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肺动脉高压血管重构的自噬相关调控通路研究进展

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摘 要:肺动脉高压(pulmonary hypertension,PH)是一种病因复杂的心肺系统疾病,以肺血管重构和肺血管阻力增高为特征,目前无法治愈。越来越多的研究显示PH与自噬失调密切相关,FoxO1、AMPK-mTOR-ULK1、NF-κB、PI3K/AKT/mTOR、ROS、LC3/Beclin-1、HIF-1α/BNIP3、BMPR2以及MAPK等自噬相关通路调控肺动脉平滑肌细胞(pulmonary artery smooth muscle cells,PASMCs)和肺动脉内皮细胞(pulmonary artery endothelial cells,PAECs)增殖或凋亡,进而调控肺血管重构,促进或改善PH。本文主要综述近年来自噬调节PH肺血管重构的相关信号通路。

关键词:肺动脉高压;肺血管重构;自噬;信号转导通路
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Research progress on autophagy-related regulatory pathways of vascular remodeling in pulmonary hypertension

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Abstract: Pulmonary hypertension (PH) is a cardiopulmonary disease with complex etiology, characterized by progressively increasing pulmonary vascular resistance and pulmonary vascular remodeling. Currently, there is no cure for PH, highlighting an urgent clinical need for novel therapeutic targets to intervene in vascular remodeling. Recent research indicates that dysregulation of cellular autophagy plays a pivotal role in the pathogenesis and progression of PH. Autophagy, a highly conserved cellular self-degradation process, precisely regulates the proliferation, apoptosis, migration, and phenotypic switching of pulmonary artery smooth muscle cells (PASMCs) and pulmonary artery endothelial cells (PAECs) through multiple signaling pathways, thereby influencing the course of pulmonary vascular remodeling. This review aims to systematically elucidate the autophagy-related signaling pathways involved in pulmonary vascular remodeling. These pathways include, but are not limited to, the FoxO1, AMPK-mTOR-ULK1, NF-κB, PI3K/AKT/mTOR, ROS, LC3/Beclin-1, HIF-1α/BNIP3, BMPR2, and MAPK signaling pathways. These pathways form a complex regulatory network. Among them, the FoxO1 and AMPK-mTOR-ULK1 pathways primarily exert protective effects in pulmonary vascular remodeling. In contrast, the NF-κB, eIF2α, LC3/Beclin-1 pathways, oxidative stress, and BMPR2 mutations predominantly contribute to detrimental effects. The HIF-1α/BNIP3, PI3K/AKT/mTOR, and MAPK pathways can play dual roles, finely tuning abnormal PASMC proliferation, migration, and anti-apoptosis, as well as PAEC dysfunction and apoptosis. This intricate regulation ultimately drives or inhibits remodeling processes such as vascular wall thickening and lumen occlusion. Furthermore, this article reviews therapeutic strategies for PH targeting autophagy. By employing pharmacological interventions to either inhibit or promote cellular autophagy, vascular remodeling can be suppressed, thereby alleviating PH. For example, the mTOR inhibitor rapamycin, chloroquine, and hydroxychloroquine are utilized to inhibit autophagy clinically. In addition to drug-based approaches, gene therapy strategies can also be applied to regulate autophagy. Targeting genes such as miR-210,

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miR-138-5p, miRNA-205-5p, miR-204, and miR-382-3p can reduce the proliferation, differentiation, and anti-apoptotic activity of PASMCs, decrease medial hypertrophy in the pulmonary vasculature in experimental PH, and consequently attenuate pulmonary vascular remodeling. An in-depth exploration of the regulatory role of autophagy in pulmonary vascular remodeling will contribute to advancing research on the molecular mechanisms of PH and facilitate the development of autophagy-related therapeutics. It is believed that with further investigation into the molecular mechanisms of autophagy in PH, autophagy is likely to become a breakthrough point and a crucial target for the prevention and treatment of PH.
Key words: pulmonary hypertension; pulmonary vascular remodeling; autophagy; signal transduction pathway

肺动脉高压(pulmonary hypertension,PH)是一种逐渐加重且无法逆转的临床病理生理综合征,其主要特征为肺血管的重塑,表现为肺血管持续收缩、管壁变厚,肺动脉血流改变,右心室代偿性肥厚,最终发展为右心功能衰竭而死亡[1,2]。2022年,ESC/ERS指南将PH血流学定义为静息状态下平均肺动脉压(mean pulmonary pressure,mPAP) >20 mmHg[1]。PH按照不同发病原因可分为五类,其中左心疾病和肺部疾病是PH最常见的病因,分别引起第2类PH和第3类PH。按发病率估计,全球每百万人中PH患者为15~48例,总患病人数约占全球人口1%[2],65岁以上人群患病率更高。若不能早期得到规范有效治疗,患者2~3年内多死于右心衰竭,故被称为"心血管恶性肿瘤"[1-3]。PH发生机制十分复杂,肺血管重构是其主要病理改变,包括肺动脉平滑肌细胞(pulmonary artery smooth muscle cells,PASMCs)过度增殖和迁移、肺动脉内皮细胞(pulmonary artery endothelial cells,PAECs)功能失调、血管外膜成纤维细胞(vascular adventitial fibroblasts,VAFs)异常增殖、血管外胶原沉积等改变,这些变化导致血管腔变窄,肺循环阻力增加,进而导致PH发生。

近年研究发现,自噬(autophagy)通过调控细胞代谢、增殖和凋亡,维持细胞内稳态,在PH血管重构中发挥重要作用,基础水平的自噬有助于维持肺血管细胞正常功能和稳态,防止细胞损伤,参与细胞自我保护。当自噬过度激活,可导致细胞成分过度降解,引发自噬性细胞死亡,进一步加剧血管重构和PH发展。本文主要综述近年来自噬调节PH血管重构的相关信号通路,并探讨其潜在治疗价值。

1 自噬的生物学基础

自噬是一种高度保守的生物过程,主要发生于真核细胞,通过溶酶体降解回收细胞质成分,发挥细胞管家的作用,但当细胞暴露于低氧、无氧或毒素等不利刺激时,自噬作为一种适应性反应被迅速激活[4,5]。哺乳动物细胞存在三种类型的自噬,主要包括巨自噬(macroautophagy)、微自噬(microautophagy)和分子伴侣介导的自噬(chaperone-mediated autophagy,CMA)[6],如图1所示。与其他两种自噬相比,巨自噬被认为是主要的自噬类型,对它的研究最为广泛,因此巨自噬通常被称作"自噬"。

哺乳动物的自噬始于吞噬泡(phagophore)的形成,随后双膜自噬小体(autophagosome)包围一部分细胞质,与核内体(endosome)对接融合,形成自噬溶酶体(autolysosome);自噬小体的内膜和内容物被自噬溶酶体内部的酸性水解酶降解,降解产物通过渗透酶被释放回细胞质中,从而得到再利用[7]。MAP1LC3(又称LC3)是哺乳动物自噬相关基因8 (autophagy-related gene 8,Atg8)同源物[8],在自噬小体形成过程中,微管相关蛋白1轻链3β (microtubule-associated protein 1 light chain 3 beta,MAP1LC3B或LC3B)和Beclin-1 (Atg6)蛋白被募集到自噬体膜上,可用于监测自噬。LC3B-II是LC3B-I的脂质化形式,维持自噬体膜的稳定性,是自噬体形成的基础,内源性LC3-II/LC3-I是自噬体敏感的、特异的标志物[9]。

2 肺血管重构中自噬的双重作用

在低氧、氧化应激或营养不良条件下,自噬通过清除受损的细胞器及错误折叠的蛋白来维持能量代谢、细胞活力及细胞内环境的稳定[10],异常自噬可破坏细胞内稳态,促进感染性疾病、癌症、神经退行性疾病、肺部疾病和心血管疾病等发生[11-13]。在PH发展过程中,血管重构是涉及血管壁细胞增殖、迁移、凋亡以及细胞外基质改变等过程的核心病理过程,持续或过度自噬可能推动血管重构[14]。

