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文献综述 REVIEW

半乳糖凝集素-9与炎症性肠病关系的研究进展

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Galectin-9 and inflammatory bowel disease

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Abstract

Galectin-9 (Gal-9), a beta-galactoside binding lectin, is a tandem-repeat-type member of the galectin family which can specifically recognize and bind to galactosidase associated with diverse biological processes. Gal-9 is widely expressed in various tissues, plays a role in cell growth, polarization, adhesion, aggregation, and apoptosis, and has important functions in inflammatory diseases, autoimmune diseases, tumors, and infections. Our recent studies showed that Gal-9 is strongly associated with the genesis and development of inflammatory bowel disease. Here we will review the progress in understanding the role of Gal-9 in the pathogenesis of inflammatory bowel disease.

Key Words: Galectin-9; Inflammatory bowel disease; Tim-3; Immunity

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摘要

半乳糖凝集素-9(galectin-9, Gal-9)是能特异性识别、结合半乳糖苷的半乳糖凝集素家族成员之一. 该蛋白广泛表达于机体组织, 参与细胞生长、分化、黏附、聚集、凋亡等, 与炎症性疾病、自身免疫性疾病、肿瘤、细菌病毒感染等多类疾病密切相关. 近年研究发现, Gal-9与炎症性肠病的发生、发展关系密切, 本文就Gal-9与炎症性肠病的关系进行综述.

关键词: **半乳糖凝集素-9**; **炎症性肠病**; Tim-3; **免疫**

核心提示: 半乳糖凝集素-9(galectin-9, Gal-9)负性调控Th1/Th17细胞免疫应答, 介导相应免疫细胞细胞凋亡, Gal-9及其相关调控因子表达异常参与炎症性肠病(inflammatory bowel disease)的发生发展.

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■背景资料
早期研究发现半乳糖凝集素-9(galectin-9, Gal-9)参与细胞生长、分化、黏附、聚集、凋亡等多种生物学活动, 与炎症性疾病、自身免疫性疾病、肿瘤、细菌病毒感染等多类疾病密切相关, 近年来研究显示, Gal-9在免疫调节中发挥广泛且复杂的作用, 与炎症性肠病(inflammatory bowel disease, IBD)的关系受到越来越多学者的关注.

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■研发前沿
Gal-9与IBD的发生、发展关系密切, 但不同学者提出不同的信号通路, 何种信号通路在IBD中起决定作用尚不清楚, 这是当今乃至今后的研究热点.

0 引言

炎症性肠病(inflammatory bowel disease, IBD)是一种发病机制不明确, 与环境、遗传、免疫等因素相关反复发作的慢性肠道炎症性疾病, 包括溃疡性结肠炎(ulcerative colitis, UC)、克罗恩病(Crohn's disease, CD). 近年来IBD发病率有逐渐增高的趋势, 但其确切发病机制还不十分清楚. 肠道内环境与宿主不恰当的免疫应答正受到密切关注, 目前一般认为IBD是遗传易感人群肠道黏膜损伤后, 过量细菌侵入黏膜下层, 激发固有及适应性异常免疫应答所致. 半乳糖凝集素-9(galectin-9, Gal-9)是能特异性识别、结合半乳糖苷的半乳糖凝集素(galectin)家族成员之一, 可与多种糖蛋白连接发挥作用, 并参与细胞生长、分化、黏附、聚集、凋亡等多种生物学活动, 与炎症性疾病、自身免疫性疾病、肿瘤、细菌病毒感染等多类疾病密切相关[1], 尤其与炎症性肠病的发生、发展的关系受到越来越多学者关注.

1 Gal-9的生物学功能

1.1 Gal-9概述 半乳糖凝集素-9(galectin-9, Gal-9)是1997年由Wada等[2]从鼠胚肾组织中首次分离出来的能特异性识别、结合半乳糖苷, 具有嗜酸性粒细胞趋化性[1]的半乳糖凝集素(galectin)家族成员之一, 他存在于多种物种, 并在组织分布上具有广泛性. 他由2个串联的糖识别结构域(carbohydrate-recognition domains, CRD)通过一条肽链相连而成, 其中C-CRD是受体识别、诱导T细胞凋亡的最主要决定区域[3,4], 而N-CRD在激活树突状细胞(dendritic-like cells, DCs)方面更有效[4]. 在结构上可分为膜结合型、可溶型两种, 根据CRD连接肽段的长短可分为L、M、S三种亚型, T细胞有选择性的高表达Gal-9(M)、Gal-9(L), 低表达Gal-9(S), 而在结肠癌细胞血管黏附上Gal-9(L)具有抑制作用, Gal-9(S)、Gal-9(M)具有促进作用[5]. 人*Gal-9*基因位于人类染色体17q11.1, 包括11个外显子, 转录区长度约为1.7 kb, 编码蛋白相对分子量约34-39 kDa, 在人体肝脏、脾脏、小肠、肾脏、肺脏、骨骼肌、免疫细胞等组织中广泛表达. 不同位置的Gal-9其功能或是相反的, 如胞内的Gal-9可触发单核细胞释放促炎因子[1], 而胞外的Gal-9可诱导单核细胞凋亡[6].

