肺表面活性物质与相关呼吸道疾病

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摘要 肺表面活性物质是由肺泡II型上皮细胞产生的脂质和蛋白质的复合物。肺表面活性物质覆盖在肺泡区域中气体–液体交换的界面, 具有维持肺表面张力从而防止肺泡过度膨胀或坍塌、维持正常的肺泡形态和进行宿主防御的功能。肺表面活性物质的缺陷可能会导致多种呼吸道疾病, 包括呼吸窘迫综合征、间质性肺炎、胎粪吸入综合征、肺纤维化和肺泡蛋白沉积症等。该文综述了肺表面活性物质的组成、合成代谢和功能, 讨论肺表面活性物质缺陷与呼吸道疾病之间的关系, 期望为肺表面活性物质缺陷造成的呼吸道疾病的研究提供理论参考。

关键词 肺表面活性物质; 脂质; 肺表面活性蛋白; 呼吸道疾病

Pulmonary Surfactant and Related Respiratory Diseases

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Abstract Pulmonary surfactants are lipid protein complexes produced by alveolar type II epithelial cells, cover the gas-liquid exchange interface in the alveolar region. They are maintaining the surface tension of the lungs to prevent alveoli against excessive expansion/collapse, maintaining normal alveolar morphology and performing host defense. Defects in pulmonary surfactant may cause a variety of respiratory diseases, including respiratory distress syndrome, interstitial pneumonia, meconium aspiration syndrome, pulmonary fibrosis, and alveolar proteinosis. This article reviews the composition, anabolism and function of pulmonary surfactants, as well as the relationship between pulmonary surfactant deficiency and respiratory diseases, and provides a theoretical basis for respiratory diseases caused by pulmonary surfactant deficiency.

Keywords pulmonary surfactant; lipid; pulmonary surfactant protein; respiratory disease

肺表面活性物质(pulmonary surfactant, PS)是稳定呼吸气–液界面的一个重要系统。肺表面活性物质具有避免肺泡在呼吸过程中过度膨胀或坍塌的表面活性, 为肺泡在肺部气体交换过程中提供了结构和功能基础。早在1959年, AVERY和MEAD[1]就证明了缺乏肺表面活性物质会导致新生儿罹患呼吸窘迫综合征(neonatal respiratory distress syndrome, NRDS)。近年来, 许多动物模型研究发现, 肺表面活性物质与多种呼吸道疾病直接相关[2-4]。因此, 了解肺表面活性物质的功能与合成代谢机制, 将有助于进一步了解肺表面活性物质在相关呼吸道疾病中的作用。本综述将介绍肺表面活性物质的组成、功能与合成代谢, 并深入剖析肺表面活性物质与呼吸道疾病的关系。

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1 肺表面活性物质的组成和功能

1.1 肺表面活性物质的组成

肺表面活性物质由90%的脂质和10%的蛋白质组成。其中, 脂质含80%~90%的磷脂(phospholipid, PL)和约2%的中性脂质(neutral lipid)。磷脂酰胆碱(phosphatidylcholine, PC)在磷脂中含量最高, 约占70%, 其次为磷脂酰甘油(phosphatidylglycerol, PG)。而在PC中, 二棕榈酰磷脂酰胆碱(dipalmitoyl phosphatidyl choline, DPPC)作为PC的主要成分, 占50%以上(图1)。另外, 相关蛋白则主要由肺表面活性蛋白A(surfactant protein A, SP-A)、SP-B、SP-C和SP-D组成。SP-A和SP-D是亲水性表面活性蛋白, 属于集合素蛋白家族中的成员, 与肺的先天宿主防御直接相关[5-6]。SP-B和SP-C是疏水性表面活性蛋白, 与磷脂一起储存和分泌[7], 在呼吸循环期间可保持脂质膜的稳定性[8]。

1.2 肺表面活性物质的功能

肺表面活性物质在呼吸的过程中为肺泡提供了表面活性, 其作用过程包括: (1)吸气时, 肺表面活性物质形成表面活性膜并且吸附到气–液界面, 覆盖肺泡区域; (2)呼气时, 肺表面活性物质形成具有压缩性的多层膜结构, 表面活性膜被表面活性成分填充, 主要是磷脂, 但其需要一些特定的肺表面活性物质相关蛋白的参与共同作用从而大幅度降低肺泡表面张力; (3)再次吸气导致肺泡扩张时, 表面活性膜重新膨胀, 气–液界面磷脂重新横向分布覆盖肺泡区域[9]。