2.1 保护性自噬

自噬在PH发病机制中的作用尚存争议,有研究表明自噬促进PH发展[15,16];而另一些研究则表明自噬可防止PH发生,如PASMCs自噬激活通过抑制

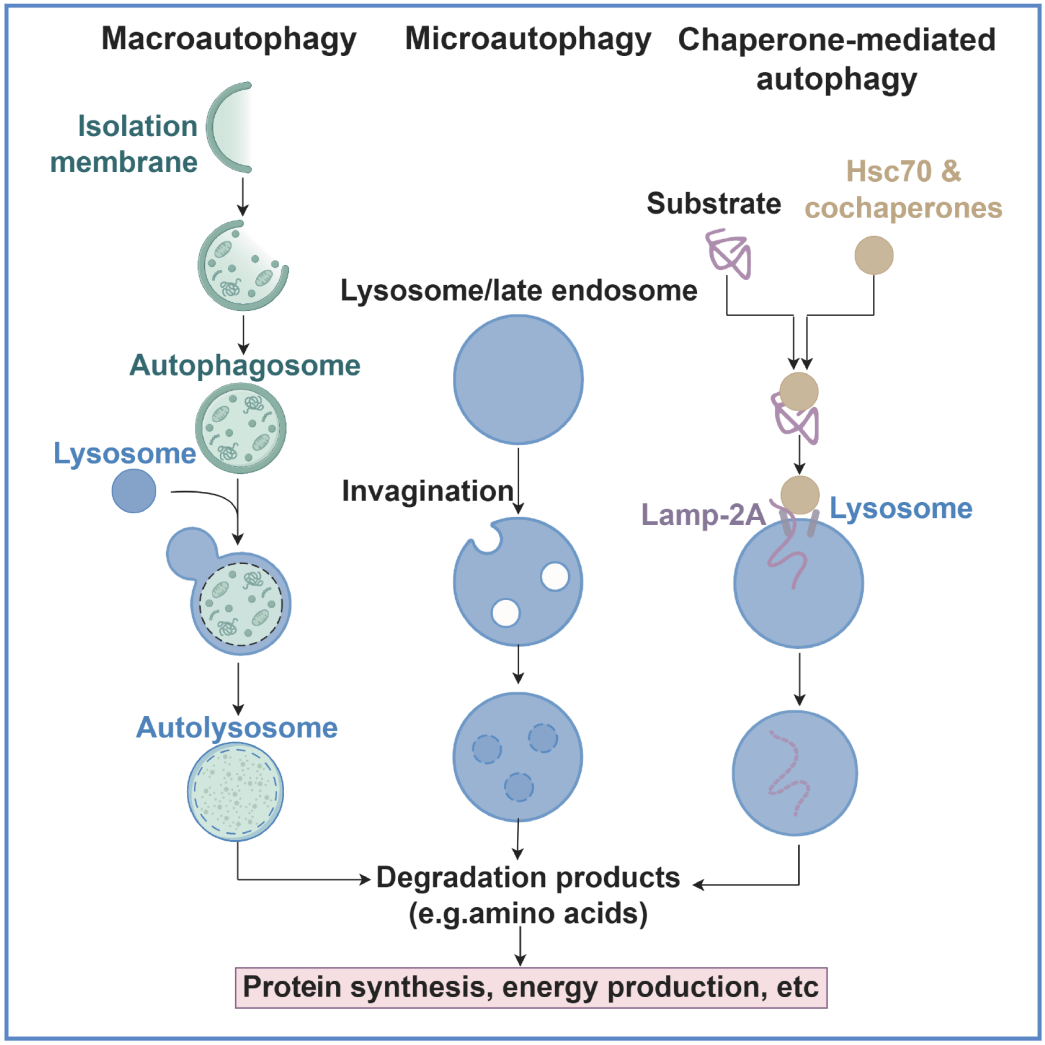

图1　自噬的3种类型

巨自噬：依赖溶酶体途径对胞质蛋白和细胞器进行降解，部分细胞质可被吞噬泡包围，形成自噬体，自噬体的外膜与溶酶体融合，内部物质在自噬溶酶体中降解。微自噬：溶酶体膜或后期核内体膜内陷，直接吞噬细胞质成分。分子伴侣介导的自噬：含有KFERQ样五肽序列的底物蛋白首先被细胞质中的Hsc70及其共伴侣蛋白识别，通过与溶酶体膜上的Lamp-2A结合被转运到溶酶体内。经过这三种类型的自噬产生的降解产物可用于新蛋白质合成、能量产生等等。由Figuredraw绘制。

Figure 1　The three types of autophagy

Macroautophagy: Relies on the lysosomal pathway to degrade cytoplasmic proteins and organelles. Some cytoplasm can be surrounded by phagosomes, forming autophagosomes. The outer membrane of the autophagosome fuses with the lysosome, and the internal material is degraded in the autolysosome. Microautophagy: The lysosomal membrane or late endosomal membrane is invaginated, directly engulfing the small components of the cytoplasm. Chaperone-mediated autophagy: The substrate proteins containing a KFERQ-like pentapeptide sequence are first recognized by cytosolic Hsc70 and cochaperones. Then they are translocated into the lysosomal lumen after binding with lysosomal Lamp-2A. The degradation products produced by these three types of autophagy can be utilized for new protein synthesis, energy production, and other purposes. Drawn by Figuredraw.

细胞增殖发挥保护作用[17]。在PH患者及低氧诱导的PH（hypoxia-induced pulmonary hypertension，HPH）小鼠模型中，肺和肺血管组织中LC3B表达升高，人PAECs和PASMCs中的细胞自噬也明显增加；过表达LC3B可抑制PAECs低氧依赖性增殖，但敲除*LC3B*基因的小鼠PH表型明显加重，表明在HPH中自噬蛋白LC3B可抑制血管重构的增殖过程[18]。以上提示，自噬过程是肺血管对低氧应激的一般反应；严重PH患者自噬发生率升高可能提示本身修复反应不足[18]。

此外，在慢性血栓栓塞性肺动脉高压（chronic thromboembolic pulmonary hypertension，CTEPH）大

鼠模型中，发现肺动脉内膜存在自噬缺陷，表现为Beclin-1和LC3B的mRNA与蛋白表达均降低，而组织因子（TF）蛋白表达升高，TF可通过丝裂原活化蛋白激酶（MAPK）信号途径上调VEGF表达，促进血管重塑，提示CTEPH中的自噬抑制可能促进肺血管重构和血栓形成[19]。

2.2 病理性自噬

目前越来越多的证据显示，自噬功能失调参与PH血管重构过程，并且上调的自噬与PH发生发展有关。哺乳动物摄入野百合碱（monocrotaline，MCT）后通过直接损伤内皮，引发肺血管炎和中膜层重构，是构建PH模型的经典方法之一。多项研究显示，MCT致PH大鼠模型自噬明显增强，LC3B蛋白显著增加，p62表达降低，LC3-II/LC3-I比值显著升高；抑制自噬可减轻MCT诱导的肺动脉重构[10,16,20]。Zhai等[21]发现NF-κB介导的自噬可促进PH的发展；且激活单磷酸腺苷活化蛋白激酶（adenosine monophosphate-activated protein kinase，AMPK）可通过靶向核因子-κB（NF-κB）抑制自噬及血管重构，缓解PH。

低氧本身就是一种代谢应激源，已证实可促进人PASMCs和PAECs自噬[22,23]。自噬的激活参与低氧诱导的PASMCs增殖和迁移，而采用自噬抑制剂3-MA可抑制PASMCs自噬和增殖[15]。金属硫蛋白3（MT3）可促进Atg5表达，促进低氧PASMCs的自噬小体形成[24]。特异性敲除小鼠内皮细胞*Atg7*则使肺血管重构明显缓解[23]。单细胞转录组测序发现，肺微血管内皮细胞（microvascular endothelial cells，MVECs）中的自噬通量明显高于PAECs，自噬可能介导不同类型内皮细胞对低氧产生差异性反应，最终导致PAECs增殖并伴随MVECs凋亡，促进PAECs取代凋亡的MVECs，从而驱动远端血管平滑肌化，促进PH进展[23]。此外，在暴露于阿片类药物的HIV相关PH患者肺组织及PAECs中，自噬被明显激活，自噬小体和自噬溶酶体数量明显增加，提示肺血管重构加重与自噬加剧有关[25]。抑制自噬有望成为一种新的PH治疗手段。

