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文献综述 REVIEW

外周血中CD4$^+$CD25$^+$Tregs与慢性乙型肝炎抗病毒治疗相关性的研究进展

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■背景资料
慢性乙型肝炎患者在抗病毒治疗过程中外周血CD4$^+$CD25$^+$Tregs呈现的变化以及发挥的作用备受关注.

Advances in understanding relationship between peripheral blood CD4$^+$CD25$^+$ regulatory T cells and antiviral treatment in CHB patients

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Abstract
The immunosuppressive function of CD4$^+$CD25$^+$ regulatory T cells may closely associate with the occurrence, development and prognosis of CHB patients. The change and function of CD4$^+$CD25$^+$ regulatory T cells in CHB patients undergoing antiviral treatment have aroused the attention of scholars. Here we review the types, immunophenotypes, and function of CD4$^+$CD25$^+$ regulatory T cells, as well as the relationship between peripheral blood CD4$^+$CD25$^+$ regulatory T cells and antiviral treatment in CHB patients.

摘要
CD4$^+$CD25$^+$调节性T细胞(T regulatory cells, Tregs)发挥的免疫负调作用与慢性乙型肝炎发生、发展及预后密切相关, 慢性乙型肝炎患者在抗病毒治疗过程中外周血CD4$^+$CD25$^+$Tregs呈现的变化以及发挥的作用备受诸多学者关注, 本文就CD4$^+$CD25$^+$Tregs的分类、免疫标志、功能及其与CHB抗病毒的相关研究进行综述.

关键词: 慢性乙型肝炎; T淋巴细胞; 调节性; 抗病毒; 治疗

核心提示: 本文对外周血中CD4$^+$CD25$^+$调节性T细胞(T regulatory cells)与慢性乙型肝炎(chronic hepatitis B)抗病毒治疗的研究相关进行了总结, 并指出目前相关研究存在的不足, 为未来寻找抗乙型肝炎病毒(hepatitis B virus)治疗新靶点的研究提供思路.

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0 引言
乙型肝炎病毒(hepatitis B virus, HBV)感染仍然是一个严重的健康问题, 每年约有100万人死于

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■研发前沿
近年来研究表明, $CD4^+CD25^+$调节性T细胞可能为抗乙型肝炎病毒(hepatitis B virus, HBV)疗效判断提供可靠参考.

HBV感染相关的肝衰竭、肝硬化及肝癌[1]. 我国慢性乙型肝炎(chronic hepatitis B, CHB)患病基数较大, 抑制HBV、减轻肝脏炎症损害及肝纤维化, 阻断或延缓肝硬化、肝癌的发生是当前CHB治疗的总体目标, 抗病毒是治疗关键, 目前国内外公认的有效抗HBV药物包括核苷(酸)类似物和干扰素, 但是疗效还不尽人意, 治疗过程中的一些难题(如耐药、停药后病情加重、不良反应大等)客观存在, 寻找新疗法任重道远. $CD4^+CD25^+$调节性T细胞(T regulatory cells, Tregs)是目前备受国内外关注的一群免疫负调细胞, 研究表明$CD4^+CD25^+$Tregs与CHB的发生、发展及预后有关[2,3]. 而$CD4^+CD25^+$Tregs在CHB抗病毒治疗过程中呈现什么变化, 发挥何种功能, 能否为寻找CHB新疗法开拓新视野, 成为治疗CHB的靶点或预测抗HBV疗效的参考指标? 本文就目前外周血中$CD4^+CD25^+$Tregs与CHB抗病毒治疗的相关研究作一综述.

