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综 述

15-脂氧合酶/15-羟廿碳四烯酸在缺氧性肺动脉高压中的作用和机制

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摘 要：肺动脉高压是一种病因复杂的罕见病，以肺动脉阻力增高，引起右心室后负荷增大，最终导致右心室功能衰竭而使患者死亡为特征。肺血管花生四烯酸信号通路异常在肺动脉高压中发挥重要作用。肺动脉高压患者肺动脉内皮细胞、平滑肌细胞和成纤维细胞中15-脂氧合酶(15-lipoxygenase, 15-LO)及其代谢产物15-羟廿碳四烯酸(15-hydroxyeicosatetraenoic acid, 15-HETE)水平均升高。在缺氧条件下，15-LO/15-HETE引起肺动脉收缩，促进肺动脉内皮细胞和平滑肌细胞增殖，抑制肺动脉平滑肌细胞凋亡，促进肺血管外膜纤维化，进而导致肺动脉高压的发生。本文主要对15-LO/15-HETE与缺氧性肺动脉高压相关性的研究进行综述，以阐明15-LO/15-HETE在缺氧性肺动脉高压中发挥的核心作用。

关键词：缺氧性肺动脉高压；15-脂氧合酶；15-羟廿碳四烯酸；血管收缩；血管重塑
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Role of 15-lipoxygenase/15-hydroxyeicosatetraenoic acid in hypoxic pulmonary arterial hypertension

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Abstract: Pulmonary arterial hypertension (PAH) is a rare disease with a complex aetiology characterized by elevated pulmonary artery resistance, which leads to progressive right ventricular failure and ultimately death. The aberrant metabolism of arachidonic acid in the pulmonary vasculature plays a central role in the pathogenesis of PAH. The levels of 15-lipoxygenase (15-LO) and 15-hydroxyeicosatetraenoic acid (15-HETE) are elevated in the pulmonary arterial endothelial cells (PAECs), pulmonary smooth muscle cells (PASMCs) and fibroblasts of PAH patients. Under hypoxia condition, 15-LO/15-HETE induces pulmonary artery contraction, promotes the proliferation of PAECs and PASMCs, inhibits apoptosis of PASMCs, promotes fibrosis of pulmonary vessels, and then leads to the occurrence of PAH. Here, we review the research progress on the relationship between 15-LO/15-HETE and hypoxic PAH, in order to clarify the significance of 15-LO/15-HETE in hypoxic PAH.

Key words: hypoxic pulmonary arterial hypertension; 15-lipoxygenase; 15-hydroxyeicosatetraenoic acid; vasoconstriction; vascular remodeling

肺动脉高压是与多种临床症状和广泛组织病理学异常改变相关的疾病类型的总称，以静息状态下平均肺动脉压高于 20 mmHg、肺动脉楔压 ≤ 30 mmHg、肺血管阻力 ≥ 3 Wood Units 为特征 [1]，是

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导致成人与新生儿多种肺部疾病和心脏疾病发病和死亡的原因。2018 年德国第六届肺动脉高压大会将肺高压分为五种类型：肺动脉高压、左心疾病引起的肺高压、肺部疾病和 (或) 缺氧引起的肺高压、肺动脉阻塞引起的肺高压、不明原因和 (或) 多种因素引起的肺高压 [1]。肺动脉高压的病理改变涉及肺动脉内皮细胞 (pulmonary arterial endothelial cells, PAECs) 功能异常和平滑肌增殖，其发生机制与肿瘤十分相似 [2]。缺氧与肺癌和肺动脉高压的发生密切相关 [3, 4]。急性缺氧诱导的肺血管收缩 (hypoxia-induced pulmonary vasoconstriction, HPV) 有利于肺大部分区域的通气与血流相匹配，提高气体交换效率。长时间缺氧可引起缺氧性肺血管重塑 (hypoxic pulmonary vascular remodeling, HPVR)[4]。血管收缩、血管壁重塑和原位血栓形成是肺血管功能紊乱的主要特征 [5]。

