文章编号: 1005-6661(2018)05-0588-04 DOI: 10.16250/j.32.1374.2018001 ·综述·

Treg/Th17平衡与血吸虫感染免疫

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[摘要] 血吸虫感染可诱导调节性T细胞(Treg)和Th17型免疫反应。研究表明,Treg和Th17细胞及其平衡在血吸虫感染中具有非常重要的作用。Treg细胞抑制宿主体内过度病理反应,并有助于血吸虫逃避宿主的免疫攻击;而Th17细胞促进血吸虫感染过程中的免疫病理发展。本文就Treg/Th17平衡与血吸虫感染免疫关系的研究进展作一综述。

[关键词] 血吸虫;Treg/Th17平衡;免疫病理;免疫调节

[中图分类号] R383.24 [文献标识码] A

Treg/Th17 balance and immunology of schistosome infection: a review

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[Abstract] Many factors are reported to be involved in regulating the immunopathogenesis of schistosome infection. $CD4^+$ T cell is one of the key players in the regulation of the liver granuloma formation by differentiation into different effector subsets including T helper (Th) 1, Th2, Th17, and T regulatory cells (Treg cells). Treg cells play an important suppressive role in immunopathology control and favor the pathogen to escape from the host immune assault. The functional activity of Tregs has been related to some autoimmune diseases including asthma and inflammatory bowel disease, which suggests that the manipulation of Tregs to restore their numbers and function may be therapeutic. However, interleukin-17 (IL-17) is a pro-inflammatory cytokine involved in the pathogenesis of many inflammatory and infectious conditions, including schistosomiasis. Therefore, a deeper understanding of the mechanisms of these immune regulations is necessary for the better control of pathology in schistosomiasis. In this paper, we review the Treg/Th17 balance and the immunology of schistosome infection.

[Key words] Schistosome; Treg/Th17 balance; Immunopathology; Immune regulation

血吸虫病是一种严重危害人类健康的感染性免疫疾病[1],最主要的病理损伤是由沉积在肝脏中的虫卵导致的肝脏虫卵肉芽肿及继发的肝纤维化[2],引起肝脾肿大、上消化道出血及腹水等症状,严重者可危及生命[3]。研究表明,$CD4^+$ T细胞应答在纤维化发生发展过程中发挥关键作用[4]。机体内的辅助性T细胞根据其表达细胞因子谱差异,可分为Th1、Th2、Th19、Th17[5]和滤泡辅助性T细胞(Follicular T helper cells,Tfh)。研究表明,除Th1/Th2细胞极化及其免疫调节与血吸虫肝脏纤维化的发生发展密切相关外[6],在不同微环境下可相互转化的Treg细胞与Th17细胞也在血吸虫感染免疫中具有重要作用[7-9]。本文就Treg/Th17平衡与血吸虫感染免疫的关系研究进展作一综述。

1 Treg细胞与血吸虫感染免疫

Treg细胞最早于1995年由Sakaguchi等[10]发现。根据细胞来源及产生效应机制的不同,可将Treg细胞分为诱导性调节性T细胞(Inducible regulatory T cells, iTregs)和天然调节性T细胞(Natural regulatory T cells, nTregs)[11]。iTregs主要由外周初始$CD4^+$T细胞在抗原诱导下分化而成,通过直接接触和/或分泌细胞因子TGF-β和IL-10等来发挥其免疫抑制作用[12]。nTregs来源于胸腺并持续维持于外周,主要通过与靶细胞直接接触而发挥作用[13]。叉头状转录因子P3(Forkhead transcription factor 3, Foxp3)在调控Treg分化发育和功能上具有至关重要的作用,因此被认为是Treg细胞的特异性标志物[14]。

1.1 Treg细胞抑制宿主体内过度病理反应 在血吸虫感染过程中,通常会诱导宿主体内Treg细胞增殖,缓解由血吸虫诱导的Th1/Th2/Th17免疫反应造成的相关病理损伤,从而起到保护宿主的目的[15]。研究表明,血吸虫成虫抗原主要引起Th1型

