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溃疡性结肠炎发病机制研究进展

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[摘要]溃疡性结肠炎的发病率逐年增加,但发病机制仍未完全明朗,广大学者分别从遗传因素、环境因素、肠道微生态失衡、肠黏膜屏障紊乱、异常免疫应答和线粒体病等方面进行研究,为进一步了解溃疡性结肠炎可能存在的发病机理,现将其研究进展进行综述,以期更好地指导临床用药,同时为进一步研究其发病机制提供新思路。

[关键词]溃疡性结肠炎;发病机制;遗传;环境;肠道微生态;肠黏膜屏障;免疫应答;线粒体病
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Research progress on pathogenesis of ulcerative colitis

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View from specialist: It is creative, and of certain scientific and educational value.

[ABSTRACT] The incidence of ulcerative colitis is increasing year by year, yet the pathogenesis is still not clear. Many scholars have studied the genetic factors, environmental factors, intestinal microecological imbalance, intestinal mucosal barrier disorder, abnormal immune response and mitochondrial diseases, and abundant achievements have been made. In order to further understand the possible pathogenesis of ulcerative colitis, this paper reviews its research progress, in order to better guide clinical medication, and provide new ideas for further study of its pathogenesis.

[KEYWORDS] Ulcerative colitis; Pathogenesis; Heredity; Environment; Intestinal microecology; Intestinal mucosal barrier; Immune response; Mitochondrial disease

溃疡性结肠炎(ulcerative colitis, UC)是全世界常见的一种特发性炎症性肠病(inflammatory bowel disease, IBD),发病机制受多因素影响,涉及遗传易感性、上皮屏障缺陷、免疫反应失调和环境因素[1]。在发达国家发病率较高(>0.3%),在新兴工业化国家发病率增加迅速(年百分比变化增加14.9%)[2,3]。预计到2025年,全球流行率将达3 000万人[4]。UC患者发病具有年龄依赖性,在年龄分布上呈双峰,第一高峰在15~30岁,第二高峰在50~70岁[5,6]。UC患者患结直肠癌的风险增加,诊断10年后患结直肠癌的几率为2%,20年后为8%,30年后为20%~30%[1]。UC严重影响人们的生活质量,关于其发病机理的学术成果日新月异,笔者在UC领域研究多年,现将其发病机制学说作一综述。

1 遗传学

遗传学从全基因组关联(genome-wide associa-

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tion study，GWAS）、全基因组测序和精细定位3个方面对IBD进行基因层面的研究，鉴定出多个基因位点与IBD有关，其中有很大一部分基因是UC和克罗恩病（Crohn′s disease，CD）所共有的。广大学者通过潜心研究先后发现了1p36、12q15[7]基因位点；免疫球蛋白受体基因FCGR2A（rs1801274）、13q12（rs17085007）和糖蛋白基因SLC26A3（rs2108225）[8]；20q13（HNF4A）、16q22（CDH1、CDH3）和7q31（LAMB1）[9]；7q22和22q13上的（IL17REL）[10]；6q22.1[11]等基因易感位点在遗传方面影响UC的发生、发展，后续报道相继增多。目前鉴定出260种易感位点与IBD相关[12]，有研究发现163个（67%）易感性位点中就有110个是UC与CD同时相关[13]，关于不同种族之间的基因关联，UC表现出明显的种族依赖性[14]。6号染色体中编码人类白细胞抗原基因区域在UC遗传学发病机制中具有明显的特异性[15,16]，新的研究发现在腺苷酸环化酶-7中发现了一个0.6%频率的错义变体，它使溃疡性结肠炎的风险增加了一倍[17]，UC患者家族遗传史为8%～14%，一级亲属患该病的风险是常人的4倍[18,19]。使用免疫芯片（iChip）和估算的GWAS数据分别解释了15%和19%的易感性变化，密集的iChip区域解释了iChip和GWAS数据中10%和9%的单核苷酸多态性遗传率[20]。可见，与UC有关的易感基因位点从遗传学解释了UC可能存在的发病机制。

2 环境因素

2.1 饮食

食用蔬菜和水果与UC和CD的风险呈负相关[21]，大量饮用饮料可能会增加UC的风险[22]，酒精可直接引起黏膜损伤，增加细菌移位，是UC的危险因素[23]，而咖啡因通过下调壳多糖酶3样蛋白-1能推迟葡聚糖硫酸钠诱导的小鼠结肠炎[24]，喝茶能降低UC的风险[22,25,26]。肉食消费者比素食消费者患UC的风险显著增加，而肉食消费者中红肉与UC的关系更加显著[27]。饮食中n-3多不饱和脂肪酸（n-3 polyunsaturated fatty acids，n-3 PUFAs）的含量与UC程负相关，进食含n-3 PUFAs越丰富的食物，患UC的风险越低[28]，人体必需脂肪酸OMEGA-3（a-亚麻仁油酸）和OMEGA-6（亚油烯酸）是保证健康的必需品，机体不能制造，必须从外源性饮食中获取，但过多地摄入OMEGA-3和OMEGA-6会增加UC的发病风险[29]。饮食中的蛋白质与UC的关系微妙，除鸡蛋和奶制品以外的动物蛋白中，大量食用肉类或鱼类与IBD风险相关[30]。H_2S在低水平时具有抗炎作用，而浓度较高时就会作为毒素损伤肠道黏膜，富含硫的食物以及硫酸盐还原菌的丰富与UC的发展和病情的活跃有关，虽然结肠腔内的代谢环境受多因素影响，但是过多地摄入含硫的食物会损伤肠腔的黏膜屏障[31-33]。

