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·综述·

磷脂酰肌醇3激酶/蛋白激酶B/雷帕霉素靶蛋白信号通路在肺部疾病中的研究进展

杨春兰[1] 综述 戴爱国[2] 审校

(1. 南华大学附属省老年医院呼吸科/湖南省老年医学研究所呼吸疾病研究室，长沙 410016；
2. 湖南省长沙医学院呼吸系统疾病研究所，长沙 410219)

[摘 要] 磷脂酰肌醇3激酶/蛋白激酶B/雷帕霉素靶蛋白(phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin，PI3K/Akt/mTOR)是细胞内重要信号通路，在细胞生长、增殖、分化和蛋白合成等过程中起重要作用。肺癌、哮喘、肺动脉高压、肺纤维化、慢性阻塞性肺疾病(chronic pulmonary obstructive disease，COPD)等疾病是呼吸系统常见疾病，其病理机制涉及细胞增殖及凋亡等，与PI3K/Akt/mTOR信号通路关系密切。

[关键词] 磷脂酰肌醇3激酶/蛋白激酶B/雷帕霉素靶蛋白信号通路；呼吸系统疾病；病理机制

Research progress of phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin signal pathway in pulmonary diseases

YANG Chunlan[1], DAI Aiguo[2]

(1. Department of Respiratory, Hunan Geriatric Hospital Affiliated to University of South China/Hunan Geratic Respiratory Disease Institute, Changsha 410016; 2. Respiratory Disease Institute, Changsha Medical University, Changsha 410219, China)

Abstract Phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) signal pathway is an important intracellular signal pathway, playing pivotal role in cell growth, proliferation, differentiation, DNA synthesis. Pulmonary carcinoma, asthma, pulmonary artery hypertension, pulmonary fibrosis, chronic pulmonary obstructive disease (COPD) are common chronic respiratory diseases, and their patho-mechanisms involve cell proliferation and growth, which have intimate relationship with PI3K/Akt/mTOR.

Keywords PI3K/Akt/mTOR signal pathway; pulmonary disease; pathogenesis

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通信作者 (Corresponding author)：戴爱国，Email: daiaiguo2003@163.com

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磷脂酰肌醇3激酶/蛋白激酶B/雷帕霉素靶蛋白(phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin，PI3K/Akt/mTOR)是细胞体内的经典信号通路，参与细胞增殖、细胞凋亡、细胞自噬等多个环节，影响许多疾病的预后与转归。近年来，PI3K/Akt/mTOR在呼吸系统疾病如肺癌、支气管哮喘、肺动脉高压、肺纤维化、慢性阻塞性肺疾病(chronic pulmonary obstructive disease，COPD)等疾病的研究越来越多，但迄今为止，PI3K/Akt/mTOR信号通路在呼吸系统疾病中的作用尚未有系统的报告，本文就PI3K/Akt/mTOR信号通路在呼吸系统疾病中的研究做一综述。

1 PI3K/Akt/mTOR 信号通路组成及功能

1.1 PI3K/Akt/mTOR 信号通路的组成

PI3K是存在于细胞质的一种能催化磷脂酰肌醇D3位磷酸化的脂类激酶。PI3K家族成员根据其一级结构、调节功能等分为3型，其中研究最广泛的是I型PI3K，由调节亚基p85和催化亚基p110组成。Akt是PI3K下游的关键蛋白之一，是一种进化上高度保守的丝氨酸/苏氨酸蛋白激酶，约由480个氨基酸残基组成[1]。雷帕霉素靶蛋白(mammalian target of rapamycin，mTOR)是存在于胞质中的一种丝/苏氨酸蛋白激酶，属于磷脂酰肌醇3-激酶(PIKK)相关激酶家族。

1.2 PI3K/Akt/mTOR 信号通路的功能

当细胞受生长因子等刺激后，激活PI3K将导致3,4-二磷酸磷脂酰肌醇(PIP2)转化为3,4,5-三磷酸磷脂酰肌醇(PIP3)，募集PDK1和Akt丝氨酸/苏氨酸激酶，活化Akt，激活其下游诸多靶位点，包括mTOR，诱导p70S6K磷酸化S6核糖体，诱导细胞增殖与内皮细胞分化[2-4]，抑制细胞凋亡[5]，促进上皮细胞间质转化[6-7]，诱导新生血管形成[8-9]，参与许多疾病的病理过程，影响预后与转归。

