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文献综述 REVIEW

干扰上皮细胞能量代谢对炎症性肠病发病的影响

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Abnormal epithelial cell energy metabolism influences pathogenesis of inflammatory bowel disease

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Abstract

Etiology and pathogenesis of inflammatory bowel disease (IBD) are not clear, but colonic mucosal damage is known to be a critical factor. In recent decades, many studies suggest that interfering with the energy metabolism of epithelial tissue could result in the widening of intestinal epithelial cell gap, increased bacterial translocation across the epithelium, decreased mucus secretion, and intestinal mucosal barrier dysfunction. Bacteria and antigens adhere to the intestinal mucosa, enter into the lamina propria, activate inflammation, and initiate the pathogenesis of IBD. The lack of energy fuel butyrate and mitochondrial dysfunction are the causes of abnormal energy metabolism of the intestinal epithelium. Improving energy metabolism and protection of mitochondrial function can alleviate the seriousness of IBD, reduce recurrence, and provides a new strategy for the treatment of IBD.

Key Words: Inflammatory bowel disease; Colonic mucosal barrier; Energy metabolism; Mitochondria

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摘要

炎症性肠病(inflammatory bowel disease, IBD)的病因和发病机制尚不明确, 结肠黏膜屏障损伤是关键因素. 近几十年研究认为, 干扰上皮组织的能量代谢会引发肠上皮细胞间隙增宽, 细菌跨膜易位增多, 黏液分泌减少等肠黏膜屏障功能紊乱. 细菌、抗原等物质穿过肠黏膜屏障, 进入固有层激活炎症

背景资料
肠上皮细胞依赖高能量维持细胞极性, ATP水平下降, 上皮间隙增宽, 黏液分泌减少, 上皮细胞更新减慢, 细胞结构蛋白合成减少, 上皮凋亡增多等, 严重削弱了结肠黏膜屏障功能, 细菌、抗原等进入黏膜下层, 启动了炎症性肠病(inflammatory bowel disease, IBD)的发病.

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研发前沿
肠上皮线粒体形态、生化、功能的改变也能影响肠黏膜屏障的紧密性, 用线粒体靶向抗氧化剂MitoTEMPO对IBD有治疗作用.

反应, 启动炎症性肠病. 能量燃料丁酸盐缺乏, 线粒体病理改变是肠上皮能量异常的原因. 改善能量代谢, 保护线粒体功能等方法, 能缓解IBD的严重性, 减少复发, 为IBD的治疗提供了新的策略.

关键词: 炎症性肠病; 结肠黏膜屏障; 能量代谢; 线粒体

核心提示: 结肠上皮细胞能量代谢对结肠黏膜屏障的形态和功能有重要影响, 干扰上皮组织的能量代谢会引发肠黏膜屏障功能紊乱, 促进炎症性肠病(inflammatory bowel disease, IBD)发生. 改善能量代谢, 保护线粒体等方法, 能缓解IBD的严重性, 为IBD的治疗提供了新的策略.

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0 引言

炎症性肠病(inflammatory bowel disease, IBD)包括克罗恩病(Crohn's disease CD)和溃疡性结肠炎(ulcerative colitis, UC), 病因和发病机制尚未完全明确. 肠黏膜屏障损伤是本病发病的关键因素已得到认可. 肠黏膜屏障由肠黏膜细胞、细胞间相互连接及其分泌黏液层构成, 形成了一个完整的生物屏, 有效阻止肠腔内细菌、抗原等物质进入肠黏膜固有层激活固有层免疫细胞[1-3]. IBD发病时肠黏膜屏障功能异常, 肠腔内抗原物质向肠黏膜固有层移位并激活固有层免疫细胞, 导致大量炎症细胞因子及介质的产生, 所产生的炎症分子进一步损伤肠黏膜屏障功能[2,4].

近几十年的研究发现, 能量代谢对肠黏膜屏障的完整性有重要的影响, 肠上皮细胞是极性细胞, 依赖高能量维持细胞的极性, 干扰上皮组织的能量代谢的因素会引发肠黏膜屏障异常, 从而启动IBD发病[5-8]. 因此, 研究肠上皮组织的能量代谢, 为缓解IBD症状和减少复发有着重要的意义, 为临床治疗IBD提供新的思路. 国内关于这方面研究不多, 本文将IBD患者结肠黏膜的能量代谢异常的研究进展进行综述.

