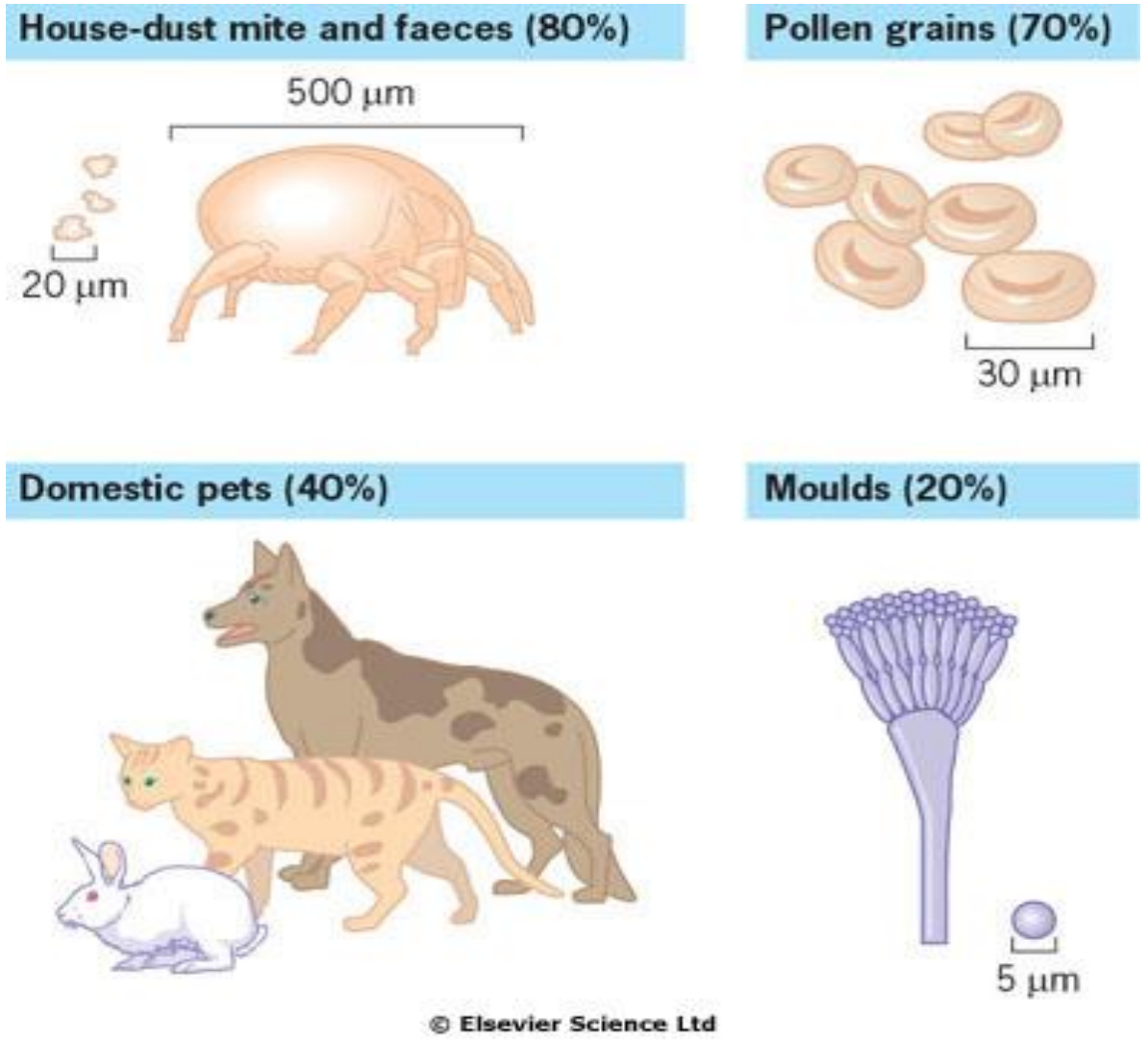
