

PATHOGENESIS OF BRONCHIAL OBSTRUCTION - ASTHMA, CHRONIC OBSTRUCTIVE LUNG DISEASE

1. ASTHMA

Definition by GINA (Global Initiative for Asthma):

Asthma is a chronic inflammatory disorder of airways. Many cells and mediators are involved in this process – eosinophils, mast cells and T-lymphocytes. Chronic inflammation is connected with bronchial hyperreactivity and leads to episodes of wheezing, coughing, tightness in the chest, breathlessness, shortage of breath specially at night and in the morning. This episodes are usually connected with variable obstruction which is reversible spontaneously or by treatment.

- A) Allergic asthma = asthma induced by immunological mechanisms. IgE induced asthma – IgE antibodies triggers early and late-phase of response, T-lymphocytes late and opozděné responses.
- B) Non-allergic asthma = asthma induced by non-immunological triggers
Intermittent x persistent

Inflammation causes obstruction of airways by:

- ❑ Acute bronchoconstriction
- ❑ Swelling of bronchial wall
- ❑ Chronic production of mucous
- ❑ Remodeling of airways walls

Risk factors:

- individual predisposition (genetic variability – 5. a 11. chromosome - atopy, bronchial hyperreactivity, male or female, nation)
- environment – exposition to allergens and professional chemicals which lead to sensitivity, viral and bacterial infection, food, smoking, social and economic society, number of family members, psychosomatic influence

Cells involved in chronic allergic inflammation

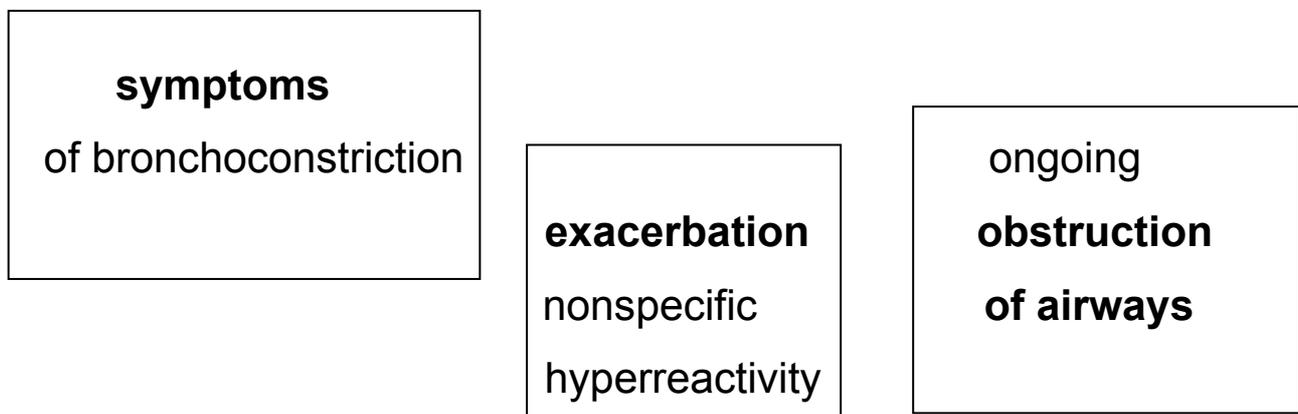
1. Eosinophils
2. Mast cells
3. T-lymphocytes
4. Neutrophils
5. Basophils

Histopathology findings during biopsy examination have not clear affinity to course of disorder and changes of pulmonary function. Also bronchial hyperreactivity does not correlate with histology findings.

Acute inflammation

**Remodeling
of airways**

Chronic inflammation



Changes of **ventilation parameters** exist in patients with proper anti-inflammatory therapy x **the obstruction of airways** is not proven in all asthmatic patient.