花生四烯酸 (arachidonic acid, AA) 级联反应在血管内皮和平滑肌细胞稳态中发挥重要作用。肺动脉高压患者和动物模型 AA 下游通路均存在异常。越来越多的数据显示脂氧合酶 (lipoxygenase, LO) 来源的 AA 代谢物在肺动脉高压病理进展中发挥关键作用。Al-Naamani 等研究显示，血浆中 15- 羟廿碳四烯酸 (15-hydroxyeicosatetraenoic acid, 15-HETE) 和 12-HETE 水平可作为肺动脉高压生存率的预测因子 [6]。Fülöp 等研究发现敲除 *Cyp2c44* 基因可降低 12-HETE 产生，导致 $CD133^+$ 造血干细胞数量增多，增多的 $CD133^+$ 细胞在肺动脉外膜沉积引起肺高压 [7]。Ruffenach 等在小鼠饮食中添加 15-HETE，引起 PAECs 内氧化脂质增多，促进了 PAECs 凋亡 [8]。本研究组多项研究显示，15- 脂氧合酶 (15-lipoxygenase, 15-LO) 及其代谢产物 15-HETE 在缺氧性肺动脉高压 (hypoxic pulmonary arterial hypertension, HPAH) 中发挥重要作用，本文就该领域研究进展作一综述。

1 15-LO概述

LO 是多不饱和脂肪酸 (polyunsaturated fatty acids, PUFAs) 代谢的关键酶 [9]，通过将 PUFAs 转化为具有生物活性的产物，影响细胞结构、代谢和信号转导 [10]。目前发现与血管功能相关的 LO 主要有三种亚型：5-LO、12-LO 和 15-LO，源于这些 LO 的代谢物可影响血管的收缩和舒张状态 [11]。

在人体内，目前已鉴定出两种不同类型的 15-LO，即 15-LO-1[12] 和 15-LO-2[13]，二者分别由 *ALOX15* 和 *ALOX15B* 编码 [14, 15]。*ALOX15* 基因位于 17 号染色体 p13.3 位点，包含 14 个外显子；*ALOX15B* 基因位于 17 号染色体 p13.1 位点，也含有 14 个外显子。在生理条件下，15-LO-1 表达于嗜酸性粒细胞 [16]、血管内皮细胞 [17]、气道上皮细胞 [18] 和软骨细胞 [19]；15-LO-2 表达于中性粒细胞、单核细胞、淋巴细胞 [16] 和肺动脉平滑肌细胞 (pulmonary arterial smooth muscle cells, PASMCs) [20]。

ALOX15 的表达调控存在多种机制，包括转录水平和表观遗传学的调节 [21]。Chen 等研究显示，双乙酰布里丹内酯通过抑制 STAT6 和 JAK3 的活化抑制白细胞介素 -4 (interleukin-4, IL-4) 诱导的 *ALOX15* mRNA 表达 [22]。Ho 等研究显示，在成神经细胞瘤细胞中，*ALOX15* 的表达受组蛋白乙酰化修饰的调节 [23]。

15-LO 是脂质过氧化酶，可将双氧分子加到 AA 的第 15 个碳原子上 [9, 24]，催化 AA 生成 15- 羟基二十碳 -5Z,8Z,11Z,13E- 四烯酸 [15(S)-HPETE]，15(S)-HPETE 不稳定，可被过氧化物酶还原为 15-HETE。在炎症、细胞分化、肿瘤发生和动脉粥样硬化等过程中均有 15-LO 及 AA 代谢产物的表达。15-LO 及 AA 代谢产物的生理作用因组织和种属不同而不同。

2 15-LO/15-HETE与HPAH

2.1 15-LO在HPAH中的分布和表达

在严重肺动脉高压患者肺血管样本中，15-LO-1 和 15-LO-2 在 PAECs 和 PASMCs 中的表达水平均上调 [25]。本研究组研究显示，正常大鼠 PAECs 表达 15-LO-1 和 15-LO-2，而 PASMCs 只表达 15-LO-2，水平均较低；在缺氧条件下，15-LO-1 和 15-LO-2 均上调 [20]。Zhu 等研究显示，缺氧肺组织微粒体中活化的 15-LO 催化 AA 生成 15-HETE，15-LO 的激活与酶从胞浆向膜转位有关 [26]。15-LO 抑制剂 NDGA (N-dihydroguaiac acid) 可明显下调 PASMCs 和 PAECs 中 15-LO 蛋白水平 [27]。

