支气管肺发育不良发生机制中肺泡上皮细胞转分化关键信号通路的研究进展

张梦玥[1] 周建国[1,2△]

([1]国家儿童医学中心/复旦大学附属儿科医院新生儿科 上海 201102;
[2]复旦大学附属儿科医院安徽分院/安徽省儿童医院新生儿科 合肥 230022)

【摘要】 支气管肺发育不良(bronchopulmonary dysplasia,BPD)是早产儿严重呼吸系统并发症,重症病例仍缺乏有效治疗手段。BPD是多因素疾病,发病机制主要包括肺泡简单化和肺微血管发育障碍。肺泡上皮细胞是肺泡的主要构成部分,包括肺泡Ⅰ型(alveolar type 1,AT1)和肺泡Ⅱ型(alveolar type 2,AT2)细胞,其中AT1细胞参与气血屏障构建,发挥气体交换作用,AT2细胞具有增殖分化的干细胞特性,维持肺内环境稳态、修复肺损伤。肺损伤修复的核心是AT2细胞向AT1细胞的转分化,而激活转分化的信号转导机制尚未明确。本文通过文献检索和分类总结,探讨肺泡上皮细胞转分化的关键信号转导通路及研究进展,为阐述BPD发病机制及探索BPD新的治疗方案提供参考。

【关键词】 肺泡上皮细胞; 转分化; 信号通路; 支气管肺发育不良(BPD)
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Research progress on key signaling pathways of alveolar epithelial cell transdifferentiation in the pathogenesis of bronchopulmonary dysplasia

ZHANG Meng-yue[1], ZHOU Jian-guo[1,2△]

([1]*Department of Neonatology, Children's Hospital, Fudan University/National Children's Medical Center, Shanghai* 201102, *China*; [2]*Department of Neonatology, Anhui Provincial Children's Hospital/Anhui Affiliated Children's Hospital of Fudan University, Hefei* 230022, *Anhui Province*, *China*)

【Abstract】 Bronchopulmonary dysplasia (BPD) is a detrimental respiratory complication associated with prematurity that still lacks effective treatment. BPD is a multifactorial disease with a pathogenesis involving alveolar simplification and impaired vascularization. Alveolar epithelial cells are the main components of alveoli including alveolar type Ⅰ (AT1) and alveolar type Ⅱ (AT2) epithelial cells. AT1 cells are involved in constructing the air-blood barrier and facilitating gas exchange, while AT2 cells, characterized by proliferative and differentiated stem cell properties, maintain lung homeostasis and contribute to lung injury. The transdifferentiation of AT2 cells into AT1 cells is a core mechanism in the repair of lung injuries, although the key signaling pathway activating transdifferentiation remains unclear. This article introduces the key signaling pathways and research progress in alveolar epithelial cell transdifferentiation through literature retrieval and classification summary, providing a foundation for elucidating the pathogenesis of BPD and exploring new therapeutic regimens for BPD.

【Key words】 alveolar epithelial cells; transdifferentiation; signaling pathway; bronchopulmonary

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△Corresponding author E-mail:joezhou@fudan.edu.cn

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dysplasia (BPD)

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肺具有强大的再生和修复功能。肺泡上皮细胞是肺实质主要组成部分,分为肺泡Ⅰ型(alveolar type 1, AT1)细胞和肺泡Ⅱ型(alveolar type 2, AT2)细胞。AT1细胞又称鳞状肺泡上皮细胞和小肺泡细胞,占肺泡总表面积的95%以上,是气血屏障的主要组成部分,参与气体交换[1]。AT2细胞具有增殖和分化功能,参与肺泡形成及损伤后修复,修复过程由具有干细胞性的AT2细胞转分化为AT1细胞,因此转分化障碍将会导致不良后果[2-4]。研究表明肺泡上皮细胞转分化障碍与支气管肺发育不良(bronchopulmonary dysplasia, BPD)[5]、慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)[6]、特发性肺纤维化(idiopathic pulmonary fibrosis, IPF)[7]等多种呼吸系统疾病密切相关。其中BPD是早产儿重要并发症,也是当前新生儿诊疗的难点问题,其发病机制、治疗策略亟待进一步深入研究。虽然肺泡上皮细胞转分化障碍及相关信号通路在BPD的研究中一直是热门问题,但缺乏BPD发生机制中AT2细胞转分化为AT1细胞的关键信号通路的综述。本文重点聚焦BPD转分化过程的关键信号通路,以期为进一步阐述BPD发病机制、探索BPD新的治疗方案提供理论基础。

