世界华人消化杂志 2013年3月8日; 21(7): 591-596
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

缺氧在肠黏膜炎症损伤过程中的病理生理机制

邱骅婧, 吴 维, 刘占举

邱骅婧, 吴维, 刘占举, 同济大学附属第十人民医院消化内科 上海市 200072
邱骅婧, 硕士, 主要从事炎症性肠病的研究.
国家自然科学基金资助项目, No. 81270470, No. 81061120521
作者贡献分布: 本文综述由邱骅婧与吴维完成; 刘占举审校.
通讯作者: 刘占举, 教授, 主任医师, 200072, 上海市延长中路301号, 同济大学附属第十人民医院消化内科.
zhanjuliu@yahoo.com
电话: 021-66301164
收稿日期: 2012-12-10 修回日期: 2013-01-29
接受日期: 2013-02-21 在线出版日期: 2013-03-08

Role of hypoxic injury in pathophysiology of intestinal mucosal inflammation

Hua-Jing Qiu, Wei Wu, Zhan-Ju Liu

Hua-Jing Qiu, Wei Wu, Zhan-Ju Liu, Department of Gastroenterology, Shanghai Tenth People's Hospital, Tongji University, Shanghai 200072, China
Supported by: National Natural Science Foundation of China, Nos. 81270470 and 81061120521
Correspondence to: Zhan-Ju Liu, Professor, Chief Physician, Department of Gastroenterology, Shanghai Tenth People's Hospital, Tongji University, 301 Yanchang Middle Road, Shanghai 200072, China. zhanjuliu@yahoo.com
Received: 2012-12-10 Revised: 2013-01-29
Accepted: 2013-02-21 Published online: 2013-03-08

Abstract
Hypoxia influences the normal metabolism of cells and normal functions of organs, eventually causing diseases. Various degrees of hypoxia can be seen in the intestinal mucosa of both experimental mouse models and patients with inflammatory bowel disease (IBD), whose oxygen supply and oxygen consumption are damaged. A number of hypoxia inducible factors, such as HIF-1, HIF-2 and HIF-3, can regulate different physiological responses via different mechanisms. Proline hydroxylasedomain (PHD) is a two-dioxygenase oxygen sensor that can mediate degradation of proline residues of HIFs. IBD is closely related to hypoxia. In recent years, researchers have paid more attention to improving the body's reaction to hypoxia in IBD, which is considered a novel treatment concept. This review will analyze the role of hypoxic injury in the pathophysiology of intestinal mucosal inflammation in IBD.

Key Words: Hypoxia; Inflammatory bowel disease; Hypoxia-inducible factor-1; Proline hydroxylasedomain

Qiu HJ, Wu W, Liu ZJ. Role of hypoxic injury in pathophysiology of intestinal mucosal inflammation. Shijie Huaren Xiaohua Zazhi 2013; 21(7): 591-596 http://www.wjgnet.com/1009-3079/21/591.asp DOI: http://dx.doi.org/10.11569/wcjd.v21.i7.591

摘要
细胞缺氧影响细胞的正常代谢, 影响组织器官正常功能, 导致疾病发生. 在实验小鼠模型和人类炎症性肠病(inflammatory bowel disease, IBD)患者的肠黏膜上均可见不同程度的缺氧, 氧供给和氧消耗之间的平衡受到破坏. 机体缺氧时, 一些低氧诱导因子, 如低氧诱导因子(hypoxia-inducible factor, HIF)-1、HIF-2和HIF-3, 能够通过不同的调节机制调控不同的生理反应. 脯氨酰羟化酶(proline hydroxylasedomain, PHD)是一种双加氧酶的氧感受器, 通过催化HIF脯氨酸残基发生羟化反应介导其降解. IBD与缺氧有着密切的联系, 在IBD中如何提高机体对缺氧的反应逐渐被研究人员重视, 并被看做为一种新颖的治疗理念, 本文就缺氧在IBD肠道黏膜炎症损伤过程中的病理生理变化进行综述分析.

关键词: 缺氧; 炎症性肠病; 低氧诱导因子-1; 脯氨酰羟化酶

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0 引言
炎症性肠病(inflammatory bowel disease, IBD)在欧美等西方国家有着较高的发病率, 但近几年随着人们生活方式的日趋西化, 在我国的患病率也逐

■背景资料
炎症性肠病(inflammatory bowel disease, IBD)包含有克罗恩病和溃疡性结肠炎, 近几年随着人们生活方式的日趋西化,在我国的患病率也逐渐上升. 人体自身免疫调节、环境因素、遗传因素及肠道菌群微生态是影响IBD疾病发生和进展的4大主要因素, 缺氧是其中一个不可忽视的重要影响因子.