相关报道
摄入麦麸、燕麦、黄豆及高纤维素谷类等食物, 可被肠腔共生菌转化为丁酸等, 改善结肠上皮能量, 促进上皮细胞增殖, 加强丁酸盐对结肠黏膜的保护作用.

1 IBD的发病与能量关系密切

1.1 UC患者能量燃料丁酸的缺乏, ATP水平低于正常 研究[9]发现, 以丁酸为主的短链脂肪酸(short fatty acid, SFA)是结肠上皮细胞的能量主要能源, 他们主要来自大肠中厌氧杆菌对粪便纤维素的酵解作用, 提供结肠上皮细胞>70%的能量, 而且远端的结肠黏膜较之近端更依赖于丁酸盐作为呼吸燃料. 1980年Roediger等[10]观察由6例静止期UC和4例急性期UC以及7名健康者的降结肠黏膜制备的结肠上皮细胞悬浮液, 发现静止期和急性期UC患者的结肠细胞丁酸代谢为CO_2显著减少. 由此推测: 丁酸盐氧化减少, 结肠黏膜尤其是远端结肠和直肠出现黏膜屏障功能减退, 肠腔内细菌、抗原等物质进入肠黏膜固有层激活免疫细胞, 诱发炎症反应的发生.

这一推测陆续得到其他研究者的验证[11,12]. 用丁酸盐氧化抑制剂灌肠大鼠5 d, 抑制丁酸盐的氧化代谢, 大鼠出现体质量减轻、血性腹泻、组织缺损等病理变化, 与UC病变相似[13,14]. 1984年Kameyama等[15]检测UC病灶周围结肠黏膜, 用酶联免疫法证实UC结肠黏膜ATP和能荷水平明显低于对照组. 改道性结肠炎是因手术使粪便改道后, 引起闭锁结肠段非特异性炎症, 类似非特异性或UC, 用相当于正常粪便所含的相似浓度短链脂肪酸液局部注入改道结肠段, 结果可使炎症消退[16]. 以上研究和观察说明, SFA的来源不足或利用障碍, 导致结肠上皮能量水平低于正常, 与UC发病和缓解关系密切.

1.2 某些致病因素干扰肠上皮能量代谢, 诱发CD发病 CD的发病与呼吸燃料SFA缺乏的关系并不密切, 因为CD病变部位多见于末端回肠和邻近结肠[17], 其能量主要来源是谷氨酰胺和葡萄糖而非SFA[9]. 然而, 干扰能量代谢对CD的发病也有重要影响, 感染、缺血以及药物等致病因素皆能干扰肠上皮细胞的能量代谢. Nazli等[18]观察取自于CD的结肠切除组织, 发现了上皮内肿胀和不规则的线粒体. 因此他们推测扰乱上皮的能量代谢, 能导致屏障功能削弱, 以促进细菌易位. 通过实验说明, 用氧化磷酸化解偶联剂二硝基酚诱发上皮细胞能量亏损4 h, 无毒无致病性大肠细菌更容易被结肠上皮细胞内吞, 进入固有层, 激

活免疫反应.

2 能量与结肠黏膜屏障

2.1 上皮ATP不足时影响细胞连接, 通透性增高 许多上皮细胞系研究说明ATP耗竭是细胞旁路高通透性和紧密连接重新分布的原因[7,19-21]. 细胞连接是结肠黏膜屏障重要组成, ATP耗竭首先引起actin细胞骨架的改变, 在细胞与细胞连接区域的F-actin明显地减少和破坏[19,22,23], actin细丝与细胞连接相联, actin的异常可以引起细胞连接分布和功能的改变, 细胞间隙增宽[24], 结肠黏膜屏障通透性增加. 肠腔的细菌和抗原进入黏膜下层, 诱发炎症反应.