Remodeling

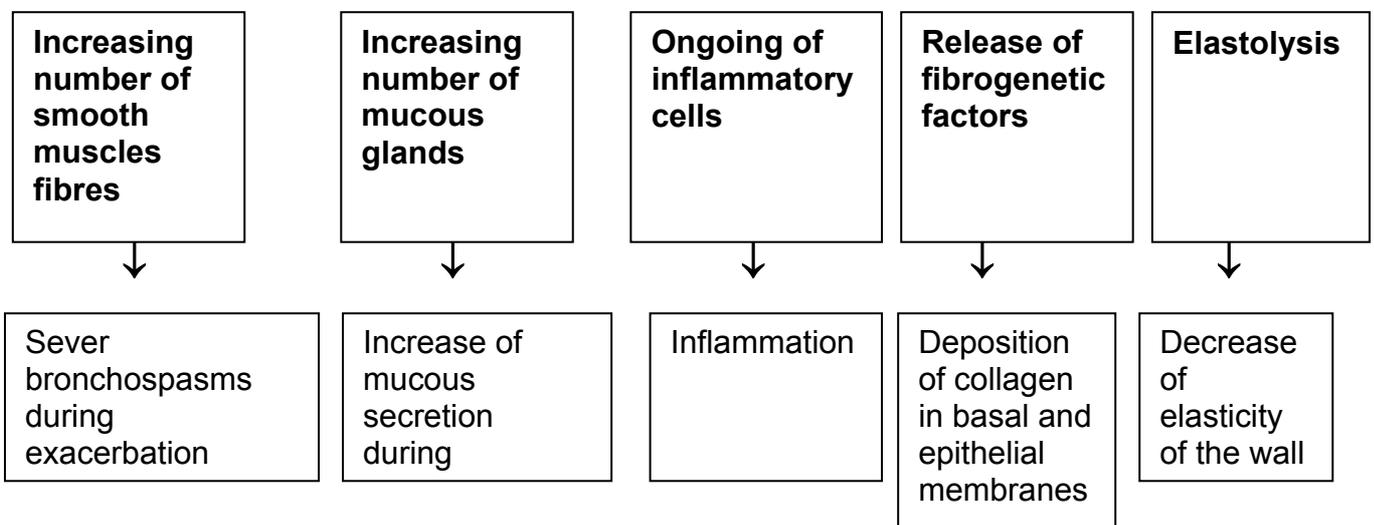
- ❑ **destruction of brush epithelium in airways**
- ❑ **swelling of the bronchial wall**
- ❑ **stimulation of proliferation of fibroblasts**
- ❑ **deposition of collagen in lamina reticularis of basal membrane**
- ❑ **hypertrophy of smooth muscles**
- ❑ **hyperplasia of goblet cells**

The process of remodeling is involved by:

- ❑ **Th2 lymphocytes (CD25+, production of IL-4,13,5,6,10)**
- ❑ **antigen presenting cells**
- ❑ **mast cells (tryptase-converting angiotensin I to angiotensin II, hypertrophy of smooth muscles, histamin – fibrogenetic effect)**
- ❑ **eosinophils (long-living in epithelium and submucoses, create lipids –PAF, LTC₄,LTD₄, LTB₄, peptides, cytokines, TGF- α , TGF- β , IL-1,3, GM-CSF, ECP)**
- ❑ **alveolar macrophages (production of TNF- α , IL-6)**
- ❑ **epithelial cells (desquamation of epithelium, lost of integrity, TGF- β , IGF-1, KGF- β , alteration of differentiation and proliferation of epithelial cells, apoptosis)**
- ❑ **endothelial cells**
- ❑ **myocytes (proliferation of myocytes - after stimulation with IL-11, which is produced by mezenchymal cells after stimulation with allergen, PGDF, EGF, the effect of gelatinase A (MMP-2) and B (MMP-9), production of IL-6,8, eotaxin, PGE₂, RANTES, MCP-1,2,3, expression of ICAM-1, VCAM-1, production of NO, GM-CSF, IL-5)**
- ❑ **fibroblasts (activation of fibroblasts, creation of myofibroblasts, release of GM-CSF and TGF- β , increasing pro-inflammatory activity of eosinophils)**