1.2 Gal-9与免疫调节 Gal-9是一种新发现的以Tim-3、CD44为主要受体分子的嗜酸性粒细胞趋化因子, 其以浓度依赖的方式延长嗜酸性粒细胞的存活, 并抑制其凋亡[7]. 因Tim-3表达于特异性T细胞[8]、固有免疫细胞[9], 故Gal-9在免疫调节中发挥着重要作用. 在单纯疱疹病毒感染中Gal-9对$CD8^+$ T细胞具有抑制作用, 潜伏感染时上调的Gal-9表达可致$CD8^+$ T细胞免疫活性减弱, 而*Gal-9*基因敲除的小鼠, $CD8^+$ T细胞免疫活性较强[10,11]. Gal-9/Tim-3反应可激活$CD4^+$ T细胞, 在HIV-1感染中抑制持续的免疫激活及相关的组织损伤. 丙型病毒性肝炎患者的肝脏库普佛细胞有更多的Gal-9表达, 并伴有循环血中Gal-9升高[12], 通过与Tim-3结合参与固有免疫应答及适应性Th1/Tc1功能失调, 最终导致HCV持续感染[13].

1.3 Gal-9与细胞黏附、聚集 Gal-9在机体组织中广泛表达, 其黏附、聚集作用在多种生物活动中发挥重要的调节作用. 成纤维细胞胞膜上的Gal-9在干扰素-γ(interferon-γ, IFN-γ)的诱导下表达增多, 这些胞膜Gal-9表达量升高的细胞即可被嗜酸性粒细胞有选择性地黏附[14]. 而该蛋白对CD44依赖的白细胞识别、黏附细胞外基质发挥调节作用, 是其抑制气道过敏性炎症和气道高反应的重要机制[15]. 除参与炎症反应外, Gal-9在肿瘤转移中也发挥重要作用. 有研究指出, 当Gal-9表达降低时, 乳癌细胞聚集表现被抑制, 而增殖、黏附、侵袭作用增强[16], 与之前有关黑色素瘤的研究结果类似[17].

1.4 Gal-9与细胞凋亡 Gal-9在细胞凋亡中发挥重要作用, 如在丙型肝炎病毒(hepatitis C virus, HCV)感染患者肝库普佛细胞表面, Gal-9可通过活化Caspase8途径诱导HCV特异性$CD8^+$ T细胞凋亡[12], 而抗蛋白酶的重组Gal-9(hGal-9)可通过Caspase8、9、3诱导5种骨髓瘤细胞的凋亡[18]. 此外, Gal-9还可促使DC、Tim-3^+CD8^+ T细胞活化增殖, 产生更多的穿孔素、颗粒酶B诱导肿瘤细胞凋亡[19]. 而Gal-9通过钙-钙蛋白酶-Caspase1信号通路诱导如MOLT-4(T细胞)、THP-1(巨噬细胞)等多种免疫细胞凋亡[20,21], 是其参与机体炎症反应的重要机制之一.

2 Gal-9与IBD的关系

IBD是一种发病机制不明确, 与环境、遗传、免疫等因素相关反复发作的慢性肠道炎症性疾病[22]. 近年来, 其发病率有逐渐增高的趋势, 但其确切发病机制还不十分清楚. 目前一般认为IBD是遗传易感人群肠道黏膜损伤后, 过量细菌侵入黏膜下层, 激发固有及适应性异常免疫

反应所致, 其中涉及肠道感染, 肠上皮屏障破坏, 固有及适应性免疫激活等.

2.1 Gal-9与Th1/Th17 近年来, 炎症性肠病的发生、发展与免疫应答异常尤其是与Th1/Th17失调的关系已受到越来越多学者的密切关注. Rovedatti等[23]对IBD患者进行组织病理学研究发现, IBD患者肠黏膜炎症处比非炎症处Th17、Th1/Th17均增加, IL-17表达上调. 后有学者在动物实验中也发现了类似结果, 并且应用Th1型细胞因子IL-12的抗体对炎症性肠病动物模型进行治疗, 炎症可在一定程度上得到缓解, 而Th1型细胞因子IFN-γ缺陷小鼠不能诱导结肠炎的发生[24,25]. Gal-9对Th1、Th2、Th17、Tregs、嗜酸性粒细胞等免疫细胞具有调节作用已得到大量研究的支持; 其与Tim-3结合, 下调自身免疫性疾病, 诱导免疫耐受也成为近年来免疫异常类疾病的研究热点. 因Gal-9与Tim-3结合可诱导Th1细胞凋亡, 阻止Th1、Th17细胞因子的释放(保护作用), 负性调节Th1/Th17, 上调调节性T细胞(Tregs)[26], 可推测Gal-9/Tim-3与炎症性肠病的发生发展密切相关, Gal-9与Tim-3结合或有下调IBD炎症反应的作用.

