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“蓝嘴唇”: 缺氧性肺动脉高压肺血管重构研究进展

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摘要 缺氧性肺动脉高压是一种肺动脉压异常升高的综合征, 起因是长期慢性缺氧诱发肺动脉血管收缩和重构, 发病率高、生存期短, 尚无有效治疗方法, 是临床面临的巨大难题和挑战. 慢性炎症和氧化应激反应诱导的肺小动脉血管重构是缺氧性肺动脉高压的典型病理学特征. 本文针对肺动脉血管重构的病理生理学特点、病理生理学发病机制、治疗现状及展望等方面的最新研究进展进行总结, 并讨论肺动脉血管重构的机制研究和相关治疗药物研发进展, 为缺氧性肺动脉高压的治疗提供思路.

关键词 肺动脉高压, 缺氧, 肺动脉血管重构, 炎症, 氧化应激

肺动脉高压(pulmonary hypertension, PH)是一种复杂的进行性心肺系统疾病, 确切发病机制尚不清楚, 患者生存期有限, 临床上暂无有效治愈手段, PH也被认为是心血管领域的“癌症”. PH患者因长期缺氧所致嘴唇呈现不同程度的蓝紫色, 被称为“蓝嘴唇”, 大部分患者遭受过误诊经历, 甚至无法得到确诊却因病情过于严重而去世[1], 因此, 需要给予该疾病更多的重视与关注.

依据《中国肺动脉高压诊断与治疗指南(2021版)》, “pulmonary hypertension”名词定义为肺动脉高压, 血流动力学定义为, 于海平面、静息状态下, 经右心导管检测的肺动脉平均压≥25 mmHg. 临床上将PH分为5类, 其中肺部疾病和(或)低氧所致PH属于第3类, 长期慢性低氧是此类PH的重要特征和发病诱因. 缺氧性肺动脉高压(hypoxic pulmonary hypertension, HPH)不仅是PH中常见类型之一, 也是阻塞性肺疾病、限制性肺疾病、高原心脏病等多种心肺疾病发生发展中的关键环节, 是临床面临的巨大难题和挑战[2~5]. 肺动脉血管重构(pulmonary vascular remodeling)在HPH的发病机制中发挥重要作用, 本文将从HPH肺血管重构的病理学特点、病理生理学机制、治疗现状及展望四个方面对HPH的研究进展作一综述.

1 病理学特点

缺氧性肺血管收缩(hypoxic pulmonary artery vasoconstriction)及肺动脉血管重构是HPH的两大典型病理特征, 其过程主要发生于肺小动脉血管(<500 μm)[6,7]. 肺动脉血管壁有3层, 包括单层内皮细胞组成的内膜、平滑肌细胞和弹力板组成的中膜以及成纤维细胞

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(fibroblasts)组成的外膜. 血管重构过程涉及血管壁三层的变化, 是细胞肥大、增生、炎症改变的结果, 影响细胞分化、凋亡、过度迁移, 以及细胞外基质沉积(图1).

1.1 肺动脉内膜内皮细胞

肺动脉血管内皮细胞(pulmonary artery endothelial cell, PAEC)是排列在血管内膜的单层扁平状细胞, 作为血流与肺动脉中、外膜之间屏障, 能保护肺动脉中层的平滑肌细胞及外层的成纤维细胞免受血液中各种细胞因子、毒素的直接刺激作用. 同时兼具内分泌功能, 生成多种血管活性物质和细胞因子, 调节血管舒张及收缩[8,9]. 正常生理状态下, PAEC被认为是遗传稳定的“静止状态”, 一旦被激活, 将诱导疾病的发生, 参与疾病的进展.

