•综述•

靶向肠道细菌呼吸及能量代谢调控炎症性肠病进程的治疗策略分析

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摘要: 肠道菌群失衡与多种宿主疾病密切相关, 靶向肠道菌群中的代谢通路也成为当前防治宿主疾病的前沿策略和研究热点。炎症性肠病 (inflammatory bowel disease, IBD) 是一组病因不明的慢性进展性肠道炎症疾病。已有研究证实IBD的发生和发展与肠道菌群紊乱以及细菌的呼吸能量代谢之间存在一定联系, 本文将结合最新的研究进展, 对三者之间的关系进行整理分析, 并提出调控肠道菌群呼吸与能量代谢, 缓解宿主肠道炎症新的治疗策略。在IBD发生发展时, 肠道菌群稳态失衡, 其原因主要包括两方面: ① 宿主肠道炎症发生时, 肠腔内氧气含量增加, 致使兼性厌氧菌尤其是肠杆菌科细菌异常增殖, 而绝对厌氧菌如厚壁菌门等细菌的生长则受到抑制; ② 肠道炎症副产物也会支持兼性厌氧菌的扩增, 最终加剧肠道菌群失衡。失调的肠道菌群会进一步加剧肠道免疫稳态失衡, 加重肠道炎症反应。最新研究证实可通过干扰细菌呼吸及能量代谢, 抑制促炎细菌的异常增殖进而恢复菌群稳态, 减轻IBD炎症反应。通过以上分析, 提示可聚焦肠道菌群中的代谢通路, 调控肠道细菌呼吸以及能量代谢, 探索缓解宿主肠道炎症的治疗策略, 对于IBD的临床治疗以及创新药物研究具有重要意义。

关键词: 炎症性肠病; 肠道菌群; 肠杆菌科; 细菌呼吸; 能量代谢

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Analysis of the strategy to intervene the progress of inflammatory bowel disease by targeting intestinal bacterial respiration and energy metabolism

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Abstract: Gut microbiota dysbiosis is closely related to a variety of host diseases. Recently, targeting the metabolic pathways of gut microbiota for the prevention and treatment of host diseases has become a frontier strategy and research hotspot. Inflammatory bowel disease (IBD) is a group of chronic progressive intestinal inflammatory diseases of unknown etiology. The relationship between IBD and gut microbiota disorders and bacterial respiratory/energy metabolism has been confirmed in recent research. This article will introduce the relationship among them, and propose a new treatment strategy to alleviate host gut inflammation by regulating gut microbiota respiration and energy metabolism based on the latest research progress. In the progression of IBD, the gut microbiota homeostasis is disturbed. The main reasons include two aspects: on the one hand, when the intestinal inflammation of the host occurs, with increasing of oxygen concentration in the intestinal cavity, facultative anaerobic bacteria, especially Enterobacteriaceae bacteria would proliferate abnormally; while the growth of absolute anaerobic bacteria such as

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Firmicutes is inhibited. On the other hand, intestinal inflammation by-products also support the expansion of facultative anaerobic bacteria, which ultimately exacerbates the imbalance of gut microbiota. Dysregulated intestinal flora will further disturb intestinal immune homeostasis and exacerbate intestinal inflammation. The latest research proposed the possibility that IBD can be alleviated by interfering with the respiration of bacteria, inhibiting the abnormal proliferation of bacteria, or increasing the level of "beneficial" metabolites of gut microbiota. The above studies suggest that alleviating host intestinal inflammation can be explored by focusing on the metabolic pathways of gut microbiota and regulating the intestinal bacterial respiration and energy metabolism, which is of great significance for the clinical treatment of IBD and the research of innovative drugs.

Key words: inflammatory bowel disease; gut bacteria; Enterobacteriaceae; bacterial respiration; energy metabolism

炎症性肠病 (inflammatory bowel disease, IBD), 包括溃疡性结肠炎 (ulcerative colitis, UC) 和克罗恩病 (Crohn's disease, CD) 两种主要类型, 是一种病因暂不明确的肠道慢性炎症性疾病。UC发病部位主要在结肠黏膜与黏膜下层, 临床表现主要为腹泻、腹痛和血便等。CD可影响从口腔到肛门的整个胃肠道的各个部分, 临床表现取决于疾病位置, 可能包括腹泻、腹痛、发烧和肠梗阻等临床特征[1,2]。目前, IBD的发病率与患病率在全世界范围内不断增加, 在西方发达国家较为多发[3]。据估计, 在美国有多达140万人, 在英国有25万人患有IBD[4]。但随着越来越多的国家采用“西化”的生活方式, 发展中国家或地区的发病率也逐渐上升[5]。

