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文献综述 REVIEW

T细胞免疫球蛋白黏蛋白3与消化系炎症疾病的关系

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Role of Tim-3 in pathogenesis of inflammatory diseases of the digestive system

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Abstract
T cell immunoglobulin mucin domain-containing molecules (Tim)-3 is a type I cell membrane glycoprotein that is expressed on the surface of cells involved in innate and adaptive immunity. As the first discovered member of Tim family, Tim-3 participates in T cell-induced immune responses. By interacting with its ligands galectin-9 or Ptd-Ser, Tim-3 induces cell apoptosis and clearance of apoptotic cells in autoimmune disorders, allergic diseases and virus infection-associated diseases. Tim-3 can act as a negative regulator of Th1/Th17 immune responses. Current research has shown that Tim-3 is involved in the pathogenesis of inflammatory diseases of the digestive system. Here we will review the progress in understanding the role of Tim-3 in the pathogenesis of inflammatory diseases of the digestive system.

Key Words: Tim-3; Galectin-9; Immune; Inflammatory; Digestive system diseases

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摘要
T细胞免疫球蛋白黏蛋白(T cell immunoglobulin mucin domain containing molecules, Tim)-3是一种Ⅰ型细胞表面糖蛋白, 表达于多种固有及适应性免疫应答细胞表面. Tim-3作为Tim家族中参与T细胞免疫应答的首位成员, 他通过与配体半乳凝集素(galectin-9, Gal-9)及磷脂酰丝氨酸(PtdSer)相互作用, 介导细胞凋亡及清除凋亡细胞, 负性调控Th1/Th17细胞免疫应答, 参与自身免疫性疾病、过敏性疾病、病毒感染相关性疾病等多种疾病. 目前研究表明Tim-3与消化系统炎症疾病密切相关, 本文将就相关文献报道进行综述.

关键词: T细胞免疫球蛋白黏蛋白-3; 半乳糖凝集素-9; 免疫; 炎症; 消化系疾病

核心提示: Tim-3负性调控Th1/Th17细胞免疫应答, Tim-3与配体gal-9结合介导细胞凋亡, 两者及其相关调控因子表达异常参与消化系疾病的发生发展.

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0 引言
T细胞免疫球蛋白黏蛋白家族(T cell immuno-

■背景资料
早期研究认为Tim-3特异性表达于Th1细胞表面, 他可作为区分Th1和Th2细胞的表面标志物, 并参与Th免疫调控. 近年来研究显示Tim-3在多种类型细胞表面均有表达, Tim-3与配体结合可调控免疫反应的多个环节, 并诱导细胞凋亡及清除凋亡细胞.

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■研发前沿
Tim-3信号通路异常参与消化系疾病的发生发展, 激活或阻断此通路可改善或治愈相关疾病, 何种因素或机制导致Tim-3信号通路异常, 目前尚不清楚, 这是当前乃至今后的研究热点.

globulin mucin domain containing molecules, Tim)最初于2001年由McIntire等[1]在鼠的气道高反应调控位点区(Tapr)被发现, 该家族包含8个成员, 定位于鼠染色体11B1.1上, 在人类染色体上已鉴定表达的Tim家族成员是Tim-1、Tim-3和Tim-4, 定位于染色体5q33.2. Tim家族与T细胞免疫应答密切相关, T细胞免疫球蛋白黏蛋白(T cell immunoglobulin mucin domain containing molecules, Tim)-3作为Tim家族中的重要一员, 大量研究显示Tim-3参与以T细胞应答异常为主的多种疾病. 目前研究表明Tim-3与消化系炎症疾病密切相关, 包括肝炎病毒及幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)、炎症性肠病、食物过敏所致肠道炎症浸润等, 现将Tim-3与他们的关系综述如下.