肺动脉系统功能紊乱是HPH重要病理特征之一, 缺氧诱导的内皮细胞损伤是HPH肺动脉内皮功能障碍发生的始动环节. 慢性缺氧破坏肺动脉血管内膜的完整性, 紊乱内皮屏障功能, 血液中的各种刺激因子跨过细胞内皮屏障直接作用于肺动脉的中、外膜, 刺激肺动脉平滑肌细胞(pulmonary artery smooth cell, PASMC)和成纤维细胞异常增殖, 造成细胞外基质(extracellular matrix, ECM)过度沉积, 诱导肺动脉中膜及外膜增厚[10]; 缺氧还能促进内皮细胞分泌血管收缩因子(例如内皮素-1,5-羟色胺等), 减少舒张因子(例如一氧化氮NO、前列环素、心房钠尿肽等)的分泌, 加剧肺动脉血管的收缩程度, 造成肺动脉血管重构[11,12]. 此外, 长期缺氧能直接激活内皮细胞, 导致PAEC过度增殖, 内膜增厚, 管腔狭窄, 肺血管阻力增加, 肺动脉压升高, 而肺动脉压的升高又能诱导细胞分泌大量细胞外基质, 促进肺血管的增厚、重构和狭窄, 形成恶性循环, 加重HPH的发生发展[9].

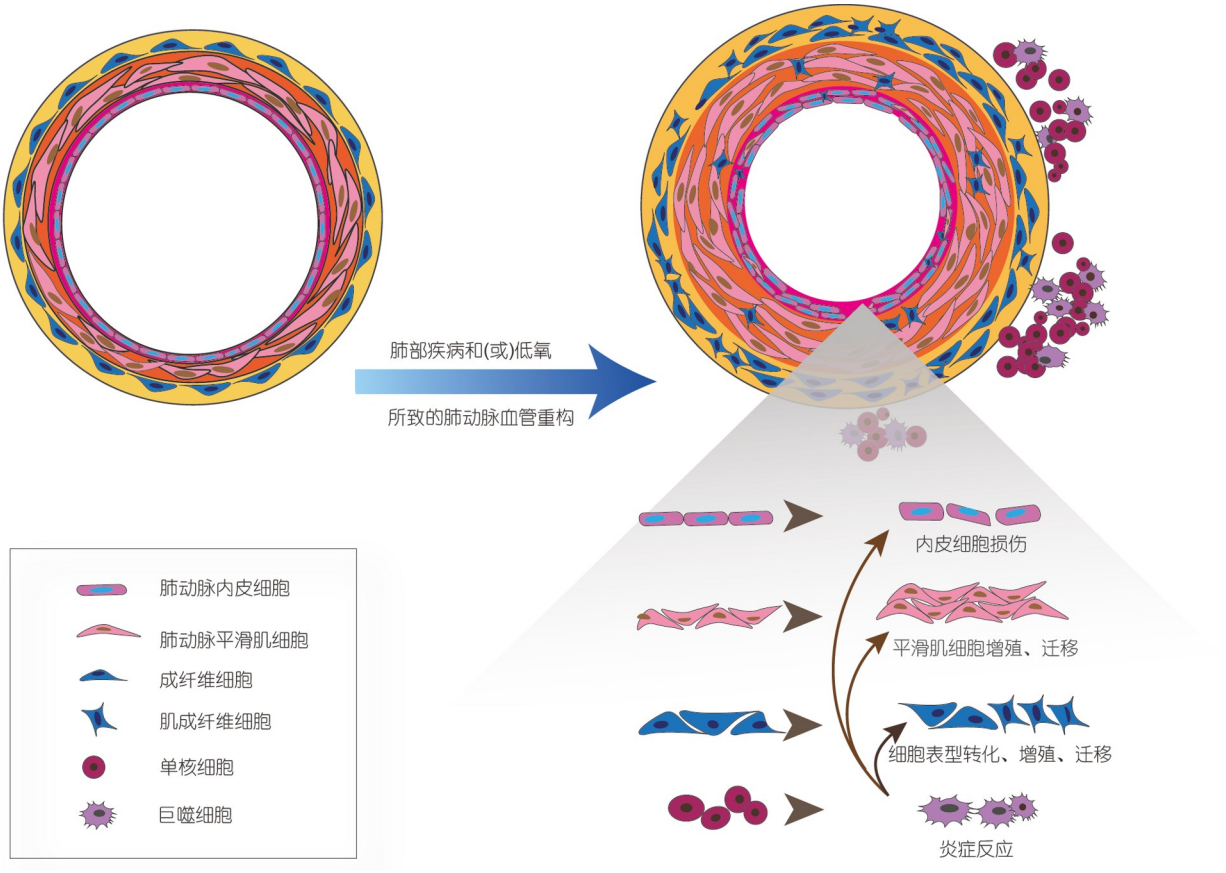

图 1 缺氧性肺动脉高压肺动脉血管重构病理特征示意图

Figure 1 Schematic diagram of pathological features of remodeled pulmonary arterioles in hypoxic pulmonary hypertension

