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文献综述 REVIEW

炎症性肠病肠道淋巴细胞归巢研究进展

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Progress of gut associated lymphocyte homing in inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) is characterized by chronic inflammation of intestinal tract, and it is classified into 2 subtypes traditionally, namely ulcerative colitis (UC) and Crohn's disease (CD). Many investigations have shown that intestinal lymphocyte homing (lymphocyte homing, LH) is closely related to IBD. This paper reviews the advances in the relationship between inflammatory bowel disease and lymphocyte homing.

Key Words: Inflammatory bowel disease; Lymphocyte homing; Adhesion molecules

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摘要

炎症性肠病(inflammatory bowel disease, IBD)是慢性肠道炎症疾病, 传统上分为溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(Crohn's disease, CD). 诸多研究表明, IBD与肠道淋巴细胞归巢(lymphocyte homing, LH)密切相关, 本文就IBD与LH研究进展作一综述.

关键词: 炎症性肠病; 淋巴细胞归巢; 黏附分子

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0 引言

20世纪60年代, Gowans和Knight *et al*[1-2]从正常鼠的输出淋巴管分离出淋巴细胞, 用放射性物质标志后注入受体动物的血循环, 再通过闪烁显像术和放射自显影术来探测这些细胞的分布, 观察到小淋巴细胞分布于全身次级淋巴组织, 而激活的免疫母细胞则选择性的迁移至黏膜部位. 受这个实验的启发, 随后多个小组的科学家进行了一系列活体研究. 这些试验奠定了淋巴细胞再循环和归巢概念的基础. 目前认为炎症性肠病(inflammatory bowel disease, IBD)发病与基因易感性个体对正常肠道共栖菌群的异常免疫反应有关[3-4], 肠道淋巴细胞归巢(lymphocyte homing, LH)作为免疫反应的一个关键环节, 在IBD的发病和复发中发挥重要作用.

1 基本概念

成熟淋巴细胞离开中枢免疫器官后, 经血液循环趋向性迁移并定居于外周免疫器官或组织特定区域, 称为LH. LH的分子基础是淋巴细胞与内皮细胞黏附分子的相互作用. 介导LH的黏附分子称为淋巴细胞归巢受体(lymphocyte homing receptor), 其相应配体为血管地址素(vscular addressin), 主要表达于血管内皮细胞表面[5].

2 淋巴细胞归巢机制,淋巴细胞归巢受体、地址素、趋化因子

淋巴细胞从循环募集到目标组织是一个高度调节的过程, 依赖一系列黏附分子的相继作用.

■背景资料
目前认为炎症性肠病(IBD)发病与基因易感性个体对正常肠道共栖菌群的异常免疫反应有关. IBD传统上被分为两个亚型: 即溃疡性结肠炎(UC)和克罗恩病(CD). 失控的肠道炎症是他们共同的路径. 自循环中增强的淋巴细胞归巢在肠道炎症的发病和复发中发挥重要作用.

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胃肠病学家和药物学家一直致力于开发出更加安全有效的拮抗淋巴细胞归巢药物来治疗IBD及相关疾病. 因此必须进一步深入研究淋巴细胞归巢的分子和信号传导机制, 探讨可能影响淋巴细胞归巢的因素, 选择合适的药物作用靶点.

需经历贴壁, 滚动(rolling); 趋化因子对整合素的激活(activing); 整合素介导的淋巴细胞牢固黏附(adhereing); 淋巴细胞于高内皮静脉(high-endothelial venules, HEV)内皮细胞间隙的游出. 该过程涉及到一系列归巢受体、地址素及趋化因子的级联作用[6-7]. 各亚群的具体归巢步骤有所不同[8-12].

2.1 淋巴细胞归巢受体 主要包括选择素家族的L-选择素[13]、整合素家族的α4β7和淋巴细胞功能相关抗原LFA-1(αLβ2) 等. 其与相对应的地址素相互识别、相互作用可介导淋巴细胞与内皮细胞间的黏附和游出过程.