[基金项目] 湖北省武汉市卫生和计划生育委员会重点项目(WX17A08);湖北省卫生和计划生育委员会一般项目(WJ2017X30)

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[数字出版日期] 2018-10-17 09:13:22

[数字出版网址] http://kns.cnki.net/kcms/detail/32.1374.R.20181011.1246.001.html

免疫反应;而虫卵抗原主要引起Th2型免疫反应,并通过上调*Fizz1*、*Ym-1*、*Arg-1*基因激活巨噬细胞,造成肝脏纤维化病理损伤[16]。因而,调控Th1、Th2型免疫反应及分泌IL-17的淋巴细胞间的平衡对于防止严重宿主肝脏病理损伤具有重要作用[15]。同时,肝脏内有大量$CD4^+Foxp3^+$Treg细胞聚集,可平衡免疫反应并减轻免疫病理损伤。Turner等[17]研究发现,和急性期感染小鼠比,曼氏血吸虫感染慢性期小鼠结肠组织中Th2型细胞因子(IL-4和IL-5)分泌和肉芽肿面积均明显减少,而Treg细胞数量及TGF-β表达明显增多;当采用抗CD25单克隆抗体剔除其体内Treg细胞时,慢性期局部病理反应加重,提示增多的Treg细胞可抑制曼氏血吸虫感染慢性期小鼠局部病理结肠组织中Th2型免疫炎症反应。与感染对照组比较,日本血吸虫感染*AQP4*基因敲除小鼠肝脏中虫卵周围大量聚集嗜酸性粒细胞和巨噬细胞,导致肝虫卵肉芽肿形成明显增强,其机制可能是通过增强Th2型免疫反应、减弱Th1型免疫反应、降低Treg细胞数量来实现[18]。以上资料均表明,Treg细胞强大的免疫调节功能有利于机体控制寄生虫感染后引起的免疫病理反应。

1.2 Treg细胞在血吸虫逃避宿主免疫应答中的作用 病原体具有逃避宿主免疫攻击的能力,如干扰抗原提呈细胞而影响效应细胞的激活或其本身抗原产生变异等,从而在机体内长期存在导致持续感染[19]。日本血吸虫感染诱导的Treg细胞增多,是其逃避宿主免疫的窗口之一[20]。既然血吸虫可利用Treg细胞及其分泌的细胞因子逃避宿主的免疫应答,若采用相应的删除抗体(Depletion antibody)或者干扰其抑制功能,则可能利于机体清除寄生虫。例如,anti-CD25单克隆抗体可部分剔除Treg细胞,导致虫荷下降、Th1型细胞因子IFN-γ明显上升、细胞因子IL-10明显下降[21]。Layland等[22]提前向小鼠注射anti-CD25单克隆抗体,用于剔除其体内的Treg细胞,结果发现经过此处理的小鼠感染曼氏血吸虫后,小鼠肠道、肝脏和粪便中虫卵数均明显减少。以上研究结果表明,机体内Treg细胞的存在有利于血吸虫在体内长期存活,从而使其得以逃避宿主的免疫反应。