另外值得注意的是，在低氧、炎症等刺激下，外膜成纤维细胞被激活，表型发生改变并过度增殖，进而激活单核/巨噬细胞，促进炎症反应、细胞外基质（ECM）产生，并促进血管壁增厚和纤维化[26]。同时也有报道指出，VAFs可能是肺动脉成纤维细胞（pulmonary artery fibroblasts，PAFs）的主要来源，且PAFs更易发生增殖[26,27]。PAFs缺氧时，转化生长因子-β（TGF-β）、磷脂酰肌醇3-激酶（PI3K）、蛋白激酶B（protein kinase B/Akt）、哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）和p70核糖体蛋白S6激酶之间协同作用，对于PAFs的低氧增殖至关重要[28-30]。在动脉中过表达TGF-β1还可致内膜增生和纤维化，促进胶原蛋白和ECM生成[28]。近来研究发现，以旁分泌方式作用于VAFs的Omega-3脂肪酸衍生环氧化物（ω-3环氧化物）来源于肺组织肥大细胞，可通过抑制TGF-β/Smad2信号通路抑制肺成纤维细胞活化、增殖和迁移，从而减轻肺血管重构，有利于PH的治疗[29]。

外周炎症免疫细胞不仅通过炎症途径参与PH血管重构过程，其自噬调控也被证实参与血管病变[31]。在肥胖相关HFpEF肺动脉高压（PH-cHFpEF）小鼠肺组织中，肺泡巨噬细胞转录组分析显示自噬通路基因表达显著失调，Dusp1高表达伴随Atg7、Atg14水平下降，代谢应激通过上调c-Fos/Dusp1抑制肺泡巨噬细胞自噬，而自噬缺陷的巨噬细胞可分泌IL-6、TNF-α炎症因子诱导内皮细胞功能障碍[32]。在HPH小鼠模型中，低氧诱导的血小板活化因子乙酰水解酶II型（type II platelet-activating factor acetyl hydrolase，PAF-AH2）表达下降，可致肥大细胞产生的保护性ω-3环氧化物减少，失去对成纤维细胞增殖的抑制，从而使胶原沉积和血管重构加重[29]。

2.3 自噬作用方向的影响因素

自噬对PH的作用可随其被激活的程度、阶段、细胞类型以及涉及信号通路的不同等出现变化[33]。在PH发病初期，适度的自噬可清除受损细胞器，维持PAECs功能，而自噬过强时可造成PAECs细胞凋亡[34]；随着疾病进展，持续或过度激活的自噬导致PAECs功能紊乱、PASMCs增殖、内皮-间质转化（endothelial-mesenchymal transition，EMT）和血管肌化等，加重肺血管重构和右心衰竭风险[35]。不同细胞自噬表现出不同的效应，如PASMCs自噬能抑制细胞凋亡，促进增殖和肺血管重构[15]。巨噬细胞自噬可促进炎症、驱动内皮损伤，往往是病理性自噬[32]。不同的信号通路调控可使自噬发挥保护性或病理性作用，如适度激活AMPK-mTOR通路可促进自噬，抑制PASMCs增殖，减轻血管重构[33]；但持续的低氧可激活PI3K/Akt/mTOR信号通路，抑制自噬活性，从而促进PASMCs

增殖和抗凋亡,促进PH发展[36]。

3 关键自噬相关通路与PH血管重构

3.1 FoxO1通路

FoxO1 (forkhead box O1)是属于FoxO家族成员的转录因子,FoxO1磷酸化后从细胞核转运至细胞质,失去调控靶基因能力而抑制自噬;而细胞核FoxO1活化可增强Atg表达,促进自噬。在PH血管重构中,FoxO1主要通过促进自噬活性发挥保护作用,而FoxO1功能受损或表达减少则导致自噬抑制,加剧血管重构。在CTEPH大鼠模型PAECs中,FoxO1活性明显降低,Beclin-1表达及LC3-II/LC3-I下降,自噬减少,导致PAECs功能障碍和血管重构[37]。目前用于治疗特发性肺纤维化的吡非尼酮(pirfenidone)已被证实在Sugen/低氧(SuHx) 联合构建的PH大鼠模型中可增加PASMCs中核定位的FoxO1水平,从而减弱PASMCs增殖和迁移能力,这意味着吡非尼酮有望以FoxO1为靶点通过促进自噬来抑制PH的形成,可联合其他药物治疗严重PH[38]。

然而也有研究得到相反的结果。如FoxO1在MCT致PH模型中被显著磷酸化而失活,胞质FoxO1表达升高可激活PH大鼠PASMCs自噬;紫杉醇可降低FoxO1磷酸化,使其核积累增加,通过抑制自噬减轻肺血管重构[39]。Li等[40]以紫杉醇纳米晶颗粒(NPs)作为载体,开发了一种靶向共递送紫杉醇与凋亡蛋白Caspase-3的系统。该系统可通过精准靶向PASMCs并抑制其增殖,有效缓解MCT诱导的肺血管重构,改善心功能与血流动力学。

3.2 AMPK-mTOR-ULK1通路

AMPK是一种丝氨酸/苏氨酸蛋白激酶,由 α、β 和 γ 亚基组成,其中α亚基是催化亚基,通过磷酸化苏氨酸172残基激活AMPK,调节细胞代谢,维持能量稳态,在多种疾病中起保护作用[41]。mTOR是细胞自噬的负调节因子,抑制mTOR活性可促进自噬的发生。当低氧、ROS、细胞内ATP水平降低或AMP/ATP比值增加时,AMPK被激活,通过磷酸化mTOR复合体1 (mTORC1)抑制其活性,解除mTORC1对ULK1复合体(ULK1-Atg13-FIP200)的抑制,从而启动自噬[33]。AMPK也可通过直接磷酸化mTOR结合的伴侣蛋白Raptor以及蛋白结节性硬化复合物(tuberous sclerosis 2,TSC2),抑制mTORC1活性,诱导自噬[42]。unc-51样激酶1 (unc-51-like kinase 1,ULK1)是酵母Atg1的同源蛋白,可直接与AMPK结合并使其磷酸化激活,抑制mTORC1对细胞的抑制作用,促进自噬小体形成[34,43]。

AMPK-mTOR-ULK1通路在PH血管重构中主要发挥促进自噬、抑制病变进展的保护作用[44,45]。在低氧PASMCs模型中,salidroside通过激活AMPK-mTOR-ULK1通路显著增强自噬,进而抑制PASMCs增殖并促进其凋亡,减轻血管重构[45]。二甲双胍也对实验性PH呈现良好的治疗效果,既可以通过激活AMPK信号途径抑制低氧诱导的自噬和PASMCs增殖,减轻肺血管重构[46];也可通过AMPK信号增强NO通路,直接作用于PASMCs缓解MCT大鼠的血管收缩[47]。

此外,mTORC2可降低AMPK活性,激活mTORC1,从而抑制自噬,促进人特发性肺动脉高压(idiopathic pulmonary arterial hypertension,IPAH)PASMCs增殖和存活;在HPH大鼠模型中,抑制mTORC1/2 (双抑制剂PP242)可促进PASMCs自噬,逆转肺血管重构,改善肺血管密度,为靶向mTORC2治疗PH提供了新机制与策略[48]。

3.3 HIF-1α/BNIP3通路

研究发现,低氧引起的自噬可在多种血管疾病中被激活,包括肺动脉高压、心肌病、心肌损伤和动脉粥样硬化以及心脏和其他器官的缺血-再灌注损伤[49-51]等。前面已讨论的促死亡自噬主要是通过AMPK依赖性mTOR通路介导,除此之外,促生存自噬还可能涉及hypoxia-inducible factor-1α (HIF-1α)/Bcl-2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3)途径[52]。