2 PI3K/Akt/mTOR信号通路与肺部常见疾病的关系

2.1 PI3K/Akt/mTOR 与肺癌

2.1.1 PI3K/Akt/mTOR 与肺癌的浸润与转移

上皮–间质细胞转化是肿瘤发生远处转移的关键起始步骤，包括癌症细胞的运动、侵袭和迁移[10]。PI3K/Akt通路的激活是调节上皮间质细胞转化的关键信号通路，与肿瘤的浸润与转移关系密切[11]。Baek等[12]证实：银杏酚酸通过抑制PI3K/Akt/mTOR信号通路，阻遏TGF-β_1诱导的上皮间质转化，抑制肺癌浸润和转移。抑制PI3K表达和Akt磷酸化，NCI-H1650和A549细胞的侵袭性明显降低[13]。Chen等[14]发现：抑制Akt，p-Akt，mTOR和p-mTOR蛋白水平，对铂类化疗药物抵抗的A549细胞上皮间质细胞转化降低。

2.1.2 PI3K/Akt/mTOR 与肺癌细胞的增殖和迁移

PI3K/Akt/mTOR参与小细胞肺癌细胞的增殖、存活和迁移[15]。Umemura等[16]从基因层面分析了PI3K/Akt/mTOR信号通路在小细胞肺癌中促细胞增殖的作用。用比较基因分析法发现36%的小细胞肺癌患者中PI3K/Akt/mTOR通路基因有改变，与抽烟、性别、年龄没有关系，而PI3K/Akt/mTOR抑制剂能显著抑制小细胞肺癌细胞增殖。Wang等[17]证实：Stellettin B呈剂量依赖方式减少Akt，mTOR，p70S6K磷酸化水平，减少周期素D1表达和pRB磷酸化水平，增加周期素依赖激酶抑制酶p27表达，诱导细胞停滞于细胞周期G_1期，抑制A549细胞增殖，促进细胞凋亡。Yu等[18]证实：磷脂酰乙醇胺结合蛋白4(PEBP4)显著升高p-Akt，p-mTOR，促进HCC827型肺癌细胞增殖和迁移，PI3K抑制剂则可抑制PEBP4诱导的Akt，mTOR磷酸化，减少细胞增殖和迁移。Zhang等[19]发现：上调p-Akt，p-mTOR可增加A549细胞活性，促进细胞增殖，抑制p-Akt，p-mTOR，A549细胞活性和增殖亦可减少。研究[20]表明：过表达Period2通过抑制PI3K/Akt/mTOR通路，促进A549细胞凋亡，抑制细胞增殖。

2.1.3 PI3K/Akt/mTOR 与肺癌的自噬

百花丹素抑制PI3K/Akt/mTOR信号，诱导A549和H23细胞发生自噬，抑制细胞增殖[21]。Zhao等[22]发现：桔梗皂苷-*D*呈时间和剂量依赖性减少磷酸化Akt和mTOR表达，诱导A549细胞发生自噬，提示PI3K/Akt/mTOR信号通路参与非小细胞肺癌自噬，影响癌症细胞的增殖。麦冬提取物黄酮类和甾体皂苷通过抑制PI3K/Akt/mTOR通路，增加自噬标志物如LC3-II的生成，促进A549细胞的自噬[23]。此外，内质网应激通过抑制PI3K/Akt/mTOR的磷酸化，促进人小细胞肺癌细胞NCI-H446和H69细胞的自噬及凋亡，逆转细胞对化疗药物的抗药性[24]。

