

DOI: 10.13376/j.cblls/2021346

文章编号: 1004-0374(2021)04-0527-07

肺干/祖细胞代谢与呼吸系统疾病研究进展

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摘要: 呼吸系统疾病的全球死亡率居高不下, 多种疾病至今仍缺乏根治手段。其中, 肺癌、哮喘、特发性肺纤维化和慢性阻塞性肺疾病等难治性疾病都与肺干/祖细胞的调节和功能异常密切相关。在呼吸系统中, 不同区域分布着不同类型的肺干/祖细胞。肺干/祖细胞具有自我更新、增殖与分化功能, 肺部的损伤修复离不开肺干/祖细胞的这些功能。因此, 负责肺脏再生的肺干/祖细胞受到越来越多的关注。研究表明, 肺干/祖细胞的功能与糖酵解、脂质合成、磷酸戊糖途径、氨基酸代谢和氧化磷酸化等主要代谢途径密切相关, 其代谢发生改变可能与肺脏衰老和多种呼吸系统疾病有关。该文对正常、衰老和疾病状态下的肺干/祖细胞的代谢调控进行了综述。

关键词: 肺干/祖细胞; 代谢调控; 肺癌; 哮喘; 肺纤维化; 慢性阻塞性肺疾病

中图分类号: Q251; R714; R734

文献标志码: A

Metabolic regulation of lung stem/progenitor cells and respiratory diseases

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Abstract: The global mortality rate of respiratory diseases remains high. Among them, refractory diseases such as lung cancer, asthma, idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease are all closely related to the altered regulation and functional abnormalities of lung stem/progenitor cells. Lung stem/progenitor cells are region-specific and exhibit the ability to self-renew, proliferate and differentiate, contributing to the repair of epithelium after lung injury. Therefore, lung stem/progenitor cells have attracted more and more attention. Previous studies have shown that the fate and the function of lung stem/progenitor cells are regulated by metabolic pathways including glycolysis, lipid synthesis, pentose phosphate pathway, amino acid metabolism, oxidative phosphorylation and other major metabolic pathways. In addition, there are many links between metabolic pathways and functions of lung stem/progenitor cells. Metabolic alteration in lung stem/progenitor cells may be related to lung aging and diseases. This article reviews the metabolic regulation of lung stem/progenitor cells under normal, aging and disease states.

Key words: lung stem/progenitor cells; metabolic regulation; lung cancer; asthma; pulmonary fibrosis; chronic obstructive pulmonary disease

干细胞是一类具有自我复制和多向分化能力的细胞, 可增殖分化进而代替因疾病或损伤而丢失的成熟细胞^[1]。干细胞具有自我更新能力, 可对称分裂或者不对称分裂, 至少产生一个保留干细胞特性的子细胞。干细胞在彻底分化前, 能转化成某种中间细胞, 这种中间细胞被称作祖细胞(progenitor cell), 其分化更具明确性。肺干/祖细胞具有组织特

异性, 保留了分化和自我更新的能力。肺损伤后的组织修复和疾病恢复需要干/祖细胞的增殖分化和

收稿日期: 2020-10-06; 修回日期: 2020-11-01

基金项目: 国家自然科学基金项目(81773394, 81970001, 82070001)

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自我更新,这一过程与细胞功能的转变和能量的重新分配相关^[2]。物质代谢显著影响细胞功能和能量供应,受与干/祖细胞增殖和分化相关的信号调控,代谢途径和活性在不同的肺脏干/祖细胞类型中有所不同,并且也随着细胞生长分化而变化。肺脏上皮干/祖细胞主要包括:基底细胞(basal cells, BCs)、Club细胞(以前称为Clara细胞)、vClub细胞、神经内分泌细胞(pulmonary neuroendocrine cells, PNECs)、支气管肺泡干细胞(bronchioalveolar stem cells, BASCs)、谱系阴性肺上皮祖细胞(lineage-negative epithelial progenitors, LNEP)和II型肺泡细胞(type 2 alveolar cells, AT2)^[3-6]。解析肺脏干/祖细胞的代谢调控网络有助于揭示呼吸系统疾病发生发展的机制。