1 $CD4^+CD25^+$Tregs的概述、功能及意义

调节性T细胞(regulatory T cell, Tregs)是一群专职免疫负调细胞, 根据是否来源于胸腺可将其为天然型调节性T细胞(nTreg)和诱导型调节性T细胞(aTreg或iTreg)[4]. Sakaguchi等[5]将占正常人外周血$CD4^+$T细胞5%-10%的这群$CD4^+CD25^+$胸腺细胞定义为nTreg. 人类的$CD4^+CD25^+$Tregs除细胞标志CD25外, 还有叉头翼螺旋转录因子3(forkhead box protein 3, Foxp3)[6]、细胞毒性T淋巴细胞相关抗原4(cytotoxic T lymphocyte-associated antigen-4, CTLA-4)[7]、糖皮质激素诱导的肿瘤坏死因子(glucocorticoid-induced tumor necrosis factor receptor, GITR)[8]、CD127(IL-7受体α链)[9,10]等, 其中Foxp3可作为$CD4^+CD25^+$Tregs的特征性细胞标志[11,12], 对其发育、活化及功能发挥起关键作用[13], 且不受活化状态影响. 有研究[14]表明Foxp3剔除的小鼠体内不能表达$CD4^+CD25^+$Tregs, 并伴随炎症性疾病发生.

$CD4^+CD25^+$Tregs具有免疫抑制及免疫无能功能, 一方面由CTLA-4介导[15,16]$CD4^+CD25^+$Tregs通过细胞间接触抑制方式抑制T细胞的增殖与活化, 实现免疫抑制; 另一方面, $CD4^+CD25^+$Tregs还能在效应性T细胞活化早期抑制白介素-2(interleukin-2, IL-2)的产生[17]从而介导免疫无能; 此外, $CD4^+CD25^+$Tregs通过分泌转化生长因子-β(transforming growth factor-β, TGF-β)、IL-10等[18], 抑制自然杀伤细胞、$CD4^+$和$CD8^+$ T细胞等多种免疫细胞的功能从而参与体内免疫应答调节[19-21], 保持免疫反应与免疫耐受间的平衡, 发挥免疫自稳功能[22]. 某些外源或内源性因素致$CD4^+CD25^+$Tregs数量和功能改变或异常将会导致机体疾病的发生, 如Tregs表达频率或活性降低, 机体自身免疫耐受缺陷从而导致自身免疫性疾病发生[23,24]; 反之, 频率或活性过度升高的Tregs会抑制机体抗肿瘤免疫应答, 介导免疫逃逸, 导致恶性肿瘤发生[25-27]. 另外, $CD4^+CD25^+$Tregs与感染性疾病[28-30]、移植免疫相关疾病[31,32]、内分泌性疾病[33,34]等也息息相关.

2 $CD4^+CD25^+$Tregs与CHB

慢性乙型肝炎发病机制极为复杂, 与体内T淋巴细胞、自然杀伤细胞(natural killer cell, NK)、树突状细胞(dendritic cells, DCs)及Tregs等多种免疫细胞及相互间作用有关. $CD4^+CD25^+$Tregs发挥的免疫负调功能在HBV感染发病机制中的作用日益受到关注, Tregs通过维持机体保护性免疫避免肝脏受到过度免疫损伤[35], 同时导致HBV持续感染[36,37]. 前期我们对HBV携带者与其他HBV感染状态外周血中$CD4^+CD25^+$Tregs的频率差异比较做Meta分析[38]结果表明: HBV携带者外周血Tregs频率较健康对照高(P = 0.01). 另外Aalaei-Andabili等[39]就国内外符合纳入标准的12篇$CD4^+CD25^+$Tregs与HBV感染相关研究进行系统评价及Meta分析, 结果显示: CHB外周血中$CD4^+CD25^+$Tregs频率均较AHB及健康对照高, HBV DNA高于10^7拷贝/mL的CHB外周血中Tregs频率高于HBV DNA低拷贝CHB, 并推论Treg细胞可能成为影响HBV感染预后的重要因素. 推测可能机制为HBV携带者外周血中升高的$CD4^+CD25^+$Tregs抑制DCs分化与成熟, 削弱DCs和其他抗原递呈细胞的活性, 从而抑制T细胞的增殖与活化发挥免疫负调功能[40], 与此同时, 这种不成熟的DCs能诱导Tregs的表达[41,42], 这样的恶性循环造就$CD4^+CD25^+$Tregs持续表达和HBV感染慢性化, 机体表现为肝脏无免疫损伤的免疫耐受状态. 此外, CHB外周血中上调的$CD4^+CD25^+$Tregs抑制HBV特异性$CD4^+$和$CD8^+$ T细胞活化与增殖[3,43], 同时抑制IL-2、IFN-γ分泌[44], 从而实现免疫抑制, 使得机体清除HBV的能力下降, HBV DNA病毒载量随之升高[18].

