•综述•

细胞色素P450及类二十烷酸代谢物: 高原疾病治疗的新靶点

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摘要: 细胞色素P450 (cytochrome P450, CYP450) 是机体中存在的最重要的代谢酶家族, 在类二十烷酸的生物合成与代谢调控中发挥关键作用。高原低氧影响CYP450的表达和活性, 进一步导致类二十烷酸代谢发生变化。低氧下类二十烷酸代谢物的改变可能是高原疾病发生和机体缺氧适应的重要机制, 然而, CYP450和类二十烷酸在高原疾病病理生理过程中的具体作用及低氧调控CYP450的分子机制, 目前仍不清楚。本文综述了高原低氧环境中CYP450和类二十烷酸代谢物的变化及细胞因子、核受体和表观遗传修饰等在低氧下对CYP450的调控作用, 并探讨了CYP450和类二十烷酸代谢物通过血管调节、炎症反应及氧化应激等途径参与高原疾病发生发展的可能机制, 以期为高原疾病的预防和治疗提供新的理论依据和潜在靶点。

关键词: 高原疾病; 细胞色素P450; 类二十烷酸; 缺氧; 代谢调控

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Cytochrome P450 and eicosanoid metabolites: novel therapeutic targets for high-altitude disease

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Abstract: Cytochrome P450 (CYP450) is the body's most important family of metabolic enzymes and plays an important role in eicosanoid metabolism. High-altitude hypoxia affects the expression and activity of CYP450, which further leads to changes in eicosanoid metabolism. The alteration of eicosanoid metabolites under hypoxia may be an important mechanism for the development of high-altitude diseases and the body's adaptation to hypoxia; however, the specific roles of CYP450 and eicosanoids in the pathophysiological processes of high-altitude diseases, as well as the molecular mechanisms by which hypoxia regulates CYP450, are still unclear. In this paper, we reviewed the changes of CYP450 and eicosanoid metabolites and the mechanisms of CYP450 regulation by cytokines, nuclear receptors, and epigenetic modifications under hypoxic environment and explored the possible mechanisms by which CYP450 and eicosanoid metabolites are involved in the development of high-altitude diseases through the pathways of vasoregulation, inflammation, and oxidative stress. This article aims to provide a new theoretical basis and potential targets for the prevention and treatment of high-altitude diseases.

Key words: high-altitude disease; cytochrome P450; eicosanoid; hypoxia; metabolic regulation

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高原环境具有低压、低氧、强辐射、寒冷等特征, 对机体平衡有着重要影响, 其中低氧是影响机体细胞代谢的主要因素。高原低氧环境会对机体的许多系统产生深远影响, 包括呼吸系统、中枢神经系统、心血管系统及内分泌系统等, 这种系统性病理生理改变会显著增加高原肺动脉高压 (high-altitude pulmonary hypertension, HAPH)、高原肺水肿 (high-altitude pulmonary edema, HAPE)、高原脑水肿 (high-altitude cerebral edema, HACE) 等一系列高原疾病的发病风险[1,2]。细胞色素P450 (cytochrome P450, CYP450) 是机体中存在的最重要的代谢酶家族, 研究发现高原低氧环境中CYP450的表达和活性发生改变, 导致药物的药代动力学特征发生变化[3-6]。除了参与外源性物质的代谢外, CYP450还参与内源性物质的代谢, 如花生四烯酸、维生素和类固醇等的氧化代谢[7]。越来越多的研究表明, 高原病患者体内CYP450的内源性代谢物特别是类二十烷酸的生物合成发生变化[8,9], 且抑制CYP450及相关代谢物的变化可以影响高原疾病的发生发展[10,11], 这表明CYP450及类二十烷酸代谢物可能是高原疾病发生发展和机体缺氧适应的重要机制。本文综述了CYP450及类二十烷酸代谢物在高原低氧环境中的变化及低氧下细胞因子、核受体和表观遗传修饰对CYP450的调控机制, 并探讨了CYP450及类二十烷酸代谢物在高原疾病中的作用及其病理生理机制, 以期为合理解释高原低氧相关疾病的发病机制提供参考依据, 同时为高原疾病的靶向精准治疗策略提供研究基础。

1　CYP450及类二十烷酸代谢物

CYP450酶是一类催化多种化合物代谢的含血红素酶, 在生物体内源性或外源性物质的代谢过程中起着关键作用。其中1～4家族主要参与药物、环境毒素等外源性物质的生物转化, 而5～51家族主要参与内源性物质的生物合成或分解代谢。值得注意的是, 某些具有外源性物质代谢功能的CYP450亚型如CYP2C、CYP2J、CYP3A和CYP4A等也同时参与内源性物质的代谢过程[12,13]。

长链多不饱和脂肪酸 (polyunsaturated fatty acids, PUFAs) 是构成磷脂膜的重要组分, 根据第一个双键出现的位置可分为*n*-3 PUFA和*n*-6 PUFA, 二十碳五烯酸 (eicosapentaenoic acid, EPA) 和二十二碳六烯酸 (docosahexaenoic acid, DHA) 是典型的*n*-3 PUFA, 亚油酸 (linoleic acid, LA) 和花生四烯酸 (arachidonic acid, AA) 是典型的*n*-6 PUFA, 由这些PUFA代谢生成的生物活性脂质介质称为类二十烷酸, 常见的有前列腺素、白三烯、脂氧素、环氧脂肪酸等。类二十烷酸的生成主要包括环氧合酶 (cyclooxygenase, COX)、脂氧合酶 (lipoxygenase, LOX) 和CYP450三种代谢途径, 其中COX和LOX途径研究较多, 分别催化生成前列腺素、凝血烷酸等和白三烯、羟基脂肪酸等。近年来, CYP450途径催化生成的环氧脂肪酸等类二十烷酸引起广泛关注, 越来越多的证据表明它们在多种疾病的病理生理过程中具有重要的生物学功能, 特别是低氧相关疾病[14,15]。CYP450环氧酶和ω羟化酶是CYP450途径中主要的代谢酶, 其中环氧酶主要有CYP2C和CYP2J, 此外, CYP1A、CYP2B、CYP2D等也具有环氧化能力。花生四烯酸是最具特征的PUFA底物, 在内皮细胞中, 环氧酶代谢花生四烯酸产生5,6-EET、8,9-EET、11,12-EET和14,15-EET四种主要的环氧二十碳三烯酸 (epoxyeicosatrienoic acid, EET) 区域异构体, 随后通过可溶性环氧化物水解酶 (soluble epoxide hydrolase, sEH) 代谢为相应的具有较低生物学效应的二羟基二十碳三烯酸 (dihydroxyeicosatrienoic acid, DHET)。除花生四烯酸外, 亚油酸经CYP450环氧酶代谢产生9,10-EpOME、12,13-EpOME等环氧辛烷酸 (epoxyoctadecamonoenic acid, EpOME), 在sEH的作用下进一步水解为9,10-二羟基-12*Z*-辛烷烯酸 (9,10-DiHOME) 和12,13-二羟基-9*Z*-辛烷烯酸 (12,13-DiHOME)。二十碳五烯酸经CYP450代谢可产生环氧二十碳四烯酸 (epoxyeicosatetraenoic acid, EEQ), 二十二碳六烯酸经CYP450代谢可产生环氧二十二碳五烯酸 (epoxydocosapentaenoic acid, EDP)。ω羟化酶主要包括CYP4A和CYP4F, 在平滑肌细胞中, ω羟化酶主要负责花生四烯酸的代谢, 生成19-或20-羟基二十碳四烯酸 (hydroxyeicosatetraenoic acid, HETE) (图1)。

2　高原低氧环境CYP450的表达和活性变化及调控机制

2.1　高原低氧环境CYP450的表达和活性变化

研究发现, CYP1A1[16]、CYP1A2[3,17]、CYP2B6[16]、CYP2E1[18]和CYP3A4[18-20]等药物代谢酶的表达和活性在低氧下降低, 导致高原低氧环境中大部分临床药物的代谢和清除速率减慢。而与类二十烷酸代谢相关的CYP450由于参与了低氧适应与高原疾病发展过程, 其在低氧下的表达和活性变化可能与其他CYP450酶存在一定差异, 如CYP2C8在低氧下的表达和活性升高[21], CYP2C19则表现为表达和活性降低[16], 而CYP2C9在低氧条件下的表达变化规律, 目前尚无共识。Duan等[22]研究表明, 当SD大鼠暴露在4 300 m高原缺氧环境中时, 无论是急性暴露 (24 h) 还是慢性暴露 (30天), 其肝脏组织中CYP2C9的表达水平均显著降低。类似的, Gola等[23]将SD大鼠置于模拟7 620 m

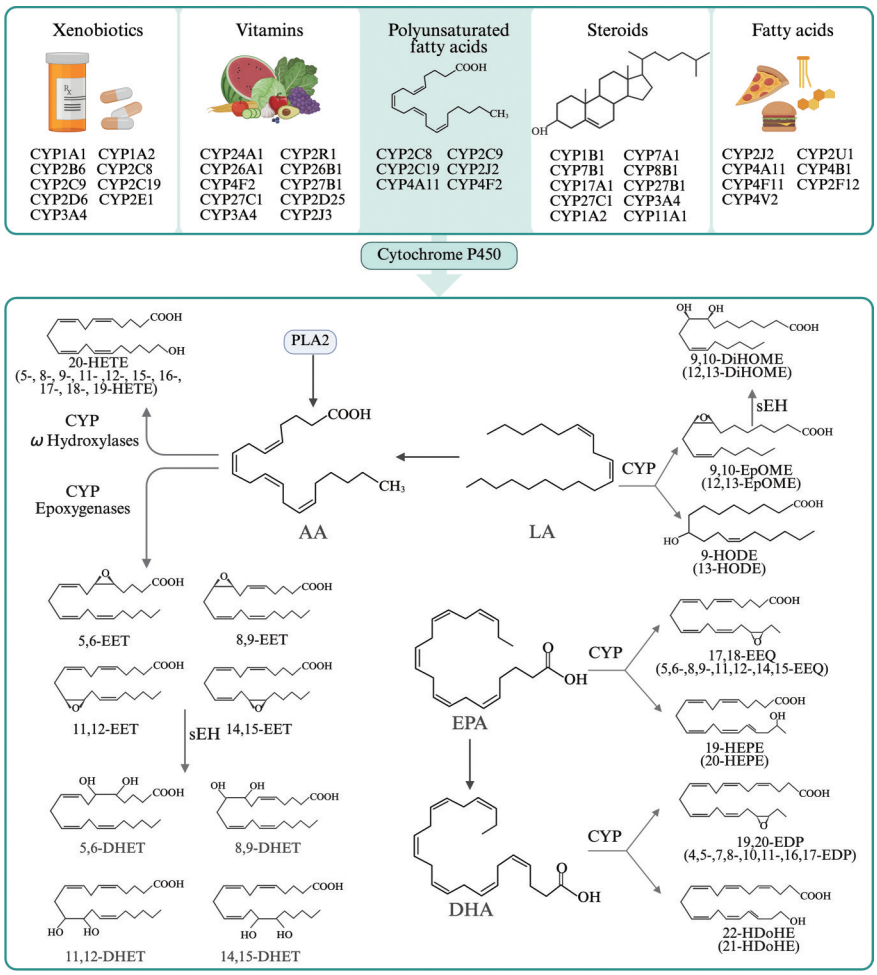


Figure 1 Cytochrome P450-dependent pathways involved in the biological transformation of eicosanoid. PLA2: Phospholipase A2; AA: Arachidonic acid; LA: Linoleic acid; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; EET: Epoxyeicosatrienoic acid; DHET: Dihydroxyeicosatrienoic acid; sEH: Soluble epoxide hydrolase; HETE: Hydroxyeicosatetraenoic acid; EpOME: Epoxyoctadecamonoenic acid; DiHOME: Dihydroxyoctadecenoic acid; HODE: Hydroxyoctadecadienoic acid; EEQ: Epoxyeicosatetraenoic acid; HEPE: Hydroxyeicosapentaenoic acid; EDP: Epoxydocosapentaenoic acid; HDoHE: Hydroxydocosahexaenoic acid

