PULMONARY SURFACTANT

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THE PULMONARY SURFACTANT

- The agents that decrease surface tension are called surface active agents or surfactants.

- Surface tension can be defined as the cohesive force of attraction experienced by the molecules present at the interphase of two media.

- The surface tension may develop between solid-liquid, liquid-liquid or liquid- gas media. Surface tension tends to pull the molecules at the interphase inwards thereby reducing the interaction between two phases.

- The surfactants are amphipathic molecules that form a film between the two media in such a way that their interactions are thermodynamically stable and result in reduced surface tension.

- In our body, lungs offer a large surface area where atmospheric air (gaseous media) comes in contact with body fluids (aqueous media) for gaseous exchange.

- The presence of pulmonary surfactant at the gaseous-aqueous interphase reduces the surface tension facilitating the diffusion of gases

History of surfactant

- Von Neergard in 1929 gave the concept of surface tension in lungs for the first time while performing experiments with porcine lungs.

- He demonstrated that surface tension existing between the air-water interphase of lungs is important factor for the recoil of lung and reduced surface tension facilitates respiration.

- He also suggested the relevance of surface tension with the first breath of new born.

❑ In 1946, Thannhauser *and colleagues* reported that lung tissue has remarkably high content of lecithin a lipid now called as dipalmitoylphosphatidylcholine

❑Gruenwald in 1947 in a paper " surface tension as a factor that affects neonate lung aeration" stated that surface tension offers resistance to aeration of the neonate lungs and surface-active agents reduce such resistance

❑ In 1955 Pattle, while working with the nerve gases that damage the lungs, observed fairly stable air bubbles that were ineffective to anti-foaming agents. He postulated that the bubbles might be lined by some surface active agents/substances and deficiency of such surface- active material might be responsible for infant respiratory distress syndrome (IRDS)

- Clements (1955) and Macklin (1954) showed that various lipid fractions especially those rich in dipalmitoyl phosphatidylcholine have surface tension reducing properties similar to the naturally occurring pulmonary surfactant.

- In late 1950's, Avery and Mead demonstrated that IRDS or hyaline membrane disease of the new born is due to high surface tension or surfactant deficiency.

- Various studies have shown that phosphatidylcholine is an important component of pulmonary surfactant as it remarkably decreases the surface tension compared to other lipids like cholesterol, phosphatidylinositol, phosphatidylethanolamine

Cells lining the airways - Review

- The respiratory airways are lined by various types of cells originating from the basement membrane.

- They include ciliary cells, goblet cells, basal cells, clara cells, serous cells, chemosensory cells, brush cells, alveolar pneumocytes and other epithelial cells.

