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文献综述 REVIEW

调节性T细胞在炎症性肠病中的研究进展

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Progress in research the roles of regulatory T cells in inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) is a nonspecific intestinal inflammatory disease. Its causes and pathogenesis have a close relationship with disorder of autoimmune function. The imbalance of the Th1/Th2 paradigm is an important factor for IBD. However, the pathogenesis of IBD cannot be interpreted on the basis of the Th1/Th2 paradigm alone. Recent research has highlighted the substantial role of regulatory T cells in the nosogenesis of IBD. This review will explore the relationship between regulatory T cells and IBD, and the progress in the study of regulatory T cells.

Key Words: Inflammatory bowel disease; Regulatory T cell; Autoimmunity

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摘要

炎症性肠病(IBD)是一种非特异性肠道炎症性疾病, 其发病与自身免疫功能紊乱有关. Th1/Th2失衡是导致IBD的重要因素之一. 然而, Th1/Th2理论并不能充分阐明IBD的发病机制. 近几年来, 越来越多的研究显示, 调节性T细胞在炎症性肠病的发生发展中起重要的作用. 本文就近年来调节性T细胞在炎症性肠病中作用的研究进展作一综述.

关键词: 炎症性肠病; 调节性T细胞; 自身免疫

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■背景资料
炎症性肠病是一种累及胃肠道的自身免疫性疾病, 近年来患病率呈逐渐上升趋势, 炎症性肠病发病机制不明, 近年来发现调节性T细胞在IBD中起重要作用.

0 引言

炎症性肠病(inflammatory bowel disease, IBD)是一种累及胃肠道的自身免疫性疾病, 包括溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(crohn's disease, CD). 近年来患病率呈逐渐上升趋势. IBD发病机制不明, 目前认为Th1/Th2失衡是导致IBD肠黏膜损害的重要因素之一. 近年来发现一类有别于Th1/Th2的特殊细胞调节性T细胞(regulatory T cell, Tr), 在IBD中起重要作用.

1 Tr细胞的生物学特性

Tr细胞具有高度异源性, 目前仍不清楚他们的前体、分化过程. 根据其来源、表位特性及发挥效应机制, Tr可划分为自然发生的$CD4^+CD25^+$ Tr细胞(natural regulatory T cells, nTreg)和适应性Tr细胞(induced regulatory T cells or adaptive regulatory T cells)[1-5], 后者有Tr1、Th3等多种亚型. $CD4^+CD25^+$ Tr细胞是目前研究较多的一类亚群, 可从人的胸腺和外周血中分离到, 且实验证实人和小鼠的Tr具有相似的特性.

自然发生的Tr细胞主要是指在胸腺发育成熟后进入外周淋巴组织, 抑制自身反应性T细胞, 以维持自身免疫平衡, 在预防病理性自身免疫反应方面起作用[2-3,6]. $CD4^+CD25^+$ Tr细胞拥有独特的细胞表型和功能, 是一种功能成熟的T细胞亚群, 约占正常人和小鼠的外周血及脾脏组织中$CD4^+$ T细胞的5%-10%, 具有免疫抑制性和免疫无能性. $CD4^+CD25^+$ Tr细胞的免疫抑制性

■研发前沿
对调节性T细胞在炎症性肠病发病中的作用, 以及对以调节性T细胞为靶点治疗炎症性肠病的策略研究是现在和今后研究的重点.

表现为经TCR信号刺激活化后能抑制$CD4^+$和$CD8^+$淋巴细胞的活化和增殖, 这种抑制作用无抗原特异性, 不具有组织相容性复合体(MHC)限制性[7-8]; 免疫无能性表现在对高浓度IL-2的单独刺激, 固相包被或可溶性抗CD3单抗, 以及抗CD3单抗、抗CD28单抗的联合作用呈无应答状态, 也不分泌IL-2[7-8]. $CD4^+CD25^+$ Tr介导免疫抑制的确切分子机制尚不清楚, 目前发现细胞因子(IL-10、TGF-β等)的分泌、与同源的抗原递呈细胞(APCs)的接触(既细胞与细胞特定表面共刺激分子的结合)、以及对APCs功能的下调等多种机制可能参与$CD4^+CD25^+$ Tr的抑制[9]. $CD4^+CD25^+$ Tr具有独特的表型, CD25(IL-2受体的α链)是早期发现的标志[10], 但因其也表达在活化T细胞表面, 对活动状态的免疫性疾病单靠CD25表达鉴定Tr不够特异. Foxp3是$CD4^+CD25^+$ Tr相对较特异性的标志物. Foxp3属于foxhead家族成员的转录因子, 组成性表达于机体的$CD4^+CD25^+$ Tr, 对nTreg细胞的发育和功能起关键作用[11-15]. 但是因为Foxp3属于胞内蛋白, 其检测和分离有所不便. 近来报道, 表面分子CD127低表达可以取代Foxp3, 作为Tr细胞特异标记[16-17]. 另外, Neuropilin-1(Nrp1)也可能是$CD4^+CD25^+$ Tr的相对特异标志物. Nrp1是与轴突导向、血管生成和T细胞激活有关的受体. Bruder *et al*[18]发现其组成性表达于$CD4^+CD25^+$ Tr表面. 其他标志物还有$CD45RB^{low}$, CD62L等, 但都不是$CD4^+CD25^+$ Tr的特异性标志. 此外与$CD4^+CD25^+$ Tr抑制功能相关的分子还有GITR[19]、lag-3[20]、瘦素[21]、Toll样受体-8(TLR-8)[22].

