Molecular and Physiological Determinants of Pulmonary Developmental Biology: a Review

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Abstract   The lungs undergo an extensive endodermal diverging morphogenesis along with alveogenesis, angiogenesis, and vasculogenesis to secure a sufficient diffusion surface for gaseous exchange. Any aberration in the course of normal development inculcating structural and functional abnormalities of lungs in antenatal life has potential morbidity in adult life. Factors such as IUGR, nutrient deficiency, FLM, Hypoxemia, ETS, surfactant deficiency, allergy and infections can adversely affect in-utero lungs development. Peculiar local and systemic inflammatory immune responses may elicit persistent architectural and physiological abnormalities. Lung surfactant produced by AEC-II cells is a mixture of phospholipids, surfactant proteins, and neutral lipids. Surfactant lowers alveolar surface tension, a crucial step for the prevention of alveolar collapse. Surfactant proteins are part of the innate immune defense of the lung. Surfactant deficiency and dysfunction is known to implicate a number of respiratory diseases especially allergic asthma and NRDS. The present article provides a state of the art review of the current knowledge of biology of normal lung development, its anatomical and molecular aspects, factors that regulate normal organogenesis of pulmonary system and molecular basis of respiratory allergic disorders including asthma.

Keywords: *respiratory diseases, allergic disorders, pulmonary development, lung surfactants*

1. Introduction

In depth understanding of pulmonary developmental biology has profound and substantial impact on human health outcomes. Lungs are the sole organ, exclusively performing the function of exchange of gases to enable an organism to acclimatize to terrestrial life. Any malfunctioning in the conversion of this fluid filled organ, apparently unimportant to intrauterine survival, into air filled hollow structure endangers perinatal survival. Respiratory disorders in early life stages contribute to major morbidity and mortality causes the world over [1]. Despite the fact that normal adult lungs can undergo repair, it is seen that prenatal deficits cannot be resolved in perinatal life resulting in morbidity and clinical burdens [2]. Understanding of lungs developmental biology holds the key which could be used to aid lungs-repair and regeneration.

Various studies on human and animal models have shown that the development and later function of lungs can be influenced by in-utero environmental compromises (including physical, endocrine, maternal tobacco smoking during pregnancy, maternal diabetes, metabolic disturbances and reduced amniotic fluid volume and inflammatory factors [3] during fetal and early postnatal life [4]. These factors are not limited to individual responses; in fact abnormality of one component can alter the reaction of others. Moreover a number of early life factors including atopy, lower respiratory infections, low SES, active and passive smoking during childhood and nutrition are also shown to be associated with disturbed pulmonary function over whole life span [5,6,7,8,9,10,11,12]. Many of the factors that affect fetal growth cause intrauterine growth restriction (IUGR) causing preterm birth (PB) and low birth weight. Numerous epidemiological studies have indicated that low birth weight is associated with an increased risk of respiratory symptoms or illnesses after birth [4].

Most of the studies investigating developmental paradigm of lungs are done on animal models having very different timing of morphological growth stages compared with humans. The animals mostly subjected to such studies include Drosophila, rabbits, sheep, rats and mice. The most useful information is mined from research work done in rats and mice as most of their alveolar development occurs postnatally like that of humans. The research conducted on animal models has abetted to identify potential and actual fetal and neonatal pulmonary disorders and their solutions to alleviate neonatal morbidity and mortality [13].

The present article provides a concise review on the current knowledge of biology of normal lung development, its anatomical and molecular aspects and factors that regulates normal organogenesis of pulmonary system. A brief overview of developmental anomalies and acquired pathologies is included, outlined with experimental and

epidemiological evidences showing that the exposure to certain factors, precarious to fetal and neonatal lung can cause detrimental effects on lung architecture and physiology, can result in persistent alterations in respiratory function. The effort is done to provide a separate and summarized discussion on development of lung surfactants system and immunity, effect of allergen exposure on surfactants-system of developing respiratory system in antenatal and postnatal life and its detrimental outcomes.

2. Methods

This review extracts the information from peer-reviewed English-language publications and research articles identified from MEDLINE/PubMed, Tylor and Francis online, Science Direct, Wiley Interscience, and Elsevier data bases up to the year 2012. Search strategy was use of keywords along with various combinations of developmental biology, pulmonary system, growth factors, environmental exposure anomalies, allergies and lung surfactants. The PubMed function of "related articles" was used to get relevant articles not accessed from initial searches. Other searches were carried out by using names of authors of relevant articles. The original articles from review material were accessed through references where possible. The tables in this review are limited to studies that provide the basic understanding and pathology of stated diseases. The discussion and material in this review is restricted to most investigated and accepted knowledge in the concerned field.