2.2 地址素 L-选择素、α4β7和LFA-1的配体(地址素)分别为黏膜地址素细胞黏附分子-1(mucosal addressin cell adhesion molecule-1, MAdCAM-1)和细胞间黏附分子-1(intercellular adhesion molecule-1, ICAM-1)/血管细胞黏附分子-1(vascular adhesion molecule-l, VCAM-l), 均属于免疫球蛋白超家族(immunoglobulin super family, IgSF), 具有与Ig相似的结构特征. 外周淋巴结地址素(peripheral lymph node addressin, PNAd)是一种特殊形式的MAdCAM-1, 即为碳水化合物抗原决定簇修饰的MAdCAM-1.

2.3 趋化因子 趋化性细胞因子是一个蛋白质家族, 分子质量多为8-10 kDa. 与淋巴细胞归巢相关的趋化性细胞因子很多[14-19], 按半胱氨酸的位置、排列方式和位置可分为四个亚家族, 其中最具代表性的是CCR9. CCR9和整合素α4β7联合表达于归巢至肠道的淋巴细胞, 选择性运输至小肠. 通过活体显微镜检查能直观的观察到在正常和TNF-α刺激条件下淋巴细胞依赖CCR9/CCL25黏附于鼠小肠内皮[20].

3 炎症性肠病中淋巴细胞归巢

3.1 淋巴细胞 有研究表明IBD中炎症浸润部位的肠黏膜中T、B细胞总数量增加, 各具体亚群有增有减. SAMP1/Yit小鼠能自发性发生回肠炎症, 是研究IBD的重要动物模型. Matsuzaki *et al*[21]用荧光标记T细胞, 再从尾静脉注入受体小鼠, 并用活体显微镜监测派伊尔淋巴结(peyer patches, PP)毛细血管后微静脉、黏膜下层微血管和末端回肠绒毛毛细血管内的T细胞归巢, 发现与AKR/J小鼠和15 wk龄的SAMP1/Yit小鼠相比, 35 wk的SAMP1/Yit的小鼠HEV内T淋巴细胞归巢明显增强, 免疫组化技术证实CD4、CD8和β7整合素阳性的细胞浸润增加. 与此相似, Teramoto *et al*[22]把从脾脏提取的T和B淋巴细胞用荧光标记后注入受体小鼠, 再用右旋葡聚糖硫酸钠 (dextran sulfate sodium, DSS)诱导结肠炎, 活体显微镜观察提示受体结肠黏膜及黏膜下层内T和B淋巴细胞的黏附均显著增强. 诸多文献认为, LH增多是肠道淋巴细胞数目增加的重要机制之一[21-22].

3.1.1 $CD4^+$ T细胞: CD和UC中$CD4^+$T细胞归巢显著增加, 其中CD以分泌IFN-γ和IL-2的Th1型细胞为主, 而UC以非典型的Th2型细胞占优势, 其分泌TGF-β和IL-5而不分泌IL-4[4].

大量的实验性结肠炎模型都表现为Th1型炎症, 其炎症特征在肉眼和光镜水平下均和CD相似. 研究的较多的有三硝基苯磺酸(trinitrobenzene sulfonic acid, TNBS)结肠炎和IL-10基因敲除小鼠发生的结肠炎. IL-10是Th2型反应的促进因子, Th1型反应的抑制因子. 通过动物试验技术把编码IL-10的基因敲除后,小鼠可自发肠道炎症, 病变以直肠和结肠为主, 病理学特征与人类CD十分相似, 炎症部位T浸润, 分泌高水平IFN-γ和TNF-α, 表现为显著的Th1型免疫反应.