2.2 吸烟

吸烟会显著增加肺癌的发病风险，影响心肺功能[34]，但意外的是，吸烟能改善急性期UC的症状，降低其发病率[35]。后续的研究发现吸烟可能是通过增加肠黏膜内受损的血管的灌注从而改善UC急性期的症状，但在UC缓解期则会使症状加重[36]。吸烟能预防UC的发生，并缩短其病程，降低结肠切除术的手术率[37]。新的研究发现，有吸烟史但目前未吸烟的人较从未吸烟的人患病率高；当前吸烟者患UC的风险显著降低，在目前的吸烟者中，UC发展的风险与终生累积吸烟量无关，至于吸烟对UC有预防作用也仅在男性人群中得到了验证[38]。后来学者又发现吸烟年龄与UC发病风险之间存在正向因果关系[39]，虽然吸烟对UC有保护因素，但吸烟的风险远远超过任何可能的益处，因此，医生还是建议、鼓励和帮助吸烟的UC患者戒烟。

2.3 阑尾

阑尾切除史是UC的危险因素[40]，同时阑尾切除能增加UC的肠外症状[41]。阑尾淋巴滤泡在出生5 d后开始发育，逐渐成熟，是防御肠腔微生物感染的重要免疫器官，阑尾通过向肠道提供一个共生生物膜对抗肠道炎症活动因子、修复肠腔的微小损害，维持肠道内环境的稳定，同时阑尾也是维持肠外黏膜免疫组织多样化的必要条件[42]。组织学分析显示，衰老可引起阑尾淋巴组织脂肪变性，UC患者的阑尾淋巴组织更易发生脂肪变性，阑尾淋巴组织变性失活后会进一步加剧UC的发生、发展[43]。通过对肠道菌群和肠黏膜免疫系统的深入了解，阑尾被认为是维持肠道菌群稳态的“护城河”，正常的肠道菌群为机体提供了丰富的营养物质，保护肠腔免受致病菌的损害[44]。由此可见，阑尾不仅通过淋巴组织修复肠腔炎症损害，而且通过维持肠道微生物多样性，防止UC的发生、发展。

3 肠道微生态

越来越多的研究发现肠道菌群失调在UC的发病机制中起重要作用，肠道微生物群是一个复杂而丰富的生态系统，结肠为微生物群提供了丰富的营养环境而成为肠道菌群的主要定居场所[45]，肠道微生物群通过代谢产物向宿主提供能量和营养物质[46]，保护宿主[47]并调节宿主的免疫系统[48]。肠道

细菌在消化食糜中的纤维素时产生短链脂肪酸(SCFA),SCFA能有效对抗UC的炎症反应[49],同时肠道微生物群能促进肠腔分泌上皮细胞修复因子白细胞介素-18,增加上皮细胞的完整性,促进杯状细胞产生黏蛋白进一步加固细胞间的紧密连接[50],预防致病菌的入侵。肠道微生物群通过介导多种相关的免疫炎症途径,参与UC的发生、发展。肠腔上皮屏障是抵御细菌入侵的第一道防线,结肠上皮屏障损伤会导致肠腔通透性增加,从而引起宿主免疫反应发生变化[51]。随着UC肠腔黏膜炎症的产生,抗原呈递细胞的数量增加,T细胞的稳态失衡,导致炎症进一步加剧。肠道微生态失衡引起T细胞亚群介导非特异性Th2免疫反应释放白细胞介素-13并损伤肠腔上皮细胞[52]。同时,在UC的发展过程中肠系膜淋巴结微生物群也扮演一个重要的角色,UC和CD肠系膜淋巴结微生物群之间存在明显差异,这一发现有助于鉴别诊断UC[53]。尽管UC的发病机制还未完全清楚,但肠道微生态失衡从多个层面影响UC的发生。