海拔的低压氧舱中, 发现持续暴露 7 或 14 天后, 肝组织 CYP2C9 的表达量同样明显下调。但在另一项研究中, 研究者将 Wistar 大鼠急性暴露在 4 010 m 海拔环境 24 h 后, 肝脏 CYP2C9 的表达反而出现上调现象[24]。关于 CYP2J2 的研究显示, 在 1% O_2 条件下培养 16 h 的 HepG2 细胞中, *CYP2J2* 的 mRNA 下调至常氧对照的 25%[25]。此外, 在缺氧再氧合诱导的细胞模型中, CYP2J2 蛋白表达也减少[26,27], 且相关研究表明, CYP2J2 在缺氧下的这种下调与 c-Jun 有关, 缺氧激活 c-Fos 的表达, 促进 c-Jun/c-Fos 异源二聚体的形成, 从而降低 c-Jun 与 CYP2J2 上游区域的结合, 导致基因表达下调[28,29]。

值得注意的是, 尽管 ω 羟化酶 CYP4A11 和 CYP4F2 在类二十烷酸代谢中发挥关键作用, 但关于其在低氧条件下的研究仍存在知识空白。早期在角膜器官培养模型中发现缺氧可上调 *CYP4A* 的 mRNA 表达水平[30], 但该研究未区分具体亚型, 此后 Chen 等[31]发现缺氧 (2% O_2) 可增加循环内皮祖细胞 CYP4A11 基因和蛋白质表达, 但针对 CYP4F2 在低氧下的表达变化仍缺乏系统研究。

以上研究表明, 高原低氧会影响体内 CYP450 的表达和活性, 其中, 环氧酶 CYP2C19 和 CYP2J2 的表达和活性在低氧下降低, 而 CYP2C8 的表达和活性在低氧下升高, ω 羟化酶 CYP4A 的表达和活性在低氧下同样降低, 其余 CYP450 的变化有待进一步研究。CYP450 在低氧下的表达和活性变化结果见表 1[3,16-24,31-33]。

2.2 高原低氧调控 CYP450 的机制

研究表明, 高原低氧环境中细胞因子、核受体和表观遗传修饰是调控 CYP450 的主要机制 (图 2), 这些调控机制相互交织, 共同维持 CYP450 的正常功能, 在低

Table 1　Effects of hypoxia on CYP450 expression and activity. ↑: Increase; ↓: Decrease

Family	CYP450	Endogenous substrate	Species	Effect	Hypoxia model	Ref
CYP1	CYP1A1	Steroid hormones, melatonin, AA, EPA	Rabbit	Protein ↓	Normobaric hypoxia chamber (FiO_2 = 8%, 48 h)	[16]
	CYP1A2	Hydrocarbons, steroids	Rat	Protein ↓, mRNA ↓, activity ↓	High-altitude hypoxic environment (4 300 m/2 800 m, 24 h/30 d)	[3,17]
	CYP1B1	Eicosanoids, fat-soluble, vitamins, steroids, bile acids	Mouse	Protein ↑, mRNA ↑	Hypobaric hypoxia chamber (10% O_2, 14 d)	[18,32]
CYP2	CYP2B6	AA, lauric acid, 17β-estradiol, estrone, ethinylestradiol, testosterone	Rabbit	Protein ↓	Normobaric hypoxia chamber (FiO_2 = 8%, 48 h)	[16]
	CYP2C8	AA, EPA, DHA	Human umbilical vein endothelial cells	Protein ↑, mRNA ↑	1% O_2 for 1, 4, 12, and 24 h	[21]
	CYP2C9	Steroids, melatonin, retinoids, AA	Rat	Protein ↓, activity ↓	High-altitude hypoxic environment (4 300 m/2 800 m, 24 h/30 d)	[22]
			Rat	Protein ↓	Hypobaric hypoxia chamber (7 620 m, 6 h/24 h)	[23]
			Rat	Protein ↑	High-altitude hypoxic environment (4 010 m, 24 h)	[24]
	CYP2C19	AA	Rabbit	Protein ↓	Normobaric hypoxia chamber (FiO_2 = 8%, 48 h)	[16]
			Rat	Protein ↓, activity ↑	High-altitude hypoxic environment (4 300 m/2 800 m, 24 h/30 d)	[3]
	CYP2D6	AA	Human	Activity ↓	High-altitude hypoxic environment (4 559 m, 7 d)	[33]
			Rat	Protein ↑, mRNA ↑, activity ↑	High-altitude hypoxic environment (4 300 m/2 800 m, 24 h/30 d)	[3]
	CYP2E1	AA	Rat	Protein ↓, mRNA ↓, activity ↓	High-altitude hypoxic environment (4 300 m/2 800 m, 24 h/30 d)	[18]
CYP3	CYP3A4	Steroids, bile acids, cholesterol, lipid, hormones, vitamin D	Rat	Protein ↓, mRNA ↓, activity ↓	High-altitude hypoxic environment (4 300 m/2 800 m, 24 h/30 d)	[18-20]
CYP4	CYP4A11	AA, fatty acid, lauric acid	Endothelial progenitor cells	Protein ↑, mRNA ↑	2% O_2 for 2 and 6 h	[31]

氧下药物代谢、毒物解毒及内源性物质的代谢合成等生理过程中发挥重要作用。

2.2.1　细胞因子　炎症是非遗传因素之一, 已被证明肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)、白细胞介素 (interleukin, IL)-1β、IL-6和转化生长因子-β等炎症因子会降低CYP450的表达和活性, 特别是在一些炎症或感染模型中, CYP450蛋白及mRNA的表达水平降低[34-36], 此外, CYP450的下调与核因子κB (nuclear factor-kappa B, NF-κB) 表达增加也有关系[37]。由急性和慢性缺氧引起的全身性炎症, 提供了低氧下CYP450变化的复杂机制。Fradette等[38]指出急性中度缺氧 (FiO_2为8%的环境中缺氧48 h) 会降低CYP1A1、CYP1A2的活性和表达, 增加CYP3A6表达和活性, 而干扰素-γ、IL-1β和IL-2等的释放促成了CYP450的这些变化。此外, 低氧诱导因子 (hypoxia inducible factors, HIF) 可介导CYP450表达的改变。HIF是慢性缺氧反应的主要效应因子, 能够调节各种下游靶基因以增加氧气供应或减少氧气消耗, 从而促进机体对低氧的适应。常氧条件下, 脯氨酸羟化酶 (proline hydroxylase, PHD) 激活, HIF-1被蛋白酶水解, 而在缺氧条件下, PHD被抑制, 使HIF-1得以稳定存在。研究表明, HIF-1和CYP450之间的相互作用可能是低氧调控CYP450变化的主要机制。Liu等[39,40]将星形胶质细胞在1% O_2缺氧条件下孵育1、3和6 h, 发现CYP2C11 mRNA和蛋白水平显著增加。有趣的是, 研究发现缺氧1 h后, 在CYP2C11表达增加之前, HIF-1α蛋白表达增加, 并且CYP2C11启动子DNA和HIF-1α之间存在特异性且直接的相互作用。另一项研究还报道了HIF和CYP450之间存在的间接调节作用, 研究者发现缺氧下HIF信号的激活导致CYP7A1负调节因子E4BP4的表达增加, 从而导致CYP7A1表达下调[41]。这些结果表明, 缺氧诱导的CYP450表达水平的下调是由炎症因子和HIF水平的变化共同介导的。

2.2.2　核受体　核受体是调节CYP450的重要转录因子, 低氧条件下孕烷X受体 (pregnane X receptor, PXR)、组成型雄烷受体 (constitutive androstane receptor, CAR)、芳香烃受体 (aryl hydrocarbon receptor, AHR) 和肝核因子 (hepatocyte nuclear factor, HNF) 等核受体参