1 Tim-3的生物学性能及配体

人Tim-3分子由301个氨基酸组成, 其基因长约23 kb[2], 与鼠Tim-3具有63%的同源性, 表达在终末分化的$CD4^+$Th1, $CD8^+$Tc1细胞及Th17表面[3-5]. 此外, Tim-3也表达在人固有免疫细胞上, 如树突状细胞[6]、自然杀伤细胞[7]、单核巨噬细胞表面[8]. Tim-3是一种Ⅰ型细胞表面糖蛋白, 他由信号肽、胞外免疫球蛋白结构域、黏蛋白结构域、跨膜结构域及胞质尾区组成[2]. 其免疫球蛋白晶体结构分析显示, 该结构域的4个保守半胱氨酸之间形成的2个独特袋状结构, 为Tim-3与其配体结合及发挥效应提供了作用位点[9]. 现已明确Tim-3负性调控Th1免疫应答, 他通过与配体半乳凝集素(galectin-9, Gal-9)相互作用介导细胞凋亡, 参与自身免疫性疾病[10]、过敏性疾病[11]、病毒感染相关性疾病等多种疾病[12]. 而在固有免疫应答中, Tim-3可与Toll样受体(toll-like receptor, TLR)协同作用启动固有免疫应答, 通过刺激巨噬细胞活化参与自身免疫性[13]及感染性疾病[14]. Tim-3在固有及适应性免疫应答中发挥不同作用的现象, 是与树突状细胞(dendritic cells, DC)和Th1细胞表面Tim-3胞内段去酪氨酸磷酸化形式不同相关[6].

Gal-9作为Tim-3的天然配体[15], 他是一种大小约36 kDa的S型凝集素, 属于半乳糖凝集素家族中的一员, 1997年首次从霍奇金淋巴瘤中克隆出来[16], 广泛分布在肝脏、小肠、脾脏、心脏、胸腺、骨骼肌等处[17], 表达于多种类型细胞表面. Th1细胞通过分泌干扰素(interferon-γ, IFN-γ)上调Gal-9的表达[18], 后者与Tim-3相互作用介导抑制性信号, 促进钙内流, 选择性诱导Th1细胞凋亡[15,18,19]. 此外, Gal-9可促进T细胞分化成调节性T(regulatory T cells, Treg)细胞, 抑制其分化成Th17细胞[20], 同时可与Tim-3相互作用诱导Th17细胞凋亡[21]. DeKruyff等[22]发现Tim-3与其另一个配体磷脂酰丝氨酸(PtdSer)之间具有高达50%的亲和力, 两者相互作用可介导凋亡细胞吞噬, 维持内环境稳定, 参与自身免疫调节及免疫耐受诱导[23].

