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文献综述 REVIEW

IL-33/ST2系统在溃疡性结肠炎中的免疫调节

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Immune modulation by the IL-33/ST2 system in ulcerative colitis

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Abstract
The immune system prevents pathogens from entering and spreading in the body. Dysfunction of the immune system can activate an intestinal inflammatory response, leading to chronic diseases including inflammatory bowel diseases (IBD). Ulcerative colitis (UC) is a form of IBD of unknown etiology with increasing prevalence. There is an imbalance in the interleukin-33/homolog of sulfotransferase 2 (IL-33/ST2) axis in UC intestinal mucosa. This paper reviews the role of the IL-33/ST2 system in immunity of the intestinal mucosa and its importance in IBD, especially UC.

Key Words: IL-33/ST2 system; Ulcerative colitis; Immune modulation

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摘要
免疫系统防止病原体进入人体及体内传播, 免疫系统受损可以引起肠道炎症反应, 导致包括炎症性肠病(inflammatory bowel diseases, IBD)在内的慢性疾病. 溃疡性结肠炎(ulcerative colitis, UC)是一种患病率增加且病因不明的炎症性肠病, UC患者肠黏膜中IL-33/ST2轴失衡. 本文就IL-33/ST2系统在肠道免疫中的作用及在IBD特别是UC中的重要性进行综述.

关键词: IL-33/ST2系统; 溃疡性结肠炎; 免疫调节

核心提示: 肠道固有免疫系统防止病原体入侵, 免疫系统受损可引起肠道炎症反应. 总结各项研究结果认为: IL-33/ST2系统在上皮细胞炎症中具有抗炎和促炎的双重作用, 在炎症性肠病(inflammatory bowel diseases)特别是溃疡性结肠炎的病理过程中起到重要作用.

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0 引言
胃肠道自口腔延伸至肛门, 内含大量共生菌, 对食物进行物理性和化学性消化并摄取养分. 肠道免疫系统能识别微生物及食物蛋白质, 避免良性抗原引起炎症反应, 称为肠耐受. 该过程被破坏, 可激活免疫反应, 导致疾病发生, 如食物过敏、乳糜泻和包括溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(Crohn's disease, CD)在内的炎症性肠病(inflammatory bowel diseases, IBD). UC是发生在结肠和直肠的炎症和黏膜溃疡, 而CD则累及全胃肠道. 近年来, 白介素33(in-

■背景资料
炎症性肠病(inflammatory bowel diseases, IBD)是一种全球性疾病, 病因不明且患病率逐年增加. IBD的发病机制主要概括为: 环境因素作用于遗传易感因素, 在肠道菌群的参与下, 启动肠道免疫和非免疫系统, 免疫炎症反应表现为过度亢进和难以自限.

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■研发前沿
研究认为, IL-33/ST2系统是上皮细胞炎症反应平衡的关键, 本文主要阐述了IL-33/ST2系统在IBD特别是UC中的作用, 旨在为UC的治疗提供指导作用.

terleukin-33, IL-33)及其受体(homolog of sulfotransferase 2, ST2)被认为是上皮细胞炎症反应平衡的关键, UC患者血清ST2以及肠黏膜IL-33水平均增高[1], 血清ST2水平与疾病严重程度相关, 可能是疾病活动的标志[2]. 本文中, 我们将评价IL-33/ST2系统在肠黏膜和IBD特别是UC固有免疫中的作用.

1 肠道免疫和UC免疫改变

肠道免疫系统包括黏液层、黏膜上皮、固有层三道屏障, 屏障被破坏时, 免疫耐受性将会受到影响.