■同行评议者
陆伦根, 教授, 上海交通大学附属第一人民医院消化科

■研发前沿
炎症性肠病与缺氧有着密切的联系，在实验小鼠模型和人类IBD患者的肠黏膜上均可见不同程度的缺氧，氧供给和氧消耗之间的平衡受到破坏. 机体缺氧时一些低氧诱导因子能够通过不同的调节机制调控不同的生理反应，在IBD中如何提高机体对缺氧的反应被看做为一种新颖的治疗理念.

渐上升. IBD包含有克罗恩病(Crohn's disease, CD)和溃疡性结肠炎(ulcerative colitis, UC), 人体自身免疫调节、环境因素、遗传因素及肠道菌群调节是影响IBD疾病发生和进展的4大主要因素, 缺氧是其中一项不可忽视的重要影响因子[1-4], 以下就缺氧条件下的氧调节因子、缺氧对IBD的病理生理影响及未来治疗新方向逐一展开介绍.

1 缺氧环境下氧调节因子

机体缺氧时, 一些低氧诱导因子[如hypoxia-inducible factor, (HIF)-1、HIF-2和HIF-3]和脯氨酰羟化酶, 能够通过不同的调节机制调控不同的生理反应, 发挥对机体的保护或破坏作用.

1.1 低氧诱导因子-1 HIF-1在低氧诱导的哺乳动物细胞中广泛表达, 为低氧应答的全局性调控因子. HIF-1能与人红细胞生成素基因的3增强子序列结合, 促进其转录[5]. HIF-1在低氧时通过对靶基因的诱导表达, 使缺氧的组织细胞保持一定的氧浓度, 维持机体氧的自我平衡与氧稳定. HIF-1活性调节主要有: (1)HIF-1 mRNA表达水平调节; (2)HIF-1蛋白表达水平调节; (3)HIF-1二聚化和DNA结合活性调节; (4)HIF-1α转录活性调节. HIF-1是一种异源二聚体, 主要由120 kDa的HIF-1α和91-94 kDa的HIF-1β两个亚单位组成. HIF-1β亚基又称芳香烃受体核转运子(aryl hydrocarbon receptor nuclear translocator, ARNT), 基因定位于人的1号染色体q21区, 在细胞内稳定表达, 起结构性作用; HIF-1α基因定位于人的14号染色体q21-24区, 缺氧信号的调控, 是HIF-1的活性亚基[6]. HIF-1β亚基在细胞浆中稳定表达, 而HIF-1α亚基在翻译后即被泛素-蛋白酶水解复合体降解. 因此, 在正常氧饱和度下的细胞中基本检测不到亚基的表达, 而在缺氧状态下, 亚基的降解被抑制, HIF-1α和HIF-1β亚基形成有活性的HIF-1, 转移到细胞核内调节多种基因的转录. HIF-1α在正常的肠组织中不表达或者很微弱的表达, 而在IBD的肠腔和腺体的上皮细胞、肠黏膜组织内的淋巴细胞和巨噬细胞中表达明显增强, 还可在血管的内皮细胞、基质的结缔组织细胞中表达, 特征为胞浆或胞核显黄色或棕褐色[7].

1.2 低氧诱导因子-2 HIF-2是bHLH-PAS蛋白家族新成员[8], HIF-2与HIF-1在结构上极其相似, 由诱导表达的HIF-2α亚基和持续表达的HIF-1β亚基所组成的异源二聚体结构. HIF-2α只表达于内皮细胞、肾脏、心脏、肺以及小肠, 而HIF-1α广泛地表达于各类细胞; HIF-2α能够加快细胞周期进程, 而HIF-1α起阻止作用[9], 且HIF-2α不能表达MDR、CD73等保护性基因. HIF-1α介导的对肠黏膜屏障的保护机制在IBD的发病早期起着保护作用, 而当肠黏膜屏障受到破坏时, HIF-2α能增强慢性炎症反应, 恶化疾病进程[10].

1.3 低氧诱导因子-3 HIF-3[11]主要表达于心脏、肺、骨骼肌和胎盘中, 在肝脏和肾脏中的表达量较低, HIF-3α与HIF-1α、HIF-2α结构上有较大的差异, 功能上也有明显的不同. HIF-3α能与HIF-1α、HIF-2α竞争性结合HIF-1β亚基, 导致HIF-1、HIF-2的表达水平降低, 从而抑制HIF-1、HIF-2对目标基因表达的上调作用[12], 可能是缺氧调控靶基因表达的负性调节因子.

