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· 文献综述 ·

高原低氧与胆囊结石发生机制的研究进展

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摘要

高原地区低氧环境被认为是影响人体代谢与疾病谱的重要环境因素。近年来流行病学研究发现, 高海拔地区胆囊结石患病率明显高于平原地区, 但其潜在机制尚未完全阐明。研究提示, 高原低氧可能通过多种途径参与胆囊结石形成, 包括影响肝脏脂质与胆固醇代谢、改变胆汁成分、降低胆囊收缩功能、破坏肠道菌群稳态及激活炎症反应等。此外, 低氧还可通过氧化应激、DNA损伤及表观遗传调控等机制进一步促进成石过程。与此同时, 高原人群对低氧的遗传适应性(如EPAS1等基因多态性)可能影响个体对胆囊结石的易感性。本文系统综述高原低氧与胆囊结石发生发展的研究进展, 重点总结其在代谢调控、胆囊动力、肠道菌群及炎症-表观遗传调控等方面的可能机制, 以期高原地区胆囊结石的防治及相关研究提供参考。

关键词

胆囊结石病; 高原病; 低氧; 胃肠道微生物组; 表观基因组学; 综述
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Research progress on the mechanisms linking high-altitude hypoxia and gallbladder stone formation

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Abstract

Hypoxia at high altitude is an important environmental factor influencing human metabolism and disease patterns. Recent epidemiological studies have shown that the prevalence of gallbladder stones is significantly higher in high-altitude regions than in low-altitude areas, yet the underlying mechanisms remain incompletely understood. Emerging evidence suggests that high-altitude hypoxia may promote gallstone formation through multiple pathways, including alterations in hepatic lipid and cholesterol metabolism, changes in bile composition, impairment of gallbladder contractility, disruption of gut microbiota homeostasis, and activation of inflammatory responses. In addition, hypoxia-induced oxidative stress, DNA damage, and epigenetic regulation may further contribute to lithogenesis. Genetic adaptation to hypoxia, such as polymorphisms in EPAS1 and related genes, may also influence individual susceptibility to gallstone disease among high-altitude populations. This review summarizes current research progress on the relationship between high-altitude hypoxia and gallbladder stones,

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focusing on potential mechanisms involving metabolic regulation, gallbladder motility, gut microbiota alterations, and inflammatory-epigenetic pathways, with the aim of providing insights for prevention and future research on gallstone disease in high-altitude regions.

Key words

Cholelithiasis; Altitude Sickness; Hypoxia; Gastrointestinal Microbiome; Epigenomics; Review

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在医学上,海拔 $\geq 2\ 500\text{ m}$ 的地区被定义为高原。中国的高原面积占国土总面积的1/3,是全球高原面积最大且人口最多的国家。此外,有逾1.4亿人常住高原,每年还有超4 000万人因旅游、工作等原因进入高海拔地区,使得面临高原低氧环境威胁的人口接近1.8亿^[1],因此深入研究高原低氧对人体健康的影响至关重要。较平原地区,处于高海拔的居民胆囊结石患病率高,而知晓率、治疗率、控制率低;在高原地区,由胆囊结石导致的急性化脓性胆囊炎、胆囊坏疽、穿孔、继发性胆总管结石合并急性化脓性胆囊炎,以及胆源性胰腺炎等疾病,已成为常见的住院病因,并且高原地区因胆囊结石而行胆囊手术是高海拔地区普通外科择期手术中最常开展的手术^[2]。因此探讨高原低氧与胆囊结石的发病机制尤为重要,本文就高原低氧与胆囊结石关系的研究进展进行综述。