3. Development of Respiratory System

3.1. Programming and Growth

In humans and some other mammals who have long-gestation periods, development of the pulmonary architecture is an ongoing process till early postnatal life [14]. The lung mostly comprises of two highly branched tubular systems 'the airways and the vasculature' working in conjunction to efficiently perform the gas exchange. As the most critical time of birth reaches, the airways are formed and terminal air sacs mainly function as prototypes of definitive alveoli. Alveolar formation continues till 18-36 months of postnatal life [15]. Later lung growth largely occurs by the enlargement of existing alveoli (see Figure 1).
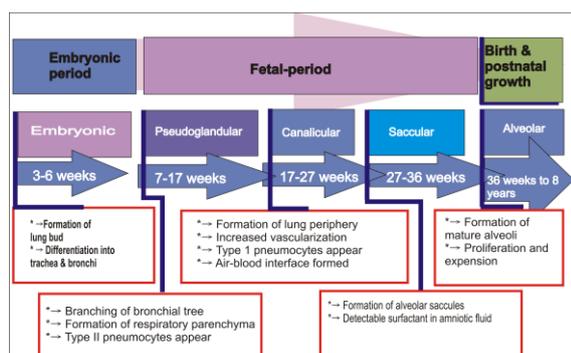
Figure 1. Summary of various stages and structural organizations in the development of lungs in prenatal and postnatal life

The four major levels of development are recognized, first of which is *Embryogenesis* (the progress of fertilized ovum to an embryo). Second is *Morphogenesis* involving tissue complexion and maturation and starts from formation of main frame of pulmonary system to development of specialized gas exchange surfaces (alveoli). During the third level, *Differentiation* of specialized cells (alveolar type-II cells) from precursor cells occur [16,17,18,19]. The *Growth* includes Volume expansion which starts in prenatal stage [20] and extends to postnatal life [21]. Factors controlling lung growth during these phases are reviewed later in this article.

The formation of primary germ layers, the ectoderm, the mesoderm and the endoderm occurs during gastrulation period. The endoderm then undergoes morphogenesis orchestrating to form primitive gut tube [22]. The broad gene expression patterns, in precise domains of fore, mid and hindgut regulates development of specific organs. The endodermal patterning is also controlled by conjoint interactions with surrounding mesodermal tissue [22].

The development of respiratory tract starts as a ventral out pouching from foregut called laryngotracheal groove, at fourth week of gestation [23]. The margins of this groove fuse to form laryngotracheal tube which grows caudally into splanchnic mesoderm forming right and left lung buds. These lung buds further divides to form an analog for main bronchi. In the mesenchyme of the laryngotracheal tube, cartilage develops with conversion of upper part of tube with larynx and lower part with trachea. Each bronchus then continues to subdivide laterally in a dichotomous way till terminal bronchioles and alveoli are formed. The pattern of branching is highly stereotyped and can be categorized in three sequences called "domain branching", "planar branching", "orthogonal bifurcation" depending on the plane along which branching occurs [24].

Lobes of lungs are formed by fifth week while bronchi keep on dividing in 6th week of gestation. This branching results in formation of bilobed left and trilobed right lung. The branching pattern is highly influenced by neighboring mesenchyme [25,26,27], various growth factors and epithelial-mesenchymal interactions and their dependence on maturity of type II alveolar cells [28,29,30,31,32].

3.1.1. Pseudoglandular Phase

Classically, the prenatal developmental phase of lung is described by distinct histological characters on basis of which different stages are [33,34,35,36,37] recognized. This phase extends from 7 to 17th Week (see Figure 1). The main frame of pulmonary system is formed including bronchial tissue, cartilage, ciliated epithelium and scarce capillaries. The branching from bronchial buds and preacinar structures complete by 17th week. Airways terminate blindly with columnar or cuboidal epithelium, yet alveoli are not formed [38]. By 3 months of gestation, lungs are of definitive shape.

3.1.2. Canalicular Phase

From 17 weeks to 27 weeks of gestation, Canalicular Phase continues in which development of bronchioles, alveolar ducts, primary acini and increased vascularization is involved. The epithelial cells' glycogen diminishes from 20th week. Type I and II pneumocytes are

identifiable by 24 weeks of intra uterine life and Lamellar bodies containing surfactant proteins and phospholipid can be seen [39]. The first air-blood interface develops by the end of this stage [35,36,37] in form of cylindrical saccules (in intermediate saccular stage) divided by crests known as secondary septae made of collagen and elastin [23].

3.1.3. Alveolar Phase

The next phase of respiratory system development called Alveolar phase (28 weeks to term: see Figure 1) is characterized by rapid growth and maturation of acini with remodeling of the double capillary layer and thinning of the alveolar walls, mesenchymal proliferation, and distinct increase in well differentiated type I and II pneumocytes [40].

