高原适应遗传学缺氧诱导因子通路相关基因及其药理学研究进展

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摘要: 人类对高原缺氧环境的适应表现、机制及相关药理学研究一直是科研探索的热点。一个世纪以来, 主要集中于青藏高原、南美洲安第斯高原和埃塞俄比亚高原的高原世居人群对于慢性缺氧所具有的独特生理适应已经得到了科学验证, 而近10年来的基因研究也证实高原适应具有遗传学基础, 尤其与缺氧诱导因子 (hypoxia inducible factor, HIF) 通路及缺氧反应基因 (hypoxia response elements, HREs) 具有密切关系。但有趣的是, 对高原缺氧的适应表现和遗传机制在上述三大高原世居人群中却并不完全相同, 其中西藏人具有更好的高原适应表现, 并且HIF通路是其最关键的适应机制。同时, 由于HIF通路涉及广泛, 可调节数以百计的下游基因表达, 并与癌症、炎症、缺血、急性脏器损伤和感染等多种疾病密切相关, 因此HIF通路的激活剂和抑制剂研究也取得了很大进展。本文就三大高原世居人群对高原环境的不同适应反应、HIF及HREs在不同种族高原适应中的遗传学作用机制、HIF通路的药理学研究进展进行了综述, 以期为高原低氧遗传性适应及HIF相关性疾病的进一步研究提供参考。

关键词: 缺氧; 高原; 适应; 缺氧诱导因子; 脯氨酸羟化酶

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Hypoxia inducing factor related genetic adaptation in high-altitude and pharmacological modulation

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Abstract: Adaptation to hypoxia of the plateau environment has been a focus of scientific research in decades. The geographical distributions of such living environment include the Qinghai-Tibet Plateau, Andean Plateau in South America and Ethiopian Plateau. Over the past century, the unique features of physiological adaptation to high-altitude chronic hypoxia have been documented scientifically. The genetic studies of hypoxic adaptation in the past decade have revealed genetic bases of human high-altitude adaptation, with a close relationship to the hypoxia inducible factor (HIF) pathway and hypoxia response elements (HREs). Interestingly, the genetic pattern of adaptation to hypoxia is not the same among the three plateau populations. Tibetan has developed the best high-altitude adaptation, with modification of the HIF pathway as the key genetic element. Due to the wide range of HIF pathways, HIFs could regulate hundreds of downstream genes and are closely related to various diseases such as cancer, inflammation, ischemia, acute organ damage and infection, etc. The treatment researches of these diseases through HIFs-related regulations have led to the development of stabilizers and inhibitors of HIF pathway. We review here the adaptive responses of the three plateau populations to the hypoxic environment, and the genetic

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mechanism of HIF and HREs in the different ethnic high-altitude populations. Classes of HIF inhibitors, such as PI3K and/or mammalian target of rapamycin (mTOR) inhibitors, DNA-binding inhibitors, histone deacetylase inhibitors, heat-shock protein 90 inhibitors, cardiac glycosides, transcription inhibitors, topoisomerase inhibitors, and HIF activators including 2-OG mimics, Fe^{2+} chelators, prolyl hydroxylase (PHD) active-site blockers and CUL2 deneddylators have been presented with the drug examples. In addition, the top 3 chemical-disease and chemical-gene (protein) co-occurrences have been presented from the Pubmed literature search. The review could serve as references for research of hypoxia adaptation and HIF-related diseases.

Key words: hypoxia; altitude; adaptation; hypoxia-inducible factor; prolyl hydroxylases domain