1 高原低氧与胆囊结石的流行病学研究

高原低氧条件下,胆囊结石发病率远高于平原地区,在一项纳入全球115项研究的Meta分析^[3]中发现高海拔区域胆囊结石患病率全球最高(11.2%),显著高于平原地区(5.1%)。Abdu等^[4]调查发现,在高原地区胆囊结石发病率显著高于平原;Ma等^[5]总结出,高海拔地区的青海省胆囊结石发病率明显高于平原;Alessa等^[6]发现,与平原地区相比,高原地区居民胆囊结石的发病率呈显著增高趋势;沙特阿拉伯人群中胆结石病的患病率研究证实,高原与平原地区间胆囊结石发病率存在显著差异,高原地区为高发区^[7];在中国那曲人群体检中发现胆囊结石患病率高达24%,明显高于全国及低海拔人群水平;上述研究证实,高海拔与胆囊结石密切相关,高原低氧环境能显著影响胆囊结石的患病率。

2 高原低氧影响肝脏、血脂等代谢

缺氧是胆囊结石形成的重要启动因素,低氧通过多条分子通路调控肝脏脂质代谢、胆固醇代谢、胆汁成分分泌等,促进胆结石形成。低氧诱导肝脏中低氧诱导因子1(hypoxia-inducible factor 1 α , HIF-1 α)表达上调,HIF-1 α 作为高原低氧应答的核心调控因子,通过转录激活胆固醇与脂质代谢关键基因,直接驱动致石性胆汁形成^[8-9];HIF-1 α 结合HMG-CoA还原酶基因启动子,显著提升其表达,促进肝细胞胆固醇从头合成,导致胆汁胆固醇过饱和;低氧环境下,HIF-1 α 通过表观遗传沉默胆固醇7 α -羟化酶(cytochrome P450 family 7 subfamily A member 1, CYP7A1)^[10],抑制胆固醇向胆汁酸转化,使胆汁酸池缩小 $>25\%$,削弱胆固醇溶解能力;HIF-1 α 可促进含黄素单加氧酶3(flavin containing monooxygenase 3, FMO3)表达,增加氧化三甲胺(trimethylamine N-oxide, TMAO)生成,扰乱胆汁和血浆脂质比例,促进胆固醇结石形成;低氧环境下,肝脏脂肪酸 β -氧化能力下降,脂质合成增强,导致肝内脂质积聚、胆固醇分泌增加^[11];低氧抑制肝细胞胆汁酸转运蛋白Ntcp(Na⁺-taurocholate cotransporting polypeptide)、胆汁酸盐输出泵(bile salt export pump, BSEP)和多药耐药相关蛋白2表达,导致胆汁分泌减少、成分异常,易形成结石^[12];HIF-1 α 可下调水通道蛋白8重组蛋白(recombinant aquaporin 8, AQP8)表达,减少肝细胞向胆道的水分分泌,使胆汁浓缩,促进结石形成^[13];高原低氧诱导肝脏氧化应激反应增强,谷胱甘肽等抗氧化物下降,脂质过氧化产物升高,导致肝细胞损伤和功能障碍,诱发胆囊结石^[14];低氧抑制肝脏线粒体功能,降低三磷酸腺苷生成,促使肝细胞代谢重编程,影响脂肪酸和胆固醇的合成与分解,促成胆囊结石形成^[15]。

