microRNA介导低氧对药物代谢酶和转运体的调控

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摘要: 低氧条件下机体的循环系统、神经系统、内分泌系统等的功能发生显著改变, 这些变化影响药物在体内的吸收、分布、代谢和排泄。药物代谢酶和转运体是影响药物代谢的主要因素, 微小RNA (microRNA, miRNA) 除调控与药物代谢相关的基因如缺氧诱导因子、炎症因子、核受体等, 还可直接作用于药物代谢酶和转运体, 影响药物的体内代谢。本文通过综述低氧对miRNA及药物代谢酶和转运体的调节, miRNA调控药物代谢酶和转运体及药物代谢相关基因, 低氧调节药物代谢酶和转运体的相关机制等, 探讨miRNA在低氧调节药物代谢酶和转运体中的作用, 提出以miRNA为核心的低氧影响药物代谢的分子机制。

关键词: miRNA; 低氧; 药物代谢酶; 药物转运体

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Effect of hypoxia on drug metabolizing enzymes and transporters and the role of microRNA

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Abstract: The function of circulatory system, nervous system and endocrine system is significantly changed in hypoxic environments. These changes affect the absorption, distribution, metabolism, and excretion of drugs in the body. Drug metabolizing enzymes and transporters are the main factors affecting drug metabolism; microRNA (miRNA) can act directly on drug metabolizing enzymes and transporters and can regulate their genes through hypoxia-inducible factor, inflammatory cytokines, and nuclear receptors. This article reviews the effect of hypoxia on drug metabolizing enzymes and transporters and the mechanisms by which miRNA modulates these proteins and their expression during hypoxia.

Key words: miRNA; hypoxia; drug metabolizing enzyme; drug transporter

低氧是指可利用的氧减少或氧分压降至临界值以下的状态, 包括宏观低氧环境和微观低氧环境, 如高原低氧、高空飞行、潜水作业等属于宏观低氧环境, 肿瘤、炎症、休克等疾病状态属于微观低氧环境。低氧条件下机体产生一系列的生理性变化, 部分为病理性变化, 这些变化影响内源性物质如氨基酸、胆红素等和外源性物质如药物、毒素等的代谢[1,2]。早在20世纪80年代就有研究发现, 低氧条件下茶碱和地尔硫䓬的代谢减慢[3-5], 随后更多研究表明低氧显著影响普萘洛尔[6]、氨茶碱[7]、乙酰唑胺[8]、强的松[9]、呋喃苯胺酸[10]、磺胺甲噁唑[11]的体内代谢, 证实低氧环境中大多数药物的体内代谢减慢。药物代谢酶和转运体是药物在体内进行生物转化的主要因素, 低氧条件下药物代谢酶和转

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运体发生显著变化[12-14], 其机制与低氧调节炎症因子、缺氧诱导因子 (hypoxia inducible factors, HIF) 和核受体通路并进一步调控药物代谢酶和转运体的基因表达有关[15,16]。miRNA是具有调控功能的非编码RNA, 低氧条件下miRNA的表达发生显著变化, 并且miRNA的变化与药物代谢酶和转运体具有一定的相关性[17,18], 本文从不同角度综述了miRNA在低氧条件下对药物代谢酶和转运体的调控作用。

1 低氧调控miRNA的表达

miRNA是一类小分子非编码RNA, 长度约为19～25个核苷酸。miRNA通过与靶基因mRNA 3'端非编码区 (3'-untranslated region, 3'-UTR) 特定序列的碱基完全或不完全互补配对, 引起mRNA降解或翻译抑制来调控靶基因的表达[19-21]。miRNA在很多生物学过程中具有重要的调节作用, 如参与调节细胞增殖、分化与凋亡、肿瘤发生与发展、脂类代谢、免疫等各种生命活动[22-25]。迄今为止, 人类基因组中已经发现2 500多种成熟miRNA, 而三分之一以上的人类蛋白编码基因都是miRNA的保守靶基因, 表明miRNA在基因调控中发挥重要作用[26]。肠、肝和肾组织是药物吸收、代谢、排泄的重要器官, miRNA、药物代谢酶和转运体广泛分布其中, 低氧条件下这些组织器官中的miRNA表达发生显著变化。

1.1 低氧调控肝组织中miRNA的表达 肝脏是药物代谢的重要器官, 存在大量药物代谢酶和转运体。miRNA-122是哺乳动物肝损伤的一种有效生物标志物, 研究发现低氧降低肝脏miRNA-122-5p的表达, 推测低氧条件下药物代谢的变化与miRNA介导的肝脏功能改变有关[27,28]。Zhu[29]发现低氧训练可显著降低肝脏miRNA-27的表达。低氧微环境中的肿瘤细胞研究表明, 与正常人肝细胞比较, miRNA-375和miRNA-196-5p在肝癌细胞中的表达均显著降低[30,31]。体内研究发现, 在13.6% O_2浓度下, 大鼠肝脏miRNA-92a-2-5p、miRNA-378a-3p和miRNA-1224表达均显著降低[32]。以上研究结果显示低氧对肿瘤细胞和肝组织中的miRNA具有显著调节作用, miRNA-92、miRNA-122、miRNA-196、miRNA-375和miRNA-378的表达均呈下降趋势。