1 代谢调控肺干/祖细胞功能

营养物质代谢是维持细胞生存和正常功能的能量来源。细胞代谢途径包括:糖酵解、磷酸戊糖途径、脂质合成和氨基酸代谢等。糖酵解在增强生物合成以满足细胞增殖需求方面的功能已获得广泛的证据支持^[7]。磷酸戊糖途径可减少氧化应激和活性氧(reactive oxygen species, ROS)生成^[8]。线粒体丙酮酸载体缺失或抑制会减少糖的氧化作用,干扰干细胞稳态,但会促进干细胞增殖^[9]。多不饱和脂肪酸及其代谢产物(如前列腺素)是影响干细胞增殖分化和自我更新的内源性因素之一。

面对环境的侵扰和自身的衰退,个体存活需要一种维持组织功能完整性的机制,这一机制称为再生。许多组织,如血液和上皮,受损时可以大量再生,这一过程被称为损伤诱导再生。肺上皮在正常情况下更新很慢,然而,它有多个具有高度可塑性的干/祖细胞群,在急性肺损伤后可发挥修复损伤的强大功能^[10]。肺脏的代谢变化可影响肺脏干/祖细胞功能。

利用类器官模型进一步研究发现,AT2的细胞增殖功能与糖酵解途径成正相关,与脂代谢途径成负相关^[11]。糖皮质激素具有促进糖酵解和抑制脂肪合成的作用。在糖皮质激素受体缺失的小鼠胎肺中,Cole等^[12]使用电镜观察到AT2细胞的比例增加约30%,而AT1的比例下降约50%,提示AT2向AT1分化需要糖皮质激素信号,但是其下游代谢通路有待揭示。AT2细胞还具有表面活性物质分泌功能,降低表面张力以防止肺泡在呼气时塌陷,这一重要过程需要丙酮酸和柠檬酸的参与^[13]。表面活性剂磷

脂在肺中的周转率非常高,因此即使在代谢不利的条件下(如饥饿),也必须继续产生脂质^[14]。在AMP(adenosine monophosphate)/ATP(adenosine triphosphate)比值升高时,脂肪酸合成是不可行的^[14]。高水平的5'-腺苷单磷酸激活蛋白激酶(adenosine 5'-monophosphate-activated protein kinase, AMPK)使AT2细胞快速感知ATP水平的下降,通过低耗能的途径产生表面活性物质^[15]。这是AT2细胞控制表面活性物质生成的机制。

在气道部位,本课题组研究发现,vClub和Club两种气道上皮细胞的增殖分化均受到糖酵解的双向调控,适当水平的葡萄糖促进vClub和Club细胞的增殖,抑制其向纤毛细胞和杯状细胞分化;葡萄糖耗竭时,Club细胞向纤毛细胞和杯状细胞分化加快^[16]。Club祖细胞存活需要还原性环境,N-乙酰半胱氨酸(N-acetylcysteine, NAC)具有抗氧化作用,可通过增加Club细胞分泌蛋白的合成和分泌,减少香烟烟雾诱导的氧化反应对Club细胞的损伤作用^[17]。

2 代谢与肺干细胞衰老

与静止状态细胞相比,衰老细胞具有高代谢活性。研究表明,衰老细胞的糖酵解增加。细胞衰老时,丙酮酸代谢方向是决定糖酵解能否产生足够能量的关键。苹果酸与许多氧化还原反应有关,其缺乏会导致细胞衰老^[18]。此外,包括乙酰辅酶A在内的多种关键代谢物在衰老过程中均有所增加^[19]。在氧化磷酸化过程中,少量电子过早地还原氧气会形成ROS,引起氧化应激反应,加快细胞衰老^[20]。细胞可以通过糖的有氧氧化和磷酸戊糖途径减少ROS^[21]。AMPK作为一种生物能量感受器,其激活可导致细胞周期停滞,最终导致衰老。细胞自噬可显著影响干细胞的衰老,因为它在联系新陈代谢与表观遗传变化的过程中发挥了重要作用^[19]。

ROS过量产生可触发肺脏干细胞衰老。研究发现,ROS增加将损害AT2细胞的自我更新能力和增殖功能^[11]。但是,AT2细胞衰老后的分泌功能得到增强^[22]。BCs细胞在高水平ROS环境中发生衰老,同时启动自我反馈机制控制ROS的水平^[23]。Duox1和Duox2是烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate, NADPH)氧化酶家族的成员,在气道上皮细胞中表达并参与H₂O₂的释放^[24]。此外,谷胱甘肽可直接使强氧化性的自由基还原为容易代谢的酸类物质,加速自由基的释放,从