最新的流行病学调查显示, 我国的IBD发病率居亚洲首位, 并且呈逐年上升的趋势[4]。2015年《自然评论: 胃肠病学与肝病学》杂志发表评论文章指出, 在未来的10年中, 中国的患病率最高可能达到0.1%, 2025年的患病人数将超过150万, 几乎追平西方国家, 这必将给我国的医疗系统和社会经济带来巨大负担[6]。目前IBD的治疗仍缺乏安全有效的药物, 主要依赖于非特异性抗炎和免疫抑制治疗, 常用药物有糖皮质激素、氨基水杨酸和免疫抑制剂等, 但是这些药物均具有较多不良反应, 多数患者不能坚持长期服用, 导致疾病的反复发作和迁延不愈[7-9]。因此, 探究IBD的病理机制, 寻找IBD的治疗新靶点和新药物, 对于应对当前的IBD防治挑战具有重要意义。

关于IBD的病因学研究主要集中于遗传、环境、肠道菌群以及宿主免疫等方面[10-12]。其中, 肠道菌群被证明是与IBD肠道炎症密切相关的重要因素[13,14]。肠道炎症期间, 肠道菌群组成发生改变, 某些细菌呼吸方式也发生了变化。例如, 在IBD动物模型盲肠提取物的细菌基因组学分析中发现, 其硝酸盐呼吸、氧化三甲胺 (trimethylamine *N*-oxide, TMAO) 呼吸和甲酸氧化相关代谢酶的基因水平过度表达[15]。与此同时, 特定的细菌代谢产物也随之发生变化, 例如IBD患者粪便提取物中观察到短链脂肪酸 (short-chain fatty acids, SCFA) 浓度降低[16]。由此可见, 肠道菌群组成以及肠道菌群的能量代谢方式与IBD的发生发展密切相关。关于肠道菌群能量代谢与IBD具体的联系, 将在下文进行综述。

1 IBD发生发展时肠道菌群稳态失衡

人类肠道中有着数量众多的肠道细菌, 健康状态下, 肠道处于无氧状态, 不同类型的肠道细菌之间互相制约, 保持肠道菌群动态平衡。肠道免疫系统对共生的肠道菌群产生免疫耐受, 二者共同维持着肠道稳态。遗传、环境、饮食等多种因素会诱发肠道免疫稳态失衡进而导致肠道炎症反应。在肠道炎症微环境下, 肠杆菌科细菌显著增加[17,18] (菌群稳态失衡), 并进一步加剧肠道免疫稳态失衡, 加重肠道炎症反应, 形成肠道内免疫稳态失衡与菌群稳态失衡之间的恶性循环, 最终导致IBD的发生发展[19,20]。

1.1 IBD发生时肠道内专性厌氧菌相对丰度减少而兼性厌氧菌相对丰度增加

在过去几十年中, 关于健康人体的肠道菌群组成, 人们一直在不懈探索, 并通过宏基因组分析得到了进一步的结果[21]。通过焦磷酸测序, 对编码16S核糖体RNA进行基因分析得知厚壁菌门、拟杆菌门、变形菌门以及放线菌门在肠道中占主导地位。其中, 厚壁菌门和拟杆菌门细菌主要是专性厌氧菌, 是肠道细菌的优势种, 占肠道细菌的90%[22,23]。

然而, 在IBD患者中, 无论是UC患者还是CD患者, 均观察到肠道菌群失衡现象 (表1), 主要表现为细菌多样性减少、专性厌氧菌丰度降低以及兼性厌氧菌数量增加[24]。在CD患者中, 可以观察到*Faecalibacterium*和*Roseburia* (专性厌氧菌) 水平降低, 兼性厌氧菌肠杆菌科细菌数量增加[25]。Zhou等[26]在IBD患者中观察到专性厌氧菌拟杆菌的减少。在UC患者中, 其细菌多样性减少, 且变形菌门和放线菌门细菌增多[27]。而且, Morgan等[28]的研究也证明, 与健康受试者相比,

Table 1 The changes of intestinal flora in inflammatory bowel disease (IBD)

Bacteria	Phylum	Class	Family	Genus	Species	Comment
Obligate anaerobic bacteria	Firmicutes	Clostridia	Ruminococcaceae	*Faecalibacterium*	*Faecalibacterium prausnitzii*	Decrease
			Clostridiaceae	*Clostridium*	–	Decrease
			Lachnospiraceae	*Roseburia*	*Roseburia hominis*	Decrease
	Bacteroidetes	Bacteroidia	Bacteroidaceae	*Bacteroides*	–	Decrease
Facultative anaerobic bacteria	Proteobacteria	–	Enterobacteriaceae	*Escherichia*	*Escherichia coli*	Increase
				Klebsiella	*Klebsiella pneumoniae*	Increase

IBD患者的肠道微生物群落的特征是变形菌门 (尤其是肠杆菌科) 的细菌过度生长以及伴随着专性厌氧菌厚壁菌门细菌数量的减少。

1.2 IBD发作时肠腔内升高的氧气浓度促进兼性厌氧菌变形菌门细菌的生长 正常情况下, 肠道处于无氧状态, 肠道中的专性厌氧菌将复杂的化合物发酵成较小分子的化合物, 并将许多发酵产物转化为SCFA, 其中乙酸盐、丙酸盐和丁酸盐是最丰富的产物[29]。乙酸盐和丙酸盐主要由拟杆菌门细菌产生, 而丁酸盐主要为厚壁菌门细菌的代谢终产物[30], 并可作为结肠细胞主要的能源物质。