IFN-γ是Th1型炎症的关键因子, 其产生过度主要与两个分子有关, 一个为T-bet, 另一个为STAT4(signal transducer and activator of transcription 4). Furuta *et al*[23]比较同一遗传背景下T-bet(-/-)、STAT4(-/-)及T-bet(-/-)和STAT4(-/-)小鼠发现, 单独敲除T-bet或STAT4基因, Th1型反应均显著降低, 若同时敲除两基因, 则几乎检测不到Th1型反应. Thieu *et al*[24]发现T-bet促进Th1型分化, 需要STAT4的参与. 有学者报道CD患者表达特征性受体IL-12Rβ2的Th1细胞数量显著增加, 炎症组织中的T细胞的核提取物中的STAT4和T-bet含量也显著增加[25].

从目前资料来看, UC类似于一种缓和的Th2型免疫反应[26], Th2介导的B细胞激活的证据是自身抗体的出现, 包括核旁型抗中性粒细胞胞质抗体(perinuclear antineutrophil cytoplasmatic antibodies, pANCA)和抗IgG1、IgG4亚类抗体[27-28]. 最近有研究发现, IL-13在UC的发病中起重要作用, 可影响肠道上皮细胞的紧密连接、凋亡和再生[29-30].

3.1.2 $CD8^+$ T细胞: IBD的发生发展与上皮内淋巴细胞含量也密切相关. 外周血及肠黏膜固有层以$CD4^+$ T细胞占优势, 而上皮内淋巴细胞(intraepithelial lymphocytes, IELs)90%以上是

CD3$^+$的T细胞, 其中主要是CD8$^+$ T细胞, 而CD4$^+$ T细胞极少. 肠黏膜固有层中一部分CD8$^+$ T淋巴细胞可迁移至绒毛顶部附近形成IELs. CD8$^+$ T IEL群包括CD8αα和CD8αβT细胞, 可表达γδ或αβ受体. Natascha *et al*[31]报道CD患者肠上皮内淋巴细胞对上皮来源的靶细胞的细胞溶解活动明显加强, CD8$^+$IEL较正常人明显升高; CD患者T细胞表型和功能上的改变只限于肠黏膜的淋巴细胞, 而血液中T细胞的功能没有变化, IEL对肠组织的细胞溶解活动明显加强.

不同于CD4$^+$ T细胞促炎作用, γδT细胞在IBD的发生和发展过程中起保护调节作用[32-35], 其一般均为CD8αα+. Inagaki-Ohara *et al*[36]报道γδT基因敲除小鼠能自发结肠炎, 其幼鼠表显出对TNBS诱导结肠炎的高度敏感性. Hoffmann *et al*[37]把提取自野生型或IL-10转基因小鼠的γδT细胞, 预防性转移至同类系TNBS诱导的结肠炎小鼠,发现TNBS小鼠肠道和脾脏淋巴细胞分泌TNF-α减少, IL-10和TGF-β增加, 从而使小鼠生存时间延长, 组织损伤减轻. Kühl *et al*[38]研究了在多种IBD动物模型中删除或敲除γδT, 发现早期干预使黏膜固有层中淋巴细胞及脾细胞IFN-γ分泌增加, 提示γδT细胞在肠道炎症的早期发挥重要作用, 可能的机制是影响IFN-γ分泌和上皮细胞再生.另有研究表明γδT细胞是细胞因子Th17的重要来源, 有细菌感染时, 可快速诱导Th17型反应, 保护肠黏膜[39-40].

3.2 LH相关分子

3.2.1 MAdCAM-1: IBD中LH显著增强, 淋巴细胞及上皮细胞表面归巢相关分子表达也伴随增加, 其中最重要的是α4β7/MAdCAM-1分子. 多种IBD动物模型中均能检测到显著增加的MAdCAM-1蛋白. 近年来开发出一种可增强超声成像的胶囊, 其内含有可与MAdCAM-1特异结合的微气泡(microbubbles, MB). Bachmann *et al*[41]给SAMP1/Yit结肠炎小鼠服用此种胶囊后作腹部超声, 发现MB可聚集于肠道炎症部位, 产生显著增强的回声.