1.2.1 *肺表面活性物质脂质的功能* 肺表面活性物质脂质的生物物理特性一直是人们研究的热点。磷脂中含量最高的DPPC与膜的表面活性有直接的关系。DPPC是一种饱和磷脂, 其含量约占肺表面活性物质的40%, 在呼气时, DPPC促进肺表面活性物质在气–液界面形成多层膜结构, 可降低肺泡表面张力, 防止呼气时肺泡出现萎缩[10]。肺表面活性物质中, 脂质是维持肺部免疫的生物活性分子[11]。研究表明, 占脂质含量第二的PG, 是肺内先天性免疫调节因子, 其主要分子种类棕榈酰–油酰磷脂酰甘油(palmitoyl oleoyl phosphatidylglycerol, POPG)可抑制促炎Toll样受体(Toll-like receptors, TLRs)中TLR2和TLR4的活化[12]。此外, POPG对呼吸道合胞病毒(respiratory syncytial virus, RSV)和甲型流感病毒(influenza A virus, IAV)具有抗病毒特性, POPG具有在细菌和病毒感染的情况下治疗急性或慢性肺部疾病的重要潜力[13-14]。

1.2.2 *亲水性肺表面活性蛋白的功能* 亲水性表面活性蛋白SP-A和SP-D能够调节肺部炎症反应和保护肺免受病原体侵害。SP-A和SP-D直接与包括细菌和病毒在内的多种微生物相互作用, 并可阻碍革兰氏阴性菌、荚膜组织胞浆菌和肺炎支原体的生长[15]。SP-A和SP-D蛋白前体的C-端凝集素结构域优先暴露并与病毒和细菌上的非宿主寡糖结合, 形成的聚集蛋白还通过刺激Fc受体(Fc receptors, FcR)和人红细胞补体受体1(complement receptor type 1, CR1)介导巨噬细胞激活吞噬作用, 帮助细菌清除[16]。SP-A和SP-D可以与包括Toll样受体、钙网蛋白CD91以及信号调节蛋白α1(signal regulatory protein α1, SIRPα1)等细胞表面受体结合, 并以微生物配体特异性方式减弱或增强炎症。有实验研究表明, 肺内缺乏SP-A的动物会导致肺部频繁地发生感染[2]; 条件性敲除*SP-D*基因(*Sftpd*$^{-/-}$)的小鼠会出现肺部炎症并逐渐恶化, 进而发生肺气肿和肺表面活性物质磷脂积累[3]。近些年, 在尿道组织中也发现了SP-A和SP-D这两种经典的聚集蛋白, 它们被认为是激活泌尿道和肾脏疾病中先天免疫和宿主防御的体液免疫的关键因素[17]。目前, SP-A和SP-D在肺系统外的作用是一个活跃的研究领域。

1.2.3 *疏水性肺表面活性蛋白的功能* 疏水性表面活性剂蛋白SP-B和SP-C在肺表面活性物质膜的形成和稳定中发挥着重要作用[9,18]。SP-B和SP-C与肺表面活性物质磷脂组装成双层膜, 储存在板层体(lamellar bodies, LBs)中, LBs在生理刺激下分泌后, 能够以板层体颗粒(lamellar body-like particles, LBPs)的形式保持密集的结构, 并且有效地被转运到肺泡气–液界面, 这过程与LBPs外表面蛋白SP-B和SP-C的存在及其功能状态密切相关[19]。有研究提出, 表面张力会使表面活性蛋白构象发生变化, 从而调控肺表面活性物质的活性[20]。吸气时, SP-B作为二聚体在磷脂膜或单层膜表面形成一个环, 环与相邻膜对接并且形成疏水管, 能够促进表面活性脂类在肺表面活性物质膜与界面之间快速流动[21]。SP-C氨基酸序列主要包括两个相邻的半胱氨酸, 即Cys5和Cys6, 它们均由硫代酯键共价棕榈酰化, 研究表明, 这种棕榈酰化翻译后修饰有助于保持SP-C蛋白和磷脂与界面膜的紧密联系, 保证呼气时界面膜在压缩过程中的完整性[22-23]。SP-B和SP-C对于脂质在气–