另有学者研究发现, 溃疡性结肠炎患者及结肠炎模型小鼠体内Tim-3、Gal-9较正常者明显降低, 并伴有Th17响应升高, Treg细胞响应衰减, Th1反应明显降低. 应用外源性Gal-9干预可改变不同T细胞亚群间的平衡, 减轻小鼠结肠炎症状[27], 这与Veenstra等[28]在GVHD的研究中发现, 应用Tim-3抗体或利用*Tim-3*基因敲除方法阻断Tim-3/Gal-9反应, 可增高T细胞增殖及GVHD肠道炎症表现的结果一致. 提示了Tim-3/Gal-9通路异常与结肠炎症关系密切, 或是UC的发病机制之一. Li等[29]在TNBS-结肠炎建模前12 h腹腔注射重组Tim-3蛋白能够明显加重小鼠结肠炎症状, 且结肠炎症状与小鼠体内Tim-3$^+$细胞成正相关, 前炎性因子IFN-γ、IL-17、IL-23水平明显升高, 而抗炎性因子IL-4、TGF-p水平明显下降; 经典的Treg细胞群表达CD25、FoxP3的CD4$^+$ T细胞数目减少, 肠系膜淋巴结细胞CD80表达水平下降, 同时CD4$^+$ T细胞CTLA-4的表达降低, 而CD28的表达升高. 提示了Tim-3分子可能通过对共刺激分子CD28、CD80、CTLA-4的调节, 影响CD4$^+$ T效应细胞不同亚群的极化, 发挥对结肠炎的负调节作用, 提示了Gal-9相对减少或增加结肠炎的炎症反应. 同样有研究发现, CD患者黏膜下及外周血中Th1表面Tim-3表达较对照组明显降低, 并伴有Th1表面Tim-3上调异常, Tim-3的相对减少或致CD发病[30]. 提示Tim-3/Gal-9通路或在UC、CD的发病中发挥不同的调节作用, 或为IBD治疗提供新思路.

2.2 Gal-9与固有免疫 大量研究证明, 肥大细胞增殖、脱颗粒增多可激活固有免疫、适应性免疫, 介导神经免疫相互作用, 进而破坏肠上皮屏障, 而参与IBD发病[31,32]. 我们前期研究发现, 肥大细胞还可通过Fc-γ受体与鞭毛蛋白特异性结合后脱颗粒, 在肠道炎症反应中发挥重要作用[33]. 而已有学者在过敏性肠炎的研究中发现, 肠上皮细胞、血清中Gal-9表达与急性过敏的皮肤反应, 肥大细胞脱颗粒, Th1、Treg细胞分化成负相关[34]. 而Gal-9调节作用是通过参与调节外周血单个核细胞(peripheral blood mononuclear cell, PBMC)分泌IFN-γ、IL-10的过程实现的[35]. 另有研究发现, 肥大细胞产生的类胰蛋白酶可激活T84细胞的PAR-2受体, 进而诱导T84细胞表达Gal-9增多, 应用外源性Gal-9抗体阻断Gal-9作用则可抑制抗原特异性Th2反应, 小鼠肠道炎症减轻[36], 这与前文Shi、Li等[2-29,33]指出的Gal-9具有抑制结肠炎症的作用不一致, 或许是Gal-9在不同类型的结肠炎中参与的免疫通路不同, 对于不同类型肠道炎症的调节作用或许相反, 因此Gal-9在IBD中的具体免疫调节机制有待进一步研究. 此外, 肥大细胞也可分泌Gal-9, 且可发挥自分泌调节作用, 抑制IgE与抗原结合后诱导的肥大细胞过度脱颗粒[37]. 由此可推测Gal-9或是通过调节肥大细胞免疫功能从而调节IBD发病. 我们前期研究发现, 应用美沙拉嗪治疗溃疡性结肠炎后, 患者血清TNF-α及IL-8较柳氮磺吡啶对照组降低, 且临床症状缓解、镜下黏膜修复优于对照组[38]. 后进一步研究发现实验性结肠炎小鼠结肠黏膜有大量炎性细胞浸润并TNF mRNA水平明显升高, 抗TNF-单克隆抗体治疗可有效地阻断慢性结肠炎的发生, 降低CD4$^+$ T细胞和单核巨噬细胞浸润及CD4$^+$ T细胞效应应答[39]. TLR2介导HMC-1细胞对PGN的吸收, 致T84单层屏障功能破坏, 阻断TLR2可阻断HMC-1被激活, 及其引起的T84单层屏障功能减退[40]. 人固有免疫的单核/巨噬细胞特异性受体(刺激性的有TLR, 抑制性的有Tim-3)与微生物产物结合后, 进行识别、应答. 有研究发现, 其他细胞表达的Gal-9与单核/巨噬细胞表达的Tim-3结合后, 可负性调节TLR介导的IL-12表达. 而单核细胞表达的强效的或沉默的Gal-9可通过