1.2　肺动脉中层平滑肌细胞

PASMC是肺动脉血管中层的主要细胞, 是诱发肺动脉血管重构的细胞学基础. 正常生理状态下, PASMC的增殖与凋亡处于动态平衡状态, 成熟的PASMC分化成为收缩表型. 病理情况下, 各种生长因子诱导PASMC发生去分化, 转化成为具有增殖、迁移能力的合成表型. 远端肺微小动脉重构血管的PASMC部分来源于收缩表型, 去分化并迁移至远端小动脉血管, 进行增殖和再分化等一系列细胞生物学活动, 参与并促进HPH肺动脉血管重构与疾病发展[13~15].

大量研究广泛证实, PASMC的异常过度增殖在肺动脉血管重构中处于主导性地位, HPH肺动脉血管中层增厚的组织形态学标准是肥大和增生, 即PASMC体积增大和数量增多[16]. 慢性缺氧状态下, PASMC的增殖与凋亡比例失衡, 导致PASMC过度增殖, 最终造成肺血管壁的不可逆性增厚、管腔狭窄甚至闭塞, 以及肺动脉压的持续升高[17~20]. 已有研究报道, 生活在高原(海拔高于3500 m)的居民与生活在海平面的居民相比, 远端肺动脉血管和小动脉中层的平滑肌细胞数量增多[21]. 缺氧诱导的PASMC的增殖性改变是导致缺氧性肺动脉重构的重要环节, 探究PASMC过度增殖的潜在确切分子机制, 应用有效策略进行针对性干预, 已经成为近年来防治HPH的研究热点.

1.3　肺动脉外膜纤维细胞

成纤维细胞是构成肺动脉血管外膜的主要细胞, 其活化能造成外膜微环境的改变, 在HPH的发生发展过程中具有重要作用[22]. 缺氧条件下, 成纤维细胞对低氧的感知及增殖反应较PASMC更为敏感, 扮演“感受器”角色率先被激活, 成纤维细胞迅速增殖并发生表型转化为肌成纤维细胞(myofibroblast), 进而诱导肌成纤维细胞从血管外膜向中膜、内膜迁移, 最终造成肺小血管动脉血管壁的内、中、外膜呈现不同程度的结构性增厚[23,24].

无肌型小动脉主要由内皮细胞和成纤维细胞组成, 是肺循环中的重要容量型血管. 慢性缺氧条件下, 转化生长因子-β、血管紧张素 Ⅱ、凝血酶、内皮素和纤连蛋白等表达增加, 诱导肺动脉外膜成纤维细胞的胸腺细胞分化抗原(thymocyte differentiation antigen-1, Thy-1)启动子发生甲基化, Thy-1表达下调, 成纤维细胞表型转化为肌成纤维细胞, 进而诱发无肌型小动脉肌化, 同时加速肌成纤维细胞增殖[25~27]. 除了成纤维细胞异常增殖外, ECM的沉积及胶原蛋白的交联重排均能造成血管外膜增厚、血管硬度增加, 参与HPH进展[28]. 成纤维细胞还能招募巨噬细胞通过促炎信号转导通路发生慢性炎症, 而巨噬细胞也能反过来促进成纤维细胞产生胶原及生长因子, 诱导成纤维细胞增殖, 参与肺动脉血管重构[29~31].

2　病理生理学机制

2.1　慢性炎症

慢性炎症反应是诱发HPH疾病的极其重要机制之一, 缺氧能造成肺动脉结构性与功能性的炎症反应发生, 炎症能导致肺组织的氧气供需失衡, 形成局部低氧微环境, 进一步加重机体的缺氧程度, 因此低氧(hypoxia)与炎症(inflammation)一直是研究者的关注热点[32,33]. 既往研究认为, HPH的血管炎症是以血管内膜为中心, 由“内”向“外”进行, 近年来研究发现, 由成纤维细胞启动炎症反应, 由“外”向“内”进行, 低氧条件下, 肌成纤维细胞分泌大量炎症因子(巨噬细胞趋化因子、刺激因子、黏附蛋白), 诱导单核巨噬细胞、淋巴细胞、树突状细胞等多种炎性细胞浸润, 导致肺小动脉炎症的发生[29,34,35].