而减轻自由基对肺脏的损害。Chen等^[25]研究发现, 老年小鼠肺中的谷胱甘肽浓度降低了30%。这些研究提示, 与抗氧化相关的代谢活性及其信号通路调控可能与肺干细胞衰老息息相关, 亟待研究证实。

衰老干细胞线粒体会出现氧化损伤和大量突变的迹象。衰老AT2细胞中出现功能失调的线粒体聚集, 其特征是磷酸酶及张力蛋白同源物诱导的蛋白激酶1(PTEN-induced putative kinase 1, PINK1)的低表达^[26]。Yanagi等^[27]研究发现, 线粒体结构和功能障碍与内质网应激标志物蛋白的表达增加也有关。2018年, 有研究发现高脂饮食会对肺脏产生潜在的有害影响, 包括减少线粒体的数量和功能, 增加肺部炎症。高脂饮食产生的这些效应可能与肺泡干细胞老化相关^[28]。

3 肺干细胞代谢与肺癌

肺癌是指起源于肺泡或支气管黏膜上皮的恶性肿瘤, 是世界范围内最常见的致死病因之一。不同肺癌亚型起源于不同类型的肺上皮干细胞。Desai等^[29]证明肺泡干细胞AT2是肺腺癌的起始细胞。Claudins是调节细胞旁通透性和细胞极性的紧密连接蛋白家族。Claudin 18在肺泡上皮中高度表达, Zhou等^[30]证明Claudin 18敲除小鼠AT2细胞增殖加快, Yes相关蛋白(Yes-associated protein, YAP)被激活, 最终导致肺癌发生。AT2细胞和支气管肺泡干细胞肿瘤基因*K-ras*活化都能导致肺腺癌发生^[31]。鳞癌细胞表达多种BCs的特异性标志物, 暗示鳞癌主要发生在BCs富集的气管和支气管部位^[32]。目前, 尚不确定突变导致的环境和细胞变化如何影响肺鳞癌的进展^[32]。小细胞肺癌主要出现在PNECs分布的细支气管部位, 并表达特异性标志物^[33]。约15%的非小细胞肺癌肿瘤表现出神经内分泌特性, 并被认为具有与小细胞肺癌相似的生物学特性^[34]。IL-6激活的STAT3信号通路促进PNECs分化, 而IL-6激活的p38 MAPK信号通路促进PNECs增殖^[34]。这两种途径在非小细胞肺癌的发病机理中都起着至关重要的作用, 为未来的治疗提供了新的分子靶标。

由于肺癌早期诊断的困难以及对基本机制了解不足, 多数患者预后不良。目前, 代谢重塑已被广泛接受为新型肿瘤生物标志物的基础^[35]。在肺癌中, 癌细胞的糖酵解增加促进了细胞增殖, 抑制糖酵解代谢酶的表达可以通过Akt信号通路抑制肺腺癌癌细胞增殖^[36]。胶原XVII-层黏连蛋-332激活的Oct4-己糖激酶2(hexokinase 2, HK2)通路可诱导糖

酵解上调并维持肺癌干细胞的干性^[37]。酪氨酸激酶Fyn相关酶的基因敲除能够显著抑制Warburg效应(抑制葡萄糖摄取以及乙酰辅酶A和乳酸的产生), 损伤非小细胞肺癌癌细胞的干性表达^[38]。磷酸戊糖途径的激活可以诱导大量的NADPH和谷胱甘肽产生, 导致癌细胞的抗凋亡能力增强^[39-40]。此外, 癌细胞中大多数脂肪酸合成的关键酶, 如ATP柠檬酸裂合酶、脂肪酸合成酶和乙酰辅酶A羧化酶等, 都被高度激活, 酶抑制剂可能会抑制癌细胞增殖^[41]。肺癌细胞的生长是谷氨酰胺依赖性的。谷氨酰胺的摄取由肺癌细胞中SLC1A5的转运活性介导, 对该活性的阻断会增加细胞内ROS的释放, 阻碍癌细胞生长^[42]。多种肺癌亚型起源于肺上皮干细胞, 而癌细胞的代谢与肺癌的发生发展关系密切, 可以认为是肺上皮干细胞来源的癌细胞发生了与肺癌相关的代谢异常, 如糖酵解增加、脂肪酸合成增加和磷酸戊糖途径的激活。尽管如此, 肺脏干/祖细胞代谢异常与肺癌发生的直接联系需要进一步证实。