长期生活在高原的人在循环、呼吸和血液方面呈现出对高原环境的独特适应性。高原适应 (high-altitude adaptation) 是高原世居人群或动物经过世世代代的自然选择所获得的, 是通过长期基因突变使其功能结构发生深刻改变或重建, 而这些特性又通过生殖传给后代而巩固下来。这也称之为具有遗传适应 (genetic adaptation) 基础的自然习服 (natural acclimatization)[1]。已知全世界高原居住历史最长的两个民族为青藏高原喜马拉雅山的藏族 (约3～5万年) 和南美洲安第斯高原的印第安人 (约9千年), 而人类对低氧适应生理反应的研究早在1890年从Francois-Gilbert Viault就已开始, 这些早期研究重点主要为安第斯山人对高原的生理性适应。从20世纪70年代开始, 研究重点多集中于青藏高原藏族对高原的生理性适应, 而近年来则较多的关注于埃塞俄比亚人的高原适应方式研究[1]。人们通过对三大高原世居人群对高原低氧的生理性适应研究发现, 缺氧诱导因子 (hypoxia inducible factor, HIF) 及缺氧反应基因 (hypoxia response elements, HREs) 是人类缺氧适应的关键遗传学机制, 并与人体多种疾病具有密切关系。而基于HIF通路的药理学研究, 包括HIF激活剂和抑制剂的研究也取得了很大进展。本文就三大高原世居人群对高原环境的不同适应反应、HIF及HREs在不同种族高原适应中的遗传学作用机制、HIF通路稳定剂和抑制剂的药理学研究进展综述如下。

1 三大高原世居人群的高原适应性变化

1.1 红细胞系变化

从平原到达高原短期逗留的人群, 体内的红细胞压积和血红蛋白浓度随海拔升高而增加, 红细胞增殖也随海拔升高而活跃, 使红细胞携带更多氧气以克服因海拔升高引起的环境氧分压的降低。安第斯山人群就表现出与海拔高度相关的血红蛋白浓度升高这种高原适应行为[2]。相反地, 尽管藏族人血红蛋白浓度在海拔超过4 000 m时才随之升高, 但仍低于安第斯人, 这种特性呈现出藏族人对低氧引起的红细胞增多反应性较低[3]。此外, 在相同海拔高度, 藏族人促红细胞生成素 (erythropoietin, EPO) 含量也稍低于安第斯人[4], 而埃塞俄比亚人体内的血红蛋白量则保持在平原人群的较高水平范围内[5]。因为高黏血症对心脏和慢性高原病都有影响, 所以藏族人的低血红蛋白浓度是被动适应低氧高原环境的结果, 这种相对较低的血红蛋白浓度是藏族人良好高原适应的最重要表型之一。

1.2 血氧饱和度 (oxygen saturation, SaO_2)

在相同海拔高度, 青藏高原世居藏族比新进入高原的平原人保持着更高的静息状态SaO_2, 但与在青藏高原出生并长大的中国汉族人相比却没有明显差异, 并且用同样的仪器和测量方法, 藏族人SaO_2低于同条件下的安第斯人水平[6]。值得注意的是在藏族女性人群中, SaO_2等位基因高表达者所生育后代的存活率高于SaO_2等位基因低表达的人[7]。而埃塞俄比亚人的SaO_2均比同海拔高度的平原移居者高, 其动脉氧含量比从平原移居者高出约16%[8]。

1.3 静息通气量与低氧通气反应

当平原人快速暴露在高原环境后其通气量会立即升高, 即低氧通气反应 (hypoxic ventilatory response, HVR)。这是短期逗留在高原的人所表现出的重要适应反应, 但这种反应不会持续太久, 经过数天后, 其在静息状态下的通气量会恢复到平原水平[9]。而世居高原人群对其持续暴露的低氧环境却有两种截然不同的肺部反应: 安第斯山人静息状态下的通气水平与低海拔人群静息和运动状态下的通气水平无明显差异[10]; 而在同海拔高度, 藏族人比已经高原习服的亚洲人和欧洲人保持着更高的静息状态通气水平, 表现出HVR增强[11]。值得注意的是, 世居藏族人静息状态通气水平是居住在安第斯山的艾玛拉人的1.5倍。此外, 世居藏族人的HVR与急性暴露在低氧环境下的新移居者和低海拔人群有一致性, 显示藏族人已经适应低氧所引起的肺通气量的增加[3]。

1.4 肺血管收缩反应与肺动脉压 (pulmonary artery pressure, PAP)

