

• 科技评述:2025年诺贝尔奖评述 •

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从“免疫平衡”到“免疫震荡” ——2025年诺贝尔生理学或医学奖解读及展望

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[摘要] 2025年诺贝尔生理学或医学奖授予布伦科、拉姆斯德尔及坂口志文,表彰其解析外周免疫耐受机制的突破:坂口发现CD4⁺CD25⁺调节性T细胞(Treg),布伦科和拉姆斯德尔等发现FOXP3基因突变致自身免疫病,且FOXP3是Treg发育与功能的主控基因。该成果完善了“中枢耐受+外周Treg监控”的免疫调控理论,推动了免疫学原创发现在自身免疫、癌症免疫、器官移植等临床疾病治疗实践中显效。当下Treg疗法尚未正式获批上市,基础理论及新药创制依然有待突破。我国在FOXP3修饰调控、组织特异性Treg亚型、Treg功能的代谢调控及免疫震荡理论等领域均有原创发现,未来需强化Treg领域基础与转化衔接,力争在Treg疗法理论及实践领域实现新突破。

[关键词] FOXP3; 调节性T细胞; 免疫平衡; 免疫震荡

1 研究背景:免疫系统的“敌我识别”难题

健康人体免疫系统可以识别自我和非我,且具有记忆性,可以“精准攻防”,防范病原感染,同时也不会伤及自身,这是免疫学最基本也是最重要的科学问题。20世纪60年代末,日本科学家西冢泰章(Yasuaki Nishizuka)对3日龄小鼠进行胸腺切除术会导致小鼠卵巢持续炎症,胸腺移植可以预防这种情况的发生,提示胸腺来源的免疫细胞可以抑制炎症^[1]。20世纪80年代确立的“中枢免疫耐受”理论认为,T细胞在胸腺发育成熟过程中会清除具有自身攻击性的T细胞,但临床中自身免疫病的频繁高发(全球各类自身免疫病患者超5亿),揭示中枢免疫耐受机制存在漏洞。1995年,坂口志文(Shimon Sakaguchi)实验室发现一类高表达细胞表面受体CD4⁺CD25⁺的T细胞亚群,可以阻止小鼠外周自身免疫病的发生和进展^[2]。

2 获奖原因:外周免疫耐受机制的突破性解析

诺贝尔委员会2025年将奖项授予美国科学家玛

丽·布伦科(Mary E. Brunkow)、弗瑞德·拉姆斯德尔(Fred Ramsdell),以及日本科学家坂口志文(Shimon Sakaguchi),因为其构建了从“关键免疫细胞亚群(CD4⁺CD25⁺ T细胞)、到发现核心转录因子基因(FOXP3),实现免疫平衡调节”的关键功能。坂口志文1995年首次鉴定出CD4⁺CD25⁺调节性T细胞(Treg),证实其可抑制自身反应性T细胞,为“外周免疫耐受”理论奠定了科学基础^[2]。布伦科与拉姆斯德尔等发现FOXP3基因突变导致小鼠多发自身免疫病,且人类同源基因突变引发致命性IPEX综合征,揭示FOXP3为免疫调控“开关(刹车)”^[3]。坂口志文实验室证实FOXP3是Treg发育与功能的主控基因,体外过表达FOXP3可以让CD4⁺ T细胞获得免疫抑制表型^[4]。此外,鲁坚斯基(Alexander Y. Rudensky)实验室及拉姆斯德尔实验室分别敲除FOXP3基因导致小鼠体内无法产生功能性Treg,直接诱发全身炎性自身免疫反应^[5,6]。诺贝尔委员会主席欧莱·卡珀评价:“这一发现彻底改写了免疫学教科

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书,解释了人类免于自身免疫病的核心原理”。

3 科技意义:从基础理论到临床革命

从基础科学突破的角度来看,本次诺贝尔生理学或医学奖发现完善免疫调控理论:确立“中枢耐受筛选+外周Treg监控”的双重防御体系,填补了免疫耐受领域空白。开创了全新的免疫调节研究领域:当下外周免疫耐受已成为免疫学、细胞生物学交叉研究的核心方向,在调节性T细胞领域全球已发表相关科学论文超6万篇。