The mature respiratory epithelium develops a diversity of cell types including ciliated, goblet, basal, Clara cells, pulmonary and alveolar macrophages. These Epithelial cell lineages are organized distally in airways. The Squamous epithelium lines larynx, upper airways are lined with ciliated columnar and mucus secreting cells while Clara cell lines lower respiratory tract. Small foci in epithelial cells of upper airways contain PNE cells (pulmonary endocrine cells). The Pulmonary interstitium also contain mesenchyme derived cell lineages like fibroblasts, myofibroblasts and smooth muscles. The Vascular set up includes endothelial cells and vessel wall smooth muscles of arteries, veins and capillaries along with lymphatic endothelial cells for lymphatic system [41]. Fetal lung is filled with liquid which prevents airways and developing alveoli from collapse. The liquid secretion of fetal lung is controlled by active secretion of chloride ion from pulmonary epithelium, which carries positive sodium and water along with it [42]. The production of lung liquid ceases under influence of adrenaline [43] as the term approaches.

As the fetus prepares to take its first breath, transition from intrauterine environment to extra-uterine life is an important challenge that respiratory system has to face. To make a successful adaptation, biochemical maturation of specialized enzyme system is also critical. Any immaturity of main biochemical systems (surfactants, antioxidant enzymes and lung liquid secretion) can contribute subsequent pathology of respiratory disorder particularly in preterm infants. Hyperoxia can cause production of free radicals hence damage endothelial cells and epithelial lining of lungs. The protective mechanisms include antioxidant enzymes and Vitamin A, C and E. The enzymes which provide defense against free radicals include catalase, glutathione peroxidase and superoxide dismutase. These systems mature as the gestation proceeds [44].

4. Molecular Basics of Pulmonary Development

The major challenge for researchers in understanding lung development is to trace the actual mechanisms that control the highly sophisticated orchestration from an outgrowth of endodermal foregut to a highly specialized organ. An insight to these mechanisms is important to find clues of genetic mutations, adverse effects associated with environmental toxins, drugs and intra-uterine infections that develop anomalies and help in designing solutions to improve developmental outcome.

The study of highly refined and systematically assimilated cellular and molecular mechanisms of development in human fetus is practically and ethically challenging to perform. Though some researches provide such intervention studies, the main contribution of knowledge and understanding comes from detailed study of molecular mechanisms of pulmonary development in animal models of *Drosophila*, mouse and sheep [41,45,46].

The process of lung development during endodermal organogenesis is controlled by a variety of multiple stage specific growth regulators including BMP, Wnt, Hedgehog factor, RA (retinoic acid) and Notch, Fibroblast growth factor-8 (FGF-8), Keratinocyte growth factor-7 (FGF-7), Platelet derived growth factor B, Epidermal growth factor, Insulin-like growth factor, Transforming growth factor, Vascular endothelial growth factor, Platelet derived growth factor (A) and Granulocyte macrophage-colony stimulating factor. Amazingly similar growth factors and signaling pathways are utilized during different growth stages but the impression produced varies depending on the phase. Some transcription factors such as Hhex, Cdx, Foxa2 have diversity of roles in forming regional identity and later Organogenesis [47]. Foxa2, which is selectively expressed in respiratory epithelium is also known to regulate Th-2 mediated innate defense and inflammation in developing lungs [48].

Table 1. Summary of various growth and transcription factors expressed in different phases of lung development

Roles of Certain Mediators in Embryonic Development	
Phases of lungs development	Growth/transcription factors involved
Formation of Lung Primordium	FOXA 1/2, GATA 4/6, Gli, Tbx4
Tracheal Morphogenesis	Gli, HNF-3beta, RA, Tbx 4, FGFs
Branching, Differentiation and control	FGF-10, Tbx4/5, Gli, Nkx 2.1, GATA, BMP-4, Shh, HOX genes
Alveogenesis	Nkx 2.1, GATA, BMP-4, Shh, FGF-10, PDGF, IGF, RA
Surfactant induction and regulation	FGFs, Nkx 2.1
Vascular growth and angiogenesis	VEGF, EMAP II, Extracellular matrix proteins, Cell adhesion receptors

The cellular initiation of lung organogenesis starts as result of increased FGF and Wnt signals from mesoderm, establishing localized domain of Nkx2-1 gene expression setting a mark for future trachea. Lung bud arises by a localized expression of Fgf10 for which RA and Hedgehog signaling is required to suppress TGFβ signaling that promotes the expression of Tbx4/5 and Hoxa4/5 as well as FGF10 [49,50]. The growing lung bud experiences a highly categorized branching to generate a highly integrated tree-like structure of the lung. Experimental evidences prove that a fine balance of collaborations between positive regulatory signals FGF10 and Tbx4/5 in the mesenchymal distal tip with negative feedback modulators Shh, BMP4, Fgfr2, and the FGF-antagonist sprout in the growing distal tip epithelium, and this balance regulates branching pattern and equilibrium [50,51].