适应性Tr细胞由初始(navie)T细胞在抗原和某些特定因素(如未成熟DC, 成熟DC, IL-10, TGF-β, 抗CD4 或抗CD8 mAb, IFN及维生素D3等)刺激下产生[4]. 研究较多的有$CD8^+CD28^-$ T细胞、Tr1细胞[23]和Th3细胞、某些表达γδT细胞受体的$CD4^-CD8^-$ T细胞、NKT细胞[3,24].

2 $CD4^+CD25^+$ Tr细胞在IBD免疫紊乱中的作用及其机制

肠道是人体与外界抗原接触的主要场所, 因此肠道的局部反应需要精密地调节以避免对食物性抗原和正常菌群产生免疫反应, 同时又能有效地防御病原体. 在人体以及动物模型中的研究显示, Tr细胞在保持肠道稳态中起重要作用.

$CD4^+CD25^+$ Tr数量的减少, 表面分子表达的缺陷, 抑制功能的受损, 都与IBD的发生相关. Maul *et al*[25]分析IBD患者外周血和肠黏膜组织的Tr细胞, 结果显示在疾病活动期外周血$CD4^+CD25^+$和$Foxp3^+$ Tr细胞下降, 而在疾病缓解期上升; IBD病变肠黏膜Tr细胞较非病变处升高, 但这种升高仍然低于健康对照组. Takahashi *et al*[26]也得到类似的结果: 活动期UC外周血$CD4^+CD45RO^+CD25^+$ T细胞显著降低, 且与疾病的严重程度呈反比, 但CD患者无统计学差异. 然而仍有报道显示IBD患者的Tr细胞抑制功能没有减低, 且有少数报道活动期IBD外周血、肠黏膜Tr细胞升高[27-28], 这可能是体内环境的不同, 炎症细胞数量的优势, 或是其他Tr细胞的拮抗机制, 使其无法抗衡IBD的肠黏膜炎症.

在T细胞缺陷的小鼠与大鼠中, 输注$CD4^+CD45RB^{high}$ T细胞可以诱发IBD. 如果与此同时输入$CD4^+CD25^+$ Tr则能预防IBD的发生; 若在此之后, IBD的病理变化已建立, 输注$CD4^+CD25^+$ Tr, 可被招募到肠淋巴组织、固有层, 迁移到脾脏而发挥免疫调节作用, 治疗IBD[29]. CCR4在$CD4^+CD25^+$ Tr的迁移中起重要作用, 对这一模型中$CD4^+CD25^+$ Tr的抑制功能起关键作用[30]. 尽管$CD4^+CD25^+$ Tr的调节机制还不清楚, 但进一步研究初步显示, $CD4^+CD25^+$ Tr细胞大致可通过细胞接触及分泌抑制性细胞因子等方式实现对$CD4^+/CD8^+$ T细胞的非特异性抑制效应, 以预防治疗IBD.

2.1 细胞接触依赖机制 在体外, $CD4^+CD25^+$ Tr细胞介导的免疫抑制是通过Tr细胞与反应细胞同细胞接触实现. 多种配体-受体参与此过程, 其中包括介导信号的共刺激分子, 如细胞毒性T淋巴细胞相关抗原-4(cytotoxic T-lymphocyte antigen, CTLA-4)、糖皮质激素诱导的肿瘤坏死因子受体(glucocorticoid-induced TNF-receptor, GITR)、OX40(CD134)、淋巴细胞活化基因3(LAG-3)等.