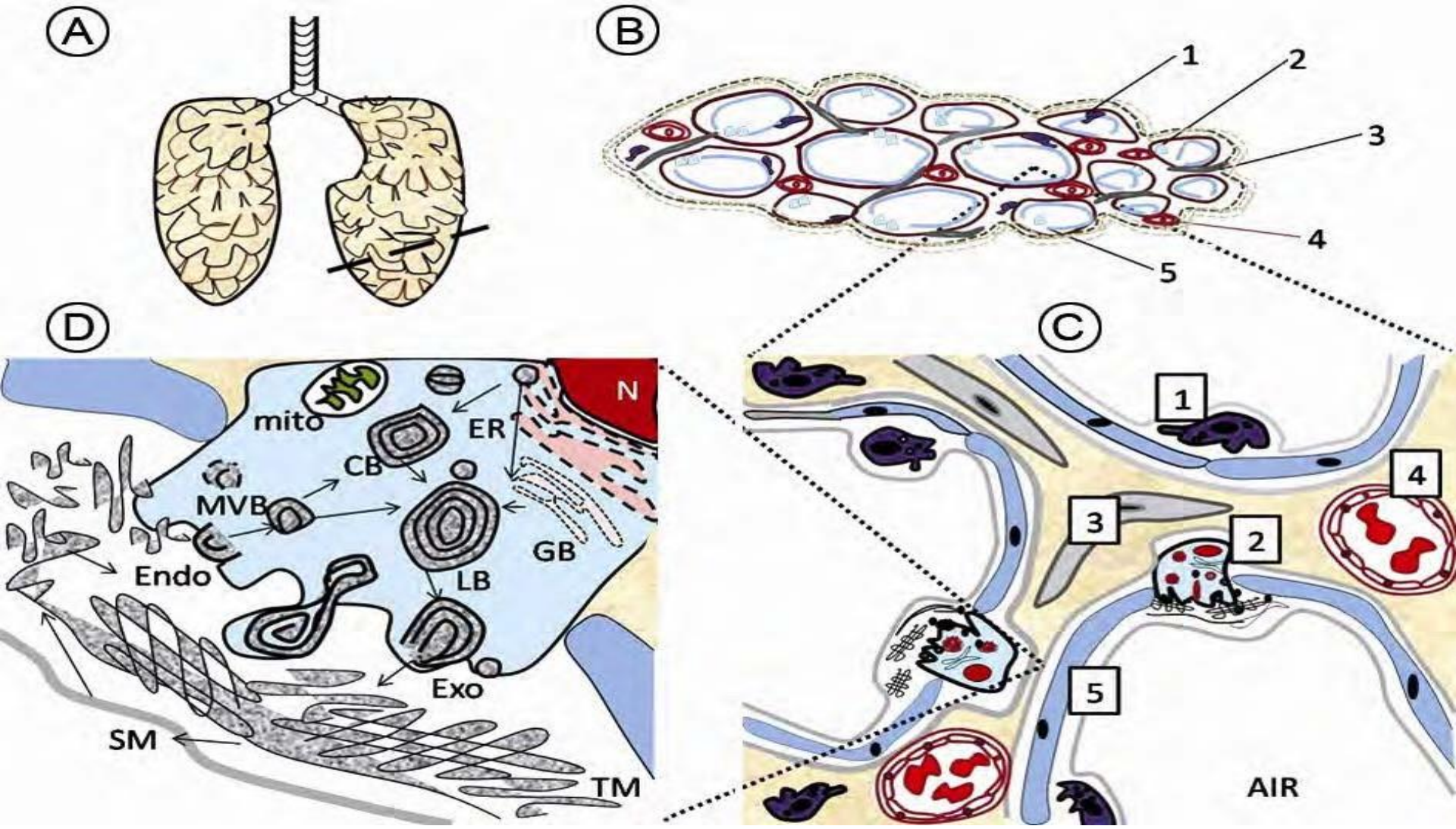
- Ciliated cells are cuboidal cells with a layer of cilia present on the apical side. Basal cells are undifferentiated epithelial cells that can be differentiated into other cell types at the time of tissue injury

- Clara cells, goblet cells, serous cells and alveolar epithelial cells secrete various immuno- protective proteins, mucous, phospholipids and surfactant that lines the epithelium.

- They also contain various channels (sodium channels, potassium channels, chloride channels, aquaporins) that help to regulate the fluid volume lining the pulmonary epithelium

- *The alveolar pneumocytes:* The epithelial cells covering the alveoli are called alveolar pneumocytes and are of two types viz.; alveolar type I (AT-I) and alveolar type II (AT-II).

- They can be distinguished morphologically and functionally.



Schematic showing the alveolar pneumocyte type-II in lungs. (A) lungs showing the level of sectioning, (B) section of lungs taken at the dashed line, (C) gross features of the lung section at the level of alveoli and (D) AT-II cell and surfactant metabolism are shown. In B and C, 1 alveolar macrophages, 2 alveolar pneumocyte type-II, 3 fibroblasts, 4 capillaries with endothelial layer and RBCs and 5 alveolar pneumocyte type I. In D, CB=composite body, endo=endocytosis; exo=exocytosis; GB=Golgi bodies; LB=lamellar bodies, mito=mitochondria, MVB=multivesicular bodies, N=nucleus of AT-II cell, TM=tubular myeline, SM=surfactant monolayer.

- AT-I cells are flat squamous cells originating from the basement membrane covering 95% of the alveolar surface area

- They possess fewer cell organelles and are metabolically less active

- AT-II cells are cuboidal cells covering only 5% of the alveolar surface area They possess large number of cell organelles and are metabolically active

- The AT-I cells reduce the tissue resistance and allow free diffusion of gases at the alveolar surface

- They can efficiently transport ions, water and other macromolecules in or out of the pulmonary cells, and thus play an important role in maintaining the composition and volume of the pulmonary fluid lining

- AT-II cells are small cells positioned at the corners or thickenings of the alveoli so that their morphology does not hinder the gaseous exchange.