胃肠道表面覆盖一层黏液, 保护上皮细胞免受肠道抗原伤害, 为食团推进提供润滑作用. 胃肠道不同区域黏液数量和蛋白质组成不同, 由于细菌含量较高, 结肠黏液最为丰富, 主要成分为具有不同亚型的黏蛋白(mucin, MUC). 小肠中含量最丰富的黏蛋白包括MUC2、MUC3和MUC6, 结肠主要是MUC2, 胃肠道细胞也表达其他黏蛋白如MUC1、MUC3、MUC4等[3]. 不同MUC亚型导致黏液层与上皮细胞黏附性不一. MUC1牢固吸附于上皮层, 防止细菌入侵, MUC1缺陷小鼠($MUC1^{-/-}$)无法清除空肠弯曲菌, 导致全身性感染[4]. 杯状细胞合成分泌一些易清除黏液层的MUCS, 其分化部分依赖细菌的存在, 由于微生物更多, 结肠杯状细胞比十二指肠丰富. MUC2在结肠内最为丰富, 加之硫酸和唾液, 能结合水和病原体. 高尔基体内MUC2生物合成酶缺失可导致小鼠结肠炎发生发展[5]. 此外, MUC2可被肠道菌代谢, 作为一种能量来源[6]. $MUC2^{-/-}$动物自发出现结肠黏膜炎症, 有感染性腹泻、直肠脱垂甚至癌症, 与人类UC类似[7]. 经葡聚糖硫酸钠(dextran sulfate sodium, DSS)处理的野生型小鼠, 黏液层厚度变薄, 肠上皮对细菌通透性增加, 发展为结肠炎[8]. CD患者回肠MUC1和MUC4水平下降, 而MUC2、MUC5、MUC7和MUC6在病变处检测不到[9]. UC患者O-糖基化、硫酸化及MUC2的表达减少. 其他肠黏液蛋白成分包括三叶肽3(trefoil factor 3, TFF-3)、抵抗素样分子β(resistin like molecule-β, RELM-β)和蛋白质结合的Fcγ(Fcγ protein bindin, Fcgbp). TFF-3属于三叶因子家族, 存在于杯状细胞, 能保护上皮细胞、促进细胞迁移及阻断细胞凋亡, 与 MUC2蛋白共表达时, 可以结合到MUC2D区域, 黏液黏度增加. $TFF\text{-}3^{-/-}$小鼠比野生型小鼠更易形成DSS诱导的结肠炎, 动物过度表达TFF-3不易出现损伤和肠溃疡[10]. 血清TFF-3水平在活动期UC患者升高, 经糖皮质激素治疗后则下降, 但增加的血清TFF-3水平不能反映作为细胞凋亡信号的肠黏膜TFF-3含量[11]. RELM-β是杯状细胞分泌的富含半胱氨酸的蛋白质, 受到细菌和寄生虫刺激时, 诱导MUC2分泌增加. Fcgbp也由杯状细胞分泌, 通过二硫键与MUC2和TFF-3结合, 形成更大的黏液层凝聚力和黏度. Fcgbp结合到免疫球蛋白IgG Fc部分, 在炎症反应中固定于黏液层, 提高细菌的调理素作用[12].