2.2 15-HETE和HPV

HPV 是肺血管的内在特征。外源性 15-HETE 使缺氧大鼠肺动脉紧张度增高的效应具有剂量依赖性 [26]。用 15-LO 抑制物 1 (15-lipoxygenase inhibitor 1, 15-LOXI1) 抑制内源性 15-HETE 的生成，可以抑制缺氧诱导的剥除内皮的牛肺动脉收缩，还使缺氧条件下培养的肺动脉环对苯肾上腺素的收缩反应明显

下降[28]。人类妊娠子痫时，脐动脉内增多的15-LO通过15-HETE上调钙离子水平，引起脐动脉收缩[29]，提示内源性15-HETE参与肺血管收缩过程。

胞浆内游离Ca^{2+}增多是导致肺血管收缩的主要原因[30]。PAECs膜上的机械门控通道Piezo1通过影响内皮细胞内Ca^{2+}浓度和NO产生，介导依赖内皮的肺血管舒张[31]。本研究组研究显示，15-HETE诱导的肺动脉收缩在PASMCs内Ca^{2+}浓度升高时被触发[32]。钙库操纵性钙通道(store-operated calcium channels, SOCCs)开放引起$[Ca^{2+}]_i$增多是慢性缺氧诱发HPV的原因，电压依赖性钙通道(voltage-dependent calcium channels, VDCCs)在此过程中不发挥作用[33]。15-HETE诱导大鼠远端肺动脉平滑肌内瞬时受体电位通道蛋白1 (transient receptor potential channel protein 1, TRPC1)水平升高，引起Ca^{2+}流入增多[34]。细胞内增多的Ca^{2+}与钙调蛋白形成复合体，激活肌球蛋白轻链激酶，引起肌球蛋白轻链磷酸化，磷酸化的肌球蛋白轻链通过actin刺激肌球蛋白的ATP酶活性，引起横桥摆动和肌肉收缩[35]。在缺氧条件下，15-HETE还通过PASMCs间的缝隙连接介导平滑肌内肌球蛋白重链表达，参与肺动脉持续的HPV反应[28]。以上这些研究表明，15-HETE是通过提高$[Ca^{2+}]_i$引起肺动脉收缩。

细胞膜对K^+的通透性和膜两侧K^+浓度差决定静息电位水平。亚急性缺氧抑制PASMCs的电压门控性K^+通道[36]，引起膜去极化和VDCCs开放，介导Ca^{2+}内流导致细胞内钙升高，触发肺动脉平滑肌收缩[37]。本研究组研究结果显示，抑制电压依赖性钾离子通道(voltage-dependent potassium ion channels, K_V)可完全阻断15-HETE对肺血管的效应[38]，亚急性缺氧通过内源性15-HETE下调$K_V1.5$、$K_V2.1$和$K_V3.4$的表达，抑制I_K电流[39, 40]。这些研究结果表明，缺氧可通过15-LO/15-HETE抑制K_V通道，引起PASMCs膜去极化和细胞内钙增高，导致肺血管收缩[41–43]。

肺血管细胞释放多种血管活性物质影响血管收缩。缺氧使内皮型一氧化氮合酶(endothelial nitric oxide synthase, eNOS)的活性降低，引起NO生成减少，导致肺动脉收缩[44]；血管紧张素II通过与I型受体结合促进人肺动脉平滑肌来源的$eNOS^{Ser1177}$磷酸化，对平滑肌收缩发挥自我抑制作用[45]。在慢性间断性缺氧过程中，血液单核细胞来源的肺巨噬细胞通过肾上腺素型β3受体/诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)通路缓解肺动脉HPV反应[46]。15-HETE使去内皮(抑制NO生成)的肺动脉血管环收缩效应增强，抑制内源性15-HETE可诱导肺血管内皮细胞NO生成，其机制与15-HETE通过磷酸化$eNOS^{Thr495}$位点抑制eNOS活性有关[47]，提示15-HETE可影响肺血管内皮细胞释放血管活性物质，从而引起血管收缩。