- These cells are rich in membrane bound organelles known as lamellar bodies which are the site of synthesis, storage and secretion of the pulmonary surfactant

- AT-II cells are involved in intracellular as well as extracellular surfactant metabolism

- AT-II cells are considered as stem cells for AT-I cells

- In addition, they have role in alveolar fluid balance, cellular (epithelial) repair, removal of dead (apoptotic) cells, immuno-regulation and host defense.

- They communicate with various other cells of the alveoli directly (cell-cell contact) or indirectly (through signaling molecules) and integrate various components of the alveoli functionally

Airway surface liquid and alveolar lining fluid

- The cells covering the respiratory tract are lined by a film of fluid that forms a barrier between the cells and air.

- It contains mucous, immuno-protective proteins, phospholipids, surfactant

- The composition of the airway surface liquid varies with the population of constituent cell types in different regions of the respiratory tract.

- Airway lining fluid of the upper respiratory tract contains more of mucous and immuno-protective proteins whereas the airway surface liquid lining the alveoli is rich in surfactant

- The airway surface liquid present at the alveoli is called alveolar lining fluid and it protects the underlying cells from desiccation, pathogens, tissue damage and facilitates the diffusion of gases.

- The lining fluid volume is maintained by ion channels and water channels of various cells. Decreased surfactant with decreased volume of fluid lining results in lung atelactasiste (collapse)

- On the other hand decreased surfactant with increased fluid produces pulmonary edema. Both of them decrease the gaseous exchange resulting in hypoxia and hypoxia-induced stress as seen in various lung disorders.

Functions of pulmonary surfactant

- Lungs offer a large surface area that comes directly in contact with air for gaseous exchange into the body fluids.

- The surface tension at the gaseous-aqueous interphase of lung is reduced by the presence of a pulmonary surfactant.

- It is a heterogenous mixture of lipids (90%) and proteins (10%) that forms a stable monolayer at the gaseous-aqueous interphase.

1. The presence of surfactant is important to maintain the surface tension at reduced levels to prevent collapse of lung at the end of expiration thus allowing proper exchange of gases.

2. It increases the lung compliance (by decreasing the elastic force exerted by the surface tension), thus helping lung expansion during inspiration.

3. It also maintains the volume of fluid lining the alveoli and size of the alveoli in different phases of respiratory cycle.

- The lung volume is not constant; it continuously undergoes inflation and deflation during respiration.

- Accordingly, the surface area exposed to air keeps on changing. The interrelation between the surface tension (T), deflating pressure (P) and radius of the alveoli (r) obeys the Laplace law, $P = 2T/r$; according to which, the surface tension increases with increase in radius of the alveoli and vice versa

- Therefore, the smaller alveoli develop more deflating pressure and may get emptied into the larger alveoli. The presence of surfactant prevents the emptying of smaller alveoli into the larger ones.

- The surface tension effect of surfactant is *directly proportional to its concentration but inversely proportional to the surface area of the fluid* (so it is *more marked in the small alveoli)*

- Surfactant undergoes cyclical changes (with respect to its composition and structural conformation) to maintain low surface tension at the time of inspiration and to prevent the alveolar collapse at the time of expiration

4. It helps keeping the alveoli dry i.e. free from fluids (thus it prevents easy production of pulmonary edema).

- This is because it decreases the suction force exerted by the alveolar fluid surface tension (such force renders the *interstitial hydrostatic pressure to be negative,* which favours fluid filtration from the pulmonary capillaries into the alveoli)

4. It plays a major role in maintaining *alveolar stability*

Composition of surfactant

- The exact composition of the surfactant *in vivo* is not known but most of the studies are done using the endotracheal lavage fluid and *in vitro* lung preparations.

- Based on these studies, it has been demonstrated that surfactant is mainly composed of 90% lipids and 10% proteins.

- Phospholipids form the bulk of lipids present in the surfactant. Phosphatidylcholine (PC) is the main phospholipid with surface active properties that makes 70-80 % of the total lipids.

- Phosphatidylglycerol (PG) accounts for 7% and is the next most abundant lipid which is important for even spreading of the surfactant monolayer on the surface of alveoli (PC as such has very less spreading properties).

- Apart from these two, traces of phosphatidylinositol (PI; 2%), phosphatidy lethanolamine (PE; 5%), sphingomyeline (Sph; 2%), other phospholipids (PL; 3%) and other neutral lipids (in traces; 5%) constitute the lipid part of the surfactant

- The protein part of surfactant constitutes four types of surfactant-associated proteins viz., SP-A, SP-B, SP-C and SP-D.