研究表明, 剥脱掉外膜的肺动脉血管丧失激活巨噬细胞的功能[29]; 表观遗传修饰能够调控成纤维细胞发生促炎表型转换, 其潜在机制可能与组蛋白去乙酰化酶(histone deacetylase, HDAC)的表达升高及催化活性增强相关[30]; 炎性因子肿瘤坏死因子α(tumor necrosis factor α, TNFα)诱导PASMC转化成为促增殖和抗凋亡表型, 白介素6(interleukin 6, IL-6)通过活化T细胞, 诱导巨噬细胞向M2型极化, 释放趋化因子CXCL12等可溶性细胞因子进而促进PASMC的过度增殖, 参与肺动脉中膜重构[35]. HPH模型小鼠中, NALP3炎症小体激活, IL-1β等促炎症细胞因子分泌增加, 激活的炎症细胞能进一步招募更多的炎症细胞, 释放大量的炎症因子, 加剧炎症反应的发生, 进而导致肺动脉内皮细胞功能障碍, 应用超氧化物歧化酶(superoxide dismutase, SOD)模拟物能有效缓解小鼠的HPH进展, 提示炎症反应非独立存在, 与氧化应激的发生密切相关[36].

2.2 氧化应激

活性氧(reactive oxygen species, ROS)簇是指在生物体内与氧代谢相关的含氧自由基, 以及易形成自由基的过氧化物的总称, 主要包括超氧阴离子自由基、脂氧自由基、羟自由基及过氧化氢(H_2O_2)等. ROS是体内氧化代谢的重要分子, 线粒体及NADPH氧化酶(nicotinamide vadenine dinucleotide phosphate oxidase, NOX)系统为其主要来源. 正常生理条件下, 机体精准控制ROS的生成, 参与细胞信号转导, 调节信息传递. 慢性缺氧情况下, 机体产生大量ROS, 诱导氧化应激(oxidative stress)反应, 导致细胞内及细胞间信息传递混乱, 诱发脂质过氧化, 损伤细胞正常生理功能, 参与HPH疾病进程[34,37~41].

已有研究证实, 缺氧诱导的ROS过度生成能够造成内皮细胞一氧化氮合酶(endothelial nitric oxide synthase, eNOS)发生解偶联反应, 降低NO生成量[42]. ROS作为第二信使在PASMC中直接或间接介导信号转导通路, 例如P13K/Akt, MAPK/ERK, AMPK/STAT3等, 导致PASMC过度增殖, 参与肺动脉血管重构[40,41]. ROS能诱导内皮素-1、血栓素A2、前列环素等收缩血管物质的释放, 导致肺动脉系统的持续收缩[8], 还能增强缺氧诱导因子-1(hypoxia-inducible factor-1, HIF-1)、核因子-κB(nuclear factor kappa-B, NF-κB)、AP-1等氧化还原敏感性转录因子的转录活性, 启动肺组织的炎症反应, 促进HPH的发生与发展[43]. 此外, 缺氧还能降低机体内抗氧化酶的表达和(或)活性, 包括调控红血球核因子相关因子-2(nuclear factor erythroid-2 related factor 2, Nrf2)、SOD、硫氧还蛋白(thioredoxin, Trx)、谷胱甘肽(glutathione, GSH), 削弱ROS的清除作用, 降低抗氧化系统的防御功能, 导致氧化应激水平增加, 促进HPH的发生与发展[44~47]. 因此, 如何有效清除缺氧诱导产生的ROS成为HPH潜在治疗方法之一, 近年来备受关注.

2.3 HPH发生相关分子

HPH发生机制至今尚未阐明, 近年来, 国内外应用HPH动物模型探究HPH发生发展机制的研究取得了一定的进展. 尽管啮齿类动物模型(慢性低氧、慢性低氧联合VEGF抑制剂等)不能完全模拟临床HPH的发病过程, 但是对于研究信号转导通路探究发病机制具有重要意义[48].

