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述评 EDITORIAL

Th17、Treg及其平衡在肝癌治疗中的意义

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Significance of Th17/Treg balance in pathogenesis and treatment of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in China, and it is characterized by high malignancy, rapid progression, and easy metastasis. Current treatment options include liver transplantation, surgical resection and local ablative therapy. However, for all except transplantation, tumor recurrence rates are up to 70% after 5 years. In recent years, due to unsatisfying therapeutic effects of conventional therapies, the immune therapy of HCC has gradually become a hot research area. However, there exists a severe tumor immune microenvironment in HCC, which affects the immune therapeutic effects. Regulatory T (Treg) cells and T helper 17 (Th17) cells are two newly discovered subsets of $CD4^+$ T cells. They play crucial roles in the maintenance of immune homeostasis and antitumor immunity, and they are important in forming microenvironmental immune suppression in HCC. Immunotherapy targeting Th17 or Treg cells in HCC appears to have potential feasibility. More evidence show that clarification of Th17/Treg balance and imbalance mechanisms may provide a new strategy for the immunotherapy of HCC.

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Key Words: T helper 17 cells; Regulatory T cells; Hepatocellular carcinoma; Therapy

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背景资料
肝癌早期诊断率低, 常规治疗如肝移植、手术切除、射频消融等效果不佳; 肝癌的免疫治疗逐渐成为研究热点, 肿瘤微环境的免疫抑制状态成为免疫治疗研究的瓶颈, Th17细胞及调节性T细胞(regulatory T cell, Treg)是肿瘤微环境中的重要组成部分, 在肝癌的发病过程中发挥关键作用, 故研究Th17、Treg及两者的平衡对于突破肝癌免疫治疗瓶颈有重大意义.

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■研发前沿
免疫治疗近来成为肝癌治疗的研究热点, 如何突破肝癌的免疫耐受成为目前研究的挑战.

摘要

肝细胞癌是我国常见的恶性肿瘤之一, 具有恶性程度高、发展快、易转移等特点. 当前治疗方法主要有肝移植、手术切除和局部消融治疗. 然而, 对于除移植外的所有治疗中, 5年后肿瘤复发率高达70%. 近几年来, 由于常规治疗效果不满意, 肝癌的免疫治疗逐渐成为热点. 但是肝癌存在严重的肿瘤免疫微环境抑制, 影响了肝癌免疫治疗效果. Th17细胞、调节性T细胞(regulatory T cell, Treg)是近年来新发现的$CD4^+$ T细胞亚群, 在一定条件下, 两者存在相互转化的关系, 在维持人体自身免疫稳定和抗肿瘤免疫过程中起着重要作用, 他们是形成肝癌微环境免疫抑制的重要成员. 以Th17或Treg为靶点的肝癌免疫治疗具有潜在可行性, 更多证据表明, Th17/Treg的平衡、失衡机制将为肝癌的免疫治疗提供新的策略.

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关键词: Th17细胞; 调节性T细胞; 肝细胞肝癌; 治疗

核心提要: Th17细胞、调节性T细胞(regulatory T cell, Treg)是近年来新发现的$CD4^+$ T细胞亚群, 目前动物实验及临床研究表明, Th17、Treg及其平衡在人体自身免疫稳定和抗肿瘤免疫过程中起着重要作用, 深入研究有助于进一步揭示机体对肝癌免疫耐受的原因, 并寻找免疫治疗的靶点.

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0 引言

肝细胞癌(hepatocellular carcinoma, HCC)是临床上最常见的恶性肿瘤之一, 早期诊断困难, 手术切除率低, 在我国HCC的发病率和病死率均高于西方发达国家和其他发展中国家[1], 死亡率仅次于胃癌、肺癌[2]. 近来随着肿瘤免疫的研究进展, 发现Th17细胞及调节性T细胞(regulatory T cell, Treg)是肿瘤微环境中的重要组成部分[3,4], 在肝癌的发病过程中发挥关键作用. 关于Th17细胞、Treg细胞及两者失衡关系在肝癌发病和治疗中意义是目前研究的热点, 现将相关研究综述如下, 以期为肝癌的临床治疗提供新思路.

■相关报道
Treg在肝癌患者外周血和肝癌组织均呈高表达, 高表达的Treg很可能通过抑制某些免疫细胞、因子的肿瘤杀伤效能而营造了免疫抑制微环境, 介导了肝癌的免疫逃逸.