肺泡化障碍在BPD发生发展中的作用 肺泡化是肺泡形成过程。孕晚期胎儿肺发育,肺泡数量增加,肺泡体积减小,肺中隔形成。BPD是早产儿慢性呼吸系统疾病,由多种因素共同作用导致。BPD的发生发展主要原因包括肺发育障碍[8]、机械通气[9]、围产期感染[10]、氧化应激反应[11]、遗传易感性[12]等。肺泡化障碍和肺微血管发育不良是BPD的主要病理表现。Coalson等[13]基于新生儿大样本BPD病例的肺组织病理学多中心回顾性研究显示,BPD病例常见的肺部病理学特征包括肺泡数量减少、体积增大、结构简单化、毛细血管畸形、肺泡壁毛细血管纤维化等。Rößler等[14]通过研究高氧环境下兔肺肺泡和微血管变化,发现高氧损伤对肺泡化有十分显著的抑制作用。诸多研究[15-16]证实多种损伤因素作用导致的肺泡化障碍是BPD发生发展的关键机制。

肺泡上皮细胞转分化在BPD发病机制和肺损伤修复中的作用 BPD发病机制复杂,高氧暴露肺损伤是BPD常用的动物模型。Sun等[17]通过构建高氧新生大鼠模型发现,肺损伤后AT2细胞转分化为AT1细胞的活动增强,AT2细胞具有修复小鼠肺损伤和刺激肺血管发育作用。但AT2细胞只占肺泡上皮细胞的16%,肺泡总面积的5%,维持肺正常气体交换过程的肺泡上皮细胞的95%由AT1细胞构成。在肺损伤发生后,AT1细胞数目减少,为维持肺正常生理学功能,AT2细胞发挥干细胞性增殖作用[2-4],分化为AT1细胞,修复肺组织结构和功能[18]。但肺泡上皮细胞转分化的机制仍未明确,因此探讨肺泡上皮细胞转分化的关键信号通路,对于揭示BPD发病机制、探索BPD治疗新方案具有重要意义。

肺泡上皮细胞转分化的关键信号通路

FGF信号通路 Brownfield等[19]通过对小鼠肺泡上皮细胞单细胞RNA测序分析、标记表达、谱系追踪和克隆分析,首次阐述了成纤维细胞生长因子(fibroblast growth factor, FGF)信号通路在肺泡祖细胞分化及维持AT2细胞形态结构中发挥关键作用。AT1细胞和AT2细胞是由一个共同的芽尖祖细胞(bud tip progenitors, BTPs)分化而来[20]。发育过程中的BTPs和新生AT2细胞持续表达Fgfr2受体[21]。此外,在肺泡分化过程中,Fgfr2的配体Fgf7和Fgf10在周围间充质中高表达[22]。调节FGF信号通路可以促进肺泡细胞增殖、分化,改善肺功能。Bellusci等[23]的研究显示,将Fgf10加入小鼠胚胎肺中,远端间充质中的Fgf10可诱导肺内胚层扩张、出芽,进而促进小鼠胚胎肺发育。

TGFβ和BMP信号通路 利用人肺移植体和体外培养的类器官模型,Frum研究团队发现转化生长因子β(transforming growth factor β, TGFβ)信号通路和骨形态发生蛋白(bone morphogenetic protein, BMP)信号通路在AT2细胞分化中发挥相反的作用[24-25]。在BTPs和RSPO2-阳性间充质细胞之间,表现为抑制TGFβ信号通路可以促进BTPs向AT2细胞分化,而激活BMP信号通路则抑制BTPs向AT2细胞分化。除了以上研究结果,Frum研究团队[26]还发现了在高Wnt环境下,抑制

TGFβ和激活BMP信号,可观察到体外培养的人肺组织BTPs大量分化成AT2细胞,并分泌AT2细胞板层体。该团队的研究为理解人类肺发育过程中AT2细胞转分化机制提供了新思路。

此外,TGFβ与BMP信号通路还是介导药物修复肺损伤和促进肺发育的重要信号通路。如倍他米松、地塞米松等糖皮质激素促进胚胎肺发育的药理机制研究[27-28],发现激素通过抑制肺的TGFβ信号通路,促进BTPs分化为AT2细胞,修复肺损伤、刺激胎肺发育。Kobayashi等[29]的IPF机制研究,也发现TGFβ和BMP信号通路会导致AT2细胞转分化异常与基底细胞错位。

Wnt信号通路与IGF-1 Nabhan等[30]通过对肺成纤维细胞的单细胞RNA测序、小鼠动物实验、单分子荧光原位杂交,发现Wnt信号通路通过抑制BTPs向AT1细胞分化来维持AT2细胞的干细胞性。大量研究已证实,Wnt信号通路参与细胞增殖、分化和凋亡。而胰岛素样生长因子-1(insulin-like growth factors-1,IGF-1)在肺泡细胞的分化和修复中也起关键作用[31],但IGF-1影响转分化的机制尚不明确。有研究[32]显示IGF-1可以直接通过促进AT2细胞增殖和分化,介导肺泡细胞修复和再生。另一些研究[33]则认为抑制Wnt信号通路是IGF-1影响AT2细胞分化的重要信号通路。Wnt5a是Wnt家族的一员,本课题组[34]前期通过建立高氧诱导的大鼠BPD模型并运用单细胞测序技术,在AT2细胞转分化过程Wnt5a信号通路作用的研究中得出以下结论:Wnt5a的mRNA和蛋白质是AT2转分化的关键因子,具体表现为间充质干细胞来源的细胞外囊泡通过Wnt5a信号通路,抑制AT2细胞转分化为AT1细胞。