15-HETE还通过蛋白激酶途径激活不同的信号转导通路影响肺血管收缩。在缺氧条件下，15-HETE激活PASMCs内蛋白激酶C (protein kinase C, PKC)的δ和ε亚型，使其由胞浆向细胞膜进行转位[48]；15-HETE上调核和胞浆内的细胞外信号调节激酶1和2 (extracellular signal-regulated kinases 1 and 2, ERK1/2)磷酸化水平[49]；15-HETE上调Rho相关激酶(Rho-associated kinase, ROCK)表达，通过G蛋白和酪氨酸激酶途径，促进ROCK2由细胞核向胞浆转位，导致肺血管收缩[50]。

2.3 15-LO/15-HETE和HPVR

细胞增殖与死亡的稳态失衡在肺动脉高压病理改变中发挥关键作用。Yu等研究表明，血管平滑肌细胞增殖增加和凋亡被抑制是导致肺动脉中膜增厚、血管重塑和管腔狭窄的主要原因[51]。HPVR是HPAH病理改变的主要机制。研究显示，肺动脉高压患者PAECs和PAMSCs中15-LO-1和15-LO-2表达上调，15-LO/15-HETE途径部分介导缺氧引起的肺血管重塑[25]。

本研究组研究显示，用15-LO抑制剂NDGA对HPAH大鼠进行灌胃处理，可有效降低体内15-HETE水平，逆转缺氧引起的肺动脉病理改变，如胶原沉积和中膜增厚；15-LO抑制剂CDC (cinnamyl-3,4-dihydroxy-α-cyanocinnamate)可抑制PAECs中内源性15-HETE的生成，并抑制PAECs迁移和血管形成[25, 27]。

15-HETE参与细胞抗凋亡机制。饮食中添加15-HETE触发小鼠PAECs凋亡，导致肺动脉高压的发生[8]。本研究组研究显示，15-HETE通过ROCK、热休克蛋白90、磷脂酰肌醇激酶3 (phosphatidylinositol 3-kinase, PI3K)/Akt、ERK1/2和iNOS等通路提高Bcl-2表达水平，下调caspase-3、Bax、FasL、Bad和caspase-9表达，抑制肺动脉平滑肌凋亡；低氧诱导因子1α (hypoxia inducible factor 1α, HIF-1α)和15-LO/15-HETE形成的反馈环路使缺氧诱导的PASMCs抗凋亡效应增强[52]；细胞水平的多项研究显示，15-HETE可

抑制肺动脉平滑肌凋亡，促进细胞存活，引起HPVR[53–55]。活化的K_V通道在PASMCs凋亡、存活和增殖中发挥重要作用[51, 56, 57]，K_V电流和多种K_V通道蛋白表达下调可抑制PASMCs凋亡[58, 59]。在无血清培养的PASMCs中，15-HETE可部分逆转K^+通道开放诱导的细胞凋亡，说明15-HETE通过(至少部分通过)使K^+通道失活发挥抗PASMCs凋亡的作用[60]。本研究组研究还显示，在缺氧条件下，15-HETE通过上调沉默信息调节因子1 (silent information regulator 1, SIRT1)抑制PASMCs凋亡[61]。以上这些研究表明，15-LO/ 15-HETE参与了PASMCs的凋亡过程。