此外,低氧通过调控过氧化物酶体增殖物激活受体(peroxisome proliferators-activated receptor,

PPAR)^[16]、血管生成素样蛋白家族 (angiotensin-like protein, ANGPTL)^[17]等关键因子, 引发脂代谢紊乱。具体而言, 低氧抑制PPAR信号通路, 导致肝脏脂肪酸 β -氧化减弱与甘油三酯清除受阻; 同时, 低氧上调ANGPTL3、ANGPTL8的表达, 有效抑制脂蛋白脂肪酶活性, 从而减少外周组织对甘油三酯的摄取与水解。这些途径协同作用可导致甘油三酯及胆固醇水平升高, 从而促进血脂代谢紊乱。血脂异常导致肝脏摄取过多低密度脂蛋白胆固醇, 肝细胞合成内源性胆固醇增多、同时高甘油三酯血症可抑制肝脏CYP7A1酶活性, 减少胆汁酸合成, 导致胆汁中胆固醇过饱和是胆固醇结晶和胆结石形成的重要条件^[18-19]。胆固醇过饱和胆汁中, 胆囊黏膜分泌黏蛋白、钙离子等促石因子增多, 促进胆固醇单水结晶析出, 而载脂蛋白A1、AQP8等抗结石因子减少, 削弱对结晶形成的抑制作用^[20]。高脂血症诱发胆囊壁氧化应激, 激活NF- κ B通路, 促进炎症因子(如TNF- α 、白细胞介素6)释放, 炎症反应刺激胆囊黏膜过度分泌黏蛋白, 包裹胆固醇结晶形成结石核心。血脂异常常伴随胆囊平滑肌细胞脂质沉积, 干扰胆囊收缩素(cholecystokinin, CCK)受体信号传导, 导致胆囊排空延迟^[21], 并且胆汁淤积为结晶聚集生长提供时间, 微小结晶逐渐融合成结石, 结石一旦形成, 机械刺激胆囊壁, 加剧炎症和黏液分泌, 形成恶性循环。血脂异常加剧胰岛素抵抗进一步损害胆汁酸肠肝循环效率, 降低胆汁酸池总量, 促进结石成核和生长^[22]。

3 高原低氧降低胆囊收缩功能

低氧环境下, 机体交感神经活性代偿性增强, 而副交感神经功能相对受抑, 迷走神经是调控胆囊周期性收缩与排空的主要自主神经通路, 其张力降低直接削弱胆囊平滑肌的基础张力与收缩幅度, 同时, 交感神经兴奋释放的去甲肾上腺素可直接作用于胆囊平滑肌上的 β 受体, 产生舒张效应, 进一步抑制胆囊收缩^[23]。CCK是餐后刺激胆囊强力收缩、Oddi括约肌松弛的关键激素, 低氧环境可导致CCK受体下调或功能受损、胆囊壁CCK受体表达减少、信号转导效率降低, 使平滑肌细胞对CCK刺激的反应性显著下降^[24-25]。此外, 低氧干扰细胞能量代谢和钙离子稳态, 影响CCK触发

的胞内Ca²⁺释放与肌球蛋白轻链磷酸化等关键收缩信号转导步骤^[26]。低氧还能影响胃动素、胃泌素等其他调节胃肠动力的激素水平或效应, 协同导致胆囊排空动力不足。高原低氧通过多种途径协同削弱胆囊收缩功能: 神经调节失衡、关键激素CCK效应减弱、平滑肌细胞直接损伤等机制共同导致胆囊排空延迟和胆汁淤积。

4 高原低氧破坏肠道菌群

肠道菌群是寄居于消化道的微生物群落, 参与营养代谢、维生素合成、免疫调节和屏障维护, 维持微生态平衡, 并与胆囊结石形成关系密切。低氧破坏肠道稳态, 诱发菌群失调。肠道上皮细胞对氧气变化极为敏感, 低氧会损害其屏障功能, 增加通透性并削弱黏液层保护。低氧环境显著改变肠道菌群的组成和丰度, 研究显示, 缺氧条件下肠道拟杆菌属、脱硫弧菌目等厌氧菌丰度增加, 双歧杆菌、乳杆菌等有益菌显著减少, 这种菌群结构改变直接影响胆汁酸代谢相关酶的产生^[27-28]。肠道菌群负责将肝脏分泌的初级胆汁酸转化为次级胆汁酸。低氧下, 这些关键转化菌群减少, 导致次级胆汁酸水平显著下降。低氧介导的肠道菌群失调导致胆盐水解酶、CYP7A1活性异常, 使7 α -脱羟基细菌显著增加, 促进次级胆汁酸(脱氧胆酸、石胆酸)生成增多。次级胆汁酸浓度升高激活G蛋白偶联胆汁酸受体1(G protein-coupled bile acid receptor 1, GPBAR1), 导致胆囊平滑肌松弛, 胆汁淤积, 为结石形成创造条件^[29-30]。同时, 病原菌利用硫酸盐和有机底物产生大量硫化氢损伤肝细胞和胆管上皮细胞, 同时抑制胆汁酸合成与转运、抑制肝脏合成胆汁酸的关键酶如CYP7A1, 并下调胆汁酸转运蛋白: BSEP、牛磺胆酸钠共转运蛋白(sodium taurocholate co-transporting polypeptide, NTCP)的表达, 影响胆汁酸在肝肠循环中的流通与组成^[31]。缺氧诱导活性氧(reactive oxygen species, ROS)产生, 促进胆红素自由基形成和脂质过氧化。氧化应激破坏肠道屏障功能, 增加肠道通透性, 导致细菌移位和内毒素血症, 内毒素激活Toll样受体4信号通路, 抑制肝脏胆固醇代谢, 促进胆固醇结晶^[32]。菌群失调影响短链脂肪酸, 特别是丁酸减少, 削弱其对胆固醇合成的抑制作用^[33]; 缺氧导致胆囊壁黏蛋白过度分泌,