1.4 脯氨酰羟化酶 脯氨酰羟化酶(proline hydroxylasedomain, PHD)是调节HIF-1的关键分子, 通过催化HIF脯氨酸残基发生羟化反应介导其降解, 他能够直接感受氧分压、是一种双加氧酶的氧感受器[3]. 目前研究发现了PHD1、PHD2、PHD3和PHD4这4种编码脯氨酰羟化酶的基因, 其中编码PHD1、PHD2、PHD3的基因与线虫的Egl-9基因同源, 在有氧条件下, 能催化人HIF特定脯氨酸残基发生羟化反应[13], 并且研究发现HIF-1α与PHD1、PHD3, 相比较PHD2而言, 有着更紧密的联系, PHD1与血管生长因子也有着密切的联系[14]. 2002年Epstein等[15]发现了PHD4, 但在HIF-1α过表达时PHD4才能发挥其调节作用. 与其他Fe^{2+}、α-酮戊二酸依赖的双加氧酶超家族成员一样, PHDs需要O_2作为底物, 一个氧原子加载到HIF-1α ODD区Pro402或Pro564形成脯氨酰残基; 另一个氧原子与α-酮戊二酸发生去碳羧基反应, 生成延胡索酸和二氧化碳. 同时, PHD羟基化HIF-1α的反应还需要铁和维生素C作为辅助因子. 常氧状态时, HIF-1α被PHD羟基化后进而被泛素蛋白酶水解, 因此细胞内无HIF-1聚集; 低氧状态时, 脯氨酰羟化酶活性受到抑制, PHD羟基化HIF-1α反应受阻, HIF-1α亚基大量积累, HIF-1聚集并入核诱导多种靶基因表达, 启动低氧应答反应, 以维持细胞和机体的氧自稳平衡及能量代谢平衡. 体外实验已证实PHD对氧的亲和力很低, 因此在低氧环境中, 细胞内HIF-1α表达量增加、DNA结合能力增强[3].

2 缺氧对IBD的病理生理影响机制

2.1 缺氧与肠道黏膜屏障损伤 缺氧、组织损伤及强烈的代谢应激在肿瘤坏死因子(recombinant human tumor necrosis factor-α, TNF-α)及其他促

炎因子的协助下, 能够迅速激活机体的固有免疫应答[16], 吞噬细胞的吞噬功能和自由基的产量在缺氧条件下会得到显著提高[17]. 同时缺氧能够在细胞、组织、系统水平上诱发适应性免疫应答以促进组织器官功能的顺利发挥, 缺氧和缺氧诱导因子是T细胞生长、分化及其功能发挥的重要调节者[18]. 已有很多证据表明缺氧介导的腺苷信号途径在正常和病态的肠黏膜中都发挥着重要作用, 而且HIF和缺氧信号决定了腺苷受体信号旁路和腺苷酸代谢中的多个步骤[19]. 腺苷主要通过其4大主要受体-ADORA1、ADORA2A、ADORA2B、ADORA3发挥作用, 细胞外的腺苷主要来源于三磷酸腺苷或一磷酸腺苷, HIF-1A诱发的基因改变会促进炎症组织分泌腺苷, 研究表明腺苷会抑制过度炎症反应和促进损伤组织的愈合[20]. 虽然至今IBD病因仍不明确, Hollander等[21]首先通过对CD患者及其家属肠道炎症发生前的肠黏膜渗透性改变的研究发现, 肠道渗透性的改变、肠黏膜完整性的破坏可能是CD的易患因素, 这也在之后的研究中得到了证实, 同时认为半胱氨酸蛋白酶募集域家族15号基因(CARD15)突变体可能与CD有关. Buhner等[22]选取了128例非活动性CD患者, 129例一级亲属(CD-R), 66例非血缘性家族成员(CD-NR)和96例健康对照人群. 分析3个最常见的CARD15多态现象(R702W、G908R、3020insC), 并用乳果糖/甘露醇比例确定肠黏膜通透性, 结果发现CD和CD-R组肠黏膜的通透性明显增加. 44%CD、26%CD-R和6%CD-NR人群的乳果糖/甘露醇比例在正常范围以上, 而对照组则全部在正常范围之内. 在IBD的动物模型上同样能够证实肠黏膜渗透性的增加, 白介素-10(interleukin-10, IL-10)敲除小鼠的肠黏膜在发生组织学异常之前就出现了渗透性的增加[23]. 在无菌环境中的小鼠并无屏障损伤, 提示肠黏膜屏障损害可能由于对肠微生物群不正常的免疫反应所引起. 屏障完整性的损害促进了大量非选择性的肠腔抗原的涌入, 持续刺激固有层的免疫细胞, 引起炎症持续时间的延长, 使之转化为慢性炎症. 就这点而言, 炎症缺氧和缺氧炎症是相互促进的[3].