肠黏膜上皮包括肠上皮细胞、杯状细胞和肠内分泌细胞, 通过紧密连接结合, 分隔身体和肠内容物. 肠上皮细胞吸收养分并分泌杀菌蛋白如防御素与抗菌肽; 杯状细胞分泌黏液; 肠内分泌细胞产生激素如5-羟色胺、P物质、促胰液素. 这些细胞和潘氏细胞位于隐窝基底, 分泌α防御素、磷脂酶A2、溶菌酶和其他抗菌肽[13]. 参与肠道免疫功能的还有存在于小肠淋巴滤泡中M细胞, 可转运和呈递微生物衍生的抗原给树突状细胞和巨噬细胞. 吞噬细胞表达受体感受病原相关分子模式(pathogen associated molecular patterns, PAMPs), 识别自体和异体分子. 病原体识别受体(pathogen recognition receptors, PRRs)表达于上皮细胞、巨噬细胞、中性粒细胞、树突状细胞, 激活吞噬作用、趋化性及效应分子产生, 有助于迟发免疫应答. 肠道PRRs中最重要的是膜Toll样受体(Toll-like receptor, TLRs)和细胞内核苷酸寡聚化结构域受体(nucleotide oligomerization domain receptor, NOD), TLR2、TLR4和TLR5分布于细胞表面, TLR3、TLR7和TLR9分布于胞内体膜, 识别某些PAMPs并激活NF-κB信号通路诱导促炎性基因. TLRs在肠腺隐窝特异表达[14]. TLR4在高尔基体内聚和上皮细胞辅助受体MD2低表达提示可能存在接触肠道抗原后防止TLRs激活促炎症信号的其他机制. TLR9位于肠上皮细胞质膜, 激活耐受性反应或核因子κB(nuclear factor kappa B, NF-κB)相关促炎性通路[15]. NOD受体能结合微生物产物. 这些受体表达在暴露于细菌的上皮细胞、巨噬细胞和树突状细胞中, 激活NF-κB和丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)途径协同TLRs产生细胞因子[16]. 报道称, UC患者肠上皮细胞细胞比例、杯状细胞含量与内质网应激反应均有变化, 对照组杯状细胞占结肠上皮细胞总数的55%, 活动期UC患者占33%[17]. 潘氏细胞通常存在于小肠中, 而UC患者结肠存在异位潘氏细胞, 分泌异常抗

菌蛋白如β-防御素和抗菌肽. UC患者肠黏膜存在非典型杯状细胞蛋白质, 内质网应激水平高于对照组[18], 可能改变细胞内钙水平和NF-κB信号通路的激活, 增加上皮通透性.