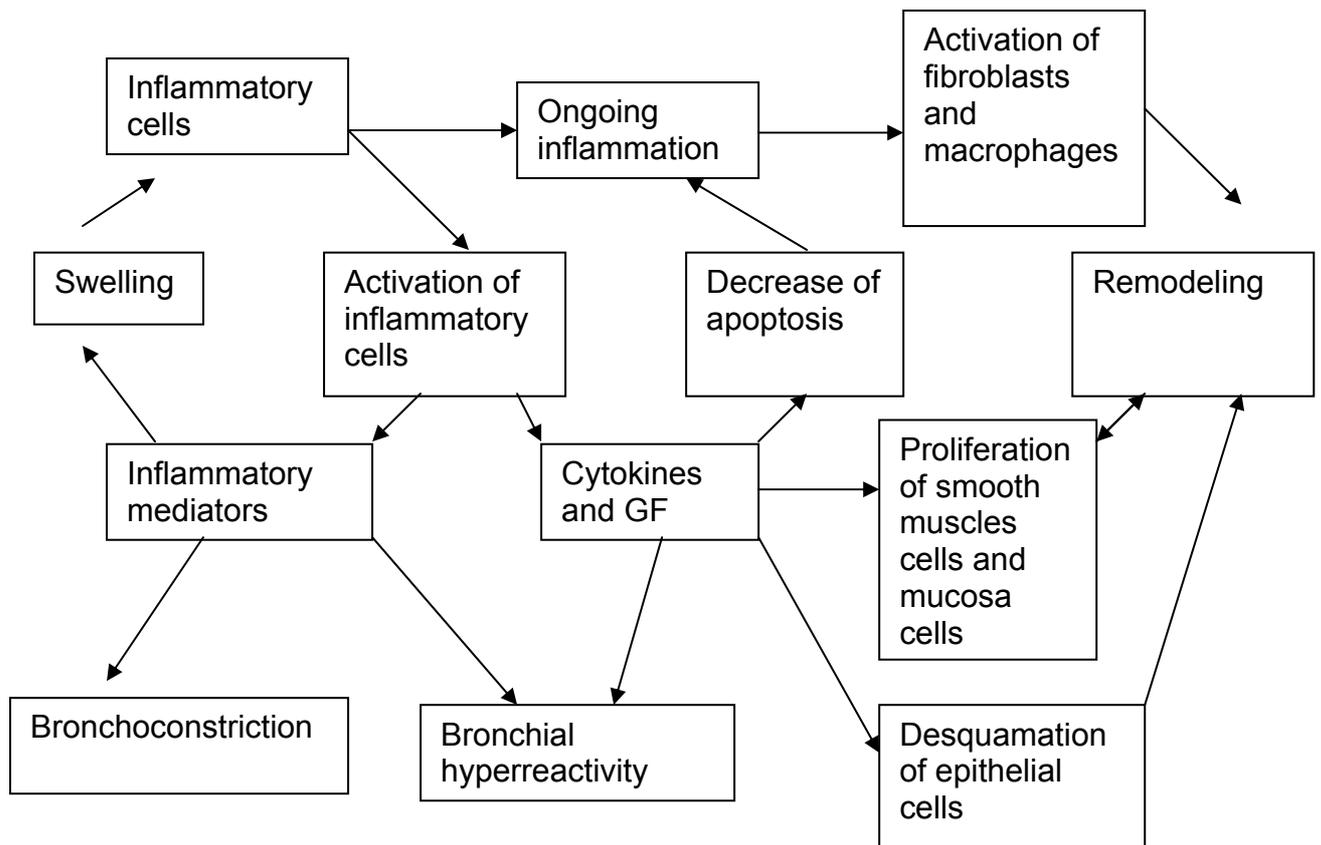
Subepithelial structures:

- ❑ **thickness of basal membrane**
- ❑ **increasing deposition of extracellular matrix under epithelium**
- ❑ **deposition of collagen I., III., IV., V. and VII. in reticular membrane**
- ❑ **increasing deposition of proteoglycans (lumican, biblycan, decorin, fibromodulin, hyaluron, versica)**
- ❑ **tenascin (corresponds with activity of chronic inflammation)**
- ❑ **fibronectin**



Pathophysiological and clinic consequences:

- in some patients the grade of remodeling not necessarily correlates with bronchial hyperreactivity
- remodeling correlates with plasma level of eosinophils, but does not correlate with the grade of bronchial hyperreactivity nor with period and severity of asthma
- long period of asthma is connected with collagen and fibronectin deposition and with lowering of bronchial hyperreactivity
- decrease of FEV1 although the proper therapy
- no correlation between thickening of the reticular membrane and the period of asthma and decrease of FEV1 in adults