1.2 低氧调控肠组织中miRNA的表达 肠道是药物吸收的主要部位, 其分布的药物转运体对药物吸收起着至关重要的作用, 低氧条件下肠组织中的miRNA发生显著变化。Nijhuis等[33]研究了DLD-1、HCT116和HT29等6种肠癌细胞系中miRNA在20.9%、1.0%和0.2% O_2浓度中的表达情况, 发现miRNA-210、miRNA-30d、miRNA-320b、miRNA-320c、miRNA-320a、miRNA-21、miRNA-141和miRNA-147的表达显著升高, 其中miRNA-210最为明显。高原低氧环境中miRNA的表达变化研究较少, 研究发现高海拔地区的汉族人和藏族人血浆中miRNA-210-3p浓度显著高于平原地区汉族[34], 与文献[33]研究结果一致, 提示实际低氧环境下, miRNA-210表达显著升高。肿瘤低氧微环境和实际低氧环境存在一定差异, Toshihiro等[35]发现miRNA-320a、miRNA-320b、miRNA-320c、miRNA-320d在结直肠肿瘤低氧微环境中的表达显著降低, 与前述研究结果相反。以上研究结果表明, 低氧条件下肠组织miRNA的变化存在一定争议, 基本变化趋势是肿瘤低氧微环境中表达显著降低, 而在实际低氧环境中表达显著升高。

1.3 低氧调控肾组织中miRNA的表达 肾脏是药物排泄的重要器官, 肾脏中的转运体对内源性和外源性物质的分泌和重吸收具有重要作用。Liu等[36]采用低压氧舱模拟7 500 m海拔和9.0% O_2高原环境, 测定了大鼠脑、肺、心、肝和肾脏中miRNA-210的表达, 发现不同组织中miRNA-210的表达均显著升高, 其中肾脏中升高近5倍, 研究结果与低氧肠组织中miRNA-210的变化一致。Wu等[37]对小鼠进行24%～7% O_2和周期60 s的间歇性缺氧造模, 发现肾脏中miRNA-155的表达显著升高了25%。Xu等[38]发现小鼠肾脏缺血再灌注后引起的缺氧损伤能够明显升高miRNA-21的表达, 另外在1% O_2浓度下, 人脐静脉内皮细胞中miRNA-21的表达同样显著升高。

低氧对肝、肠和肾组织中的miRNA均有调控作用, 其中肝脏中miRNA-92a、miRNA-122、miRNA-375、miRNA-378和miRNA-1224表达显著降低, 肠组织中miRNA-21、miRNA-30d、miRNA-141、miRNA-147、miRNA-210和miRNA-320的表达显著升高, 肾组织中miRNA-21、miRNA-155和miRNA-210表达显著升高, 见表1[28-34,36,38]。miRNA-320为特殊miRNA, 其在肿瘤低氧微环境中表达降低, 与实际低氧环境研究结果恰好相反。有关低氧对肠组织和肠肿瘤细胞中miRNA-320的调控研究还有待进一步证实。

2 低氧对药物代谢酶和转运体的影响

2.1 低氧对药物代谢酶的影响 药物代谢酶分为两类, I相代谢酶主要参与氧化、还原、水解等反应, II相代谢酶主要催化葡萄糖醛酸化、硫酸化、乙酰化等反应。细胞色素P450 (cytochrome P450, CYP450) 是最主要的I相代谢酶, 目前已确定了人类57个CYP450基因, 根据序列的相似性分为18个家族, 42个亚家族[39]。CYP1A2、CYP2C9、CYP2C19、CYP2D6、CYP2E1和CYP3A4代谢90%以上的药物, 其中CYP3A4是人体中最重要的药物代谢酶, 代谢50%以上的药物[40]。II