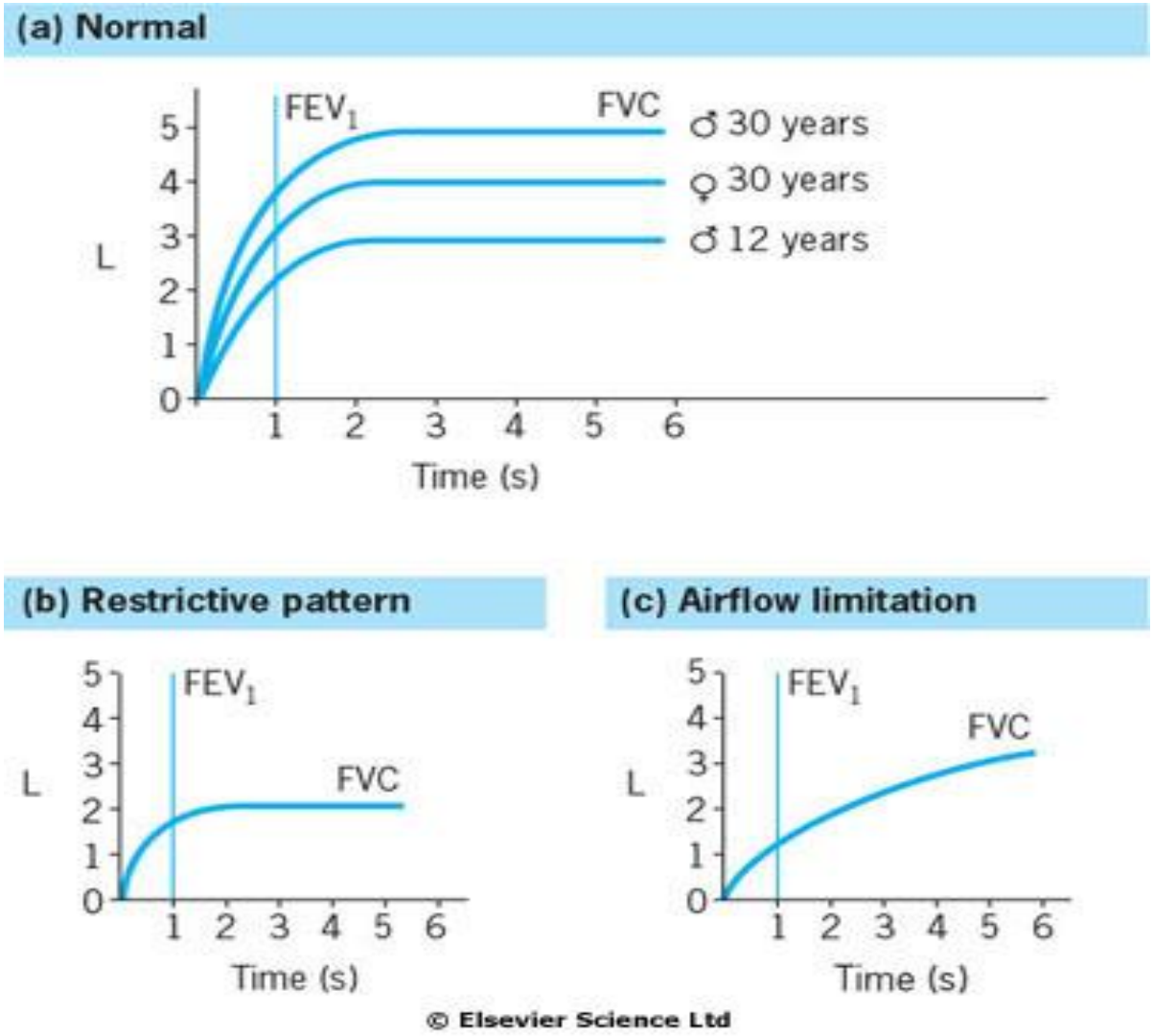