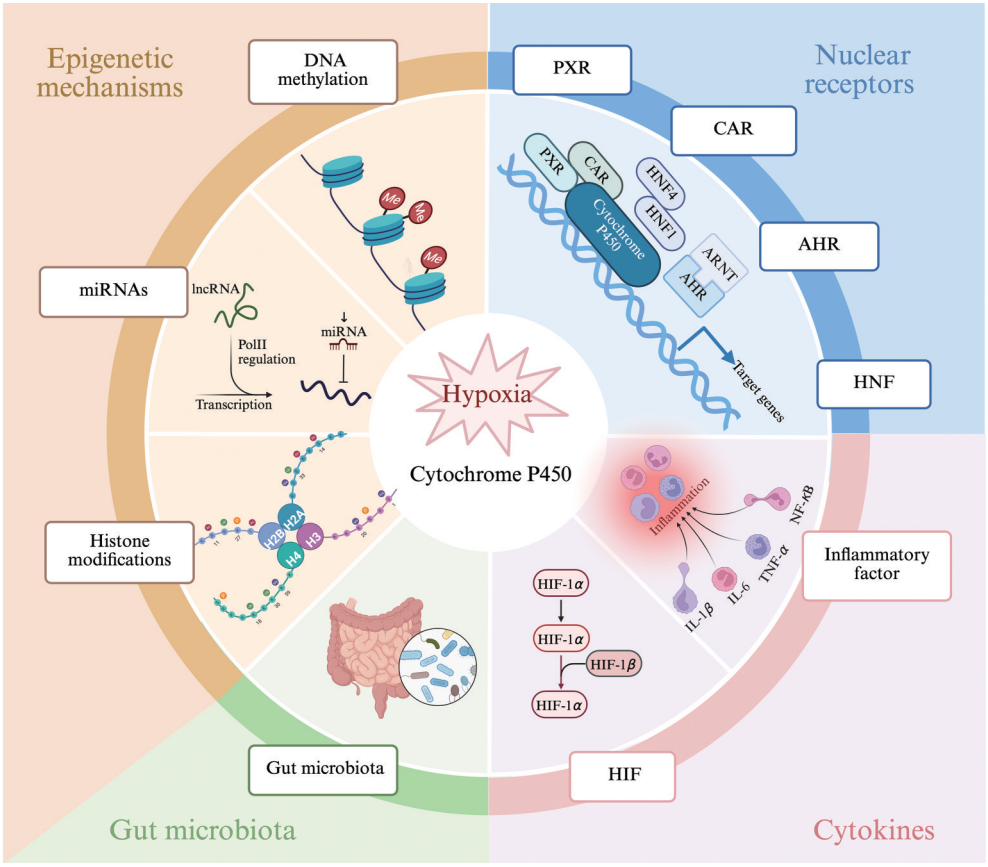


Figure 2 Regulatory network of cytochrome P450 under hypoxia. Four main mechanisms are involved: ① Hypoxia reduces the expression of nuclear receptors such as PXR, CAR, AHR, and HNF, and further regulates the activity and expression of CYP450. ② Hypoxia induces epigenetic changes, miRNA and lncRNA expression are suppressed under hypoxia, while hypoxia induces DNA methylation and histone modification, which together regulate CYP450 expression. ③ High-altitude hypoxia activates inflammatory factors and NF-*κ*B signaling pathway to negatively regulate CYP450 expression; meanwhile, HIF-1 binds to hypoxia-responsive elements of downstream genes under hypoxia to regulate CYP450 and nuclear receptor expression. ④ High-altitude hypoxia alters the structure and diversity of the gut microbiota, mediating changes in CYP450 expression through the release of extracellular vesicles. PXR: Pregnane X receptor; CAR: Constitutive androstane receptor; AHR: Aryl hydrocarbon receptor; ARNT: Aryl hydrocarbon receptor nuclear translocator; HNF: Hepatocyte nuclear factor; miRNAs: microRNAs; lncRNA: Long non-coding RNA; TNF-*α*: Tumor necrosis factor-*α*; IL-1*β*: Interleukin-1*β*; IL-6: Interleukin-6; NF-*κ*B: Nuclear factor-kappa B; HIF-1: Hypoxia inducible factor-1

与CYP450表达的调控。

PXR和CAR是孤儿受体亚家族的成员, 在细胞核中充当转录因子, 保护细胞免受毒性损伤。研究发现, 低氧影响PXR和CAR的表达[42], 而PXR或CAR在缺氧下的这种变化可能是介导缺氧期间CYP450变化的潜在机制。Legendre等[43]在1% O_2缺氧条件下培养24 h的高度分化的人类肝瘤HepaRG细胞中发现CAR、PXR和AHR的表达下调, 同时CYP3A4、CYP1A2、CYP2E1和CYP2C9的活性降低。本课题组的研究也进一步证实缺氧会通过PXR和CAR调节途径抑制CYP1A2、CYP2C9、CYP2E1和CYP3A4的表达[22]。AHR是一种配体依赖型转录因子, CYP1A1和CYP1A2是AHR典型靶基因, AHR通过与ARNT结合形成AHR/ARNT复合物, 促进CYP1A1和CYP1A2的转录, Zhang等[44]发现缺氧 (1%或2.5% O_2) 显著减少*CYP1A1*和*AHR*的mRNA, AHR siRNA也显著减少*CYP1A1* mRNA。缺氧联合AHR siRNA的组合比单独治疗更能减少*CYP1A1* mRNA, 但减少幅度小于相加, 这表明缺氧和AHR缺乏可能在减少CYP1A1表达方面具有共同的途径, 而这种途径可能与低氧下HIF的表达相关。因为ARNT不仅是AHR的配体, 也能与HIF-1*α*二聚化, 因此, 由于低氧下HIF-1*α*与ARNT的竞争性结合增加, 减少了AHR与ARNT的结合, 导致AHR对CYP450的靶向减少[45-47]。

HNF1*α*和HNF4*α*是肝脏中最重要的一类肝脏富集因子, 参与调节人肝脏中大多数CYP450基因的组

成性表达, 研究发现HNF4α和HNF1α的敲低改变了*CYP2B6*、*CYP2C8*、*CYP2C9*、*CYP2C19*、*CYP2E1*、*CYP1A2*和*CYP3A4*的mRNA水平[48,49]。缺氧会抑制HNF的表达, Mazure等[50]发现缺氧下调了HepG2细胞中的HNF4蛋白和基因表达, Sato等[51]发现缺氧会降低β细胞中的HNF4α蛋白表达和稳定性。而缺氧环境下, HNF1α和HNF4α的表达变化可能是调控CYP450表达的重要机制。Yang等[52]通过测定高原缺氧环境中大鼠体内HNF和CYP450的表达以及体外验证实验, 证实HNF1α和HNF4α在低氧条件下通过相互抑制的方式协同下调CYP1A2的表达。

2.2.3　表观遗传修饰　DNA甲基化和微小RNA (microRNA, miRNA)是研究最广泛的表观遗传机制, 表观遗传调控的改变发生在多种病理过程中, 而低氧条件诱导的表观遗传修饰可能调控CYP450表达。

DNA甲基化是指甲基通过DNA甲基转移酶添加到CpG二核苷酸内胞嘧啶环的C5位置的过程。一些CYP450酶中含有关键的CpG岛, 因此CYP450的表达水平受到DNA甲基化修饰的精确调控[53-55]。DNA甲基化是缺氧反应中不可或缺的调控机制, 有研究发现藏族和非藏族之间的差异甲基化基因在高海拔基因周围富集, 这表明DNA甲基化的改变在高海拔适应中起着重要作用[56]。Zhang等[57,58]的研究又进一步证实低氧下DNA甲基化与学习记忆能力的改变及缺氧耐受性的增强有关。CYP450的DNA甲基化在低氧反应中也同样重要, Jin等[59]对中国HAPE患者进行甲基化分析, 发现HAPE患者*CYP2S1*基因启动子区的多个CpG位点异常甲基化, 但DNA甲基化在低氧下是否还调节其他CYP450表达, 需要更多的研究来验证。

miRNA是研究最为广泛和深入的非编码RNA。研究发现, 缺氧可上调或下调miRNA的表达[60,61], 而miRNA负向调节CYP450的表达, Krkoška等[62]在人类肝脏HepaRG细胞中发现miR-653和miR-29c是CYP1A2表达的有效抑制剂。Tantawy等[63]使用全基因组miRNA分析来识别与CYP3A表达相关的miRNA, 确定并验证了miR-107和miR-1260与CYP3A4、CYP3A5和CYP3A43的表达密切相关。miRNA对CYP2C8、CYP2C9、CYP2E1同样具有负调节作用[64-66]。由此说明miRNA是缺氧介导的CYP450表达变化的关键分子机制[67]。本课题组研究发现, 在2% O_2下培养24 h后Caco-2细胞中的miR-873-5p显著降低, 并可调控MDR1和PXR的表达, 进一步介导缺氧下药物转运体的功能和表达水平的改变[68], 但miRNA对CYP450的功能和表达是否具有类似的影响, 仍需进一步探索。此外, 近年的研究表明, 组蛋白修饰作为关键的表观遗传调控机制, 同样可以调控CYP450的表达[69,70], 同时缺氧又会诱导组蛋白酶的表达发生变化[71], 因此缺氧下CYP450的表达变化与组蛋白修饰的相关性也是未来研究的另一重要方向。

3　CYP450及类二十烷酸代谢物在高原疾病中的变化及作用

3.1　缺氧性中枢神经系统损伤

在人体所有组织中, 神经系统组织对低氧的耐受能力最差, 正常成年人脑重占体重2%左右, 但其耗氧量却达到全身耗氧量的20%, 因此对缺氧十分敏感。高原低氧尤其是急性高原低氧会引发中枢神经系统功能障碍, 引起高原性头痛、急性高山病和高原性脑水肿等脑损伤[72-74]。越来越多的研究表明, 缺氧会显著影响脑组织中CYP450的表达水平, Jacob等[45]将人脑微血管内皮细胞系(hCMEC/D3)暴露于缺氧条件下6 h, 发现CYP1A1和CYP1B1的表达显著降低。另一项研究指出, 在低氧环境下, 大西洋黄花鱼下丘脑中CYP19a1b的活性、CYP19a1 mRNA和蛋白质表达量均显著下降[75]。然而, 并非所有脑CYP450酶都对缺氧表现出相同的反应模式, 如CYP46A1的表达在低氧条件下反而上调[76]。这些研究表明, 脑中CYP450在缺氧条件下的表达调控具有复杂性和多样性, 但可以确定的是缺氧通过调控脑中CYP450的表达及类二十烷酸的生物合成, 进而参与脑功能调节。本课题组通过DIA测序发现, 高原低氧环境中大鼠脑内CYP450表达发生变化, 且这种变化可能与血脑屏障结构和功能的变化相关[77-79]。此外, 缺氧下的脑血管扩张也与CYP450及类二十烷酸的变化相关。缺氧通过扩张脑血管以维持大脑的氧气和能量供应, Leffler等[80]最早发现CYP450环氧合酶抑制剂咪康唑可以降低新生猪缺氧时脑微血管扩张程度, 这表明CYP450在调节缺氧下脑血管扩张中具有重要作用, 此后的研究进一步确定了CYP2C11及EET的血管扩张作用。Yamaura等[81]发现缺氧(2% O_2)增强星形胶质细胞钙激活钾(K^+_{Ca})通道电流的开放状态概率(NPo)和CYP2C11及EET的表达, K^+_{Ca}通道的激活能使血管平滑肌细胞膜电位超极化, 进而引起血管扩张, 而CYP环氧酶抑制剂抑制了K^+_{Ca}单通道电流的NPo增加, 外源性11, 12-EET增加了K^+_{Ca}单通道电流的NPo, 这表明CYP2C11及EET可能是低氧下通过调节K^+_{Ca}通道电流活动引起血管扩张的关键机制[82]。除EET外, 低氧下HETEs生物合成的变化也与脑功能调节有关, 研究发现缺氧降低脑中20-HETE的基础内源性水平, 而外源20-HETE减弱了缺氧诱导的大鼠脑动脉肌细胞中K^+_{Ca}电流的激活, 这说明20-HETE也参与缺氧诱导的

动脉 K^+_{Ca}通道电流激活和脑血管舒张, 但与CYP2C11不同的是, 缺氧下的脑血管扩张与CYP4A无关[83]。尽管缺氧下CYP450及相关的类二十烷酸代谢物参与脑功能的调节分子机制尚未完全确定, 但可以确定的是它们对低氧下脑血管收缩功能的调节至关重要。