Eosinophils

- ❑ terminal cells developing from bone marrow under stimulatory effects of GM-CSF, IL-3 and IL-5, which activates only eosinophils and basophils in humans
- ❑ eosinophils migrate shortly in tissues and get through the mucous of GIT tract. The process is regulated by eotaxin and homing gastrointestinal adhesive receptor $\alpha 4\beta 7$ which binds to MAdCAM-1 molecule expressed in gastrointestinal tissue.
- ❑ live 2 weeks in tissue (GIT parasites)
- ❑ eosinophilia in peripheral blood is not a result of migration to the tissues but is under the surveillance of migratory signals from vasculature of targeting organ
- ❑ IL-4, IL-13 induce the expression of VCAM-1 which binds to very late antigen-4, the receptor of eosinophils, and to P-selectin
- ❑ CC chemokines like eotaxin bind CC chemokine receptor 3, target eosinophiles to the tissue where they stay alive long time due to IL-5 which diminishes apoptosis and due to the effects of GM-CSF

- Mediators released by eosinophils: major basic protein (MBP), eosinophilic cationic protein (ECP), peroxidase, neurotoxin, sulfidic peptic leukotrienes, PAF, GM-CSF, TGF- α , TGF- β
- Degranulation of eosinophils – supposing by crossing Fc γ , Fc α , together with adhesive receptor of macrophage antigen-1 – Mac-1

Cytokines involved in pathogenesis of asthma

IL-4

- cross-linking of immunoglobulines in B lymphocytes – production of IgE and IgG4
- increases of expression of VCAM-1 and mucous secretion
- inhibits of activation of Th1 and production of IFN γ

IL-13

- induces production of IgE a IgG4
- activates mast cells
- increases bronchial hyperreactivity and contractility of smooth muscles, affects the differentiation of cilia
- induces the production of eotaxin, VCAM-1
- supress production of pro-inflammatory cytokines

IL-5

- produced by mast cells and Th2 lymphocytes, epithelial cells and eosinophils
- affects the proliferation and the differentiation of B lymphocytes
- induces expression of IL-2R
- proliferating and differentiating factor for eosinophils

IL-12

- produced by macrophages, dendritic cells and monocytes
- decreases production of Th2 cytokines and then production of IgE and IgG1
- decreases number of eosinophils in peripheral blood and in sputum

IL-10

- large immunosuppressive and anti-inflammatory effect
- decreases expression of iNOS, COX2

- decreases release of IL-2, expression of MHC class II., CD80, CD86 and CD32 on the surface of APC and then presentation of allergen, RANTES, IL-5
- correlation with asthma severity

IFN γ

- low levels in atopic people
- stimulatory effects on Th1 cells, inhibitory effects on Th2 cells
- the nebulisation of IFN γ decreases the number of eosinophils in BAL but this effect is not significant

TGF- β

- remodeling
- induction of expression of Fas receptor on the surface of epithelial cells, activation of apoptosis, fagocytosis by macrophages, exsudation of plasma, fibrosis

Classification of asthma:

A. Atopic (allergic) asthma

- in combination with allergic rhinitis, atopic dermatitis, genetic predisposition
- confirmation of spec. IgE antibodies, prick tests, inhalation challenge

B. Endogenous asthma

- without specific known influence, obviously in women after exposition to cold weather, refract to the standard therapy

C. Exercise induced asthma

- physical exercising, provocation by inhalation of chemicals, cold or hot weather

D. Aspirin induced asthma

- typical triads-nasal polyps, urticaria and asthma induced by application of aspirin
- other drugs

E. Allergic bronchopulmonary aspergillosis

- aspergillus acts as an allergen challenge in atopic people and induces aspergillus asthma or allergic bronchopulmonary aspergillosis
- in the chest radiography are intermittent infiltrates in lungs, the viscosity of mucous is increased and mucous plugs, bronchiectasia

F. Gastroesophageal reflux

- bronchospasm induced by reflex

G. Sinobronchial syndrome

- combination of sinusitis with nasal polyps and with asthma

H. Professional asthma

- induced by inhalation and exposition to industry chemicals

CH. Asthmatic equivalent

- dry cough, irritating, without breathlessness

Classification of asthma grading:

Grade 1. Intermittent asthma

- rare symptoms < than 1x per week, short episodes of worsening
- night symptoms 2x monthly
- no symptoms between attacks
- PEF or FEV1 > 80%, variability < 20%