许多研究均发现兼性厌氧菌中的变形菌门在IBD患者肠道内异常增殖的现象, 尤其以肠杆菌科的过度繁殖为主要表现[23,31,32]。关于此现象, 科学家提出了一种“氧假说”: 氧气是肠道菌群从专性厌氧菌转变为兼性厌氧菌或需氧菌的重要原因。例如小肠移植患者的回肠造口术为氧气进入肠道提供了一个门户, 该门户允许氧气到达原本无氧的远端回肠, 在回肠造口术时观察到肠杆菌科的相对丰度增加, 并且微生物群落会在手术关闭后恢复到其正常组成[33]。

正常情况下 (图1), 结肠表面处于低氧状态; 从低氧结肠表面释放出的有限量的氧气可在结肠上皮细胞内进行丁酸盐β氧化反应被消耗, 生成CO_2, 最终导致结肠上皮缺氧, 从而维持肠腔内的厌氧状态[34,35]。然而, 在慢性炎症期间, 血液经常进入胃肠道, 其血红蛋白携带的氧气在肠道细菌所处的肠黏膜和管腔中释放[22], 肠腔内氧气含量增加。与此同时, 因肠道炎症期间肠黏膜细胞受损, 导致SCFA吸收和代谢受损以及肠道产丁酸菌的减少[36-38], 结肠细胞利用丁酸盐的能力降低。结肠细胞缺乏能源物质, 削弱了肠上皮执行β氧化的能力, 导致氧气无法被利用并在肠腔中扩散[39]。肠腔内的氧气进一步促进了兼性厌氧菌的生长, 而抑制专性厌氧菌的繁殖。作为一种代表性的兼性厌氧菌, 变形菌门细菌在此期间过度生长。

1.3 肠杆菌科细菌借助独特的呼吸方式在肠道炎症微环境下过度生长 肠道炎症期间, 一些炎症因子 (如interferon-γ, IFN-γ) 可刺激相关酶表达, 从而产生抗微生物的自由基产物: 活性氧和活性氮, 如超氧化物[40]、过氧化物[41]、次氯酸盐[42]、一氧化氮[40,43]和过氧亚硝酸盐[44]等。这些自由基在肠腔中反应形成无害的氧化产物, 即*S*-氧化物、*N*-氧化物和硝酸盐[45-47], 这些产物的存在会导致肠内生长条件发生明显变化 (图2)。作为宿主炎症反应的副产物, *S*-氧化物, *N*-氧化物和硝酸盐可为兼性厌氧微生物在这种环境下的生长提供新的选择。肠杆菌科细菌可以分别通过表达二甲基亚砜 (dimethyl *S*-oxide, DMSO) 还原酶、TMAO还原酶[48]和硝酸还原酶[49]来分别使用*S*-氧化物、*N*-氧化物和硝酸盐作为厌氧呼吸的末端电子受体, 从而支持其生长。而Clostridia和Bacteroidia细菌缺乏使用这些外源电子受体所需的末端氧化还原酶[50,51], 因此其生长缺乏优势。所以, 肠道发生炎症时可通过无氧呼吸支持肠杆菌科细菌的生长, 即导致IBD期间肠道菌群紊乱的机制之一是宿主选择性地供给兼性厌氧细菌。

为了研究在炎症发作期间驱动肠杆菌科细菌种群扩展的机制, Hughes等[32]将大肠杆菌作为模型生物进行了研究。大肠杆菌有3种MoCo依赖性甲酸脱氢酶: 甲酸脱氢酶N (formate dehydrogenase-N, FDN)、甲酸脱氢酶O和甲酸脱氢酶H[52]。在Hughes等[32]的实验中发现, 甲酸脱氢酶在发炎的肠道中为大肠杆菌的生长提供了适宜的优势。通过进一步的研究结果表明, 大肠杆菌主要依赖于FDN酶, 而氧气很可能充当末端电子受体, 并提出甲酸盐的氧化和氧呼吸可能是肠道微生物种群失调的代谢特征。因此, 甲酸氧化与呼吸作用一起构成了肠道炎症期间肠杆菌科细菌过度生长的机制。

总之, UC和CD患者的肠道菌群总体特征表现为肠道细菌多样性减少、厚壁菌门细菌丰度降低以及变形菌门中肠杆菌科细菌的异常增多[53]。但是, UC与CD患者之间肠道菌群的变化也存在一些差异。有研究者检测了IBD患者以及健康个体肠道黏膜和粪便中菌群的差异, 发现埃希氏菌属、志贺氏菌属、*Sutterella*菌属以及梭状芽胞杆菌XI等细菌在UC患者中更多; 而梭杆菌属、*Halomonas*菌属、不动杆菌属、希瓦氏菌属以及链球菌属在CD患者中更多[54]。与健康宿主相