Table 1 Changes in the expression of miRNA at hypoxia. ↑: Increase; ↓: Decrease

Species	Object	miRNA	mRNA expression	Reference
Human	Huh7	miR-375	↓	[30]
	Huh7	miR-196-5p	↓	[31]
	Hep3B	miR-375	↓	[30]
	Hep3B	miR-196-5p	↓	[31]
	HCCLM3	miR-196-5p	↓	[31]
	SMMC7721	miR-196-5p	↓	[31]
	HepG2	miR-196-5p	↓	[31]
	DLD-1	miR-210	↑	[33]
	DLD-1	miR-320	↑	[33]
	HCT116	miR-210	↑	[33]
	HCT116	miR-320	↑	[33]
	HT29	miR-210	↑	[33]
	HT29	miR-320	↑	[33]
	HT29	miR-320	↓	[34]
	HT55	miR-210	↑	[33]
	HT55	miR-320	↑	[33]
	SW837	miR-210	↑	[33]
	SW837	miR-320	↑	[33]
	VACO4S	miR-210	↑	[33]
	VACO4S	miR-320	↑	[33]
	SW480	miR-320	↓	[34]
	HUVEC	miR-21	↑	[38]
	Plasma	miR-210	↑	[36]
Rat	Liver	miR-122	↓	[29]
	Liver	miR-27	↓	[28]
	Liver	miR-92a-2-5p	↓	[32]
	Liver	miR-378a-3p	↓	[32]
	Liver	miR-1224	↓	[32]
	Liver	miR-210	↑	[36]
	Brain	miR-210	↑	[36]
	Heart	miR-210	↑	[36]
	Renal	miR-210	↑	[36]
Mouse	Renal	miR-155	↑	[36]

相代谢酶主要有*N*-乙酰基转移酶 (*N*-acetyltransferase, NATs)、谷胱甘肽巯基转移酶 (glutathione S-transferase, GSTs) 以及葡萄糖醛酸转移酶 (UDP-glucuronyl transferases, UGTs) 等。

研究已证实, 低氧显著改变药物代谢酶CYP450的活性和表达[40]。Kurdi等[41]发现急性缺氧显著下调家兔CYP1A1和CYP1A2的活性和蛋白表达。Fradette等[42]研究证实家兔急性缺氧48 h后, CYP3A6和CYP3A11的表达显著升高, CYP1A1、CYP1A2、CYP2B4、CYP2C5和CYP2C16的表达显著降低。课题组研究发现高原低氧对CYP450也有一定影响, 大鼠急进2 800 m高原地区3天后, CYP1A2的活性、蛋白和mRNA表达分别降低62.3%、60.4%和51.1%, 30天后分别降低60.8%、62.0%和32.9%。大鼠急进4 300 m高原地区3天后, CYP1A2的活性、蛋白和mRNA表达分别降低60.8%、65.8%和37.2%, 30天后分别降低53.8%、64.8%和30.7%[12]。在海拔2 800 m和4 300 m高原地区, 慢性缺氧使CYP2D1的活性和表达显著升高, 而急性缺氧无明显影响[12]。高原急性缺氧对CYP3A1和CYP2E1的活性和表达也无明显影响, 但在高原慢性缺氧条件下CYP3A1和CYP2E1的活性和表达显著降低[13]。高原低氧条件下II相药物代谢酶也发生一定变化, 如大鼠*N*-乙酰基转移酶II的活性在4 600 m高原地区显著降低38.7%[40]。

以上研究结果表明, 不同低氧方式对动物体内CYP450酶影响的结果较为一致, 其中CYP1A1、CYP1A2、CYP2E1和CYP3A1的活性和表达降低, CYP3A6和CYP2D1的活性和表达升高, 见表2[12,13,40-42]。与急性缺氧相比, 慢性缺氧对动物体内药物代谢酶的影响较大。

Table 2 Changes in the activity and expression of drug metabolizing enzymes at hypoxia. ↑: Increase; ↓: Decrease

Species	Drug metabolizing enzyme	Effect	Reference
Rabbit	CYP1A1	Protein expression, ↓	[41]
	CYP1A2	Protein expression, ↓	[41]
	CYP3A6	Protein expression, ↓	[41]
	CYP2B4	Protein expression, ↓	[42]
	CYP2C5	Protein expression, ↓	[42]
	CYP2C16	Protein expression, ↓	[42]
Rat	CYP1A2	↓	[12]
	CYP2C11	−	[12]
	CYP2C22	Activity, ↑	[12]
	CYP2D1	↑	[12]
	CYP2E1	↓	[13]
	CYP3A1	↓	[13]
	NAT2	Activity, ↓	[12]
	GST	Activity, ↓	[40]
	UGT	−	[40]
Human	CYP1A2	−	[40]
	CYP2C19	−	[40]
	CYP2D6	Activity, ↓	[40]
	CYP3A4	Activity, ↓	[40]

2.2 低氧对药物转运体的影响 药物转运体是一类存在于细胞膜上的蛋白质或多肽, 影响着药物在体内的吸收、分布、代谢和排泄。药物转运体分为两类, 第一类是ABC族转运蛋白, 又称ATP结合 (ATP-binding cassette, ABC) 转运蛋白, 由*ABC*基因编码, 如*ABCB1*编码MDR1、*ABCC2*编码MRP2等。ABC家族主要有多药耐药蛋白 (multi-drug resistance protein, MDRs) 又称P-糖蛋白 (P-glycoprotein, P-gp)、多药耐药相关蛋白 (multidrug resistance-associated protein, MRPs)、乳腺癌耐药蛋白 (breast cancer resistance protein, BCRP) 等, 其大部分蛋白的功能是将底物从细胞内外排至细胞外。第二类是可溶性载体 (solute carrier, SLC) 转运蛋白, 又称可溶性载体, 由*SLC*基因编码, 如*SLCO1B1*编

