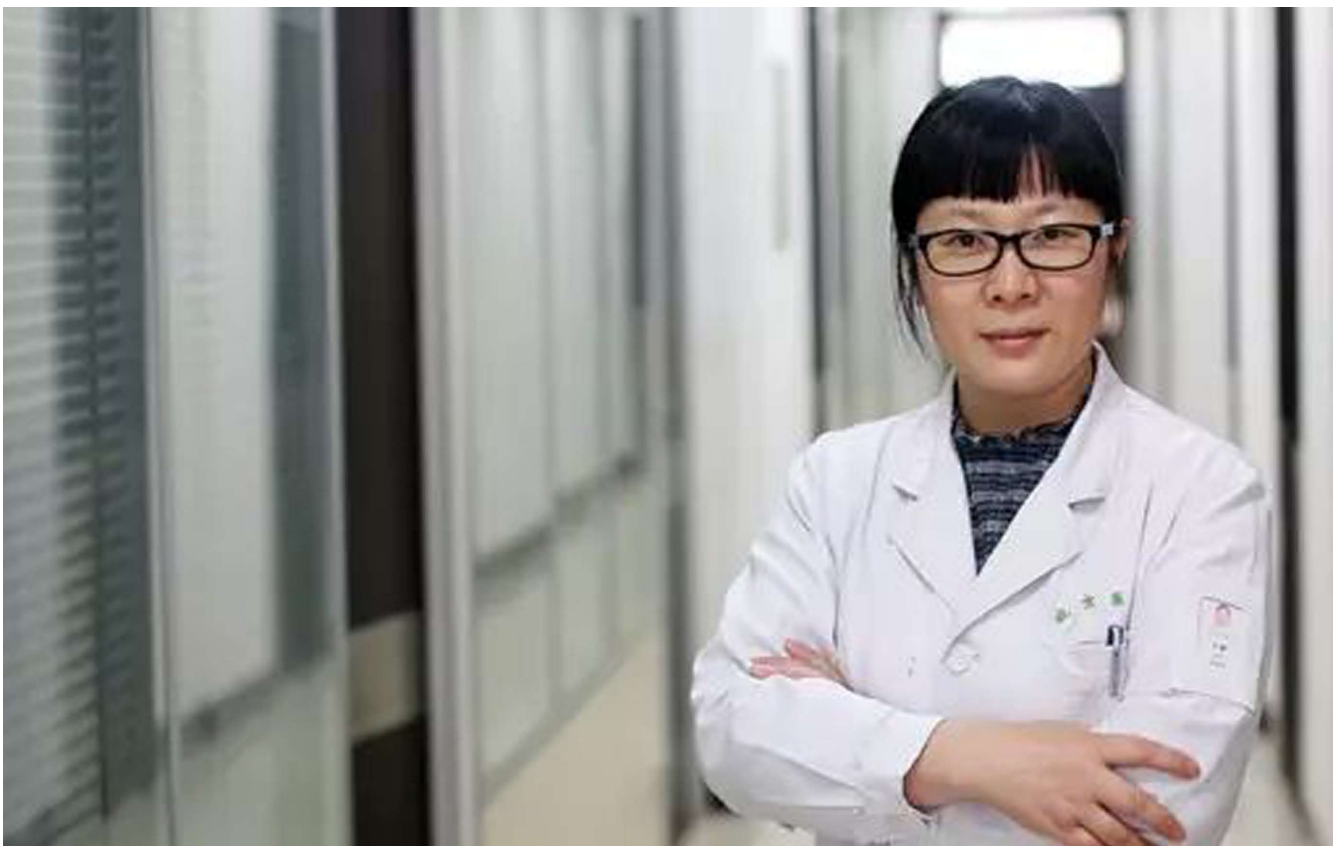
ISSN 1009-3079 (print)
ISSN 2219-2859 (online)