3.2 缺氧性肺损伤

在急性缺氧环境下, 肺血管收缩, 肺动脉阻力增加, 同时缺氧肺泡周围的血流减少, 使这部分血流向通气良好的区域重新分布。长期缺氧会使机体产生一种病理状态, 导致肺动脉重塑, 动脉压力升高, 最终发展成为肺动脉高压, HAPH就是常见的慢性高原病之一[84,85]。研究表明, CYP450与缺氧相关的肺损伤的发生发展存在显著关联。Si等[86]开展的针对中国汉族人群的研究发现, *CYP4F2*基因多态性与HAPE易感性密切相关, 在另一项多中心病例对照研究中, 研究人员发现*CYP19A1*的基因多态性在肺动脉高压的发展中同样起着重要作用[87]。此外, White等[32,88]的研究则从临床和分子层面证实CYP1B1和肺动脉高压的相关性, 发现在慢性缺氧小鼠和肺动脉高压患者肺中CYP1B1的表达增加, 并在肺血管壁中高度表达, 而$CYP1B1^{-/-}$小鼠及使用了CYP1B1抑制剂的小鼠肺血管重塑和肺动脉收缩减弱, 说明缺氧下肺CYP1B1表达增加促进了PAH的发展。此后在一种使用同源和部位定向重组策略建立的*CYP2J2*基因缺失小鼠中发现, 缺氧导致肺血管收缩和全身氧合功能受损, 而递送了编码*CYP2J2*的BAC序列补体的小鼠则没有发生这种损伤, 这表明*CYP2J2*也参与了缺氧下肺血管功能的调节[10,89]。此外, 缺氧下肺中CYP4A、CYP2C9等的表达变化也与缺氧时的肺血管收缩紧密相关[44,90,91], 而CYP450的这种调节作用实际上与类二十烷酸代谢物的变化有关。Kiss等[92]开发了一种类二十烷酸分析技术, 发现在缺氧肺血管收缩条件下游离EETs及其水合产物游离DHETs的生成大大增加, 因此推测EETs/DHETs可能对延长缺氧性肺血管收缩反应做出重大贡献。Pokreisz等[91]进一步证实EETs在缺氧性肺血管收缩中的作用, 他们发现慢性缺氧 (7天) 引起Swiss Webster小鼠肺动脉高压和肺血管重塑, 同时增加CYP2C29 (CYP2C9同工酶) 的表达。此外, 缺氧小鼠肺微粒体合成的8,9-、11,12-和14,15-EET/DHET增加, 而环氧化酶抑制剂处理后缺氧性肺收缩减弱, 可溶性环氧化物水解酶抑制剂处理后收缩增强, 这表明CYP450环氧化酶衍生的EETs可引起低氧下的肺血管收缩。尽管很多研究都证实缺氧下EETs对缺氧肺动脉高压发展的调节作用[93-95], 但这种作用又是复杂的, 在离体灌注的小鼠肺中, 11,12-EET引起肺动脉压力增加, 但14,15-EET没有作用, 而11,12-EET又不影响猪肺动脉的张力, 此外, 5,6-和11,12-EET可分别舒张家兔和仔猪的肺动脉[96-98], 产生这些差异的原因尚不清楚, 但可以确定的是EETs对肺血管的调节作用可能与K^+_{Ca}通道调节及下游血管收缩调节剂的生成有关, 这将在后续进行进一步讨论。此外, 肺中HETEs特别是15-HETE和20-HETE的生物合成也受到缺氧的调控, 而HETEs又进一步通过促进肺血管重塑或者改变肺血管张力来调控缺氧性肺血管收缩的持续发展[99,100]。

3.3 缺氧性心脏损伤

在处于急性高原缺氧环境时, 心率和心输出量增加, 而经过一段时间的适应, 心率及心室功能可能会回到正常状态[101,102], 尽管目前没有直接证据表明高原缺氧下心脏功能的变化直接参与了高原病包括急性高原反应、高海拔肺水肿或高海拔脑水肿等的发展, 但对心血管疾病患者来说, 心血管功能的受损加之氧气运输变化可能会加重脑卒中、心肌损伤和血栓形成。研究发现, CYP1A1、CYP1A2、CYP1B1、CYP2B6、CYP2C8、CYP2C9、CYP2E1、CYP2J2、CYP4A11和CYP4B1均在心脏表达[103], 而位于心脏内的CYP450及类二十烷酸代谢物具有心脏保护作用。Zhao等[104]研究发现, CYP2J2在急性心肌梗死和陈旧性心肌梗死患者中的表达明显增加, 随后通过转基因大鼠及体外研究, 进一步证实CYP2J2和EETs对心功能的改善作用。此后, 一系列的研究证明, 在心血管系统中, EETs能够通过抑制炎症、舒张血管、抑制凋亡等作用防止缺血性损伤、非缺血性心肌病、糖尿病性心肌病、心脏纤维化和心律失常, 因此, 防止EETs降解的药物已被证明可逆转疾病状态下心脏的病理改变[105,106]。而羟基化的代谢物HETEs特别是20-HETE则通过调节血管收缩物 (内皮素-1、血管紧张素II、心房利钠肽、5-羟色胺和一氧化氮等) 的释放控制血管收缩及血压变化进而间接影响心脏功能[107-109]。此外, 其他的类二十烷酸如EEQ、EDP以及水合产物特别是DiHOME等也具有心脏保护作用[14]。然而, 目前对心脏特异性CYP450及类二十烷酸代谢物在缺氧下心脏生理和病理学中的作用的认识水平是有限的。早期研究采用蛋白质组学方法发现高原牦牛心脏组织中的差异丰度蛋白富集于CYP450[110], 说明高原低氧导致心脏内的CYP450发生变化促进机体对低氧的适应, 但缺氧下CYP450及类二十烷酸代谢物的心脏保护或毒性作用还需要更多的研究去证实。

总之, 在高原缺氧环境下, CYP450/类二十烷酸代谢通路发生显著紊乱, 这一代谢网络的失调与高原疾病的病理生理过程密切相关。基于现有研究证据, 本

课题组推测CYP2C9[81,82,91]、CYP2J2[10,25,89]和CYP4A[31,83]可能是参与高原疾病发生发展和机体低氧适应性调节的关键代谢酶, 而EETs[81,82,91,92]和HETEs[83,100]是介导低氧下机体功能失调的重要基础。

4　CYP450及类二十烷酸代谢物参与高原疾病病理生理过程的可能机制

CYP450参与高原疾病病理生理过程的核心机制, 主要源于类二十烷酸的关键调控作用, 特别是EETs和HETEs对血管稳态调节网络的广泛影响。EETs和HETEs作为血管反应的核心, 参与低氧下血管张力的调节并促进血管生成[10,111-113]。在内皮细胞中, EETs激活K^+_{Ca}通道, 诱导平滑肌细胞超极化, 抑制L型Ca^{2+}通道, 从而诱导松弛, 因此EETs在全身脉管系统中作为内皮源性血管舒张剂舒张血管, 故而缺氧下脑中CYP450表达和EETs合成的增加有助于增强平滑肌细胞超极化, 进而使血管反应性减弱。但在肺循环中, EETs由血管平滑肌细胞产生, 其可以增强血管收缩, 因此, 缺氧下肺组织中EETs的合成增加导致肺动脉压力的升高进而引发高原肺动脉高压[93]。而HETEs降低K^+_{Ca}通道的开放概率并抑制Na-K-ATP酶, 导致平滑肌细胞膜去极化, L型Ca^{2+}通道激活, 从而诱导收缩, 尽管缺氧下HETE的变化目前尚未形成统一定论, 但可以确定的是, 缺氧下肺中HETE合成增加促进了肺血管的收缩和重塑, 而脑中HETEs生物合成的抑制可能与脑血管扩张有关。除了调节血管张力, 类二十烷酸还能促进血管生成, 改善血液供应。血管内皮生长因子 (vascular endothelial growth factor, VEGF) 是一种依赖一氧化氮的全身动脉扩张剂, 缺氧通过转录VEGF刺激血管生成, EETs和HETEs可以增强VEGF诱导的血管生成作用。反之, VEGF可增加内皮细胞中CYP450酶启动子活性, 诱导CYP450的表达, 导致细胞内EETs和HETEs水平升高[104,114]。

除血管调节作用以外, 类二十烷酸还具有一定的炎症调节作用, 低氧下机体会发生炎症反应, 而EETs具有抗炎作用, 可以直接下调COX和LOX酶及其相应代谢产物的活性降低炎症反应, 或通过抑制NF-κB途径降低TNF-α、IL-1α和C反应蛋白 (C reactive protein, CRP) 等炎症介质的水平[115-117], 而HETEs则是一种促炎介质, 可显著刺激内皮细胞中炎症细胞因子和趋化因子的产生, 包括IL-8、IL-13、IL-4和前列腺素E2等[118-120]。因此, 缺氧通过改变EETs和HETEs的合成, 进而调控促炎因子和抗炎因子生成, 加剧缺氧诱导的炎症反应, 然而, EETs和HETEs在调节炎症反应中表现出截然相反的作用, 低氧环境如何调控二者的动态平衡以影响高原病的生理过程仍需进行系统解析。

而另一种机制可能与活性氧 (reactive oxygen species, ROS) 的生成有关, 类二十烷酸代谢过程中可能产生ROS, ROS不仅可直接诱导细胞和组织的氧化应激, 而且还能充当影响局部或全身血流分布的信号分子。先前的研究证实, 暴露于急性缺氧会诱导超氧化物的产生, 而缺氧下星形胶质细胞在产生EET的过程中也同样促进超氧化物的产生, 这些超氧化物可以激活K^+_{Ca}通道电流, 进而提供针对缺氧诱导的组织损伤的保护[83]。此外, 缺氧下20-HETE的生物合成也受到缺氧诱导的ROS产生增加的负调节, 这是一种反应机制, 被认为是与急性缺氧相关的代偿性脑血管舒张的可能介质[82]。CYP450及类二十烷酸代谢物参与高原病病理生理过程的可能机制如图3所示。

5　小结与展望

高原低氧环境会影响人体的呼吸系统、中枢神经系统、心血管系统等的结构和功能, 进而引发一系列高原疾病。近年来, 越来越多的研究表明低氧影响体内CYP450的表达, CYP450作为体内重要的内源性的代谢酶, 其变化影响着类二十烷酸的生物合成, 这些变化有些可能有利于促进机体对低氧的适应, 有些则进一步加重低氧对机体的损伤, 因此, 探讨高原疾病-CYP450-类二十烷酸之间的关系, 不仅为全面了解高原疾病的发病机制提供了依据, 同时也为靶向治疗缺氧疾病提供了新视角。