Antigens causing allergic rhinitis and asthma

Chronic obstructive pulmonary disease (COPD)

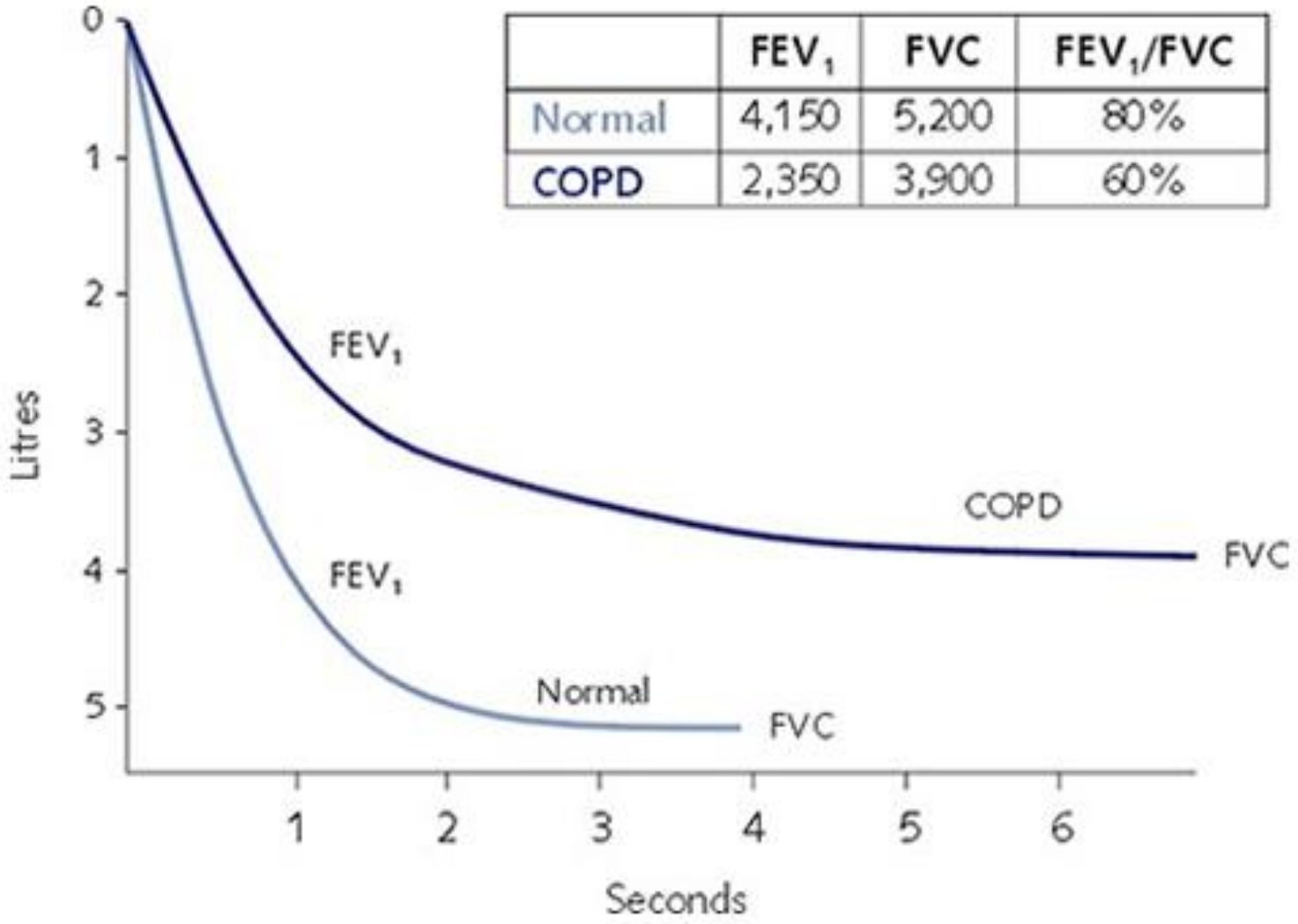
- ***Symptoms***

- 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



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

FVC - forced expiratory vital capacity

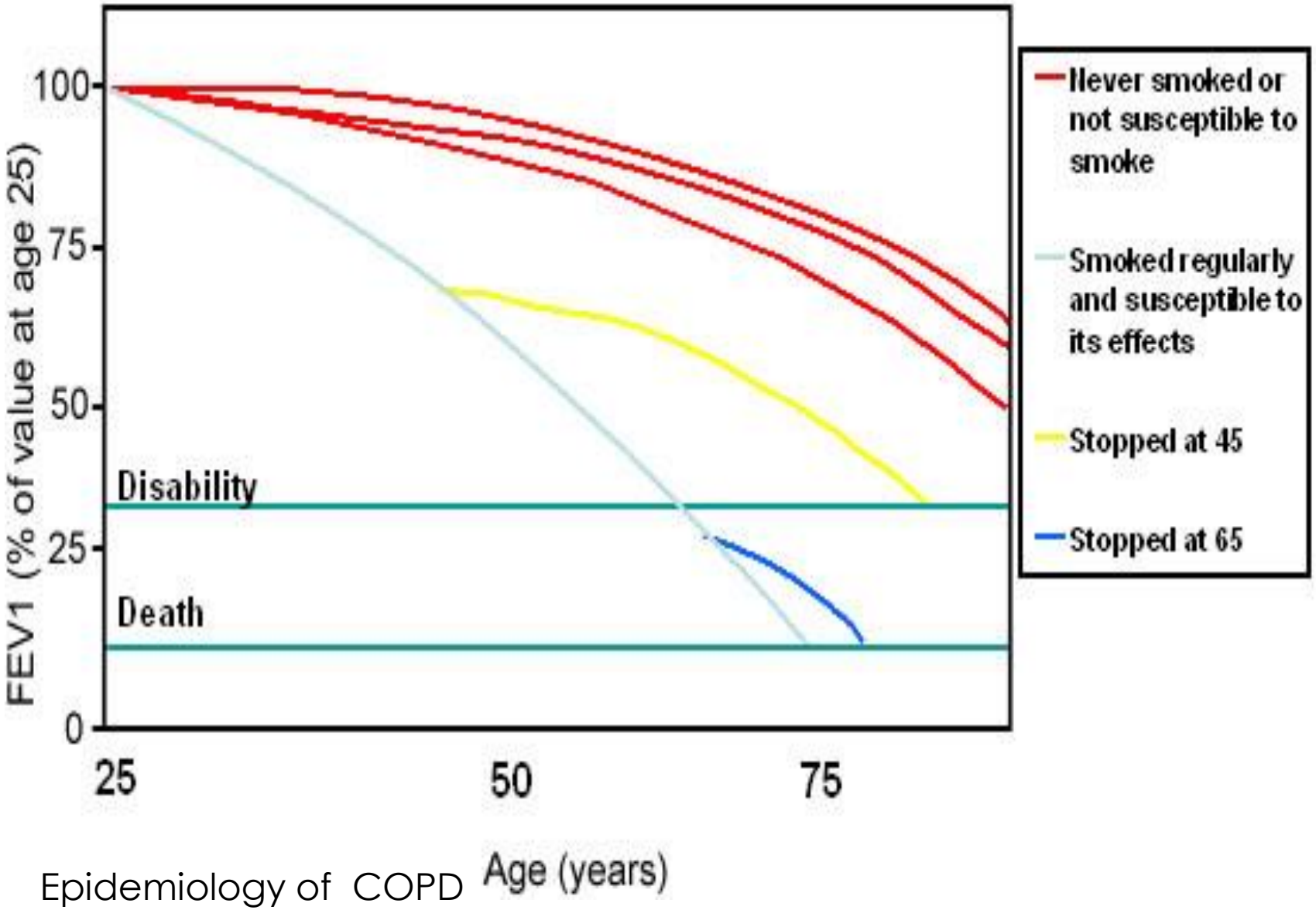


	FEV_1	FVC	FEV_1/FVC
Normal	4,150	5,200	80%
COPD	2,350	3,900	60%