固有层作为肠道第三道屏障, 含有巨噬细胞、中性粒细胞、多形核细胞、树突状细胞、自然杀伤细胞和淋巴细胞等. 树突状细胞是粒细胞吞噬细胞, 能维持上皮完整性、吞噬管腔抗原, 在结合到CX3CR1的上皮细胞质膜表达, 还通过胞饮作用吞噬细胞外液, 参与淋巴结内T细胞抗原呈递, 启动适应性免疫反应, 包括免疫反应之间的中心环节[19]. IBD患者具有非典型树突状细胞表型[20], 树突状细胞聚集于发炎的肠道组织中, 可能与趋化因子CCL20表达增加有关, 该分子通过NF-κB调节诱导树突状和T细胞聚集. 与缓解期患者或健康人相比, UC和CD患者结肠$CD11c^+$树突状细胞表达TLR2、TLR4、CD40水平升高[21]. IBD患者树突状细胞识别细菌产物能力增强, 引起对共生细菌免疫应答的激活, 导致肠耐受缺失. 巨噬细胞和中性粒细胞、树突状细胞都是免疫系统主要的吞噬细胞, 通过吞噬体和溶酶体内的溶酶体酶降解捕获的病原体, 降解的肽片段结合到细胞表面的MHC-Ⅱ类分子, 结合树突状细胞, 发起抗原呈递. 单核细胞是存在于外周血的未成熟型巨噬细胞, 受到趋化因子IL-8和TGF-β刺激后成熟并迁移到组织, 活化后表达一些PRRs增加[22,23]. 肠道巨噬细胞有耐受性特点, PRRs和其他表面蛋白如CD14、CD80和CD86表达较低[24], 分泌IL-1、IL-6、IL-8数量有限, 当暴露于微生物时可表达高水平IL-1前体, 表明他们对黏膜耐受有积极作用[25]. 肠巨噬细胞与CX3CL1含量有关[26], 缺乏趋化因子受体的小鼠($CX3CR1^{-/-}$)由于巨噬细胞无法聚集到固有层易受到沙门氏菌感染[27]. IBD患者肠巨噬细胞分子表面CD14含量增加, NF-κB转录途径活化, 失去肠道免疫耐受. 粒细胞包括中性、嗜碱性及嗜酸性粒细胞. 中性粒细胞含量最丰富, 具有吞噬活性, 在免疫反应中有重要作用, 活化的中性粒细胞分泌抗菌分子、活性氧、炎性细胞因子和趋化因子, 吸引树突状细胞和巨噬细胞到黏膜[28], 与细菌成分相互作用. 中性粒细胞特异趋化因子IL-8主要由上皮细胞产生, IBD患者受损的上皮细胞IL-8分泌升高, 大量中性粒细胞聚集, 加剧肠道黏膜免疫应答[29]. 钙卫蛋白在IBD中浓度显著增加, 粪便钙卫蛋白可作为患者结肠镜检查前的筛选试验, 也作为监测UC和CD疗效的指标[30]. 嗜酸和嗜碱性粒细胞分泌的促炎性细胞因子及蛋白质对宿主防御寄生虫非常重要. IBD患者中嗜酸和嗜碱性粒细胞相关趋化因子如MCP-3表达增加, 表明他们在IBD中可能有重要作用[31]. IBD患者粪便嗜酸性粒细胞阳离子蛋白含量增加、小肠液及外周血嗜酸性粒细胞颗粒蛋白浓度增加以及活动期CD患者肠黏膜嗜酸性粒细胞含量增加[32]. 肥大细胞保护黏膜免受病原体和寄生虫损害, 在过敏性反应中有重要作用, 胞浆颗粒中含有大量的组胺、类胰蛋白酶、前列腺素PGD2、白三烯LTC4和趋化因子, 类胰蛋白酶通过激活PAR-2受体调节细胞间紧密连接, 影响肠上皮通透性. 活动期IBD患者肠黏膜肥大细胞数增加, 而对照组和缓解期患者尽管受损的黏膜组织可能有少量肥大细胞, 但细胞含量无显著差异[33]. 冷加压试验中, 缓解期IBD患者肥大细胞活化增加, 提示其活化与应激有关[34]. 上皮内γ/δT淋巴细胞是颗粒状胞浆的淋巴样细胞, 位于各器官尤其是肠、皮肤、肺和生殖道的上皮细胞. IBD患者上皮内淋巴细胞(intraepithelial lymphocytes, IELs)活化增加、IL-23产生和趋化因子含量增加, 导致干扰素-γ(interferon-γ, IFN-γ)、肿瘤坏死因子α(tumor necrosis factor alpha, TNF-α)、IL-2增加[35]. 为缺乏上皮内淋巴细胞γ/δ的结肠炎小鼠接种IELs, 可导致IFN-γ、TNF-α减少和TGF-β水平增加[36], 表明这些细胞在黏膜耐受中起到关键作用. 自然杀伤(natural killer, NK)细胞是一种颗粒状胞浆的淋巴样细胞, 能识别感染病毒或其他病原体的异常细胞, 活化后释放穿孔素和酶, 激活细胞凋亡. IBD患者肠黏膜固有层NK细胞数量增加[37], 可能是IBD患者肠黏膜细胞因子和生长因子含量失衡所致. NK细胞发育的关键分子如IL-15、IL-21和IL-23和其同源受体在UC患者肠黏膜中升高, 可能部分导致NK细胞活化. 有研究以IL-21R为靶点治疗IBD, 效果较好[38].

■创新盘点
关于IBD免疫调节异常的研究较多, 但并无统一定论, 目前大家逐渐关注到IL-33/ST2系统在IBD特别是UC中的调节作用, 我们对此进行总结阐述, 便于读者了解.

2 IL-33/ST2系统在UC中的作用

近年来, IL-33/ST2系统在IBD中的作用越来越受到重视. 研究认为, UC患者肠黏膜IL-33及ST2表达增加[1,39]. 血清可溶性ST2亚型(sST2)与肠黏膜ST2均与疾病严重程度相关, 作为反映UC活动的标志物[2]. IL-33和IL-1α、IL-1β及IL-18一样, 属于IL-1超家族, 分布在内皮细胞、成纤维细胞、平滑肌细胞、巨噬细胞和树突状细胞, 而ST2主要分布于肥大细胞、巨噬细胞和Th2淋巴

■应用要点
我们阅读总结了近年来部分相关文献, 对肠道固有免疫调节及IL-33/ST2在IBD特别是UC中的作用进行阐述, 旨在让大家认识、了解该系统, 对以后选择新的治疗靶点提供思路.