对急性高原环境的另一个重要的肺部反应是肺血管收缩, 随之导致的结果是肺动脉高压。低氧性肺动

脉高压是与海拔高度有关的肺功能紊乱, 其最主要的病理变化为肺血管收缩和重构, 最终可引起PAP增高及右心衰竭, 也是导致高原肺水肿的主要病理生理机制[12]。久居高原者对低氧引起的肺血管收缩反应与平原人不同, 藏族人静息和运动状态下的PAP与平原人平均水平相符或只是稍有升高, 这也是藏族人肺动脉高压发病率低的一个直接证据。而汉族和藏族婴幼儿在肺动脉高压的形成上也存在着明显差异。研究发现, 与世居藏族婴儿相比, 居住在青藏高原的汉族婴儿更容易出现亚急性高原病的表现, 如呼吸困难、晕厥、发绀、肺动脉高压及右心衰[13], 相反地, 肺动脉高压在安第斯山成年人和青少年群体中确有发生, 其根本原因与包括肺动脉管壁增厚的动脉结构变化有关[12]。

1.5 新生儿出生体重(birth weight)

对安第斯山人和藏族已妊娠女性的研究发现, 高海拔会导致胎儿宫内生长受限, 进而导致新生儿低体重, 这是导致新生儿病死率升高的一个很重要因素[14]。妇女在高海拔地区居住几代后, 由高海拔导致的胎儿宫内生长受限发生率会随着其在高原居住时间的延长而降低, 其所生新生儿低体重发生率会少于短期移居到高原的人[14]。对相同海拔高度居住人群的研究显示, 与欧洲人和中国汉族妇女相比, 安第斯人和藏族妇女所生胎儿的出生体重较高, 表明安第斯人和藏族世居人群都受到上述与缺氧暴露时间有关的低体重儿保护[15]。此外, 安第斯人祖先的来源情况与新生儿出生体重密切相关, 表明后者受到了遗传的影响[16]。

1.6 一氧化氮 (nitric oxide, NO) 水平

以往对高原低氧适应的表型因子研究多集中在肺和血液相关因子上。而最近的研究指出血管因子也是高原适应的核心表型因子。NO是很强的血管舒张因子, 在包括血管内皮细胞的很多细胞上都有表达, 可调节血流量和血管阻力, 还参与其他的细胞反应如动脉平滑肌细胞的松弛。研究表明, 相比平原人, 藏族人具有更高的血循环NO水平, 其虽有更大的前臂血流量但并未出现高血压或血管阻力的升高[17]。

2 HIF通路基因

HIF信号通路中一系列相关基因在高原适应中具有非常重要的作用, HIF通路基因涉及广泛, 在细胞缺氧应答中可调节数以百计的下游基因[18]。HIF基因普遍存在于人和哺乳动物细胞内, 虽然在常氧浓度 (21% O_2) 下可表达, 但合成的HIF蛋白质分子很快会被细胞内氧依赖性泛素蛋白酶途径所降解, 故只有在缺氧条件下才会稳定表达, 且主要通过羟基化、磷酸化和乙酰化等途径提高蛋白稳定性和活性[19]。HIF途径是一个复杂的氧敏感系统, 对维持低氧环境下细胞的能量代谢、生长和增殖等方面起重要作用, 促使下游基因对细胞缺氧做出反应, 与机体适应高原环境有密切联系[20]。HIF是低氧反应的转录调控器, 由β亚单位 (HIF-β) 和3个α亚单位 (HIF-1α、HIF-2α和HIF-3α, 前两者的研究较多) 组成的异源二聚体[21]。HIF通过α亚单位特定区域上的脯氨酰羟化基来调控其对氧浓度变化发生的反应, 可激活数百个与低氧适应相关的细胞基因。