BNIP3属于Bcl-2家族BH3-only蛋白,但与其他BH3-only蛋白不同,其BH3结构域不能与抗凋亡Bcl-2家族成员相互作用,因此缺失BH3结构域不影响BNIP3诱导细胞死亡[53];而缺失TM结构域会阻断BNIP3诱导细胞死亡, 使得BNIP3成为Bcl-2家族中具有独特特征的BH3-only成员[54]。目前已知BNIP3是HIF-1下游靶基因,低氧条件下HIF-1α可与BNIP3近端启动子中的缺氧反应元件(HRE)结合,诱导BNIP3表达升高[55]。BNIP3通过与Beclin-1竞争结合Bcl-2,解除对Beclin-1的抑制,从而激活自噬体形成,诱导细胞自噬而死亡[4](图2)。BNIP3还可与Rheb结合并阻断其激活mTOR,导致细胞自噬[56]。目前尚不清楚BNIP3是直接导致自噬,还是

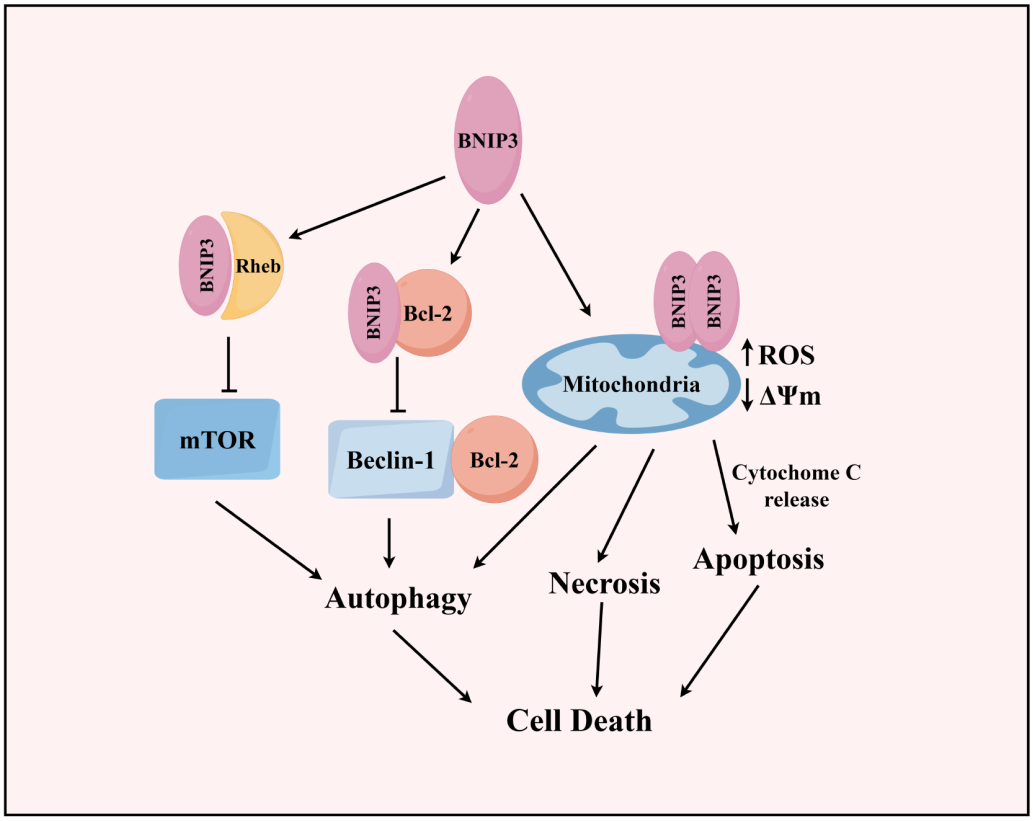

图2 BNIP3诱导细胞死亡的机制

BNIP3可通过凋亡、坏死和自噬途径诱导细胞死亡。BNIP3的TM结构域整合到线粒体外膜，可导致ROS增加、渗透转换(permeable transition，PT)孔开放及Δψm丢失，引起细胞色素C释放，从而激活凋亡蛋白Caspase，导致细胞凋亡。由Figuredraw绘制。

Figure 2 Mechanisms of BNIP3-induced cell death

BNIP3 can induce cell death via apoptotic, necrotic, and autophagic pathways. The integration of the TM domain of BNIP3 into the outer mitochondrial membrane can lead to an increase in ROS, the opening of the permeability transition (PT) pore, and the loss of Δψm, which triggers the release of cytochrome C, subsequently activates Caspases, and ultimately results in cell apoptosis. Drawn by Figuredraw.

通过BNIP3引起线粒体损伤而诱导自噬。

在慢性低氧条件下，PAECs需要完整且激活的HIF-1α/PDGF-B来维持病理性的远端小动脉肌化和肺动脉高压[57]。经PDGF-B处理的人PASMCs可上调Atg5、Atg7、Beclin-1 和LC3B 表达，进而促进远端小动脉肌化、PH及右心室肥厚[57]。在PASMCs或心肌细胞中，HIF-1α/BNIP3介导的线粒体自噬可以清除受损线粒体，减少ROS的生成和细胞死亡，在疾病早期起适应性保护作用[58]；研究发现，在MCT致PH模型右心室失代偿阶段(MCT 5~6周)，BNIP3和Beclin-1表达显著升高，提示在晚期病理阶段HIF-1α/BNIP3通路过度激活自噬，使心肌细胞死亡和心室功能衰竭加重[59]。

已有多项研究表明，靶向HIF-1α或HIF-2α可减轻慢性低氧诱导的肺血管重构[60-63]。但HIF-2α在内皮细胞中的病理作用比HIF-1α更明确，而在SMC中主要是HIF-1α起作用[63]。肺内皮细胞*Hif2α*基因缺陷可预防小鼠HPH发生及肺血管重构[60,64]。平滑肌特异性HIF-1α缺失可使持续低氧诱导的血管重构明显缓解，但其缺失并不能完全逆转这一反应，表明SMC HIF-1α并不是肺血管重构的唯一决定因素[63]，其他细胞途径或类型也可能参与HPH中低氧诱导的远端肺小动脉肌化，例如：缺乏T细胞的无胸腺大鼠发生PH和血管重构的风险增加[65]，慢性低氧可导致成纤维细胞表型改变等[66]。

3.4 PI3K/AKT/mTOR 通路

大多数研究认为，低氧环境下PI3K/Akt/mTOR信号通路可抑制自噬活性，促进PASMCs增殖和抗凋亡，是血管重构的重要驱动机制[33,67]，靶向该通路可恢复自噬，缓解病变。mTORC1位于通路下游，通过

磷酸化ULK1复合体，阻止自噬体形成，从而抑制自噬活性[33]。在HPH模型中，骨桥蛋白（osteopontin，OPN）激活PI3K/AKT/mTOR通路，显著下调自噬标志蛋白LC3B和Beclin-1，同时促进PASMCs增殖；下调PI3K或OPN表达可恢复LC3B和Beclin-1水平，诱导自噬并抑制细胞增殖[36]。

PH血管重塑发生和进展的关键是血管内皮损伤，研究显示肺血管内皮改变先于肺动脉肌肉化。在PH的早期阶段，PAECs由于PI3K/Akt通路被抑制而发生细胞凋亡[68]，随着疾病进展，触发PI3K/Akt信号过度激活，导致PAECs和PASMCs过度增殖，进而驱动血管重构，形成复杂肺血管病变[68,69]。低氧条件下增加半乳糖凝集素3（galectin-3，Gal-3）可激活Akt/GSK-3β/mTOR通路，促进PAECs凋亡，抑制自噬[70]。也有研究显示，PI3K/Akt/mTOR可通过促进自噬参与PH发生发展。在HIV相关PH中，自噬促进PAECs从细胞凋亡表型向过度增殖表型转变[25]。在PH患者肺组织中mTOR的表达明显下调，进而激活自噬[71]。在HPH小鼠模型中，过表达mTOR可抑制低氧诱导的PAECs自噬和增殖，明显缓解肺小动脉壁增厚和右心室肥大，在PH进展中起保护作用[71]。糖酵解蛋白ENO1在PH患者、HPH小鼠模型及PAECs中表达升高，靶向ENO1可通过PI3K/Akt/mTOR信号通路改善内皮、线粒体功能障碍和肺血管重构，从而缓解HPH[67]。

