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文献综述 REVIEW

炎症性肠病与免疫学关系研究进展

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Advances in studies on relation between inflammatory bowel disease and immunity

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Abstract
Inflammatory bowel disease is a chronic inflammatory disease of the gastrointestinal tract. Its main clinical manifestations are abdominal pain and diarrhea. Its etiology is complicated. Immune system is very important. Following factors, such as intestinal environment, immune cells, human leukocyte antigens, antibodies, anti- laminaribioside antibody, anti-chitobioside antibody IgA, cytokines, cell adhesion molecules, NO and NF-κB, play a key role in the pathogenesis of inflammatory bowel disease. Inflammatory bowel disease is related to all these factors. This paper reviews the possible role of these immune factors in the pathogenesis of inflammatory bowel disease.

Key Words: Immune factors; Inflammatory bowel disease

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摘要
炎症性肠病是一组病因未明的慢性肠道炎症性疾病, 其临床症状以腹痛和腹泻为主, 病因和发病机制错综复杂, 包括多种因素, 其中与机体免疫系统关系密切, 目前研究发现免疫异常是炎症性肠病发病的重要因素, 包括肠道内环境、免疫细胞、人类白细胞抗原、自身抗体、抗Laminaribioside糖抗体(ALCA)和抗Chitobioside IgA糖抗体(ACCA)、细胞因子、黏附分子、一氧化氮和核因子NF-κB等, 他们在炎症的起始和持续发展中起重要的作用, 本文就免疫因素在炎症性肠病中的作用作一综述.

关键词: 免疫因素; 炎症性肠病

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■背景资料
炎症性肠病(inflammatory bowel disease, IBD)包括溃疡性结肠炎和克罗恩病, 其发病机制和病因涉及多方面的因素, 目前研究发现免疫异常是IBD发病的重要因素, 在炎症的起始和持续发展中起重要的作用.

0 引言
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), 其病因和发病机制仍不清楚. 目前认为IBD发生与多因素有关, 即在遗传物质基础上, 由于抗原刺激和体内免疫系统的激活, 各种环境因素相互作用而引起的慢性肠道炎症[1-5]. 本文就IBD与免疫学关系的研究进展作一综述.

1 IBD与肠道内环境
目前研究表明, 肠内细菌的存在是IBD发病的必要条件, 同一种小鼠在普通环境和无特定病原体环境中可以建立结肠炎模型, 而在无菌环境中无法形成炎症模型, 黏膜炎症经抗生素治疗后改善, 表明肠道内定居的微生物与本病的启动有关[6-8]. Van *et al*[9]证实微生物的代谢产物丁酸盐、异戊酸盐和铵能影响肠上皮细胞代谢的完整性, 从而诱发黏膜免疫反应. 胃肠道内有大量的抗原物质存在, 如致病菌、正常菌群、细菌毒素及病毒等, 肠免疫系统具有两个方面的

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IBD病因和发病机制仍不清楚, 目前认为IBD发生与多因素有关, 即在遗传物质基础上, 由于抗原刺激和体内免疫系统的激活, 各种环境因素相互作用而引起的慢性肠道炎症. 但究竟哪一种免疫因素起主要作用, 各免疫因素之间有哪些相互联系及针对哪一免疫因素治疗更有效, 都有待于进一步研究.

功能, 既要保护肠黏膜, 抵御致病因子的入侵, 又要吸取营养物质, 耐受正常的肠道菌群, 所有这些肠内容物均可能是潜在的免疫原, 上皮细胞黏膜屏障的破坏为大量摄取肠抗原创造条件, 无节制的免疫反应及免疫调节失衡是IBD的免疫学特性[10].

2 IBD与免疫细胞

引起炎症反应的T细胞与调节性T细胞平衡是机体调节免疫反应的主要模式, 其紊乱可诱发IBD等免疫性疾病. 肠道共生的微生物抗原刺激肠黏膜T细胞, $CD4^+$ T细胞在IL-12的作用下分化为Th1细胞, 分泌干扰素-γ(IFN-γ)介导肠黏膜炎症, IFN-γ活化单核巨噬细胞, 使之释放前炎性细胞因子肿瘤坏死因子-α(TNF-α)、IL-6和IL-1参与炎症过程, 形成IFN-γ、TNF-α升高的Th1型黏膜炎症, 表现与CD相似[11-14]. $CD4^+$ T细胞分泌IL-4、IL-5和IL-13, 形成Th2型黏膜炎症, 表现与UC相似, 因此推测UC可能是Th2细胞介导的疾病, 目前支持该观点的证据有: (1)UC患者比CD患者体内存在更多自身抗体, Th2细胞有助于B细胞活化产生抗体; (2)UC中增加的自身抗体主要为Th2相关的抗体类型; (3)EB病毒诱导的产物现在被鉴定为Th2型细胞因子, 这种细胞因子增加见于UC[15-17].