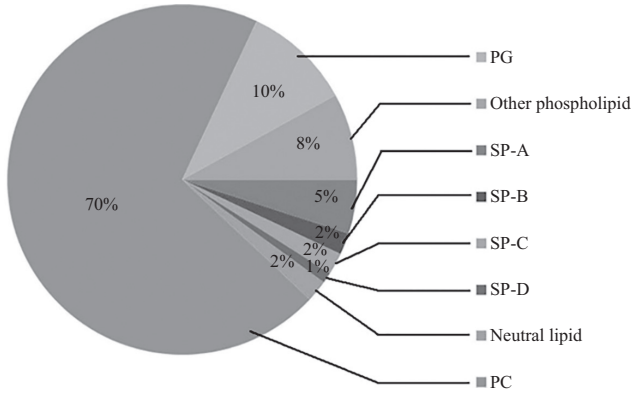

图1 肺表面活性物质的组成

Fig.1 Composition of pulmonary surfactant

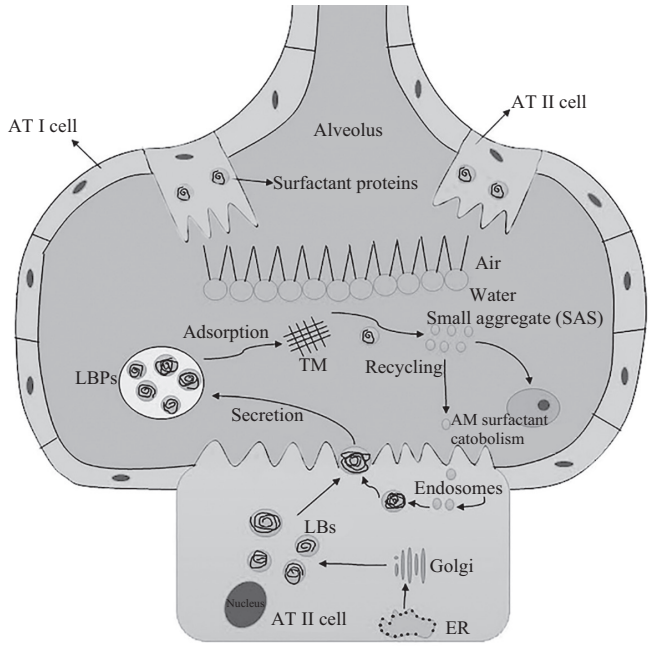

图2 肺表面活性物质的合成代谢(根据参考文献[31]修改)

Fig.2 Synthesis and metabolism of pulmonary surfactant(modified from reference [31])

液界面的吸附具有促进作用, 可通过形成蛋白脂孔来诱导膜的通透性变化, 由于蛋白可以作为支架来诱导脂质孔的形成, 脂质极性头排列在孔壁上, 所以可极大地促进肺表面活性物质脂类对气–液界面的吸附[24-25]。

此外, 在敲除*SP-B*(*Sftpb*$^{-/-}$)遗传修饰转基因小鼠中发现: SP-B对于SP-C的合成有重要的作用, SP-B的缺失会导致SP-C前体蛋白的加工不完全, 进一步导致肺泡空腔中缺失成熟的SP-C[26]。SP-B和SP-C与呼吸道疾病有重要的联系, SP-B的缺失会导致成年小鼠呼吸衰竭[27]。靶向敲除*SP-C*(*Sftpc*$^{-/-}$)会导致小鼠在出生后一段时间内发生严重的进行性肺炎[9]。临床上发现, 人体中SP-C的缺乏会导致慢性肺间质疾病[28]。

2 肺表面活性物质的合成代谢

肺表面活性物质的代谢过程是: 表面活性剂脂质和蛋白质在肺泡II型上皮细胞的内质网中合成并且存储在高度致密的膜状细胞器–板层体中[29]。受生理刺激后分泌到肺泡空间, 在肺泡空间中以LBPs或管状髓鞘(tubular myelin, TM)的形式有效地吸附到呼吸空气–水界面, 形成稳定的肺表面活性物质膜。肺泡II型上皮细胞和肺泡巨噬细胞会对废弃的肺表面活性物质进行摄取或者清除, 最终导致肺表面活性物质组分进行再循环利用或直接降解[30](图2)。