该通路还参与调节血管外膜成纤维细胞（VAFs）自噬，促进肺血管重构。盘状结构域受体2（discoidin domain receptor 2，DDR2）通过激活 PI3K/Akt/mTOR通路抑制自噬，导致ROS堆积，继而激活VAFs，使外膜纤维化、重构[72]。沉默调节蛋白1（Sirtuin 1，SIRT1）可抑制Akt/mTOR信号通路使VAFs发生自噬，再通过自噬-溶酶体途径降解NLRP3，从而抑制炎症反应[73]。

3.5 氧化应激与肺血管重构

氧化应激在PH发病机制中至关重要，而ROS是与氧化应激密切相关的自由基[74]。在病理条件下，氧化还原稳态失调使ROS产生增加，引起氧化应激，导致相关细胞成分氧化损伤；氧化应激还可通过多种机制诱导自噬[14]。疾病早期ROS可激活AMPK和FoxO诱导保护性自噬，但长期过度的自噬转变为病理性自噬，使肺血管重构加重、细胞异常增殖，促进PH进展[14]。自噬亦可通过p62介导、线粒体自噬等方式调节ROS水平，从而影响ET-1、TXA2、前列环素和PPAR-γ等血管活性因子的释放和作用，严重影响血管张力，调节细胞增殖和凋亡，进而导致肺血管重构[75]。

有研究表明ROS通过氧化Atg4的半胱氨酸残基抑制其蛋白酶活性，从而阻断磷脂酰乙醇胺（PE）从其与LC3的偶联物中裂解释放，使膜结合态LC3持续保留在自噬体膜上，进而促进自噬进程[76]。细胞在低氧和氧化应激时分泌的亲环蛋白A（cyclophilin A，CyPA）在PH中可参与诱导自噬和调节内皮细胞功能。在低氧或MCT诱导的PH大鼠中发现，抗肿瘤药物厚朴酚（honokiol，HNK）可减少自噬标志物表达，通过抑制CyPA减轻PAECs自噬、肺血管重构[77]。ROS还可通过激活NLRP3炎症小体促进自噬发生，而激活ROS-NLRP3通路可调节细胞自噬，进而影响PH血管重构过程[14]。

3.6 NF-κB通路

NF-κB是心肌梗死、肥大和扩张型心肌病、PH等多种疾病的重要转录调节因子，可调控炎症、免疫反应、细胞存活和增殖相关基因表达。目前已有研究证明，该通路可激活自噬，促进肺血管重构；自噬也可影响NF-κB信号通路的表达[34,78]。低氧可通过NF-κB激活自噬，从而促进PASMCs细胞周期从G_1期向S期转换，促进PASMCs增殖及肺血管重构[78]。在MCT致PH大鼠中，NF-κB被显著激活，并伴有Rho家族GTP酶3（Rho family GTPase 3，RND3）表达下降[21]。NF-κB调控基因Snail是EMT、细胞黏附和增殖的关键调节因子，研究显示IL-1β可通过激活NF-κB/Snail通路诱导人脐静脉内皮细胞（human umbilical vein endothelial cells，HUVECs）EMT[79]。

NF-κB通路可与AMPK、HIF-1α、MAPK、氧化应激等多条通路交互作用。激活AMPK可抑制NF-κB p56亚基向细胞核易位，降低自噬标志物水平，进而抑制自噬和血管重构，抑制PH进展[21]。在PH中AMPK常被抑制，其失活可解除对NF-κB的抑制，从而增强炎症与自噬。在HPH模型中，增多的ROS可直接激活NF-κB信号通路，上调自噬相关蛋白，促进PASMCs线粒体自噬；NF-κB激活进一步抑制细胞凋亡，增强细胞增殖与迁移能力，加重血管重构[69]；NF-κB激活还可诱导IL-1β、IL-6、TNF-α等炎症因子的释放，进一步加重氧化应激，形成“氧化应激-NF-κB-自噬”正反馈环路[69]。

3.7 eIF2α与肺血管重构

真核翻译起始因子2α激酶(eukaryotic initiation factor 2α,eIF2α)是翻译起始因子家族的调节亚基,主要负责催化蛋白质翻译起始。有文献报道,在PH肺血管重构过程中,eIF2α作为调控细胞增殖的关键分子发挥重要作用。在MCT致PH大鼠模型中,eIF2α高表达激活自噬,促进PASMCs增殖,并导致大鼠肺血管重构;而eIF2α siRNA可有效抑制LC3B表达、恢复p62水平,明显抑制PASMCs增殖和自噬。另外,使用自噬溶酶体抑制剂氯喹(chloroquine)抑制自噬溶酶体降解过程,可逆转eIF2α介导的增殖效应,进一步证实eIF2α通过自噬途径促进PASMCs增殖和血管重构[80]。

3.8 LC3/Beclin-1通路

自噬体形成由Beclin-1和LC3启动,参与调节PH肺血管重构。LC3B与成熟的自噬体呈正相关,Beclin-1作为抗凋亡介质Bcl-2的结合伴侣,对于细胞抵抗凋亡或自噬至关重要[81]。目前绝大多数研究支持LC3/Beclin-1在PH血管重构中主要发挥病理性作用[57,82-85]。在低氧、氧化应激等刺激下,人和小鼠的PAECs和PASMCs中LC3B、Beclin-1、Atg5、Atg7等自噬相关基因表达升高,启动自噬体形成[18,57]。MCT活性代谢产物野百合碱吡咯(monocrotaline pyrrole,MCTP)处理可显著提高PAECs自噬水平,加重PAECs功能障碍,促进PAECs增殖和迁移,从而促进血管生成[82]。

Beclin-1缺失可减少纤溶酶原诱导的自噬,加速细胞凋亡,提示自噬抑制可能对内皮细胞产生抗血管生成作用[83]。此外,Beclin-1可与抗凋亡蛋白Bcl-2形成复合物,因此缺乏Beclin-1可能会加速caspase依赖性细胞凋亡[84]。最近的研究显示,在*Beclin-1*缺陷小鼠中肺动脉平滑肌细胞(SMCs)中Beclin-1缺失可通过下调低氧诱导的Atg5、Atg7,促进SMCs细胞凋亡和减少细胞增殖,从而减轻已形成的远端小动脉肌化、PH及右心室肥厚;值得注意的是,肺动脉内皮细胞(ECs)中 Beclin-1缺失不改变慢性低氧小鼠的肺血管重构,因此,SMCs (而不是ECs)中的Beclin-1是维持病理性远端动脉肌化和PH所必需的[57]。

3.9 BMPR2通路

骨形态发生蛋白II型受体(bone morphogenetic protein (BMP) type 2 receptor,BMPR-II/BMPR2)主要表达于PAECs、PASMCs和外膜成纤维细胞中,可特异性识别TGF-β超家族。BMPR2表达减少是PH的重要致病因素,BMPR2异常可调节PAECs从早期促细胞凋亡状态到抗凋亡状态的转化,并促进PASMCs过度增殖,促进血管肌肉化和丛状病变的形成,在肺血管重构中发挥关键作用[69]。BMPR2可通过Smad信号通路抑制PASMCs增殖,其功能缺失可导致细胞过度增殖[16]。超过70%的家族性PAH患者以及约26%的IPAH患者携带BMPR2杂合突变。然而,BMPR2 突变不完全外显,说明其他遗传和环境因素也可导致PH。在MCT和SuHx两种PH大鼠模型肺组织、人类PAECs和PASMCs、IPAH患者肺MVECs中均发现BMPR2水平降低且自噬活性增强,LC3B水平显著升高[85]。BMPR2杂合突变蛋白主要经自噬-溶酶体途径降解,其表达下降可激活自噬,诱导肺动脉平滑肌细胞过度增殖,导致血管壁平滑肌层病理性增厚[20,85]。经氯喹或羟氯喹治疗的MCT大鼠,自噬明显被抑制,BMPR2蛋白表达增加,显著减轻肺动脉肌化和血管壁增厚[16];同时体外研究证实,氯喹可抑制PASMCs增殖并诱导凋亡,而不影响PAECs[16]。在一项II期临床试验中发现,他克莫司(tacrolimus,FK506)可显著上调PH患者BMPR2表达,从而改善TGF-β诱导的血管重构[86]。