- SP-A is the most abundant protein followed by SP-B, SP-C and SP-D . SP-A and SP-D are hypdophillic proteins whereas SP-B and SP-C are hydrophobic in nature.

- The hydrophobic proteins play a direct role in structural organization of the surfactant at the interphase whereas the hydrophilic proteins play a regulatory role in surfactant metabolism along with immunological functions.

- The interaction between lipids and proteins is important for the surface-active properties and homeostasis of the surfactant

Surfactant proteins

- *Hydrophillic proteins:* SP-A and SP-D are the two hydrophilic proteins present in the surfactant.

- They are large glycosylated proteins belonging to collectin family, characterized by the presence of collagen like domain and carbohydrate binding properties

- These proteins are found in the multivesicular bodies of the AT-II cells

- They regulate the surfactant secretion and reuptake by the AT-II cells

- These proteins also play important role in host defense

- They bind to specific sites (carbohydrate moieties) on the foreign pathogens and stimulate immunological reactions like oposonisation and phagocytosis

- *Hydrophobic proteins:* SP-B and SP-C are the two hydrophobic proteins present in the surfactant.

- They are synthesized by proteolytic cleavage of a precursor molecule and specific post translational modifications.

- They are found aggregated along with the phospholipids in the lamellar bodies and are important for the surface active properties of the phospholipids

- These proteins help in the stabilization of tubular myeline and adsorption of lipids onto the surfactant monolayer

Surfactant lipid biosynthesis

- The biosynthetic pathway for the surfactant lipids and the membrane lipids is the same.

- The surfactant is synthesized mainly in the AT-II cells and few other cells of the respiratory airways whereas membrane lipid biosynthesis as such is common for all cell types.

- The specific composition of lipids and proteins gives surfactant its characteristic properties. As compared to plasma membrane, saturated PC, PG and PI are present in larger amounts in the surfactant

- Therefore, the biosynthesis of lipids constituting the surfactant is basically the biosynthetic pathway for PC, PG and PI biosynthesis from precursors like dihydroxyacetone phosphate (DHAP), glyceraldehydes-3 phosphate, phosphatidic acid, choline and some acyl derivatives of these

- The important enzymes involved in the PC biosynthesis are: choline kinase, choline phosphate cytidyl transferase, choline phosphotransferase, acyltransferase and the enzymes of fatty acid synthesis for synthesizing non-lipid precursors.

Regulation of lipid biosynthesis

- **Enzymatic regulation:** The biosynthesis of PC is mediated by sequential actions of different enzymes. The reaction catalysed by phosphocholine cytidyl transferase (CT) is the rate limiting step for PC biosynthesis

- **Hormonal regulation:** The physiological regulation of phosphatidylcholine biosynthesis is primarily hormonal

- Various hormones like glucocorticoids, thyroid hormone, estrogen and prolactin have been shown to increase the surfactant lipid biosynthesis

- The biosynthesis can be increased by two mechanisms: either by increasing enzyme activity or by increasing enzyme mass.

- The hormones can also modulate the cellular metabolism to increase the availability of precursors like DAG and other lipids for enzyme (increasing the substrate availability and enzyme activity indirectly).

- Glucocorticoids: Glucocorticoids predominantly increase the enzymatic activity (not enzyme mass) to increase surfactant lipid synthesis

❑ Glucocorticoids stimulate fatty acid biosynthesis resulting in increased availability of precursors that act as substrates for the enzymes involved in PC synthesis

❑Supporting this, the increased production of cortisol in 30-32 weeks of gestation has been associated with the fetal lung maturation and surfactant production

❑Estrogen: The effect of estrogen is similar to glucocorticoids. It increases surfactant biosynthesis by increasing the activity of enzymes like phosphocholine cytidyltransferase and lysolecithinacyl transferase involved in PC biosynthesis

- The increase in level of estrogen during pregnancy has been linked with the fetal lung maturation and surfactant production

- Prolactin: Prolactin is an anabolic hormone that is important for the fetal growth. Some studies correlate the increased prolactin levels in the last phase of pregnancy and lung maturation

- They state that prolactin increases phospholipid content of the surfactant specifically PC and PG. However, some other studies report that there is no effect of prolactin on surfactant biosynthesis and lung maturation

- Further studies are required to establish the relationship between prolactin and surfactant biosynthesis

- Thyroid hormone: Thyroid hormones increases surfactant production and number of lamellar bodies in the AT-II cells

- Thyroxine is thought to accelerate the translocation of lipids into the lamellar bodies and increases the incorporation of precursors into PC and helps fetal lung maturation

- Respiratory distress syndrome is shown to be associated with decreased thyroid hormone levels or its receptor abnormalities

- Insulin: Insulin has a dual role in surfactant biosynthesis.