HIF-1α可抑制氧化磷酸化和线粒体生物合成, 对维持红系造血干细胞的稳定必不可少。HIF-2α可调节成年人肾间质细胞EPO基因, 而EPO是红系的核心调节剂。转基因小鼠的研究显示, HIF-2α在贫血状态下会丧失功能, 而HIF -2α获得功能时会产生红系细胞[22]。在缺氧反应中, HIF-1α和HIF-2α可作为有利因素协同作用, 两者可激活血管内皮生长因子 (vascular endothelial growth factor, VEGF), 从而诱导血管生成。小鼠研究显示, HIF-1α和HIF-2α表达降低可延迟或防止低氧性肺动脉高压的发生, 而HIF-2α突变可导致肺动脉高压, 显示HIF-1α和HIF-2α与肺动脉高压的发生密切相关[23]。同时, HIF-1α和HIF-2α也具有相互拮抗性。HIF-1α促进细胞周期停滞, 而HIF-2α促进细胞周期进展。在鼠巨噬细胞、角质形成细胞和内皮细胞中, HIF-1α通过激活一氧化氮合酶2 (nitric oxide synthase 2, NOS2) 基因促进NO产生, 而HIF-2α则通过抑制精氨酸酶 (arginase, Arg) 基因抑制NO产生[24]。HIF通路中的脯氨酸羟化酶 (prolyl hydroxylase domain, PHD) 主要包含PHD1、PHD2和PHD3, 可在其氧依赖降解结构区羟化HIF-α[25]。而在低氧情况下, PHD家族这种内在的氧依赖调节除了对氧浓度改变敏感外, 还可识别铁、抗坏血酸盐浓度和三羧酸循环等, 即其蛋白区域能对各种信号做出反应, 该位置上的羟化基可调控HIF对氧浓度变化的反应, PHD2基因活动减弱可激活HIF途径[26]。

3 HIF通路基因在三大高原世居人群高原适应中的遗传分析

3.1 西藏人高原适应的HIF通路遗传学机制

青藏高原世居藏族是全世界高原适应生存历史最久的人类群体。对藏族世居人群的多项基因组扫描研究显示HIF通路基因在藏族人高原适应中发挥了重要作用[27-29], 而其中的两个HIF通路基因 (HIF-2α基因和PHD2基因) 在不同研究结果中具有一致性[28,30], 显示西藏世居人群与缺氧有关的基因与汉族低海拔人群明显不同。

3.1.1 HIF-2α基因 即内皮PAS区域蛋白1 (endothelial Per-Amt-Sim domain protein 1, EPAS1) 基因。HIF-2α基因是HIF通路中的重要基因, 在人体应对低氧环境的细胞生化调节通路中起核心作用, 但其中藏族人

群特有的HIF-2α基因可能尤其关键, 87%以上的藏族人携带该基因型, 而汉族人的携带率仅9%[29,30]。为进一步揭示其机制, 研究者基于此基因进行了关联性分析, 从与红细胞数量相关的单核苷酸多态性 (single-nucleotide polymorphism, SNP, 指在基因组水平上由单个核苷酸变异所引起的DNA序列多态性) 差异能够看出该基因型与藏族人群的血红蛋白浓度有关, 进一步佐证了该基因型与藏族人高原适应的相关性[31]。汪建课题组[32]通过对50例世居藏族的外显子 (包含92%的人类基因) 进行测序, 发现HIF-2α基因46441523位点等位基因G在世居藏族人群中的频率远高于汉族, 且该位点的基因型与血红蛋白含量密切相关。藏族和汉族人中存在明显差异的SNP位点均位于HIF-2α基因的非编码区, 且该SNP位点的基因型与世居藏族的低血红蛋白浓度显著相关, 提示HIF-2α基因与高原适应相关[28,30,31]。青藏高原世居藏族人除HIF-2α基因的多态性与其低血红蛋白浓度密切相关外, 其血红蛋白浓度明显低于同海拔高度的安第斯人群, 而与低海拔人群的血红蛋白水平接近, 表明世居藏族人群对于高原适应的机制与祖先同样来自亚洲的安第斯人群不同[33]。上述全基因组研究一致显示世居藏族人HIF-2α基因具有积极的定向选择性, 从而能发生有利突变以增强机体对高原环境的适应性。

3.1.2 PHD2基因 PHD2也称为EGLN1, 是HIF通路中的脯氨酰羟化基蛋白域基因, 多项研究证实支持藏族人群高原适应的第二个关键HIF通路候选基因是PHD2, 它可通过减少细胞缺氧状态下HIF-1α亚基的羟基化作用从而调节HIF转录通路[28,29]。其中犹他大学Tatum S. Simonson与青海大学格日力教授[34]合作, 通过全基因组关联研究 (genome-wide association study, GWAS) 对30例世居藏族的研究发现, PHD2和位于22号染色体上的过氧化物酶体增殖物激活型受体A (peroxisome proliferator-activated receptor A, PPARA) 两个低氧相关基因的单倍型与世居藏族的低血红蛋白含量密切相关, 认为正是这种原因导致藏族人具有特别的高原适应性, 而其他多项研究也显示西藏人PHD2基因与其低血红蛋白浓度之间存在关联[30,34,35]。研究表明, 在缺氧状况下, 西藏人PHD等位基因与血浆EPO的迟钝反应相关, 从藏族人分离的淋巴细胞研究显示藏族人具有较低的HIF-1α和HIF-2α靶基因选择, 而PHD2等位基因也可能是通过增加NO的水平而参与低氧环境下的呼吸调节[11,30,34-36]。