2.1 肺表面活性物质的合成与转运

肺表面活性物质脂质在肺II型上皮细胞中的合成过程有两种途径, 一种是在内质网中从头合成途径, 另外一种是回收再利用途径。从头合成途径是在内质网中合成, SP-B与SP-C合成后会经过高尔基–多泡体途径进入LBs, 磷脂是通过转运蛋白直接转运到LBs, 它们以高度填充和部分脱水的形式储存在LBs中[29,32]。ABC转运蛋白(ATP-binding cassette transporters)家族中的ABCA3水解的ATP能量能促进各种基质穿过细胞膜, 在磷脂和胆固醇转运中起重要作用。研究表明, ABCA3转运的功能紊乱会导致肺泡II型上皮细胞被游离的胆固醇诱导发生细胞死亡, ABCA3可以通过调控胆固醇调节元件结合蛋白(sterol-regulatory element binding protein, SREBP)降低细胞游离胆固醇的水平, 使细胞对外源性胆固醇更具抵抗力[33]。SP-C突变与蛋白沉积症有关, 即导致磷脂和蛋白质在肺泡内的积累。因此, SP-C可能参与了多泡体中肺表面活性物质的脂质摄取和降解[34]。亲水性蛋白SP-A和SP-D的合成加工, 其过程还包括糖基化与寡聚作用, 都在肺泡II型上皮细胞的内质网中进行, 但其分泌途径似乎不需经过LBs的储存, 直接到达表面活性膜[35]。

2.2 肺表面活性物质的分泌

促进肺表面活性物质分泌主要的生理刺激是吸气时肺泡的机械拉伸, 而机械拉伸会导致细胞质内钙离子浓度升高, 这也是肺表面活性物质分泌所必需的离子信号[36]。Ca^{2+}信号会触发LBs与质膜融合。LBs与质膜融合后, ATP介导细胞外的Ca^{2+}进入融合膜中的离子通道P2X4嘌呤受体通道。融合活化增加的Ca^{2+}导致融合孔扩张, 在融合后阶段, 肌动蛋白和肌动蛋白相关蛋白包裹融合的囊泡。肌动蛋白膜的收缩导致整个囊泡的压缩, 促进肺表面活性物质释放[37]。LBs能够将肺表面活性物质包装成板层体颗粒状的形式释放出来, 并且这些颗粒在与气–液界面或其他表面活性膜接触之前一直保持着高度填充的结构, 其分泌的量是通过一个复杂的过程来高度调控的[38]。肺表面活性物质释放后吸附到气–液界面, 并且迅速沿界面扩散, 形成多层表面活性剂膜。SP-B和SP-C不仅参与吸附和扩散过程, 而且还参与膜的形成和稳定[39-40]。肺表面活性物质一旦被LBs分泌出来, 表面活性剂膜就会展开, 从而使磷脂能够有效地被吸附到气液界面中[29]。

2.3 肺表面活性物质的降解和回收

肺表面活性物质会随着呼吸循环从肺表面活性物质膜或LBs中分离出大团聚体(large aggregate, LA), 小团聚体(small agglomerate, SA)则从代谢产物中分离出来。它们的去向有几种途径, 包括肺泡II型上皮细胞的再内化、肺泡巨噬细胞清除, 还有少部分通过粘膜纤毛向上呼吸道扩散而降解。在肺损伤、炎症和肺泡毛细血管通透性屏障改变的情况下, 一些肺表面活性物质也可能泄漏到血液中[41]。因此, 血液中肺表面活性蛋白的存在可以作为肺损伤和呼吸病理的早期标志物[42]。SP-A不仅能够增加肺表面活性物质的回收率, 而且还能通过与抑制过氧化物酶6直接作用来调节磷脂降解[43]。磷脂的回收和循环利用也受SP-C和SP-D调控, SP-C和SP-D通过对LA到SA结构转换过程的作用, 也参与调节肺表面活性物质的回收。因此, 这些肺表面活性蛋白可能在后天调整动物体内肺表面活性物质稳态的发育过程中起重要作用, 能提高肺表面活性物质的回收率, 也能对特定的环境需求做出反应[23]。巨噬细胞可以清除肺表面活性物质, 对于维持肺表面活性物质的稳态具有重要意义。粒细胞–巨噬细胞集落刺激因子(granulocyte-macrophage colony-stimulating factor, GM-CSF)是负责体内清除肺表面活性物质的信号通路, 能够调节脂质转运蛋白家族中的ABCG1和ABCA1介导的磷脂或胆固醇外排[44]。此外研究发现, 转录调节蛋白(BTB and CNC homolog 2, Bach 2)是巨噬细胞的调节因子, 缺乏这些蛋白会导致肺泡腔内的脂质和蛋白积累[45]。