Grade 2. Mild persistent asthma

- symptoms <1x per day >1x per week
- night symptoms > 2x per month
- exacerbation can affect daily activity or sleeping
- PEF or FEV1 > 80%, variability 20-30%

Grade 3. Moderate persistent asthma

- Everyday symptoms
- Exacerbation affects daily activity and sleeping
- Night symptoms > 1x per week
- Everyday use of releasing drugs
- PEF or FEV1 between 60- 80%, variability > 30%

Grade 4. Severe persistent asthma

- Continuous symptoms
- Frequent exacerbation
- Physical activity is decreased
- Frequent night symptoms
- PEF or FEV1 < 60%, variability > 30%

Examination methods:

History

- variable – seasonal, diurnal, exercise
- breathlessness, cough, wheezing, rhinitis
- physical examination – normal, hyperinflation with sounding se percussion, prolonged breath-out, dry phenomenon, pulsus paradoxus, running of supraclavicular area, silent lungs

Spirometry

- diagnosis, to monitor treatment, estimation and prevention, examination before an operation
- basic– searching – PEF (Peak Expiratory Flow)
index of variability PEF = $\frac{\text{the highest} - \text{the lowest}}{0,5 \times (\text{the highest} + \text{the lowest})} \times 100$
 - FVC, FEV1, FEV1%FVC
- enlarged – spirometry, curve of flow-volume, bronchial challenge tests
puls oxymety, rhinomanometry

Pletysmography

- referential method for measuring of resistance, breathing work, compliance and DLCO
- isotherm conditions , two phases- measuring of intrathoracal volume of gas and measuring of airways resistance

Bronchomotoric challenge

- bronchodilatation test – test of reversibility of bronchial obstruction
salbutamol 200-400 ug, ipratropium 80 ug
- bronchoconstriction test – bronchial hyperreactivity
histamin 1g na 100 ml of 0,9% NaCl, methacholin, acetylcholin, adenosin-5-monofosfát, hypertonic NaCl

RTG

- normal, hyperinflation

Bronchoscopy

- Endobronchial biopsy – submucosis
- Bronchoalveolar lavage – phenotypic differentiation from peripheral blood, express CD69

Induced sputum

- Hypertonic NaCl
- Number of eosinophils in sputum corresponds to bronchial biopsy and BAL

ECP

- ECP levels in induced sputum corresponded to symptoms score and inversely proportional to PEF.
- Significant inflammation –15 ug/l, compensation of asthma - 23 ug/l

Measuring of breath-out condensated gas

- LTB₄, cysteinyl leukotrienes, NO –increased in untreated patients, dependent on flow, lower flow-higher NO, constantly 50 ml/s
- Low production of NO in cilia dyskinesia, cystic fibrosis, correlation with findings in biopsy and eosinophils in sputum

Blood gases

2. COLD

Definition by GOLD (Global Initiative for Chronic Obstructive Lung Disease):

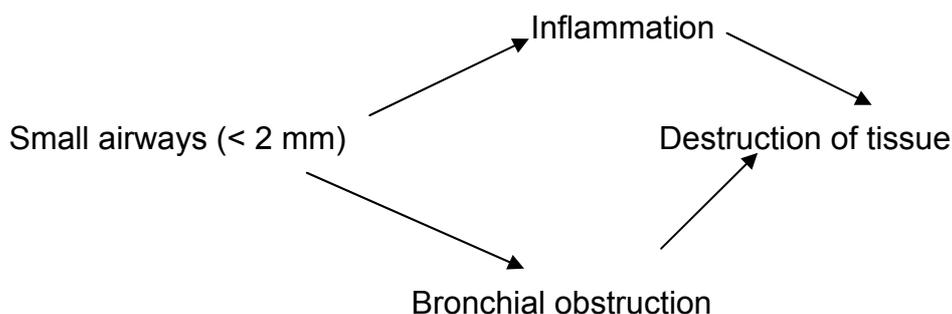
COLD is characterized by decreasing flow in airways (bronchial obstruction) which is not completely reversible. Bronchial obstruction is in the progress and is connected with abnormal inflammatory response of lungs caused by toxic pollutants.