3.2 安第斯人和埃塞俄比亚人高原适应的HIF通路遗传学机制

安第斯人的基因组分析显示至少40个HIF通路与缺氧相关候选基因参与其高原适应机制[11,27], 这些候选基因与西藏世居人群高原适应的相关基因并不完全重叠。尽管PHD2是安第斯人和西藏世居人群共同的高原适应候选基因, 但与血红蛋白浓度有关的西藏人高原适应关键基因PHD2在安第斯人群中则未显示出类似的相关性[28,30,35]。与西藏人高原适应的最关键基因HIF-2α和PHD2不同, 安第斯人高原适应的关键基因是磷酸腺苷激活蛋白激酶α-1催化亚基 (α-1 catalytic subunit of adenosine monophosphate-activated protein kinase, AMPKα1, 也称为PRKAA1) 和参与红细胞生成的类泛素化蛋白酶1 (sentrin specific peptidase 1, SENP1)[37,38]。安第斯山人基因组分析显示AMPKα1基因SNP上游部分的母系变异与新生儿的出生体重和母体的子宫动脉直径相关, 提示该基因可能通过影响妊娠生理反应促进胎儿生长来达到对高原环境的人群遗传性适应[14]。此外, 安第斯山人慢性高原病患者的全基因组测序显示SENP1也参与其慢性高原病的发展调节[37]。

对埃塞俄比亚高原世居人群的遗传学研究显示缺氧相关及非相关基因在其高原适应过程中均有表达, 而这些候选基因与藏族人和安第斯人相比表现出明显不同[38,39]。包括螺旋−环−螺旋家族基本成员E41 (basic helix-loop-helix family member e41, BHLHE41)、线粒体钙摄取1基因 (mitochondrial calcium uptake 1, MICU1)、VAV 3鸟嘌呤核苷酸交换因子 (VAV 3 guanine nucleotide exchange factor, VAV3)、芳香烃受体核转运蛋白2 (aryl hydrocarbon receptor nuclear translocator 2, ARNT2) 和甲状腺激素β受体 (thyroid hormone receptor β, THRB) 等候选基因都与埃塞俄比亚人的血管生理反应或缺氧反应相关。值得注意的是, 埃塞俄比亚人的ARNT2和THRB两个基因与其血红蛋白浓度变化有密切关联[40]。而藏族人群的HIF-2α和PHD2基因与其血红蛋白水平相关, 但在安第斯山人群中并没有发现这种关联, 这也提示安第斯山人是通过不同的遗传位点进行高原适应。

4 HIF通路基因药理学研究

如上所述, 三大高原世居人群中, 青藏高原人类活动的时间早于其他高原世居人群, 有更长的进化时间, 因而表现出更好的高原适应反应, 而其PHD2和HIF-2α的基因变化也经历了数千年的自然选择过程[41-43]。大量研究表明HIF通路基因是缺氧适应性转录反应和环境氧浓度变化的关键调节剂, 可调节数百个下游基因并诱导EPO、VEGF和NOS等多种HREs的表达[44]。由于HIF通路与癌症、炎症、缺血、心肌缺血再灌注损伤、急性肺损伤 (acute lung injury, ALI)、急性肾损伤

(acute kidney injury, AKI)、感染和伤口愈合等密切相关, 因此, 通过药理学方式调节这一缺氧适应途径引起了许多关注, HIF通路靶向药物在目前药物研究领域中也取得了很大进展[44-46]。

