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Sphingolipids in Lung Growth and Repair

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Sphingolipids comprise a class of bioactive lipids that are involved in a variety of pathophysiologic processes, including cell death and survival. Ceramide and sphingosine-1-phosphate (S1P) form the center of sphingolipid metabolism and determine proapoptotic and antiapoptotic balance. Findings in animal models suggest a possible pathophysiologic role of ceramide and S1P in COPD, cystic fibrosis, and asthma. Sphingolipid research is now focusing on the role of ceramides during lung inflammation and its regulation by sphingomyelinases. Recently, sphingolipids have been shown to play a role in the pathogenesis of bronchopulmonary dysplasia (BPD). Ceramide upregulation was linked with vascular endothelial growth factor suppression and decreased surfactant protein B levels, pathways important for the development of BPD. In a murine model of BPD, intervention with an S1P analog had a favorable effect on histologic abnormalities and ceramide levels. Ceramides and S1P also regulate endothelial permeability through cortical actin cytoskeletal rearrangement, which is relevant for the pathogenesis of ARDS. On the basis of these observations, the feasibility of pharmacologic intervention in the sphingolipid pathway to influence disease development and progression is presently explored, with promising early results. The prospect of new strategies to prevent and repair lung disease by interfering with sphingolipid metabolism is exciting and could potentially reduce morbidity and mortality in patients with severe lung disorders.
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Abbreviations: ASMase = acid sphingomyelinase; BPD = bronchopulmonary dysplasia; CF = cystic fibrosis; LPS = lipopolysaccharide; nSMase = neutral sphingomyelinase; S1P = sphingosine-1-phosphate; SP-B = surfactant protein B; VEGF = vascular endothelial growth factor

Sphingolipids are structure-bearing components of the cell membrane that have been shown to function as messenger molecules, exhibiting effects on cell proliferation, apoptosis, cell contact and adhesion, and endothelial barrier function during the immune response.[1-9] They have been identified as an important class of molecules involved in a variety of diseases, such as atherosclerosis, chronic heart failure,[5] asthma,[10] diabetes, sepsis, cystic fibrosis (CF), COPD,[11] Alzheimer disease,[12] and cancer.[13] Emerging evidence also suggests an important role for sphingolipids in lung development and in damage and repair processes after early lung injury. An important process in the development of the human lung is alveolarization, which occurs between 36 weeks gestation and 2 years postnatally when secondary septa subdivide the immature saccules into smaller alveolar units[14-16] to increase the surface area for gas exchange. Between birth and age 3 years, the capillary monolayer is formed in these septa, thereby reducing the septal thickness to improve gas exchange properties.[17] A host of growth factors, morphogens, receptors, transcription factors, hormones, cellular processes, and physical determinants are crucial during the various stages of lung development.[15,18] Disruption of any of these processes results in structurally and functionally abnormal lungs, such as can be seen in bronchopulmonary dysplasia (BDP). The present review focuses on the role of sphingolipids during lung development, damage, and repair.

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Biologic Importance of Sphingolipids in the Lung

Sphingolipids comprise a hydrophobic sphingoid long chain base (sphingosine, sphinganine, or phytosphingosine) and a hydrophilic fatty acid that varies in chain length, degree of hydroxylation, and saturation, creating a large possible variety in sphingolipid composition.[19,20] Two important sphingolipids are ceramide and sphingosine-1-phosphate (S1P). Ceramide is the center of sphingolipid metabolism,[21] acts as precursor for the creation of all other sphingolipids, and functions as a stress signal for multiple stimuli, such as radiation, ischemia and reperfusion, chemotherapeutics, and cytokines.[22,23] S1P functions as a prosurvival signal and promotes cell proliferation and differentiation. Because S1P is generated from ceramide through sphingosine, it has been proposed that these two sphingolipids determine the apoptotic balance.[7] The regulation of sphingolipid metabolism is complicated and involves many enzymes (Fig 1). There are three main pathways to create ceramide: (1) de novo synthesis from serine and palmitoyl coenzyme A by serine palmitoyltransferase, (2) breakdown of sphingomyelin by acid sphingomyelinase (ASMase) or neutral sphingomyelinase (nSMase), and (3) production from sphingosine by ceramide synthase. Sphingosine can also be converted into S1P by sphingosine kinase.

