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文献综述 REVIEW

肠神经胶质细胞在炎症性肠病发生发展中作用的研究进展

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■背景资料
炎症性肠病(inflammatory bowel disease, IBD)包括克罗恩病和溃疡性结肠炎, 其病因和发病机制目前尚不清楚, 大多数学者认为持续肠道感染、肠黏膜屏障缺损、肠黏膜免疫调节异常、遗传和环境等因素共同参与了其发生过程. 肠神经胶质细胞(enteric glial cell, EGC)可通过自身及分泌的细胞因子等在维护肠黏膜屏障完整、纠正肠黏膜免疫异常方面起重要的作用.

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Role of enteric glial cells in inflammatory bowel disease

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Abstract
The etiology and pathogenesis of inflammatory bowel disease are currently unknown. It is generally believed that persistent intestinal infection, intestinal mucosal barrier defect, intestinal mucosal immune dysregulation and genetic and environmental factors together contribute to the pathogenesis of inflammatory bowel disease. Several studies have demonstrated that enteric glial cells play an important role in maintaining the integrity of intestinal mucosal barrier. Enteric glial cell deficiency in mice leads to the destruction of integrity of intestinal mucosal barrier, increases mucosal permeability, and results in intestinal inflammation, hemorrhage and necrosis. This article discusses the role of enteric glial cells in the occurrence and development of inflammatory bowel disease.

Key Words: Enteric glial cells; Inflammatory bowel disease; Ulcerative colitis; Crohn's disease

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摘要
目前炎症性肠病(inflammatory bowel disease, IBD)病因及发病机制尚不清楚, 大多数学者认为持续肠道感染、肠黏膜屏障缺损、肠黏膜免疫调节异常、遗传和环境等因素共同参与了其发生过程. 近来有研究显示肠神经胶质细胞在维持肠黏膜屏障的完整方面发挥重要作用, 肠神经胶质细胞的缺失会导致小鼠肠黏膜屏障完整性丧失, 通透性增加, 产生肠道炎症, 出血及坏死等IBD的表现. 本文就肠神经胶质细胞在IBD发生发展中的作用研究现状作一综述.

关键词: 肠神经胶质细胞; 炎症性肠病; 溃疡性结肠炎; 克罗恩病

核心提示: 神经胶质细胞(enteric glial cell, EGC)可能在肠道炎症-不典型增生-癌变演进序列中发挥重要作用, 肠道慢性炎症时EGC网络逐渐遭破坏, EGC数量减少, 保护性作用减弱, 使得炎-癌进程得以进行. 如果在炎症性肠病(inflammatory bowel disease)发病后, 能够保护EGC或者适时补充EGC分泌的各种因子, 很有可能阻断炎-癌进程, 缓解肠道炎症反应, 减小癌变几率.

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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

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炎(ulcerative colitis, UC), 其病因和发病机制尚不清楚, 目前大多学者认为持续肠道感染、肠黏膜屏障缺损、肠黏膜免疫调节异常、遗传和环境等因素共同参与了IBD发生过程[1-4]. 研究发现肠神经胶质细胞(enteric glial cell, EGC)的缺失会导致肠黏膜屏障完整性丧失, 通透性增加, 产生肠道炎症, 出血及坏死等炎症性肠病的表现[5-8], 提示EGC在维持肠黏膜屏障的完整性、IBD发病方面发挥重要作用. 此外, 越来越多研究表明EGC在肠道神经-内分泌-免疫网络中扮演重要角色, 可能通过自身及分泌的神经营养因子、神经多肽及细胞因子等对IBD的发生发展有错综复杂的影响[9,10], 现就其在IBD发生发展中的作用研究进展作一综述.

1 EGC概述

EGC来源于神经外胚层, 是肠神经系统(enteric nervous system, ENS)的主要成员之一, 主要分布于肠壁黏膜下丛和肠肌间丛神经节[11]. 此外, EGC伸出多个突起与神经元和EGC之间相互连接, 在整个胃肠道形成广泛的网络[12], 不仅分布于肌层、黏膜下层, 黏膜固有层也有, 最远可达肠绒毛的顶端[13-15]. 成熟EGC表达肠胶质原纤维酸性蛋白(glial fibrillary acidic protein, GFAP)、钙结合蛋白S100B、p57NGFR、Sox8/9/10等[16,17]. 先前认为EGC主要有营养和支持神经元, 参与肠道内神经活动的整合和调节, 维持内环境稳定, 调节肠黏膜血管等功能[18,19]. 而现在研究证实EGC缺失会导致肠黏膜屏障破坏, 通透性增加, 产生严重的肠道炎症反应[8,20]. EGC还可通过分泌多种神经营养因子、神经多肽和细胞因子, 包括GDNF、NGF、neurotrophin-3、GSNO、P物质、NPY、CCK、VIP、甘丙肽、生长抑素、白介素-1β(interleukin-1β, IL-1β)、IL-6和肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)等, 在IBD的发生发展中发挥更为广泛的作用[21-24].