4.1 HIF抑制剂

HIF抑制剂的开发主要基于化合物的筛选, 霍普金斯药物库中已获得美国食品药品管理局 (FDA) 批准或已进入II期临床试验的HIF基因抑制药物有20余种, 而最有效的11种HIF抑制剂都是强心苷类 (cardiacglycosides), 如地高辛、哇巴因和前列腺素A等。研究发现棘霉素 (NSC-13502) 可有效抑制*HIF1A*与其同源HREs的结合而成为HIF1靶向药物, 其他HIF抑制剂包括磷酸肌醇3-激酶 (phosphoinositide 3-kinase, PI3K) 和哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR) 抑制剂、热休克蛋白90抑制剂 (heat-shock protein 90 inhibitors)、组蛋白脱乙酰基酶抑制剂 (histone deacetylase inhibitors) 和拓扑异构酶抑制剂 (topoisomerase inhibitors) 等。目前用于癌症治疗临床试验的HIF抑制剂有度他雄胺、拓扑替康、PX-478、地高辛及反义寡核苷酸EZN-2968等[9]。然而动物实验研究发现HIF抑制剂的潜在局限性, 如有研究用HIF抑制剂棘霉素治疗呼吸机诱导的ALI小鼠, 结果显示小鼠存活时间减少且肺部炎症增加[47]。尽管目前尚无关于HIF抑制剂对炎症性或缺血性疾病作用的人体试验证据, 但临床试验设计仍然需要重点关注这些潜在风险, 比如可能抑制组织保护反应、导致炎症性肠病 (inflammatory bowel disease, IBD) 患者肠道炎症的恶化、长期服用HIF抑制剂的患者在心肌梗塞期间可能导致更严重的缺血−再灌注损伤, 或更严重的AKI和ALI等。HIF通路抑制剂的分类及代表药物见表1[48-60], 表中同时列出了Pubmed已发表文献中报道数量位于前三的与该药物共同出现、具有密切相关性的疾病及基因 (蛋白)。

4.2 HIF激活剂和PHD抑制剂

研究证明HIF激活剂在不同肠道炎症模型中具有保护作用。有研究使用HIF激活剂DMOG (dimethyloxaloylglycine, 为2-OG加氧酶及PHD的非特异性抑制剂) 治疗化学诱导性结肠炎; 还有研究使用特异性HIF激活剂FG-4497干预2,4,6-三硝基苯磺酸 (2,4,6-trinitrobenzenesulphonic acid, TNBS) 诱导的肠道炎症[61,62]。两项研究均表明HIF激活剂治疗与肠道炎症多种参数的显著改善相关, 包括体重减轻、肠道炎性变化和组织学损伤[61,62]。同时, 研究表明HIF激活与促进肿瘤血管形成有关, 因此使用HIF激活剂治疗炎性或缺血性疾病时的一个重要问题是对肿瘤性疾病的影响, 但HIF激活剂是否可能导致人类癌症或肿瘤进展的问题目前尚无明确证据[63]。临床前和临床研究都表明肢体如手臂或腿的缺血再灌注的短暂周期可以保护心脏免受随后的缺血性心肌损伤, 而将编码组成型活性形式的HIF-1α重组腺病毒注射到小鼠后肢肌肉中, 可以在药理学上引发这种效应, 这些研究提示HIF激活剂的缺血性心脏保护作用[63,64]。同时, 由于HIF刺激的VEGF释放可能与血管渗漏增加和败血症样综合征有关, 一项研究HIF激活剂治疗支气管肺发育不良 (一种影响早产新生儿的慢性肺病) 的实验以早产狒狒新生儿的血管生成和改善肺部生长和功能为指标, 发现通过PHD抑制剂FG-4095的HIF刺激可改善支气管肺发育不良, 但FG-4095治疗组所有死亡动物都出现涉及面部和头皮的红斑性丘疹性皮疹, 且FG-4095治疗组与未治疗组相比, 死亡和皮疹之间存在显著相关 ($P = 0.002$)[61,62]。除了癌症领域, HIF作为炎症和缺血性疾病的药理学靶点, 临床研究则尝试通过HIF通路激活剂来治疗慢性血管闭塞性疾病如外周动脉疾病和间歇性跛行, 但尚未证实明确有效[65]。