Hippo-YAP信号通路 Hippo-YAP是一种十分稳定的信号通路,对肺组织发育和肺泡干细胞的行为具有重要调控作用,在肺泡上皮细胞的增殖和分化中扮演重要角色[35]。具体表现为YAP蛋白维持肺泡上皮细胞内环境稳态、Hippo信号通路通过控制肺泡干细胞活性限制肺器官大小[36]。通过研究调控肺泡再生的机制,Digiovanni等[37]应用机械张力诱导Hippo信号相关蛋白YAP蛋白激活,促进小鼠肺泡再生。Hippo-YAP信号通路是近年来肺发育和疾病研究的热点。如Mahoney等[38]通过研究胎儿肺泡上皮细胞发育过程,发现倘若缺失YAP蛋白,Sox2的水平和分布将会无法控制,上皮祖细胞也无法正确响应局部TGFβ信号通路的调控,最终导致肺发育不良和肺囊性纤维化;并且提示YAP蛋白在肺组织形成的早期阶段具有显著影响Sox2的表达与分化以及调节肺泡上皮细胞的作用。

Hedgehog信号通路 Hedgehog信号通路与多种肺部疾病的发生和发展密切相关。例如BPD导致肺损伤时,AT2细胞转分化为AT1细胞的启动须通过旁分泌的方式激活Hedgehog信号通路[39]。在IPF发生的过程中,Hedgehog信号通路影响肺成纤维细胞增殖、凋亡、迁移、胶原和纤维蛋白生成以及AT2细胞转分化的过程[40]。Peng等[41]通过特异性删除成年小鼠肺脏中*Shh*基因,靶向抑制Hedgehog信号通路后发现相邻肺间质细胞增殖扩张,而AT2细胞转分化被抑制,提示Hedgehog信号通路在通过维持小鼠远端气道的上皮和间质稳态方面具有重要作用。Hedgehog信号通路还具有促进AT2细胞转分化的作用[42],发挥促进胎儿肺形成、维持肺内环境稳态和促进肺再生的功能。Ingham等[43]对Hedgehog信号通路作用的分子机制研究显示,Hedgehog蛋白与Patched 1受体结合,激活Smoothened蛋白,进而引起下游信号转导。

Notch信号通路 Notch信号通路主要通过4个Notch受体(Notch1~Notch4)和5个配体(Jag1、Jag2、Dll1、Dll3和Dll4)发挥作用[44]。Notch信号通路在AT2细胞转分化与肺部疾病的发生发展中扮演重要角色,遗传和单细胞RNA测序数据显示,Notch信号转导在IPF蜂窝状囊性病变中表现活跃[45]。Notch信号通路调节肺泡上皮细胞转分化、维持胎儿肺泡和远端细支气管发育和稳态[46]。而Wozniak等[47]通过整理成人BPD病例预后情况,总结出Notch信号通路和远端气道形态发育不良与早产儿BPD有关。肺损伤后肺泡和小气道的异常修复也会导致成人COPD的发生[48]。通过单细胞测序、谱系追踪研究、建立各种肺损伤和小鼠3D类器官模型,Kopan等[49]发现Notch信号通路在肺发育过程中可以影响肺泡和气道上皮细胞、促进肺泡干细胞的分化及肺损伤后修复。

关键信号转导通路之间的相互作用 通过单细胞测序技术可以发现关键信号通路在不同的细胞类型中呈现不同的组合表达,并以多对混杂的方式与相应配体及下游蛋白相互作用[50]。研究[51]表

明BMP信号通路通过促进Smad1-Dvl1复合物形成来抑制Wnt信号通路的活性。Notch信号通路可以增强Wnt经典途径β-catenin及其下游的基因表达[52]。FGF信号通路通过灭活GSK-3β来上调Wnt经典途径β-catenin的表达,Wnt信号通路反过来刺激FGF23启动子的活性[53]。现有研究中BPD发病机制涉及的信号通路众多,信号通路相互作用的方式有待进一步研究,准确阐明关键信号通路的相互作用网络,有助于我们发现治疗BPD的潜在靶点。

结语 支气管肺发育不良作为早产儿重症呼吸系统并发症,主要表现为肺泡化障碍和肺泡简单化,肺泡上皮细胞转分化在肺泡形成及肺损伤修复过程中发挥关键作用,但肺泡上皮细胞转分化的分子机制复杂,涉及信号通路繁多。随着技术的发展,更加精细的单细胞测序技术、建立类器官模型、人工智能、组学分析等已经被运用在肺癌的研究中,并取得了一定的成果。但在BPD领域尚未有此类报道,未来可以结合新技术深入研究参与肺泡AT2细胞转分化的的信号通路,探索信号通路下游关键分子,寻求BPD治疗新策略。

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