Chronic bronchial obstruction

- Combination of disorder of small airways (**obstructive bronchiolitis**) and destruction of lung tissue (**emphysema**)
- Chronic inflammation – remodeling and narrowing of small airways
- Destruction of lungs and inflammation lead to lose of connection of alveoli with small airways
- Decrease of elasticity

Risk factors

- **Genetic factors (e.g. deficiency of α_1 - antitrypsin, ABO secretion status, microsomal epoxid hydroxylase, glutathion S-transferase, α_1 - antichymotrypsin, complementary part GcG, TNF- α , microsatelit instability), hyperreactivity of airways, growth of lungs**
- **Exposition to tobacco smoke, professional dust and chemicals, air pollution in environment and in buildings, infection, social and economic status**



Cells involved in inflammation:

Neutrophils

- BAL and sputum contain activated neutrophils but their number is not increased in sections from bronchi or lung tissue
- Induced sputum contains increased level of myeloperoxidase and human neutrophil lipocalin
- Secretion of proteases- neutrophil elastase, cathepsin G neutrophil protease-3

Macrophages

- Production of IL-8, LTB₄, TNF- α

T lymphocytes CD8+

- Release of perforin, granzym B, TNF- α

Eosinophils

- The role is unknown, usually increase during acute exacerbation
- Increase of ECP, EPO in induced sputum

Epithelial cells

- Production of inflammatory mediators (eicosanoids, cytokines, adhesive molecules)
- E-selektin-attraction and adhesion of neutrophils
- TNF- α , IL-8

Mediators involved in COLD pathogenesis:

Leukotriene B₄

- Strong attraction of neutrophils
- Secreted by macrophages

IL-8

- Selective attraction of neutrophils
- Secreted by macrophages, neutrophils and epithelial cells in bronchi

TNF- α

- activates NF- κ B which activates gene for pro IL-8
- in sputum, bronchial biopsy

Macrophages Chemotactic protein-1 (MCP-1)

- attraction of macrophages to the lungs

Macrophage inflammatory protein-1 (MIP-1)

Macrophage inflammatory protein -1 α (MIP-1 α)