BMPR2突变可致PAECs凋亡增加,促炎因子和生长因子分泌增多,造成内皮损伤。已有多项研究证实,下调PAECs中BMPR2可促进细胞凋亡[87-89]。BMPR2异常还与特异性的ECM成分重塑有关。抑制BMPR2信号通路可减少PASMCs中IV型胶原蛋白的生成,促进内皮损伤及后续的血管重构[90]。此外,自噬诱导的BMPR2降解还可促进EMT,进一步加重血管重构[91,92]。

3.10 MAPK信号通路

MAPK信号通路主要包括细胞外信号调节激酶(extracellular signal-regulated kinase,ERK)通路、c-Jun N-末端激酶(c-Jun N-terminal kinase,JNK)通路、p38丝裂原活化蛋白激酶(p38 mitogen-activated protein kinase,p38 MAPK)通路,均可调节细胞自噬。JNK通路不仅可介导抗凋亡蛋白Bcl-2磷酸化,上调Beclin-1促进自噬,还可协调自噬相关基因表达上调,如增强DNA损伤调节自噬调控因子(DNA damage-regulated autophagy modulator,DRAM)表达,诱导自噬发生[93]。ERK5可以直接磷酸化ULK1,下调自噬,其

抑制自噬与内质网未折叠蛋白反应有关,不依赖于AMPK和mTOR[94]。

p38 MAPK通路可通过激活不同的下游分子对细胞自噬发挥双向调控作用。p38 MAPK激活可诱导ULK1磷酸化,破坏ULK1-Atg13复合物,进而减弱自噬[95]。通过体内和体外研究显示,Notch4-ERK/JNK/p38 MAPK轴在低氧性肺血管重构中发挥重要作用,上调PASMCs中的Notch4可激活ERK/JNK/p38 MAPK通路,诱导肺血管重构[96]。黄芩苷通过下调p38 MAPK/基质金属蛋白酶9 (MMP-9)通路减轻慢性HPH[97]。OPN不仅可通过激活PI3K/AKT/mTOR通路下调自噬,促进PASMCs增殖[37],还可通过p38 MAPK通路抑制PASMCs自噬,进而促进HPH[98]。p38 MAPK通路亦可激活细胞自噬,破坏血管内皮紧密连接结构,造成屏障功能障碍;也可下调血管通透性相关关键屏障蛋白,最终导致肺血管病理改变,发生血管重构。此外,血红素氧合酶1 (hemin oxygenase-1,HO-1)抑制剂ZnPPIX可通过激活p38 MAPK途径诱导Beclin-1非依赖性自噬[95]。

ERK1/2信号通路可活化动力蛋白相关蛋白1 (dynamin-related protein 1,Drp1)介导的线粒体分裂-自噬轴,促进BMPR2进入溶酶体降解,并使DNA结合抑制蛋白1 (inhibitor of DNA binding 1,Id1)表达下调,从而增强PASMCs增殖与迁移能力,参与PH血管重构的发生发展过程[99]。值得注意的是,Chang等[100]研究发现,乙醛脱氢酶2 (ALDH2)基因缺失可显著激活ERK1/2磷酸化并激活自噬,提高肺组织和PASMCs内自噬小体和自噬溶酶体的数量,并促进PASMCs迁移、增殖,从而加重SuHx诱导的PH肺动脉肌化,提示ALDH2通过抑制ERK1/2-Beclin-1介导的自噬通路,抑制PASMCs增殖与迁移,从而缓解肺血管重构与PH进展,表明ALDH2可能成为PH潜在的治疗靶点[100]。

3.11 其他通路

此外,激活ROS-HIF1α通路、促进程序性细胞死亡因子4 (PDCD4)溶酶体降解、提高泛素化细胞凋亡诱导因子(AIF)水平和促进FOXM1介导的FAK磷酸化[13]等,都可激活自噬,促进PH发生发展。这些通路并非彼此孤立,而是存在错综复杂的互作调控关系。长期低氧诱导的自噬增强可能反过来导致程序性细胞死亡[101]。在婴儿血管瘤研究中发现,低氧诱导的自噬可通过调控HIF-1α和mTOR信号转换,使细胞由促生存转向促死亡:即短时间低氧可诱导HUVECs HIF-1α/BNIP3依赖性自噬,促进内皮细胞存活及增殖;而低氧应激作用持续较长时间后,则会引起AMPK/mTOR信号通路依赖性自噬激活,造成细胞损伤,进而导致后续的内皮细胞程序性死亡[49]。

4 靶向自噬的治疗策略

4.1 药物干预

针对自噬相关通路进行药物治疗是当前PH研究的重点。常用的治疗策略包括抑制细胞内的自噬和促进自噬。氯喹和羟化氯喹还通过阻止自噬小体成熟来抑制自噬,并可抑制低氧暴露的小鼠平滑肌细胞增殖,从而抑制PH发病[102]。低氧诱导的PASMCs增殖可被另一种自噬抑制剂3-MA逆转[15]。对已发生肺血管重构的大鼠给予两次多烯紫杉醇(docetaxel,DTX)腹腔注射治疗后,可观察到肺血管重构完全恢复至正常水平,右心室压(RVP)降低,其机制主要是DTX通过肌球蛋白重链9 (MYH9)调控Beclin-1,促进Beclin-1降解,抑制自噬,进而促进PASMCs死亡[103]。新型小分子溶酶体自噬抑制剂ROC-325具有较好的治疗前景,抗癌活性比抗疟药羟化氯喹更强,初步临床前研究显示该抑制剂对自噬有明显抑制作用,促进NO生成,促进血管舒张,抑制血管重构,从而缓解PH[20]。

由于PH血管重构机制复杂,促进细胞自噬的治疗策略不容忽视。黄酮槲皮素通过FoxO1-SENS3-mTOR通路诱导PASMCs细胞凋亡并增强低氧诱导的自噬[104]。采用自噬抑制剂处理PASMCs更易发生槲皮素诱导的细胞凋亡,提示联合槲皮素和自噬抑制剂可能是HPH治疗的一种新策略。荜拨酰胺(piperlongumine)可显著降低HPH大鼠右心室收缩压,缓解右心室肥厚、肺动脉壁增厚和肺小动脉肌肉化,并抑制低氧诱导的PASMCs增殖,通过增强自噬缓解HPH血管重构[105]。

目前这些药物仍处于研究阶段,尚未在临床广泛应用。只有少数调节自噬的化合物被用于临床,如雷帕霉素(mTOR抑制剂)、氯喹和羟化氯喹已被广泛用于临床抑制自噬[106]。

4.2 基因治疗

较多研究表明非编码RNA (non-coding RNAs,ncRNA)在PH血管重构中扮演关键角色。通过抑制miR-210[107]、miR-138-5p[108]、miRNA-205-5p[109]可

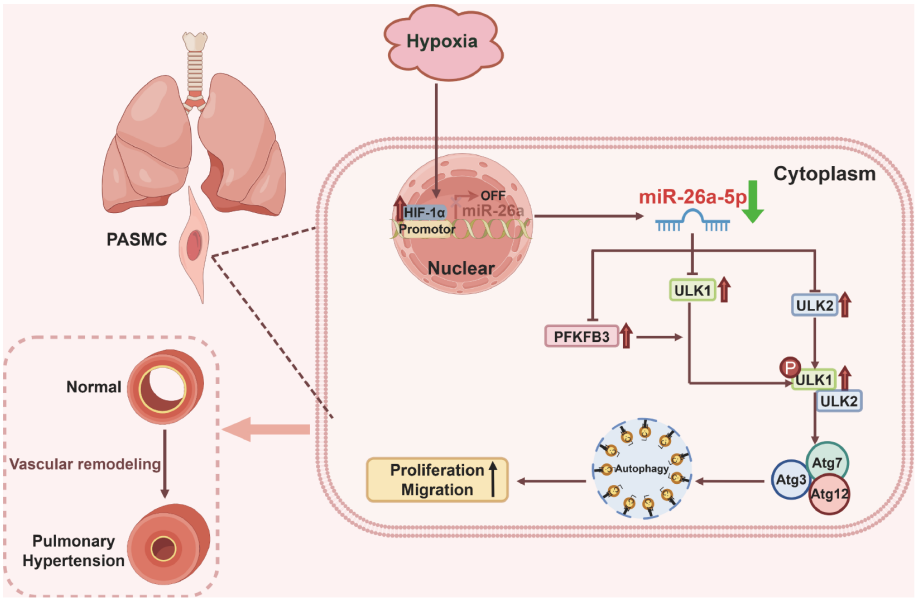

图3 低氧诱导的HIF-1α/miR-26a-5p/PFKFB3/ULK1/2信号通路调控及其对PH肺血管重构的影响

HIF-1α:低氧诱导因子1α（hypoxia inducible factor 1α);PFKFB3:6-磷酸果糖-2-激酶/果糖-2,6-双磷酸酶3（6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3);ULK1/2:unc-51样自噬激活激酶1/2（unc-51 like autophagy activating kinase 1/2);PASMC:肺动脉平滑肌细胞(pulmonary artery smooth muscle cell);Atg3/7/12:自噬相关3/7/12（autophagy related 3/7/12)。本图由Figuredraw绘制。