2.2 缺氧与肠黏膜血管炎症 IBD患者的结肠中可广泛存在血管炎症, 血管炎既是疾病的发病机制, 又可作为疾病活动性的一项重要指标[24]. 肠壁中的血管炎分布范围常取决于肠黏膜炎症严重程度, 炎症程度越高, 分布越广泛[25]. VEGF与受体在血管内皮细胞中相互作用, 促进血管内皮细胞分裂[26]. VEGF基因是HIF-1α的重要靶基因, 活化的HIF-1能直接启动VEGF的转录, 上调VEGF受体Flt1的转录[27], 通过增强VEGF mRNA的稳定性来提高VEGF的表达[28], 并且研究发现缺氧激活Dll4-Notch-Hey2信号参与内皮前体细胞的分化[29]. Wood等[30]发现缺氧能够增加处于清醒状态下小鼠的白细胞迁移和血管渗透性. 他们将异硫氰基荧光素(fluorescein isothiocyanate, FITC)标记的白蛋白分别注射到处于常氧状态和10%氧气状态下的小鼠肠系膜血管中, 4 h后发现在缺氧状态下的小鼠血管周围FITC标记的白蛋白依赖的荧光信号显著增加, 提示了血管渗透性增加; 并且发现呼吸常氧状态下小鼠肠系膜微血管内很少有黏着的或迁徙的白细胞, 而处于10%氧气状态下的小鼠肠系膜微血管内白细胞迁徙则有明显的增加, 白细胞迁徙的量和时间成正比. Steiner等[31]发现在组织缺氧状态下, 肥大细胞通过活性氧(reactive oxygen species, ROS)/氮氧化物(nitrogen oxides, NO)平衡系统等对调节微血管炎症反应发挥着重要作用. 原始淋巴细胞易聚集于IBD患者的肠微血管内皮, 而正常肠道微血管更易与记忆淋巴细胞结合[32]. 缺氧能够引起肠黏膜血管炎症, CD的症状可首先表现为血管炎, 因此在临床上可将肠黏膜炎症与疾病进展程度相联系.

2.3 HIF-1及其他因子在IBD肠黏膜炎症发生时的作用 肠黏膜在发生炎症时会出现严重缺氧, 虽然已有研究发现, 相较于健康人群, 处于炎症活动期的IBD患者的血清HIF-1表达量上升[7], 但是目前所有支持HIF-1在肠黏膜炎症中发挥作用的证据仅来源于动物实验. 在动物IBD模型中, 通过增加或抑制HIF-1在小鼠体内的表达, HIF-1能够改善由2,4,6-三硝基苯磺酸诱导的大肠炎的多项临床指标, 如体质量下降、结肠长度、肠黏膜渗透性. HIF-1在维持肠黏膜的完整性中发挥着固有保护作用, 因此增加HIF-1的表达量, 被视为一种新颖的治疗理念[33]. HIF-1能够调节许多具有肠道屏障保护作用的基因, 包括肠三叶因子(ITF)、CD73、多药耐药基因1(MDR1)[34-36], 其中ITF和CD73已在动物活体内被证明是机体缺氧时具有肠黏膜屏障保护作用因子, 敲除MDR1基因的小鼠会自发发生肠道炎症[37], ITF通过维持肠黏膜上皮细胞的完整性及恢复正常的肠黏膜渗透性来保护和修复肠黏膜, 缺少肠三叶因子的小鼠对肠道炎症的易感性大大增加[38]. 转录核因子-κB(nuclear factor-κB, NF-

■相关报道
Hollander等首先发现肠道渗透性的改变、肠黏膜完整性的破坏可能是克罗恩病的易患因素, 白介素10敲除小鼠的肠黏膜在发生组织学异常之前就出现渗透性的增加, 而缺氧与肠道黏膜屏障损伤、肠道黏膜血管炎症有着密切的联系.

■创新盘点
本文就缺氧在IBD肠道黏膜炎症损伤过程中的病理生理变化进行分析, 在缺氧条件下的氧调节因子、缺氧对IBD的病理生理影响及未来治疗新方向等3个方面逐一展开详细的介绍.