The epithelium of developing saccules differentiate to form various cell types among which AEC-1 (alveolar epithelial cell) that express aquaporin 5 and T1-alpha on maturation, and AEC-2 which secrete surfactant proteins and lipids when mature, are included. Crest formation and alveolar maturation requires elastin and myofibril [52]. Regulation of vascular and mesenchymal components involved in alveolization is governed by multiple signaling pathways and intercellular interactions including Pdgf-alpha, ephrin B2, Fgf and RA. The Fgf-2 and Fgf-18 are important for late stage lung development [53].

The ongoing research in embryology has shown importance of interactions in endodermal epithelium and splanchnic-mesodermal-mesenchyme growth, morphogenesis and cell differentiation in developing lungs. These epithelial mesenchymal interactions consequently are regulated by key signaling mediators as, FGF and their receptors, Wnt genes and β- catenin, BMP4, sonic hedgehog and Gli genes [54].

In early stages of pulmonary development, multipotent epithelial cells differentiate to form pulmonary neuroendocrine cells under influence of MASH-1. The differentiation of these epithelial phenotypes also occurs under discrete transcriptional regulatory mechanisms. It is becoming clear that angiogenesis and vasculogenesis of the pulmonary circulation and capillary network are closely linked with each other and may be necessary for lung epithelial morphogenesis. The pulmonary vascularization involves a fine balance between positive angiogenic and vasculogenic factors (VEGF) [55,56,57], which signals through cognate receptors flk, flt [57,58] and negative regulators (EMAP II) [57,59]. Growth factors, extraxcellular matrix proteins and cell adhesion receptors, all play important role in differentiation, commitment, and relocation of endothelial cells [60]. Research have shown that inhibition of VEGF cause cessation of vascular growth and altered epithelial proliferation but does not affect cell differentiation [61]. The detailed reviews on the cellular and molecular aspects of lung morphogenesis and development, done by various researchers [21,27,45,50,62,63] can be consulted separately to obtain further insight in this aspect.

5. Developmental Abnormalities of Respiratory System

The normal pattern of developing pulmonary system can be disturbed by imbalance of various growth factors and genetic mutations or acquired pathology (infection, allergy, ETS) producing faulty gene expressions. In either case the result is in the form of structural and functional abnormality of lungs. Defect at each stage of development of the pulmonary tree can produce a different set of aberrations and hence pathological complications [64].

Abnormal developmental outcomes of embryonic stages may appear in the form of tracheo-oesophageal fistula, laryngeal, tracheal, or oesophageal atresia; tracheal stenosis; pulmonary agenesis or congenital lung cysts. Congenital anomalies like pulmonary hypoplasia, pulmonary sequestration, Lymphangectasia, Pulmonary adenomatoid malformation and Congenital diaphragmatic hernia (CHD) may evolve during the pseudoglandular stage. Pulmonary hypoplasia may also develop in

canalicular phase, the underlying causes of which may be skeletal Dysplasias, Pleural space lesions, CNS damage, oligiohydramnios, or Congenital muscular disease [13,29,38]. The types of anomalies of pulmonary system alongwith reference of their detailed discussion on each disorder, its presentation, pathophysiology and factors contributing it are stated in Table 2.

Table 2. Developmental Anomalies of Respiratory Systema-d

Anatomical region	Anomaly
Upper Respiratory tract	Anterior and posterior nares
	Clefts of lips and palate
Lower Respiratory tract	
Larynx	Laryngeal artesia
	Laryngeal Stenosis and Obstruction
	Laryngeal clefts
	Laryngeal Cysts
	Laryngomalacia
Trachea	Tracheal agenesis
	Tracheal Stenosis
	Tracheoesophageal Fistula
	Trachea-Bronchomalacia
Lungs	Bronchial Isomerism
	Bronchial Artesia
	Bronchial Stenosis
	Pulmonary Agenesis
	Pulmonary Lobar Anomalies
	Lung Hypoplasia
	Pulmonary Cystic Disease
	Bronchogenic Cysts
	Congenital Lobar Emphysema
	Congenital Pulmonary Adenomatoid Malformation
	Pulmonary Sequestration langstone
	Pulmonary Hamartomas
	Alveolar Capillary Dysplasia
	Lymphangiectasia

a-d [65,66,67,68]

The respiratory disorders of newborn especially preterm birth may be due to acquired pathology occurring mainly through immaturity, infection, exposure to environmental toxins or birth asphyxia. These problems can manifest themselves in the form of Respiratory Distress Syndrome, Hyaline membrane disease, Bronchopulmonary dysplasia (Chronic Lung Disease), Pulmonary interstitial emphysema (PIE), Pulmonary hemorrhage, and Meconium aspiration syndrome [29].