世界华人消化杂志®

WORLD CHINESE JOURNAL OF DIGESTOLOGY

Shijie Huaren Xiaohua Zazhi

2019 年 6 月 8 日　　第 27 卷　　第 11 期　　(Volume 27 Number 11)



11/2019

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ISSN 1009-3079
9 771009 307056 11 >

世界华人消化杂志 https://www.wjgnet.com 二零一九年六月八日 第二十七卷 第十一期

WCJD 世界华人消化杂志®

目　次　2019年6月8日 第27卷 第11期 (总第631期)

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编务 李香; 送审编辑 崔丽君; 组版编辑 刘继红; 英文编辑 王天奇; 形式规范审核编辑部主任 马亚娟; 最终清样审核总编辑 马连生

世界华人消化杂志

Shijie Huaren Xiaohua Zazhi

吴阶平　题写封面刊名
陈可冀　题写版权刊名

(半月刊)

创　刊 1993-01-15
改　刊 1998-01-25
出　版 2019-06-08
原刊名 新消化病学杂志

期刊名称
世界华人消化杂志

国际标准连续出版物号
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

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Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Fax: +1-925-223-8242
Telephone: +1-925-223-8243
E-mail: wcjd@wjgnet.com
http://www.wjgnet.com

出版
百世登出版集团有限公司
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Fax: +1-925-223-8242
Telephone: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

制作
北京百世登生物医学科技有限公司
100025, 北京市朝阳区东四环中路62号, 远洋国际中心D座903室
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《世界华人消化杂志》正式开通了在线办公系统(https://www.baishideng.com), 所有办公流程一律可以在线进行, 包括投稿、审稿、编辑、审读, 以及作者、读者和编者之间的信息反馈交流.

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定价
每期136.00元 全年24期3264.00元

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WCJD 世界华人消化杂志®

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Volume 27 Number 11 Jun 8, 2019

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Indexed/Abstracted by Chemical Abstracts, EMBASE/Excerpta Medica, Abstract Journals, Scopus, CNKI, CSTJ and Superstar Journals Database.

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Shijie Huaren Xiaohua Zazhi

Founded on January 15, 1993
Renamed on January 25, 1998
Publication date June 8, 2019

NAME OF JOURNAL
World Chinese Journal of Digestology

ISSN
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

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E-mail: wcjd@wjgnet.com
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Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Fax: +1-925-223-8242
Telephone: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
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PRODUCTION CENTER
Beijing Baishideng BioMed Scientific Co., Limited Room 903, Building D,
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Chaoyang District, Beijing 100025, China
Telephone: +86-10-85381892
Fax: +86-10-85381893

PRINT SUBSCRIPTION
RMB 136 Yuan for each issue
RMB 3264 Yuan for one year

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WCJD 世界华人消化杂志®

在线投稿: https://www.baishideng.com

世界华人消化杂志 2019年6月8日; 27(11): 665-670

DOI: 10.11569/wcjd.v27.i11.665

ISSN 1009-3079 (print) ISSN 2219-2859 (online)

述评 EDITORIAL

调节性T细胞在自身免疫性肝病中的作用机理及治疗进展

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基金项目: 天津市科委慢性病防治科技重大专项, No. 17ZXMFSY00210; 天津市卫计委卫生行业重点攻关项目, No. 15KG149.

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收稿日期: 2019-03-22
修回日期: 2019-04-16
接受日期: 2019-05-15
在线出版日期: 2019-06-08

Role of regulatory T cells in pathogenesis and therapy of autoimmune liver disease

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Supported by: Tianjin Science and Technology Major Project of Chronic Disease Control, No. 17ZXMFSY00210; Key Scientific and Technological Project of Tianjin Municipal Commission of Health and Family Planning, No. 15KG149.