3 肺表面活性物质相关呼吸道疾病

如前所述, 肺泡内严格调控并且维持肺表面活性物质各成分的量, 对于肺表面活性物质的在气–液界面上的功能实现至关重要。因此, 肺表面活性物质在合成、成熟或降解过程中的突变, 会导致肺部产生复杂的病理情况。表1总结了肺表面活性物质各组分和参与肺表面活性物质合成代谢的重要因子及通路, 它们的功能和与它们的缺失或突变相关的呼吸道疾病。

3.1 新生儿呼吸窘迫综合征

NRDS是一种严重的呼吸道疾病, 主要发生于妊娠少于37周出生的早产婴儿, 也是新生儿重症监护入院的最常见疾病之一。该疾病主要是由于肺器

官发育不成熟, 缺乏肺表面活性物质, 导致肺泡高表面张力, 从而发生肺不张[59]。NRDS是一种致命的综合征, 死亡率超过80%[60]。研究表明, 肺表面活性物质的遗传缺陷会导致NRDS, 主要原因是肺泡中*Sftpb*基因突变引起SP-B不足[47]。*ABCA3*的突变也可能是导致NRDS的遗传因素[61]。参与远端肺形成的转录因子Nkx2.1对于调节合成表面活性蛋白具有重要的作用[62]。*Nkx2.1*的突变在早期发育阶段不会危及生命, 但导致的肺表面活性物质缺陷会对肺泡上皮细胞造成慢性机械应力, 随着时间的推移会导致不同程度的新生儿或儿童间质性肺病。近年来, 外源性肺表面活性物质替代疗法使得新生儿呼吸窘迫综合征的死亡率降低了50%[63]。

3.2 胎粪吸入综合征与急性呼吸窘迫综合征

胎粪吸入综合征(meconium aspiration syndrome, MAS)、急性呼吸窘迫综合征(acute respiratory distress syndrome, ARDS)等呼吸疾病与肺表面活性物质脂质的缺陷有关[58]。MAS是指胎儿吸入被胎粪污染的羊水, 导致气道发生阻塞、肺内炎症和一系列全身性疾病[57,64]。由于胎粪中含有大量的胆固醇、胆汁酸和磷脂酶, 它们会与肺表面活性物质膜相互作用, 使后者功能失调[65]。胎粪主要会导致DPPC等肺表面活性物质磷脂的破碎和表面活性蛋白的裂解, 可以使肺表面活性物质膜直接失活并通过受体刺激启动炎症级联反应, 从而影响肺表面活性物质的性质[66]。ARDS是一种严重的慢性疾病, 50%~70%的患者存在严重的神经肌肉、呼吸和精神功能障碍, ARDS的发生与许多严重的疾病有关, 死亡率高达40%[67-68]。肺泡II型上皮细胞与巨噬细胞中的肺表面活性物质磷脂由分泌磷脂酶A2(secretory phospholipase A2, sPLA2)水解。研究表明, 在ARDS期间, 人肺中的sPLA2含量增高会导致肺表面活性物质磷脂PC和PG含量显著下调, sPLA2的含量与肺表面活性物质失衡有关[69-70]。有研究表明, SP-B和SP-A对于ARDS患者中sPLA2介导的PC和PG水解具有保护作用[71]。因此, ARDS中SP-B和SP-A的缺失会加剧肺表面活性物质的损伤[72]。

3.3 特发性肺纤维化

特发性肺纤维化(idiopathic pulmonary fibrosis, IPF)是最常见和最严重的特发性间质性肺炎, 患者大多数会发展为呼吸衰竭[73-75]。肺纤维化是一种十分复杂的疾病, 主要是由于细胞外基质的沉积和肌成纤维细胞的迁移和活化, 已有研究提出, 肺表面活性物质功能障碍是触发和促进纤维化发生的原因之一[76-77]。在肺纤维化的早期阶段, SP-B和SP-C缺乏导致肺表面活性物质发生功能性障碍, 进一步导致表面张力升高和肺泡塌陷[77]。肺表面活性物质失活引起肺泡塌陷和硬化最终导致肺功能退化, 是人类IPF的重要致病原因[78]。此外, 研究发现, SP-C的错