2 Tim-3与消化系统炎症疾病

2.1 Tim-3与肝脏疾病

2.1.1 Tim-3与病毒感染相关性肝病: 病毒持续感染以适应性免疫应答受损为特征, 尤以$CD8^+$ T细胞功能受损明显[24], 而有效的病毒特异性$CD8^+$ T细胞应答在病毒清除中起重要作用[25].

Wu等[26]研究发现, 慢性乙肝病毒(chronic hepatitis B, CHB)感染患者外周血$CD4^+$和$CD8^+$ T细胞表面高表达Tim-3, 其水平与传统肝脏损伤标志物丙氨酸转移酶(alanine transaminase, ALT), 门冬氨酸转移酶(aspartate transferase, AST), 总胆红素(total bilirubin, TB)和国际标准化比率(International Normalized Ratio, INR)呈正相关, 经有效抗病毒治疗Tim-3表达下调, 提示Tim-3过表达参与持续乙型肝炎病毒(hepatitis B virus, HBV)感染, Tim-3可作为评估肝脏损伤程度的一个有效指标. $Tim\text{-}3^+CD8^+$ T细胞数目与转录因子T-bet mRNA及细胞因子IFN-γ水平呈负相关, 与病毒载量无关, 故研究者推测Tim-3通过下调Th1/Tc1细胞应答, 负性调控宿主免疫系统, 最终导致HBV持续感染. 此外, 有研究显示自然杀伤(natural killer, NK)细胞表面上调的Tim-3可与Gal-9相互作用, 抑制NK细胞的免疫活性, 导致HBV持续感染[27]. Wu等[28]进一步研究发现, 封闭Tim-3信号通路可修复部分分泌、增殖功能受损的$Tim\text{-}3^+CD8^+$ T细胞, 提示Tim-3信号通路负性调控病毒特异性$CD8^+$ T细胞介导的免疫应答, 推测细胞功能修复与否受细胞本身损伤程度及抑制分子如PD-1、CTLA-4和CD244等影响, 具体机制尚不清楚. 此外, 急性乙肝病毒(acute hepatitis B, AHB)感染患者外周血$CD8^+$ T细胞表面Tim-3呈一过性上调, 其表达水平与肝损标志物、转录因子及细胞因子水平无明显相关[26], 提示Tim-3在AHB和CHB感染致病中发挥效应不同, 导致了HBV感染结局的多样性. 与CHB感染类似, Tim-3在丙型肝炎病毒(hepatitis C virus,

HCV)特异性$CD8^+$ T细胞表面呈高表达[29,30], 慢性HCV感染患者肝内$PD\text{-}1^+Tim\text{-}3^+CD8^+$ T细胞占肝总$CD8^+$ T细胞比例远高于正常人群[29], 而大部分Tim-3在缓解晚期才降至正常水平[30], 提示$PD\text{-}1^+TIM\text{-}3^+CD8^+$ T细胞可作为慢性HCV感染的一种主要肝内细胞显型[30], 同时Tim-3表达水平可作为感染转归的一个预测指标. 虽然封闭PD-1/Tim-3均可改善HCV特异性$CD8^+$ T细胞的增殖功能[29-31], 但只有封闭Tim-3才能杀死HCV感染肝细胞[30], 提示Tim-3和PD-1在T细胞功能衰竭介导的不同阶段发挥作用. Zhang等[32]研究推测, Tim-3/Gal-9与PD-1和细胞因子信号传导抑制因子-1(suppressor of cytokine signaling-1, SOCS-1)相互作用, 限制STAT-1磷酸化, 负性调控TLR介导的白介素(interleukin, IL)-12分泌, 使固有免疫应答失调, 进而诱导适应性Th1/Tc1功能失调, 最终导致HCV持续感染. 此外, Mengshol等[33]研究显示, HCV感染患者肝枯否细胞表面高表达Gal-9, Gal-9可通过活化caspase8途径诱导HCV特异性$CD8^+$ T细胞凋亡.

肝细胞癌(hepatocellular carcinoma, HCC)与HBV及HCV感染密切相关[34]. Li等[35]采用流式细胞术检测150例临床确诊HCC患者的癌及癌旁组织发现, Tim-3主要表达在肿瘤浸润T细胞表面, Gal-9主要在HBV相关HCC的枯否细胞表面呈高表达, Tim-3/Gal-9相互作用可介导HBV相关HCC的T细胞衰竭. HBV阳性HCC患者$Tim\text{-}3^+$ T细胞在T细胞中所占比例远高于HBV阴性HCC患者, 提示Tim-3表达水平在一定程度上与肿瘤微环境相关. 此外, $Tim\text{-}3^+$ T细胞数与肿瘤大小呈正相关, 与患者生存期呈负相关, 提示$Tim\text{-}3^+$细胞数可作为判断HCC患者生存预后的一个指标.

此外, Li等[36]对789例中国汉族人口Tim-3基因启动子区-1541C/T, -1516G/T, -882C/T, -574G/T及外显子3区进行基因分型发现, -1516G/T位点与HBV易感性及HBV相关HCC特性(肿瘤分级、淋巴细胞转移)相关. 另一项相关性分析显示-1516基因显型GT/TT可能参与HCC的发展及转归[37].