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



Epidemiology of COPD

Chronic obstructive pulmonary disease (COPD)

Two main forms

- ✖ Chronic bronchitis is an ongoing inflammation of the airways.

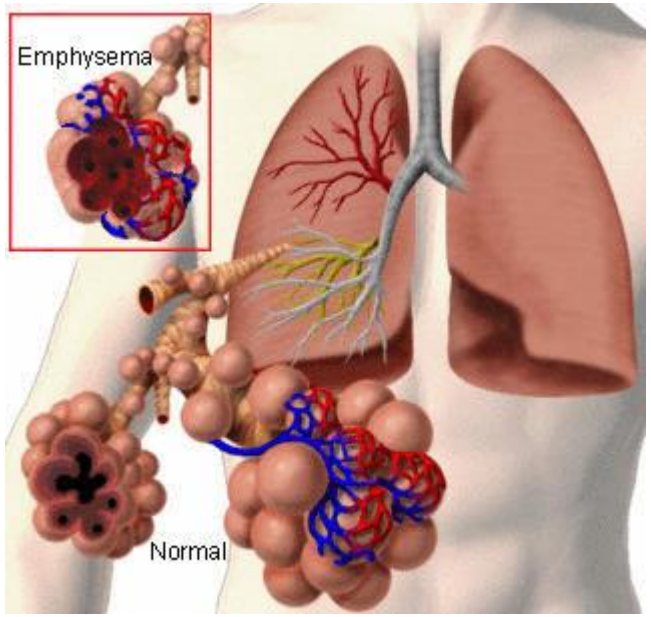
Definition according to the specializations:

- **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 terminal bronchioli in order not to collapse.