如前所述, PHD2基因活动减弱可激活HIF途径, 即PHD抑制剂具有HIF激活作用。对肾性贫血患者进行的II期临床试验中, 口服PHD抑制剂FG-2216可激活HIF通路从而显著增加患者血浆EPO水平, 表明通过药理学途径调节HIF系统可以刺激内源性EPO的产生[65]。然而, 由于FG-2216的安全性问题如可导致致命性肝坏死和肝酶水平异常已经被停止使用, 第二代PHD抑制剂FG-4592对终末期肾病患者的肾性贫血的临床试验在后续进行。但研究者也认为这种通过HIF通路激活促进的红细胞生成可能存在不可控制性风险, 尤其是在HIF2α激活剂长期治疗期间[66]。同时, 动物实验研究通过肌内注射AdCA5 (HIF1α的一种活性形式的编码组成型腺病毒) 和静脉应用PHD抑制剂DMOG参与培养的骨髓来源血管生成细胞, 分析提升缺血肢体中HIF1α水平的作用, 研究表明这种联合治疗可保护股动脉结扎的老年小鼠的血液灌注、运动和肢体功能[67]。然而, 特定PHD抑制剂的药理研究尚未见相关报道。由于PHDs基因的表达和功能可能因组织不同而异, 因此发展特异性PHD抑制剂可以更有效地达到目标效应, 并降低脱靶效应的风险。HIF通路激活剂的分类及代表药物见表2[68-76], 表中同时列出了Pubmed已发表文献中报道数量位于前三的与该药物共同出现、具有密切相关性的疾病及基因 (蛋白)。

5 研究展望

从上述研究可以发现, 高原适应机制在不同高原世居人群中是不同的, 也无疑是非常复杂的。此外, 越

Table 1 Classes and examples of hypoxia inducible factor (HIF) inhibitors

HIF inhibitors class	Example drug name	Molecular formula	Chemical-disease co-occurrences in literature (top 3 in Pubmed)	Chemical-gene (protein)co-occurrences in literature (top 3 in Pubmed)
PI3K and/or mammalian target of rapamycin (mTOR) inhibitors	Wortmannin[48]	$C_{23}H_{24}O_8$	Neoplasms, ischemia, whooping cough	AKT serine/threonine kinase 1 (AKT1), phosphatidylinositol-4,5-bisphosphate 3-kin-ase catalytic subunit alpha (PIK3CA), insulin
	LY294002[48]	$C_{19}H_{17}NO_3$	Neoplasms, ischemia, inflammation	AKT1, PIK3CA, protein kinase cAMP-dependent type I regulatory subunit beta (PRKAR1B)
	Temsirolimus[49]	$C_{56}H_{87}NO_{16}$	Neoplasms, carcinoma, renal cell, neoplasm metastasis	Mechanistic target of rapamycin kinase (mTOR), AKT1, PIK3CA
DNA-binding inhibitors	Echinomycin[50]	$C_{51}H_{64}N_{12}O_{12}S_2$	Neoplasms, hypoxia, drug-related side effects and adverse reactions (DRSEAR)	HIF-1α subunit, SET domain containing 2 ($SETD_2$), HIF 1
Histone deacetylase inhibitors	Romidepsin[51]	$C_{24}H_{36}N_4O_6S_2$	Neoplasms, DRSEAR, lymphoma	Histone deacetylase 9, histone deacetylase 1, tumor protein p53
	Trichostatin A[52]	$C_{17}H_{22}N_2O_3$	Neoplasms, carcinogenesis, breast neoplasms	Histone deacetylase 9, histone deacetylase 1, tumor protein p53
Heat-shock protein 90 inhibitors	Radicicol[53]	$C_{18}H_{17}C_lO_6$	Neoplasms, DRSEAR, carcinogenesis	Heat shock protein 90 alpha family class A member 1 (HSP90AA1), ATPase H^+ transporting V1 subunit A (ATP6V1A), thirty-eight-negative kinase 1
	Apigenin[54]	$C_{21}H_{20}O_{10}$	Neoplasms, DRSEAR, diabetes mellitus	Tumor necrosis factor, interleukin 6, serine protease 1
	Geldanamycin[55]	$C_{29}H_{40}N_2O_9$	Neoplasms, DRSEAR, carcinogenesis	HSP90AA1, AKT1, receptor tyrosine-protein kinase erbB-2
Cardiac glycosides	Digoxin[56]	$C_{41}H_{64}O_{14}$	Heart failure, arrhythmias, DRSEAR	ATP6V1A, ATP binding cassette subfamily B member 1, TBC1 domain family member 9
Transcription inhibitors	Amphotericin B[57]	$C_{47}H_{73}NO_{17}$	Infection, mycoses, DRSEAR	CD4 molecule, tumor necrosis factor, albumin
	Chetomin[58]	$C_{31}H_{30}N_6O_6S_4$	Hypoxia, neoplasms, DRSEAR	HIF-1αsubunit, E1A binding protein p300, SET domain containing 2
Topoisomerase inhibitors	Camptothecin[59]	$C_{20}H_{16}N_2O_4$	Neoplasms, DRSEAR, colonic neoplasms	DNA topoisomerase I, tumor protein p53, caspase 3
	Topotecan[60]	$C_{23}H_{23}N_3O_5$	Neoplasms, DRSEAR, ovarian neoplasms	ATP binding cassette subfamily G member 2, DNA topoisomerase I, tumor protein p53