Souza *et al*[42]以激惹性肠炎为对照组, 通过内窥镜及经口空肠活检取得CD和UC患者的结肠和空肠标本后, 做免疫组织染色并用计算机软件分析图像, 发现IBD患者α4β7整合素和MAdCAM-1表达水平显著增加; 日本学者Arihiro *et al*[43]等收集CD(40例)和UC(24例)手术切除标本作冰冻切片, 用免疫组化技术分析也发现CD和UC炎症部位的黏膜中MAdCAM-1阳性血管含量增加.

CD和UC患者炎症部位的肠黏膜中都含大量的MAdCAM-1阳性的的血管, 并且在炎症部位的溃疡底部E-选择素表达相似, 但前者溃疡底部MAdCAM-1阳性的的血管明显比后者丰富. MAdCAM-1阳性的的血管在肠道深层表达, 主要在集合淋巴结, 是CD的特征之一. MAdCAM-1在CD中的广泛表达可导致肠道透壁性炎症[43].

3.2.2 ICAM-1: 在UC急性期, 内皮细胞表达ICAM-1也明显增加[44-46], 同时伴有其配体LFA-1表达增加, 提示其在炎性细胞进入病变组织过程中起重要作用. 有研究表明嗜酸性粒细胞在结肠的聚集依赖于β2整合素/ICAM-1而不是α4β7[47], 在ICAM-1-/-的小鼠, 嗜酸性粒细胞性的结肠炎表现明显缓解. 另外, ICAM-1基因的多态性与IBD的发病密切相关[48-50].

3.2.3 趋化因子: CCL25/CCR9是生理条件下调节小肠LH的重要趋化因子, 随着CD炎症进展, CCL25和CCR9在调节小肠淋巴细胞归巢中的显著作用减弱. 针对CCL25和CCR9的靶向治疗只有在SAMP1/Yit小鼠模型疾病的早期有效, 提示在疾病后期非特异的炎症信号起主要作用[51]. 在CD的炎症部位趋化因子Fractalkine(CX3CL1)表达增加, 其两种同质异型配体之一的T280M能影响克罗恩病的临床表现和发病部位[52].

3.3 树突状细胞(dendritic cells, DC)与LH 生理和炎症状态下的LH都与DC细胞密切相关, DC和T细胞的相互作用参与IBD的发病过程. Drakes *et al*[53]通过输入CD45RBhiCD4$^+$ T细胞至重症联合免疫缺陷小鼠建立结肠炎模型, 分离结肠的DC细胞与同系基因型、同种异体基因型脾脏CD4$^+$T细胞和自体结肠分离T细胞的免疫反应, 发现结肠DC与自体固有层的T细胞共同培养时所产生的IFN-γ和IL-6数量显著高于与同系基因或同种异体基因型脾脏T细胞共同培养的含量. Hart *et al*[54]用多色流式细胞计量术分析IBD患者黏膜固有层中DC细胞表面分子, 并用胞内染色分析DC在无外源性刺激下产生的细胞因子, 发现IBD时, DC细胞激活, 表面微生物识别受体上调并产生更多的促炎细胞因子. 与此相对应, Baumgart *et al*[55]研究了活动性和非活动性IBD患者及其正常人类浆DC(PDC)和髓系DC(MDC), 观察到IBD急性期外周血中未成熟的DC细胞显著减少, 缓解期IBD患者PDC和MDC数量与正常对照组基本接近.

■相关报道

拮抗淋巴细胞归巢新药的临床应用需要特别小心, 有报道指出, 作用于α4整合素的新药那他珠单抗(natalizumab), 可破坏了大脑的正常免疫监视功能, 导致JC-多瘤病毒属的感染, 引起进行性多病灶性脑白质病(PML).

■创新盘点
本文就淋巴细胞归巢(LH)相关淋巴细胞、LH相关分子、树突状细胞、及其在IBD作用等进行了综述, 并对可影响IBD中LH的因素及如何拮抗LH治疗IBD进行了初步综述, 介绍了目前研究进展情况和发展趋势. 希望能为更深入的研究提供文献参考.