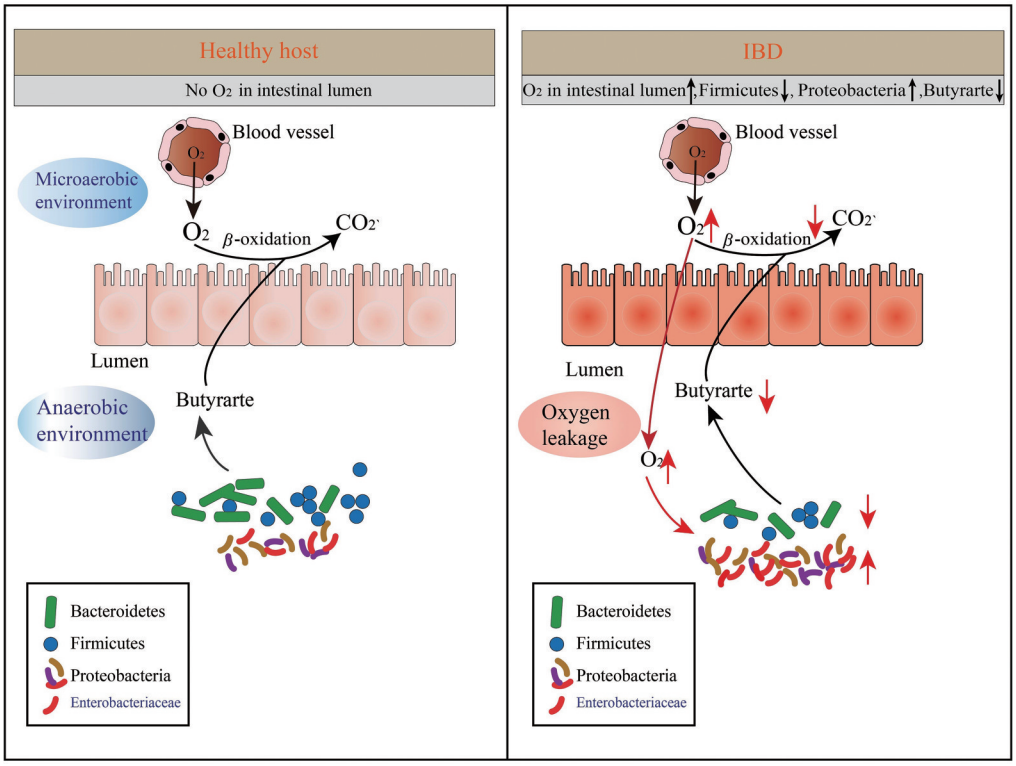

Figure 1 During gut homeostasis or during gut inflammation, the β-oxidation mechanism diagram of the host colonic epithelial cells. During gut homeostasis (left), β-oxidation of microbiota-derived butyrate causes epithelial hypoxia, which drives a dominance of obligate anaerobic bacteria within the gut microbiota. During gut inflammation (right), epithelial dysfunction leads to increased epithelial oxygenation and disrupts anaerobiasis in the lumen, thereby driving an expansion of facultative anaerobic Proteobacteria by aerobic respiration

比, UC 患者结肠中变形菌门细菌丰度增加[55], 且 UC 样本活检出的相关细菌数量也比 CD 患者多。然而当宿主处于 CD 状态时, 仅在回肠中发现变形菌门细菌数量的增加, 而且 CD 患者中的未分类细菌类成员比 UC 患者中更为普遍[56, 57]。

2 IBD 中肠道菌群稳态失衡导致的后果

研究已经证实肠道菌群可以通过调节各种细胞因子的分泌来影响肠道屏障状态, 从而对 IBD 的发病机制和进程产生影响[58-60]。Weng 等[54]基于弹枪基因组学以及代谢途径研究发现, 在 UC 患者粪便样品中, 与酸酐相关的途径较为丰富; 而在 CD 患者粪便样品中[57], 参与生物合成途径的细菌易于富集, 而参与降解途径的细菌却被耗尽。例如支链和芳香族氨基酸的生物合成途径在 CD 患者中很丰富, 而与氨基酸有关的降解途径的细菌却被耗尽了。以上现象表明, IBD 患者体内的能量代谢也有潜在的转变。

2.1 肠道菌群失调导致免疫稳态失衡并加剧肠道炎症 抗原递呈细胞 (antigen-presenting cell, APC) 主要包括单核-巨噬细胞、树突状细胞 (dendritic cell, DC)、B 细胞及内皮细胞等。在 IBD 期间, 一些病原体, 例如微生物抗原[61,62]大肠杆菌外膜蛋白、荧光假单胞菌相关蛋白、细菌鞭毛蛋白和克雷伯氏菌相关抗原等, 可被 APC 捕获并将抗原呈递给 T 细胞; 或是直接激活肠上皮细胞以及 DC 中 Toll 样受体, 诱导肿瘤坏死因子 (tumour necrosis factor, TNF)、白细胞介素 (interleukin, IL)-6、IL-1β 和 IL-18 等促炎因子的表达。被呈递的抗原信号以及诱发的炎症因子可促进幼稚 $CD4^+$ T (naive T cell, Th0) 细胞分化为效应 T 辅助细胞 (T-helper cell, Th)[63-66], 如 Th1、Th2、Th17 或 Treg (regulatory T cells) 细胞[67]。Th1 细胞主要分泌 IFN-γ、TNF 和 IL-2; Th2 细胞主要分泌 IL-4、IL-5 和 IL-13; Th17 细胞特征是分泌 IL-17A、IL-17F、IL-21 和 IL-22[68-70]。这些炎症因子对肠上皮屏障功能具有负面作用, 可导致炎症性疾病。而 Treg 细胞通过分泌抗炎细胞因子 IL-10 和 TGF-β (transforming growth factor-β), 维持肠道稳态以避免肠道炎症反应过度, 从而避免自身免疫性疾病的发生发展[71]。