总之, Tim-3在病毒感染相关肝病的发展、转归中发挥重要作用. 虽然大量研究已证明, Tim-3负性调控Th免疫应答, 但病毒感染相关肝病中高表达Tim-3的功能衰竭$CD8^+$ T细胞是否发生凋亡, 发生凋亡又跟何种因素相关, 目前尚不清楚, 仍有待于进一步研究.

2.1.2 Tim-3与自身免疫性肝炎: 自身免疫性肝炎(autoimmune hepatitis, AIH)是一种慢性进行性肝脏炎症性疾病. 他主要由$CD4^+$ T细胞通过识别自身抗原介导免疫应答. AIH与Treg功能缺陷及$CD4^+$ T细胞低应答相关[38,39]. Liberal等[39]研究发现, AIH患者外周血$Tim\text{-}3^+CD4^+$ T细胞和$Gal\text{-}9^+$ Treg细胞较健康人群少, 疾病复发组$Tim\text{-}3^+$细胞数较缓解组少, 提示$Tim\text{-}3^+$与$Gal\text{-}9^+$细胞数与AIH相关. $Tim\text{-}3^+$ T细胞较$Tim\text{-}3^-$ T细胞而言, 前者对Treg细胞的负性调控作用更易感, 尤其是CD127-Treg细胞, 表明Tim-3参与$CD4^+$ T细胞与Treg细胞介导的免疫调节. 而用siRNA封闭Treg细胞表面Gal-9可使Treg细胞对$CD4^+CD25^-$ T细胞的抑制能力显著下调, 推测Gal-9低表达可能是Treg功能受损的一个机制. 据此推断, AIH中$CD4^+CD25^-$ T效应细胞表面Tim-3与Treg细胞表面Gal-9可能是通过降低免疫易感性和损伤Treg细胞功能, 参与免疫调节受损.

2.1.3 Tim-3与原发性胆汁性肝硬变及硬化性胆管炎: 原发性胆汁性肝硬变(primary biliary cirrhosis, PBC)是一类以T细胞介导为主的慢性肝脏损害性疾病[40]. Lv等[41]建立小鼠肝损伤模型发现大量肝细胞凋亡, 大块肝组织出血坏死, $CD4^+$ T细胞数目多, 且Tim-3表达上调. 用抗Tim-3单克隆抗体封闭Tim-3信号通路可加重肝脏损伤的病理学程度, 伴$Tim\text{-}3^+CD4^+$ T细胞数目显著增多, 提示Tim-3信号通路参与慢性肝损伤. 而用Gal-9预处理可显著改善肝脏病理学特征, 伴$CD4^+$ T细胞数目及炎症因子分泌减少, 推测Tim-3与Gal-9结合可诱导$CD4^+$ T细胞凋亡, 从而减少肝脏炎症因子浸润, 改善肝脏受损程度.

2.1.4 Tim-3与肝移植: 肝移植是治疗终末期肝病的一种有效治疗手段, 缺血再灌注损伤(ischemia/reperfusion injury, IRI)可致约10%的早期肝移植失败, 而Toll样受体4(toll-like receptor4, TLR4)信号是诱发肝IRI的关键因素[42]. Uchida等[43]研究显示Tim-3/Gal-9信号通路可通过减少IFN-γ的分泌来抑制TLR4表达, 负性调控肝IRI. Tim-3/TLR4信号互为调节决定肝IRI的严重程度, 故调节Tim-3/Gal-9信号通路有望提高肝移植成功率.

2.2 Tim-3与*H. pylori*感染相关胃疾病 *H. pylori*是与慢性胃炎、胃溃疡、胃癌发病密切相关的病原微生物. Hu等[44]建立*H. pylori*感染Balb/c小鼠模型后发现, *H. pylori*感染组Tim-3 mRNA水平显著上调, 其表达与胃黏膜内Th1细胞因子

■相关报道
大量研究证实, Tim-3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
本文较系统体现了Tim-3在消化系统疾病发生发展中的表现及功能, 指出Tim-3与TLR4信号通路相关.