1 Th17细胞与Treg细胞

Th17细胞一种高分泌白介素-17(interleukin-17, IL-17)的$CD4^+$ T细胞亚群, 表达IL-17A、IL-17F、IL-6和肿瘤坏死因子-α等细胞因子, 具有促炎作用[5,6], 已证实在多种恶性肿瘤患者外周血中Th17细胞分泌的相关因子明显升高[7,8]. Treg细胞, 前身为抑制性T细胞, 具有免疫负调节作用, 在自身免疫性疾病、炎症、肿瘤等疾病中发挥免疫调节功能[9].

Th17细胞与Treg细胞都是由$CD4^+$ T细胞分化而来, 在生理状态下, 两者的分化发育相互制约, 处于动态平衡. 初始T细胞在TGF-β独立诱导下向Treg细胞分化, 而在TGF-β与IL-6联合作用下, $CD4^+$ T细胞分化为Th17 细胞[10,11], 说明Th17细胞与Treg细胞相互联系, 且IL-6是$CD4^+$ T细胞向两者分化方向的关键细胞因子. 有学者[12]发现IL-2也可以调节Th17/Treg平衡, 以刺激Treg细胞分化的方式减少Th17细胞的分化. 两者不仅在分化方向上有联系, 而且能互相转化, 研究[13]表明Th17在IL-12、IL-4的作用下能向Treg转化; 同时, Treg细胞在促炎条件齐备情况下可以分化成Th17细胞[14]. Th17/Treg在生理条件下处于动态平衡, 维持稳态, 两者的失衡促进了炎症、肿瘤等疾病进展[15,16].

2 Th17/Treg与肝癌的临床联系

HCC恶性程度高、治疗棘手、预后相对较差, 肿瘤微环境的改变是肝癌转归的关键所在[17-19]. 研究[20,21]发现Th17细胞通过其标志性细胞因子IL-17对肿瘤产生影响. Treg细胞被认为通过抑制抗肿瘤免疫应答介导免疫逃逸, 从而促进肿瘤进展[22].

Foxp3是叉状头转录因子家族中的一个成员, 被认为是Treg的特异性标志性分子[23,24], $Foxp3^+$ Treg作为Treg细胞的主要亚型之一, 近几年来研究较多. 通过小鼠建立肝癌模型行对照实验后发现, 肝癌模型肿瘤组织$Foxp3^+$ mRNA表达水平高于对照组[25], 进一步临床研究[26]中, $Foxp3^+$ mRNA在肝癌患者外周血表达显著上升, 肝癌射频消融术患者外周血中$CD4^+CD25^+Foxp3^+$ Treg在术后降低, 并与术后生存时间相关, 对于判断肝癌的预后有一定价值[27]. 肝移植患者中, 术后$Foxp3^+$ Treg越高, 复发风险越大[28]. 这些研究提示Foxp3作为Treg活性的一个指标, 是HCC的肿瘤进展和复发的独立因子, 但是目前Foxp3的检测方法及试剂

可能对结果的稳定性产生较大影响[29].

有学者[30]发现肝癌患者较健康者外周血中Treg显著升高, Th17明显减少, 这意味着Th17细胞与Treg细胞参与了肝癌的发生和发展. 进一步研究发现, Th17/Treg比例在肝癌浸润淋巴细胞中高于非肿瘤浸润淋巴细胞, 且Th17和Treg百分比与肝癌的TNM分期呈直线关系, 说明Th17/Treg与肝癌的发展密切相关, 比例越高, 肝癌分期越晚. Bouchliou等[31]通过实验证明了实体瘤的分型与Th17/Treg比值呈正相关. 在肝癌预后方面, 有研究人员[32]对术后病理确诊为HCC患者进行长期随诊, 通过监测术后患者Th17、Treg水平发现, Treg和Th17均表达者死亡率高, 随着肝癌进展, Treg与Th17细胞相关因子比例升高, 可作为判断肝癌预后的一个可靠指标.

3 与肝癌治疗的研究

临床研究[33]证实, 在肝癌患者治疗过程中, Th17细胞呈上升趋势. Th17细胞分泌的多种细胞因子在肿瘤免疫治疗中有重要研究价值[34]. 研究[35]发现, IL-17可以通过募集特定的免疫细胞诱导肿瘤细胞的凋亡. IL-21的抗肿瘤作用已应用在黑色素瘤[36,37]和非霍奇金淋巴瘤[38]的早期临床试验.

