General Toxicology

Toxic Responses of the Respiratory System (I)

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Objectives of this lecture are to:

- determine the respiratory tract structure & function, &
- determine acute & chronic responses of the lung to injury.

Overview of the respiratory system:

- The respiratory system has direct contact with the inhaled air.

  Inhaled air contains a variety of environmental pollutant (e.g., gas, dust, fiber & tobacco smoke). Air also contains air borne viruses, bacteria & fungi.

- The respiratory system is also exposed to inhaled drugs which are used for local or systemic effect.

:Respiratory tract structure & function

I. Oronasal passages:

- The respiratory tract is divided into the upper respiratory tract (from the nostril or mouth to the pharynx) & lower respiratory track (airway passages & lung parenchyma below the pharynx) (Fig. 1).

- The upper respiratory track functions to conduct, heat, humidify, filter, & chemosense incoming air.

- Nasal epithelia can metabolize many foreign compounds by cytochrome P450 & other enzymes.

- The olfactory epithelium contains specialized chemosensory olfactory neurons located in the superior portion of the nasal passage.

- The main nerve endings that perceive irritants, the chemical nociceptors also discern temperature & mechanical stress.
  Two protein families, the transient receptor potential (TRP) channels & the taste (TAS) receptors, perform these functions in the upper respiratory tract.

- TRP channels are ion channels that are permeable to cations, including calcium, magnesium, & sodium.

- Among the subfamilies of TRP receptors, are TRP subfamily A (TRPA) & TRP subfamily V (‘’V” for vanilloid) (TRPV).
  TRPA1 & TRPV1 are the major irritant receptors in the nasal passage & are primarily within the trigeminal nerve.