- *In vitro* experiments have shown that very low doses of insulin increase surfactant biosynthesis whereas high doses inhibit surfactant biosynthesis, the later effect being pronounced in case of developing fetus

- The fetuses of diabetic mothers experience hyperglycemia, hyperinsulinaemia and hyperlipidemia. All of these result in altered surfactant lipid metabolism.

- Diabetes is associated with hyperglycemia, hyperglycemia-induced oxidative stress and release of various inflammatory mediators. These factors can exacerbate or ameliorate surfactant metabolism leading to RDS

- However, insulin administration postnataly or in adults with surfactant deficiency improves the surfactant synthesis by improving the energy metabolism

Packaging of surfactant: Lamellar bodies

- Alveolar type II cells possess characteristic lamellar bodies involved in surfactant metabolism
- Lamellar bodies are lysosome like membrane bound organelles
- Previously, lamellar bodies were considered as the site of surfactant synthesis
- However, studies have shown that the actual surfactant synthesizing enzymes are not present in the lamellar bodies
- Therefore, it can be expected that different components of the surfactant (proteins and lipids) are synthesized by cellular organelles like the endoplasmic reticulum and Golgi apparatus

- From here the components are packed into small vesicles (multivesicular bodies) and are transported to the pre- lamellar or composite body by various transporter proteins.

- In the pre-lamellar bodies different components of the surfactant get assembled to form the lamellar bodies

- The lamellar bodies undergo exocytosis form AT-II cells to secrete the surfactant components into the extracellular matrix.

- The surfactant components get recycled in AT-II cells periodically.

Surfactant secretion

- Various physical and chemical stimuli can induce surfactant secretion.

- The physical stimuli include mechanical stretch or contraction of the AT-II cells during breathing.

- The chemical agents include cathecholamines (β-adrenoceptor agonists), purinoceptor agonists, cAMP, histamine, vasopressin, and some calcium ionophores

- The surfactant lipids and proteins are secreted in different manner

- The surfactant lipid secretion has been extensively studied but little is known about surfactant protein secretion

- Upon stimulation the lamellar bodies are translocated to the apical side of the AT-II cell by cytoskeletal proteins (actin and microtubules) where they undergo exocytosis to release their contents into the extracellular matrix

- Though the underlying mechanism is not exactly delineated, the stimuli directly or indirectly increase the intracellular cAMP and calcium levels that in turn activates protein kinases like PKA, PKC and CaMK

- Phosphorylation of cellular proteins by various protein kinases is a crucial step for the surfactant lipid secretion.

- The hydrophobic surfactant proteins (SP-B and SP-C localized within the lamellar bodies) are secreted in lamellar body-dependent manner along with the lipids

- The hydrophilic proteins (SP-A and SP-D) are secreted in lamellar body- independent manner

- These surfactant proteins help in the intracellular vesicular trafficking, fusion of lamellar body with cell membrane and exocytosis

- The secreted form of surfactant as such is non- functional but after secretion it undergoes structural/conformational changes to give rise to an intermediary lattice structure known as tubular myeline

- The presence of surfactant associated proteins, phospholipids and calcium are important for the structural organization of tubular myeline
- The tubular myeline then forms the surfactant monolayer by adsorbing the lipid components into the air-water interphase
- The surfactant associated proteins also help in adsorption of the lipid moieties into the monolayer and stabilization of the monolayer
- This monolayer is the functionally active form of surfactant and has the surface-active properties
- Deficiency in surfactant associated proteins results in the aggregation of surfactant components and improper formation of tubular myelines thus impairs the surface-active properties of the surfactant

