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文献综述 REVIEW

Th17、IL-17在幽门螺杆菌相关性胃癌中的研究进展

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■背景资料
近年来, 人们对幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)与宿主之间的相互作用关系进行了大量研究, 而辅助性T细胞17(T helper cell 17, Th17)在*H. pylori*致癌过程中所扮演的角色显得日益重要.

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Role of Th17 and IL-17 in *Helicobacter pylori*-related gastric carcinogenesis

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Abstract
T helper 17 (Th17) cells are a newly defined subset of $CD4^+$ effecter T cells characterized by the secretion of interleukin 17 (IL-17) and transcription factor RORγ. They play significant roles in the pathogenesis of various tumors and bacterial infectious diseases. Gastric carcinoma is closely related to *Helicobacter pylori* (*H. pylori*) infection and has a very high mortality. Evidence shows that both Th17 and IL-17 play critical roles in the pathogenesis of *H. pylori*-associated gastric carcinoma and precancerous lesions. Elucidation of the roles of Th17 and IL-17 in *H. pylori*-related gastric carcinogenesis will provide new clues to the early diagnosis, personalized prevention and immunotherapy, vaccination and prognostic evaluation of gastric carcinoma.

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Key Words: T helper cell 17; Interleukin 17; *Helicobacter pylori*; Gastric carcinoma; Precancerous lesions

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摘要
辅助性T细胞17(T helper cell 17, Th17)是一种新发现的$CD4^+$ T细胞亚型, 他以分泌白介素17(interleukin 17, IL-17)和表达转录因子RORγ为特征, 在机体各种肿瘤和感染性疾病中起着重要作用. 胃癌是一种与慢性幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)感染密切相关的恶性肿瘤, 死亡率极高. 研究发现, Th17及其分泌的IL-17在*H. pylori*感染所致的慢性萎缩性胃炎、胃溃疡、不典型增生、肠上皮化生及胃癌的发生、发展中起着不可忽视的作用, 相关研究为胃癌的早期诊断、个性化防治、瘤苗开发和预后评价提供了新思路.

关键词: 辅助性T细胞17; 白介素17; 幽门螺杆菌; 胃癌; 癌前病变

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0 引言
胃癌是一种最常见的消化系恶性肿瘤, 死亡率高居全球癌症第2位, 其发生是一个多因素、多步骤的过程. 幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)作为体内最常见的一种慢性感染, 与胃癌及癌前病变的关系密切[1]. 目前, *H. pylori*致癌的确切机制尚不明晰, 加之早期胃癌的诊断困难、临床治疗的效果不佳, 使得*H. pylori*相关性胃癌的防治工作任重道远[2]. 辅助性T细胞17(T helper cell 17, Th17)是一种新发现的$CD4^+$ T细胞亚型, 与其分泌的白介素17(interleukin 17, IL-17)共同参与了*H. pylori*感染的胃黏膜炎症反应[3]. 研究发现, *H. pylori*感染患者体内IL-17 mRNA表

达水平显著升高[4], IL-17A、IL-17F基因多态性与*H. pylori*感染性胃癌密切相关[5]. 此外, 胃腺癌患者肿瘤内IL-17低表达还可提示预后不良[6]. 近年来, Th17及IL-17在*H. pylori*相关性胃癌中所发挥的作用越发受到关注, 本文就相关研究报道作一综述.

1 Th17细胞及其细胞因子IL-17概述

Th17细胞是一类新发现的辅助性$CD4^+$ T细胞亚型, 活化后可分泌IL-17A、IL-6、TNF-α等细胞因子, 并且表达转录因子RORγ, 在机体多种肿瘤和慢性感染性疾病中起着关键性作用[7,8]. IL-17家族包括IL-17A(即通常所说的IL-17)、IL-17B、IL-17C、IL-17D、IL-17E(IL-25)和IL-17F, IL-17可以上调IL-6、转化生长因子β(transforming growth factor β, TGF-β)、肿瘤坏死因子α(tumor necrosis factor α, TNF-α)的表达, 启动炎症级联反应. 此外, IL-17还可以参与中性粒细胞的增殖、成熟和趋化, 激活T细胞防御功能, 在肿瘤防御方面起着重要作用[9]. 研究发现, IL-17在*H. pylori*导致的胃黏膜恶性病变中起着不可忽视的作用[10].