Ascending *infection* may cause still birth or even spontaneous abortion mostly before 24 weeks of gestation. Infective organisms in case of ascending infection may be E. coli, GBS, Candida [69,70], Mycoplasma, Ureaplasma or Chlamydia in some cases [71,72,73].

The causative agents in case of viral infections include Herpes Simplex, Congenital Cytomegalovirus, RSV and Metapneumovirus. Herpes Simplex virus and Enteroviruses are known to be transmitted to neonate antenatelly or during passage through birth canal [74,75].

Bronchopulmonary dysplasia (BPD) and CLD are specifically perinatal disorders that occur in infants who are born preterm with some acute lung disease and receive intensive care therapies for respiratory assistance through Ventilators [76,78].

A single insufficiency of inadequate surfactant may culminate in increased work of breathing by raised vascular functional resistance, limiting residual capacity and decreasing alveolar ventilation, which in turn can give rise to Respiratory distress syndrome, Meconium aspiration syndrome, appearance of Pulmonary air-leak syndromes (pulmonary interstitial emphysema, subcutaneous

emphysema, pneumomediastinum, pneumoperitoneum, pneumopericardium, pneumothorax) and transient tachypnea of the newborn in preterm infants.

6. Factors Effecting Pulmonary Development

The research over past few decades has provided a great insight regarding factors regulating the pulmonary development .But revealing the actual underlying mechanism can be challenging as well as promising to design manipulative strategies that may prevent and resolve fetal and neonatal morbidity and mortality.

The key physical factor regulating lung maturation is the *stretch force* exerted by luminal fluid which acts as a stent to maintain partially expanded lung [79,80]. The fetal lung liquid is developed from two main sources including secretions of epithelial cells themselves and amniotic fluid [81] Removing the stretch stimulus of luminal liquid causes simulated termination of fetal lung growth while over-distension leads rapid tissue growth and structural development, of the alveolar wall [82,83]. This stretch exerting factor in turn is controlled by transpulmonary pressure gradient and the resistance of the upper respiratory tract. *Fetal lung movements* also play major role in maintaining lung expansion to elicit a positive signal for lung growth [84].

An *impaired nutrient supply* proves to have damaging effect on antenatal and postnatal lung development [85,86] The effects of malnutrition include compromised maturation of type ll alveolar epithelial cells [87] causing decreased surfactant production and increased surface tension [88-89], reduction in lung weight and decreased DNA, protein and elastin content, an increase in lung to bodyweight ratio [90,91,92], decreased alveolar formation with underdeveloped air-blood boundary providing a reduced surface area for gaseous exchange and compromised action of acid phosphatase in alveolar macrophages, thus resulting in altered pulmonary resistance [87,92,93,94,95,96]. Lung function is also reduced in preterm infants however impact of *IUGR* on later lung physiology is more pronounced in children born after 26th gestational week [97].

Hypoxia can be established as sole factor to cause IUGR resulting in surfactant deficiency induced acute and chronic pulmonary disorders of developing lung [98,99,100]. Hypoxia inducible factors are key regulators for adaptation to hypoxic milieu throughout and after intrauterine life. HIF-1α and HIF-2α protein serve distinct and specific roles in vascular and epithelial morphogenesis [101,102]. Loss or insuffency of HIF-2α culminate in impaired pulmonary development, decreased surfactant production, ARDS and even neonatal death [103]. Prenatal and post natal exposure to *glucocorticoids* (betamethasone, dexamethasone and cortisol) have been demonstrated by various studies, to be helpful for epithelial cell maturation and improved amounts of pulmonary surfactant and suppressed inflammatory response[104,105,106,107]. Other elements that retard IUG include Chest wall anomalies, diaphragmatic hernia, Oligohydroamnios, Rhesus Isoimmunization, Renal anomalies, Myotonic Dystrophy, Anecephaly, Maternal diabetes, Alcohol and Nicotine, while sex hormones and several growth factors discussed in molecular mechanisms

of lung growth are also known to affect fetal and neonatal lung development [23]. The IUGR in turn can result in low BW which is shown to have strong association with childhood asthma and respiratory indisposition and mortality [108-109].

7. Allergy and Lungs

7.1. Developing Immune System of Respiratory Tract and Early Origins of Allergic Disorders

The preservation of sterility at distal end of respiratory tract (alveoli) is very critical as exposure to pathogens from oral end of respiratory tract is a constant threat. This necessitates the importance of specialized immune set up in respiratory machinery. This combat infantry consists of innate immunity, mucus secretion, fluid and electrolyte transport and surfactant balance.