κB)在固有免疫、应激反应和细胞生长中发挥着各自不同作用, 同时也是炎症反应的重要调节者[39], 他能够在缺氧时被激活. HIF-1在缺氧反应中起着主导作用, 如上文所述, 在缺氧状态下, HIF-1α亚基的降解被抑制, HIF-1α和HIF-1B亚基形成有活性的HIF-1, 转移到细胞核内调节多种基因的转录. 虽然在缺氧时NF-κB被激活的能力要远小于HIF-1, 但是NF-κB在缺氧炎症中能够产生促进肠黏膜细胞生存的信号[40]. Figueroa等[41]在研究红细胞生成素表达时最早提出HIF-1和NF-κB的联系, 并认为两者间存在着重要的相互作用机制. 含氧量正常时, IL-1β能够通过包含有NF-κB和环氧合酶2信号旁路, 提高HIF-1α蛋白表达量. 缺氧时, 中性粒细胞的凋亡受到抑制, 其中HIF-1α依赖的NF-κB的信号途径发挥着重要作用[42]. HIF除能够被缺氧激活之外, LPS、TNF-α、肝细胞生长因子、活性氧物质和IL-18等许多非缺氧性因素也能激活HIF和NF-κB, 促进HIF-1α mRNA表达[43]. 凝胶迁移滞后实验和染色体免疫共沉淀实验显示, NF-κB的二个亚基p50和p65能够与HIF-1α启动子的197、188二个碱基对结合, 构成位于转录起始上游的关键的调节点, 并且如果HIF-1α启动子的197、188碱基对发生了突变, 会直接破坏由NF-κB介导的HIF-1α的产生[44]. 在IBD发生时, 肠黏膜组织内HIF-1表达升高, 参与肠黏膜屏障和炎症修复功能.

3 结论

在缺氧导致肠黏膜出现炎症的动物模型中, 激活的HIF-1被证明是具有保护作用的, 能够减轻临床症状, 改善疾病结果, 但相较于各项指标受到严格控制的实验动物, IBD患者有更多的不可预测性, 如年龄、疾病进展程度等, 因此关于HIF-1对机体的保护作用需要进一步探讨. 虽然HIF-2和HIF-3的负性调节作用在实验中得到了初步证实, 但目前国内外对HIF-2和HIF-3研究仍较少, 关于他们的作用机制有待我们做进一步深入研究. 低氧状态时由于脯氨酰羟化酶活性受到抑制, 导致HIF-1大量积聚, 但在常氧状态下, TCR信号和一些促炎因子(如IL-6)也会上调$CD4^+$ T细胞中HIF-1表达[45]. 研究人员通过对HIF-1缺陷小鼠和正常小鼠对比发现, HIF-1既可通过激活RORγt转录及与RORγt和p300形成复合体上调Th17分化, 又可通过结合Foxp3和促进蛋白酶对Treg的降解作用减少Treg表达, 拥有HIF-1α缺陷T细胞的小鼠对Th17依赖的自身免疫性脑炎具有抵抗力[46]. 因此, HIF-1与T细胞分化, 缺氧对T细胞的影响, HIF-1、缺氧、T细胞三者之间的相互作用需要进一步的阐明. 大量积聚的HIF会编码生成VEGF, 他是肿瘤血管生成的重要刺激因子, 内皮细胞在VEGF的刺激下, 会增殖形成新的毛细血管网, 即血管生成, 有利于肿瘤的转移[47]. 而PHD作为HIF的重要调节分子, 可借助HIF, 影响肿瘤的发生发展. 高压氧治疗(HBOT)常用于治疗潜水减压病和一些伤口的愈合等, 而自1989年由Brady等[48]报道了第一例用高压氧治疗的CD之后, 陆陆续续有报道HBOT方法治疗IBD的病例, Rossignol[49]对此进行了总结, 发现HBOT治疗效果显著, 引起的不良反应也非常小, 因此用高压氧改善由缺氧导致的IBD, 不失为一种有效的治疗手段, 应得到我们的重视. 总之, 在IBD中提高机体对缺氧的反应, 如何提高HIF的表达量, 利用好PHD对HIF的影响作用, 是一种新颖的治疗理念.

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■应用要点
在IBD中提高机体对缺氧的反应，如何提高HIF的表达量，利用好PHD对HIF的影响作用，是一种新颖的治疗理念.

■同行评价
本文论述角度较为新颖，具有一定指导意义.

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编辑 田滢 电编 鲁亚静

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