IFN-γ和IL-12水平呈显著正相关, 而根除后小鼠脾脏Tim-3 mRNA的表达显著下降; 体外实验通过*H. pylori*活菌与Balb/c小鼠原代淋巴细胞共培养发现, 实验组Tim-3$^+$ T细胞所占比例远高于对照组, 提示*H. pylori*感染可诱导Th1优势免疫反应, 而Tim-3的表达可反映Th1免疫反应, 因此可以通过调控Tim-3信号来防治*H. pylori*相关性疾病. Xie等[45-47]进一步用Tim-3单抗阻断Tim-3信号通路发现, Tim-3阻断对*H. pylori*疫苗接种小鼠和*H. pylori*感染小鼠免疫反应调控最终导致的结局不同, 前者在加剧炎症反应的同时, 有利于*H. pylori*的清除, 后者加剧炎症反应, 却不能清除*H. pylori*感染, 同时还发现Tim-3阻断可上调TLR4、髓样分化因子88(myeloid differentiation factor 88, MyD88)的表达和核因子-κB p65(nuclear factor-κB, NF-κB p65)活化, 降低CD4$^+$CD25$^+$Foxp3$^+$Treg的数量, 增强了Th1免疫反应, 抑制了Th2免疫反应, 这可能是他增强*H. pylori*疫苗的免疫保护作用的机制, 但并不影响*H. pylori*自然感染小鼠胃黏膜内*H. pylori*定植密度, 以上研究证实Tim-3信号通路可通过调控TLR信号通路、Treg和Th免疫反应来影响*H. pylori*疫苗的免疫保护和*H. pylori*感染的免疫致病作用.

2.3 Tim-3与肠道炎症性疾病

2.3.1 Tim-3与炎症性肠病: 炎症性肠病(inflammatory bowel disease, IBD), 主要包括溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(Crohn's disease, CD), 目前其病因和确切的发病机制并不明确, 一般认为是环境、遗传、免疫等因素共同作用于遗传易感个体, 产生过度免疫反应, 最终导致持续性肠道炎症. Morimoto等[48]研究发现, CD患者Th细胞表面Tim-3表达失调, 推测改变Th细胞表面Tim-3的表达可减轻IBD所致的炎性浸润. Li等[49]用重组Tim-3胞外蛋白封闭Tim-3预处理小鼠实验性结肠炎模型, 发现结肠炎症程度加重, Tim-3$^+$CD4$^+$ T细胞数量增多, Treg细胞数量减少, 促炎因子IFN-γ、IL-17、IL-23水平增高, IL-4水平下降, 提示Tim-3信号封闭加重结肠炎症可能与Treg细胞相关, 且Tim-3封闭启动Th1/Th17优势免疫应答. 同时, 淋巴细胞表面CD80/CD86和胞内CTLA-4表达下调, 推测Tim-3信号封闭介导的Th1优势免疫应答通过下调CD80和CTLA-4的表达, 活化Th1细胞功能, 进而抑制Treg细胞功能, 这些结果表明Tim-3可影响效应T细胞分化, 负性调控IBD的发展. 虽然大量研究表明Tim-3信号通路封闭可减少Gal-9/Tim-3介导的Th1细胞凋亡, 但是此研究并未发现这一现象, 具体原因尚不清楚. 钟玫君[50]用Tim-3单抗预处理小鼠实验性结肠炎模型, 证实了Li等的研究结果, 但与上述研究结果不同的是, 小鼠结肠炎症程度减轻. 进一步检测发现肠黏膜中MyD88、NF-κB p65蛋白表达下降, 而TLRs信号通路的负性调控因子单免疫球蛋白IL-1受体相关分子(single immunoglobulin IL-1R-related molecule, SIGIRR)蛋白表达上升. 结合前人研究, Tim-3信号通路在固有应答中可激活免疫应答, 推测该研究中Tim-3抗体通过增强对固有免疫应答TLRs/NF-κB信号通路的负性调控, 抑制TLRs/NF-κB信号通路激活, 从而减轻肠道炎症程度.