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Received: 2019-03-22
Revised: 2019-04-16
Accepted: 2019-05-15
Published online: 2019-06-08

Abstract

Autoimmune liver disease (AILD) is a group of autoimmune-mediated hepatobiliary injuries, including autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis. It has been demonstrated that gene susceptibility, molecular mimicry, and abnormal immune regulation networks contribute to the occurrence and progression of AILD, while the mechanism of the related abnormal immune environment remains undetermined. It is currently believed that autoimmune diseases are mainly caused by the destruction of autoimmune tolerance mechanisms. Regulatory T cell (Treg), as a key factor to peripheral immune tolerance, may play a critical role in AILD. This article aims to elucidate the pathogenesis of AILD from the perspective of Treg cells and provide insight into the application of Treg cells in the therapy of AILD.

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Key Words: Autoimmune liver disease; Regulatory T cells; Pathogenesis; Immunotherapy

Sun MY, Liu WT. Role of regulatory T cells in pathogenesis and therapy of autoimmune liver disease. Shijie Huaren Xiaohua Zazhi 2019; 27(11): 665-670
URL: https://www.wjgnet.com/1009-3079/full/v27/i11/665.htm
DOI: https://dx.doi.org/10.11569/wcjd.v27.i11.665

摘要

自身免疫性肝病(autoimmune liver disease, AILD)是一组由自身免疫介导的肝胆损伤, 其包括自身免疫性肝炎, 原发性胆汁性胆管炎和原发性硬化性胆管炎. 多项研究表明基因易感性、分子模拟、异常的免疫调节网络对AILD的发生与发展具有促进作用, 但其自身免疫环境异常的原因至今尚未明确. 目前认为, 自身免疫性疾病的发生主要由自身免疫耐受机制破坏所致. 调节性T细胞(regulatory T cells, Treg)是外周免疫耐受的关键, 故可能在AILD中发挥重要的作

用. 本文从Treg细胞角度阐述AILD的发病机制, 并对Treg细胞在AILD治疗中的应用作一阐述.

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关键词: 自身免疫性肝病; 调节性T细胞; 发病机制; 免疫治疗

核心提要: 调节性T细胞(regulatory T cells, Treg)细胞在自身免疫性肝病(autoimmune liver disease, AILD)中的发病机制是目前研究的热点, 本文简要综述了目前关于Treg在AILD发病机制中的研究, 并总结了目前以Treg为靶点相关治疗的进展.

孙孟宇, 刘文天. 调节性T细胞在自身免疫性肝病中的作用机理及治疗进展. 世界华人消化杂志 2019; 27(11): 665-670
URL: https://www.wjgnet.com/1009-3079/full/v27/i11/665.htm
DOI: https://dx.doi.org/10.11569/wcjd.v27.i11.665

0 引言

自身免疫性肝病(autoimmune liver disease, AILD)是免疫系统介导的肝脏细胞或胆管细胞损伤的一类疾病总称. AILD发病机制尚不明确, 可能与遗传和环境因素有关. AILD的早期阶段多数患者无临床症状或伴随非特异性症状, 随疾病进展许多患者需要进行肝移植. 目前治疗AILD的策略以抑制免疫系统的免疫调控为主.

调节性T细胞(regulatory T cells, Treg)在维持体内免疫环境稳态与阻止自身免疫性反应中发挥重要的作用[1]. Treg细胞通过调节抗原提呈细胞(antigen presenting cells, APC)的成熟与功能, 干扰代谢途径和分泌抗炎因子(TGFβ、IL-10和IL35)等途径来调节免疫功[2]. 研究表明, 其他自身免疫性疾病如系统性红斑狼疮(systemic lupus erythematosus, SLE)、类风湿关节炎(rheumatoid arthritis, RA)、多发性硬化症(multiple sclerosis, MS)中, Treg细胞的数量减少、免疫抑制功能受损并且与疾病的发生有密切的联系[3-5]. AILD病人的Treg在数量与功能上也存在着异常[6-8]. 目前基于Treg细胞的自体过继治疗已经开展临床实验, 用于治疗移植物抗宿主疾病(graft-versus-host disease, GVHD)和SLE[9].