调节性T细胞被认为是一类能产生免疫抑制作用的相对独立的T细胞亚群. 调节性T细胞Tr1可分泌高水平的IL-10, 肠道内环境的稳定需要Tr1, 当肠道病原体被清除后, Tr1可通过IL-10下调炎症反应[18]. 在研究口服诱导耐受过程中发现的Th3细胞可通过分泌转化生长因子-β(TGF-β)在黏膜免疫中承担调节作用, TGF-β具有广泛的抗炎症作用, 能抑制Th1和Th2细胞的活化, 是自身免疫调节的重要因素. $CD4^+CD25^+$ T调节细胞是目前研究的热点, 在正常个体体内, 生理性 $CD4^+CD25^+$ T细胞约占$CD4^+$ T细胞的5%-10%, 其数量及活性足以抑制自身免疫性疾病的发生. $CD4^+CD25^+$ T细胞的免疫抑制作用主要是抑制自身反应性T细胞, 以维持自身免疫平衡, 研究表明$CD4^+$ $CD25^+$ T调节细胞功能失调与IBD发病有关[19-21].

3 IBD与人类白细胞抗原(human leucocyte antigens, HLA)

IBD的发病具有遗传倾向, 研究表明UC的发病与HLA-DR2呈正相关, CD患者$HLA\text{-}DR_1$和$HLA\text{-}DQ_{W5}$明显升高. 国外研究表明, CD患者的$HLA\text{-}DR_1$出现率增加, UC患者的$HLA\text{-}DR_2$出现率增加, 而$HLA\text{-}DR_4$与$HLA\text{-}DR_{W6}$出现率均减少. 无论细胞免疫还是体液免疫, HLA在免疫反应中起了关键作用[22-26].

4 IBD与自身抗体

抗中性粒细胞胞质抗体(antineutrophil cytoplasmic antibodies, ANCA)是一类作用于中性粒细胞胞质成分的自身抗体, 最先发现于肾小球肾炎和系统性脉管炎等患者的血清中. ANCA可通过毛细血管中的中性粒细胞、单核细胞或肠上皮细胞引起溶菌酶释放, 导致大面积血管或肠组织损害; ANCA亦可引发T细胞介导的细胞免疫协同作用造成组织损伤[27-29]. 近几年ANCA与IBD的关系是研究热点之一, Preda *et al*[30]测定UC患者和CD患者血清, 发现36.4%的UC患者血清ANCA阳性, 而仅15% CD患者阳性, 且均限于结肠受累的情况. ANCA可分为胞质型(cANCA)和核旁型(pANCA), 后者与IBD相关. 研究发现普遍人群中pANCA阳性率为2.9%, CD患者阳性率为10%-20%, 而UC患者的阳性率达50%-85%, 反映了病变过程中机体存在免疫功能紊乱. 由于ANCA在UC患者中呈家族聚集现象, 有望成为UC较特异的血清标记物[31-32].

近年来研究报道抗酿酒酵母抗体(anti-sacchromyces cerevisia antibody, ASCA), 是大多数CD患者的血清学标志物. 进一步研究表明, ASCA在CD的特异性表达, 不仅是肠道受侵犯时的一种简单副现象(epiphenomenon), 而且是CD患者的一种家族免疫性的表达. 文献报道, ASCA在CD患者阳性率为48%-69%, 在UC患者中的阳性率达6%-15%. ASCA研究的意义在于: (1)CD患者亲属中罹患CD易感性增高, ASCA水平可作为有价值的CD标志物; (2)CD患者ASCA阳性与阴性亚群, 可能在预后、治疗反应以及明确的遗传学标志物上均不同[33-36].

5 IBD与抗Laminaribioside糖抗体(ALCA)和抗Chitobioside IgA糖抗体(ACCA)

以色列Dotan *et al*[37]报道, ALCA和ACCA是两种与CD密切相关的新的血清学标志物, 他们首次应用多聚糖间接免疫荧光芯片技术检测了72例CD患者、56例UC患者和41例健康对照者血清中的抗多聚糖抗体谱, 再用ELISA技术对124例CD患者、106例UC患者和101例健康对照者的

血清学进行筛查, 发现ALCA和ACCA是鉴别CD和UC最有诊断价值的两种新抗体, 其在CD患者的阳性率显著高于UC患者, 且在44% ASCA阴性的CD患者中, ALCA或ACCA检测呈阳性. 如IBD患者对ALCA和ACCA中至少一种呈阳性结果, 其诊断CD敏感性为77.4%, 特异性为90.6%, 在CD患者中, 高水平的ALCA与小肠病变密切相关.