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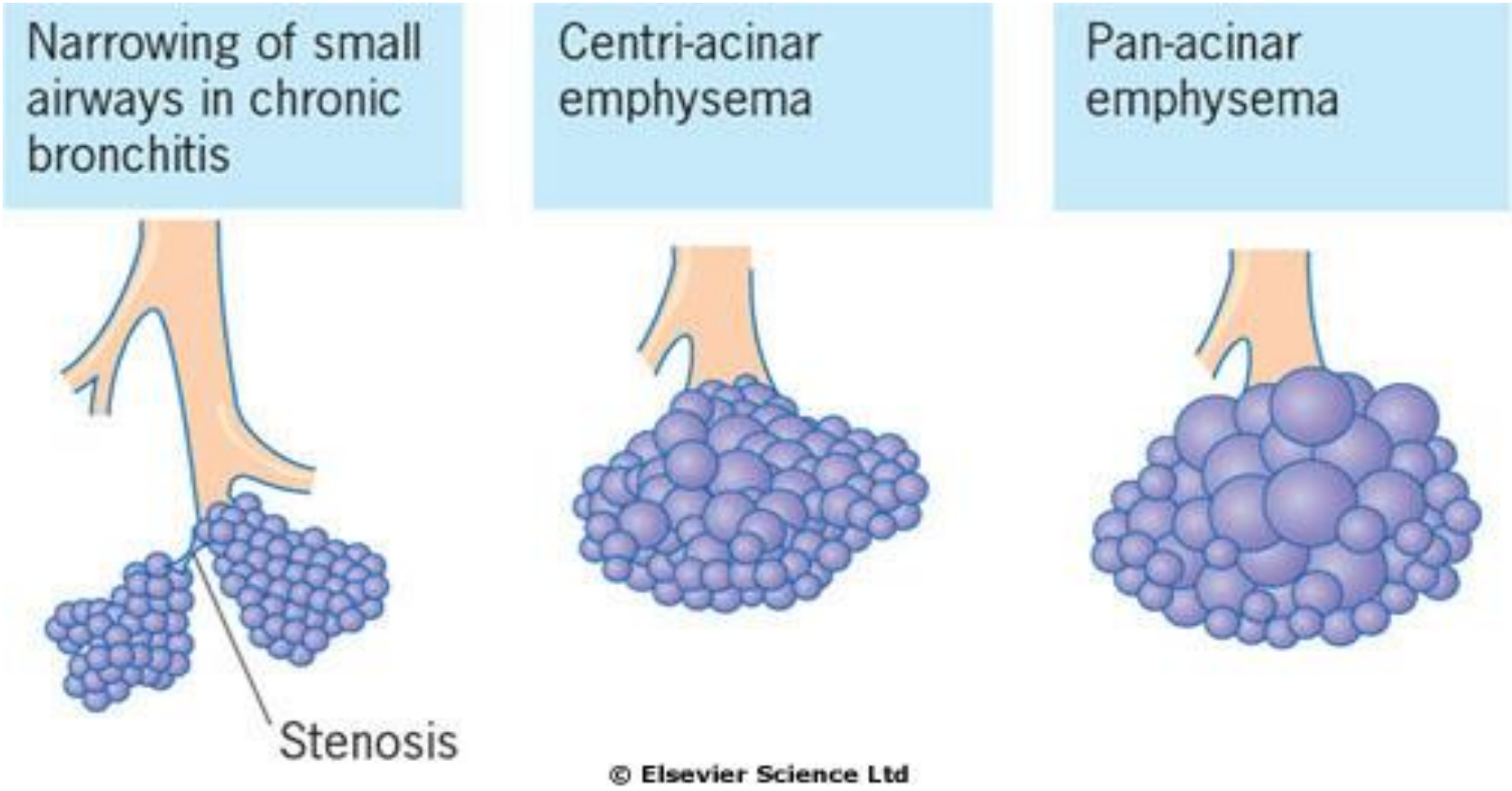
Emphysema: types

- **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).