本文将从Treg细胞角度阐述AILD的发病机制, 并对Treg细胞在AILD治疗中的应用作一阐述.

1 自身免疫性肝炎

自身免疫性肝炎(autoimmune hepatitis, AIH)是一种免疫系统介导的慢性炎症性疾病. 目前, 发病机制不清, 主要影响肝脏细胞[10]. 其特点是界面性肝炎, 高丙种球蛋白血症和血清抗核抗体(anti-nuclear antibodies, ANA)升高. 在西方国家中, AIH的发病率为5-20例/10万[11]. 多数患者在早期出现非特异性症状, 如疲劳、关节痛和厌食症. 大约25%病人无临床症状, 患者晚期出现肝硬化和门脉高压症[12].

1.1 AIH AIH的确切发病机制尚不明确, 宿主易感性、环境、遗传等多种因素均可参与发病过程. T细胞和B细胞在适应性免疫应答中起重要作用[13]. Treg细胞在免疫稳态与阻止自身免疫反应中至关重要[1]. Vento等[14]于1982年首次报道AIH病人中“抑制性”细胞缺陷. 后续研究表明, AIH病人Treg细胞数量减少[6,15]. 此外, AIH病人Treg细胞抑制T细胞增殖的能力下降, 且抑制T细胞产生炎症因子的能力下降[16,17]. 这些现象表明, AIH病人Treg细胞不仅数量减少并且免疫抑制功能也存在缺陷.

1.1.1 AIH-1: AIH-1约占AIH病人总数的90%, 其特点为ANA, 抗平滑肌抗体(smooth muscle antibody, SMA)阳性.

最近的研究从分子水平揭示了AIH病人Treg细胞免疫调节受损的原因. Gal9-TIM-3通路在免疫调节中发挥了重要的作用, Galectin-9与TIM-3结合后引起短暂的钙内流, 导致Th1细胞的死亡, 从而抑制Th1细胞的增殖[18]. AIH病人Treg细胞中Galectin-9的表达水平和CD4+T细胞中TIM-3的表达水平均低于正常人, 表明AIH的发生可能与Treg细胞免疫调节功能受损有关[19]. CD39(NTPDase)通过水解ATP和ADP调节免疫应答平衡[20]. Treg细胞通过ATP–CD39–CD73–腺苷轴发挥免疫抑制功能[21]. AIH病人$CD39^{pos}$Treg细胞数量减少, 导致Treg不能水解前炎症因子ATP, 抑制效应T细胞分泌IL17的能力受损, 并且AIH病人$CD39^{pos}$Treg在炎症环境中表型失去稳定性[22]. 对AIH-1型病人肝脏标本进行免疫细胞分析发现病人肝脏中存在大量Teff细胞(effector of T cell)并且Treg细胞在肝脏大量的富集. 激素治疗后肝脏内Treg细胞数量减少, 与达到临床缓解的病人相比, 未缓解病人肝脏内Treg/Teff比例下降更加明显. 这表明治疗期间肝内Treg细胞比例减少可能与免疫抑制治疗中断后的复发相关. 以免疫调节为主的治疗方法可能是未来治疗的新方向[23].

1.2.1 AIH-2: AIH-2是一种罕见的AIH类型, 占到AIH病人的10%, 其特点是肝肾微粒体抗体-1(liver-kidney microsomal antibody type-1, LKM-1)和抗肝胞质1型抗原(anti-liver cytosol type 1 antigen, LC1)水平升高[24]. 在AIH-2病人体内发现NK细胞数量减少, 但是活化受体表达升高; IFNγ分泌增多但是IL2分泌下降. 这种体内细胞因子谱系的改变导致Treg细胞的功能发生损害并且伴随数量的减少[25].