2.2 PI3K/Akt/mTOR 与支气管哮喘

2.2.1 PI3K/Akt/mTOR 与哮喘的气道重塑

Su等[25]发现：抑制p-PI3K和p-Akt表达，可以抑制哮喘小鼠的新生血管形成和血管重塑，减轻

哮喘症状。PI3K/Akt信号通路参与IL-25诱导的人气道平滑肌细胞血管生成[26]。胞浆素诱导人气道平滑肌细胞Akt磷酸化水平升高，促进气道平滑肌细胞增殖；抑制PI3K/Akt，可以减轻由胞浆素诱导的这一反应[27]。Ge等[28]证实：在人气道上皮细胞中，香叶木素可以减少PI3K/Akt信号通路磷酸化，从而减轻TGF-β_1诱导的人气道上皮-间质细胞转化，改善气道重塑。Wang等[29]发现：FIZZ1重组蛋白上调小鼠肺上皮细胞中Akt磷酸化，促进α-SMA和I型胶原纤维表达，抑制FIZZ1引起 p-Akt降低，α-SMA和I型胶原纤维表达量减少。从气道滴注PI3K和Akt抑制剂可下调α-SMA、I型胶原纤维、纤连蛋白-1，上调E型黏附素。作为FIZZ1的功能同源物，RELM-β同样通过PI3K/Akt信号通路促进哮喘的人肺上皮细胞增殖和生长因子的释放，从而促进气道重塑[30]。Singh等[31]证实：PI3K/Akt信号通路还参与了高胰岛素血症诱导的人原代气道平滑肌细胞增殖与胶原蛋白的释放，从而参与哮喘的气道重塑。

2.2.2 PI3K/Akt 与支气管上皮细胞的凋亡

PI3K/Akt的活化形式能抑制哮喘支气管上皮细胞的凋亡。胰岛素可上调PI3K/Akt和ERK通路活性，调节非依赖蛋白质合成机制，从而抑制聚肌胞诱导的人支气管上皮细胞凋亡[32]。

2.2.3 PI3K/Akt 与哮喘炎症

Lin等[33]发现：在小鼠哮喘模型转导间充质干细胞后，卵清蛋白诱导的PI3K/Akt通路磷酸化程度有所降低，其炎症浸润随之降低。由此推测，卵清蛋白可能通过间充质干细胞抑制PI3K/Akt激活，抑制哮喘的炎症反应。Choi等[34]证实：用LY294002和雷帕霉素抑制PI3K和mTOR，卵清蛋白诱导的小鼠哮喘模型的肺泡灌洗液中IL-4，IL-5，IL-13，TNF-α和IL-β等促炎因子含量增加，且嗜酸性粒细胞含量明显减少，同时减少卵清蛋白诱导的IgE表达，减轻气道高反应性，减少周围支气管和周围血管炎症细胞浸润和气道黏液分泌。

2.3 PI3K/Akt/mTOR 与肺动脉高压

2.3.1 PI3K/Akt/mTOR 与平滑肌细胞增殖

肺动脉平滑肌细胞增殖是肺动脉高压的主要病理特征。PI3K/Akt/mTOR信号通路参与肺动脉高压平滑肌细胞增殖[35-38]。Teng等[35]证实：在小鼠慢性低氧性肺动脉高压模型中，用^{3}H-胸苷渗入法发现低氧诱导促有丝分裂因子(hypoxia induced mitogenic factor，HIMF)强烈刺激Akt磷酸化，促进肺动脉平滑肌细胞增殖；PI3K抑制剂LY294002则抑制HIMF激活Akt的磷酸化，抑制小鼠肺微血管平滑肌细胞增殖。Zhang等[36]发现：线粒体融合蛋白2可增加Akt活性，诱导低氧性肺动脉高压大鼠肺动脉平滑肌细胞从G_0/G_1期进入S和G_2/M期，启动细胞周期，促进细胞增殖。在低氧性肺动脉高压大鼠模型中，PI3K/Akt/mTOR磷酸化水平随着低氧时间延长而逐渐增加，肺血管重塑越明显[37]。Xie等[38]发现野百合碱可诱导大鼠Akt磷酸化增加，促进大鼠肺动脉平滑肌细胞增殖。Aghamohammadzadeh等[39]发现醛固酮也可诱导Akt/mTOR信号通路激活，促进p70S6K表达增加，诱导人肺动脉平滑肌细胞增殖，促进细胞存活，抑制其凋亡。此外，PI3K/Akt也参与野百合碱诱导的肺动脉高压的肺血管重塑[40]。

2.3.2 PI3K/Akt/mTOR 与肺动脉平滑肌细胞凋亡

肺动脉平滑肌细胞凋亡减少也是肺动脉高压的一个发病环节。TGF-β1通过激活PI3K/Akt，抑制肺动脉平滑肌细胞凋亡，从而促进肺部血管中层增厚，参与低氧性肺动脉高压[41-42]。