从临床转化价值来看,本次诺贝尔奖也意义重大。比如在自身免疫病治疗方面:针对Treg功能缺陷,通过IL-2信号通路激活或细胞移植恢复其活性,已在类风湿关节炎、1型糖尿病临床试验中显示疗效,在炎性驱动小儿自闭症疾病模型治疗等方面取得新进展。在癌症免疫疗法革新方面:肿瘤微环境中过度积累的Treg会抑制抗肿瘤免疫,通过CCR8单抗等药物靶向清除这类细胞可增强PD-1抑制剂疗效,相关联合疗法响应率及患者生存期获得提升。在器官移植排斥防护方面:输注体外扩增的Treg可降低肾移植等排斥反应风险。但是,人源Treg疗法目前尚未获得正式批准成为上市药物,还需要基础理论及临床医药实践的多方面突破,如图1所示,左图是体外TCR信号和细胞因子IL-2及TGF-beta刺激诱导产生的诱导型Treg,右图是人源外周血用CD4⁺CD25^{hi}CD127^{low}分子标识分离得到的外周Treg。

4 国内研究:成果与展望

2025年诺贝尔生理学或医学奖三位获奖科学家及其代表的众多基础与临床研究者,揭示了“外周免疫耐受”的百年谜题。然而,要真正实现Treg免疫疗法,仍需在人类免疫学及Treg作用机制等方面取得更多的理论

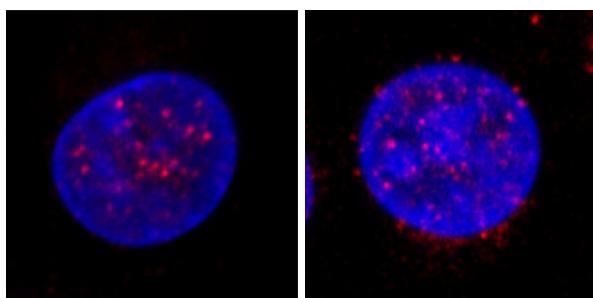


图1 两个人源FOXP3⁺调节性T细胞的免疫荧光染色:红色为FOXP3,蓝色为细胞核DAPI染色(图片来源:李斌课题组博士生徐湛)

Fig.1 Immunofluorescence Staining of Two Human FOXP3⁺ Regulatory T Cells: Red Represents FOXP3 and Blue Represents Cell Nucleus DAPI staining (Image Source: Dr. Zhan Xu from Bin Li's Group)

突破。过去二十年,在FOXP3翻译后修饰调控、肿瘤与脂肪组织特异性Treg功能、Treg发育代谢特征,以及从免疫稳态到免疫失衡的表观遗传可塑性等领域^[7-13],我国多支科研团队取得了一系列原创性成果,标志着我国在该领域实现了由“跟跑”向“并跑”的跨越。未来,应进一步强化基础研究与转化医学的衔接,在Treg精准调控和新药创制领域实现从“并跑”到“领跑”的突破,推动具有自主知识产权的创新药物从“0”到“1”加速进入临床应用,为疾病治疗开辟全新路径。

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From “Immune Homeostasis” to “Immune Perturbation” ——Insights and Perspectives on the 2025 Nobel Prize in Physiology or Medicine

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Abstract The 2025 Nobel Prize in Physiology or Medicine was awarded to Brunkow, Ramsdell, and Sakaguchi in recognition of their breakthroughs in elucidating the mechanism of peripheral immune tolerance. Specifically, Sakaguchi discovered CD4+CD25+ regulatory T cells (Treg), while Brunkow, Ramsdell and their colleagues identified that mutations in the FOXP3 gene cause autoimmune diseases and confirmed that FOXP3 is the master gene governing the development and function of Treg. This achievement has refined the immune regulation theory of “central tolerance + peripheral Treg surveillance” and promoted the application of original immunological discoveries in the clinical treatment of autoimmune diseases, cancer immunotherapy, organ transplantation and other inflammatory diseases. At present, Treg-based therapies have not yet been officially approved for marketing, and breakthroughs in basic theories and new drug development are still needed. Domestic research teams have made original discoveries in areas such as FOXP3 posttranslational modification and regulation, tissue-specific Treg subsets, metabolic regulation of Treg function, and the theory of immune perturbation. In the future, it is necessary to strengthen the connection between basic research and translational medicine in the field of Treg, and strive to achieve new breakthroughs in the theory and practice of Treg-based therapies.

Keywords FOXP3; regulatory T cells; immune homeostasis; immune perturbation

李斌 余㵎学者、上海交通大学特聘教授、上海市免疫学研究所资深PI、*European Journal of Immunology*期刊执行副主编。长期研究FOXP3翻译后修饰及Treg稳定性,近年来提出Treg免疫震荡理论假设。主持国家自然科学基金重点项目、青年科学基金项目(A类)等项目。

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