4 肺干细胞代谢与哮喘

哮喘是一种难以治愈的气道疾病, 严重危害人类身体健康, 其特点是气道上皮重塑、杯状细胞增生和炎性细胞浸润等。2014年, 研究发现, 哮喘累及大气道和小气道所有上皮细胞, 其自身修复能力减弱, 产生杯状细胞, 并导致黏液分泌增多^[43]。

哮喘患者气道黏液中葡萄糖水平增高。葡萄糖进入细胞后, 可通过磷酸戊糖途径参与核酸合成以满足细胞增殖的需要。葡萄糖的摄取与细胞自噬水平有关。李敏敏^[44]研究发现, 哮喘过程中vClub细胞自噬功能的减弱破坏了细胞对葡萄糖的摄取, vClub和Club细胞摄糖能力丧失, 导致其增殖受阻, 杯状细胞分化增强, 这可能是促进哮喘早期急性炎症反应向慢性进展的动力之一。

哮喘患者的肺中PNECs明显增加。肺脏PNECs的增殖和分泌增加能够加重哮喘反应。黏液分泌过多是由多种因素协同作用引起的, 这些因素包括炎症细胞因子和γ-氨基丁酸(γ-aminobutyric acid, GABA)水平的变化, 其中, GABA主要由PNECs产生^[45]。PNECs还可以通过神经递质GABA诱导杯状细胞增生^[46]。

哮喘的气道炎症与一氧化氮(nitric oxide, NO)有关。在哮喘患者的气道上皮细胞中发现, 其乳酸水平升高, M2型丙酮酸激酶和乳酸脱氢酶的表达增加, 这可能是由NO介导的线粒体呼吸抑制作用所

致^[39, 47-49]。哮喘气道上皮中的精氨酸代谢增加,这可能是一种保护机制,因为精氨酸酶2可以抑制NO合成^[50]。高水平的Th2炎症细胞因子可对气道多种细胞产生不利影响^[51]。Xu等^[52]研究发现,哮喘小鼠模型和人类支气管上皮中精氨酸酶2的水平升高,导致TCA循环周期延长和 α -酮戊二酸产量增加。这一途径能够在保证能量供应的同时,驱动下游元件反应,减少Th2细胞因子的产生。可见,精氨酸可能是恢复氧化磷酸化和糖酵解之间的平衡以及减轻哮喘炎症的靶标。然而,精氨酸代谢不良究竟与哪一种或哪几种气道上皮干/祖细胞有关亟待研究揭示。

5 肺干细胞代谢与肺纤维化

肺纤维化无法根治,其特征包括肺上皮干细胞损伤、线粒体功能障碍和蛋白质稳定性丧失等^[53]。活性氧离子经脂质过氧化作用产生丙二醛刺激胶原纤维合成,降低肺泡功能并引起细胞损伤^[54]。在博来霉素诱导的小鼠肺纤维化模型中,肺泡干细胞AT2细胞和AT1细胞均出现损伤^[55]。

在博来霉素诱导的肺损伤中,AT2细胞糖酵解途径多个酶基因表达水平显著上调,但是脂代谢相关基因表达下降,这有利于肺脏修复^[11]。在二氧化硅或博来霉素损伤后,AMPK的激活与小鼠肺泡上皮细胞脂质合成机制的明显下调有关^[14]。AT2细胞中线粒体融合蛋白Mfn1/2的丢失或脂肪酸合成酶的缺陷均抑制脂质合成,加剧博来霉素诱导的肺纤维化^[56]。可见,在AT2细胞中,促进脂质合成能够抑制纤维化发展。Bueno等^[26]在AT2细胞中发现了畸形和功能障碍的线粒体。线粒体功能障碍也与肺泡上皮中的代谢紊乱有关,包括AMPK激活和乳酸产生的增加^[57-58]。特发性肺纤维化患者的AT2细胞的内质网中还出现错误折叠或未折叠的蛋白质的积累^[59-60]。