3 CD4$^+$CD25$^+$Tregs与CHB核苷(酸)类似物抗病毒治疗

核苷(酸)类似物已广泛用于抗HBV治疗, 其主要作用机制为药物进入机体经病毒胸腺嘧啶核苷激酶作用, 转化成有活性的三磷酸盐后取代病毒复制时聚合酶链延长所需的结构相似核苷, 终止DNA链延长, 从而抑制HBV DNA复制. 目前常用于临床的核苷(酸)类似物有拉米夫定、恩替卡韦、阿德福韦酯、替比夫定等. Yu等[45]采用流式细胞术检测44例核苷(酸)类似物抗病毒治疗前后CHB外周血中CD4$^+$CD25$^+$Tregs频率, 结果发现治疗后生化和病毒学应答的CHB外周血中Tregs频率较治疗前明显降低, 而治疗无应答的CHB外周血中Tregs频率无明显变化, 且 CD4$^+$CD25$^+$Tregs频率与HBV DNA(r = 0.272, P = 0.016)及丙氨酸转移酶(alanine transaminase, ALT)(r =0.241, P = 0.034) 均呈正相关. 赵彩彦等[46]动态检测90例CHB服用拉米夫定抗HBV治疗前后外周血CD4$^+$CD25$^+$Tregs频率, 发现治疗应答组CD4$^+$CD25$^+$Tregs频率明显低于无应答组, 完全应答和部分应答组治疗24、36、52 wk时Tregs频率均低于治疗前, 差异均有统计学意义, 无应答组治疗前后Tregs频率差异无统计学意义. 吴金国等[47]采用流式检测到恩替卡韦治疗后4、12、24 wk CHB外周血CD4$^+$CD25$^+$Tregs比率显著递减, Tregs频率与血清中ALT呈正相关. 史为涛等[48]检测92例阿德福韦酯抗病毒治疗前后CHB外周血CD4$^+$CD25$^+$Tregs频率, 比较Tregs在完全、部分应答及无应答组间的表达差异, 结果治疗48 wk Tregs在完全应答组、部分应答组及无应答组表达依次递增, 组间差异均有统计学意义; 完全应答组与健康对照外周血Tregs频率无统计学差异. Nan等[49]研究表明替比夫定抑制HBV DNA复制会伴随CHB外周血CD4$^+$CD25$^+$Tregs频率下降. Evans等[50]检测36例CHB替比夫定抗病毒治疗前后外周血中CD4$^+$CD25$^+$Tregs比例, 发现随着治疗时间延长, CHB外周血Tregs比例下降, 治疗6、9 mo时基本降至正常; 治疗3 mo Tregs降至正常人水平的CHB在治疗后9 mo发生HBeAg血清学转换. 总之, CHB经核苷(酸)类似物抗病毒治疗后外周血中CD4$^+$CD25$^+$Tregs频率降低, 且在治疗应答组Tregs频率降低幅度更大, HBV复制活跃的CHB体内Tregs频率越高, Tregs频率与血清中ALT呈正相关. 治疗应答的CHB通过核苷(酸)类似物抑制HBV复制使机体的免疫环境有所改善[51], CD4$^+$CD25$^+$Tregs频率下降, 其免疫抑制功能削弱, HBV特异性CD4$^+$和CD8$^+$ T细胞得以活化与增殖, IL-2、IFN-γ分泌增多, HBV特异性细胞免疫应答得以重建, 更加利于机体清除病毒; 而治疗无应答者可能与频率较高的Tregs免疫抑制功能的过度发挥有关, 不易激发机体打破免疫耐受进入免疫清除, HBV特异性细胞免疫应答难以重建, 影响核苷(酸)类似物抗HBV疗效. CD4$^+$CD25$^+$Tregs表达降低与HBeAg血清学转换密切关联.