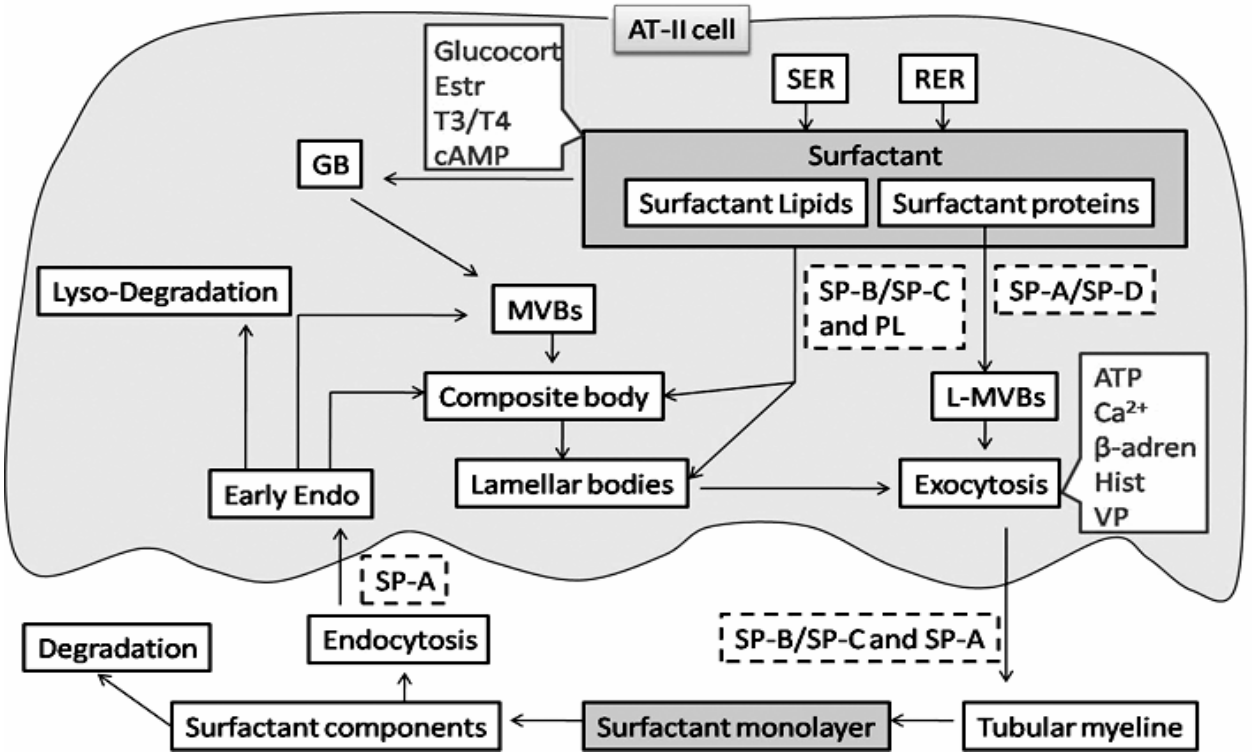


Fig. 3— Schematic representation of the surfactant metabolism in the AT-II cell. The surfactant components (lipids and proteins) are synthesized from smooth endoplasmic reticulum (SER) and rough endoplasmic reticulum (RER), respectively. Physiological agents like glucocorticoids (Glucocort), estrogen (Estro), thyroid hormones (T3/T4), and others that increase cAMP levels promote surfactant biosynthesis. After synthesis the components are transported to the Golgi bodies (GB) from where they bud-off to form multivesicular bodies (MVB). These MVBs may fuse with pre-lamellar bodies or composite bodies or directly with lamellar bodies. Some of the surfactant components (PL = Phospholipids; SP-B and SP-C) may directly be translocated from ER to composite body or lamellar bodies whereas some components (SP-A and SP-D) are found outside the lamellar body in the form of light-multivesicular bodies (L-MVBs). Upon stimulation by various agents like ATP: purinoceptor agonists, β-adrenoceptor agonists (β-adren), Ca^{2+}, histamine (Hist) and vasopressin (VP), the lamellar bodies and L-MVBs containing surfactant proteins undergo exocytosis. The exocytosed surfactant components form the intermediate lattice structure known as tubular myeline. The surfactant proteins (SP-B, SP-C and SP-A) promote the formation of tubular myeline and also assist the adsorption of surfactant lipids into the air-water interphase to form a stable surfactant monolayer. Then the surfactant monolayer gets degraded into its components, some of them are endocytosed (SP-A receptor mediated endocytosis) while some are degraded by the cells of the respiratory airways. The endocytosed contents again form early endosomes (early endo) that can fuse with composite body, lamellar body or lysosome. The early endosomes fusing with composite body or lamellar body re-enter the surfactant cycle whereas the endosomes fusing with lysosome gets degraded.