Treg细胞具有抑制抗肿瘤免疫的能力, 治疗研究主要在两方面: 耗竭肿瘤微环境中Treg细胞和抑制其功能[39]. 环磷酰胺, 是许多化疗方案的标准化疗剂, 研究[40]表明低剂量环磷酰胺可以降低小鼠血液中的Treg细胞水平, 肝癌患者的临床试验[41]也已得到证实. 抗CD25单克隆抗体可以抑制$CD4^+CD25^+$ Treg的表达[42], 显著抑制某些恶性肿瘤细胞的生长[43,44], 但是需要更进一步的研究, 以明确他是否对肝癌治疗有效. 索拉非尼是一种新型多靶向性的治疗肿瘤的口服药物, 是目前唯一被临床证实可以显著延长晚期肝癌患者生存时间[45], 研究[46,47]发现, 索拉非尼可以通过减弱Treg细胞相关细胞因子表达以抑制Treg细胞的功能, 从而抗血管生成抑制肿瘤生长. TGF-β通过破坏T细胞的再生达到肿瘤抑制效果, 然而, TGF-β的具体作用仍有争议[48].

在肝癌的免疫治疗中, 调节Th17/Treg的平衡成为新途径. miRNA(miR)-21作为免疫调节因子参与多种疾病的演变, 有研究者[49]使用二乙基亚硝胺构建大鼠肝癌模型, 通过检测和分析外周血miR-21含量与Treg/Th17比值的相关性, 数据显示miR-21在肝癌大鼠外周血中明显增加, 且与Treg/Th17的比值正相关, 提示miR-21有望成为肝癌治疗的新靶点. 研究[50]发现, 在细胞因子诱导的杀伤细胞(cytokine-induced killer, CIK)的细胞培养基中Th17/$CD4^+$ T细胞百分比增加, 加入IL-6, Treg/$CD4^+$ T细胞的百分比显著下降, 推测IL-6可以改变Th17/Treg平衡发挥CIK的抗肿瘤效应. 动物肝癌实验中, IL-18也能通过调节Th17/Treg平衡抑制肿瘤生长. 临床治疗[51]发现, 重组人血管内皮抑素在介入栓塞治疗后肝癌患者Th17/Treg比例大于常规栓塞治疗患者, 并达到更佳的肝癌治疗效果. 目前较多的动物实验和临床研究提供了肝癌免疫治疗可能的切入点, 下一步应深入针对靶点及改变Th17/Treg失衡状态的药物研究.

4 结论

我国的肝癌发病率在全世界位居第一, 大多数原发性肝癌患者早期无明显症状, 早期诊断困难, 常规治疗效果不佳, 提高肝癌的治疗效果迫在眉睫. 近年来研究发现, Th17、Treg及其平衡对肝癌的发病、治疗及转归有重大价值, 有可能打破肝癌免疫治疗的瓶颈, 但是仍有问题亟待解决, 如Th17、Treg在肿瘤发展中的精确机制; Treg细胞需要被抑制还是清除; Th17/Treg的失衡能否逆转等. 深入研究有助于进一步揭示机体对肝癌免疫耐受的原因, 并寻找免疫治疗的靶点. 随着研究的进展, 相信会给肝癌患者带来福音.

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创新盘点
本文对Th17、Treg及两者的平衡在肝癌患者的发病机制、临床实验以及药物治疗的靶点进行了综述.

应用要点
本文对突破肝癌的免疫微环境抑制状态及肝癌的靶向治疗有一定指导意义.

名词解释

肿瘤微环境: 肿瘤的发生和转移与肿瘤细胞所处的内外环境有着密切关系. 他不仅包括肿瘤所在组织的结构、功能和代谢, 而且亦与肿瘤细胞自身的(核和胞质)内在环境有关.

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同行评价

Th17、Treg特别是Foxp3$^+$ Treg与肝癌的发生、发展、预后具有密切的关系, Foxp3$^+$ Treg是近年研究的热点, 与肝癌的预后有明确的相关性, 作者重点阐述了Th17/Treg的平衡关系在肝癌发生及治疗中的作用, 比较清楚, 具有临床指导意义.

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