2 Th17及IL-17表达的上游调控因子

2.1 TGF-β和IL-6是Th17细胞分化的必需因子 Veldhoen等[11]提出, TGF-β在诱导初始T细胞分化为Th17细胞过程中起着关键作用. IL-6是信号转导及转录激活因子3(signal transducers and activators of transcription 3, STAT3)的激活物, 而STAT3的激活能够诱导IL-17的高表达, TGF-β和IL-6能够取代活化的树突状细胞(dentritic cell, DC)培养液, 诱导初始T细胞分化为Th17[12].

2.2 IL-23是Th17细胞分化的诱导因子 IL-23由DC等分泌, 参与介导STAT3磷酸化, 刺激Th17细胞分泌IL-17[13]. 但IL-23只能促进记忆性Th17细胞增殖并维持其活性, 却不能诱导初始T细胞分化为Th17细胞[14,15].

2.3 IFN-γ、IL-4和IL-27是Th17细胞分化的抑制因子 干扰素γ(interferon γ, IFN-γ)和IL-4可以通过抑制TGF-β1下游Smad3的磷酸化作用, 从而抑制TGF-β1对Th17分化的诱导作用[16]. IL-27通过与IL-27受体链和gp130受体链组成的复合物结合, 对Th17进行负反馈调节[17].

2.4 ROR-γt是促进Th17分化的主要转录因子 研究发现, ROR-γt可以通过染色体重塑开放IL-17基因座位, 并促进其他因子与IL-17启动子相结合, 由此上调IL-17的表达水平[18]. 此外, ROR-γt还可以通过调节IL-23/IL-23R轴来诱导Th17的分化[19].

此外, IL-1β、IL-21对Th17、IL-17表达水平的上调作用和IL-2、IL-10对Th17分化的负调节作用, 均有所报道[8-14].

3 Th17及IL-17在*H. pylori*致癌过程中的作用

胃癌的发病是由*H. pylori*、环境、宿主等多种因素共同决定的, 且*H. pylori*与宿主之间的相互作用在*H. pylori*致癌过程中起着关键性作用[20]. 近年来, 大量论著证实了以Th17/IL-17为中心的免疫反应与*H. pylori*相关的胃黏膜恶性病变关系密切.

3.1 *H. pylori*与胃黏膜组织病理损伤 目前, *H. pylori*致癌的确切机制仍疑云重重. 现有研究主要围绕着宿主免疫介导的黏膜损伤、*H. pylori*毒力因子(尿素酶、黏附素、CagA、VacA、iceA等)、*p53*基因突变、ROS致DNA损伤、环氧合酶-2(COX-2)高表达等方面展开[21,22]. 就宿主抗感染的免疫损伤方面来说, *H. pylori*诱发胃癌的可能机制包括慢性炎症、免疫逃避和免疫抑制3部分[23]. Müller等[24]指出, *H. pylori*能够破坏并操纵Th细胞的信号转导通路从而抑制免疫应答, 利于持续感染, 导致不同程度的胃黏膜损伤.

3.2 *H. pylori*免疫逃逸 近年来, 不少学者针对*H. pylori*能够在免疫功能完好的宿主胃黏膜长期定植的机制进行了研究. Lewis等[25]发现, *H. pylori*可以通过诱导精氨酸酶-Ⅱ的表达来下调巨噬细胞一氧化氮合酶(NOS)的翻译水平, 从而进行免疫逃逸. Solnick等[26]认为, *H. pylori*能够积极地改变胞壁表面抗原, 以逃避宿主T细胞介导的免疫反应. 此外, Kao等[27]指出, *H. pylori*能够促进调节性T细胞(Treg)的分化, 从而使Th17所驱动的免疫反应受抑制, 利于持续感染.