Surfactant recycling

- After secretion and incorporation into monolayer, surfactant undergoes dissociation into its components.

- Most of the components are recycled back through receptor mediated endocytosis into the alveolar cell while some components are cleared by the airway lining and alveolar macrophages

- Recycled components are present in the apical side of AT-II cell in the form of light and dense multivesicular bodies which are nothing but early endosomes

- These can fuse with the pre-lamellar bodies or may get degraded within the cell

- The recycling helps to maintain the surfactant pool at the alveolar level and conserves energy required for synthesizing the components again

- The signaling mechanism and details of recycling are not known but SP-A is considered important for signaling the uptake of surfactant (SP-A mediated endocytosis)

Effect of physical parameters on the surfactant metabolism

- The interaction between the lipids and proteins is very critical for the functioning of surfactant for the functioning of surfactant.

- Environmental factors like temperature, pressure and hypoxia affect the physical state of the surfactant components, their structural stability and functioning directly or indirectly.

- Depending upon the temperature and hydrostatic pressure, composition of surfactant lipids and proteins is altered so as to maintain the optimal fluidity/rigidity of the surfactant film

- For example, more of unsaturated phospholipids and cholesterol are synthesized so as to retain surfactant fluidity at lower body temperatures

- More of short chain fatty acids and surfactant associated proteins SP-B and SP-C are produced to increase the spreadability of surfactant at greater hydrostatic pressure

Hypoxia

- Hypoxia is another physical factor that is important for lung development in fetus and lung functioning in adults.

- Hypoxia induces the expression of a transcription factor called hypoxia-inducible factor 2α, that is crucial for fetal lung (AT-II cells) development and production of phospholipids

- Increased sympathetic activity induced by hypoxia (via peripheral chemoreceptors) also increases the surfactant lipid biosynthesis

- Hypoxia triggers lung expansion and maturation of lungs at the time of birth.

Hypoxia

- Prolonged fetal hypoxia associated with maternal anemia, hypertension and placental infarction causes fetal growth retardation leading to impaired lung development

- Acute hypoxia as experienced at high altitude in adults alters the surfactant system

- Hypoxia is associated with hemodynamic alterations, pulmonary hypertension and pulmonary edema.

- Edematous fluid is rich in plasma proteins and proteolytic/lipolytic enzymes that degrade the surfactant

Effect of inhaled toxicants on surfactant metabolism

- Toxicants like ozone, nitrogen dioxide, sulphur dioxide, hydrogen sulfide, chemical exhausts and dust damage the lung tissues and cause alterations in the surfactant system directly or indirectly

- The damage to lung tissue and inflammation are the main outcome of exposure to these inhalants lead to metabolic alterations in the surfactant system

- Edematous fluid is rich in plasma proteins and proteolytic/lipolytic enzymes that degrade the surfactant

- Acute hypoxia as experienced at high altitude in adults alters the surfactant system

Ozone: In the biological systems, ozone induces excessive oxidative damage to the tissues

- Surfactant alteration can be considered a consequence of tissue damage and inflammation induced by exposure to ozone.

- Ozone alters fatty acid composition of the surfactant phospholipids and decreases surfactant secretion

- It also causes ultrastructural alterations in the lamellar bodies and prevents the structural organization of lamellar body contents into tubular myeline

- It impairs the activity of SP-A that is important for the formation of surfactant monolayer

Nitrogen dioxide (NO_2): Nitrogen dioxide is an air pollutant released from the automobile exhausts can cause damage to the lung tissues.

- Nitrogen dioxide causes lipid auto-oxidation and alters the lipid composition of the surfactant

- Acute exposure of AT-II cells to nitrogen dioxide increases lipid synthesis and results in lipid accumulation whereas chronic exposure decreases the ability of the cells to synthesize lipids

Sulphur dioxide (SO_2): It is another common of air pollutant present in automobile exhausts.

- Sulphur dioxide interacts with water present in the fluid linings of the respiratory tract, eyes, throat etc and readily forms sulphuric acid which damages the epithelial layers of the respective tissues.