为了维持体内稳态, 特定的肠道细菌会促进不同 T 细胞亚群的生长 (图 3)。例如 Clostridia 可促进 Treg 细胞的增殖[72], 并抑制 Th1 和 Th17 细胞的应答[73]; 脆弱拟杆菌中的细菌多糖可以纠正 Th1/Th2 失衡[74]。拟杆菌属细菌还可通过调节 NF-κB (nuclear factor-κB) 的活化来减轻黏膜炎症[75]。由此可见, 厚壁菌门以及拟

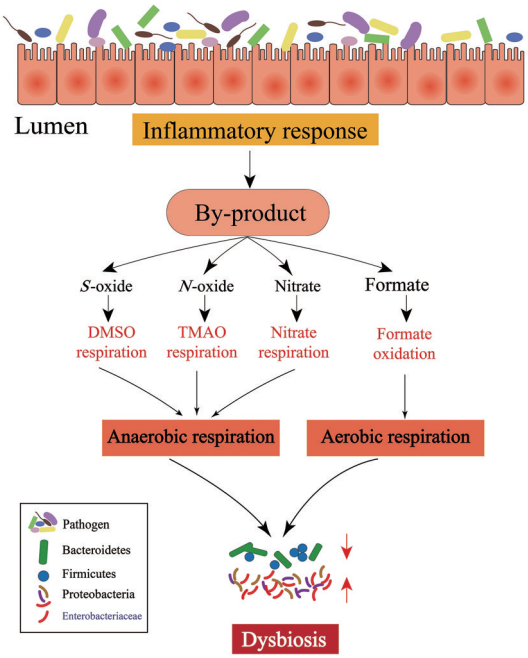

Figure 2 During gut inflammation, the inflammatory factors produced by the inflammatory response can stimulate the expression of related enzymes, thereby producing some inflammatory response products such as *S*-oxide, *N*-oxide, nitrate, and formate. These by-products can promote the growth of facultative anaerobic bacteria (Proteobacteria, especially Enterobacteriaceae) during gut inflammation. For example, Enterobacteriaceae can use these by-products to support their DMSO respiration, TMAO respiration, nitrate respiration, and formate oxidation, thereby promoting their growth. While Bacteroidetes and Firmicutes bacteria lack the ability to utilize these by-products, which puts their growth at a disadvantage and ultimately leads to gut dysbiosis. DMSO: Dimethyl *S*-oxide; TMAO: Trimethylamine *N*-oxide

杆菌门细菌的存在对维持肠道稳态具有一定意义。而IBD期间, 这两类细菌的丰度降低, 这可能也是导致肠道免疫稳态失衡的重要原因。

IBD期间肠杆菌科细菌过度生长, 会加重肠道炎症。多项研究表明, 在CD患者中可观察到黏附侵袭性大肠杆菌 (adherent-invasive *E coli*, AIEC) 水平的升高[76-78], 在UC患者中也可观察到此现象[79], 但UC中AIEC的流行程度不如CD中明确[80]。AIEC能够侵入肠道上皮细胞并在细胞内复制, 还可广泛复制到巨噬细胞中, 诱导大量的TNF-α分泌。TNF-α通过与受体TNFR1 (TNF receptor 1) 和TNFR2 (TNF receptor 2) 结合, 在细胞内激活NF-κB, 可进一步加重炎症[64,76]。多位研究者提出[81-83], 克雷伯氏菌是IBD的致病菌, 无论在患者还是动物模型中均可检测到其在肠道中的定植。Atarashi等[83]研究表明, 克雷伯氏菌可通过诱导DC产生促炎因子IL-18, 从而进一步放大了Th1细胞介导的免疫应答, 加重肠道炎症反应。大肠杆菌与克雷伯氏菌均属肠杆菌科, 此现象证实, IBD期间肠杆菌科细菌的过度生长可进一步加重肠道炎症的严重程度 (图3)。

2.2 肠道菌群失调导致SCFA含量降低并促进肠道免疫稳态失衡 前文已经讲述, 经肠道菌群代谢碳水化合物而产生的SCFA主要分为乙酸盐、丙酸盐和丁酸盐。SCFA已被证明可以改善IBD, 主要通过增强肠上皮屏障作用促进Treg的增殖分化, 激活G蛋白偶联受体, 从而抑制炎症通路如NF-κB和JAK-STAT (the Janus kinase-signal transducer and activator of transcription pathway) 来控制炎症的发生和发展[84-87]。因此SCFA是维持肠道稳态的重要代谢产物。