随着高原旅游和高海拔体育训练等活动的日益普及, 急性缺氧暴露引发的呼吸急促、心率加快及低氧性肺血管收缩导致的肺动脉压升高, 已成为诱发急性器官损伤的重要因素, 亟待引起重视。此外, 对于长期暴露于低氧环境的高原世居人群而言, 尽管机体已逐渐适应低氧状态, 但仍可能引发潜在的长期病理改变。因此, 充分了解机体在低氧环境下的代偿及适应机制, 优化高原缺氧疾病的治疗策略, 具有重要的科学意义和实际应用价值。目前, 越来越多的证据表明低氧下CYP450及类二十烷酸生成和代谢的紊乱可能介导高原环境中脑损伤[45,75-83]、肺损伤[32,44,86-100]及心脏损伤[103-110]的发生。类二十烷酸是一类具有重要生物活性的脂质介质, 其中EETs和HETEs可能是调节高原疾病病理生理过程的主要物质, 这些物质可能通过调节血管稳态、炎症反应及ROS生成来参与高原疾病的病理过程。鉴于CYP450及类二十烷酸代谢物在高原病中的重要作用, 深入探究类二十烷酸代谢谱在高原疾病中的动态变化, 有望为高原疾病的早期诊断和精准防治提供特异新型生物标志物。同时, 针对该通路的干预策略还可能为高原病的预防提供新的思路, 通过采用CYP450模拟物或拮抗剂增加或减少类二十烷

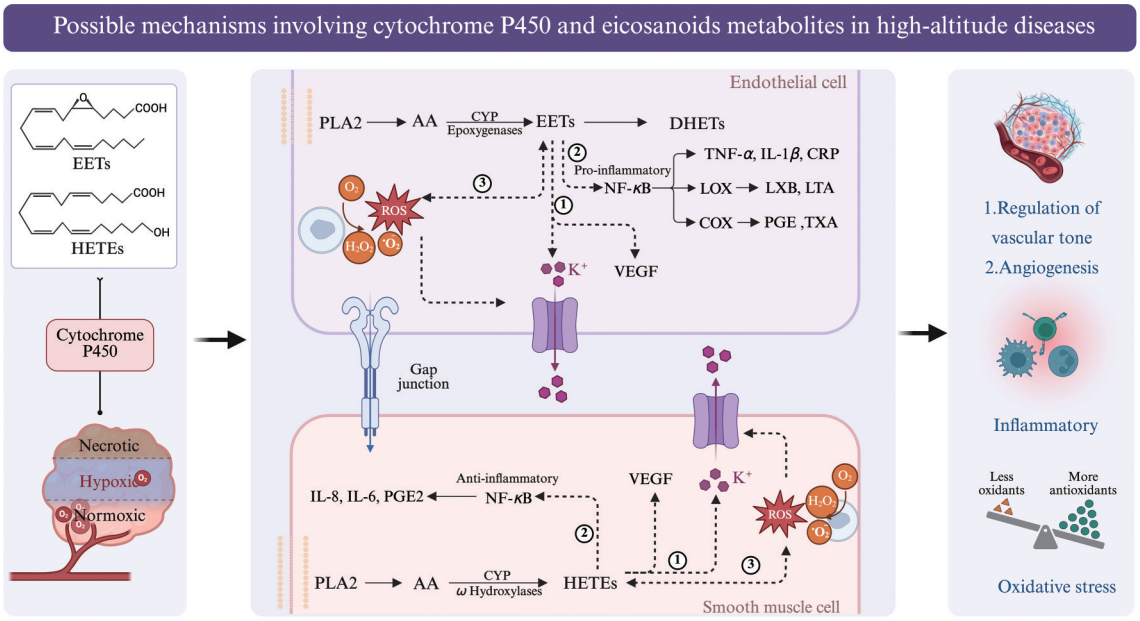


Figure 3 Possible mechanisms for the involvement of eicosanoids in the pathophysiological processes of high-altitude disease. Cytochrome P450 and eicosanoid metabolites (mainly EETs and HETEs) may contribute to the body's response to hypoxia by altering vascular tone, promoting angiogenesis, modulating inflammatory responses and oxidative stress. CRP: C reactive protein; LOX: Lipoxygenase; COX: Cyclooxygenase; ROS: Reactive oxygen species; VEGF: Vascular endothelial growth factor; LXB: Lipoxin B; LTA: Lipoteichoic acid; PGE2: Prostaglandin E2; TXA: Thromboxane A

酸代谢物在缺氧组织中的表达, 或者直接补充内源性代谢物, 或许是未来预防或治疗高原疾病的新方法。

高原低氧环境中各种高原病的发生与CYP450和类二十烷酸的变化密不可分, 而CYP450表达又受细胞因子、核受体及表观遗传修饰的调控, 随着对CYP450研究的深入, 本课题组发现这些不同的机制并不是独立工作的。如核受体的表达受表观遗传修饰、炎症因子及HIF的影响, 炎症因子及HIF又受到表观遗传修饰的调控, miRNA除调控CYP450和核受体的表达, 也调控表观遗传酶, 而miRNA的表达反过来又受到DNA甲基化和组蛋白修饰的影响。此外, 近年来研究发现肠道菌群也参与CYP450表达的调节, 高海拔缺氧改变肠道微生物群的结构和多样性, 肠道菌群又通过释放细胞外囊泡介导CYP450蛋白和mRNA表达的变化[121,122]。总之, 这些机制与遗传因素相互作用, 构成对CYP450复杂基因调控网络 (图2)。

当前的研究表明, 低氧可显著影响CYP450的表达和活性, 而不同研究报道的结果存在明显异质性, 这种差异可能源于造模方式、实验条件及个体遗传背景等多种因素的协同作用。首先在造模方法方面, 相比于模拟低压低氧的实验室环境, 高原实地环境整合了低氧、低压、强辐射、寒冷、干燥等多种环境特征, 这些因素共同作用, 增加了CYP450酶表达和活性调控的复杂性。其次, 不同的海拔高度和缺氧时间可能激活不同的生理调控机制, 急性或较高海拔的缺氧暴露会造成机体对缺氧的应激反应, 而低中海拔和慢性缺氧则触发适应机制, 这种高度和时间双依赖的调控模式同样引起CYP450表达的差异性。再者, 种属差异、细胞特异性及体内体外模型系统的不同也会影响CYP450的表达, 如低氧下HepG2细胞中CYP2C9的蛋白和mRNA表达降低[22], 而内皮细胞和星形胶质细胞中CYP2C9的表达升高[40,111]。更重要的是, 基因多态性或许也参与CYP450表达的调控。*CYP2C9*在人类中存在30多种等位基因, 其基因多态性使酶的表达和活性发生变化[123], 有研究指出藏族人群的*CYP2C9*基因存在一些独特的单核苷酸多态性 (SNPs)[124], 尽管目前的证据尚未完全阐明藏族*CYP2C9*的SNPs是否直接导致其在低氧下的表达或活性降低, 但依据现有证据推测, *CYP2C9*的基因多态性加剧了其在低氧下变化的复杂性。因此未来需要建立统一的低氧模型, 采用基因组学及基因编辑模型技术, 开展临床研究去解析这些复杂调控网络。

本课题组的研究表明EETs和HETEs是调控机体低氧适应的关键物质, 但值得注意的是, 这两类代谢物在血管张力调节、炎症反应等多个生理过程中表现出相互拮抗的作用特性, 因此, 维持EETs和HETEs之间

的动态平衡对维持低氧下的机体稳态至关重要。大量证据表明, EETs具有血管舒张、抗炎、抗凋亡和促血管生成作用, 是脑、心脏和肾脏中的强效血管扩张剂, 而HETEs可促进血管收缩和炎症反应。在缺氧条件下, 不同组织通过特异性调节EETs/HETEs平衡来实现适应性改变。在脑组织中, 低氧促使EETs合成增加而抑制HETEs合成, 这种协同变化导致脑内小动脉血管舒张, 进而可精确调控脑血流量以适应缺氧引起的神经活动和代谢需求的增加, 同时, 通过抑制细胞凋亡和活性氧的产生, 以及增强抗炎因子的表达, 来减少缺氧下的脑组织损伤, 这些效应共同构建了对缺氧性脑损伤的防御体系。而在肺循环中则呈现不同的调节模式, 由于肺循环中的EETs发挥血管收缩作用, 因此, 缺氧同时增加肺中EETs和HETEs合成, 两者协同加剧氧化应激和肺血管收缩, 从而促进高原肺水肿和高原肺动脉高压的发生。然而, 正如CYP450的表达和活性受多种因素的影响一样, EETs/HETEs在低氧适应中的调节作用同样也是复杂的, 现有研究尚不足以全面阐明这两类代谢物在各类缺氧相关疾病中的特异性机制, 这亟待通过更深入的研究来系统解析。

目前, 对低氧下CYP450表达和活性的研究多集中在动物和细胞水平, 但CYP450的表达和活性在人体和动物以及体内和体外可能不同[125,126], 类似的, EETs和HETEs的生物合成也存在种属差异。Imaoka等[127]研究了人和大鼠CYP450对花生四烯酸的催化活性, 结果发现虽然人和大鼠CYP450代谢花生四烯酸产生的EETs和HETEs的种类大致相似, 但其相对含量存在显著差异。在另一项研究中[128], 比较人CYP1B1和小鼠CYP1B1对花生四烯酸的代谢, 结果表明人和小鼠的代谢特征截然不同, 人CYP1B1的主要代谢物是75%的长链HETE、54%的中链HETE和52%的EET, 而鼠CYP1B1的主要代谢物是50%的EETs和37%的中链HETEs。临床样本与动物模型的对比研究进一步证实了这种物种差异。对蛛网膜下腔出血患者脑脊液和大鼠脑组织的分析显示, 人脑脊液中可检测到8,9-DiHETrE、20-HETE、15-HETE和12-HETE等代谢物, 而在大鼠脑组织中除了这些成分外, 还可检测到8, 9-EET、14, 15-DiHETrE和11-12-DiHETrE等代谢物[129]。总之, CYP450和类二十烷酸代谢物均存在显著的种属差异性, 这提示不能仅以动物实验结果外推至人类生理病理过程, 而需开展更多的临床试验。然而, 值得注意的是, 尽管CYP450和类二十烷酸代谢物在高原疾病中有着重要的作用, 但临床研究缺乏是当前CYP450和类二十烷酸代谢物生理作用研究中普遍存在的问题。因此, 未来应开展更多针对高原人群及高原疾病的临床研究, 重点解决基础研究向临床应用的转化问题。

综上所述, CYP450和类二十烷酸代谢物对高原疾病的发生发展和低氧适应有着十分重要的作用。虽然近年来该领域研究已取得一定进展, 但由于物种差异、实验模型系统差异及临床数据缺乏, 目前的研究还未形成统一定论, 特别是参与类二十烷酸代谢的CYP2J2、CYP4A11和CYP4F2在低氧下的表达和活性变化还鲜有研究。此外, 关于类二十烷酸在高原疾病中作用, 目前只有对缺氧造成的肺损伤中的类二十烷酸有较为清晰的理解, 但这些代谢物如何调节其他组织的缺氧过程, 还值得进一步验证。同时当前的研究多集中于AA代谢产生的EETs和HETEs的生物学作用上, 但实际上EpOME、EEQ、EDP等对机体的功能同样有着重要的影响, 还需要开展更多的研究。另外, 当前对低氧下CYP450调控机制的研究也存在诸多不足, 且现有模型在模拟高原低氧复杂环境时存在的差异也限制了研究的深入。因此, 未来的研究应聚焦于低氧环境下CYP450酶的分子调控网络, 此外, 采用灵敏、准确的分析仪器和技术如多组学联合等也将有助于更准确地预测和阐明类二十烷酸在高原缺氧疾病中的调节作用, 从而为高原医学研究人员提供有价值的见解, 促进缺氧疾病靶向药物的开发和临床应用。

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References

[1] Zubieta-Calleja GR, Zubieta-DeUrioste N. High altitude pulmonary edema, high altitude cerebral edema, and acute mountain sickness: an enhanced opinion from the High Andes-La Paz, Bolivia 3 500 m [J]. Rev Environ Health, 2022, 38: 327-338.