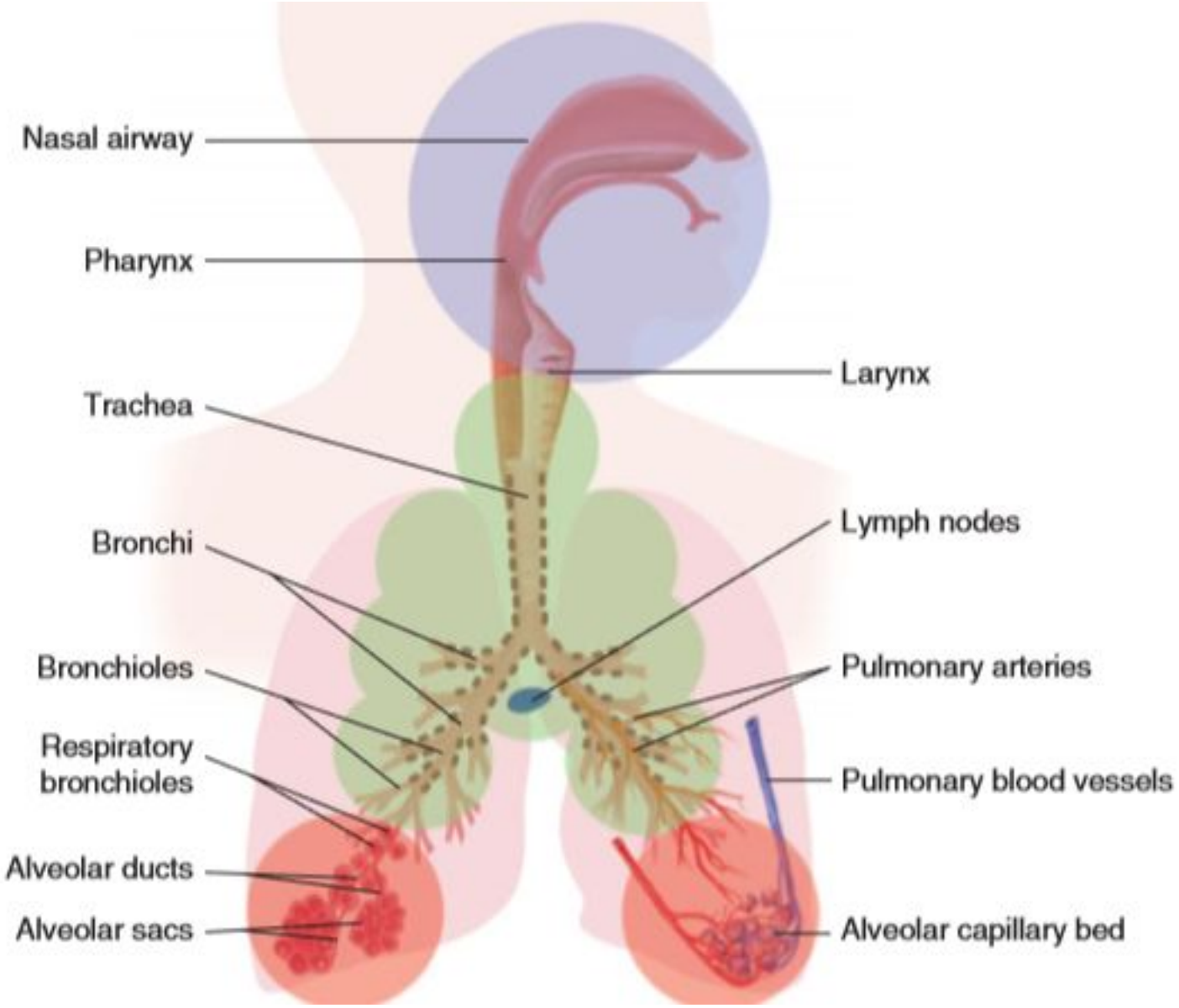

Figure 1. ***Major regions of the respiratory tract.***

II. Conducting airways:

- The conducting airways of the lower respiratory tract can be divided into:
  - proximal (trachea & bronchi), &
  - distal regions (bronchioles).

- The epithelium of the proximal airway & a portion of the nasal passage has specialized cells. These cells include ciliated, mucous& basal cells.

- These cells work together to form a mucous layer that traps & removes inhaled material via mucociliary clearance.

- In humans, the bronchiolar secretoglobin cells (BSCs), previously called the Clara cell, are found mainly in the distal airways.
  BSCs are known to inhibit phospholipase A2 & limit inflammation.

III. Gas exchange region:

- The gas exchange region consists of terminal bronchioles, respiratory bronchioles, alveolar ducts, alveoli, blood vessels, & lung interstitium. Gas exchange occurs in the alveoli.

- The alveolar epithelium consists of two cells, the alveolar type I & type II cell.

- Alveolar type I cells cover 95% of the alveolar surface, & have a role in gas exchange.

- Functions of alveolar type II cells:
- They produce & secrete suractant, a mixture of lipids, & four suractant associated proteins.
- They can undergo mitotic division & replace damaged type I cells.

- Particles deposited in the alveolar region are removed by specialized cells, the alveolar macrophage.

Responses of the lung to injury:

- Acute responses, &
- Chronic responses.

Acute responses of the lung to injury:

- Trigeminally mediated airway reflexes.
- Bronchoconstriction, airway hyperreactivity, & neurogenic inflammation.
- Acute lung injury (pulmonary edema).

Trigeminally mediated airway reflexes:

- Nasal & airway irritation represents a common response to inspired toxic compounds.

- Nasal irritation is mediated by irritant receptors [eg, transient receptor potential cation channel-A1(TRPA1)] that trigger trigeminal nerves characterized by tickling, itching & painful nasal sensations.

- TRPA1 is sensitive to several irritants including acrolein, allyl isothiocyanate, chlorine, & hydrogen peroxide.

- If continued exposure cannot be avoided, many irritants will produce cell necrosis.

Bronchoconstriction, airway hyperreactivity & neurogenic inflammation:

- Bronchoconstriction can be provoked by:
- irritants (e.g., acrolein)
- cigarette smoke,
- air pollutants,
- cholinomimetic drugs (acetylcholine),
- histamine,
- prostaglandins (PGs) (mainly PGF2α & PGD2), &
- leukotrienes.

- Characteristic symptoms include wheezing, coughing, a sensation of chest tightness & dyspnea.

- Irritants can prime the autonomic response by lowering the threshold dose of acetylcholine needed to induce bronchoconstriction. A lower threshold of acetylcholine-mediated bronchoconstriction is called airway hyperreactivity (or hyperresponsiveness).