■相关报道
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6 IBD与细胞因子

细胞因子(cytokines, CK)是由多种细胞产生的多肽或低分子糖蛋白. IBD活动期患者肠黏膜固有层与肠系膜淋巴结中淋巴细胞产生的IL-1、IL-6和TNF-α水平增加, 增加程度与病变的活动性有关. 这些炎性前细胞因子可能通过下列机制介导肠道炎症反应: (1)对中性粒细胞和巨噬细胞有趋化作用; (2)通过黏附分子的作用来增加白细胞对血管壁的黏附性; (3)激活巨噬细胞; (4)激活T、B淋巴细胞, 具有上调免疫反应的作用; (5)促使巨噬细胞、内皮细胞和成纤维细胞合成前列腺素E2(PGE2)、前列腺素12(PG12)增加; (6)使内皮细胞血小板激活因子(PAF)增多. 由活化的T细胞产生、与IBD发病有关的CK包括IL-1、IL-2、IL-4、IL-6、IL-8、IL-10、IL-11、IFN-γ和TNF-α等. CK既可以使大量的T细胞, 尤其是$CD4^+$ T细胞迅速分裂、增殖, 形成致敏淋巴细胞, 又可以活化粒细胞, 增强NK细胞和LAK细胞的杀伤力, 并诱导黏附分子表达及肥大细胞脱颗粒, 以增进炎症反应[38-43].

Fantini *et al*研究认为IL-1、IL-2参与IBD发生, T细胞活化产生的IL-2可通过激活T细胞、B细胞和巨噬细胞产生多种CK, 从而参与IBD的炎症过程[44]. TNF-α也是CD黏膜损伤的重要介质. 用抗TNF抗体治疗CD患者, 可以使肠道炎症很快消退[45]. T细胞分泌的IL-22作用于结肠上皮下肌纤维母细胞(subepithelial myofibroblasts, SEMFs), 可以促进前炎性细胞因子表达[46-47]. Yen *et al*对IL-23缺失模型和IL-12缺失模型的研究表明IL-23是慢性肠道炎症出现临床表现的必需因子[48]. IL-23的一个重要靶细胞群是记忆性T细胞亚群, 他们可以被IL-23特异性激活, 产生促炎性细胞介质IL-17和IL-6, 这一途径可能与慢性肠道炎症和其他慢性自身免疫性炎症性疾病密切相关[49].

IL-25由肠道T细胞分泌, 也可由嗜酸性粒细胞产生, 近年来研究表明, 他能促进Th2细胞活化增殖、分泌IL-4、IL-5和IL-13, 抑制Th1细胞分化增殖进而抑制Th1型细胞因子的产生, 说明IL-25在调节胃肠道炎症中起重要作用[50]. Whittall *et al*[51]研究发现在CD患者中分离出的树突状细胞被热休克蛋白70(HSP70)刺激后分泌的TNF-α浓度明显增高, 这与细胞外信号转导途径有关. IFN-γ诱导的蛋白-10(interferon-gamma-inducible protein-10, IP-10)是一个T细胞和单核细胞的趋化因子, Inatomi *et al*[52]研究发现IFN-γ能强烈诱导IP-10 mRNA表达, IP-10能介导IBD慢性炎症. 此外, 肾素血管紧张素系统(RAS)也与结肠的免疫系统相关, RAS可通过调节结肠内的前炎症性和抗炎症性细胞因子而参与三硝基苯磺酸(TNBS)诱导的结肠炎的发病过程[53].

7 IBD与细胞黏附分子

细胞黏附分子(cell adhesion molecules, CAMs)是一类介导免疫与内皮细胞相互作用的糖蛋白分子. 淋巴细胞功能相关抗原-1(LFA-1)与细胞间黏附分子-1(ICAM-1)结合能使吞噬细胞移出血管进入肠道病变组织, 在IBD初期, 内皮细胞表达ICAM-1明显增加, 同时伴有单核巨噬细胞表达LFA-1增加, 提示黏附分子在炎性细胞进入病变组织过程中起重要作用[54-57]. Bachmann *et al*[58]报道黏膜地址素细胞黏附分子-1(MAdCAM-1)在UC、CD和肠易激综合征的表达是不同的, MAdCAM-1丰富地表达于UC、CD的炎症黏膜, 且CD在溃疡基底部表达比UC丰富, 提示MAdCAM-1可能与CD透壁性炎症相关. Rijcken *et al*[59]研究应用UC、CD及对照的肠标本检测多种黏附分子在肠道的表达, 结果提示活动性UC患者黏膜中静脉及血管周围的单核细胞上血小板内皮细胞黏附分子-1(PECAM-1)表达明显增强, PECAM-1在炎症时淋巴细胞跨越移行中起重要作用, 与IBD炎症细胞的渗出机制有关.