[2] Richalet JP, Hermand E, Lhuissier FJ. Cardiovascular physiology and pathophysiology at high altitude [J]. Nat Rev Cardiol, 2024, 21: 75-88.

[3] Li XY, Wang XY, Li YP, et al. Effect of exposure to acute and chronic high-altitude hypoxia on the activity and expression of CYP1A2, CYP2D6, CYP2C9, CYP2C19 and NAT2 in rats [J]. Pharmacology, 2014, 93: 76-83.

[4] Tian L, Liu GQ, Han JJ, et al. Effects of high-altitude hypoxia on drug metabolism and pharmacokinetics of sedative-hypnotic drugs and regulatory mechanism [J]. Curr Drug Metab, 2024, 25: 416-424.

[5] Zhu JB, Yang JX, Nian YQ, et al. Pharmacokinetics of

acetaminophen and metformin hydrochloride in rats after exposure to simulated high altitude hypoxia [J]. Front Pharmacol, 2021, 12: 692349.

[6] Duo DL, Duan YB, Zhu JB, et al. New strategy for rational use of antihypertensive drugs in clinical practice in high-altitude hypoxic environments [J]. Drug Metab Rev, 2023, 55: 388-404.

[7] Haduch A, Daniel WA. The engagement of brain cytochrome P450 in the metabolism of endogenous neuroactive substrates: a possible role in mental disorders [J]. Drug Metab Rev, 2018, 50: 415-429.

[8] Chauhan G, Roy K, Kumar G, et al. Distinct influence of COX-1 and COX-2 on neuroinflammatory response and associated cognitive deficits during high altitude hypoxia [J]. Neuropharmacology, 2019, 146: 138-148.

[9] Al-Husseini A, Wijesinghe DS, Farkas L, et al. Increased eicosanoid levels in the Sugen/chronic hypoxia model of severe pulmonary hypertension [J]. PLoS One, 2015, 10: e0120157.

[10] Ding Y, Tu P, Chen Y, et al. CYP2J2 and EETs protect against pulmonary arterial hypertension with lung ischemia-reperfusion injury *in vivo* and *in vitro* [J]. Respir Res, 2021, 22: 291.

[11] Kandhi S, Alruwaili N, Wolin MS, et al. Reciprocal actions of constrictor prostanoids and superoxide in chronic hypoxia-induced pulmonary hypertension: roles of EETs [J]. Pulm Circ, 2019, 9: 2045894019895947.

[12] Li Y, Meng Q, Yang M, et al. Current trends in drug metabolism and pharmacokinetics [J]. Acta Pharm Sin B, 2019, 9: 1113-1144.

[13] Fanni D, Pinna F, Gerosa C, et al. Anatomical distribution and expression of CYP in humans: neuropharmacological implications [J]. Drug Dev Res, 2021, 82: 628-667.

[14] Jamieson KL, Endo T, Darwesh AM, et al. Cytochrome P450-derived eicosanoids and heart function [J]. Pharmacol Ther, 2017, 179: 47-83.

[15] Mihaljević Z, Matić A, Stupin A, et al. Arachidonic acid metabolites of CYP450 enzymes and HIF-1α modulate endothelium-dependent vasorelaxation in Sprague-Dawley rats under acute and intermittent hyperbaric oxygenation [J]. Int J Mol Sci, 2020, 21: 6353.

[16] Fradette C, Batonga J, Teng S, et al. Animal models of acute moderate hypoxia are associated with a down-regulation of CYP1A1, 1A2, 2B4, 2C5, and 2C16 and up-regulation of CYP3A6 and P-glycoprotein in liver [J]. Drug Metab Dispos, 2007, 35: 765-771.

[17] Wang R, Sun Y, Yin Q, et al. The effects of metronidazole on cytochrome P450 activity and expression in rats after acute exposure to high altitude of 4 300 m [J]. Biomed Pharmacother, 2017, 85: 296-302.

[18] Li XY, Wang XJ, Li YP, et al. The activity, protein, and mRNA expression of CYP2E1 and CYP3A1 in rats after exposure to acute and chronic high altitude hypoxia [J]. High Alt Med Biol, 2014, 15: 491-496.

[19] Zhang JL, Zhu JB, Yao XC, et al. Pharmacokinetics of lidocaine hydrochloride metabolized by CYP3A4 in Chinese Han volunteers living at low altitude and in native Han and Tibetan Chinese volunteers living at high altitude [J]. Pharmacology, 2016, 97: 107-113.

[20] Zhu JB, Duan YB, Duo DL, et al. High-altitude hypoxia influences the activities of the drug-metabolizing enzyme CYP3A1 and the pharmacokinetics of four cardiovascular system drugs [J]. Pharmaceuticals (Basel), 2022, 15: 1303.

[21] Michaelis UR, Fisslthaler B, Barbosa-Sicard E, et al. Cytochrome P450 epoxygenases 2C8 and 2C9 are implicated in hypoxia-induced endothelial cell migration and angiogenesis [J]. J Cell Sci, 2005, 118: 5489-5498.

[22] Duan YB, Zhu JB, Yang JX, et al. Regulation of high-altitude hypoxia on the transcription of CYP450 and UGT1A1 mediated by PXR and CAR [J]. Front Pharmacol, 2020, 11: 574176.

[23] Gola S, Gupta A, Keshri GK, et al. Evaluation of hepatic metabolism and pharmacokinetics of ibuprofen in rats under chronic hypobaric hypoxia for targeted therapy at high altitude [J]. J Pharm Biomed Anal, 2016, 121: 114-122.

[24] Huang L, Zhang X, Luo L, et al. Effects of high-altitude environment on pharmacokinetic parameters of gliquidone in rats [J]. J Zhejiang Univ (Med Sci) (浙江大学学报 (医学版)), 2022, 51: 389-396.

[25] Marden NY, Fiala-Beer E, Xiang SH, et al. Role of activator protein-1 in the down-regulation of the human CYP2J2 gene in hypoxia [J]. Biochem J, 2003, 373: 669-680.

[26] Yang B, Graham L, Dikalov S, et al. Overexpression of cytochrome P450 CYP2J2 protects against hypoxia-reoxygenation injury in cultured bovine aortic endothelial cells [J]. Mol Pharmacol, 2001, 60: 310-320.

[27] Wang HX, Zhang DM, Zeng XJ, et al. Upregulation of cytochrome P450 2J3/11, 12-epoxyeicosatrienoic acid inhibits apoptosis in neonatal rat cardiomyocytes by a caspase-dependent pathway [J]. Cytokine, 2012, 60: 360-368.

[28] Marden NY, Murray M. Characterization of a c-Jun-responsive module in the 5'-flank of the human CYP2J2 gene that regulates transactivation [J]. Biochem J, 2005, 391: 631-640.

[29] Cui PH, Lee AC, Zhou F, et al. Impaired transactivation of the human CYP2J2 arachidonic acid epoxygenase gene in HepG2 cells subjected to nitrative stress [J]. Br J Pharmacol, 2010, 159: 1440-1449.

[30] Mastyugin V, Aversa E, Bonazzi A, et al. Hypoxia-induced production of 12-hydroxyeicosanoids in the corneal epithelium: involvement of a cytochrome P-450 4B1 isoform [J]. J Pharmacol Exp Ther, 1999, 289: 1611-1619.

[31] Chen L, Ackerman R, Saleh M, et al. 20-HETE regulates the angiogenic functions of human endothelial progenitor cells and contributes to angiogenesis *in vivo* [J]. J Pharmacol Exp Ther, 2014, 348: 442-451.

[32] White K, Loughlin L, Maqbool Z, et al. Serotonin transporter, sex, and hypoxia: microarray analysis in the pulmonary arteries of mice identifies genes with relevance to human PAH [J]. Physiol Genomics, 2011, 43: 417-437.

[33] Jürgens G, Christensen HR, Brøsen K, et al. Acute hypoxia and cytochrome P450-mediated hepatic drug metabolism in humans [J]. Clin Pharmacol Ther, 2002, 71: 214-220.

[34] Dunvald AD, Järvinen E, Mortensen C, et al. Clinical and molecular perspectives on inflammation-mediated regulation of drug metabolism and transport [J]. Clin Pharmacol Ther, 2022, 112: 277-290.

[35] Agachi S, Beloukhova M, Mould D, et al. Inflammation-mediated drug interactions of olokizumab and cytochrome P450 activities in patients with rheumatoid arthritis [J]. Br J Clin Pharmacol, 2024, 90: 2811-2822.

[36] Klomp SD, Meziyerh S, Vissers MFJM, et al. Increased tacrolimus exposure in kidney transplant recipients with COVID-19: inflammation-driven downregulation of metabolism as a potential mechanism [J]. Transpl Int, 2022, 35: 10269.

[37] Yu H, Shao H, Wu Q, et al. Altered gene expression of hepatic cytochrome P450 in a rat model of intermittent hypoxia with emphysema [J]. Mol Med Rep, 2017, 16: 881-886.

[38] Fradette C, Bleau AM, Pichette V, et al. Hypoxia-induced down-regulation of CYP1A1/1A2 and up-regulation of CYP3A6 involves serum mediators [J]. Br J Pharmacol, 2002, 137: 881-891.

[39] Liu M, Alkayed NJ. Hypoxic preconditioning and tolerance *via* hypoxia inducible factor (HIF) 1alpha-linked induction of P450 2C11 epoxygenase in astrocytes [J]. J Cereb Blood Flow Metab, 2005, 25: 939-948.

[40] Takano H, Yamaguchi JI, Kato S, et al. Downregulation of CYP1A2, CYP2B6, and CYP3A4 in human hepatocytes by prolyl hydroxylase domain 2 inhibitors *via* hypoxia-inducible factor-*α* stabilization [J]. Drug Metab Dispos, 2021, 49: 20-30.

[41] Ramakrishnan SK, Taylor M, Qu A, et al. Loss of von hippel-lindau protein (VHL) increases systemic cholesterol levels through targeting hypoxia-inducible factor 2*α* and regulation of bile acid homeostasis [J]. Mol Cell Biol, 2014, 34: 1208-1220.