1.2 AIH 治疗的主要策略是抑制持续的炎症, 目前一线的治疗方式为类固醇联合硫唑嘌呤. 以Treg细胞为靶点的生物治疗在动物模型中已取得一些进展, 未来以Treg

为靶点的生物治疗可能成为AIH治疗的一种选择.

1.2.1 AIH-1的治疗: Treg细胞多克隆扩增回输治疗在GVHD治疗领域已经进行了多项临床实验, 2015年第一项Treg过继治疗临床实验在Ⅰ型糖尿病患者中显示出良好的治疗效果[26]. 自体Treg细胞过继治疗成为目前应用最广泛的治疗方式.

Treg细胞表达的趋化因子受体3(chemokine receptor 3, CXCR3)对其趋化到炎症部位有重要的作用. CXCR3过表达可使Treg向肝脏的趋化能力增强[27]. AIH动物模型中, 分离CXCR3+Treg细胞, 在体外扩增并证明其具有免疫抑制功能, 回输到AIH小鼠体内可以有效的到达肝脏[28]. 研究表明, AIH-1型患者Treg细胞的CXCR3通路功能正常, 故自体CXCR3+Treg细胞在体外扩增之后可以有效的到达肝脏[29]. AIH-1型患者Treg/Th17细胞的比例存在异常, 患者的Treg细胞表型发生改变, 向Th17细胞表型分化[30]. 由于AIH-1型患者Treg细胞的功能异常, 所以Treg过继治疗的关键在于能否获得表型稳定的Treg细胞. 有研究证明, 利用AIH-1患者新生Treg细胞(newly generated Tregs, ngTreg)进行扩增培养, 在Treg分化期间利用物理方法消除其产生的IL17, 可以获得表型稳定的Treg细胞[31].

IL2是T细胞的生长因子, 注射低剂量IL2可以在体内扩增Treg[32]. 但由于Treg表达高水平的CD25(IL-2高亲和力受体), 所以注射低剂量IL-2后优先扩增CD4+Treg[32]. 低剂量IL-2可以促进体内Treg数量增加并且无不良反应, 已用于治疗丙型肝炎病毒诱发的血管炎患者和SLE患者[32,33]. IL-2亦可以扩增效应T细胞, 由于AIH病程进展中存在大量的效应T细胞, 需要进一步的研究来证明低剂量IL2治疗对调节/效应T细胞平衡和疾病进展的影响.

1.2.2 AIH-2的治疗: AIH-2患者由于Treg数量与功能受损, 体内存在大量细胞色素酶P450IID6(Cytochrome P450IID6, CYP2D6)抗原特异性的Teff细胞. 将Treg细胞与表达CYP2D6多肽的树突状细胞共培养, 可以产生CYP2D6抗原特异性的Treg细胞[34]. 这种抗原特异性的Treg细胞在共培养实验中可以有效的抑制CYP2D6抗原特异性的Teff细胞.

视黄酸(retinoic acid, RA)可以诱导Foxp3+Treg的产生同时可以增强Treg细胞的免疫抑制功能[35]. 在体外利用RA扩增AIH-2型患者的Treg细胞, 这种Treg细胞在免疫稳态与炎症环境中都表现出稳定的免疫表型与免疫抑制功能[36].

2 原发性胆汁性胆管炎

原发性胆汁性胆管炎(primary biliary cholangitis, PBC)是一种以免疫系统介导的肝内胆管慢性、进行性损伤为特点的疾病. 肝内胆管进行性的破坏导致慢性胆汁淤积, 门脉炎症, 并逐渐发展为肝硬化和肝功能衰竭[37]. PBC女性高发, 男女比例1:10[38]. 西方国家发病率为2.05例/10万. 多数患者在诊断时无症状, 随着疾病的发展, 患者会出现疲劳与瘙痒, 有78%患者存在疲劳症状, 有20%-70%患者存在瘙痒症状[38]. 虽然遗传和环境因素在PBC的发病机制中起重要作用, 但PBC病人中Treg细胞也存在着异常.