来越多的研究证据表明高原生理适应是多个基因, 尤其是HIF通路多基因相互作用的结果。此外, 尽管藏族人HIF通路基因的选择主要是基于对慢性缺氧的适应结果, 但藏族人群的这种基因变化也是其对高海拔地区其他环境压力如低温和强烈紫外线暴露的适应性反应, 且PHD2和HIF-2α在藏族高原适应中的共同作用尚需进一步研究。同时,尽管基于HIF通路基因多疾病相关性的PHD抑制剂、HIF抑制剂和激活剂的药理学研究也取得了显著进展, 但仍存在很多未解的问题。高原适应是研究人类进化过程的极好的自然实验设计, 以HIF通路为关键关注点的高原遗传性适应研究及HIF通路药理学研究将更好地理解人类环境适应

Table 2 Classes and examples of HIF activators

HIF activators class	Example drug name	Molecular formula	Chemical-disease co-occurrences in literature (top 3 in Pubmed)	Chemical-gene (protein)co-occurrences in literature (top 3 in Pubmed)
2-OG mimics	Dimethyloxalylglycine[68]	$C_6H_9NO_5$	Hypoxia, neoplasms, ischemia	HIF-1α subunit, $SETD_2$, HIF1
	N-oxalyl-d-phenylalanine[69]	$C_{11}H_9NO_4$	Hypoxia	HIF-1α, erythropoietin, $SETD_2$
Fe^{2+} chelators	Desferrioxamine[70]	$C_{25}H_{48}N_6O_8$	DRSEAR, iron overload, beta-thalassemia	Ferritin, catalase
	Hydralazine[71]	$C_8H_8N_4$	Hypertension, heart failure, hypotension	Renin, calcium voltage-gated channel subunit alpha1F, albumin
	TM-6008[72]	$C_{21}H_{17}N_5O_3$	Hypoxia, inflammation, ischemia	HIF-1αsubunit, EGLN1, myosin light chain kinase
	L-Mimosine[73]	$C_8H_{10}N_2O_4$	Hypoxia, neoplasms, DRSEAR	tyrosinase, HIF-1α subunit, interleukin 6
PHD active-site blockers	Pyrazolopyridines[74]	$C_6H_5N_3$	Neoplasms, DRSEAR, asthma	PDE4, B-Raf proto-oncogene serine/threoninekinase, tumor necrosis factor
	8-Hydroxyquinolines[75]	$C_{10}H_7INNaO_7S$	DRSEAR, jaundice, neoplasms	ATP6V1A, albumin, methyl-CpG binding domain protein 2
CUL2 deneddylators	MLN4924[76]	$C_{21}H_{25}N_5O_4S$	Neoplasms, DRSEAR, carcinogenesis	Neural precursor cell expressed developmentally down-regulated 8, parkin RBR E3 ubiquitin protein ligase, cullin 1

的分子学基础, 并为缺血和慢性缺氧性疾病等HIF通路相关疾病的新疗法提供依据。

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