- It alters the structure and functions of AT-II cells and decreases the synthesis of pulmonary surfactant

- It drastically affects the physico-chemical properties of the surfactant

Aerosols: Lacrimators, tear gases and other chemicals dispersed in aerosols can produce respiratory tract irritation

- Commonly used lacrimators are 1-chloroacetophenone (CN), 2-chlorobenzylidene malononitrile (CS) and dibenz [b,f]-1,4-oxazepine (CR)

- Exposure to these gases causes inflammation, damage to the alveolar capillary membrane, pulmonary edema and destruction of the pulmonary surfactant

- Exposure to CR, decreases the phosphatidylcholine and ethanolamine synthesis and increases sphingomyeline synthesis leading to altered lipid constitution of the surfactant

Artificial ventilation: Artificial ventilation used for treatment in critical cases of ARDS or other diseases can be very harmful.

- Artificial ventilation decreases lung compliance and alters the surfactant homeostasis leading to lung dysfunction

- Excess of oxygen induces the formation of free radicals that can damage various tissues and cellular constituents

- In addition, there is alteration in the lipid content of the surfactant and therefore it fails to aggregate properly

- The release of inflammatory mediators like TNFα, IL-6, IL-10 after hyperoxia might be interfering with the signaling pathways of surfactant packaging and secretion

Smoke: Cigarette smoke or polyurethane smoke reduces the phospholipid and protein (SP-A and SP-D) content of the surfactant

- Cigarette smoke especially decreases the phosphlipid/protein ratio of the broncho-alveolar lavage fluid (BAL) obtained from humans

- The surface-active properties of surfactant (monolayer) are decreased due to altered composition and interference by smoke particles

- Long time exposure may cause tissue (AT-II cells) injury altering the surfactant system

Effect of inflammatory mediators and intracellular signaling molecules on surfactant metabolism

- TNF-α, NO, IL-1, Interferon-γ and other inflammatory molecules play critical role in surfactant metabolism. They can increase or decrease the surfactant biosynthesis.

- TNF-α released due to edema, infection, oxidative damage, or any type of tissue injury cause alteration in the surfactant homeostasis

- TNF-α decreases surfactant PC synthesis, increases PC turnover and alters the overall lipid content of the surfactant.

- Other cytokines like transforming growth factor, interferon-γ and IL-1 present in the amniotic fluid stimulate the production of surfactant (lipids as well as proteins) and helps fetal lung maturation

- Nitric oxide (NO) present at physiological concentration promotes surfactant secretion by increasing intracellular cGMP levels and activation of protein kinases.

- However, excessive production of NO due to inflammation inhibits the surfactant secretion

- Endothelin-1 increases the surfactant secretion by increasing intracellular calcium levels and activating PKC

- Prostaglandins increase the surfactant biosynthesis and secretion. Increase in prostaglandins with gestational age has been considered important for fetal lung development and maturation

- The prostaglandin levels also increase at the time of labour that is considered to facilitate surfactant release and breathing of the new born

- In adult lungs, porstaglandins like PGE_2 and PGF_2 promote PC biosynthesis. PGE_2 also promotes SP-A biosynthesis

Clinical importance

- The decrease in surfactant level/function is associated with a number of diseases like infant respiratory distress syndrome (IRDS), adult respiratory distress syndrome (ARDS), lung proteinosis, obstructive lung diseases, interstitial lung diseases and chronic lung disease

- Respiratory distress syndrome is associated with surfactant deficiency.

- It is characterized by increased work of breathing, impaired gas exchange, decreased compliance, atelactasis, hypoxia, interstitial edema, pulmonary hypertension, hemodynamic alterations and other associated complications.

- It is very common in infants, where it is called infant respiratory distress syndrome (IRDS)

- In adults, it is called adult respiratory distress syndrome (ARDS) and can occur due to multiple factors leading to lung injury, dysfunction and decreased surfactant synthesis

- In other diseases like obstructive lung diseases, chronic lung diseases and interstitial lung diseases, the surfactant deficiency is a secondary to inflammatory or metabolic abnormalities.

Infant respiratory distress syndrome (IRDS)

- This is a serious lung disease that occurs *due to deficient formation of the surfactant.* It is also called the *hyaline membrane disease.*

- IRDS is characterized by the immature lungs and failure to produce sufficient amount of surfactant.

- Genetic or acquired factors are implicated for the development of IRDS

- Genetic factors include the mutations in genes coding for the surfactant associated proteins and various other transporter proteins involved in surfactant packaging