Figure 3 Regulation of the hypoxia-induced HIF-1α/miR-26a-5p/PFKFB3/ULK1/2 signaling pathway and effect on pulmonary vascular remodeling in PH

HIF-1α: hypoxia inducible factor 1α; PFKFB3: 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; ULK1/2: unc-51 like autophagy activating kinase 1/2; PASMC: pulmonary artery smooth muscle cell; Atg3/7/12: autophagy related 3/7/12. Drawn by Figuredraw.

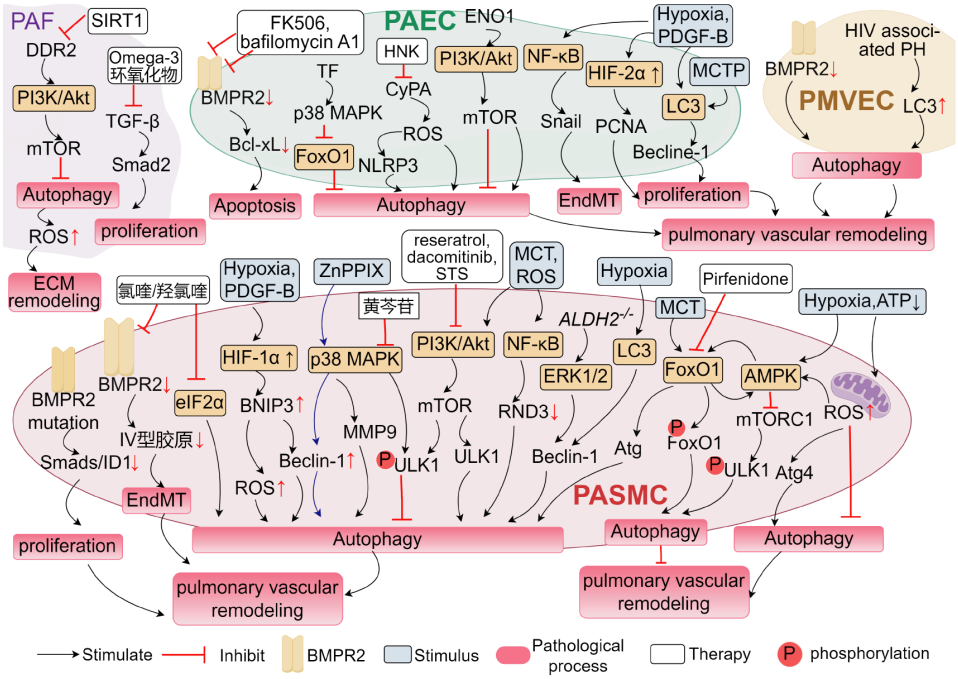

图4 调节肺血管重构的自噬相关信号通路及治疗物质

本图由Figuredraw绘制。

Figure 4 Autophagy-related signaling pathways and therapeutic substances of pulmonary vascular remodeling

Drawn by Figuredraw.

表 1 PH肺血管重构相关的自噬通路(主要起保护性作用)

Table 1 Autophagy-related pathways of pulmonary vascular remodeling in PH (mainly protective effect)

信号通路	动物模型或细胞类型	自噬相关蛋白改变	自噬水平	血管重构的影响	PH的功能结局	参考文献
FoxO1通路	CTEPH大鼠、PAECs	TF↑→p38MAPK↑→FoxO1活性↓→Beclin-1↓、LC3-II/LC3-I↓	抑制	抑制PAECs的自噬活性	组织因子抑制细胞自噬，促进血栓形成	[37]
	SuHx-PH大鼠、PASMCs	核内FoxO1↑→Beclin-1↑、LC3↑	促进	抑制PASMCs增殖和迁移，抑制血管重构	吡非尼酮可上调FoxO1表达和核转位，改善血流动力学，减轻右心室和肺血管重构，抑制PH发展	[38]
	MCT-PH大鼠、PASMCs	FoxO1磷酸化失活→胞质FoxO1↑→Beclin-1↑、LC3B/LC3A↑	促进	促进PASMCs增殖，抗凋亡	紫杉醇可减少FoxO1磷酸化，进而抑制自噬，减轻肺血管重构，抑制PH发展	[39]
AMPK-mTOR-ULK1通路	HPH大鼠、PASMCs	AMPK↑→mTOR↓→ULK1↑(AMPK↑-ULK1↑)→LC3-II/LC3-I↑、p62↓	促进	抑制PASMCs增殖，促进凋亡，减轻血管重构	Salidroside可直接激活ULK1或解除mTOR对ULK1的抑制，激活自噬，抑制PH发展	[45]
	HPH大鼠、PASMCs	AMPK↑→Beclin-1↓、LC3B-II/LC3B-I↓、p62↑	抑制	抑制PASMCs增殖，缓解血管重构	二甲双胍可激活AMPK信号通路，减轻低氧引起的血流动力学改变和右心室肥厚，抑制PH发展	[46]
	IPAH患者、HPH大鼠、PAVSMCs	Nox4↑→mTORC2↑→AMPK↓→mTORC1↑→Bim↓	抑制	促进PASMCs增殖和存活	促进PH进展	[48]
其他	HPH小鼠/人PAECs、PASMCs	低氧→Egr-1↑→LC3B↑→ ROS↓、HIF-1α↓	促进	抑制血管细胞增殖，减轻血管重构	上调自噬蛋白LC3B可减轻肺血管细胞增殖与重塑，对PH具有保护作用	[18]

表2　PH肺血管重构相关的自噬通路(病理性作用)

Table 2　Autophagy-related pathways of pulmonary vascular remodeling in PH (pathogenic effect)