1.3 血吸虫利用Treg细胞帮助宿主克服自身免疫性疾病 随着"卫生假说"的提出以及后续的深入研究,寄生虫感染通过调节宿主的免疫状态以克服某些自身免疫性疾病、过敏性疾病等逐渐受到关注[23]。早期研究表明,血吸虫感染可以缓解过敏原卵清蛋白(OVA)诱导的哮喘小鼠气道炎症症状[24]。如在OVA小鼠致敏前预先感染日本血吸虫,可以抑制OVA致敏作用导致的哮喘症状,如抑制气道嗜酸性粒细胞增多症以及黏液生成;随后发现,这种抑制作用和Treg细胞增多有关[25]。血吸虫感染后Treg细胞增多同样也可以保护炎症性结肠炎的发生[26]。重组日本血吸虫半胱氨酸蛋白酶抑制剂(rSjcystatin)对Balb/c小鼠炎症性肠病具有治疗作用,其免疫机制可能与上调Treg细胞有关[26]。与对照组比较,使用rSjcystatin的小鼠脾淋巴细胞、肠系膜淋巴结及肠道黏膜固有层单核细胞中IFN-γ明显降低,而结肠组织中IL-4、IL-13、IL-10、TGF-β水平明显升高,且肠系膜淋巴结与肠道黏膜固有层中的Treg细胞水平上调[26]。然而,血吸虫感染用于治疗自身免疫性疾病过程中存在一定自身感染的风险[27-28]。Zaccone等[27]研究发现,给予I型糖尿病模型的NOD小鼠注射曼氏血吸虫可溶性虫卵抗原后,小鼠胰腺组织中$CD4^+Foxp3^+$Treg及$CD4^+CD25^+GITR^+$Treg细胞数量均明显升高,且糖尿病模型成功率明显降低,说明曼氏血吸虫可溶性虫卵抗原对NOD小鼠的保护作用与Treg细胞数量和功能均密切相关。

2 Th17细胞促进血吸虫感染过程中的免疫病理发展

Park等[29]和Harrington等[30]于2005年发现一类新的细胞亚群,因其特征性分泌细胞因子IL-17而命名为Th17细胞。Th17细胞具有独立的分化和调节机制,孤核受体(Retinoid related orphan receptor γt,RORγt)是其分化的特异性转录因子。虽然Treg细胞和Th17细胞在许多组织中同时存在,但两者在分化和功能上互相对抗[31]。在生理状态下,TGF-β抑制Th1和Th2细胞分化、诱导$CD4^+$T淋巴细胞转化为Treg细胞,后者抑制自身免疫、维持机体免疫稳态;当感染或病原体入侵时,炎性细胞因子IL-6或IL-21大量分泌,与低浓度TGF-β共同作用,促使$CD4^+$T淋巴细胞分化为Th17细胞,后者分泌IL-17(IL-17A)等促炎因子,诱导自身免疫和炎症的发生[32]。

传统观念认为,Th1/Th2免疫极化反应是血吸虫感染过程中的主要免疫学机制[33]。而近几年研究发现,血吸虫感染还可能由IL-23驱动,特异性诱导Th17细胞分化及其相关细胞因子IL-17分泌,参与感染过程中肉芽肿形成[34]。Chen等[35]发现日本血吸虫感染小鼠淋巴细胞经过抗CD3单克隆抗体/抗CD28单克隆抗体及PMA加离子霉素刺激后表达IL-17明显高于对照组小鼠;比较IL-17在3种肝T细胞亚型即辅助性T细胞、自然杀伤T细胞及γδT细胞中的表达,结果显示IL-17在γδT细胞中表达最高,为其主要来源。小鼠模型实验同时证实,使用抗IL-17A单克隆抗体中和IL-17可降低炎症细胞浸润及胶原在肝脏中沉积,可使肝细胞坏死明显下调,同时伴有促炎症细胞因子/化学因子如IL-6、IL-1β和CXCL2下调表达[36]。Smith等[37]发现,遗传易感性小鼠感染曼氏血吸虫后,IL-17水平升高更加显著,并产生严重肉芽肿免疫病理反应,因此进一步认为血吸虫感染后产生的严重病理并发症还和宿主遗传有关。Wang等[38]研究发现,IL-17细胞有利于肝肉芽肿形成及纤维化,而*ICOSL*基因敲除小鼠存活率增加、虫卵肉芽肿炎症明显下降且抑制肝脏纤维化发展,这可能与Th17细胞下调有关。Chen等[39]亦报道,日本血吸虫感染会诱导小鼠肺部Th17细胞比例增高,采用anti-IL-17单克隆抗体阻断日本血吸虫感染小鼠体内Th17细胞,同样可以减轻肺脏肉芽肿面积及炎性细胞浸润程度。Rutitzky等[40]研究发现,Th1细胞特异性转录因子T-bet对Th17细胞在曼氏血吸虫感染过程中介导的免疫病理反应具有一定负性调节作用。在*IL-17*$^{-/-}$基因小鼠感染曼氏血吸虫第6周,即使IFN-γ分泌增高,肉芽肿形成较轻;然而在IFN-γ$^{-/-}$小鼠感染第6周,IL-17显著增高,其病理反应明显加重,*IL-17*和*IFN-γ*基因同时敲除则可以完全抑制曼氏血吸虫导致的肉芽肿形成[40]。因此,在血吸虫感染过程中,Th17和Th1共同调节肉芽肿形成,决定宿主感染的严重程度。