2.4 PI3K/Akt/mTOR 与肺纤维化

2.4.1 PI3K/Akt/mTOR 与肺纤维化的自噬

Chitra等[43]研究发现：博莱霉素激活PI3K/Akt/mTOR，导致Wistar大鼠肺纤维化模型中纤连蛋白、I型和III型胶原蛋白以及α-SMA表达增加，自噬标志物Beclin-1和LC3表达显著下降；黄连素则减少博来霉素诱导的PI3K，Akt和mTOR磷酸化，促进自噬水平，改善肺纤维化。PI3K/Akt参与了博莱霉素诱导体内、体外人肺纤维细胞的纤维化[44-45]。在特发性肺纤维化患者中，肺组织及肺泡灌洗液Akt磷酸化水平增加，活体培养的特发性肺纤维化细胞中Akt磷酸化水平显著升高，而PI3K/mTOR抑制剂GSK2126458则呈浓度依赖性抑制特发性肺纤维化中p-Akt，下调特发性肺纤维化肺组织胶原蛋白。这些研究提示：PI3K/Akt/mTOR可促进肺组织胶原蛋白合成，抑制细胞自噬，促进特发性肺纤维化发生。

2.4.2 PI3K/Akt/mTOR 与上皮细胞的增殖

博莱霉素激活PI3K/Akt/mTOR，促进上皮细胞的转化，维持上皮细胞增殖，从而导致肺纤维化[46]。Kulkarni等[47]证实VEGF抑制剂可下调博来霉素诱导的mTOR，减轻肺纤维化。

2.5 PI3K/Akt/mTOR 与 COPD

2.5.1 PI3K/Akt/mTOR 与 COPD 炎症

Numata等[32]证实：胰岛素促进PI3K/Akt激

活，抑制TLR3诱导的人支气管上皮细胞凋亡，减轻COPD气道炎症，提示PI3K/Akt通过参与抗凋亡而减轻COPD炎症。然而，Mortaz等[48]证实：香烟烟雾提取物通过抑制人浆细胞样树突状细胞(plasmacytoid dendritic cells，pDC)PI3K/Akt磷酸化，减少TLR9配体诱导的TNF-α，IL-6和IFN-α表达，从而减少COPD的炎症损伤。

2.5.2 PI3K/Akt/mTOR 与 COPD 纤维化

香烟烟雾提取物诱导PI3K/Akt磷酸化增加，促进人气道上皮细胞上皮间质转化，促进COPD患者小气道纤维化[49]，进一步加剧COPD患者气促情况；抑制PI3K/Akt则减少香烟烟雾诱导的上皮间质转化，减轻COPD肺部纤维化[50]。此外，在大鼠COPD引起的骨骼肌萎缩中，可能通过激活PI3K/Akt/mTOR信号起到代偿性作用[51]，促进骨骼肌细胞的生成。

2.6 PI3K/Akt/mTOR 与肺部其他疾病

PI3K/Akt/mTOR信号通路与肺部炎症、肺部损伤等也有密切关系。研究[52]显示：脂多糖(lipopolysaccharide，LPS)诱导的BALB/c小鼠急性肺部炎症中，p-PI3K，p-Akt和p-mTOR表达增高，提示PI3K/Akt/mTOR可能介导急性肺部炎症。然而，Li等[53]发现：上调肺泡II型上皮细胞(AT-II)中Akt，p-Akt，mTOR和p-mTOR可以减轻炎症因子如TNF-α和IL-6诱导的肺泡II型细胞损伤损伤，提示PI3K/Akt/mTOR信号通路参与抗炎症效应，减少肺部损伤。

3 结语

PI3K/Akt/mTOR信号通路作为细胞内经典的信号转导通路之一，通过其活化或者抑制作用，影响细胞增殖、迁移、上皮–间质细胞转化、细胞凋亡、细胞自噬、细胞炎症等，在肺癌、哮喘、肺动脉高压、肺纤维化、COPD等疾病中扮演着重要的角色，影响其发展与转归。尽管PI3K/Akt/mTOR信号在肺部疾病中的认识越来越清晰，但是迄今为止，尚未有相关抑制剂治疗肺部疾病的报道。因为PI3K/Akt/mTOR不仅是经典的病理信号通路，还参与着正常的机体生理功能，生理状态与病理状态的区别迄今尚未报道。能否找到病理状态与生理状态下的不同点，对阐述疾病的病理生理可能有至关重要的作用，且可能会成为今后的主要研究方向。

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