2.2 上皮细胞ATP不足, 非致病性细菌易跨上皮转运至黏膜层 ATP的匮乏促进细菌跨细胞转运, 穿过上皮细胞, 进入黏膜层. Nazli等[18]用0.1 mmol/L的线粒体解偶联剂2,4-二硝基苯酚(2,4-dinitrophenol, DNP)注射入回肠末端的肠腔内, 上皮细胞ATP水平明显下降, 黏膜屏障通透性增高. 单层的人结肠上皮细胞(T84, HT-29)用DNP与非致病性大肠杆菌处理后, 与单纯用非致病性大肠杆菌处理比较, 10倍以上的细菌通过细胞旁路途径或跨细胞途径(细胞内吞和易位)进入黏膜下层, 更多的实验资料支持跨细胞通道才是主要途径, 活细菌穿过完整的上皮单层进入固有层[8,18,25,26].

2.3 ATP水平不足, 影响上皮细胞许多功能 结肠上皮细胞许多重要功能的完成也是能量依赖过程[14], 包括肠上皮的电解质交换[14,27], 黏液层的糖蛋白合成[28,29], 细胞膜脂肪合成[30], 结构蛋白合成和解毒功能等[29], 细胞能量的匮乏可以削弱所有这些过程, 短期致使上皮细胞萎缩, 长期导致结肠黏膜屏障破坏, 发展为IBD.

3 线粒体的病理改变是能量代谢减退的原因

3.1 线粒体内许多蛋白表达在病变早期已明显减少 线粒体是细胞的动力室, 线粒体病理改变往往导致能量匮乏. Hsieh等[31]用2-DE和质谱分别鉴定UC活动期、静止期和非特异性肠炎以及正常肠黏膜表达蛋白. UC活动期结肠黏膜有13个蛋白分子下调和6个上调被确认. 在下调的蛋白中, 8个(ATP合成酶5B、抑制素PHB等)是线粒体蛋白, 三个(磷酸冰糖异构酶等)参与能量产生, 三个是细胞内抗氧化剂. 透射电子显微镜显示UC患者肠上皮细胞线粒体肿胀, 线粒体嵴紊乱, 内外膜紧密度缺失等相对早于微绒毛和细胞核的形态改变. PHB是一个重要的线粒体成分蛋白, 在UC的疾病活动期和静止期都明显下调[32]. 以上研究说明在UC发展中, 线粒体功能紊乱是早期事情[31]. Santhanam等[33]取UC患者结肠活检组织, 用分光光度法测量证明, 结肠黏膜线粒体内乙酰乙酰辅酶A硫解酶活性, 显著低于正常水平, 无论是左侧的溃疡黏膜, 还是右侧的正常组织, 而此酶是丁酸氧化的关键酶, 由此推论UC发病与线粒体内乙酰乙酰辅酶A硫解酶活性减退相关.

3.2 线粒体复合物活性在疾病早期出现减退 结肠黏膜从43个患者和35个对照者经活检采取并经过结肠镜筛选, 线粒体电子传递链(electron transport chain, ETC)的生物活性进行生化分析. 与对照组比较, 从UC患者的结肠活组织提取的线粒体复合物Ⅱ, 活性显著减退. 而其他线粒体复合物活性正常. 线粒体复合物Ⅱ活性也同样在UC发病和正常肠黏膜减退. 减退程度与临床、内镜、组织学分级无关. 结肠上皮细胞从不同患病阶段的葡聚糖硫酸钠(dextran sulphate sodium, DSS)诱导的结肠炎瑞士白化小鼠分离, 也进行ETC复合物活性分析. 复合物Ⅱ和复合物Ⅳ的活性减退, 其他复合物活性则不受影响[34].

3.3 许多致病因素能诱发线粒体异常 许多致病因素能诱发线粒体的病理改变, 如应激、感染、缺血、非甾体类药物(non-steroidal anti-inflammatory drug, NSAID)等, 而这些致病因素的长期慢性刺激往往与IBD的复发密切相关. Söderholm等[35]用大鼠避水应激试验5 d后, 超微病理观察显示结肠上皮线粒体膨大和嵴的不规则扭曲, 上皮通透性增高. Somasundaram等[36]通过电镜观察大鼠口服NSAID药物, 能明显抑制肠上皮线粒体的电子传递链的氧化磷酸化功能, 导致肠上皮ATP水平下降, 增高肠上皮通透性[37]. 病原体轮状病毒、空肠弯曲杆菌等感染也能引起线粒体肿胀、能量水平下降、actin解聚、紧密连接重新分布等与肠上皮通透性增高相关的改变[7,38,39]. 在肠黏膜缺血状态时, 肠上皮与线粒体也会出现以上类似反应[37,40].

