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文献综述 REVIEW

中性粒细胞源性粪便标志物在炎症性肠病活动度评估中的应用

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Clinical utility of fecal neutrophil-derived biomarkers in evaluating activity of inflammatory bowel disease

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Abstract
Inflammatory bowel disease (IBD) is a group of chronic, idiopathic intestinal diseases characterized by periods of remission and relapses. Evaluating the activity of IBD timely and accurately is crucial to guide treatment. The change of neutrophils in the intestinal tissue is correlated closely with the activity of IBD. This article reviews the clinical utility of fecal neutrophil-derived biomarkers in assessing the activity of IBD.

Key Words: Inflammatory bowel disease; Activity; Fecal biomarkers

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摘要
炎症性肠病(inflammatory bowel disease, IBD)是一组慢性非特异性肠道疾病, 具有反复发作的特点, 及时、准确地判断疾病活动性对于指导治疗具有重要意义. 活检组织中中性粒细胞数目变化与IBD疾病活动性密切相关, 本文就中性粒细胞源性粪便标志物在IBD活动度评价中的应用作一综述.

关键词: 炎症性肠病; 活动度; 粪便标志物

核心提示: 本文重点把几种中性粒细胞源性粪便标志物在炎症性肠病(inflammatory bowel disease)活动度评价中的应用价值及其存在的问题进行了综述.

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0 引言
炎症性肠病(inflammatory bowel disease, IBD)是一组病因不明的肠道炎症性疾病, 包括溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(Crohn's disease, CD). 近年来随着对IBD研究的不断深入, IBD治疗目标逐渐从单纯要求临床症状和血液学指标缓解转变为"黏膜愈合"甚至近来新提出的"持续深层缓解(sustained deep remis-

■背景资料
炎症性肠病(inflammatory bowel disease, IBD)疾病活动的主要组织学表现是中性粒细胞迁入胃肠黏膜和上皮细胞损伤, 其中中性粒细胞数目的变化与疾病活动度密切相关. 因此, 作为中性粒细胞源性的粪便标志物被认为可以很好的反应IBD疾病活动.

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■研发前沿
目前已有大量临床研究证实中性粒细胞源性粪便标志物在反应IBD肠道炎症程度方面具有重要应用价值, 且国内外关于IBD疾病监测的共识意见中也强调了粪便钙卫蛋白(calprotectin, Cal)乳铁蛋白(lactoferrin, Lf)的临床应用价值. 但也存在一些问题如: 上述标志物的临界值界定至今尚无定论、上述标志物的检测尚存在一定的假阳性和假阴性以及如何控制影响因素等.

sion)”[1], 由此对疾病活动度判断的要求越来越高. 内镜检查联合病变黏膜活检是反应疾病活动度的金标准[2], 但因其侵入性难以用于疾病随访; 粪便中In111标记白细胞排泄率是评价IBD活动性最可靠的检验指标[2], 但费用昂贵、辐射暴露限制了其应用[3]. 近年来研究发现粪便中中性粒细胞源性标志物在反应IBD活动性方面具有重要价值.

1 IBD发病机制及病理生理学特点

目前认为IBD的发病机制是环境因素作用于遗传易感者出现肠黏膜系统免疫功能失调, 最终导致肠道慢性炎性反应病理过程和临床表现[4,5]. IBD疾病活动的主要组织学表现是中性粒细胞迁入胃肠黏膜和上皮细胞损伤[6]. 《炎症性肠病组织病理学欧洲共识》[7]指出黏膜活检组织中中性粒细胞数量的变化与疾病活动、复发、黏膜愈合等过程密切相关, 具体为: 疾病活动时可见中性粒细胞浸润; 疾病复发时可见中性粒细胞和嗜酸性粒细胞增加; 疾病缓解时可见慢性炎症细胞、单核细胞数目减少, 中性粒细胞消失而嗜酸性粒细胞数目无变化. 由此推测中性粒细胞源性生物学标志物能准确反映疾病变化.

2 中性粒细胞源性粪便标志物与IBD活动性

中性粒细胞源性标志物主要有钙卫蛋白(calprotectin, Cal)、乳铁蛋白(lactoferrin, Lf)、促炎蛋白(S100A12)、多形核中性白细胞弹性蛋白(PMN-elastase, PMN-e)、基质金属蛋白酶(matrix metalloproteinases, MMPs)、中性粒细胞相关载脂蛋白(neutrophil gelatinase-associated lipocalin, NGAL)、髓过氧化物酶(myeloperoxidase, MPO)、溶菌酶(lysozyme, Lys)等, 研究显示上述标志物在IBD患者粪便中可测.