2 EGC与IBD

2.1 IBD时EGC的改变 研究显示IBD时EGC的数目显著减少[21,25], 而在实验性结肠炎及IBD患者的活检标本中发现EGC明显增生, 在UC及CD的炎性肠段中EGC增生较非炎性肠段显著, 且UC较CD患者EGC增生显著[24,26]. 提示IBD早期, 受漏过黏膜屏障致炎物质及免疫细胞分泌的各种炎性因子的刺激, EGC反应性增生肥大, 合成分泌大量神经营养因子或营养素, 维护肠黏膜屏障, 抑制炎症反应. 随着炎症的持续存在, EGC网络逐渐遭到破坏, EGC数目减少, 保护性作用减弱, 使得炎症反应持续加重, 甚至癌变.

2.2 IBD时EGC源性神经营养因子、神经多肽及细胞因子分泌异常 来源于EGC的神经营养因子包括神经生长因子(nerve growth factor, NGF)、胶质细胞源性神经营养因子(glial-cell-line-derived neurotrophic factor, GDNF)和神经营养因子-3(neurotrophin-3)等[27,28]. 早先研究表明在变态反应性炎症中, NGF能够引起肥大细胞趋化, 发生脱颗粒反应, 释放组胺及其他有害因子, 加重炎症反应[29]. 而近期研究发现在抗NGF治疗的大鼠结肠炎模型炎症较对照组加重2-3倍[30], 提示NGF在IBD中具有促炎和抗炎的双重作用. NGF可通过抑制T细胞的活化, 下调免疫或炎症反应[31]; 抑制单核细胞跨上皮移动, 减少淋巴细胞的浸润及活化, 减少致炎细胞因子的释放[32]; 还可降低急性炎性组织血管通透性, 减少炎性渗出[33], 调节单核细胞合成降钙素基因相关肽(calcitonin gene related peptides, CGRP)[34], 增加IL-10的分泌[35], 从而起到抗炎作用. 此外, NGF可促进结肠上皮增殖[36], 有助于损伤肠黏膜上皮自我更新和修复, 中断ENS损伤进程, 纠正免疫异常, 重新恢复肠道稳态, 在IBD时发挥以抗炎为主的综合性保护作用[37].

近年来大量研究证实GDNF直接参与了肠道炎症反应[38-40], von Boyen等[41]在体外培养EGC发现GDNF在CD中是显著增加的, 并证实了GDNF是由EGC分泌的, IL-1、TNF-α及脂多糖类等炎性因子激发其分泌GDNF, 具有抗肠上皮细胞凋亡, 维护肠黏膜屏障的完整性作用, 从而参与调节肠道炎症过程. 此外研究证实GDNF在实验性UC小鼠模型及UC患者肠黏膜中表达显著增加, 增加的GDNF在体外通过活化MAPK, PI3K/AKT途径发挥抗结肠上皮SW480细胞凋亡作用[42]. 体内GDNF也可抗上皮细胞凋亡, 并上调紧密连接蛋白ZO-1表达而保护肠黏膜屏障, 降低肠黏膜通透性, 同时GDNF在体内通过激活PI3K/AKT通路抑制肠黏膜NF-κB p65而降低致炎性细胞因子TNF-α、IL-1β, 从而降低UC小鼠疾病活动指数, 缓解肠道炎症[25]. 最新研究表明, CD中GDNF表达增加、Caspase3/7活性增强, 可能存在一个反馈性的GDNF自分泌环, 通过自分泌的方式有效防止EGC凋亡, 从而起到维持肠黏膜完整, 抑制炎症反应的作用[40].

Savidge等[43]研究发现EGC也可通过释放亚

■研发前沿
越来越多研究表明IBD时EGC可通过自身及分泌多种细胞因子改善肠黏膜屏障功能, 缓解肠道炎症. 同时其分泌的细胞因子也可作用于EGC本身, 反馈性调节其增殖、凋亡及分泌功能. 但具体作用机制尚不清楚, 亟待进一步研究.