[42] Yuan X, Xiang D, Min Q, et al. Effects of acute hypoxia on expression of pregnane X receptor in liver tissues of rats exposed to high altitude [J]. J Zhejiang Univ (Med Sci) (浙江大学学报(医学版)), 2019, 48: 603-608.

[43] Legendre C, Hori T, Loyer P, et al. Drug-metabolising enzymes are down-regulated by hypoxia in differentiated human hepatoma HepaRG cells: HIF-1alpha involvement in CYP3A4 repression [J]. Eur J Cancer, 2009, 45: 2882-2892.

[44] Zhang N, Walker MK. Crosstalk between the aryl hydrocarbon receptor and hypoxia on the constitutive expression of cytochrome P4501A1 mRNA [J]. Cardiovasc Toxicol, 2007, 7: 282-290.

[45] Jacob A, Potin S, Saubaméa B, et al. Hypoxia interferes with aryl hydrocarbon receptor pathway in hCMEC/D3 human cerebral microvascular endothelial cells [J]. J Neurochem, 2015, 132: 373-383.

[46] Vorrink SU, Severson PL, Kulak MV, et al. Hypoxia perturbs aryl hydrocarbon receptor signaling and CYP1A1 expression induced by PCB 126 in human skin and liver-derived cell lines [J]. Toxicol Appl Pharmacol, 2014, 274: 408-416.

[47] Coelho NR, Tomkiewicz C, Correia MJ, et al. First evidence of aryl hydrocarbon receptor as a druggable target in hypertension induced by chronic intermittent hypoxia [J]. Pharmacol Res, 2020, 159: 104869.

[48] Chen L, Bao Y, Piekos SC, et al. A transcriptional regulatory network containing nuclear receptors and long noncoding RNAs controls basal and drug-induced expression of cytochrome P450s in HepaRG cells [J]. Mol Pharmacol, 2018, 94: 749-759.

[49] Chiang TS, Yang KC, Chiou LL, et al. Enhancement of CYP3A4 activity in HepG2 cells by lentiviral transfection of hepatocyte nuclear factor-1 alpha [J]. PLoS One, 2014, 9: e94885.

[50] Mazure NM, Nguyen TL, Danan JL. Severe hypoxia specifically downregulates hepatocyte nuclear factor-4 gene expression in HepG2 human hepatoma cells [J]. Tumour Biol, 2001, 22: 310-317.

[51] Sato Y, Tsuyama T, Sato C, et al. Hypoxia reduces HNF4*α*/MODY1 protein expression in pancreatic *β*-cells by activating AMP-activated protein kinase [J]. J Biol Chem, 2017, 292: 8716-8728.

[52] Yang JX, Bai X, Liu GQ, et al. A transcriptional regulatory network of HNF4*α* and HNF1*α* involved in human diseases and drug metabolism [J]. Drug Metab Rev, 2022, 54: 361-385.

[53] Radhakrishna U, Ratnamala U, Jhala DD, et al. Cytochrome P450 genes mediated by DNA methylation are involved in the resistance to hidradenitis suppurativa [J]. J Invest Dermatol, 2023, 143: 670-673.

[54] Kronfol MM, Jahr FM, Dozmorov MG, et al. DNA methylation and histone acetylation changes to cytochrome P450 2E1 regulation in normal aging and impact on rates of drug metabolism in the liver [J]. Geroscience, 2020, 42: 819-832.

[55] Chen JY, Sheng L. Advances in the study of methyltransferase in drug metabolism [J]. Acta Pharm Sin (药学学报), 2024, 59: 1562-1568.

[56] Lin Z, Lu Y, Yu G, et al. Genome-wide DNA methylation landscape of four Chinese populations and epigenetic variation linked to Tibetan high-altitude adaptation [J]. Sci China Life Sci, 2023, 66: 2354-2369.

[57] Zhang S, Fu W, Jia X, et al. Hypoxic preconditioning modulates BDNF and its signaling through DNA methylation to promote learning and memory in mice [J]. ACS Chem Neurosci, 2023, 14: 2320-2332.

[58] Ruhr I, Bierstedt J, Rhen T, et al. Developmental programming

of DNA methylation and gene expression patterns is associated with extreme cardiovascular tolerance to anoxia in the common snapping turtle [J]. Epigenetics Chromatin, 2021, 14: 42.

[59] Jin T, Lu H, Zhang Z, et al. CYP2S1 gene methylation among high-altitude pulmonary edema [J]. Gene, 2022, 834: 146590.

[60] Cai W, Liu S, Liu Z, et al. Downregulation of lung miR-203a-3p expression by high-altitude hypoxia enhances VEGF/Notch signaling [J]. Aging (Albany NY), 2020, 12: 4247-4267.

[61] Chen X, Liu X, Li B, et al. Cold inducible RNA binding protein is involved in chronic hypoxia induced neuron apoptosis by down-regulating HIF-1*α* expression and regulated by microRNA-23a [J]. Int J Biol Sci, 2017, 13: 518-531.

[62] Krkoška M, Nekvindová J, Nevědělová K, et al. Role of miR-653 and miR-29c in downregulation of CYP1A2 expression in hepatocellular carcinoma [J]. Pharmacol Rep, 2022, 74: 148-158.

[63] Tantawy M, Collins JM, Wang D. Genome-wide microRNA profiles identify miR-107 as a top miRNA associating with expression of the CYP3As and other drug metabolizing cytochrome P450 enzymes in the liver [J]. Front Pharmacol, 2022, 13: 943538.

[64] Kugler N, Klein K, Zanger UM. MiR-155 and other microRNAs downregulate drug metabolizing cytochromes P450 in inflammation [J]. Biochem Pharmacol, 2020, 171: 113725.

[65] Rieger JK, Reutter S, Hofmann U, et al. Inflammation-associated microRNA-130b down-regulates cytochrome P450 activities and directly targets CYP2C9 [J]. Drug Metab Dispos, 2015, 43: 884-888.

[66] Matthews O, Morrison EE, Tranter JD, et al. Transfer of hepatocellular microRNA regulates cytochrome P450 2E1 in renal tubular cells [J]. EBioMedicine, 2020, 62: 103092.

[67] Duan YB, Zhu JB, Yang JX, et al. Effect of hypoxia on drug metabolizing enzymes and transporters and the role of microRNA [J]. Acta Pharm Sin (药学学报), 2021, 56: 50-60.

[68] Duan YB, Bai X, Yang JX, et al. Exposure to high-altitude environment is associated with drug transporters change: microRNA-873-5p-mediated alteration of function and expression levels of drug transporters under hypoxia [J]. Drug Metab Dispos, 2022, 50: 174-186.

[69] Velenosi TJ, Feere DA, Sohi G, et al. Decreased nuclear receptor activity and epigenetic modulation associates with down-regulation of hepatic drug-metabolizing enzymes in chronic kidney disease [J]. FASEB J, 2014, 28: 5388-5397.

[70] Jiang Z, Zheng X, Wang W, et al. CYP2C9 inhibits the invasion and migration of esophageal squamous cell carcinoma *via* downregulation of HDAC [J]. Mol Cell Biochem, 2021, 476: 2011-2020.

[71] Kassie F, Anderson LB, Higgins L, et al. Chemopreventive agents modulate the protein expression profile of 4-(methylnitrosamino) -1- (3-pyridyl) -1-butanone plus benzo[a] pyrene-induced lung tumors in A/J mice [J]. Carcinogenesis, 2008, 29: 610-619.

[72] Burtscher J, Mallet RT, Burtscher M, et al. Hypoxia and brain aging: neurodegeneration or neuroprotection? [J]. Ageing Res Rev, 2021, 68: 101343.

[73] Aboouf MA, Thiersch M, Soliz J, et al. The brain at high altitude: from molecular signaling to cognitive performance [J]. Int J Mol Sci, 2023, 24: 10179.

[74] Su R, Jia S, Zhang N, et al. The effects of long-term high-altitude exposure on cognition: a meta-analysis [J]. Neurosci Biobehav Rev, 2024, 161: 105682.

[75] Rahman MS, Thomas P. Molecular characterization and expression of cytochrome p450 aromatase in Atlantic croaker brain: regulation by antioxidant status and nitric oxide synthase during hypoxia stress [J]. Front Physiol, 2021, 12: 720200.

[76] Lu F, Fan S, Romo AR, et al. Serum 24*S*-hydroxycholesterol predicts long-term brain structural and functional outcomes after hypoxia-ischemia in neonatal mice [J]. J Cereb Blood Flow Metab, 2021, 41: 312-323.

[77] Liu GQ, Wang Q, Tian L, et al. Blood-brain barrier permeability is affected by changes in tight junction protein expression at high-altitude hypoxic conditions-this may have implications for brain drug transport [J]. AAPS J, 2024, 26: 90.

[78] Liu GQ, Bai X, Yang JX, et al. Relationship between blood-brain barrier changes and drug metabolism under high-altitude hypoxia: obstacle or opportunity for drug transport? [J]. Drug Metab Rev, 2023, 55: 107-125.

[79] Liu GQ, Bai X, Yang JX, et al. The modulation and mechanisms of high-altitude hypoxia in drug transport across the blood-brain barrier [J]. Acta Pharm Sin (药学学报), 2023, 58: 659-671.

[80] Leffler CW, Smith JS, Edrington JL, et al. Mechanisms of hypoxia-induced cerebrovascular dilation in the newborn pig [J]. Am J Physiol, 1997, 272: H1323-H1332.

[81] Yamaura K, Gebremedhin D, Zhang C, et al. Contribution of epoxyeicosatrienoic acids to the hypoxia-induced activation of Ca^{2+}-activated K^+ channel current in cultured rat hippocampal astrocytes [J]. Neuroscience, 2006, 143: 703-716.

[82] Halder SK, Milner R. The impact of chronic mild hypoxia on cerebrovascular remodelling; uncoupling of angiogenesis and vascular breakdown [J]. Fluids Barriers CNS, 2021, 18: 50.

[83] Gebremedhin D, Yamaura K, Harder DR. Role of 20-HETE in the hypoxia-induced activation of Ca^{2+}-activated K^+ channel currents in rat cerebral arterial muscle cells [J]. Am J Physiol Heart Circ Physiol, 2008, 294: H107-H120.

[84] Fröhlich S, Boylan J, McLoughlin P. Hypoxia-induced inflammation in the lung: a potential therapeutic target in acute lung injury? [J]. Am J Respir Cell Mol Biol, 2013, 48: 271-279.

[85] El Alam S, Pena E, Aguilera D, et al. Inflammation in pulmonary hypertension and edema induced by hypobaric hypoxia exposure [J]. Int J Mol Sci, 2022, 23: 12656.

[86] Si L, Wang H, Wang R, et al. Suggestive evidence of CYP4F2

gene polymorphisms with HAPE susceptibility in the Chinese Han population [J]. PLoS One, 2023, 18: e0280136.