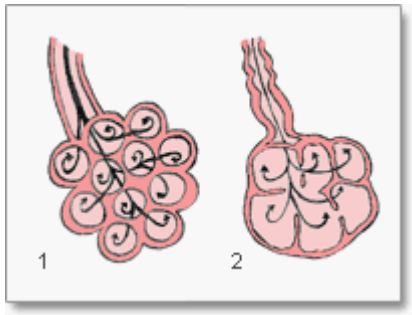
Pathological sings of chronic bronchitis and emphysema

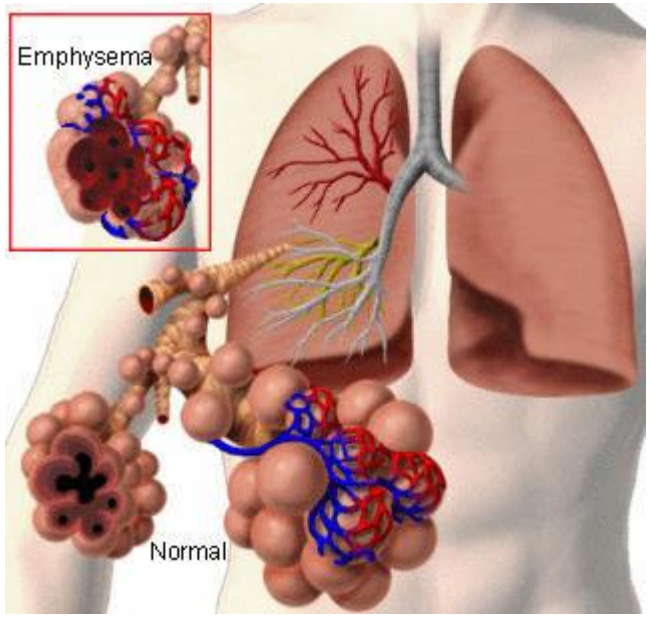
Chronic obstructive pulmonary disease (COPD)

✖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.





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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.

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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.