码OATP1B1、*SLC15A1*编码PEPT1等。SLC家族包括寡肽转运体 (oligopeptide transporter, PEPTs)、有机阴离子(organic anion transporter, OATs)、阳离子转运体(organic cation transporter, OCTs) 等, 主要功能是转运底物进入细胞[43,44]。

低氧显著影响药物转运体的表达, 家兔在8% O_2浓度下缺氧48 h, 肝组织中的MDR1蛋白表达显著升高77%[42]。Dopp等[45]也证实了低氧升高大鼠肝脏MDR1 mRNA的相对表达。大鼠在高原低氧实际环境暴露72 h后, MDR1蛋白和mRNA表达在小肠中分别下调了71.3%和50.1%, 肝组织中分别上调1.33和1.15倍, 肾组织中分别上调1.83和0.49倍[46,47], 研究结果表明低氧条件下MDR1的表达在不同组织中的变化趋势不同。低氧暴露时间也是影响药物转运体的重要因素, 随着缺氧时间的延长, MRP2在小肠和肝脏组织中的蛋白表达量有上升的趋势, 而在肾脏组织中, 缺氧24 h后MRP2的表达升高, 缺氧72 h后MRP2的表达降低[47]。大鼠在模拟海拔5 000 m的低压氧舱中暴露24 h和72 h后, PEPT1、OATP1B1、OAT1、OCT1、MDR1和MRP2的表达升高, 但随着缺氧时间的延长, 不同组织中的药物转运体变化趋势不一致[48]。

以上研究结果显示, 低氧条件下药物转运体的变化与机体组织类型和低氧暴露时间有关, 其中肝脏中MDR1、MRP2、PEPT1、OATP1B1、OAT1、OCT1的表达显著升高, OATP2和BCRP的表达无明显变化。肠组织中MRP2、PEPT1、OATP1B1、OAT1、OCT1的表达显著升高, 而MDR1的表达显著降低。肾组织中MDR1、PEPT1、OAT1、OCT1表达显著升高, MRP2的表达随低氧暴露时间先升高后降低, OATP1B1的表达随低氧暴露时间先降低后无明显变化。低氧条件下药物转运体的变化见表3[42,45-48]。

Table 3 Changes in the activity and expression of drug transporters at hypoxia. ↑: Increase; ↓: Decrease

Object	Drug transporter	Effect	Reference
Liver	MDR1	Protein expression, − mRNA expression, ↑	[42,45,47,48]
	BCRP	mRNA expression, −	[42]
	MRP2	↑	[47,48]
	OATP1B1	mRNA expression, −	[42]
	OATP1B1	mRNA expression, ↑	[48]
	PEPT1	mRNA expression, ↑	[48]
	OCT1	mRNA expression, ↑	[48]
	OAT1	mRNA expression, ↑	[48]
Intestine	MDR1	↓	[46]
	MDR1	↑	[47]
	MDR1	mRNA expression, ↑	[48]
	MRP2	↑	[47,48]
	PEPT1	mRNA expression, ↑	[48]
	OATP1B1	mRNA expression, ↑	[48]
	OAT1	mRNA expression, ↑	[48]
	OCT1	mRNA expression, ↑	[48]
Kidney	MDR1	↑	[47,48]
	MRP2	↑	[47,48]
	PEPT1	mRNA expression, ↑	[48]
	OATP1B1	mRNA expression, ↑ (hypoxia for 24 h); − (hypoxia for 72 h)	[48]
	OAT1	mRNA expression, ↑	[48]
	OCT1	mRNA expression, ↑	[48]
Heart	MDR1	↓	[45]

3 miRNA调控药物代谢酶和转运体

3.1 miRNA调控药物代谢酶 miRNA可负调控CYP450的表达[49,50]。在敲除miRNA-122的小鼠肝脏中CYP1A2的表达显著上调, 提示miRNA-122对CYP1A2有负调控作用[51]。Chen等[52]筛选出62个与CYP1A2相关的miRNA, 进一步证实miRNA-132-5p可靶向调控CYP1A2的表达。Wei等[53]用双荧光素酶实验证实了miRNA-320可靶向CYP1A2抑制股骨头缺血性坏死。Wei等[54]预测105种miRNA可能对CYP3A4的mRNA有转录调控作用, 并证实了miRNA-1、miRNA-577、miRNA-532-3p和miRNA-627可显著降低CYP3A4的表达。文献[55,56]证实了miRNA-103和miRNA-107对CYP2C8具有负调节作用, 并在CYP2C9和CYP2C19的3'-UTRs中发现了miRNA应答元件(miRNA response element, MRE), 表明miRNA-103和miRNA-107可能在转录后水平调控CYP2C9和CYP2C19的表达。此外, miRNA-128调控CYP2C9的表达, miRNA-130b和miRNA-155可调控CYP2C9和CYP2C19的表达[57-59]。Li等[60]研究了脑组织中CYP2D变化的机制, 发现miRNA-101和miRNA-128-2能与CYP2D6 3'-UTRs结合, 从而降低CYP2D6在脑组织中的表达。miRNA对CYP2E1同样具有负调节作用, 研究[61,62]发现CYP2E1的3'-UTRs中有一个潜在的miRNA-378 MRE识别元件, 并验证了miRNA-378对CYP2E1的靶向作用, 同时在人肝组织样本中观察到miRNA-378与CYP2E1的负相关性。