远端肺组织的慢性损伤会导致AT2细胞的功能改变或丧失,从而促进成纤维细胞的病理性激活和修复失调^[61]。许多细胞因子和炎症介质会加剧AT2细胞损伤,促进AT2细胞凋亡,最终导致肺表面活性物质生成减少和活性下降^[62-64]。肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)和NO浓度均与AT2细胞总损伤率呈显著正相关。

6 肺干细胞代谢与慢性阻塞性肺疾病

慢性阻塞性肺病(chronic obstructive pulmonary disease, COPD)是一种常见的呼吸道疾病,以支气

管增生为主要特征,主要与长期暴露于吸入刺激物(香烟烟雾或环境污染物)有关。在戒烟后,炎症通路仍处于激活状态,多数中度COPD患者的病程会在5~20年内进展到重度^[65]。

COPD患者肺排出空气的能力逐渐减弱,小气道上皮增生是气流受限的主要因素之一,这可能是终末细支气管干细胞过度增殖导致的^[66]。研究发现,人的终末细支气管存在p63⁺Krt5⁺的BCs^[67-68]。吸烟患者支气管上皮的BCs也出现异常增生和代谢变化,失去再生修复能力,这是造成COPD气道变化的主要原因,并且在持续的压力下会发生恶变^[67, 69-70]。Rao等^[71]将单细胞测序技术应用于COPD患者和非COPD患者的肺组织,发现COPD肺中多种与病变相关的远端气道祖细胞发生变异。当将这些变异祖细胞移植到免疫缺陷的小鼠身上时,诱导了类似于COPD的杯状细胞增生、炎症和纤维化病理^[71]。COPD患者肺中存在较多p63⁺BCs^[71-72]。与不吸烟者相比,吸烟者的BCs的乙酰辅酶A水平降低,表明TCA减弱^[73]。此外,暴露于香烟烟雾可使AT2的糖酵解减弱,这与GAPDH (glyceraldehyde-3-phosphate dehydrogenase)被抑制有关^[74]。N-乙酰半胱氨酸可以增加Club细胞分泌蛋白的合成和分泌,减少香烟烟雾诱导的氧化反应对Club细胞的损伤作用^[17]。基因工程和COPD动物模型可用来揭示气道干/祖细胞代谢改变与COPD病理学的直接关系。

7 总结与展望

代谢途径和肺脏干细胞生理相关信号的调节网络的解析不仅对了解组织的体内平衡具有重要意义,对于确定支持正常干细胞生理的体外培养条件也非常重要。更重要的是,肺脏干/祖细胞代谢变化与肺生理和病理过程,包括增殖分化、衰老和炎症反应息息相关。细胞代谢途径往往是互通的,所有代谢对肺脏干/祖细胞功能的调控不是单一的,是错综复杂的,其代谢失调可能导致许多呼吸系统疾病的发生与发展。比较肺脏干细胞生理、衰老和疾病状态的细胞代谢能够进一步揭示其代谢调控机制,对于通过纠正干细胞代谢紊乱来恢复组织器官损伤的新型治疗方法是十分必要的。对靶向代谢产物或途径的探索也有利于呼吸系统疾病治疗方法的研究。例如,对糖和乳酸等代谢物进行定量评估和控制,靶向调控ROS和H₂O₂水平等。已有研究表明,饮食干预对于疾病治疗有重要意义。肺脏干细胞代谢紊乱导致呼吸系统疾病主要也是与糖、脂质和蛋白

质三大营养物质代谢改变有关。对疾病模型进行饮食调控从而探究新的诊疗方法是值得研究的方向。

然而, 对于肺脏干细胞代谢与呼吸系统疾病仍有很多亟需解决的问题。目前, 大多是从损伤角度去研究干细胞代谢与疾病之间的关系, 而很少从修复角度去研究肺脏干/祖细胞或上皮细胞再生能力下降的机制。另外, 目前的疾病模型多为小鼠, 而小鼠和人类之间肺病生理差异巨大, 因此迫切需要建立新的呼吸系统疾病动物模型。

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