3.3 Th17、IL-17对*H. pylori*的免疫应答 近年来, 大量研究关注于Th17细胞针对*H. pylori*所产生的特异性保护作用, 认为这主要是通过诱导中性粒细胞活化来发挥作用的. Akhiani等[28]提出, 细菌抗原刺激巨噬细胞和DC产生大量的IL-6与TGF-β, 共同诱导初始T细胞分化、成熟. 另外, *H. pylori*尿素酶B(UreB)也能诱导IL-17因子的表达[29]. 此外, IL-1β和TNF-α能促进TGF-β和IL-6对Th17细胞的诱导作用, 但不能取代TGF-β和IL-6[30]. 活化后的Th17细胞分泌IL-17、IL-6、TNF-α、IL-22等细胞因子发挥抗感染免疫应答.

3.3.1 IL-17(IL-17A): Sebkova等[31]采用IL-17分别刺激胃癌细胞MKN28和*H. pylori*的正常

■研发前沿

目前, *H. pylori*致胃癌的确切机制仍不清楚, Th17细胞及其分泌的细胞因子IL-17在机体抗感染免疫反应中发挥了重要作用, 明确Th17、IL-17与*H. pylori*相关性胃癌之间的关系, 有助于进一步理解*H. pylori*致胃癌的机制, 为胃癌的防治提供有效的指导.

■相关报道
大量研究发现, *H. pylori*感染的患者体内IL-17 mRNA表达水平显著升高, 且与胃黏膜病理损伤的严重程度高度相关. 此外, IL-17A和IL-17F基因多态性与*H. pylori*相关性胃癌的关联性, 也得到了证实.

胃上皮细胞, 均发现细胞外信号调节蛋白激酶1/2(ERK1/2)、激活蛋白-1(AP-1)、核因子κβ(NF-κβ)被激活, 启动了炎症瀑布反应. IL-17还可以诱导细胞间粘附因子的表达, 促进T细胞反应[32]. 此外, IL-17可以刺激成纤维细胞过度表达MMPs, 引起黏膜损伤[33].

3.3.2 IL-6: IL-6能够促进B细胞增殖分化, 诱导抗体分泌[34], 还可以促进造血干细胞增殖, 诱导中性粒细胞活化, 参与炎症反应[35].

3.3.3 TNF-α: TNF-α能够促进IL-2α、IFN-γ的表达, 并激活CTL, 诱导肿瘤细胞凋亡. Mosaffa等[36]发现广谱抗肿瘤物ABCG2短期(72 h)作用于胃癌细胞后可以导致TNF-α、IL-6、IL-1β的表达水平下降.

3.3.4 IL-22: IL-22可以促进C-反应蛋白(CRP)和抗菌肽的生成, 参与宿主上皮屏障的防御作用[37].

3.4 Th17与IL-17在*H. pylori*致癌过程中的作用 大量动物实验发现, 在*H. pylori*感染早期, 小鼠体内IL-17A和IL-22的mRNA水平显著升高, 此外, TNF-α、IL-17的外周血水平也有所升高[38,39]. Oertli等[40]指出, 小鼠体内Th17细胞介导的免疫应答水平与*H. pylori*感染所致的慢性萎缩性胃炎、异型增生和肠上皮化生有所关联. Allen等[41]在*H. pylori*慢性感染致胃炎的小鼠模型中发现, IL-17能够通过激活Ras/MAPK信号通路, 参与调节*H. pylori*感染所激活的单核巨噬系统应答水平. Flach等[42]发现, 小鼠胃黏膜的*H. pylori*感染水平和TNF、IL-12p40、IL-17、IFN-γ表达之间呈现明显的负相关. 还有研究采用多种细胞因子抑制剂腹腔注射的方法来比较各因子在*H. pylori*感染中发挥的作用, 发现尽管Th1活性有所增强, 但只有Th17分泌的IL-17所起的中和作用与*H. pylori*定植有关, 表明以IFN-γ为基础的IL-17免疫应答在抗*H. pylori*方面比TNF更为重要[43]. 然而, De-Lyria等[44]在早期采用*H. pylori*主动免疫小鼠后, 检测到Th17细胞大量生成并发挥重要的免疫保护作用. 可进一步的实验结果却出人意料, 小鼠体内IL-17表达水平的上升反而伴随着*H. pylori*定植数量的增多. Olivares等[45]发现, 实验小鼠在中和IL-17和IL-17A受体基因靶位的控制下, 胃炎、胃溃疡、胃癌等检出率更高. Rolig等[46]采用免疫荧光法检测到, 具有诱导细胞凋亡作用的*H. pylori*趋化性突变体che(-)细胞内Th17 mRNA呈低表达, 且Th17针对*H. pylori*感染的免疫反应是由伴随着细菌感染的细胞凋亡信号所驱动的.