2.1 粪便Cal(fecal calprotectin, FC) Cal是一种钙锌结合蛋白, 主要来源于中性粒细胞, 少量见于单核细胞和反应性巨噬细胞. Cal占粒细胞胞质蛋白达60%, 故FC能成比例反应中性粒细胞肠道迁移[8]; Cal在粪便中分布均匀, 少量取样也能反映整个肠道炎症情况[9]. Cal能抗蛋白酶和细菌降解, 粪便标本室温放置1 wk仍性质稳定, 对个体来说24 h内任意时间所取标本测得FC值间有相关性(r = 0.90)[9]. IBD患者FC排泄率与In111标记白细胞排泄率相关[10]. 目前FC主要用ELISA法检测, 最近发现量子蓝快速测试法可替代ELISA用于FC检测, 该法检测快速, 弥补了ELISA耗时的不足[11]. 因此, FC用于IBD疾病监测时, 患者可随时留取标本, 结果及时可取, 在客观反映病情的同时也节约了时间.

多数研究发现FC在监测IBD疾病进程中有重要意义[12-14], 相关Meta分析结果也肯定了FC在IBD疾病活动性评估和预测复发中的价值. 在反应IBD疾病活动性方面, FC与临床疾病活动指数、内镜和组织学参数相当, 且FC对UC活动性评价作用优于CD[15], FC水平与UC和CD内镜下疾病活动指数和疾病分级相关[16]. 杨晓鸥等[17]研究显示IBD中FC水平显著高于肠易激综合征(irritable bowel syndrome, IBS)和正常对照者(P<0.001); IBS与正常对照间FC无显著差异(P>0.05). Schoepfer等[18]发现FC与UC内镜下疾病活动性相关(r = 0.821), 优于血白细胞(blood leukocytes)和C-反应蛋白(C-reactive protein, CRP); 内镜下疾病不同分级间FC有显著差异(P<0.001); 取临界值57 μg/g, FC判断内镜下疾病活动的敏感性为91%、特异性为90%. Schoepfer等[19]研究发现CD组FC显著高于健康对照组(P<0.001); 用克罗恩病简化内镜评分(simple endoscopic score for Crohn's disease, SES-CD)将CD分为非活动、轻度活动、中度活动、高活动性4级, 在FC、CRP、白细胞计数、克罗恩病活动指数(Crohn's disease activity index, CDAI)中, FC与SES-CD相关性最好(r = 0.75), 只有FC能区别非活动与轻度活动CD(P<0.001)、轻度活动与中度活动CD(P = 0.008)、中度活动与高活动CD(P<0.001). 另外, FC也是IBD疾病缓解的重要预测指标. D'Haens等[16]研究显示FC≤250 μg/g预测CD内镜下缓解的敏感度, 特异度, 阳性预测值, 阴性预测值分别为94.1%、62.2%、48.5%、96.6%; FC在预测UC内镜下缓解中也有重要价值[20]. Molander等[21]对经肿瘤坏死因子-α抑制剂治疗缓解的IBD患者(16例CD, 33例UC)进行停药后12 mo随访观察, 定期行FC测定和结直肠镜检查, 发现15例复发、34例仍缓解; 复发组FC水平较复发前明显升高, 内镜确诊复发前2 mo、4 mo、6 mo FC水平均比缓解时显著升高(分别为P = 0.0014、P = 0.0056、P = 0.0029), 说明连续监测FC能预测IBD复发.

对于单纯小肠病变的CD患者, 其疾病活动性判断是一个棘手的临床问题. 世界消化内镜组织(Organisation Mondiale d'Endoscopie Diges-

tive, OMED)与欧洲克罗恩病和溃疡性结肠炎组织(European Crohn's and Colitis Organisation, ECCO)联合提出的共识意见中肯定了小肠胶囊内镜(small-bowel capsule endoscopy, SBCE)在小肠CD疾病监测中的重要作用[22], SBCE疾病活动性指数主要有胶囊内镜CD活动指数(Capsule Endoscopy Crohn's Disease Activity Index, CECDAI)和Lewis评分. 研究[23]发现FC水平与CECDAI、Lewis评分相关. 另外, 由于儿童患者依从性差, 难以通过定期的内镜检查对IBD疾病进行监测, 研究[24]发现FC也能较好地反应IBD患儿疾病活动性. Kostakis等[25]对FC在IBD患儿疾病监测中的应用进行Meta分析, 结果显示FC水平在IBD活动期(包括新诊断未治疗者和治疗后复发者)显著高于缓解期, 非活动期显著高于IBS组; FC取临界值50 μg/g时, 判断IBD疾病活动的敏感性为96.2%-100%、特异性为71.9%-100%、阳性似然比为3.5-3.6、阴性似然比为0.0-0.1; 研究还显示FC在儿童IBD疾病复发中也有较好预测价值. 但Falvey等[26]认为FC不能预测IBD内镜下缓解, 主要原因可能为FC检测值受多种因素影响且检测结果存在一定假阳性和假阴性. 总之, FC在IBD疾病监测中具有较好的应用价值, 但不能完全替代内镜和组织学检查.