3.4 线粒体异常影响上皮细胞的更新和凋亡 线粒体不仅通过降低ATP的产生影响结肠黏膜屏

创新盘点

结肠上皮能量燃料缺乏, 或应激、药物、感染、缺血等刺激诱导的肠上皮线粒体功能紊乱, ATP水平下降, 削弱了结肠黏膜屏障功能, 是IBD发病的重要机制.

应用要点
通过改善能量代谢, 保护线粒体的功能等方法, 能缓解IBD的严重性, 减少复发, 为IBD的治疗提供了新的策略.

障的紧密度, 线粒体内膜通透性增高, 细胞色素C释放入胞浆, 也可以直接诱导上皮细胞凋亡, 破坏结肠黏膜屏障[41,42]. 线粒体的有氧代谢能促进结肠隐窝的肠干细胞的增殖和分化, 肠上皮细胞的表达[43-45]. 总之, 肠上皮线粒体形态、生化、功能的改变也能影响肠黏膜屏障的紧密性.

4 改善能量代谢能缓解IBD的发病

4.1 补充上皮能量燃料能缓解UC Harig等[16]用正常粪便所含的相似浓度SCFA灌肠4例改道性结肠炎患者2-3 wk, 明显改善结肠肉眼和组织学损伤, 停用后迅速复发. Steinhart等[46]用丁酸盐灌肠难治性结肠炎患者3-6 wk, 临床和内镜损伤评分明显改善.

4.2 提高ATP水平, 改善动物实验性结肠炎 Bär等[47]用有一致的细胞核, 和不相同的线粒体基因组的conplastic小鼠做研究对象, 通过测量结肠黏膜的ATP水平和线粒体氧化磷酸化(oxidative phosphorylation, OXPHOS)复合体活性、上皮细胞增殖和凋亡等指标, OXPHOS复合体活性和ATP水平升高的小鼠, 比较那些结肠黏膜ATP水平低的小鼠, 口服DSS或灌肠三硝基苯磺酸(trinitrobenzenesulfonic acid, TNBS)诱导的结肠炎严重度要轻, 说明增加肠上皮细胞线粒体内ATP合成可能是一个治疗UC的途径.

4.3 线粒体靶向抗氧化剂能保护线粒体, 缓解DSS结肠炎 MitoTEMPO是线粒体靶向抗氧化剂, 进入线粒体, 可减少线粒体内活性氧的产生, 保护线粒体的功能, 提高肠上皮ATP水平, 抑制结肠黏膜屏障功能紊乱, 明显缓解DSS诱导的小鼠结肠炎[48-50].

5 结论

结肠上皮能量代谢对IBD发病有重要的影响, 结肠上皮能量燃料丁酸盐的缺乏, 或应激、药物、感染、缺血等刺激诱导的肠上皮线粒体功能紊乱, ATP水平下降, 从而导致上皮间隙增宽, 通透性增加, 细菌跨细胞转运易位进入固有层增多, 黏液分泌减少, 上皮细胞更新减慢, 细胞结构蛋白合成减少, 上皮凋亡增多等, 严重削弱了结肠黏膜屏障功能, 细菌、抗原等进入黏膜下层, 启动了IBD的发病, 通过改善能量代谢, 保护线粒体的功能等方法, 能缓解IBD的严重性, 减少复发, 为IBD的治疗提供了新的策略.

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名词解释

肠上皮的细胞连接：从顶端到基膜依次为紧密连接，黏附连接，桥粒，缝隙连接，起着封闭细胞间隙的作用，防止肠腔内物质自由经过细胞间隙，穿过上皮细胞层，对调节肠道屏障的通透性发挥着重要的作用.

同行评价

上皮细胞能量代谢与IBD存在一定的联系, 本文对其进行综述可为国内相关研究工作者开阔视野、启发思路. 本文书写流畅, 条理清晰.

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