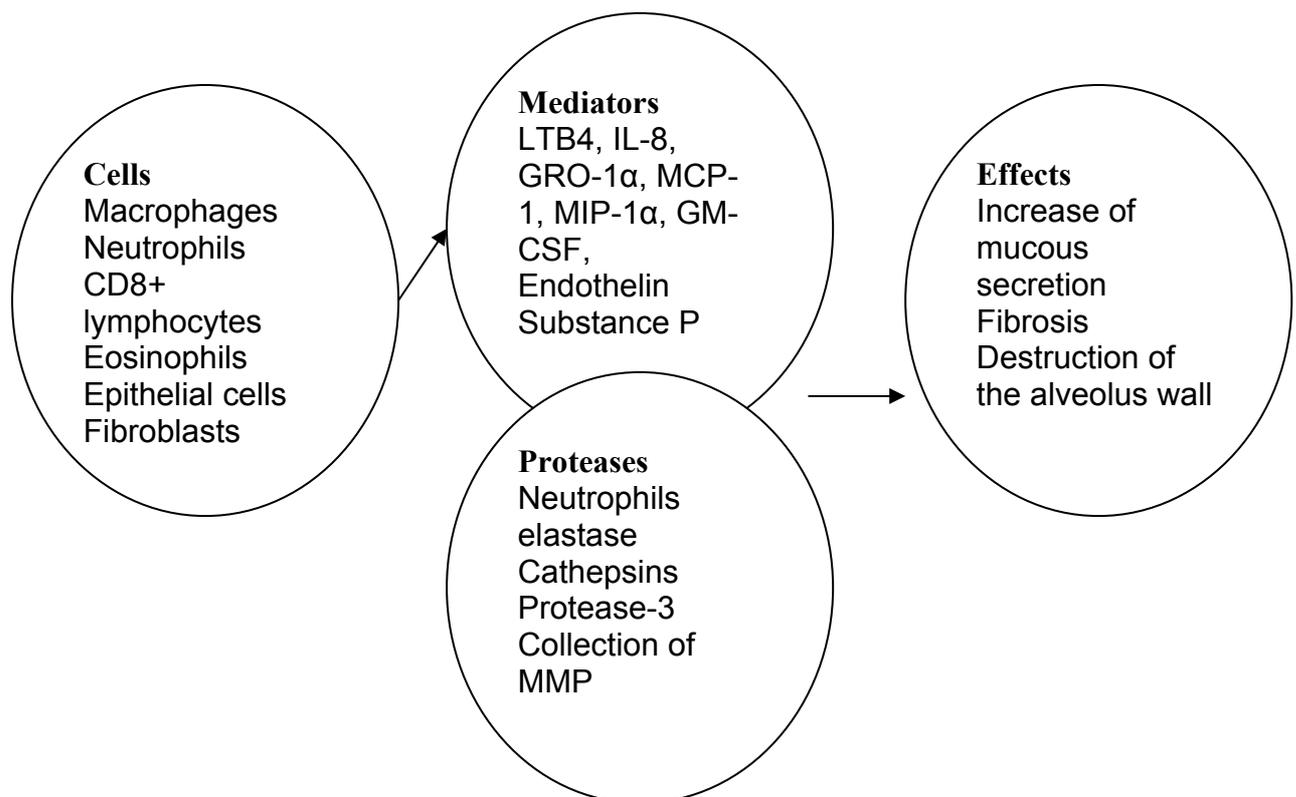
GM-CSF – increased during exacerbation

TGF- β , EGF – remodeling of bronchi

Endothelin-1 – vasoconstriction, chronic hypoxemia

Neuropeptides – substance P, VIP – influence on vessels function and secretion of mucous