选择素及他们的配体、ICAM-1、VCAM-1、VLA-4和整合素β等CAMs在UC和CD患者肠病变中有重要作用, 用于治疗IBD的经典药物糖皮质激素和5-氨基水杨酸的作用机制即部分与CAMs的合成与功能有关, 说明CAMs与IBD发病有关[60-61].

8 IBD与NO

一氧化氮(NO)是一种多效性的自由基信号分子, 他可促进和抑制氧自由基介导的组织损伤. 大量资料证实, NO参与了UC发生过程中的炎症

■创新盘点
IBD的发病机制和病因涉及多方面的因素, 其中免疫因素起重要作用, 本文通过引用国内外最新的研究资料, 对免疫因素与IBD的关系进行综述, 系统地阐明了各种免疫因素在IBD发病过程中的作用.

和组织损伤. 检测UC活动期患者结肠黏膜的还原型辅酶Ⅱ(NADPH)发现: 黏膜隐窝中NADPH依赖性酶(NADPH-diaphourase, Nd)染色增多, 表明在UC中有一氧化氮合酶(NOS)诱导存在. NOS分为原生酶(cNOS)和诱生酶(iNOS)两种, 在UC结肠黏膜层主要以iNOS为主. NO在UC炎症过程中充当了双重角色, 既有保护作用, 又有杀伤毒性和促炎作用. 在炎症初期, 可抑制激活的巨噬细胞和T细胞的功能, 并能抑制血小板聚集, 防止血栓形成, 同时抑制髓过氧化物酶的活性, 保护上皮屏障及促进上皮修复. 随着炎症的发展, 大剂量NO由iNOS催化产生, 从而一方面可通过伴随产生的自由基损伤组织, 另一方面启动机体免疫防御系统, 如巨噬细胞、中性粒细胞, 抑制靶细胞内DNA复制, 降低靶细胞内cAMP/cGMP比例, 激活NK、LAK细胞, 直接增强其细胞毒性, 若作用过强, 即可造成正常组织的损伤. 在体外实验或体内急性炎症研究中表明NO有较强的抗黏附作用, NO在IBD的抗黏附作用, 参与调节体内内皮细胞黏附分子(ECAM)表达的分子机制, 抑制所谓的趋集瀑布机制中各步骤的反应剂, 有望成为新药来控制和逆转IBD的炎症反应[62-68].

9 IBD与核因子NF-κB

血液循环和肠道细胞因子表达异常是IBD发病的重要机制, 核因子NF-κB是一种调节各种细胞因子、趋化因子、黏附分子的转录因子, 在IBD复杂的细胞因子网络失调中, NF-κB活化是一个中心环节. IBD中NF-κB活性增高的同时伴有IL-1、IL-6、TNF-α等升高, IL-1和TNF-α可促进NF-κB进一步活化, 后者通过正反馈使IL-1和TNF-α分泌进一步增加, 同时使其他细胞因子IL-6、IL-8等表达增加, 产生级联反应, 使炎症过程得以持续和放大. 研究表明, 在IBD患者肠浆膜组织纤维母细胞中 NF-κB和ICAM-1表达明显增强[69-70]. Guidi *et al*[71]研究发现活动期IBD患者的黏膜固有层单核细胞中可检测到增加的NF-κB, 说明NF-κB在IBD中调节炎症性细胞因子的分泌.

总之, IBD病因和发病机制复杂, 涉及免疫学、遗传学以及环境因素等多方面问题, 免疫因素在IBD发病过程中起重要作用, 但究竟哪一种免疫因素起主要作用, 各免疫因素之间有哪些相互联系及针对哪一免疫因素治疗更有效, 都有待于进一步研究.

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■应用要点
本文就免疫因素在IBD形成过程中的作用作一综述, 但这些因素尚未完全阐明, 进一步阐明这些问题, 将为临床治疗提供新的方法和依据, 有利于对这类疾病进行合理有效的治疗.

■名词解释
抗中性粒细胞胞质抗体(anti-neutrophil cytoplasmic antibodies, ANCA): 是一类作用于中性粒细胞胞质成分的自身抗体, 最先发现于肾小球肾炎和系统性脉管炎等患者的血清中. ANCA可通过毛细血管中的中性粒细胞、单核细胞或肠上皮细胞引起溶菌酶释放, 导致大面积血管或肠组织损害; ANCA亦可引发T细胞介导的细胞免疫协同作用造成组织损伤.

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■同行评价
本文重点突出, 参考文献新, 全面, 较好反应了当前进展, 综述水平符合发表要求.

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• 消息 •

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