CTLA-4属于CD28细胞表面受体家族, 与CD28相反, 活化的T细胞膜受体CTLA-4与APCs上的配体CD80/CD86结合, 介导免疫抑制信号, 以维持免疫自稳. 研究证实Tr细胞高表达CTLA-4. 高水平的CTLA-4与APCs上的B7结合, 诱导色氨酸裂解酶-吲哚胺2, 3-二加氧酶(IDO)活化, 介导免疫耐受[31]. CTLA-4在结肠炎中可能起重要作用. $CD4^+CD25^+$ Tr对肠炎的控制可被CTLA-4的中和抗体阻断[32]. 然而$CD4^+CD25^+$ Tr的体外免疫抑制效应不为CTLA-4阻断而逆转[33].

GITR表达在胸腺和外周血的静息$CD4^+CD25^+$ Tr细胞上. GITR可能与抗$CD4^+CD25^+$

Tr抗体结合, 使$CD4^+CD25^+$ Tr活性增强. 在$CD4^+CD45RB^{high}$ T诱发的IBD模型中, $CD4^+GITR^+$ T细胞能阻止结肠炎的发展; 给予抗GITR mAb可阻断$CD4^+CD25^+$ Tr对小鼠结肠炎的抑制作用[34]. 然而$CD4^+CD45RB^{high}$ T表达GITR起到相反的作用. GITR-/-小鼠脾脏$CD4^+CD45RB^{high}$ T诱导结肠炎的活性降低; GITR基因剔除和阻断GITR, 可预防2, 4, 6-trinitrobenzene sulphonic acid(TNBS)诱发的结肠炎. 因此GITR在IBD中的作用还有待进一步研究.

OX40分子短暂地表达于活化的$CD4^+$ T细胞上, 与APC表面OX40L结合, 介导免疫活化信号, 参与$CD4^+CD45RB^{high}$ T诱发的结肠炎产生[32]. 给予抗OX40L抗体能够阻止T细胞在小鼠结肠炎肠黏膜中积聚, 并且使结肠炎缓解[32].

LAG-3表达于活化的$CD4^+CD25^+$ Tr, LAG-3基因敲除小鼠的$CD4^+CD25^+$ Tr的抑制功能明显降低, $CD4^+$ T细胞异位表达LAG-3后可获得Tr的特性[20]. 但目前, 有关LAG-3与IBD研究的报道少见, 需进一步研究LAG-3与IBD的关系.

由此可见, 共激分子/共激分子受体在Tr细胞活化中起重要作用. 研究其表达异常的机制及如何调节这一类信号途径可能为治疗IBD带来新的曙光.

2.2 细胞因子调节机制 $CD4^+CD25^+$ Tr细胞还可通过释放抑制性的细胞因子(如IL-10, TGF-β2和IL-2等)发挥重要作用. 体外研究显示, $CD4^+CD25^+$ Tr细胞中IL-10和TGF-β mRNA的表达水平较高, 并且给予合适的刺激, $CD4^+CD25^+$ Tr细胞能直接分泌IL-10和TGF-β. 在$CD4^+CD45RB^{high}$ T诱发的IBD模型中, TGF-β和IL-10在Tr细胞对IBD的保护作用中占有较重要地位. 从TGF-β基因敲除小鼠分离的$CD4^+CD25^+$ Tr细胞[35]或来源于IL-10敲除小鼠$CD4^+CD45RB^{low}$ T则失去了抗IBD作用[36]. 在抗原脉冲细胞(antigen-experienced cells)、缠绕杆菌、利什曼原虫诱发的结肠炎模型中, Tr细胞的预防与治疗作用依赖IL-10[37]. 此外IL-10基因敲除的小鼠或用IL-10受体抗体处理野生型小鼠可产生慢性结肠炎, 可见IL-10在肠道内环境中起负性调节肠道免疫反应的作用. TGF-β也能阻断噁唑酮诱导的Th2型小鼠结肠炎[38]. 但在CD, Tr细胞分泌TGF-β的量反而增加, 可能是因为存在部分抗调节的活化机制. $CD4^+CD25^+$ Tr细胞可以通过体外TGF-β诱导$CD25^-$ T细胞产生, 这一TGF-β诱导的Tr细胞具有拮抗$CD4^+CD62L^+$ T细胞输注引发实验性结肠炎的作用[39]. IBD的TGF-β信号转导缺陷与Smad7的上调有关. *po* Smad7的反义核苷酸可改善TNBS诱导的结肠炎并防止其复发[40].