Complement – C5a - concentration of neutrophils

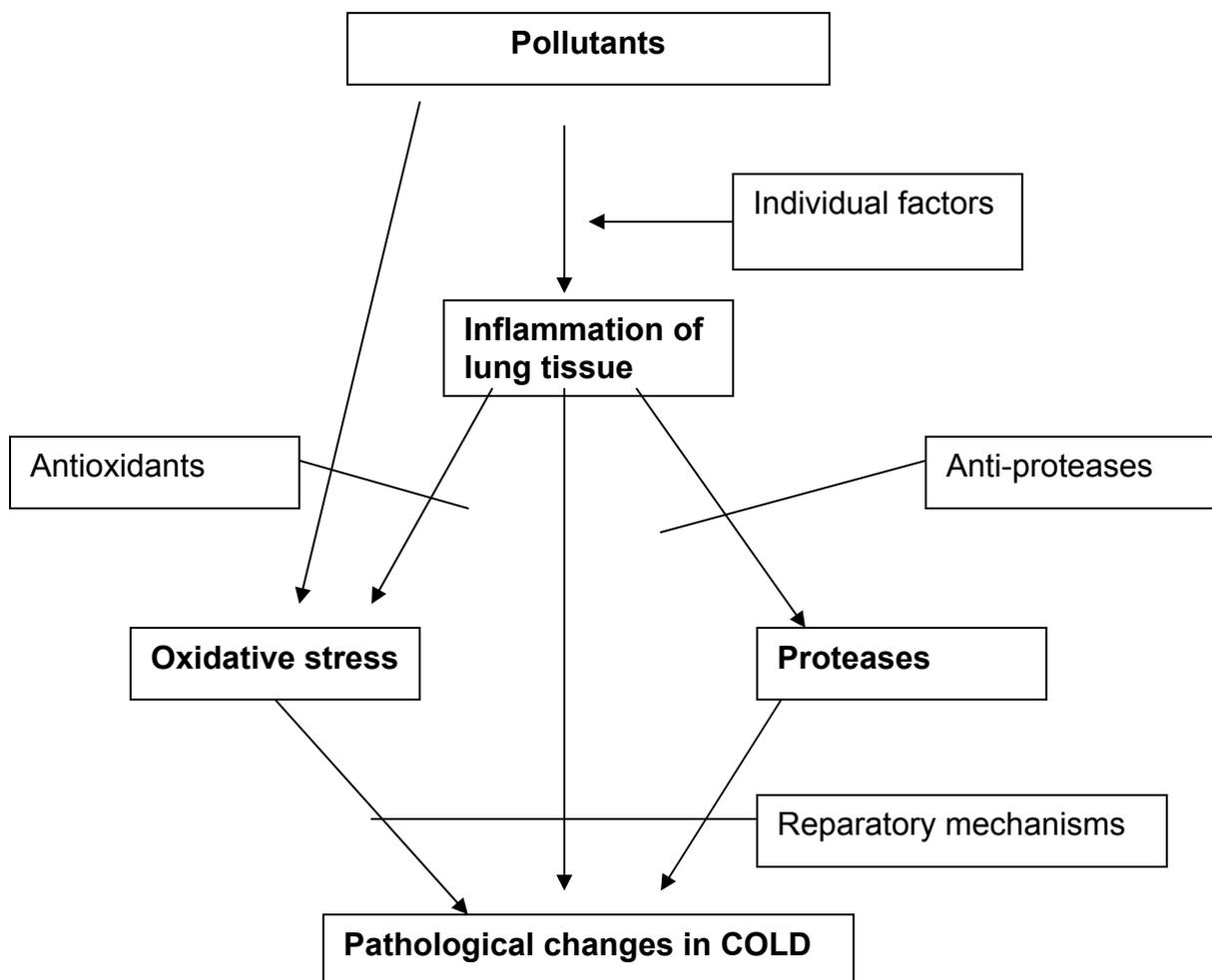


Pathogenesis of COLD

- **pollutants in environment ---inflammation**
- **smoking of cigarettes** – stimulation of macrophages and epithelial cells to produce TNF- α , IL-8 and LTB4
 - exhalations from cars, dust from grain
- **instability between proteases and anti-proteases in lungs**
 - Laurell and Eriksson –1963 – deficiency of α_1 -antitrypsin and emphysema

➤ **oxidative stress**

- hydrogen peroxide, NO – directly measured oxidants produced during smoking of cigarettes
- isoprostan F₂ α-III, marker of oxidative stress in lungs, bronchoconstriction
- changes in central and peripheral bronchi, lung tissue and vessels
- peripheral bronchi are the major place of the obstruction
- centrilobular type of emphysema
- changes include: increased secretion of mucus, the function of cilia is disturbed, obstruction, hyperinflation of lungs, disturbed gas exchange – firstly hypoxamia (due to irregularity of ventilation and perfusion), then hypercapnia, pulmonary hypertension and cor pulmonale



Classification of COLD grading:

Grade 0 – high risk

- normal spirometry
- chronic symptoms

Grade I – mild

- FEV1/FVC < 70%
- FEV1 > 80%
- Chronic symptoms are or are not present (cough, sputum)

Grade II – moderate

- FEV1/FVC < 70%
- 50% < FEV1 < 80%
- Chronic symptoms are or are not present (cough, sputum, breathlessness)

Grade III – severe

- FEV1/FVC < 70%
- 30% < FEV1 < 50%
- Chronic symptoms are or are not present (cough, sputum, breathlessness)

Grade IV – the most severe

- FEV1/FVC < 70%
- FEV1 < 30% or FEV1 < 50% and respiratory failure or clinical symptoms of cor pulmonale

Examination methods:

Clinics

- History, physical examination, inspection, palpation, percussion, auscultation

Spirometry, bronchodilatation challenge and test of reversibility by corticosteroides

- if FEV1 after application of bronchodilators is < 80% and FEV1/FVC < 70%, the bronchial obstruction is not fully reversible
- patient is treated for 6-12 month with inhalation corticosteroides and FEV1 is increased about 200 ml and about 15% before treatment, the test is positive

RTG, CT, HRCT

- hyperinflation – flat diaphragm, enlargement of retrosternal space, increased transparency of lungs, quick loosening of pulmonary vessels bed

Blood gases

- in patients with FEV1 < 40%
- in patients with clinical symptoms of respiratory failure, right heart failure

Pulmonary hemodynamics

- pulmonary hypertension, cor pulmonale

Hematocrit

Screening of deficiency of α_1 -antitrypsin

- COLD started before 45 years

Differences between asthma and COLD

	COLD	ASTHMA
Cells	Neutrophils Great increase of macrophage number Increase of CD8+ T cells	Eosinophils Small increase of macrophage number Increase CD4+ Th2 lymphocytes Activation of mast cells
Mediators	LTB4 IL-8 TNF- α	LTD4 IL-4, IL-5 And others
Results	Squamous metaplasia of epithel Destruction of tissue Mucous metaplasia Enlargement of glands	Fragile epithel Thickening of basal membrane Mucous metaplasia Enlargement of glands
Treatment efficacy	Corticosteroides have little or no effect in the treatment	Corticosteroides can cure inflammation