IBD患者与健康者相比, 其粪便样品中SCFA水平降低。研究表明, UC患者粪便样品中的乙酸盐和丙酸盐有所降低[88]。另一项研究发现IBD患者粪便样本中的丁酸盐和丙酸盐也有所降低[89]。Kumari等[90]的研究也证明了UC患者粪便中SCFA浓度降低, 尤其是丁酸盐以及乙酸盐。

同时, 也有研究者在IBD患者和相关动物模型中观察到一些产SCFA细菌的数量和多样性下降, 如产丁酸菌。人肠道中主要产丁酸菌属于厚壁菌门, 特别是*Faecalibacterium prausnitzii*、*Clostridium*菌属以及Lachnospiraceae科的*Roseburia*菌属[91,92]。Halfvarson等[36]在128名IBD患者中发现患者体内产丁酸菌*Faecalibacterium prauznitzii*的丰度明显下降。Machiels等[88]也发现类似结果, UC患者中产丁酸*Faecalibacterium prauznitzii*和*Roseburia hominis*的丰度显著降低。产丁酸菌丰度的降低与IBD期间肠道菌群紊乱有关。IBD期间, 肠腔内氧气含量上升, 专性厌氧菌数量减少, 厚壁菌门细菌的数量也有所降低, 所以产丁酸菌数量降低。

以上结果表明, IBD期间, 肠道SCFA含量的降低可能与肠道菌群紊乱密切相关。Kumari等[90]提出, 因Clostridia数量减少而导致的丁酸盐含量的降低可能是UC的病因。肠道菌群失调导致细菌生成SCFA减少, 从而促进IBD进程。

2.3 肠道菌群失调导致乳酸含量升高 研究发现, 在严重的UC患者中, 其粪便中乳酸含量较高[93]。Hove等[94]的研究也发现类似结果。Bjerrum等[95]用^{1}H NMR (proton nuclear magnetic resonance spectrometry) 光谱分析了UC和CD患者的粪便提取物代谢谱, 发现活跃期间的UC患者肠道内乳酸盐的含量更高, 导致肠道内乳酸升高的原因可能是严重的UC患者肠道内pH