2.2 粪便Lf(fecal lactoferrin, FL) Lf是一种铁结合蛋白, 主要见于中性粒细胞, 亦少量见于单核细胞、巨噬细胞、淋巴细胞和肠上皮细胞刷状缘[27,28]. 肠道发生炎症时, 中性粒细胞浸入肠黏膜引起FL增加[29]. 无论成人还是儿童, FL对IBD疾病活动度评估均有重要意义[30,31]. Langhorst等[32]研究显示FL能区别出活动期IBD与非活动期IBD和IBS; 在UC和CD中, 有肠道炎症者FL水平显著高于无炎症者(分别为P<0.01, P<0.05). Vieira等[33]发现在CD中FL与CDAI、CDEI相关(P = 0.043, P = 0.000); 在UC中FL与Mayo疾病活动指数(Mayo Disease Activity Index, MDAI)相关(P = 0.000). Yamamoto等[34]发现FL与结直肠术后CD患者内镜下疾病活动性显著相关, 术后复发组比缓解期组FL值显著升高(P = 0.025), FL临界值为140 μg/g预测临床复发的敏感性、特异性分别为67%、71%. Gisbert等[35]对FL在IBD中的应用进行系统分析指出, 在评价IBD活动性时FL与临床疾病指数、内镜和组织学方法相关, 且UC优于CD; 同时还指出FL在IBD活动期和静止期中存在大范围重叠, 这可能会影响其在IBD活动性判断中的应用.

2.3 粪便S100A12(fecal S100A12, FS100A12) S100A12是另一重要的中性粒细胞源性蛋白分子, 与Cal同属S100蛋白家族, 与钙结合[36]. 通过激活多条细胞内信号通路、增加细胞因子释放发挥促炎作用[37]. 与Cal和Lf不同, S100A12具有中性粒细胞特异性[38]. IBD患者血清和粪便中均可测得S100A12, 但粪便S100A12敏感性和特异性更好[39]. 研究[40,41]显示FS100A12可用于IBD疾病活动性评价和预测疾病复发. Foell等[42]最早证明了IBD患者肠道病变黏膜中有较高的S100A12; 且认为FL与内镜下疾病活动相关[43]. Däbritz等[44]对181例IBD患者(成人147例, 儿童34例, CD61例, UC120例)随访3年发现, IBD复发组FS100A12水平显著高于非复发组; FS100A12>0.5 mg/kg与18 mo内疾病复发相关; 疾病复发前6 mo和复发后FS100A12均明显升高; 取0.43 mg/kg为临界值, 预测8-12 wk内疾病复发的敏感性、特异性分别为70%、83%. 从现有数据来看, FS100A12确实是IBD疾病监测的良好生物学指标, 但相关的临床研究较少不足以确定其可靠性.

2.4 粪便PMN-e(fecal PMN-elastase, FPMN-e) PMN-e是另一中性粒细胞源性蛋白分子, PMN-e在胰腺炎中的应用研究较多, 近年来发现PMN-e在IBD活动性评价中也有重要作用[43]. Kayazawa等[45]对IBD患者肠道灌洗液中Lf、PMN-e、MPO、Lys进行检测发现, 四指标均与UC内镜下疾病活动度分级相关; Lf、PMN-e在判断CD内镜下黏膜炎症的敏感性方面比CDAI好. 在IBD与IBS鉴别中, 粪便中PMN-e优于Cal、MPO、Lys、Lf, 且PMN-e敏感性和特异性最高[46]. Langhorst等[47]研究显示FPMN-e与UC结肠炎活动指数(colitis activity index, CAI)相关(r = 0.604, P<0.001), 活动期显著高于缓解期(P<0.001); Silberer等[46]也认为FPMN-e与IBD内镜下活动性相关. 但Langhorst等[32]研究发现粪便中Lf、Cal和PMN-e可作为区分活动期与非活动期IBD、IBD与IBS的指标, 但三者不能很好地反映IBD内镜下炎症程度. 上述研究表明FPMN-e在判断IBD疾病是否活动方面有一定价值, 但其在准确反映内镜下疾病活动度变化方面尚存争议.

2.5 粪便NGAL(fecal neutrophil gelatinase-

■相关报道
关于粪便Cal、Lf、S100A12在IBD活动性评估中的应用研究比较多, 且应用价值得到肯定; 其他中性粒细胞源性粪便标志物的研究相关较少.