15-HETE还参与细胞增殖的调节。Porter等研究显示，慢性缺氧通过H_2O_2诱导15-LO生成，促进PAECs增殖[62]。本研究组研究显示，15-HETE通过p38 MAPK通路调节ROS生成促进PAECs迁移和PASMCs增殖，参与缺氧诱导的肺血管重塑[63]。在缺氧条件下，15-LO/15-HETE和激活蛋白-1 (activator protein 1, AP-1)形成正反馈环路促进PASMCs表型转化[64]。缺氧诱导的内源性15-HETE增加或给予外源性15-HETE，均可上调PASMCs中增殖细胞核抗原(proliferating cell nuclear antigen, PCNA)和Cyclin A的表达，该效应可被15-LO抑制剂CDC阻断。缺氧和外源性15-HETE可显著增加BrdU插入和α-tubulin微管形成数量，使更多的PASMCs处于G_2/M+S期；CDC还可抑制细胞增殖、α-tubulin聚合，并使细胞停滞于G_0/G_1期；缺氧通过15-LO-2/15-HETE促进PASMCs增殖，而ROCK通路参与15-HETE诱导的PASMCs增殖和中膜肥厚[65]，以上这些研究结果表明，抑制ROCK通路和15-HETE有望成为治疗人类肺动脉高压的新策略。

外膜纤维化也是肺血管重塑的机制之一[66]。肺动脉高压患者存在外膜纤维化[67]。氧化型低密度脂蛋白(oxidized low density lipoprotein, oxLDL)刺激ERK-cPLA$_2$-15-LO通路发挥促氧化的作用，刺激肺发生纤维化反应以对抗氧化和代谢损伤的挑战[68]。Cussac等认为肺动脉外膜成纤维细胞在肺动脉高压肺血管重塑中发挥必不可少的作用，他们发现缺氧和野百合碱诱导的肺动脉高压模型大鼠肺动脉外膜TRPV4 (transient receptor potential vanilloid 4)表达增多，TRPV4的激活上调了I型胶原蛋白和纤连蛋白的表达，引起外膜纤维化[69]。本研究组研究显示，缺氧通过c-Jun氨基端激酶(c-Jun N-terminal kinase, JNK)-Elk1通路上调肺动脉外膜成纤维细胞15-LO的表达水平，15-LO通过对p27kipl的调节促进成纤维细胞增殖导致血管外膜重塑[70]。肺动脉高压患者和缺氧诱导的肺动脉高压大鼠模型均提示缺氧引起肺动脉外膜细胞外基质沉积，导致外膜纤维化[71]；15-LO/15-HETE还可通过转化生长因子β1 (transforming growth factor β1, TGF-β1)/Smad2/3通路介导成纤维细胞表型转化和外膜纤维化[71]。

2.4 15-LO/15-HETE参与HPAH炎症过程

肺高压的病理机制尚未完全清楚，有很多因素提示炎症参与肺动脉高压的发病过程。在临床上，肺动脉高压是多种自身免疫性疾病(比如硬皮病和系统性红斑狼疮)[72–74]和感染性疾病(比如HIV和血吸虫病)的并发症[75, 76]，提示炎症刺激可引起血管发生病理改变。12/15-LO参与很多炎症相关疾病，其代谢产物12(S)-HETE和15(S)-HETE既发挥抗炎也发挥促炎的作用[77]。敲低人视网膜内皮细胞12/15-LO可有效抑制高糖诱导的白细胞黏附分子ICAM-1的表达[78]。12/15-LO活性持续增高与不可控制的炎症有关，可导致器官功能衰竭[79]；12/15-LO在脂多糖诱导的急性肾损伤中通过催化AA生成12-HETE发挥促炎作用，而通过水解底物二十二碳六烯酸(docosahexaenoic acid, DHA)发挥抗炎作用[80]；在基因水平敲低12/15-LO可有效减轻心肌梗死后的炎症，改善左心室功能，提高患者生存率[81]。Suzuki等研究显示，12/15-LO诱导的炎症和氧化应激参与糖尿病心肌病的发展过程[82]；用过敏原刺激敲除12/15-LO的动物模型，肺组织IgE的含量减少，提示12/15-LO在过敏原诱导的肺部炎症中发挥重要作用[83]。本研究组研究显示，慢性缺氧通过15-LO/15-HETE和NF-κB促进PAECs的单核细胞浸润及细胞间黏附分子增加，提示15-LO/15-HETE参与缺氧诱导的肺动脉炎症反应[84]。