2.3.2 Tim-3与食物过敏所致肠道炎症浸润: 食物过敏在全世界范围内有高达2%-8%的发生率[51]. Chen等[52]研究显示, 食物过敏患者腹泻次数增多, 以肠道肥大细胞、嗜酸性粒细胞大量浸润, 抗原特异性CD4$^+$ T细胞大量增殖, CD4$^+$IL-4$^+$ T细胞数目显著增多为特征, 且肠上皮细胞Galectin-9表达上调. 体外研究发现, 用RNA干扰技术敲除髓系未成熟树突状细胞的*Tim-3*基因, 可消除Gal-9诱导的促髓系树突状细胞成熟的效应, 显著减少Tim-4的分泌, 推测Gal-9通过与Tim-3相互作用活化肠道树突状细胞, 诱导Tim-4分泌, 介导Th2优势免疫应答, 最终导致肠道长期处于高敏状态.

3 结论

近年来随着对*Tim-3*基因研究的深入, 已经发现Tim-3与众多疾病相关, 如自身免疫性疾病、过敏性疾病、炎症性疾病、病毒感染相关疾病、肿瘤等, 用Tim-3抗体或融合蛋白封闭Tim-3, 在一定程度上可改善或加重疾病程度, 提示Tim-3有望用于相关疾病的治疗, 但是其具体的分子机制目前尚不清楚. 是何种因素导致Tim-3在不同疾病中的表达水平及功能不同? 如多发性硬化患者脑脊液及外周血中T淋巴细胞低表达Tim-3, 病毒感染特异性CD8$^+$ T细胞高表达Tim-3. Tim-3/Gal-9信通路在调控疾病的过程中是否与其他负性调控因子如PD-1、CTLA-4相关, 两者又是如何发挥效应的; 表达于固有免疫细胞表面的Tim-3是如何协调固有及适应性免疫应答反应的, 这些问题都有待今后进一步研究.

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■应用要点

Tim-3与配体及其相关调控因子在消化系疾病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的靶向治疗.

■同行评价

本文就Tim-3在肝病毒性肝炎、胃炎、炎症性肠病、消化系肿瘤等疾病发生、发展中生物学作用进行阐述, 具有一定的新颖性和临床参考价值.

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• 消息 •

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本刊讯 本刊采用“顺序编码制”的著录方法, 即以文中出现顺序用阿拉伯数字编号排序. 提倡对国内同行近年已发表的相关研究论文给予充分的反映, 并在文内引用处右上角加方括号注明角码. 文中如列作者姓名, 则需在“Pang等”的右上角注角码号; 若正文中仅引用某文献中的论述, 则在该论述的句末右上角注码号. 如马连生[1]报告……, 潘伯荣等[2-5]认为……; PCR方法敏感性高[6-7]. 文献序号作正文叙述时, 用与正文同号的数字并排, 如本实验方法见文献[8]. 所引参考文献必须以近2-3年SCIE, PubMed,《中国科技论文统计源期刊》和《中文核心期刊要目总览》收录的学术类期刊为准, 通常应只引用与其观点或数据密切相关的国内外期刊中的最新文献, 包括世界华人消化杂志(http://www.wjgnet.com/1009-3079/index.jsp)和*World Journal of Gastroenterology*(http://www.wjgnet.com/1007-9327/index.jsp). 期刊: 序号, 作者(列出全体作者). 文题, 刊名, 年, 卷, 起页-止页, PMID编号 ; 书籍: 序号, 作者(列出全部),书名, 卷次, 版次, 出版地, 出版社, 年, 起页-止页.