4 黏膜屏障

肠黏膜屏障主要由微生物群、黏液层、抗菌肽、分泌型免疫球蛋白A(sIgA)、上皮细胞层和黏膜免疫系统组成,肠黏膜屏障功能(MBF)[54]是指肠腔吸收营养物质、容纳腔内微生物和分子的能力[55]。MBF的核心组成部分是上皮细胞层,上皮细胞通过细胞间的紧密连接和细胞间质的有序填充维持肠腔内部环境的稳定,保证各种物质的有序运输,上皮外侧有黏蛋白、sIgA和抗菌肽形成的黏液层进一步加固,内侧有各种免疫细胞监测,各层有机协调,保证了MBF的完整[54,56,57]。MBF的改变主要表现在透性增加和、或细菌移位,这与UC的发生密切相关[54,55]。研究发现肠道通透性增加发生在结肠疾病发展之前[58],肠道菌群的移位和丰度的改变通过影响免疫系统而破坏肠道屏障[59]。可见MBF通过多维度影响UC的发生。

5 免疫应答

UC的免疫应答和炎症途径研究表明,抗原呈递细胞、辅助性T细胞、调节性T细胞和自然杀伤性T细胞以及促炎细胞因子上调、抗炎细胞因子下调在UC黏膜损伤中发挥重要作用[60]。效应T细胞和调节T细胞维持相对平衡在肠道免疫和炎症中占主导地位[61],自然杀伤细胞(NKT)是一类特殊的淋巴细胞,其产生的T-2辅助细胞(Th2细胞)因子介导UC的发生[62,63]。中性粒细胞作为先天免疫的效应细胞,是防御病原体入侵的活性细胞,不受调节的中性粒细胞炎症机制会加速组织损伤进一步破坏肠道内环境的平衡,中性粒细胞功能异常可作为肠道慢性炎症的早期筛查,同时还能反映适应性免疫功能,肠黏膜中的中性粒细胞浸润是UC病理生理学的一个特征,中性粒细胞迁移的程度和时间与疾病的严重程度相关,活化的中性粒细胞通过上皮细胞间隙迁移至炎症部位,并聚积在隐窝腔引起隐窝脓肿,隐窝脓肿是UC的特征性组织学病理改变[64]。新的研究从微生物与免疫的角度出发,创造性地提出了“微生物群滋养免疫”,微生物群滋养免疫赋予“定植抗性”的免疫机制,定植抗性则是由定植在肠腔的微生物群所表现出来的免疫功能,破坏微生物群滋养免疫可引起肠道炎症加剧[65]。有学者利用免疫细胞分析法分析了24种免疫细胞的组分,结果发现有18种免疫细胞在UC患者中发生了显著变化,UC患者样本中细胞毒性T细胞、耗竭T细胞、1型调节性T细胞、诱导性调节性T细胞、T-1辅助细胞、中枢记忆性T细胞、树突状细胞、B细胞、单核细胞和巨噬细胞的丰度普遍高于健康对照组;相比之下,UC患者样本中幼稚$CD8^+$T细胞、Th2细胞、效应性记忆T细胞、NKT细胞、黏膜相关不变T细胞、自然杀伤细胞、中性粒细胞和$CD8^+$T细胞的丰度低于健康对照组[66]。可见,免疫机制通过多维度影响UC的发生。

6 线粒体病

线粒体病以自身稳态失衡为主导,表现出能量产生缺陷、氧化应激增加以及释放相关促炎性损伤分子[12]。活动期UC患者的线粒体基因和功能降低,MCJ是一种线粒体内膜蛋白,在UC患者中MCJ水平降低,TIMP-3因子表达升高[67]。线粒体基因组编码13个调节ATP产生的基因,这些基因在UC中都显著减少[68]。UC是结直肠癌(carcinoma of colon and rectum, CRC)的危险因素[69],UC患者10年后并发CRC的风险开始增加[70],UC患者患CRC的风险是普通人的2.4倍[71],线粒体DNA(mtDNA)突变在溃疡性结肠炎癌前病变中很常见,mtDNA突变增加了UC患CRC的风险[72],mtDNA变异与复杂的自身免疫性疾病和炎症性疾病有关,mtDNA多态性和单倍群可能独立或协同作用于核遗传因子,而线粒体基因间的相互作用可能为UC的部分遗传缺失做出合理解释[73],多药耐药-1(MDR1)基因编码一种在结肠中高度表达的α-TP依赖性外排转运蛋白,MDR1对线粒体有保护作用,若MDR1缺乏则可导致线粒体功能障碍,导致活性氧增加,最终引起UC的发生[74]。细胞外游离

状态DNA(cfDNA)浓度增加与UC患者的临床严重程度呈正相关[75],在多种炎症性疾病和急性损伤中观察到线粒体来源的cfDNA水平升高[76-79]。可见,线粒体结构和功能的改变在UC的发病机制中起重要作用。

虽然UC的发病机制尚未完全明确,广大学者分别从遗传、环境、肠道微生态、肠黏膜屏障、免疫应答和线粒体病等方面展开研究,以期能探明UC的发病机理。笔者通过阅读相关文献,将广大学者关于UC的发病机理综述如上,望各位同仁斟酌损益,略有所得。

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