2.5 15-LO/15-HETE和血管新生

肺动脉高压是多种因素参与的病理过程，尽管其机制尚未清楚，但前毛细血管的缺失和修剪参与肺动脉高压病理过程已被公认[85]。严重肺动脉高压的特点是出现丛状病灶，病灶形成与血管新生紊乱、炎症和血栓形成有关[86]。

15-LO-1/15-HETE上调血管内皮细胞生长因子(vascular endothelial cell growth factor, VEGF)表达促进缺血脑组织的血管新生[17, 87]；15-HETE通过PI3K/Akt通路促进缺血脑微血管内皮细胞增殖和迁移[17, 87]。

本研究组研究显示，缺氧诱发肺血管新生，给大鼠体内注射 15-LO 抑制剂 NDGA 可阻断此效应；缺氧诱导的 PAECs 迁移和成管增多可被 15-LO 抑制剂 CDC 阻断 [25]；缺氧通过 15-LO/15-HETE 增加 MMP2 和 MMP9 的表达，促进 PAECs 参与血管新生 [88]。这些研究说明 15-HETE 是缺氧诱导肺血管新生的重要媒介物，通过参与血管新生影响血管阻力。

2.6 15-LO/15-HETE和血栓形成

肺微血管内广泛的血栓形成也是肺血管阻力增加的原因之一，很多危险因素 (例如内皮损伤、炎症、血小板激活和纤维蛋白溶解等) 是导致血栓形成的原因。研究显示，缺血心肌组织中 15-HETE 的增加促进了血栓的形成 [89]；巨噬细胞分泌的 15-LO-2 及其代谢产物 15-HETE 激活血小板，促进血栓形成，在动脉粥样硬化形成过程中发挥作用 [90]。本研究组研究显示，在缺氧条件下，外周血单核细胞分泌的 15-LO/15-HETE 通过抑制单核细胞趋化蛋白 1 (monocyte chemotactic protein 1, MCP-1) 的表达促进血小板激活和血液凝固，参与肺血管内血栓形成 [91]。这些研究提示 15-LO/15-HETE 促进肺微血管内血栓形成，提高肺血管的阻力。

2.7 15-LO/15-HETE介导细胞间通讯

外泌体 (exosomes) 是一种细胞分泌的微小膜泡，可携带脂质、蛋白、mRNA 和 microRNAs 等多种功能性物质 [92–94]。外泌体通过其携带的分子以远距分泌或旁分泌的方式释放到局部微环境或血液循环中，参与细胞间通讯，调节细胞的生物学活性，但 15-LO/15-HETE 是否通过外泌体参与肺动脉高压的病理过程尚不清楚。研究显示，缺氧引起牛 PAECs 15-LO-2 表达增多，15-LO-2 促进含有 15-LO-2/15-HETE 的外泌体生成；在缺氧条件下 PAECs 释放外泌体增多；15-LO-2 通过与信号转导和转录激活因子 3 (signal transducer and activator of transcription 3, STAT3) 互作激活 STAT3 下游靶点 c-Myc 介导 PAECs 增殖；采用转基因小鼠的研究显示，含有功能缺陷的 15-LO 的外泌体可明显改善缺氧诱导的肺高压功能学指标 [95]。当然，含有 15-LO-2/15-HETE 的外泌体在细胞间通讯中的作用还需进一步证明，同时外泌体在肺动脉高压中的作用和机制无疑是该领域的热点。