■相关报道
越来越多的研究证明EGC不仅通过肠神经元间接影响肠免疫系统, 更可能通过自身分泌的神经营养因子、神经多肽及细胞因子等神经递质直接作用于肠黏膜免疫细胞, 从而影响肠道炎症的发生发展.

硝基谷胱甘肽(S-nitrosoglutathione, GSNO)保护肠黏膜屏障并减轻炎症, 认为GSNO是EGC调控肠黏膜屏障的中介, GSNO通过抑制黏膜核因子-κB(nuclear factor-κB, NF-κB)活性抑制致炎细胞因子TNF-α、IL-1β、IL-6的产生, 免疫抹除(Ablate)EGC后, 小鼠肠组织炎性因子TNF-α、IL-1β和IL-6显著增加. 最新研究发现EGC可分泌GSNO促进肠黏膜紧密连接蛋白ZO-1、occludin和P-MLC表达, 降低肠黏膜通透性, 从而起到保护肠黏膜屏障, 减轻炎症作用[23,44]. 此外，研究表明EGC在免疫刺激下可表达细胞因子IL-1β、IL-6和TNF-α[45]. 而免疫细胞分泌的细胞因子亦可反作用于EGC, 其中IL-1β可通过结合IL-1受体增强IL-6的表达并反馈性抑制自身IL-1β的分泌[46], 还可作用于EGC本身抑制其增生[41]. 近期研究发现炎性细胞因子可直接激活EGC表达MHC Ⅱ和c-fos, 有效增加S100B和GFAP的表达及NO的释放, 促使EGC增生、增殖[47].

总之, IBD时EGC可通过分泌多种神经营养因子、神经多肽及细胞因子改善肠黏膜屏障功能, 缓解肠道炎症. 同时其分泌的神经营养因子、神经多肽及细胞因子也作用于EGC本身, 反馈性调节其增殖、凋亡及分泌功能.

3 EGC与结直肠癌

目前EGC与结直肠癌的相关研究较少, 且均为静态横断面研究. Bach-Ngohou等[48]认为EGC通过其分泌15dPGJ2活化PPARγ, 从而抑制Caco-2结肠癌细胞的增殖, 上调分化相关基因的表达. 而Neunlist等[49]报道EGC通过自分泌的TGF-B1途径可以抑制人结肠癌细胞Caco-2、HT-29和T84细胞的增殖, 使共培养的上述细胞数目显著减少, 外源性加入TGF-B1可影响癌细胞密度和表面积, 加入TGF-B1中和抗体后则会改变EGC这一效应. 此外, 还观察到在结肠癌组织中EGC标志物S100β表达减少, 而癌组织边缘及远处S100β表达逐渐增加[49]. 提示EGC参与结肠癌的发生发展, 很可能起到抑制癌细胞生长转移作用. 然而, EGC是否可抑制结肠癌细胞的生长, 通过何种途径发挥其抑癌作用, 能否能抑制癌细胞的侵袭转移, 目前尚不清楚.

4 结论

目前IBD的病因及发病机制尚不清楚, 研究表明肠黏膜屏障缺损、肠黏膜免疫调节异常在IBD的发生发展中具有关键作用[50,51]. 肠黏膜屏障破坏, 通透性增加, 炎性因子分泌增多, 黏膜NF-κB活化等均是IBD发病及反复发作, 迁延不愈以至癌变的主要原因. 不管在体内(EGC抹除实验)[43]还是体外(EGC与Caco-2共培养)[52], EGC都具有维护肠黏膜屏障完整, 降低肠黏膜通透性, 缓解肠道炎症作用. 因此有理由认为, 在肠道炎症-不典型增生-癌变过程中, EGC网络逐渐遭破坏, EGC数量减少, 保护性作用减弱, 使得炎-癌进程得以进行. 如果在IBD发病后, 能够保护EGC或者适时补充EGC分泌的各种因子, 很有可能阻断炎-癌进程, 缓解炎症反应, 减小癌变几率. 故未来研究应重视EGC在“炎症-不典型增生-癌变”动态进程中的作用.

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■创新盘点
本文全面回顾了近年来关于EGC在IBD发生发展中的作用研究结果，发现EGC在IBD发生发展中具有重要作用，未来研究应重视EGC在“炎症-不典型增生-癌变”动态进程中作用.

■同行评价
本文为今后的研究重点提供了方向，具有一定理论指导意义及潜在的临床诊治价值.

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