The immunological setup of lung includes both inflammatory and migratory cells responsible for immune response [110,111].These cells include Helper T cells (T_H1, T_H2), alveolar Macrophages, dendritic cells, basophils, and airway epithelial cells in lung. The distinct sets of growth factors control the fetal and perinatal maturation of the immune cells in respiratory system and play fundamental role in regulating immunological homeostasis. Any encounter of immature immune system of lungs with aeroallergens cause the development of allergen-specific immune memory through infant's T cell selection. These T-memory cells cause suppression of allergy predisposing, cytokine secreting Th2 cells via expressing Th1 pattern cytokines. Any exogenous or endogenous assault to this immunomodulatory process causes failure of Th-1 memory cells, predisposing the Th-2 mediated allergic reactions. The evidences also propose that a fetus may be prone to allergy because of intrauterine hyperactivity of control mechanisms (Thurlbeck, 1982).

The tissue and organ seeding of lung by macrophages and dendritic cells, begins by 4-7 week of gestation with substantial development and reorganization in late first trimester and throughout the second trimester [112,113]. The IgE starts at 11 week of gestation in human fetus. By 21 weeks T-cell proliferation is seen when exposed to in vitro allergens. As the term approaches, IL-1, 4, 6, 7, 8 and TNFα and IFNγ are detectable in amniotic fluid [110].

The respiratory allergens, pathogens, environmental and genetic risk factors for allergy and asthma, usually impede innate immunity in respiratory system through airway epithelial cells, DCs and basophiles [107] the epithelial cells form the first line of defense against allergens [114,115,116,117]. Members of transient receptor potential (TRP) super-family of cation channels [118,119,120,121,122] play crucial role in the development of allergic disorders of pulmonary system and hence provide important therapeutic targets [123,124]. In addition to TRP ion channels, the importance of toll like receptors has been well established [125,126,127,128,129,130] as component of innate immunity. Forexample, "T_H1 cells" are the members of first combat force and provoke T_H2-polarized immune memory of inhaled allergens. The research now focuses more on Th2 cell and eosinophilic inclination for immune

response [131] as the Th1 and Th2 clones in lung mediate through different patterns of Cytokines [132,133]. Any encounter of immature immune system of lungs with aeroallergens cause the development of allergen-specific immune memory through infant's T cell selection. These T-memory cells cause suppression of allergy predisposing, cytokine secreting Th2 cells via expressing Th1 pattern cytokines. Any exogenous or endogenous assault to this immunomodulatory process causes failure of Th1 memory cells, predisposing the Th2 mediated allergic reactions [134]. The Th2 based immune control inutero is known to produce high levels of Cytokines (IL-4, IL-13) and IgE while decreased levels of IFNγ [135,136,137,138,139,140]. The evidences also propose that a fetus may be prone to allergy because of intrauterine hyperactivity of control mechanisms [141]. The studies have shown that delayed maturation of T_H1 in early infancy increase the susceptibility to acquire inflammation through aeroallergens which restricts lung growth and maturation [142].

The Dendritic cells (DCs) play a key role in regulating T helper 2 cell (Th2) immunity to aeroallergens. Different subsets of DCs (CD11b+ and CD11b- subsets) execute anti-inflammatory response by antigen uptake, draining to Lymph Nodes, and generation of adaptive immunity. The pulmonary epithelium (TLRs) not only acts as a physical barrier to allergens and pathogens but also switches release of cytokines which promote function of lung DCs and Th2 cells. The stimulation of epithelial cells by allergens also creates an immunological microenvironment involving immature DCs in defense cascade [143]. The alveolar macrophages specialize in triggering inflammatory reactions against pathogens, exposed to alveoli [114,115].

Thus the Early-life immune insults (ELII) owing to allergy, Environmental toxins (air pollution, tobacco smoke), infections or developmental immunotoxicity (DIT) has been shown to culminate in several respiratory disorders most important of which is child hood and late asthma [144,145]. The allergen contact in pregnancy may also stimulate allergic responses in the neonate by pre-sensitizing the fetus through transplacental exposure [146,147,148].

8. Lungs Surfactant System

Since the initial recognition of surfactant role in lowering surface tension of lung [149,150] a great has been laid on the study of its nature and functions. It is remarkable to note that this surfactant system also plays a vital role in pulmonary innate immune defense system against allergic threats [151]. A single abnormality of surfactant deficiency can manifest itself directly or indirectly in the form of multiple respiratory disorders of neonates including NRDS, CLD and AA [152,153]. Moreover, inflammatory enzymes produced as a result of allergen exposure or infection, can create surfactant deficiency by degrading it. This functional diversity of lung surfactants is tempting for a researcher because a complete insight to surfactant system has unique potential to resolve many problems of respiratory insufficiency in newborns especially preterm infants. A brief overview of composition, functions and importance of lung surfactant in terms of its immunomodulatory drive to fight allergens will be reviewed in this article.