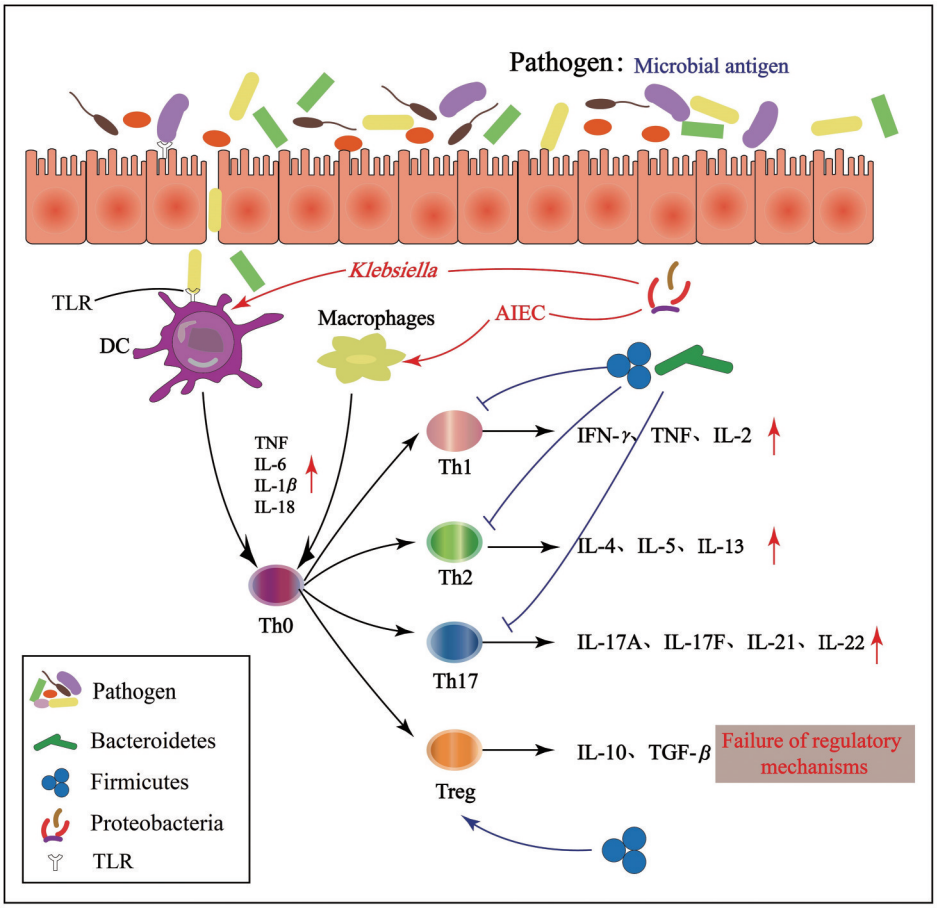

Figure 3 During IBD, some pathogenic microbial antigens can directly activate Toll-like receptors in intestinal epithelial cells or DCs, inducing the expression of some pro-inflammatory factors. These microbial antigens can also promote the differentiation of naive $CD4^+$ T cells into Th cells: Th1, Th2, Th17, or Treg cells. Inflammatory factors secreted by Th1, Th2, and Th17 cells have a negative effect on the intestinal epithelial barrier function; while IL-10 and TGF-β secreted by Treg cells can help maintain intestinal homeostasis and avoid excessive intestinal inflammation, which has a positive effect. In order to maintain homeostasis, certain gut bacteria is needed to promote the growth of different T cell subgroups. Among them, Firmicutes and Bacteroidetes bacteria can inhibit the immune responses of Th1, Th2, and Th17 cells, and Firmicutes bacteria can also promote the proliferation of Treg cells. And the Proteobacteria bacteria (AIEC, *Klebsiella*) can aggravate host inflammation by promoting the secretion of inflammatory factors. In summary, the decreased abundance of Firmicutes and Bacteroidetes, and the overgrowth of Enterobacteriaceae can further aggravate the gut inflammation. TLR: Toll-like receptor; DC: Dendritic cell; AIEC: Adherent-invasive *E. coli*; TNF: Tumor necrosis factor; IL: Interleukin; Th0: Naive T cell; Th: T-helper cell; Treg: Regulatory T cells; IFN-γ: Interferon-γ; TGF-β: Transforming growth factor-β

值的显著降低, 使细菌的代谢产物由原本的短链脂肪酸转变为乳酸[39,96]。另一个可能的原因是, IBD 期间的大量出血导致腔内氧浓度增加, 有利于兼性厌氧菌生长, 如乳酸菌和链球菌, 它们是乳酸的产生者[73], 即肠道菌群失调也可以介导乳酸的产生。

2.4 肠道菌群失调可改变肠道微环境 结肠腔的 pH 值部分取决于宿主分泌物, 部分取决于肠道微生物的发酵产物。研究表明, 健康人体结肠 pH 值接近中性, 而且人类近端结肠的 pH 值通常比远端结肠和粪便的 pH 值略低[97-99], 部分原因是饮食底物发酵的结果, 大量 SCFA 的生成导致此处 pH 值略低[100]。

而 Nugent 等[98]的研究发现: 在 40 名 UC 患者中, 一部分患者的结肠 pH 值降低; 而在 24 例 CD 患者中, 无论疾病活动或部位如何, 小肠和结肠腔的 pH 值均与健康对照组相似。Vernia 等[93]的研究发现: 在轻度 UC 患者中粪便的 pH 值正常; 但在重度结肠炎中, 粪便 pH 值降低, 暗示肠腔内 pH 值的降低。总而言之, 这些数据表明 UC 患者的结肠 pH 值降低, 特别是处于活动期的 UC, 而 CD 的肠道 pH 值尚无确切结论。

研究结果表明 UC 患者的酸性结肠腔与黏膜分泌碳酸氢盐减少、SCFA 代谢受损以及乳酸产生增加有关[93,101,102], 而 SCFA 和乳酸又与肠道菌群息息相关, 所

以肠道菌群紊乱可通过改变细菌代谢产物, 最终使肠道环境也发生相应变化。

3　通过干扰肠道细菌能量代谢干预IBD进展的治疗策略

3.1　通过干扰肠杆菌科细菌呼吸方式来减轻IBD炎症反应　在炎症过程中NO (nitric oxide) 来源于iNOS (inducible nitric oxide synthase) 的表达[103]。NO与超氧自由基反应可生成过氧亚硝酸盐, 其经进一步反应可生成硝酸盐[104]。Winter等[45]的研究表明硝酸盐呼吸可促进发炎肠道中肠杆菌科细菌大肠杆菌的生长。使用iNOS抑制剂氨基胍酸盐 (aminoguanidine hydrochloride, AG) 处理DSS (dextran sulfate sodium) 模型小鼠, 肠道内硝酸盐的产生被显著抑制, 并且大肠杆菌的生长优势减弱。Byndloss等[105]研究结果也表明, AG可消除硝酸盐呼吸作用赋予大肠杆菌的生长优势。这些研究均表明可通过介导细菌呼吸调控肠杆菌科细菌生长 (图4)。

宏基因组学分析鉴定出硝酸还原酶、TMAO还原酶和甲酸脱氢酶的活性位点含有钼蝶呤辅因子 (the molybdenum cofactor, MoCo), 即均为MoCo依赖性酶[106]。Hughes等[32]研究发现依赖于MoCo的厌氧呼吸酶和甲酸脱氢酶可以增强肠杆菌科成员在发炎肠道的适应性。钨 (tungsten, W) 在元素周期表中位于钼的正下方, 与钼化学性质相似, 可替代MoCo辅助因子中的钼, 从而使该辅助因子在肠杆菌科中失活[107], 继而可抑制肠杆菌科细菌MoCo依赖性的生长[15]。进一步研究表明, 通过W抑制MoCo依赖性酶可以抑制肠杆菌科细菌在肠道炎症微环境下的过度生长, 从而改善肠道炎症, 减轻肠组织病理损伤 (图4), 表明W可通过抑制MoCo依赖性呼吸调控肠道菌群来减轻肠道炎症[15]。