形成凝胶网络,为胆固醇结晶提供成核基质促进胆固醇结晶聚集和结石生长^[34]。

5 高原低氧环境影响炎症相关通路

低氧导致炎症介质的上调,包括白细胞介素8(interleukin 8, IL-8)和血管内皮生长因子(vascular endothelial growth factor, VEGF),这促进了免疫细胞的募集和血管生成,有助于促炎微环境;此外,缺氧会诱发环氧合酶2(cyclooxygenase 2, COX-2)表达并增加前列腺素E2的产生,放大炎症信号并在正反馈回路,加剧炎症反应^[35];HIF和NF- κ B之间相互作用是缺氧诱导的炎症的关键的另一节点,HIF-1 α 可以调节NF- κ B活性,形成一个复杂的调节环,从而增强炎症基因表达^[36]。炎症反应导致胆囊黏膜分泌大量含钙的黏液和炎性渗出物,这些物质改变胆汁成分,增加胆汁中胆红素钙、胆固醇晶体析出的风险,并可作为结石形成的核心。炎症也可刺激胆囊黏膜产生过量黏液糖蛋白,这些黏液形成凝胶状网络,有效捕获胆汁中析出的胆固醇单水结晶、胆红素钙颗粒或钙盐,促进其聚集、增大,最终形成结石^[37]。炎症会破坏胆囊平滑肌和间质Cajal样细胞,削弱收缩力并促进胆汁淤滞,并延长胆汁停留时间并增加晶体成核的机会^[38]。

6 低氧介导DNA突变及表观遗传

缺氧导致线粒体电子传递链功能障碍,大量电子泄漏生成超氧阴离子(O_2^-),经超氧化物歧化酶转化为 H_2O_2 ,最终在 Fe^{2+} 催化下产生高毒性羟自由基($\cdot OH$),这些自由基直接攻击DNA引发G \rightarrow T颠换突变;双链断裂增加,错误修复导致染色体不稳定。缺氧下ROS升高会诱导线粒体DNA变异,最明显的是线粒体12SrRNA中的827A \rightarrow G突变,这会损害氧化磷酸化,破坏三磷酸腺苷的产生,并激活AMPK/JNK通路,这些通路通过上调ABCG5/8异常增加胆固醇向胆汁的转运^[39];缺氧驱动的ROS会导致ROS的启动子或编码区出现氧化损伤和碱基错配致相关基因突变,这些突变随着时间的推移积累会降低转运蛋白功能或酶活性,

加剧胆固醇胆汁的过饱和;HIF-1 α 介导DNA修复因子BRCA1、RAD51下调进一步损害基因组完整性,促进胆囊上皮细胞中的突变积累^[40];缺氧应激上调microRNA,例如miR-210,这些RNA靶向编码胆汁酸转运蛋白的mRNA,减少它们的翻译并使胆汁成分倾向于结石形成^[41]。