3 其他亚群的Tr细胞在IBD中的作用及机制

除自然发生的$CD4^+CD25^+$ Tr细胞之外, 尚有多种T细胞群能抑制其他T细胞的效应, 例如Th3细胞、Tr1细胞、与未成熟DC共培养的$CD4^+$ T细胞、$CD8^+CD28^-$调节T细胞.

Th3细胞最早是从*po*免疫耐受的小鼠体内分离得到的, 并对Th1和Th2有抑制作用[41]. *po*免疫耐受是指*po*抗原后, 引起机体对该种抗原产生无或低免疫性反应, 但机体对其他抗原仍可产生正常免疫性应答[42]. Th3的抑制效应是抗原非特异性, 并且通过分泌TGF-β介导以“旁观者抑制”途径产生. Th3的抑制活性以受体TGF-β介导为特征, 其产生也与TGF-β相关. 与nTreg依赖IL-2相比, Th3的体外存活有赖于IL-4和IL-10[42]. 然而Th3和nTreg之间的关系还不明确. 现已证实, Th2环境诱导Th3细胞, 而Th1环境抑制Th3的诱导. 但是, 参与Th3诱导过程的确切细胞因子群还不清楚. 在$CD4^+CD45RB^{high}$细胞诱导的IBD模型中, Th3通过分泌TGF-β诱导B细胞转换为IgA的同种型, 并且能维持*po*耐受[43]. Neurath *et al*[44]证实Th3细胞能抑制TNBS诱导的结肠炎.

Tr1细胞与经典的Th1和Th2不同, 多在IL-10诱导下产生, IFN-α可增强IL-10诱导产生Tr1细胞的能力[23,45-47]. 其低增殖不分泌IL-4, 但产生高水平的IL-10, 中等量的TGF-β, IFN-γ和IL-5, 少量的IL-2, 具有旁观者抑制效应和免疫记忆力[23,45-47]. 他们在体外通过分泌IL-10和TGF-β来抑制抗原特异性免疫反应[48-49]. Tr1细胞除了在体外抑制免疫反应, 在体内也有免疫抑制作用. 在SCID鼠转入$CD4^+CD45RB^{high}$ T诱发的IBD模型中, *po*卵清蛋白(OVA)诱导的特异性Tr1细胞和致病的$CD4^+CD45RB^{high}$细胞共同传输, 可预防这一Th1细胞介导的炎症[49]. 随后的实验显示Tr1具有预防和治疗$CD4^+CD45RB^{high}$诱导的IBD作用, 且显示$CD4^+CD25^+$ Tr的免疫耐受作用部分归功于: 通过Tr1的分化而间接起作用[50].

除了$CD4^+$细胞的亚群具有调节功能, $CD8^+$的亚群细胞也同样能起到免疫调节作用. 其中$CD8^+CD28^-$的一类T细胞备受关注, 其作用机

■创新盘点
多数文章只探讨了自然发生的$CD4^+CD25^+$ Tr细胞和炎症性肠病的关系. 本文不仅对$CD4^+CD25^+$ Tr细胞在炎症性肠病中新的进展进行了总结, 还描述了其他适应性调节T细胞亚群在炎症性肠病中的作用.

■应用要点
本文对调节性T细胞在IBD中的研究, 对IBD的治疗和诊断都有重要的意义, 调节性T细胞的变化作为IBD进展的指标, 通过增强调节T细胞的功能或回输调节T细胞可能起到治疗IBD的作用, 这些都有广阔的应用前景.

制是损害CD40通路的信号传导, 抑制APC激活T辅助细胞. $CD8^+CD28^-$ T细胞可以预防输注$CD4^+CD45RB^{high}$ T细胞诱导的IBD[51]. 此外在IBD患者的肠黏膜中存在$CD8^+$调节细胞的缺陷, 表现为肠黏膜中$CD8^+$调节细胞体外抑制淋巴细胞增殖作用几乎消失, 并可能出现TCR Vβ5.1-阳性的CD8明显降低, 但$CD8^+CD28^-$ T细胞的变化不明显[52].

总之, 目前对Tr细胞的确切作用机制、不同亚型的本质和相互作用还存在争议, 和IBD的关系还不是很清楚. 但是, 在IBD中, Tr细胞无疑补充了传统的Th1/Th2理论. 对Tr细胞进一步深入研究, 不仅可以使我们加深对IBD发病机制的理解, 而且提示Tr细胞可能成为新的治疗靶点, 为IBD的治疗提供广阔的前景.

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■同行评价
本文内容新颖、全面, 有较强的理论意义和参考价值.