■相关报道
大量研究证实, Gal-9负性调控Th1/Th17细胞免疫应答, Tim-3表达失调参与自身免疫性疾病、过敏性疾病、病毒及细菌感染相关疾病等多种疾病.

■创新盘点
本文从Gal-9的生物学功能及其与IBD的关系两部分进行了较为系统的阐述，指出Gal-9在IBD发生、发展中的可能参与的信号通路，或是IBD治疗的新靶点.

加强的TLR信号通路调节*Tim-3*、*IL-12/IL-23*基因转录[41]. 另有研究也发现, Gal-9可下调巨噬细胞TNF-α、TLR2表达, 降低小鼠体内的促炎因子、趋化因子, 如TNF-α、IL-1B、IL-6及角化细胞衍生细胞因子. 而Gal-9缺陷小鼠急性炎症明显, 中性粒细胞、TNF-α升高, 应用Gal-9治疗后炎症减轻[42]. 由此可推测, Gal-9或通过在固有免疫中发挥重要的调节作用而参与IBD的发病.

2.3 Gal-9与肠道感染 IBD是一种病因及发病机制尚不完全明确的非特异性慢性肠道炎症性疾病, 目前, 肠道微生物及微生物产物因素越来越受到重视. 我们前期研究发现, 肠上皮细胞可转运肽聚糖与肥大细胞表面TLR2受体结合, 呈递于胞内NOD2受体, 进而肥大细胞活化脱颗粒释放组胺等炎症介质参与肠道炎症的发生[43]. UC患者血清中鞭毛蛋白抗体及黏膜下鞭毛蛋白量较对照组明显增多, 且与病情呈正相关[44]. 最近的流行病学分析发现, 急性弯曲菌肠炎可诱发易感人群发生IBD或使IBD患者病情加重[45,46], 这可能因为肠上皮细胞受到相应抗原刺激后发生M样细胞变化, 发挥转运、胞吞抗原的作用, 而这种可逆性分化与Caco-2细胞、淋巴滤泡相关上皮细胞Gal-9表达上调有关[47]. Kalischuk等[48]发现空肠弯曲菌可诱导非侵入性共生菌通过上皮转胞吞作用移位, 破坏肠上皮屏障功能; 而受弯曲菌感染的单层肠上皮表达Gal-9的增高, 肠绒毛结构缺失及与吸收功能相关的分子表达明显减少[49], 提示了IBD与肠道细菌感染发病相关, 而Gal-9或参与肠上皮屏障破坏及激活免疫应答, 但其确切机制还有待进一步研究.

2.4 Gal-9与凝血 已有研究发现, IBD患者体内存在与凝血激活和全身炎症反应中的血小板聚集有关的较高血栓风险[50], 应用氯吡格雷抑制血小板聚集可降低IBD模型小鼠的CMDI、DAI、MPO积分、减轻体质量降低[51], 此外, 已有学者指出, Gal-9还可激活凝血酶, 促使血小板聚集, 在凝血中发挥重要调作用[52]. 由此可推测, Gal-9或是IBD高凝状态的始动因子, 但需进一步研究证实.

3 结论

Gal-9作为一种作用复杂, 分布广泛的半乳糖结合蛋白, 在免疫调节中发挥重要重要, 为IBD的研究提供了一个新思路. 其参与固有及适应性免疫调节, 与IBD的发生、发展关系密切, 并有望成为IBD治疗的新靶点. 但因其表达广泛、作用复杂而在IBD研究中的具体机制尚不完全明确, 尚需进一步研究.

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■应用要点

Gal-9与其配体及相关调控因子在IBD中表达失调或功能异常, 有望通过改变其表达或修复其功能, 指导临床疗效评估及药物靶向治疗.

■同行评价
本文选题较为新颖，文献调研较充分，内容也较全面，具有一定指导意义.

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