1980年首次发现PBC中存在Treg细胞原发性的缺陷[7]. 从PBC病人外周血中分离得到的$CD4^{pos}CD25^{pos}$ Treg细胞没有明显的功能缺陷, 但是Treg细胞$CD8^{pos}CD28^{neg}$Treg亚群的免疫抑制功能明显减弱[39]. PBC病人的外周血单个核细胞与Th17相关的基因如IL-1β, IL-6, IL-23, RORγt和IL-17A的表达水平升高, 而与Treg相关的基因如TGF-β和FOXP3的表达水平下降, 表明在PBC病人中Treg和Th17细胞的比例失调[40]. 最近一项研究[41]表明, PBC病人的Treg细胞对IL-12敏感性增加, 失去免疫抑制表型与功能, 并可向具有促炎功能的Th1型细胞分化.

熊去氧胆酸(ursodeoxycholic acid, UDCA)是目前为止唯一批准治疗PBC的药物, 其他药物如苯丁酸氮芥, 环保菌素, 硫唑嘌呤, 沙利度胺, 甲氨喋呤, 秋水仙碱单独用药都没有显示出良好的效果[42]. 目前有多种新药在进行临床实验, 如贝特类药物. 以Treg细胞为治疗靶点的生物治疗可能为新药开发提供新的方向.

有报道Treg细胞过继治疗在动物模型中显示可以抑制T细胞的免疫应答, 从而减轻PBC的症状[43]. 万古霉素可通过影响TGF-β通路发挥免疫调节作用[44]. 一项临床实验中发现口服低剂量万古霉素可以改善PBC病人的临床症状[45]. 进一步研究表明, 万古霉素是通过增加血清TGF-β, 促进Treg数量增加, 从而治疗PBC[46].

3 原发性硬化性胆管炎

原发性硬化性胆管炎(primary sclerosing cholangitis, PSC)是一种罕见的自身免疫性肝疾病. 主要影响肝外胆管, 胆管进行性纤维化狭窄导致慢性胆汁淤积, 进而可造成肝硬化和肝功能衰竭[47]. PSC发病率为0.41例/10万[48]. 约15%-40%患者在病程早期无症状, 病程晚期最常见的症状为黄疸, 瘙痒, 疲劳, 腹痛[49]. 约60%-80%PSC患者存在溃疡性结肠炎[50]. PSC发病机制不明, 多种因素如, 遗传和环境因素都与PSC相关[50].

2004年, Sebode等[8]报道PSC病人外周循环Treg细胞数量减少, 同时免疫抑制能力受损. 对病人进行肝脏组织活检发现, 与PBC病人相比PSC病人肝内Treg细胞数量减少. PSC动物模型显示, 相比于脾脏Treg细胞, 肝脏

Treg细胞的Foxp3表达明显下降并且免疫抑制功能受损. 这可能与肝脏Treg细胞IL-12受体上调, IL-12信号通路增强有关[51].

目前为止, PSC仍然缺少有效的治疗方法, 晚期PSC唯一治疗方法是肝移植. 在PSC小鼠模型中, 低剂量IL-2c可以上调Treg细胞的CD39, 通过嘌呤途径来抑制CD8+T细胞的增殖, 改善PSC的胆管纤维化[52]. 目前临床研究表明万古霉素可改善PSC患者的临床症状[53,54]. 万古霉素作为免疫调节制剂可通过增加病人外周血中的$CD4^{pos}CD25^{pos}CD127^{neg}$Treg数量或通过消除肠道内细菌来源的有害物质[55]来治疗PSC[46,55].