Various sphingolipids play an important role in cellular homeostasis, where ceramide leads to cell cycle arrest and apoptosis and S1P plays an opposite role, namely facilitating proliferation and differentiation of cells. Therefore, ceramide and S1P are considered a proapoptotic and antiapoptotic rheostat.[24,25] The interplay between these two processes determines the formation of lung structure, on both a macroscopic and a cellular level, during all stages of lung development. On the basis of these findings, sphingolipid research has intensified. Animal models have shown altered sphingolipid levels in lipopolysaccharide (LPS)-induced macrophage dysfunction,[26] colitis,[27] melanoma,[28] ischemia-reperfusion injury,[29] and spinal cord injury.[30] In the lung, sphingolipids have been shown to be involved in vascular permeability, allergic response, and apoptosis.[31] Altered sphingolipid levels have been shown to play a role in hyperoxia-induced lung injury or BDP,[32] radiation-induced lung injury,[33] cigarette smoke-induced lung injury,[34-36] CF,[37] asthma,[38,39] and pulmonary infection, stressing the biologic importance of sphingolipid metabolism in lung disease.

Sphingomyelin as Biomarker for Fetal Lung Development

Alveolar sphingomyelin levels are believed to remain constant for the entire gestational period.[40] Dipalmitoylphosphatidylcholine is the main surface active component in the alveolar lining during fetal development, and its level remains constant for most of the gestation period and increases from weeks 32 to 33 toward term.[41] Because the alveolar compartment and the amniotic fluid are connected,[42] phosphatidylcholine (lecithin) levels also increase in the amniotic fluid toward term. The lecithin/sphingomyelin ratio in amniotic fluid is traditionally considered a marker of lung maturation.[43] In 1997, Longo et al[44] took an in-depth look at sphingomyelin levels during lung development in rats and found that sphingomyelin and sphingosine levels in lung homogenates and microsomes increased twofold and sixfold, respectively, during fetal lung development, with the highest levels at birth. This increase was caused by an increase in serine palmitoyltransferase activity, the rate-limiting enzyme of de novo synthesis of ceramide, the intermediate

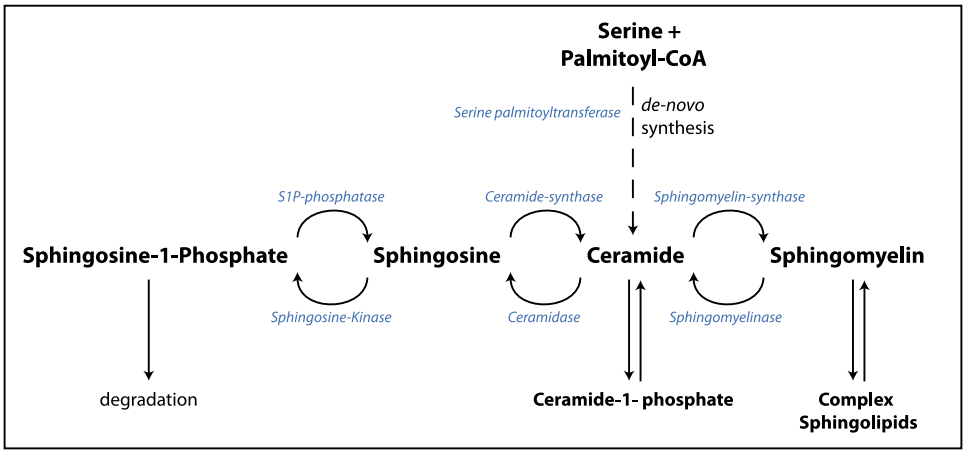

Figure 1. Pathway of sphingolipid metabolism. Enzymes are marked with italics. CoA = coenzyme A; S1P = sphingosine-1-phosphate.