8.1. The Composition of Lung Surfactant

As discussed earlier, AEC-II are involved in lung surfactant production. This surfactant system is a combination of immunomodulatory proteins (5-10%), phospholipids (PL, 80-85%) and some other lipids (5-10%). Different classes of PL in lung surfactant are PC, PI, PG, PE and SPM. [152,153] (Rau et al., 2004). Phosphatidylcholine (PC) forms the main component of PLs, while Dipalmitoyl-PC (DPPC) shares for about 50% of PC content performing main role in reducing surface tension. By 35th week of gestation, the levels of Phosphatidylglycerol (PG) reach at peak and can be used as indicator of lung maturation [154]. By this time levels of Phosphatidylinositol are also high but decreases as term approaches hence can be utilized as marker of pulmonary immaturity [154].

Protein composition of surfactant system including surfactant proteins and surface active lipid associated transporter, ABCA3, is of utmost important for both surface activity and immunological homeostasis [155,156]. The surfactant proteins are categorized according to their water affinity, in 4 major divisions, SP-A, SP-B, SP-C and SP-D [157] all of which are formed by alveolar type-II cells [152,153,158-167]. The Hydrophobic Surfactant proteins include SP-B and SP-C. SP-B are the surfactant proteins indispensable for survival due to their major role in lowering surface tension by interacting with surfactant PLs [157,168,169] with additional function of forming tubular myelin and packing Phospholipids into lamellar bodies [170] SP-C is the most hydrophobic small protein which also interacts with PLs to lower Surface tension [170].

The hydrophilic surfactant proteins belonging to collectin family are SP-A and SP-D which predominantly chip in in innate immune resistance of respiratory system.[155] both share a structural similarity of possessing N-terminal, a domain, neck region and the Carbohydrate recognition domain (CRD). SP-A is also most abundant protein while SP-D is most hydrophilic in nature [151-155, 158-167, 171-174].

8.2. Functions of Lung Surfactants

The increased surface pressure at level of small alveoli has potential to rupture them during expiration [149,150,175]. Presence of surfactants lowers the elevated pressure and ensures alveolar integrity during respiratory series and increase lung compliance. Furthermore the ability of surfactant system to counter hydrostatic forces in preventing fluid buildup and edema has also been established [149,150,175,176].

8.3. Role in Immune Defense

The hydrophilic class of surfactant proteins contributes the function of host defense in lungs [155,177]. The immune cells that perform the function of pathogen termination include neutrophils, macrophages, DCs and monocytes. SP-A and SP-D can function at different stages of immune response. They can 1) modify the release of inflammatory mediators [155,178]. 2) being the

member of collectin protein family, these surfactant proteins can opsonize various allergens and pathogens through CRD site [179,180]. 3) Ligand-activation of Immune cells [155]. 4) Direct microbicidal activity for pathogens [155,178]. 5) Increase activity of pathogen recognizing cells [181]. 6) Accelerates the activity of macrophages for Phagocytosis of apoptotic cells and in turn promotes the anti-inflammatory response of macrophages [182,183]. SP-A and SP-D are known to specifically modulate the intensities of inflammatory mediators in utero that involve preterm birth [184,185] and acute respiratory distress syndrome [186].

Although the main function of Lung surfactants is to regulate the pressure differential throughout the respiratory cycle, yet research has shown that the role they play in immune defense is not trivial. The surfactant system creates a hitch for invasion of pathogenic organisms [181]. It has ability to camouflage the antigen recognizing receptors in airways, and thus prevent the potential allergen recognition [181]. An important mode of defense to an otherwise inevitable response (bronchoconstriction) of aeroallergen is the capability of surfactants (endogenous/exogenous) to produce bronchodilation, by relaxing smooth muscles of airways [181] and clearing mucociliary secretions [187]. The role of surfactant PLs is observed to be an inhibitor of immune cell responses [188]. They down regulate the release of pro-inflammatory cytokines, signal transduction by L-selectin and activation of nuclear factor-kappa [153,189]. In the process of the macrophage induced IIA secretory phospholipase A2 synthesis, Phosphatidylglycerol and surfactant protein-A act as inhibitor [190]. Surfactant PLs also suppress immune response by blocking the synthesis of cytotoxic Oxygen intermediates by macrophages and neutrophils [191]. Though a developed surfactant system warrants the defense of pulmonary system against alveolar collapse and allergic extortions, there is yet another facet of allergy-surfactant relationship which can't be overlooked. In spite of being an important legionnaire of lung defense, surfactant itself is prone to degradation under effect of various inflammatory products such as reactive oxygen species, proteases and phospholipases [141,192,193]. This humiliation of surfactant in a developing respiratory system, in response to an ongoing inflammatory response can contribute subsequent pathophysiology of various lung defects.