低氧诱导因子(hypoxia-induced factor, HIF)是经典的氧调节转录因子, 低氧条件下, 细胞内的HIF-1α蛋白表达稳定, 是诱导PH发生的重要机制之一[49,50]. 研究报道, 在慢性低氧诱导的条件下, 平滑肌细胞特异性敲除HIF-1α能延缓小鼠肺动脉血管重构和PH疾病进程[18]. 低氧条件下, HIF-1α能激活Ras相关区域家族1A (Ras association domain family 1 A, RASSF1A)的转录, RASSF1A也能通过阻止HIF-1α的脯氨酰基化及蛋白酶体降解, 增强HIF-1α的稳定性, 形成RASSF1A-HIF-1α前馈环路, 从而增加糖酵解开关的活化, 驱动低氧信号转导通路, 参与PH进展[51]. 低氧条件下, CD146与HIF-1α的表达相互促进, 形成低氧重编程信号轴, 促进PASMC增殖、迁移, 平滑肌细胞特异性敲除CD146能够有效抑制慢性低氧诱导的小鼠肺动脉重构, 减轻PH症状[20].

2,6-二磷酸果糖激酶(phosphofructokinase-2/fructose-2,6-bisphosphatase, PFKFB)的亚型PFKFB3是一种酵解调节因子, 能促进糖降解, 参与细胞生存与增殖. 研究发现, PAEC特异性敲除*Pfkfb3*基因可显著降低糖酵解水平, 减少糖丙酮酸的生成进而下调HIF-2α的表达, 导致血小板源性生长因子β(platelet derived growth factor β, PDGFβ)、成纤维细胞生长因子2(fibroblast growth factor 2, FGF2)以及CXCL12, IL-1β等促炎细胞因子表达减少, 抑制PASMC的过度增殖及肺动脉血管周围的炎症细胞浸润, 有效阻止HPH进展[52].

硒蛋白P(selenoprotein P, SeP)广泛存在于细胞外, 具有抗氧化、解毒等作用. 研究表明, Sep通过激活HIF-1α, 干扰谷胱甘肽代谢, 增强氧化应激水平, 紊乱线粒体功能, 诱导PASMC促增殖抗凋亡; 低氧条件诱导下, PASMC特异性敲除SeP小鼠能延缓HPH进程, 进一步研究发现, 化合物血根碱能够特异性抑制Sep的表达, 对PH具有治疗作用[53].

水通道蛋白1(aquaporin-1, AQP-1)是细胞膜上运输水分子以及O_2, CO_2, NO等气体的跨膜通道蛋白. 敲除*Aqp-1*基因能破坏HIF-1α蛋白稳定性, 有效抑制PASMC过度增殖及PAEC功能紊乱, 减少缺氧性肺动脉血管重构程度, 降低肺动脉压, 有效阻止HPH疾病进程, 为HPH的治疗提供潜在靶点和新思路[54].

3　治疗现状

3.1　临床治疗局限性

目前，与HPH密切相关的3类PH暂无FDA批准治疗方法[55]，辅助长程氧疗法是3类PH治疗的首要推荐[2]，然而长期氧疗耗时长，只能改善部分肺泡缺氧，小范围内降低肺动脉压力，很多患者对于氧疗方式依从性差，导致治疗效果欠佳. 除氧疗外，利尿剂、肺部疾病的康复及潜在疾病的诊疗等辅助方法对3类PH的治疗不容忽略[56].

1类PH(动脉型肺动脉高压)靶向药物对3类PH的治疗效果尚缺乏明确论证，包括5型磷酸二酯酶抑制剂、内皮素受体拮抗剂、前列环素以及Rho激酶抑制剂等. 大多数临床研究结果表明，这些药物对3类PH的症状、运动能力、血流动力学等指标无明显改善作用. 例如，ARTEMIS-IPF试验结果显示，内皮素受体拮抗剂安立生坦无明显治疗作用，且增加不良反应事件的发生率，导致试验提前终止[57]；RISE IIP试验结果显示，利奥西呱(鸟苷酸环化酶激动剂)使用后，患者死亡率及严重不良事件发生率较高，试验提前终止以失败告终[58]；NSTAGE试验结果显示，与尼达尼布(酪氨酸激酶抑制剂)单独用药相比，尼达尼布与西地那非(5型磷酸二酯酶抑制剂)联合用药无明显作用优势[59]. 然而，最新一项大型临床试验结果显示，吸入曲前列环素能对间质性肺疾病相关HPH预后具有明显改善作用[56]. 因此，需要更多的大型临床试验论证PH靶向药物对HPH的疗效及安全性，重点关注哪种类型疾病相关的HPH能从中获益.