4 CD4$^+$CD25$^+$Tregs与CHB干扰素抗病毒治疗

干扰素是具有里程碑意义的抗HBV药物, 通过刺激机体产生抗病毒蛋白, 抑制mRNA翻译和病毒蛋白合成, 从而达到抗HBV目的. Xu等[52]动态监测27例经α-干扰素抗病毒治疗的CHB外周血中CD4$^+$CD25$^+$Tregs频率, 结果发现抗病毒治疗后HBV DNA病毒载量低于10^3拷贝, 且ALT恢复正常的应答组CHB外周血中Tregs含量逐渐降低, 而治疗无应答组Tregs含量无明显变化. Sprengers等[53]曾报道α-干扰素抗病毒无应答者外周血中CD4$^+$CD25$^+$Tregs频率较治疗前增加, 推测可能机制为干扰素治疗后增强CHB的免疫功能, CD4$^+$CD25$^+$Tregs水平降低, 其对HBV特异性CD4$^+$和CD8$^+$T细胞的负调功能被削弱, 机体对HBV的免疫耐受被打破, 抗HBV免疫应答得以增强, 从而协同干扰素抗HBV疗效. Ma等[54]检测聚乙二醇干扰素治疗前后CHB外周血中CD4$^+$CD25$^+$Tregs频率, 比较其在HBeAg血清学转换组与HBeAg未转换组间的表达差异, 分析Tregs与HBV DNA的关联. 结果发现, 发生HBeAg血清学转换CHB干扰素治疗后Tregs频率明显降低, 并在停药后一段时期维持较低水平; 而HBeAg未转阴CHB外周血中Tregs频率降低幅度较小, 且停药后有反弹现象; 治疗后4 wk(P = 0.036)、12 wk(P = 0.015)HBeAg转阴组Tregs频率均低于HBeAg未转阴组; CHB外周血中Tregs频率减低与HBV DNA病毒载量减少存在明显相关性. 其结论认为CD4$^+$CD25$^+$Tregs频率对干扰素抗病毒治疗后HBeAg血清学转换发挥一定的预测价值. 综上, CD4$^+$CD25$^+$Tregs水平降低可能协同干扰素抗HBV疗效, CD4$^+$CD25$^+$Tregs可能作为判断干扰素抗病毒疗效的参考指标.

5 结论

相关研究表明: 核苷(酸)类似物或干扰素抗病毒治疗应答组CHB外周血中CD4$^+$CD25$^+$Tregs频率

■应用要点

CD4$^+$CD25$^+$Tregs可能为抗HBV疗效判断提供可靠参考. 然而目前相关研究仍存在不足之处, CD4$^+$CD25$^+$Tregs在CHB抗病毒治疗中发挥作用的确切机制、能否成为治疗CHB的新靶点还有待于高质量研究阐明.

■同行评价
本文探讨了外周血中$CD4^+CD25^+$Tregs与CHB抗病毒治疗的研究进展，并指出目前相关研究存在一定缺陷，条理清楚，对临床治疗和科研具有一定的指导意义.

显著下降，治疗过程中Tregs频率与HBV DNA病毒载量呈正相关，$CD4^+CD25^+$Tregs频率降低与HBeAg血清学转换密切相关. $CD4^+CD25^+$Tregs可能为抗HBV疗效判断提供可靠参考. 然而目前相关研究仍存在不足之处：相关研究随访时间不够长，而更值得临床关注CHB转归的终点指标(如HBV相关肝硬化、肝癌的发生率及发生时间)需要更长时间随访研究；$CD4^+CD25^+$Tregs与CHB抗病毒治疗的相关探究，仅局限于HBV DNA病毒载量、血清ALT、HBeAg血清学转换等疗效判断中间指标的检测，不能反应$CD4^+CD25^+$Tregs对CHB抗病毒远期疗效的影响；相关研究多为治疗前后自身对照，未设置空白对照，因此对于Tregs频率及功能变化与抗病毒应答间的因果关联论证强度不够，$CD4^+CD25^+$Tregs在CHB抗病毒治疗中发挥作用的确切机制以及$CD4^+CD25^+$Tregs能否成为治疗CHB的新靶点还有待于高质量研究阐明.

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慢性乙型肝炎患者应用拉米夫定前后T淋巴细胞亚群、CD4 CD25调节性T淋巴细胞及白细胞介素-10、干扰素-γ的变化. 中华传染病杂志 2011; 29: 480-485
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