II相代谢酶UGTs参与了许多内源性物质的代谢, 并且与药物的不良反应密切相关[63]。Dluzen等[64]对UGT1A1 3'-UTRs进行生物信息学分析, 发现miRNA-491-3p的潜在结合位点, 并通过转染miRNA-491-3p的拟似物和抑制物验证了其对UGT1A1的负调控作用。其他研究表明miRNA-548d和miRNA-217分别调控UGT1A1和NAT2的表达[65,66]。

除药物代谢酶外, miRNA也可调控内源性物质的代谢酶。肝脏miRNA-122负调控CYP7A1和谷胱甘肽过氧化物酶7 (GPX7)的表达[67,68], 肠组织miRNA-

19b负调控CYP19A1的表达[69]。在淋巴细胞中过表达miRNA-125b能够显著降低谷胱甘肽合成酶 (glutathione synthetase, GSS) 的活性, 其机制与miRNA-125b能够靶向作用于GSS基因有关[70]。

3.2 miRNA调控药物转运体 miRNA负调节ABC药物转运体。MDR1的相关研究发现, miRNA-298在多个耐药细胞系中直接作用于MDR1的3'-UTR, 抑制其表达[71]。miRNA-331-5p可靶向作用于MDR1 mRNA的3'-UTR, 下调MDR1的表达[72]。He等[18]综述了miRNA-7、miRNA-19、miRNA-27a、miRNA-145、miRNA-200c、miRNA-354、miRNA-451对MDR1的靶向调控作用。miRNA-660与MRP2表达具有一定相关性, 但二者的靶向作用并未证实[73]。文献[74,75]报道, 用miRNA-379拟似物转染HepG2细胞, 发现其抑制MRP2的表达及MRP2不同二级结构的mRNA通过与miRNA相互作用对蛋白下调的程度产生影响, 证实了二者之间的靶向作用。Guo等[76]发现miRNA-495下调了耐药基因 *BCRP* 的表达, 在miRNA-495-UBE2C-BCRP/ERCC1通路中扮演了重要的角色。Li等[77]确定了BCRP mRNA 3'-UTR一个新的miRNA-519c响应元件, 并证实人乳腺癌细胞中miRNA-519c和miRNA-520h下调BCRP的表达。Jiao等[78]发现耐药细胞株中下调最为显著的miRNA-181a靶向作用于BCRP mRNA的3'-UTR, 进一步抑制BCRP的表达, 逆转细胞耐药现象。Kong等[79]研究了BCRP在耐药中的分子机制, 发现miRNA-145抑制BCRP的表达。

miRNA对SLC药物转运体的调节作用研究较少, 目前仅发现miRNA-511、miRNA-206、miRNA-613负调控OATP1B1的表达[80,81], miRNA-92b、miRNA-193a-3p负调控PEPT1的表达[82-84]。miRNA对其他SLC药物转运体的调节作用未见报道。

以上研究表明, miRNA对I相代谢酶CYP450、II相代谢酶、内源性物质代谢酶、ABC和SLC族药物转运体均具有负调控作用。miRNA调节药物转运体的研究主要集中在ABC药物转运体, SLC药物转运体还有待进一步证实。

4 miRNA调控HIF-1、核受体以及炎症因子

HIF-1、核受体以及炎症因子是调控药物代谢酶和转运体相关的基因, 这些基因的调控作用是影响药物代谢酶和转运体表达的重要机制, 因此miRNA对HIF-1、核受体以及炎症因子的调控作用会影响药物代谢酶和转运体的功能及表达。

HIF-1是细胞应答缺氧的重要调节因子, 启动下游多个与缺氧相关的基因转录。常氧条件下, 脯氨酸羟化酶 (proline hydroxylase, PHD) 激活, HIF-1被蛋白酶水解。低氧条件下, PHD处于抑制状态使得HIF-1稳定存在, 进一步调控CYP2C11、CYP3A4及MDR1的表达[85]。miRNA-18a的表达在低氧条件下显著降低, 并靶向调节HIF-1的mRNA表达[86]。另外, 研究也发现miRNA-135b、miRNA-155、miRNA-199a和miRNA-424可调节HIF-1的表达[87-90]。