4 结论

Treg细胞功能与数量异常在自身免疫性疾病中的作用是近年来的研究热点. 有研究证明Treg细胞在Ⅰ型糖尿病、红斑狼疮中存在功能异常, 并且出现与Treg相关的免疫治疗方法. 近些年大量的研究集中在Treg功能与数量异常在AILD中的作用, 为阐明AILD发病机理提供了新的方向, 同时为AILD的治疗提供了新的思路. Treg细胞在AILD中存在数量的减少, 在炎症环境中表型改变, 向促炎表型分化, 使分泌抗炎因子减少, 抑制T细胞增殖功能减弱. 抑制APC细胞抗原提呈功能减弱. Treg细胞在AILD中存在多方面的缺陷, 从而促进了AILD的发生与发展. 与Treg相关的治疗思路集中在恢复自身免疫耐受机制, 通过自身Treg细胞过继治疗, 通过细胞因子或具有免疫调节功能的抗生素恢复患者体内的Treg细胞的数量与功能. 这些新出现的免疫治疗方法为AILD病人提供了新的希望.

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编辑: 崔丽君 电编: 刘继红

ISSN 1009-3079 (print) ISSN 2219-2859 (online) DOI: 10.11569 © 2019 Baishideng Publishing Group Inc. All rights reserved.

• 消息 •

《世界华人消化杂志》正文要求

本刊讯 本刊正文标题层次为 0引言; 1 材料和方法, 1.1 材料, 1.2 方法; 2 结果; 3 讨论; 4 参考文献. 序号一律左顶格写, 后空1格写标题; 2级标题后空1格接正文. 以下逐条陈述: (1)引言 应包括该研究的目的和该研究与其他相关研究的关系. (2)材料和方法 应尽量简短, 但应让其他有经验的研究者能够重复该实验. 对新的方法应该详细描述, 以前发表过的方法引用参考文献即可, 有关文献中或试剂手册中的方法的改进仅描述改进之处即可. (3)结果 实验结果应合理采用图表和文字表示, 在结果中应避免讨论. (4)讨论 要简明, 应集中对所得的结果做出解释而不是重复叙述, 也不应是大量文献的回顾. 图表的数量要精选. 表应有表序和表题, 并有足够具有自明性的信息, 使读者不查阅正文即可理解该表的内容. 表内每一栏均应有表头, 表内非公知通用缩写应在表注中说明, 表格一律使用三线表(不用竖线), 在正文中该出现的地方应注出. 图应有图序、图题和图注, 以使其容易被读者理解, 所有的图应在正文中该出现的地方注出. 同一个主题内容的彩色图、黑白图、线条图, 统一用一个注解分别叙述. 如: 图1 萎缩性胃炎治疗前后病理变化．A: …; B: …; C: …; D: …; E: …; F: …; G: …. 曲线图可按●、○、■、□、▲、△顺序使用标准的符号. 统计学显著性用: $^{a}P<0.05$, $^{b}P<0.01$($P>0.05$不注). 如同一表中另有一套P值, 则$^{c}P<0.05$, $^{d}P<0.01$; 第3套为$^{e}P<0.05$, $^{f}P<0.01$. P值后注明何种检验及其具体数字, 如$P<0.01$, $t = 4.56$ *vs* 对照组等, 注在表的左下方. 表内采用阿拉伯数字, 共同的计量单位符号应注在表的右上方, 表内个位数、小数点、±、-应上下对齐. “空白”表示无此项或未测, “-”代表阴性未发现, 不能用同左、同上等. 表图勿与正文内容重复. 表图的标目尽量用t/min, c/(mol/L), p/kPa, V/mL, t/℃表达. 黑白图请附黑白照片, 并拷入光盘内; 彩色图请提供冲洗的彩色照片, 请不要提供计算机打印的照片. 彩色图片大小7.5 cm ×4.5 cm, 必须使用双面胶条黏贴在正文内, 不能使用浆糊黏贴. (5)志谢 后加冒号, 排在讨论后及参考文献前, 左齐.

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Fax: +1-925-223-8242
Telephone: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

ISSN 1009-3079

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