- Irritants can also stimulate TRP channels that cause neurogenic inflammation.

Acute lung injury (pulmonary edema):

- Acute lung injury (both adult or infant respiratory distress syndrome) is marked by:
  - alveolar epithelial & endothelial cell damage, &
  - inflammatory cell influx.

- These events lead to surfactant disruption & pulmonary edema.

- Pulmonary edema produces a thickening of the alveolar capillary barrier & thereby limits O_2 & CO_2 exchange.

- During acute lung injury, profibrotic growth factors, transforming growth factor beta 1 (TGFB1) is activated.

- When inhaled in high concentrations, acrolein, HCl, NO_2, NH_3, or phosgene may produce immediate alveolar damage leading to a rapid death.

- However, these gases inhaled in lower concentrations may produce very little apparent damage in the respiratory tract.

Chronic responses of the lung to injury:

- Chronic obstructive pulmonary disease (COPD)
- Lung cancer
- Asthma
- Pulmonary fibrosis

Chronic obstructive pulmonary disease (COPD):

- COPD involves an airway (bronchitis) & an alveolar (emphysema) pathology.

- Chronic bronchitis is defined by the presence of sputum production & cough for at least three months in each of two consecutive years.

- In emphysema, destruction of the gas-exchanging surface area results in a distended, hyperinflated lung that no longer effectively exchanges oxygen & carbon.

Lung cancer:

- The increased risk of developing lung cancer for average smokers compared with nonsmokers is 8- to 10-fold & for heavy smokers about 20- to 40-fold.

- The main factor responsible for smoking dependence is nicotine.

- The global burden is ~1.2 million cancer deaths per year, with 85% of lung cancer cases in men & 47% of lung cancer cases in women being attributable to tobacco use.

- Arsenic, asbestos, beryllium, cadmium, chromium, & nickel have been associated with cancer of the respiratory tract.

Asthma:

- Asthma is characterized clinically by attacks of shortness of breath, which is caused by narrowing of the large conducting airways (bronchi).

- In allergic asthma, previous exposure to an antigen typically leads to the generation of immunoglobin E (IgE).

- Upon reexposure, the antigen causes:
- cross-linking of IgE molecules
- activation of lymphocytes, eosinophils, macrophages, & mast cells
- with elaboration & release of an array of cytokines, eicosanoids, histamine, tachykinins & other mediators.

- Asthma has been associated with a number of occupations.

- Occupational asthma can be induced by high-molecular-weight & some low-molecular-weight substances.

- High-molecular-weight agents including flour-, cereals-, latex- or animal-derived proteins & enzymes cause sensitization through an IgE-mediated mechanism, such as in common atopic asthma.

- Many low molecular-weight agents that induce occupational asthma include acid anhydrides & platinum salts that induce asthma through an IgE mechanism, but most low-molecular-weight agents involve an uncertain mechanism of induction.

- Many of the low-molecular-weight agents can cross-link biological macromolecules. These agents include:
- metals (e.g., nickel, chromium, cobalt, zinc, cadmium, & aluminum),
- diisocyanates,
- cleaning agents,
- wood dusts, &
- pesticides.

Pulmonary fibrosis:

- The pathological hallmark of pulmonary fibrosis is increased focal staining of collagen fibers in the alveolar interstitium.

- Excess lung collagen is usually observed not only in the alveolar interstitium but also throughout the centriacinar region, including the alveolar ducts & respiratory bronchioles.

- The pleural surface of the lung may also become fibrotic & together with parenchymal stiffening prevent full lung inflation.

- The pathogenesis of pulmonary fibrosis involves epithelial cell injury & macrophage activation produced by a wide range of toxic insults. For example, macrophages can be activated by phagocytosis of crystalline silica which activates inflammasome receptor-mediated tumor necrosis factor (TNF) & interleukin 1 beta (IL1B) formation.
- Epithelial cells & macrophages also release chemokines that recruit & activate other inflammatory cells including neutrophils & T cells.

- These cells combine to produce excessive TGFB1, TNF, IL1B, IL13, & IL17. Of these, TNF & TGFB1 are major mediators in pulmonary fibrosis.


Thank
you