核受体是调节药物代谢酶和转运体的重要转录因子, 主要包括孕烷X受体 (pregnane X receptor, PXR)、组成型雄烷受体 (constitutive androstane receptor, CAR) 和过氧化物酶体增殖体激活受体 (peroxisome proliferator-activated receptor, PPAR)。研究发现miRNA-140-3p可抑制肝癌细胞中PXR的表达[91]。Rao等[92]研究了miRNA-148a介导雌激素对胆汁淤积症的诱导作用, 发现其可能通过PXR信号通路参与了雌激素的诱导。Takwi等[93]发现miRNA对CAR同样具有负调节作用, 有趣的是CAR可反向下调miRNA-137的表达, 形成双向调节。有研究[94,95]也证实了CAR可负反馈调控miRNA的表达。Xiao等[96]发现HaCaT细胞中miRNA-203可调控PPAR的表达, 减轻角化细胞增生。

miRNA在炎症反应中发挥着重要作用, 文献[97]报道miRNA-29c可升高炎症因子白介素-6 (IL-6) 和肿瘤坏死因子-α (TNF-α) 的蛋白和mRNA表达。Marques-Rocha等[98]发现miRNA-126、miRNA-132、miRNA-146、miRNA-155和miRNA-221可调控TNF-α、IL-1、IL-6和IL-18的表达。自身免疫疾病中的miRNA对炎症因子也有调控作用, TNF-α、IL-1β、IL-6均可被miRNA-10a、miRNA-23b、miRNA-155、miRNA-522等多个miRNA直接和间接调控[99]。

综上, miRNA对HIF-1、核受体、炎症因子均有调控作用。miRNA-18a、miRNA-135b、miRNA-155、miRNA-199a、miRNA-424下调HIF-1的表达。miRNA-140-3p和miRNA-148a下调PXR的表达, miRNA-137可下调CAR的表达, miRNA-203调控PPAR的表达。IL-6和TNF-α的表达调控与miRNA-29c、miRNA-10a、miRNA-23b、miRNA-155和miRNA-522有关, IL-1β的表达调控与miRNA-10a、miRNA-23b、miRNA-155和miRNA-522有关, 见表4[18,51-60,62,64-68,70,72,74,76-81,83,84,86-93,96,97,99]。

5 miRNA介导的低氧调控药物代谢酶和转运体的机制

低氧影响药物代谢酶和转运体的相关机制还处于探索阶段, 早期认为低氧使血液在内脏器官重分布、肝血流量降低, 阻止药物向肝脏的传递, 导致药物消除减慢, 也有文献认为低氧条件下机体肝肾功能发生一定变化, 并进一步影响药物代谢酶和转运体的活性和表达, 但都未得到进一步证实[40]。目前主要从相关因子、

Table 4 Modulation of miRNA on genes involved in drug metabolism

Gene	Classification	miRNA	Reference
CYP1A2	Phase I enzyme	miR-122, -132-5p, -320	[51-53]
CYP2C9	Phase I enzyme	miR-103, -107, -128-3p, -130b, -155-5p	[55-59]
CYP2C19	Phase I enzyme	miR-103, -107, -130b, -155-5p	[55,56,58,59]
CYP2D6	Phase I enzyme	miR-101, -128-2	[60]
CYP2E1	Phase I enzyme	miR-378	[62]
CYP3A4	Phase I enzyme	miR-577, -1, -532-3p, -627	[54]
CYP7A1	Phase I enzyme	miR-122	[67]
GPX7	Phase I enzyme	miR-122	[68]
GSS	Phase I enzyme	miR-125b	[70]
UGT1A1	Phase II enzyme	miR-491-3p, -548d-5p	[64,65]
NAT2	Phase II enzyme	miR-217	[66]
MDR1	Drug transporter	miR-7, -19, -27a, -145, -200c, -298, -331-5p, -354, -451	[18,72]
MRP2	Drug transporter	miR-379	[74]
BCRP	Drug transporter	miR-495, -519c, -520h, -181a, -145	[76-79]
OATP1B1	Drug transporter	miR-511, -206, -613	[80,81]
PEPT1	Drug transporter	miR-92b, -193a-3p	[83,84]
HIF-1	Hypoxia inducible factor-1	miR-18a, -135b, -155, -199a, -424	[86-90]
PXR	Nuclear receptor	miR-140-3p, -148a	[91,92]
CAR	Nuclear receptor	miR-137	[93]
PPAR	Nuclear receptor	miR-203	[96]
IL-6	Inflammatory cytokines	miR-29c, -10a, -23b, -155, -522	[97,99]
TNF-α	Inflammatory cytokines	miR-29c, -10a, -23b, -155, -522	[97,99]
IL-1β	Inflammatory cytokines	miR-10a, -23b, -155, -522	[99]