■创新盘点

本文系统介绍了中性粒细胞源性粪便标志物在IBD疾病活动性评价中的应用价值, 同时也对上述标志物的临床应用弊端做了简要介绍, 最后简单比较了各标志物间的优劣势, 为IBD疾病活动度判断提供了较好的临床应用参考.

associated lipocalin, FNGAL) NGAL是近来被识别的分子, 主要来源于循环中的中性粒细胞, 在组织中含量较低[48], 但当肠上皮细胞、呼吸道上皮细胞、肾小管细胞和肝血管内皮细胞受损时, 组织中NGAL含量明显增加. 研究[49]发现NGAL在IBD患者结肠上皮细胞中有过分表达. Nielsen等[50]发现在UC组缓解期、中度活动期、严重活动期3亚组中, 除缓解组外, 其余2组FNGAL值均比正常对照组显著升高(P<0.02, P<0.001); CD组中, FNGAL值在静止期与活动期有统计学差异(P<0.01); FNGAL水平随UC疾病活动性增加而显著升高(P = 0.02), 同时研究发现血NGAL水平在UC和CD组静止期与活动期间均无统计学差异. 由此推测FNGAL可作为IBD活动性评价的生物学指标. 近年来关于FNGAL在IBD疾病监测中的研究较少, 有关血NGAL的研究相对较多, 但结论不一, Oikonomou等[51]发现血NGAL水平IBD组显著高于IBS和正常对照组、活动期显著高于非活动期(均P<0.0001), 而也有研究认为血NGAL与IBD疾病活动性无明显相关[52]. 由此可见, FNGAL和血NGAL的临床价值尚待研究.

2.6 其他中性粒细胞源性粪便标志物 MMPs和MPO也为中性粒细胞源性标志物. 活动性IBD肠黏膜中的中性粒细胞释放MMPs, MMP-9在活动性UC患者结肠活检组织中明显升高[53,54]. Annaházi等[55]研究显示MMP-9能区分UC与IBS、健康对照组; MMP-9临界值取0.245 ng/mL时判断UC活动的敏感性、特异性分别为85.1%、99.9%. MMP-9在儿童IBD活动性判断中也有重要意义[54]. 粪便中MPO在监测UC治疗效果和预测IBD复发中也有重要价值[56,57], 但因MPO带正电荷易吸附于粪便颗粒表面[58], 可能会影响检验结果的可靠性, 使其应用受限.

2.7 几种标志物的比较 Foell等[43]对Cal、Lf、S100A12、PMN-e、MPO和Lys6个中性粒细胞源性粪便标志物进行对比分析显示: 除MPO外, 都可作为IBD疾病活动性评价指标, 其中Cal、S100A12、PMN-e价值更大; 在区分IBD与IBS方面, Cal、Lf、S100A12优于其他指标. 结合IBD黏膜愈合的主要组织学表现: 中性粒细胞消失、单核细胞减少、嗜酸性粒细胞数目无明显变化[7], 又因为S100A12具有中性粒细胞特异性, 而Cal、Lf也见于单核细胞, 因此推测在预测黏膜愈合方面, S100A12可能优于Cal、Lf.

3 讨论

总之, 中性粒细胞源性粪便标志物在IBD疾病活动性评价中具有重要价值, 尤其是FC和FL在国内外关于炎症性肠病诊治的共识意见中均有推荐, 但一项国外调查研究显示目前胃肠病学医师在IBD现患病例随访中最常采用的疾病监测方法是临床症状而不是内镜检查或生物学标志物[59], 原因可能为内镜检查为侵入性、生物学标志物应用经验不足且临界值选取尚存争议等. 因此, 在未来IBD疾病监测中, 寻找一种非侵入性、可靠、价廉、特异性更强的疾病评估手段仍是一个重要课题.

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■应用要点
中性粒细胞源性粪便标志物具有非侵入性、样本简便易得、检测结果可靠等特点, 有望在IBD疾病活动性评价中发挥重要作用.

■名词解释
中性粒细胞源性粪便标志物: 指一组主要来源于中性粒细胞的, 在粪便中具有一定稳定性的, 能够反映肠道炎症程度的生物学标志物.

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■同行评价
本文选题贴近临床, 具有一定的科学性、实用性, 认真进行了文献搜集工作, 有关IBD发病机制的简述为中性粒细胞源性粪便标志物用于评估IBD疾病活动度提供了理论来源, 文章重点阐述了各标志物在IBD疾病活动度评估中的应用价值. 综述条理清楚, 语言流畅, 文献新, 对临床具有一定的指导意义.

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• 消息 •

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