3.4 IBD中的白细胞募集 虽然CD和UC的发病机制和临床表现不全相同, 但他们都有大量免疫细胞浸润肠道. 在IBD中促炎症细胞因子的上调可导致血管黏附分子的表达增加, 使炎症细胞持续浸润. 与黏膜血管上的MAdCAM-1表达增加相对应, IBD患者中的炎症细胞可通过肠道特异的方式归巢至黏膜固有层.

一旦炎症已经建立, 引导器官特异归巢到组织的信号的作用往往不及一般性的炎症相关过程所起的作用. 对肠道共栖菌的免疫失调, 过多的TLR配体和促炎细胞因子的持续过分泌能激活上皮和内皮细胞, 因此能促进白细胞募集至肠黏膜间隙[3]. 激活的中性粒细胞能产生大量的超氧阴离子和活性氧(reactive oxygen species, ROS), 这些分子具有很高的反应性,可以与细菌的细胞膜、核酸分子及蛋白质发生氧化还原反应,造成微生物的损伤和死亡. 此外, ROS还可上调一些细胞因子及黏附分子如TNF-α、IL-1、ICAM-1的表达水平, 放大炎症效应. Yousefi *et al*[56]最近发现嗜酸性粒细胞一种全新的呼吸爆发机制. 嗜酸性粒细胞生理条件下在嗜酸细胞活化趋化因子的作用下在肠道黏膜固有层中维持较高基线水平. 在IBD的炎症部位内毒素(lipopolysaccharide, LPS)、C5a等可与IL-5发挥协同作用, 触发嗜酸性粒细胞瞬时弹射出线粒体DNA和阳离子蛋白, 在胞外形成黏性网络捕获并在胞外杀灭细菌, 同时造成自身组织损伤[57].

4 IBD中LH的影响因素

多种因素可通过作用于归巢受体、地址素等黏附分子的表达, 从而影响肠道淋巴细胞的归巢进而影响IBD的病理和转归.

4.1 一些酶对黏附分子的活力有作用 N-乙酰葡糖胺-6-磺化酶对L-选择素的配体活力是必须的, 前者又被表达于高内皮静脉的N-乙酰葡萄糖胺-6-O-硫基转移酶(N-acetylglucosamine-6-O-sulfotransferase-1, GIcNAc6ST-1)催化, 一旦缺乏, L-选择素的配体严重受损[58-59]. 在UC的急性期能诱导HEV样血管表达PNAd, 这与编码GIcNAc6ST-1的基因转录增加相关, 他能指导MECA-79表位的表达, 提示通过为循环中的T细胞提供额外的黏附位置, GIcNAc6ST-1在UC的发病中起一定的作用. 亦有研究指出表达于HEV的唾液酸蛋白, 当其被一系列转糖酶和转磺酶作用后, 才能够作为L-选择素的配体[60].

4.2 细胞因子 报道的最多的是TNF-α细胞因子, Ando *et al*[61]研究用TNF-α刺激一种新的结肠上皮细胞株MJC-1, 发现24 h内MAdCAM-1的表达量明显增加, 并与TNF-α呈剂量依赖性, 同时淋巴细胞的黏附增加了2-6倍, 其可运用MAdCAM-1抗体来抑制. 诱导MAdCAM-1表达增加的信号通路包括: 蛋白激酶C、酪氨酸激酶、P38丝裂原活化蛋白激酶和转录因子核因子NF-κB. 另有研究表明通过激活转录因子核因子NF-κB, TNF-α也能激活其他的细胞黏附分子: 如E-选择素、ICAM-1和VCAM-1. LPS也能够刺激鼠小肠内ICAM-1、E及P-选择素的表达.