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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.
- Interaction between fibroblasts and inflammatory cells may also play a role in fibrotic remodeling.
- 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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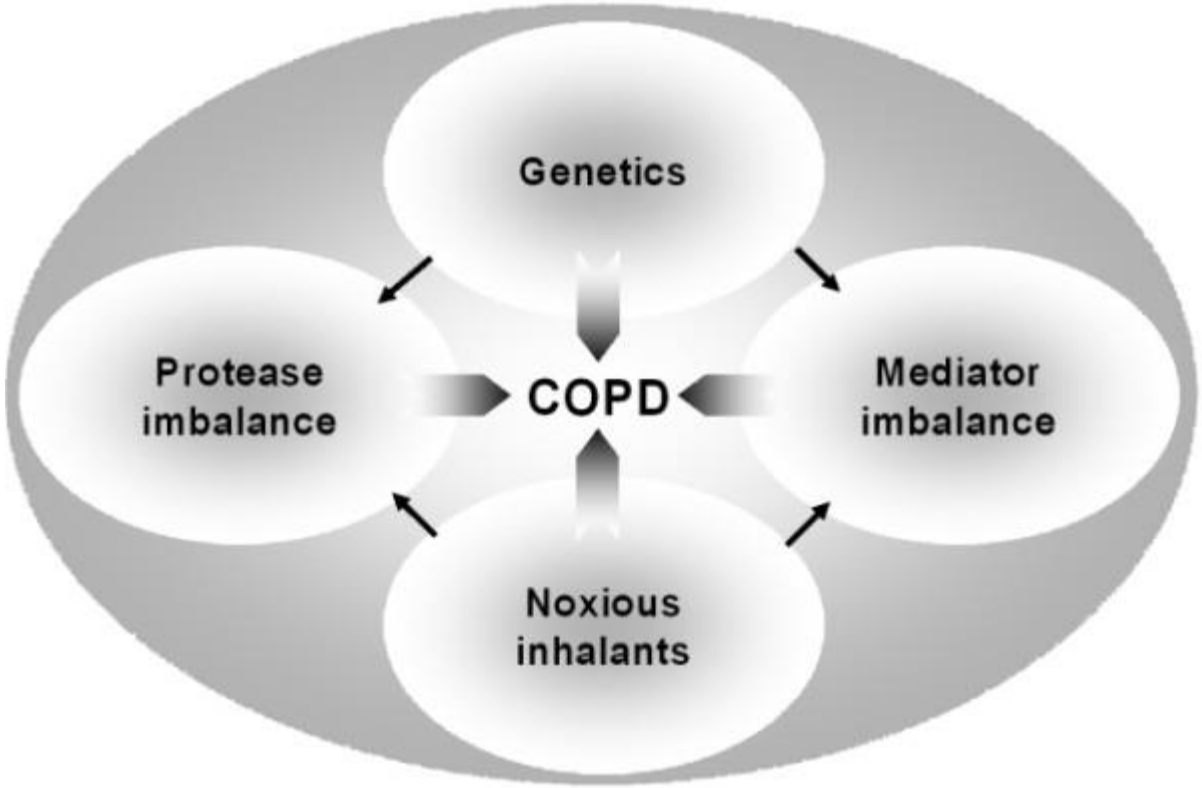
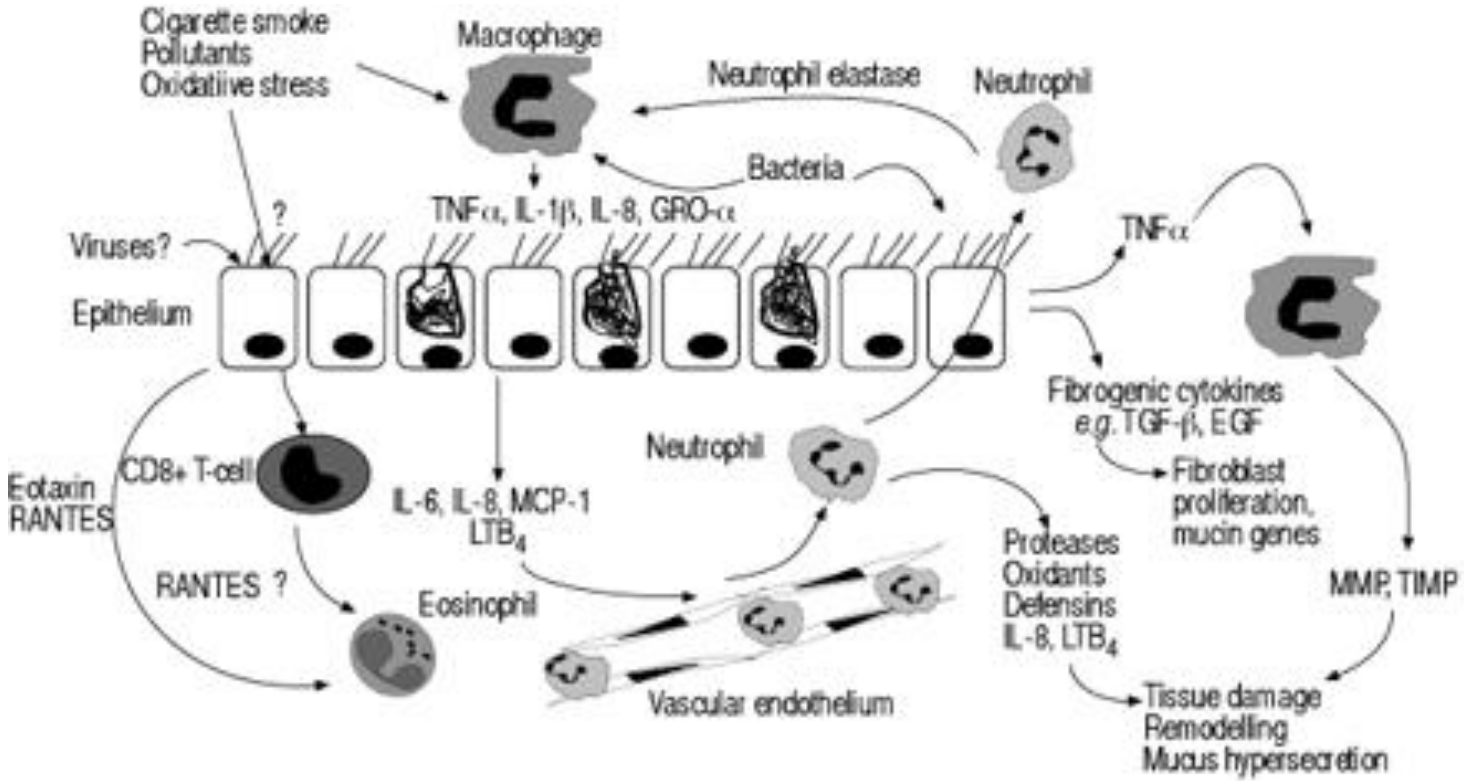


Potential pathogenetic mechanisms involved in COPD Exogenous inhaled noxious stimuli such as tobacco smoke, noxious gases or indoor air pollution and genetic factors are proposed to be the major factors related to the pathogenesis of COPD. These factors may influence protease activity and may also lead 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



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

Types of respiratory insufficiency

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

1. Severe exspiratory dyspnoe (p_aO_2 and p_aCO_2 in blood near to normal values
2. Cor pulmonale - no
3. Higher proportion of emphysema
4. Partial respiratory insuficience, normal sensitivity of central control of ventilation

- *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, alveolar hypoventilation due to decreased sensitivity of central respiratory control (no pure O2!!!)