3 Treg/Th17平衡与血吸虫感染

正常情况下,Treg/Th17细胞可以保持平衡[41];但众多研究

表明,血吸虫感染后Treg/Th17可出现失衡[42]。Mbow等[7]研究发现,与没有病理变化的埃及血吸虫感染儿童及正常儿童比,存在膀胱病理变化的埃及血吸虫感染儿童外周血中Treg、Th1和Th2细胞数量均无显著变化,而Th17数量明显增多,导致Treg/Th17细胞比例明显降低;研究人员进一步采用曼氏血吸虫分别感染CBA小鼠和C57BL/c小鼠模拟人体感染,得到类似研究结果。结果表明,在血吸虫感染过程中可能存在Treg/Th17的免疫调节失衡。Zhou等[8]研究发现,日本血吸虫虫卵来源的热休克蛋白60可特异性诱导Treg细胞,其机制可能是通过转换$CD4^+CD25^-$T细胞为$CD4^+CD25^+Foxp3^+$Treg细胞,或者以TLR4依赖的方式扩增预先存在的$CD4^+CD25^+Foxp3^+$Treg细胞;但它并不诱导其他$CD4^+$T细胞亚型,包括Th1、Th2细胞和Th17细胞,Treg/Th17失衡最终降低肝脏免疫病理反应。Herbert等[9]发现在曼氏血吸虫急性感染小鼠模型中,主要产生诱导IL-4和IL-13的活性巨噬细胞的精氨酸酶-1,可防止恶病质、中性白细胞增多症、内毒素血症产生;且精氨酸酶-1阳性的巨噬细胞促使TGF-β产生和Foxp3表达,抑制抗原特异性T细胞增殖并限制Th17分化。精氨酸酶-1缺陷可产生肠道出血及经典巨噬细胞激活(IL-6、NO、IL-12/IL-23p40产生增加);因此,急性血吸虫感染模型中通过抑制IL-12/IL-23p40产生且维持肠道黏膜Treg/Th17平衡,巨噬细胞来源的精氨酸酶-1保护宿主免受由成虫虫卵产生的过度组织损伤[9]。对于曼氏血吸虫感染所致的骨髓神经根病(SMR)患者,曼氏血吸虫可溶性虫卵抗原特异性IgE抗体可能是较有前景的生物标志物,可作为诊断性因子;与对照组比较,SMR组患者血清中Treg/Th17比例较低,Treg细胞来源的细胞因子IL-10也较低[43]。上述结果均表明,Treg/Th17失衡在血吸虫感染过程中具有重要作用。

4 结语

综上所述,具有免疫抑制功能的Treg细胞可控制自身免疫性疾病和血吸虫感染过程中机体免疫应答强度,而Th17细胞作为一种具有促炎性作用的免疫细胞参与多种炎症反应,两者在不同微环境下可以相互抑制和转化,其动态平衡关系是决定免疫耐受还是炎症发生的重要因素。血吸虫感染可调节宿主体内Treg/Th17细胞的免疫平衡,深入研究Treg/Th17细胞免疫平衡将为阐明血吸虫感染免疫学以及将血吸虫应用于其他免疫性疾病奠定理论基础。

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[收稿日期] 2018-01-02 **[编辑]** 汪伟