4.3 维生素D的衍生物 Stio *et al*[62-64]的一系列研究表明, 维生素D的衍生物(1,25-二羟维生素、DEB 1089、KH 1060、TX 527)能影响IBD中的LH相关分子的表达. 其最新的研究发现无论是否和TNF-α或LPS联合应用, 维生素D的衍生物(1,25-二羟维生素D和EB 1089)均能显著降低IBD患者和正常人ICAM-1的表达, 体外的细胞试验也得出相似的结论[65].

4.4 微生态制剂 Angulo *et al*[65]通过手术在大鼠结肠中创造一段无粪流的肠段, 用抗生素除去该肠段原有菌群后, 植入来自炎症大鼠结肠的正常菌群, 其是否含干酪乳杆菌(*Lactobacillus casei*, *L. casei*)作对照研究, TNBS诱导结肠炎, 发现*L. casei*干预能显著降低结肠淋巴细胞归巢, 同时伴有ICAM-1表达明显降低. Okada *et al*[67]报道给予DSS干预之前或之后, 在饮水中添加费氏丙酸杆菌的提取物1,4-二羟基-2-萘甲酸(1,4-Dihydroxy-2-naphthoic acid, DHNA), 均能提高DSS诱导IBD小鼠的存活率, 改善炎症评分, 并能显著缓解结肠部位增高的MAdCAM-1和β7-整合素阳性细胞数量.

4.5 超氧化物歧化酶 Seguí *et al*[68]观察到TNBS诱导结肠炎大鼠, 每天给予超氧化物歧化酶达13 mg/kg时, 能显著降低结肠HEV内淋巴细胞的黏附, 同时伴有内皮细胞VCAM-1表达明显降低. 随后他们在IL-10基因敲除和DSS模型中也得到相似的结论[69].

5 拮抗淋巴细胞归巢治疗IBD

从CD的炎症环境可知针对Th1的细胞因子的抑制治疗是有益的. 抗TNF的单抗英夫利昔(infliximab)在两个关键的临床实验中, 已证明对CD患者有效并被美国FDA批准应用于临床. 然而抗TNF-α的治疗在UC中疗效较差, 这进一

步突出了理解UC和CD之间不同的免疫病理机制的重要性. 其他一些作用于TNF的药物如CDP571、依那西普(etanercept)也在临床评估中. 其中CDP571对CD的效果与英夫利昔相似, 而依那西普在CD中的疗效有限. 相似的, 人们正满怀希望的探讨抗IL-12和抗IL-6治疗. IL-11是一种能增强肠上皮屏障功能且能抑制炎症细胞因子分泌的白介素, 但其作用仍在临床评估中.

抑制拥有CD和UC特征的破坏性免疫细胞的流入, 为IBD的治疗提供了另外的一个途径. 因为淋巴细胞募集是一个高度调节的过程, 所以潜在的可设计出有高度选择性的抗炎治疗方案. α4β7/MAdCAM-1和CCR9/CC25可作为小肠中CD的选择性靶点, 而对于UC可能需要更多的途径. Alicaforsen(ISIS 2302)是一种能抑制ICAM-1反义核苷酸[70], 已证明在公开标签的研究中对UC有效, α4β7的抑制物(MLN02, Millennium)和CCR9的抑制物(Traficet-EN, Chemocentryx)对CD的作用也在评估中. 这些药物的应用不仅有益于IBD患者, 也有益于正罹患原发性硬化性胆管炎等肠外疾病的患者.

6 结论

肠道LH是多种黏附分子参与、多步骤的反应过程, 其对肠免疫屏障的平衡有重要意义, 并且是IBD重要发病机制之一. 因此通过干预淋巴细胞归巢为该类疾病提供了新的治疗途径. 相信随着分子生物学和临床药理学研究的进展, 必将推进这一重要领域的深入研究.

■应用要点

相信随着分子生物学和临床药理学研究的进展, 更深入了解肠道淋巴细胞黏附、归巢的分子机制, 及其影响因素, 可通过干预淋巴细胞归巢为炎症性肠病(IBD)及相类似的疾病提供有效并且可靠的治疗途径.

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