信号通路	动物模型或细胞类型	自噬相关蛋白	自噬水平	血管重构的影响	PH的功能结局	参考文献
氧化应激通路	HPH/MCT-PH大鼠、PAECs	低氧/氧化应激→CyPA↑→Beclin-1↑、LC3B-II↑、Atg5↑、Atg7↑、p62↓	促进	促进PAECs增殖和肺血管内膜增厚	厚朴酚可通过抑制CyPA减轻PAECs自噬,减轻血管重构,抑制PH进展	[77]
	原代人肺微血管内皮细胞	ROS↑→ULK1↑、BECN1↑、Atg5↑、Atg7↑、LC3B-II↑	促进	PAECs从细胞凋亡表型转向过度增殖表型	Tat与吗啡协同通过ROS-自噬轴驱动肺内皮从凋亡到增殖的病理转换,导致血管闭塞性重塑,显著加重HIV相关肺动脉高压	[25]
NF-κB通路	HPH大鼠、PASMCs	低氧→NF-κB↑→LC3-II↑、LC3-II/LC3-I↑→CyclinD1↑、CDK4↑、CDK6↑	促进	促进PASMCs增殖、迁移,抑制凋亡,促进肺血管重构	低氧可通过NF-κB激活自噬,促使PASMCs细胞周期从G_1期向S期转换,促进PH进展	[78]
	MCT-PH大鼠、PASMCs	AMPK↓→NF-κB↑→LC3B↑、Beclin-1↑→RND3↓	促进	促进PASMCs增殖和肺血管重构	二甲双胍可通过激活AMPK,阻断NF-κB-自噬轴,抑制PASMCs增殖,从而减缓PH进展	[21]
eIF2α通路	MCT-PH大鼠、PASMCs	eIF2α↑→LC3B-II↑、p62↓→Ki-67↑、PCNA↑	促进	促进PASMCs增殖和肺血管重构	氯喹通过阻断自噬溶酶体降解,可逆转eIF2α介导的增殖,抑制PH的发展	[80]
LC3/Beclin-1通路	HPH小鼠、PASMCs、PAECs	HIF1/2α↑→PDGF-B↑→Beclin-1↑→Atg5↑、Atg7↑、LC3B↑、p62↓	促进	促进PASMCs增殖和远端小动脉肌肉化	促进PH及右心室肥厚	[57]
	MCT-PH大鼠、PAECs	MCTP→FDPS↑→ Rac1-GTP↑→PI3K/AKT/mTOR通路激活→Beclin-1↑、LC3b-II↑、p62↓	促进	促进PAECs增殖、迁移和血管生成	抑制FDPS或Rac1可抑制内皮自噬与增殖迁移,提高生存率	[82]
BMPR2通路	MCT-PH大鼠、SuHx-PH大鼠、PASMCs、PAECs	BMPR-II↓→LC3B-II↑、Atg5↑、p62↓	促进	促进PASMCs增殖,PAECs凋亡和功能障碍,减少PASMCs中IV型胶原蛋白的产生,促进EMT,加重血管重构	氯喹可抑制细胞自噬,抑制BMPR2的溶酶体降解,抑制PASMCs增殖并诱导凋亡,减轻肺动脉肌化和血管壁增厚,显著改善PH	[16,85,89-92]

表3 PH肺血管重构相关的自噬通路(双重作用)

Table 3 Autophagy-related pathways of pulmonary vascular remodeling in PH (dual effect)

信号通路	动物模型或细胞类型	自噬相关蛋白	自噬水平	血管重构的影响	PH的功能结局	参考文献
HIF-1α/BNIP3通路	HPH小鼠、人IPAH肺组织、PASMCs	HIF-1α↑→PDGF-B↑、BNIP3↑→Beclin-1↑、Atg5↑、Atg7↑、LC3B↑、p62↓	促进	促进远端小动脉肌化，抑制PASMCs凋亡	低氧激活自噬，平滑肌异常肌化，促进右心室肥厚和血流动力学改变，促进PH发展	[57]
	MCT-PH大鼠、6w心肌组织	HIF-1α↑→BNIP3↑→Bcl-2↓→Beclin-1↑→LC3-II/LC3-I↑、p62↑	促进	——	晚期病理阶段HIF-1α/BNIP3通路过度激活自噬，加重右心衰竭，导致PH恶化	[59]
PI3K/AKT/mTOR通路	HPH小鼠、PASMC	OPN↑→PI3K↑→PIP3↑→p-AKT↑→LC3B↓、Beclin-1↓	抑制	促进PASMCs增殖和血管重构	下调PI3K或OPN表达可恢复LC3B和Beclin-1水平，诱导自噬并抑制细胞增殖，降低平均肺动脉压，抑制PH进展	[36]
	HPH大鼠、PASMCs	Apelin↑→APJ受体↑→PI3K↑→p-Akt↑→p-mTOR↑→LC3-II↓、Beclin-1↓	抑制	抑制PASMCs增殖与迁移，减轻血管重构	外源性加入Apelin，可通过抑制自噬减轻血管重构，抑制PH进展	[15]
	HPH大鼠、肺动脉、PVECs	NF-κB↑→Gal-3↑→TRPC1/4↓→p-Akt↑→p-GSK-3β↑→p-mTOR↑→Bcl-2↓、Beclin-1↓、Atg5↓、LC3A/B↓	抑制	促进PVECs凋亡	缺氧可增加Gal-3表达，促进肺血管内皮凋亡与重塑，加速PH进展	[70]
MAPK通路	原代大鼠PASMCs	OPN↑→p38MAPK↑→Beclin-1↓、LC3B↓	抑制	促进PASMCs增殖，促进中膜肥厚与血管壁纤维化	OPN通过抑制自噬，促进PASMCs异常增殖，促进PH进展	[98]
	原代大鼠PASMCs	ERK1/2↑→Drp1磷酸化↑→线粒体分裂↑→Beclin-1↑、LC3B-II↑、p62↓、BMPR2↓、Id1↓	促进	促进PASMCs增殖与迁移，促进血管重构	HMGB1通过激活ERK1/2信号通路，促进PH进展	[99]
	SuHx-PH小鼠	ALDH2↓→4-HNE↑→ERK1/2磷酸化↑→Beclin-1↑、LC3B↑、Atg5↓、Atg7↓	促进	促进PASMC增殖与迁移，加剧肺血管重构	ALDH2通过抑制ERK1/2-Beclin-1介导的自噬，减少PASMCs增殖，缓解PH	[100]

抑制PASMCs增殖、分化和抗凋亡活性，降低实验性PH肺血管中膜肥厚。在人PAECs中下调miR-204可解除对Atg7的抑制来增强自噬水平，进一步减弱缺氧诱导的EMT，从而缓解肺血管重构，在一定程度上改善HPH[110]。在CTEPH大鼠中，lncRNA-GAS5可靶向抑制miR-382-3p进而促进自噬，降低大鼠mPAP，抑制PASMCs增殖活性和迁移能力，抑制肺动脉壁增厚及血管生成[111]。此外，环状RNA Sirtuin1 (circSIRT1)可与miR-145-5竞争性结合并激活Akt3从而促进PASMCs增殖、迁移和自噬，而下调circSIRT1通过靶向miR-145-5p/Akt3抑制PASMCs增殖、迁移和自噬从而改善PH ，已被认为是治疗PH的潜在分子靶点[112]。然而，目前仍需要更多临床数据支持及相关后续研究。

关于PH自噬途径的研究表明，在低氧诱导的PASMCs自噬和增殖中，HIF-1α/miR-26a-5p/PFKFB3/ULK1/2轴起关键作用(图3)，miR-26a-5p可抑制低氧诱导的PAMSCs自噬，减少自噬小体和自噬溶酶体的形成，减轻肺血管重构，可能是较有吸引力的标志物[113]。敲除*OPN*基因可恢复LC3B和Beclin-1水平，通过PI3K-AKT通路诱导保护性自噬，抑制 PASMCs增殖，改善HPH[36]。此外，抑制mTOR通路或激活自噬相关基因来增强自噬活性，亦可减轻PH血管重构程度[114]。

图4对调节PH的自噬相关信号通路及治疗物质进行了总结。

5 挑战与展望

肺血管重构是PH的标志性特征，也是引起PH肺血管阻力、肺动脉压力升高的重要原因。自噬失调可显著影响肺血管细胞功能，与PH发生发展、疾病进程密切相关。调节PH肺血管重构的自噬相关通路较为复杂，如FoxO1、AMPK-mTOR-ULK1通路主要发挥保护作用(表1)，NF-κB、eIF2α、LC3/Beclin-1、氧化应激、BMPR2突变主要发挥损害作用(表2)，HIF-1α/BNIP3通路、PI3K/AKT/mTOR和MAPK通路可发挥双重作用(表3)，其中ROS是连接多个通路的核心枢纽。在低氧条件下，PAECs和PASMCs自噬增强，细胞增殖增加，促进PH进展[71]。自噬也可抑制PASMCs增殖与肺血管重构，在低氧应激条件下发挥保护作用[18,115]。评估自噬在PH中的作用时，需综合考虑疾病阶段、细胞类型等多种因素的影响。由于自噬过程本身的复杂性，对于其在某些病理变化中的作用仍存在争议，目前自噬参与PH的具体机制尚未完全明晰，深入探索自噬对肺血管重构的调控作用，有利于推动PH分子机制研究，并促进自噬相关药物开发。相信随着对自噬在PH中分子作用机制的深入研究，自噬很可能成为防治PH的突破口和重要靶点。

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