3 缺氧调控15-LO/15-HETE的机制

缺氧通过 15-LO/15-HETE 参与肺动脉血管异常收缩和重塑，但缺氧引起 15-LO 发生改变的机制尚不清楚。Hultén 等发现，在缺氧条件下，动脉粥样硬化斑块的巨噬细胞中 HIF-1α 可以调节 15-LO-2 的活性，表达增多的 15-LO-2 募集更多的炎症细胞促进炎症反应 [96]。在氧化应激时，磷酸化的 STAT6 和 STAT1 与小鼠神经元中的 12/15-LOX 启动子结合，促进其表达 [97]。缺氧上调 lncRNA MALAT1 水平，通过 15-LO-1/STAT3 信号通路促进缺血再灌注脑组织血管新生 [98]。本研究组研究显示，HIF-1α/15-LO/15-HETE 通路促进缺氧诱导的人脐静脉内皮细胞增殖，参与妊娠子痫病理过程 [99]；在缺氧条件下，HIF-1α 和 15-LO/15-HETE 形成的正反馈环路参与 PASMCs 的抗凋亡机制 [52]。缺氧通过上调 PASMCs 内血红素加氧酶 1 (heme oxygenase 1, HO-1) 上调 15-LO-2/15-HETE 水平，导致肺血管收缩和肺动脉重塑 [100]；缺氧通过 TGF-β1 诱导 15-LO 表达上调，促进 PASMCs 增殖 [101]；缺氧通过 15-LO/15-HETE 和骨形态发生蛋白 4 (bone morphogenetic protein 4, BMP4)/BMPRI (bone morphogenetic protein receptor 1) 形成的正反馈环路促进 PASMCs 表型转化 [102]；TGF-β1/ 成纤维细胞生长因子 2 (fibroblast growth factor 2, FGF-2) 信号介导 15-HETE 诱导的肺动脉外膜成纤维细胞向成肌纤维细胞分化 [103]；缺氧上调 PASMCs AP-1 表达，AP-1 和 15-LO/15-HETE 形成的正反馈环路促进缺氧诱导的 PASMCs 表型转化 [64]；在肺动脉外膜纤维化过程中，依赖 JNK 的 Elk-1 信号增强促进缺氧诱导的外膜成纤维细胞 15-LO 表达 [70]。

综上所述，15-LO/15-HETE 在 HPAH 中发挥重要作用 (图 1)。

4 展望

近年来，越来越多的调节性细胞死亡方式被陆续发现，根据细胞死亡命名委员会 (NCCD) 2018 年分类，目前已定义了 11 种调节性细胞死亡方式，如焦亡和铁死亡。有研究表明，抑制 15-LO、提高谷胱甘肽含量、清除铁和脂质过氧化物可以减轻铁死亡 [104–106]；慢性间断性缺氧引起肝细胞铁死亡增多 [107]。本研究组研究显示，程序性死亡配体 1 (programmed death ligand 1, PD-L1) 与肺动脉高压 PASMCs 焦亡和肺血管纤维化有关 [108]；缺氧上调 GLI1 表达，GLI1 通过与 ASC 基因启动子区域结合促进 ASC 表达，进而引起肺动脉平滑肌焦亡 [109]。