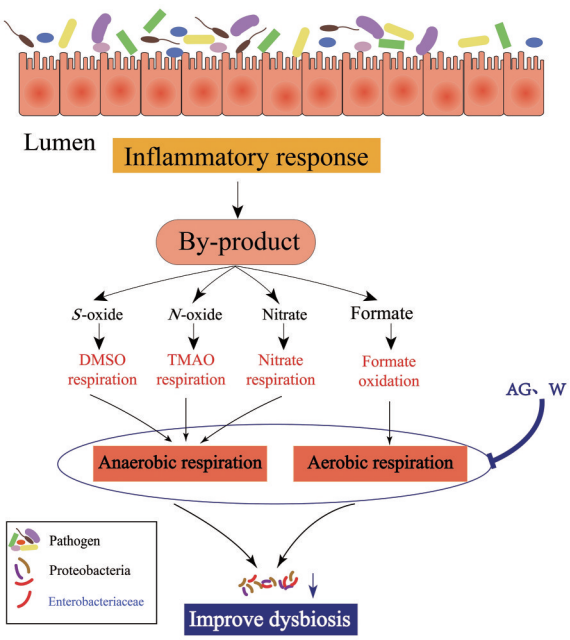

Figure 4　Schematic diagram of regulation of intestinal inflammation by interfering with the respiratory of Enterobacteriaceae bacteria. As mentioned above, during IBD, facultative anaerobes such as Enterobacteriaceae can utilize DMSO respiration, TMAO respiration, nitrate respiration, and formate oxidation to support their growth. Tungsten (W) and aminoguanidine hydrochloride (AG) can inactivate nitrate reductase, TMAO reductase, formate dehydrogenase and therefore inhibit the growth of Enterobacteriaceae, ultimately improving gut dysbiosis

兼性厌氧肠杆菌科细菌的过度生长是肠道失调的常见标志[23]。以上结果表明, 可通过干扰肠杆菌科呼吸调控肠杆菌科细菌的过度生长, 进而改善IBD。

3.2　通过增加SCFA含量发挥抗IBD作用　SCFA对维持结肠功能十分重要[108]。IBD患者中SCFA浓度降低, 而Sorbara等[109]提出总SCFA浓度与菌群内的大肠杆菌扩增之间存在负相关性, SCFA的损失可导致肠杆菌科细菌的扩增, 这提示可通过提高肠腔内SCFA浓度来进行IBD治疗。

有研究者提出用SCFA灌肠方法来治疗IBD患者, SCFA灌肠可降低远端UC患者的临床活动指数[110]。Lührs等[111]针对11例UC患者进行丁酸盐灌肠治疗, 结果表明其疾病活动指数显著下降。Scheppach等[112]在10名远端UC患者中进行了丁酸盐灌肠, 其炎症也得到改善。

除了补充外源性SCFA, 还可以通过使用益生元、益生菌补充内源性SCFA。例如补充菊粉[113]、右旋糖酐[114]和高纤维饮食[115]等益生元可改善疾病引起的消化不良症状, 增加厚壁菌门细菌数量以及增加SCFA含量, 从而达到改善IBD目的。关于益生菌, Geirnaert等[116]用产丁酸盐的细菌进行益生菌治疗, 这些细菌与活动期CD患者的粪便微生物群共培养, 结果表明培养体系中丁酸盐产量增加以及在体外可改善细胞上皮屏障功能, 这项研究证实了用益生菌治疗IBD是一种极具潜力的方式。

因此, 灌肠法可直接增加肠腔内SCFA含量, 而益生元和益生菌则通过增加产SCFA菌的数量提高SCFA含量, 最终达到抗IBD目的。

4　总结

炎症期间肠道氧含量的变化以及无氧呼吸酶、甲酸脱氢酶的过度表达可导致肠道菌群紊乱, 而肠道菌群紊乱引起的细菌代谢产物的改变也不利于肠道组织的恢复。这些最新研究表明, 可通过调控肠道菌群的能量代谢来改善肠道菌群的生态失调, 恢复肠道菌群

稳态失衡, 重建免疫稳态, 改善肠道炎症反应, 进而达到改善和治疗IBD的目的, 这也许可为IBD的治疗提供一种新的思路。

作者贡献: 李成曦为本文主要撰写者; 王颖异和李建萍负责文献查阅以及文章部分内容撰写修改; 王雨萌负责文献整理及部分绘图; 张森和段金廒为本文提出许多修改意见; 郭建明提出本文的思路并参与文章撰写及修改。

利益冲突: 所有作者均不存在利益冲突。

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