[87] Al-Naamani N, Krowka MJ, Forde KA, et al. Estrogen signaling and portopulmonary hypertension: the pulmonary vascular complications of liver disease study (PVCLD2) [J]. Hepatology, 2021, 73: 726-737.

[88] White K, Johansen AK, Nilsen M, et al. Activity of the estrogen-metabolizing enzyme cytochrome P450 1B1 influences the development of pulmonary arterial hypertension [J]. Circulation, 2012, 126: 1087-1098.

[89] Zhou GL, Beloiartsev A, Yu B, et al. Deletion of the murine cytochrome P450 Cyp2j locus by fused BAC-mediated recombination identifies a role for Cyp2j in the pulmonary vascular response to hypoxia [J]. PLoS Genet, 2013, 9: e1003950.

[90] Hashimoto R, Joshi SR, Jiang H, et al. Cyp2c44 gene disruption is associated with increased hematopoietic stem cells: implication in chronic hypoxia-induced pulmonary hypertension [J]. Am J Physiol Heart Circ Physiol, 2017, 313: H293-H303.

[91] Pokreisz P, Fleming I, Kiss L, et al. Cytochrome P450 epoxygenase gene function in hypoxic pulmonary vasoconstriction and pulmonary vascular remodeling [J]. Hypertension, 2006, 47: 762-770.

[92] Kiss L, Röder Y, Bier J, et al. Direct eicosanoid profiling of the hypoxic lung by comprehensive analysis *via* capillary liquid chromatography with dual online photodiode-array and tandem mass-spectrometric detection [J]. Anal Bioanal Chem, 2008, 390: 697-714.

[93] Strielkov I, Krause NC, Knoepp F, et al. Cytochrome P450 epoxygenase-derived 5, 6-epoxyeicosatrienoic acid relaxes pulmonary arteries in normoxia but promotes sustained pulmonary vasoconstriction in hypoxia [J]. Acta Physiol (Oxf), 2020, 230: e13521.

[94] Kandhi S, Zhang B, Froogh G, et al. EETs promote hypoxic pulmonary vasoconstriction *via* constrictor prostanoids [J]. Am J Physiol Lung Cell Mol Physiol, 2017, 313: L350-L359.

[95] Loot AE, Fleming I. Cytochrome P450-derived epoxyeicosatrienoic acids and pulmonary hypertension: central role of transient receptor potential C6 channels [J]. J Cardiovasc Pharmacol, 2011, 57: 140-147.

[96] Chen W, Yang S, Ping W, et al. CYP2J2 and EETs protect against lung ischemia/reperfusion injury *via* anti-inflammatory effects *in vivo* and *in vitro* [J]. Cell Physiol Biochem, 2015, 35: 2043-2054.

[97] Keserü B, Barbosa-Sicard E, Schermuly RT, et al. Hypoxia-induced pulmonary hypertension: comparison of soluble epoxide hydrolase deletion *vs.* inhibition [J]. Cardiovasc Res, 2010, 85: 232-240.

[98] Bihzad SM, Yousif MH. 11,12-Epoxyeicosatrienoic acid induces vasodilator response in the rat perfused mesenteric vasculature [J]. Auton Autacoid Pharmacol, 2017, 37: 3-12.

[99] Yu X, Li T, Liu X, et al. Modulation of pulmonary vascular remodeling in hypoxia: role of 15-LOX-2/15-HETE-MAPKs pathway [J]. Cell Physiol Biochem, 2015, 35: 2079-2097.

[100] Kizub IV, Lakhkar A, Dhagia V, et al. Involvement of gap junctions between smooth muscle cells in sustained hypoxic pulmonary vasoconstriction development: a potential role for 15-HETE and 20-HETE [J]. Am J Physiol Lung Cell Mol Physiol, 2016, 310: L772-L783.

[101] Heather LC, Clarke K. Metabolism, hypoxia and the diabetic heart [J]. J Mol Cell Cardiol, 2011, 50: 598-605.

[102] Richalet JP, Hermand E. Modeling the oxygen transport to the myocardium at maximal exercise at high altitude [J]. Physiol Rep, 2022, 10: e15262.

[103] ElKhatib MAW, Isse FA, El-Kadi AOS. Effect of inflammation on cytochrome P450-mediated arachidonic acid metabolism and the consequences on cardiac hypertrophy [J]. Drug Metab Rev, 2023, 55: 50-74.

[104] Zhao Q, Huang J, Wang D, et al. Endothelium-specific CYP2J2 overexpression improves cardiac dysfunction by promoting angiogenesis *via* Jagged1/Notch1 signaling [J]. J Mol Cell Cardiol, 2018, 123: 118-127.

[105] Zhou Z, Zhang M, Zhao C, et al. Epoxyeicosatrienoic acids prevent cardiac dysfunction in viral myocarditis *via* interferon type I signaling [J]. Circ Res, 2023, 133: 772-788.

[106] Neckář J, Hye Khan MA, Gross GJ, et al. Epoxyeicosatrienoic acid analog EET-B attenuates post-myocardial infarction remodeling in spontaneously hypertensive rats [J]. Clin Sci (Lond), 2019, 133: 939-951.

[107] Zeng Q, Han Y, Bao Y, et al. 20-HETE increases NADPH oxidase-derived ROS production and stimulates the L-type Ca^{2+} channel *via* a PKC-dependent mechanism in cardiomyocytes [J]. Am J Physiol Heart Circ Physiol, 2010, 299: H1109-H1117.

[108] Matsumura N, Takahara S, Maayah ZH, et al. Resveratrol improves cardiac function and exercise performance in MI-induced heart failure through the inhibition of cardiotoxic HETE metabolites [J]. J Mol Cell Cardiol, 2018, 125: 162-173.

[109] Althurwi HN, Maayah ZH, Elshenawy OH, et al. Early changes in cytochrome P450s and their associated arachidonic acid metabolites play a crucial role in the initiation of cardiac hypertrophy induced by isoproterenol [J]. Drug Metab Dispos, 2015, 43: 1254-1266.

[110] Xin JW, Chai ZX, Zhang CF, et al. Differences in proteomic profiles between yak and three cattle strains provide insights into molecular mechanisms underlying high-altitude adaptation [J]. J Anim Physiol Anim Nutr (Berl), 2022, 106: 485-493.

[111] Michaelis UR, Xia N, Barbosa-Sicard E, et al. Role of cytochrome P450 2C epoxygenases in hypoxia-induced cell migration and angiogenesis in retinal endothelial cells [J]. Invest Ophthalmol Vis Sci, 2008, 49: 1242-1247.

[112] Xia Y, Xia L, Jin Z, et al. Cytochrome P450 epoxygenase-dependent activation of TRPV4 channel participates in enhanced serotonin-induced pulmonary vasoconstriction in chronic hypoxic pulmonary hypertension [J]. Anal Cell Pathol (Amst), 2020, 2020: 8927381.

[113] Zhang J, Xiong Q, Yang L, et al. Cytochrome P450 2J2 inhibits the proliferation and angiogenesis of retinal vascular endothelial cells by regulating the Notch signaling pathway in a hypoxia-induced retinopathy model [J]. Bioengineered, 2021, 12: 10878-10890.

[114] Jandeleit-Dahm K, Meister J. Cytochrome-derived EETs, VEGF-A, and NOX4: piecing the puzzle together [J]. Diabetes, 2023, 72: 841-843.

[115] Li X, Kempf S, Günther S, et al. 11, 12-EET regulates PPAR-γ expression to modulate TGF-β-mediated macrophage polarization [J]. Cells, 2023, 12: 700.

[116] Imig JD, Hye Khan MA, Burkhan A, et al. Kidney-targeted epoxyeicosatrienoic acid analog, EET-f 01, reduces inflammation, oxidative stress, and cisplatin-induced nephrotoxicity [J]. Int J Mol Sci, 2021, 22: 2793.

[117] Pallàs M, Vázquez S, Sanfeliu C, et al. Soluble epoxide hydrolase inhibition to face neuroinflammation in Parkinson's disease: a new therapeutic strategy [J]. Biomolecules, 2020, 10: 703.

[118] Jeon KB, Kim J, Lim CM, et al. Unsaturated oxidated fatty acid 12(*S*)-HETE attenuates TNF-α expression in TNF-α/IFN-γ-stimulated human keratinocytes [J]. Int Immunopharmacol, 2023, 120: 110298.

[119] Gagnon KJ, Lefort N, Poirier SJ, et al. 5-Lipoxygenase-dependent biosynthesis of novel 20:4 *n*-3 metabolites with anti-inflammatory activity [J]. Prostaglandins Leukot Essent Fatty Acids, 2018, 138: 38-44.

[120] Ni KD, Liu JY. The functions of cytochrome P450 ω-hydroxylases and the associated eicosanoids in inflammation-related diseases [J]. Front Pharmacol, 2021, 12: 716801.

[121] Bai X, Liu GQ, Yang JX, et al. The effect of high-altitude hypoxia on drug metabolism is mediated by gut microbiota [J]. Acta Pharm Sin (药学学报), 2021, 56: 2787-2796.

[122] Bai X, Yang JX, Liu GQ, et al. Regulation of CYP450 and drug transporter mediated by gut microbiota under high-altitude hypoxia [J]. Front Pharmacol, 2022, 13: 977370.

[123] Wang L, Bao SH, Pan PP, et al. Effect of CYP2C9 genetic polymorphism on the metabolism of flurbiprofen *in vitro* [J]. Drug Dev Ind Pharm, 2015, 41: 1363-1367.

[124] Jin T, Geng T, He N, et al. Genetic polymorphism analysis of the drug-metabolizing enzyme CYP2C9 in a Chinese Tibetan population [J]. Gene, 2015, 567: 196-200.

[125] Stamou M, Wu X, Kania-Korwel I, et al. Cytochrome p450 mRNA expression in the rodent brain: species-, sex-, and region-dependent differences [J]. Drug Metab Dispos, 2014, 42: 239-244.

[126] Burkina V, Rasmussen MK, Pilipenko N, et al. Comparison of xenobiotic-metabolising human, porcine, rodent, and piscine cytochrome P450 [J]. Toxicology, 2017, 375: 10-27.

[127] Imaoka S, Hashizume T, Funae Y. Localization of rat cytochrome P450 in various tissues and comparison of arachidonic acid metabolism by rat P450 with that by human P450 orthologs [J]. Drug Metab Pharmacokinet, 2005, 20: 478-484.

[128] Choudhary D, Jansson I, Stoilov I, et al. Metabolism of retinoids and arachidonic acid by human and mouse cytochrome P450 1b1 [J]. Drug Metab Dispos, 2004, 32: 840-847.

[129] Miller TM, Donnelly MK, Crago EA, et al. Rapid, simultaneous quantitation of mono and dioxygenated metabolites of arachidonic acid in human CSF and rat brain [J]. J Chromatogr B Analyt Technol Biomed Life Sci, 2009, 877: 3991-4000.