The current knowledge about lung surfactant system and associated transcriptional guiding modules controlling gene expression for surfactant production and immunity cadence, reveals the multiple functions of surfactants and an insight to number of diseases caused by their abnormalities [156]. Each area requires a great deal of discussion that will be beyond scope of this article. On basis of epidemiological data [194,195], we will restrict our discussion to a brief overview of most prevailing allergic respiratory disorder of respiratory tract "allergic asthma" in context of surfactant abnormalities seeded during fetal, neonatal or early childhood growth period.

9. Allergic Asthma and Lung Surfactant System

There are numerous allergic conditions that involve lung, amongst which, Allergic Asthma (AA) is the most prevailing and comprehensively studied disease of early childhood and adults [195,196]. AA is a reversible airway obstruction characterized by bronchospasm, hyperresponsiveness, excessive mucus secretions, remodeling of bronchial wall and decline in respiratory function due to airway inflammation [197-200]. The initial phase of asthma is characterized by IgE mediated release of histamine, cytokines, leukotrines and interleukins (IL-4, 5)

In the fetal and early perinatal period of life, the principal defense against allergic challenges is provided via innate immunity. Research has shown that IgE which starts to develop from 11th week of gestation [110], is capable to contribute in any innate immune response as a sequence of allergen exposure. Furthermore, the immature respiratory system is already sensitive towards exogenous and endogenous vulnerabilities. This fact along with various studies reflects the latent chances of initiating early age allergic asthma in embryonic life and even in neonatal period [201,202].

The role of surfactant abnormality in instigating early origin of asthma has undergone an ardent investigation by many researchers [203-210] The predisposition to allergic coercions is known to increase in surfactant deficiency. This may occur through decreased respiratory compliance, fluid accumulation and edema of airways, diminishing mucociliary clearance, decreased masking of irritant receptors in bronchi and increased exposure to allergens, altered immunological responses and unopposed bronchoconstriction. These alterations are mainly caused by generation of eosinophilic inflammatory substances [211] causing increased degradation of surfactant molecules [209,212] and generation of protein infiltrates in bronchi [205,206,207]. The use of Surfactant Replacement therapy in allergic asthma has shown improved respiratory compliance [213,214] since the advent of synthetic and natural lung surfactants, Surfactant Replacement Therapy is included in protocols for neonates with NRDS and preterm births [108,215]. The surfactant replacement therapy is usually recommended for preterm neonates especially of less than 27 week gestational age and it has established clinical outcomes by improving SPs production [216]. The selection of surfactant therapy depends on severity of respiratory distress syndrome in more mature infants. Another approach to fight against surfactant deficiency is antenatal use of corticosteroids mainly Betamethasone and Dexamethasone. But there is insufficient evidence to show safety vs efficacy profile of steroid use for mother and the fetus [109,217].

10. Conclusion

The advent of "Molecular Embryology" has set a prospect of comprehensive knowledge about developmental programming of pulmonary system in fetal and postnatal life. The succeeding awareness has ascertained the involvement of multiple maternal/fetal endogenous or completely exogenous factors in the complex process regulating fetal lung development. A deep learning through literature till day can provide a

sound insight to physiology and morphology of lung development, yet the important prerequisite for a complete understanding to morphogenesis, growth regulation through multiple factors and transcription dynamics needs a deal of research on the progenitor cell biology of the lung. Many gaps still remain to be filled in understanding all the cellular and molecular mechanisms that lead to differentiation of multipotent progenitor cells, morphogenesis and vasculogenesis. This unleashed knowledge has potential to provide a great insight and solutions to the underline causes of respiratory disorders and congenital lung anomalies.

The advances in understanding of antenatal immune development have established the extensive role of lung surfactant system in providing resistance against pathogens and inhaled allergens. This system works in conjunction with other immunomodulators (pulmonary microphages, DCs, basophils, epithelial cells and cytokines). Both of the two major components of lung surfactant, Surfactant proteins (SP-A, SP-D) and Surfactant Phospholipids (sPL), take part in host defense mechanism. Dominance of IgE based immunity in fetal and early neonatal life has presented the evidence for contribution of surfactant abnormalities in pathophysiology of AA and its prevalence in early life, dominantly in preterm births. Lung surfactant based manipulation of immune responses has potential to target AA and CLD. Thus lung surfactants have dual role in providing defense as well as management of allergic asthma. However many underline molecular mechanisms contributing net responses are yet poorly understood. The future perspective of most efficient and safe clinical interventions lies in exhaustive research in molecular origins of lung biology.

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