HIF-1 α 引发表观遗传修饰,特别是DNA甲基化和组蛋白甲基化及去甲基化,从而破坏胆汁组成、胆囊运动和胆固醇稳态,从而促进胆固醇胆结石的形成。HIF-1 α 结合并抑制AQP8的启动子区域,降低该小管水通道的表达并减少胆汁水分泌,胆汁高浓度会提高胆固醇饱和指数,促进胆固醇结晶和结石形成。HIF-1 α 增强FMO3的表达,增加胆道胆固醇分泌和成核风,缺氧下MUC基因的启动子低甲基化并增强黏蛋白分泌,为胆固醇晶体聚集提供病灶^[42]。缺氧驱动的c-Kit信号成分甲基化耗尽Cajal间质细胞,减缓胆囊排空,延长胆固醇停留时间,促使胆囊结石^[43]。

7 低氧预适应的个体差异研究

高原人群对胆囊结石的易感性存在显著的个体差异,这与机体对低氧的适应与预适应能力密切相关。其中,EPAS1基因作为低氧应答的核心调控因子,其多态性是导致这种差异的重要遗传基础^[44]。研究^[45-46]表明,在高原低氧世居人群中,EPAS1基因的优势等位基因通过介导更为精细地HIF信号通路调控,能够优化机体的能量代谢模式、减少脂质过载与氧化应激,并维持更稳定的胆汁酸循环,从而在整体上赋予个体更强的低氧耐受性和代谢稳态维持能力。这种由遗传决定的“缺氧预适应”状态,可能显著降低其在长期低氧暴露下发生胆囊结石的风险。因此,将EPAS1等多态性纳入研究视野,不仅为阐释高原胆囊结石发病的个体差异性提供了分子证据,也为未来针对高危人群的精准预警和个体化干预策略开辟了新思路。