在临床方面, Jafarzadeh等[47]发现*H. pylori*感染阳性患者的IL-17、IL-23血清水平比阴性组明显升高, 并且IL-17的表达受cagA影响. Harris[48]和Freire[49]等研究组均发现*H. pylori*感染阳性的胃炎患者体内IL-17A、IL-23的水平以及Foxp3(+)细胞数量均大幅升高, 在儿童中尤为显著. Zhang等[50]发现胃癌患者比健康志愿者的外周血Th17检出水平更高, 且与晚期胃MALT淋巴瘤的关系尤为密切. 此外, 胃癌进展期患者接受治疗后, IL-17、IL-23p19、RORγ在肿瘤组织和外周血的浓度均显著增加. Mizuno等[51]对36例伴溃疡(GU)和29例非溃疡(NU)的*H. pylori*感染患者及*H. pylori*阴性对照者进行研究发现, IL-17和IL-8的表达水平: GU组>NU组>空白组; GU患者每个活检部位(溃疡: $R = 0.62$, $P<0.0001$; 胃窦: $R = 0.61$, $P<0.0001$). Zhou等[52]对人胃腺癌细胞AGS中IL-17A介导的细胞内信号通路进行了研究, 发现IL-17A能够激活3条MAPK通路(ERK, P38和JNK)和下游转录因子AP-1和P65 NF-κB并且可以诱导IL-8的表达, 提示IL-17与下游IL-17R的结合可以激活介导胃黏膜炎症和癌变发生的关键信号通路. Chen等[53]对192例胃腺癌手术切除标本进行研究发现, 肿瘤内IL-17高表达的胃腺癌切除患者5年存活率明显高于IL-17低表达者, COX多元风险分析提示, 肿瘤内IL-17表达水平是一个影响5年总体存活率的独立因子, 肿瘤内IL-17的低表达可能提示预后不良. Shibata等[54]对811例(胃癌287例, 非胃癌524例)*H. pylori*感染患者进行检测发现, IL-17A(rs2275913 G-197A)等位基因与胃癌病变进程显著相关, 且胃癌组的IL-17A/197A纯合子频率高于非癌组.

4 结论

一直以来, 早期胃癌的诊断较为困难, 临床就诊的胃癌患者多属中晚期, 加之治疗手段局限、*H. pylori*根除治疗后再感染现象普遍, 这大大加重了胃癌的危险性[55]. Th17细胞亚群的发现, 弥补了*H. pylori*相关性胃黏膜恶性病变过程中, 宿主Th1/Th2细胞介导免疫反应机制的不足, 相关研究对胃癌的早期检测、个性化防治、瘤苗开发和预后判断究竟具有怎样的实际意义呢? 让我们拭目以待.

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■应用要点

进一步明确Th17细胞介导的宿主抗*H. pylori*慢性感染的免疫应答机制及其在胃黏膜癌变进程中所起的调控作用, 对胃癌及癌前病变的早期监测、个性化防治、肿瘤疫苗开发和预后判断均具有重要意义.

■同行评价

本文就Th17和IL-17在*H. pylori*相关性胃癌的研究方面进行综述，资料较新颖，文献量大，有一定的可读性和科学性，并有一定的研究参考价值.

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