核受体、相关通路等几个方面开展相关机制研究。

低氧条件下HIF-1、炎症因子、核受体、P53 (protein 53)、丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK) 等对药物代谢酶和转运体具有重要调控作用。HIF-1与下游基因的低氧反应元件 (hypoxia reactive elements, HREs) 结合, 调控CYP1A、CYP2C11、CYP3A6和CYP4B1的表达[85,100]。HIF-1α亚基中有一个氧依赖降解结构域, 在常氧下极易降解, 半衰期不足5 min[85]。低氧条件下, HIF-1α的稳定性和表达都显著升高, 与HIF-1β形成二聚体, 在细胞核内与转录辅助激活因子CBP/p300、HNF4等相互作用启动转录。除HIF-1外, 炎症因子也可调控药物代谢酶的表达, 如IL-1β、IL-2β、IFN-γ可下调CYP1A1和CYP1A2的表达[40,101]。上述炎症因子与NF-κB (nuclear factor-kappa B) 通路关系密切, 低氧条件下IL-1、IL-6、TNF-α显著升高, 激活NF-κB通路, 通过磷酸化、泛素化等途径降解通路中的抑制元件IKB (NF-κB inhibitory protein), 进而调控药物代谢酶的表达, 见图1。

PXR、CAR和PPAR是核受体超家族中的重要成员, 研究发现低氧显著降低PXR和CAR的表达, 并进一步调控CYP450的活性和表达, 其中PXR调节CYP3A的表达, CAR调节CYP2B、CYP1A以及CYP3A的表达, 而CYP2C9、CYP2C19和CYP2C18由PXR和CAR共同调控[40,101]。PPAR主要介导CYP4A基因的表达, 同时也参与CY2E1的调控[102]。

低氧对药物转运体的影响机制主要与HIF、NF-κB、核受体等有关。Zhang等[103]研究发现低氧条件下HIF、P53、MAPK、NF-κB通路上调MDR1的表达。Lee等[104]发现低氧同时诱导细胞中HIF-1和MRP1的mRNA表达, 并用质粒转染方法证实HepG2细胞过表达HIF-1后, MRP1的mRNA表达显著升高。关于SLC转运体的研究较少, 仅有研究证明了在肿瘤低氧环境下OCT1可被PXR调控[105]。

低氧影响药物代谢的相关机制研究主要集中在药物代谢酶, 药物转运体的研究相对较少, 但二者的调控机制相似, 主要通过HIF、炎症因子、NF-κB、核受体等通路进行调控。低氧条件下, HIF、炎症因子、NF-κB和核受体之间是否会发生相互作用进而影响药物的代谢, 这一网络调控的关键因子尚未找到。

近年来, 越来越多的研究发现非编码RNA如miRNA、长链非编码RNA (long non-coding RNA, lncRNA) 和环状RNA (circular RNA, circRNA) 等在基因表达调控中具有重要作用。内源竞争RNA (competing endogenous RNA, ceRNA) 是RNA间相互作用的一种新机制, 主要成员是lncRNA, 有研究筛选了缺氧条件下lncRNAs的差异性表达, 发现lncRNA-H19是低氧条件下药物转运体发生变化的关键分子[106]。ceRNA可以竞争性结合miRNA来调节基因的表达, 因此ceRNA调控的核心是miRNA, miRNA可能是低氧影响药物代谢的核心机制。综合文献报道, 作者提出以下结论:

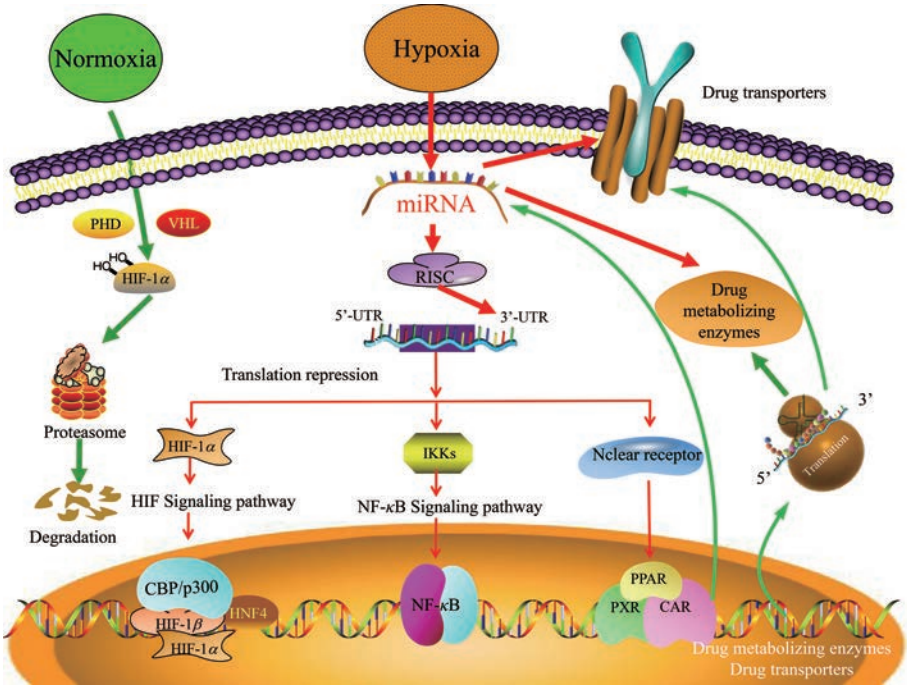

Figure 1　A hypothetical network view on the interactions between miRNA and drug metabolizing enzymes and transporters under hypoxia. The network contains miRNA and its target genes. In normoxia condition HIF is inactivated by prolyl hydroxylase enzymes (EGLN 1-3, also known as PHD 1-3) using oxygen as a substrate. Once hydroxylated it binds to a protein called Von Hippel Lindau protein (VHL) for its degradation by proteasome, whereas in hypoxia condition stabilization and nuclear translocation occur, leading to HIF pathway activation. Homeostatic response to hypoxia is primarily mediated by HIF-1 that elicits transcriptional activity through recruitment of the CREB binding protein (CBP)/p300 coactivator. Hepatic nuclear factor receptor 4 (HNF4) is interacting with HIF-1 complex, to potentiate further the cooperative effect. Inflammation activates the family of transcription factor called nuclear factor-kappa B (NF-κB). The IκB kinase (IKK) complex is the signal integration hub for NF-κB activation. IKB: NF-κB inhibitory protein; RISC: RNA-induced silencing complex

① 低氧可上调或下调miRNA的表达; ② 低氧可降低大部分CYP450酶的活性和表达; ③ 低氧对不同组织中药物转运体的表达影响不同, 并且与缺氧时间有关; ④ miRNA可负调控药物代谢酶和转运体; ⑤ miRNA可负调控与药物代谢酶和转运体相关的基因。综上, miRNA可能是低氧影响药物代谢酶和转运体的关键分子机制 (图1)。

6　小结与展望

低氧对体内物质代谢具有显著影响, 阻碍机体循环系统、神经系统、内分泌系统等的正常运行, 导致药物在体内的代谢动力学特征、药物代谢酶和转运体的活性及表达均发生显著改变, 进一步影响药物的治疗作用。在低氧环境中, 研究药物的代谢动力学特征、药物代谢酶和药物转运体的活性和表达及相关机制, 以及如何对缺氧人群进行合理有效的用药将是未来研究的热点。

肿瘤、炎症、休克等疾病状态或者高空飞行、潜水作业、高原环境都会引起机体缺氧。近年来, 人类高原活动日益频繁, 高海拔地区的人口逐渐增多, 急进高原后发生的急性肺水肿、脑水肿等疾病严重危害人们生命健康, 因此, 与其他低氧环境相比, 高原环境对人类生命活动影响较大。关注高原商贸和旅游人群、高原驻防官兵、高原体育训练的防护及高海拔地区人群的个体化用药已成为医药学科研人员研究的重点。

低氧对药物体内代谢的影响是药物代谢研究的一个新方向, 目前主要集中在部分药物的代谢动力学、I相药物代谢酶CYP450和ABC药物转运体, 且大多采用大鼠、家兔等动物模型, 难以全面客观反映人体真实特征。另外, 机制研究主要围绕细胞因子和核受体的调节进行。在低氧环境中, 大多数药物的动力学特征、II相药物代谢酶和SLC药物转运体表达及功能到底如何变化, 动物研究结果是否与人体研究结果一致, 除细胞因子和核受体外, 是否还存在其他调节机制, 都存在很大研究空间, 也值得进一步去探讨。

目前, 肿瘤、炎症等病理状态的微观低氧环境和高原实际低氧环境中的药物代谢研究有较多文献报道, 但肿瘤低氧微环境与高原实际低氧环境对药物代谢酶以及转运体的影响不同[33,34], 今后应区别对待, 重点突

破。高原环境中除低氧外, 还存在辐射、寒冷等影响因素, 近年来研究已证实辐射显著影响药物的体内代谢[107,108], 因此应综合考虑各种因素全面探讨高原低氧环境中的药物代谢。

低氧对药物代谢动力学、药物代谢酶和药物转运体有显著影响, 而HIF、炎症因子、PXR/CAR及miRNA与药物代谢酶和转运体密切相关。miRNA可直接调控药物代谢酶以及转运体的表达, 也可以作用于核受体、炎症因子、HIF等药物代谢相关基因来间接调控药物代谢酶和转运体的表达。低氧环境下miRNA的表达发生显著变化, miRNA又可调控多种基因的表达而影响药物的代谢, 基于目前研究成果, 作者提出miRNA介导的低氧对药物代谢酶和转运体影响机制。低氧条件下miRNA调控药物代谢酶和转运体是多因素调控机制, 有关miRNA介导的低氧对药物体内代谢的调控机制, 还需大量研究进一步验证。

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