综上所述,高原低氧可能通过影响脂质代谢、胆囊收缩功能、肠道菌群稳态、炎症反应及表观遗传调控等多种途径共同参与胆囊结石的发生发展,其潜在作用机制如图1所示。

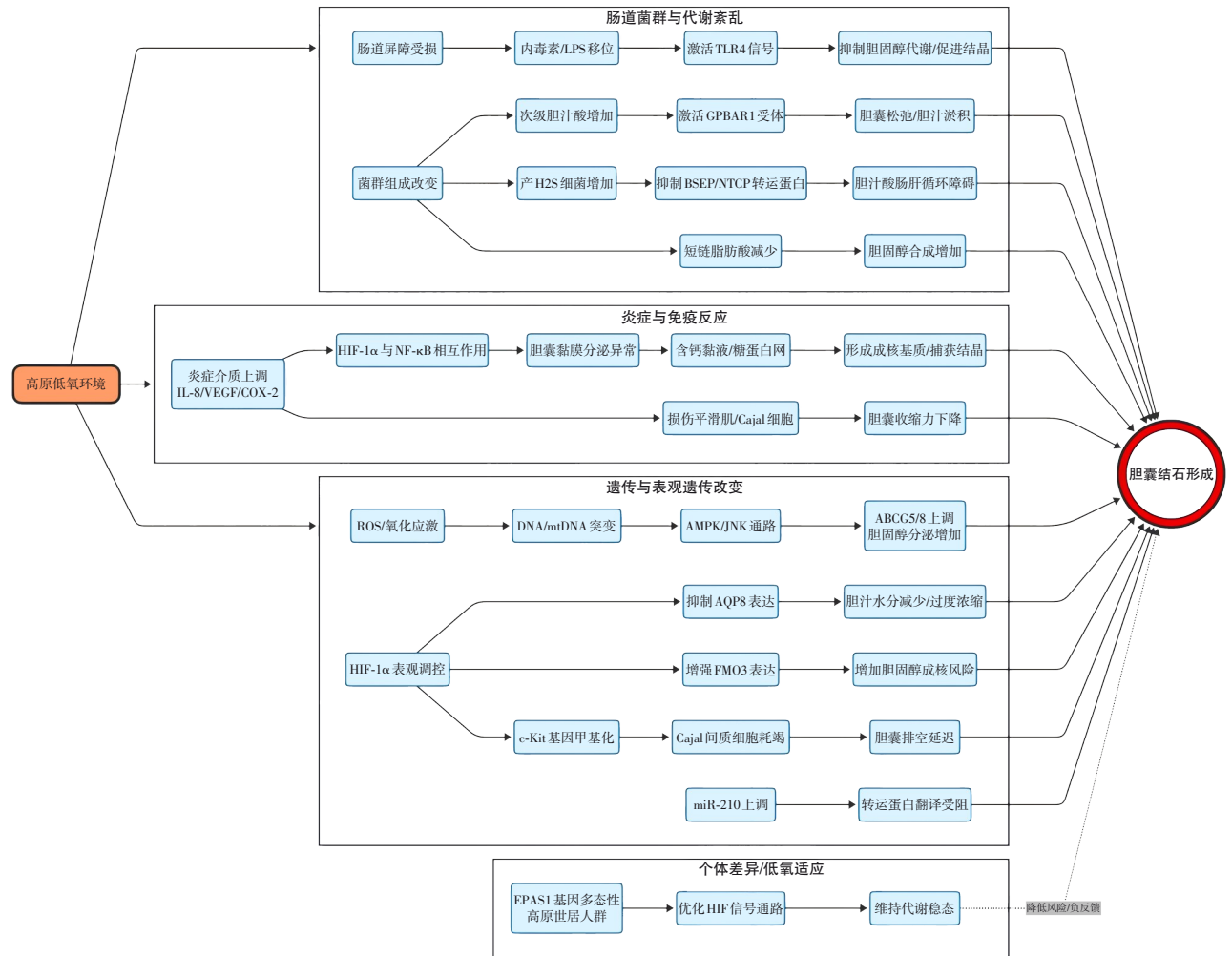


图 1 高原低氧促进胆囊结石形成的可能机制示意图

Figure 1 Schematic illustration of the potential mechanisms underlying high-altitude hypoxia-induced gallstone formation

8 展望

高原缺氧为揭示胆结石发病机制提供了一种独特的自然模型，但仍存在几个关键问题。首先，在缺氧条件下将 HIF-1α 与 FMO3 诱导联系起来的精确调控网络值得阐明。剖析上游信号如 ROS 和表观遗传修饰因子可以揭示可成药的靶点，以减轻缺氧驱动的血脂异常。其次，表征缺氧适应基因如 EPAS1、EGLN1 的患者特异性变异可以解释个体间易感性并指导高海拔居民的个性化预防策略。评估 TMAO 波动和胆结石形成的时间动态的纵向队列研究将阐明因果关系和干预的最佳时机。将药理学 HIF-1α 抑制剂或 AQP8 调节剂与 FMO3 拮抗剂一起重新利用有望恢复平衡的胆汁组成。营养干预措施：膳食补充胆汁酸螯合纤维或减少 TMAO 的益生菌可以进一步降低胆结石风险。此外，无创

成像生物标志物肝脏缺氧的超声弹性成像可能能够在结石形成之前及早发现成石性胆汁改变。最后，气候变化驱动的高海拔旅游和居住扩张凸显了有针对性的，公共卫生措施的紧迫性。未来有必要将缺氧生物学研究与胆结石流行病学数据相结合，从而为高原地区胆囊结石的风险分层及饮食干预策略提供依据。

综上，高原低氧可能通过代谢紊乱、胆囊动力障碍、肠道菌群失衡及炎症、表观遗传调控等多途径协同促进胆囊结石形成，但相关机制仍有待进一步研究。

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