3.2　挖掘天然产物治疗HPH

天然产物是指动物、植物和微生物体内的化学成分或其代谢产物，作为药物发现的一个重要来源，具有来源丰富和结构新颖多样的特点. 已有多种天然产物或其衍生物用于HPH治疗，发展前景良好，但目前大多处在基础研究阶段，距离转化成临床用药尚需大量研究.

褪黑素属于内源性吲哚胺类激素，能透过血脑屏障发挥生物学功能. 褪黑素本身及其级联代谢产物均具有强大的抗氧化活性，对HPH实验动物的肺动脉血管重构及肺动脉压升高具有显著抑制作用，潜在机制可能与抑制PASMC的过度增殖及炎症反应，抑制内皮激活相关[60~63]；原花青素B2(procyanidin B2)属于黄酮类天然产物，生物利用度高达90%以上，能通过抑制ROS过度生成，增强抗氧化酶体系，减少脂质过氧化物的生成，进而发挥抗HPH大鼠肺动脉血管重构及肺动脉压升高的作用[64]；小檗碱属于异喹啉生物碱，能通过上调骨形态发生蛋白Ⅱ型受体(bone morphogenetic protein type II receptor, BMPR2)及下游分子P-smad1/5的表达，下调TGF-β及下游分子P-smad2/3的表达，抑制PASMC过度增殖、肺动脉血管重构，从而发挥抗HPH小鼠肺动脉血管重构、右心室收缩压升高及右心肥厚的作用[65]；白藜芦醇属于非黄酮类多酚化合物，是sirtuin1(SIRT1)非特异性激活剂，通过三羧酸循环及氨基酸、胆碱、亚油酸等代谢途径对低氧诱导的肺动脉高压大鼠发挥治疗作用[66]，介导PI3K/Akt信号通路下调精氨酸酶Ⅱ(arginase II)的表达，从而抑制PASMC增殖[67]，缓解HPH进展. 药用植物在我国已有上千年历史，具有多治疗靶点特色，中国人对药用植物拥有丰富的临床经验，目前研究报道已有多种中药提取物对HPH具有良好防治作用，如积雪草苷(五环三萜类)[68]、异槲皮苷(黄酮醇类)[69]、灯盏花素(黄酮类)[70]、姜黄素(多酚类)[71]以及通心络[72]等中药复方，挖掘药用植物防治HPH具有巨大潜力[73].

4　展望

HPH疾病进展迅猛且预后不良，与多种心肺疾病密切相关. 慢性炎症、氧化应激造成肺动脉血管重构是重要病理生理学改变，以其为靶点研发有效治疗药物，有望实现延缓甚至逆转HPH的疾病进展. HPH的研究尚任重道远，发病分子机制的探索，天然产物、小分子化合物等有效药物的筛选与优化，基础科学向临床诊疗的转化与应用等研究势在必行，相信终将为HPH的防治带来曙光.

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“Blue lips”: research progress in pulmonary vascular remodeling in hypoxic pulmonary hypertension

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Hypoxic pulmonary hypertension (HPH), characterized by increased pulmonary arterial pressure, is a complex and progressive disease with a wide spectrum of hypoxic etiologies and a challenging clinical problem with high disease prevalence. Mechanism-based treatment options for HPH are still lacking, and there is currently no cure for this devastating disease. Small pulmonary artery remodeling caused by chronic inflammation and aberrant oxidative stress under hypoxia is the typical pathological feature. This review summarizes the recent progress in pulmonary vascular remodeling research, including pathophysiological characteristics, pathophysiological pathogenesis, and treatment status and prospects, and provides ideas for the treatment of HPH.

pulmonary hypertension, hypoxia, pulmonary vascular remodeling, inflammation, oxidative stress

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