表1 肺表面活性物质的组分、功能和相关呼吸道疾病

Table 1 Component, function and related respiratory disease of pulmonary surfactant

组分 Component	功能 Function	相关呼吸道疾病 Related respiratory disease	参考文献 Reference
SP-A	Pathogen binding and surfactant homeostasis	Lung infections, ARDS (acute respiratory distress syndrome)	[2,46]
SP-B	Fast interfacial adsorption and interfacial film stability	NRDS (neonatal respiratory distress syndrome), congenital PAP (pulmonary alveolar proteinosis), IPF (idiopathic pulmonary fibrosis)	[47-49]
SP-C	Interfacial film stability	IPF, ILD (interstitial lung disease), congenital PAP	[50-51]
SP-D	Pathogen binding and surfactant homeostasis	Lung infections, COPD (chronic obstruction pulmonary disease)	[3]
ABCA3	Lipid transporter, biogenesis of lamellar bodies	NRDS, ILD, congenital PAP	[52-54]
Nkx2.1	Transcription factor, development of the lung	ILD, congenital PAP[54]	[54-55]
GM-CSF	Responsible for the removal of surfactants	PAP	[56]
Phospholipids/ cholesterol	Maintain alveolar biophysical properties and interfacial film stability	MAS (meconium aspiration syndrome), ARDS	[57-58]

误折叠导致肺表面活性蛋白的异常积累引起内质网应激反应, 这与肺部炎症和特发性肺纤维化有关[79]。

3.4 肺泡蛋白沉积症

肺泡蛋白沉积症(pulmonary alveolar proteinosis, PAP)是一种未知发病机制的慢性肺疾病[80], 其特征表现为肺泡和肺泡巨噬细胞内的脂蛋白物质积累, 引起肺泡和肺末端细支气管中积累过量的肺表面活性物质。PAP包括一系列肺表面活性物质内稳态紊乱, 可分为先天性PAP、原发性PAP与继发性PAP。原发性PAP与GM-CSF信号通路有关, 可进一步分为自身免疫性PAP以及遗传性PAP[81]。自身免疫性PAP是由于体内血清抗GM-CSF的抗体水平升高而导致体内清除肺表面活性物质障碍的, 遗传性PAP是由于GM-CSF受体基因突变引起的[82]; 继发性PAP的发生是由于疾病、环境暴露或药物制剂等因素导致肺泡巨噬细胞的数量减少和功能下降[54]。先天性PAP是由于参与合成肺表面活性物质的基因包括*Sftpb*、*Sftpc*、*ABCA3*或*Nkx2.1*突变引起的[54]。

4 问题与展望

近年来, 对肺表面活性物质的研究不断深入。本文主要综述肺表面活性物质的组成及作用, 合成代谢的研究进展, 其中涉及到与肺表面活性物质相关的疾病。然而仍有一些问题未解决, 例如, 病理状况下肺损伤还会通过别的途径影响肺的生理功能, 而肺表面活性物质的影响有多大仍未确定; 肺泡II型上皮细胞和巨噬细胞是两种完全不同的细胞, 在肺器官中, 它们却具有一个共同的特征: 参与肺表面活性物质的代谢。肺泡II型上皮细胞的合成肺表面活性物质的途径已经有较深入的理解, 但其回收机制还未得到更深入研究, 而肺泡巨噬细胞的降解机制也需要进一步研究。肺表面活性物质在合成代谢的过程中是否严格遵循着某种循环利用和降解的途径, 肺表面活性物质各组分合成需求的量是通过什么途径去调控的, 其降解可能会在肺泡II型上皮细胞和巨噬细胞之间受某种调控机制去控制, 这两种细胞之间潜在的相互关系仍需进一步研究。而本综述在此做简单描述, 希望能激励该领域的研究人员更深入探索, 解决这些问题, 将使人类在未来可通过临床给予外源性肺表面活性物质来恢复肺泡肺表面活性物质的活性, 从而为治疗多种肺疾病提供无限的可能。

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