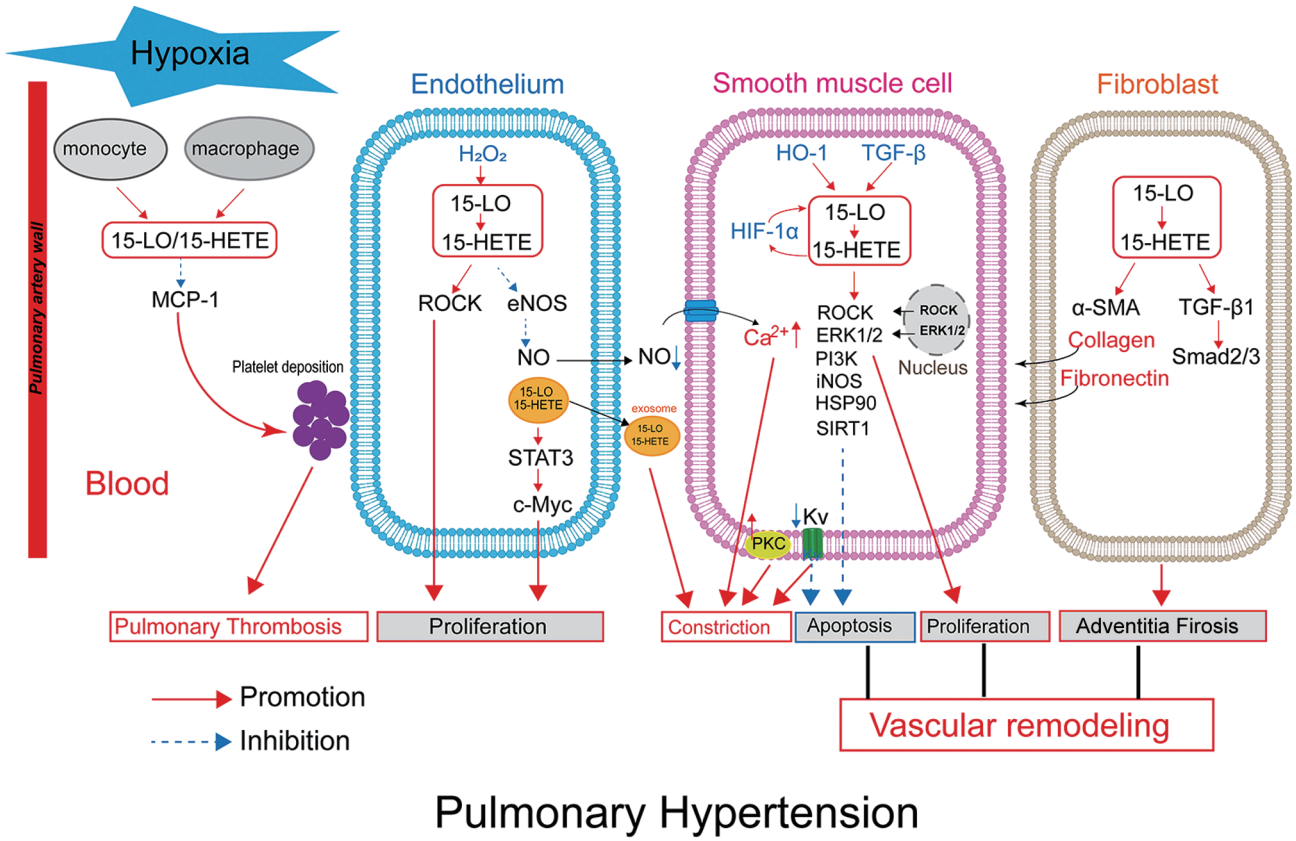

图 1. 15-LO/15-HETE在缺氧性肺动脉高压中的作用

Fig. 1. Role of 15-LO/15-HETE in hypoxic pulmonary arterial hypertension (HPAH). Hypoxia-induced 15-LO/15-HETE expression leads to platelet deposition, and stimulates pulmonary artery constriction and remodeling. The increased vascular pressure, proliferation and antiapoptosis of pulmonary arterial smooth muscle cells and adventitia fibrosis may play important roles in initiation and/or progression of pulmonary vascular remodeling. 15-LO: 15-lipoxygenase; 15-HETE: 15-hydroxyeicosatetraenoic acid; eNOS: endothelial nitric oxide synthase; iNOS: inducible nitric oxide synthase; ROCK: Rho-associated kinase; ERK1/2: extracellular signal-regulated kinases 1 and 2; TGF-β1: transforming growth factor β1; α-SMA: smooth muscle α-actin; STAT3: signal transducer and activator of transcription 3; NO: nitric oxide; HSP90: heat shock protein 90; SIRT1: silent information regulator 1; MCP-1: monocyte chemotactic protein 1; HIF-1α: hypoxia inducible factor 1α; PI3K: phosphatidylinositol 3-kinase.

但 15-LO/15-HETE 是否参与肺血管细胞的焦亡和铁死亡等细胞死亡方式及其效应分子尚不明确。其次，目前 15-LO/15-HETE 在其它疾病中的作用和机制研究较少，这无疑是相关疾病研究中需要探索的领域。再次，15-HETE 是代谢产物，通过相应的酶代谢，在疾病过程中是 15-HETE 还是催化 15-HETE 的酶发挥作用尚不清楚。15-LO 本身及其与蛋白质相互作用的网络在疾病中的作用也需要探索。此外，肺动脉高压致病因子如何调控 15-LO，调控的分子机制是什么，15-LO/15-HETE 是否可以作为潜在诊断标志物和治疗靶点，还有待进一步阐明。这些问题无疑是该领域今后研究的关键问题。

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