Pulmonary vascular disease

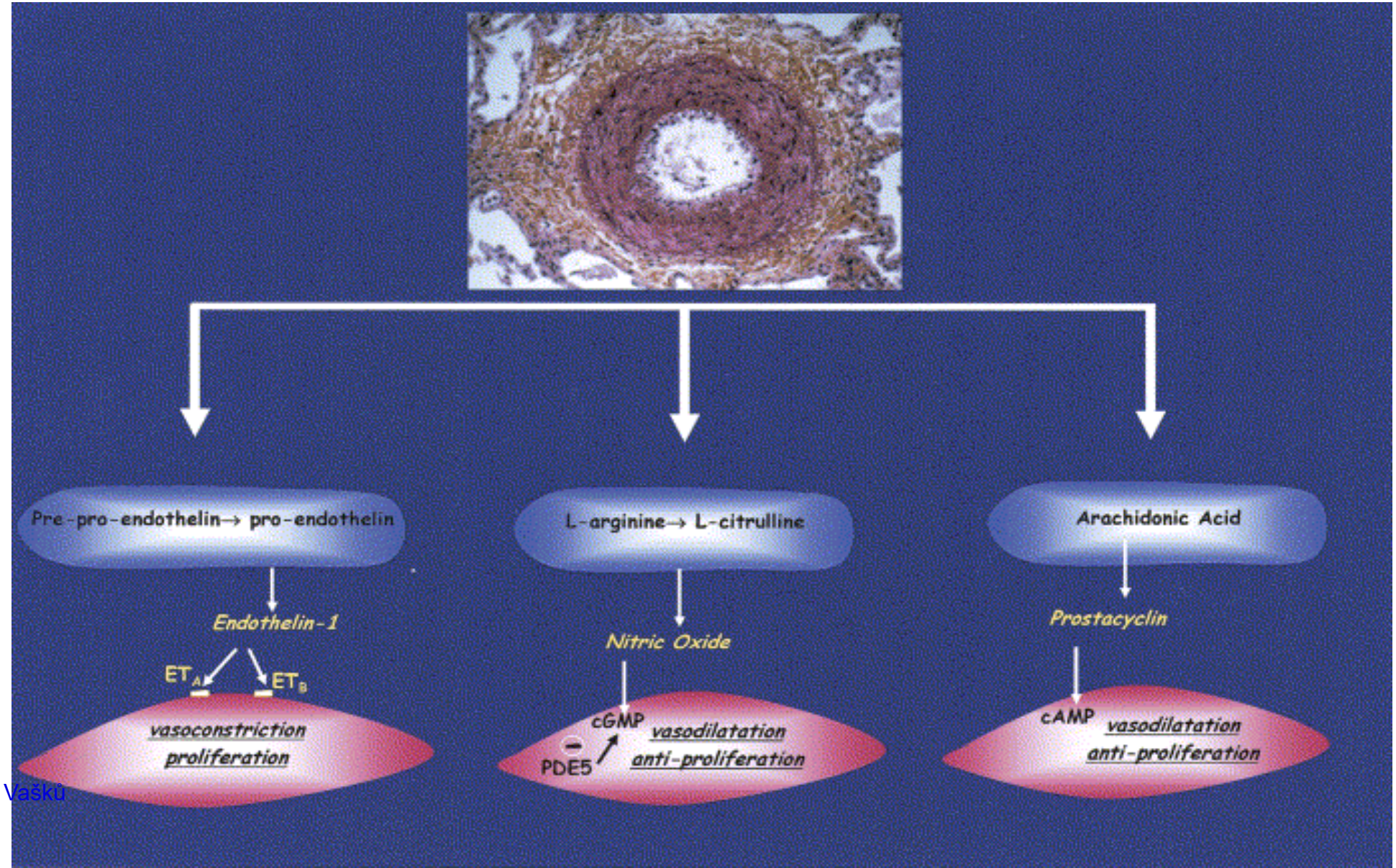
is an important risk factor for disease progression and exacerbation risk.

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.

In patients without known cardiac or pulmonary disease, the PA:A ratio is predictive of mortality; 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



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Thank you for your attention