细胞[40]. *ST2*基因属于IL-1/TLRs受体超家族, 转录产品包括四个亚型: ST2L、sST2、ST2LV和ST2V, ST2L和sST2最丰富. IL-33识别ST2L, 促进与IL-1受体辅助蛋白受体二聚化, 受体复合物胞内TIR结构域磷酸化, 吸引MyD88、TRAF6和IRAK1-4聚集, 激活NF-κB和MAPK途径[41]. ST2也可与第二受体家族受体SIGIRR形成二聚体, 负向调节IL-33/ST2信号通路[42]. 也有研究认为, IL-33移位至胞核隔离NF-κB, 抑制转录活性, 可能在上皮细胞内作为转录因子[43], 故IL-33具有促炎和抗炎的双重作用. UC患者IL-33/ST2系统失衡, 肠黏膜IL-33的主要来源是上皮细胞和肌纤维母细胞, 主要靶细胞存在于固有层. 因此, IL-33对UC的影响主要是对上皮和固有层细胞及对分泌黏液质量的影响.

IBD患者黏蛋白表达失调, 可能源于细胞因子失衡. Th1(IL-2、IL-12、IFN-γ和TNF-α)和Th2型细胞因子(IL-4、IL-5和IL-13)在IBD患者表达上调, 激发不同转录因子途径如JAK/STAT和NF-κB, 诱导黏液分泌[44]. IL-33处理后小鼠肠道杯状细胞黏蛋白含量增加, 故IL-33可能也有黏膜分泌活性. *MUC2*基因启动区包含转录因子结合位点, 这个过程可能涉及NF-κB活化[45]. IL-33调节肠道杯状细胞的分泌产物特别是TFF-3和RELM-β的机制尚无报道, 但UC患者肠黏膜中IL-33和TFF-3含量异常[11]. 固有层细胞也是IL-33的来源, LPS刺激后小鼠巨噬细胞IL-33转录和细胞外液的蛋白水平增加, IL-33$^{-/-}$巨噬细胞经LPS刺激后比野生型巨噬细胞分泌IL-6和TNF-α水平降低, 用特异性抗体拮抗野生型巨噬细胞IL-33, 可部分恢复LPS诱导的细胞因子分泌[46]. IL-33在细胞因子如TNF-α、IL-1β、CXCL1和CCL3对中性粒细胞的趋化效应中起协同作用, 并直接调节中性粒细胞动员[47]. IL-33刺激后, 肥大细胞和嗜碱性粒细胞表面ST2表达增加, 分泌Th2细胞因子和趋化因子, 协同增加IgE介导的脱颗粒. 此外, IL-33诱导趋化因子介导的肥大细胞迁移[48]. 嗜酸性粒细胞表面表达低水平ST2, IL-33刺激后可诱导IL-8、IL-3、IL-5和GM-CSF(granulocyte macrophage colony stimulating factor)的产生, CD11b表达增加, 但趋化因子介导的细胞迁移未受影响[49]. 受到IL-33、IL-6、CD86和MHC Ⅱ刺激时, 树突细胞表达ST2增加[50], 使幼稚T细胞分化成Th2细胞, 直接刺激表面缺乏ST2表达的T细胞并不会出现这种情况.

近年来, 有关IL-33/ST2在上皮细胞的作用及其表达失衡对组织功能影响的研究取得了巨大进步, 但该系统在IBD病理过程的许多问题没有得到合理解释, 了解该炎症通路在肠道炎症中的影响, 对疾病的评估、治疗有一定价值.

3 结论

IL-33/ST2系统参与肠道免疫系统的调节, 被认为是上皮细胞炎症反应平衡的关键, 在UC等慢性炎症性肠病中, 主要通过对上皮细胞、固有层细胞及分泌黏液质量的影响起到促炎和抗炎的双重作用, 如何利用该靶点进行治疗是我们以后研究的方向.

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