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Smad3对Th17细胞分化与转分化的调控作用与机制

刘思远，戴　岳*

中国药科大学中药学院，江苏　南京

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摘　要

Th17细胞属于效应T细胞亚群，能够保护机体免受外来病原体的侵害，维持组织的完整性，但其数目增多或过度活化可导致和加剧自身免疫性疾病。转化生长因子β (TGF-β)是诱导Th17细胞分化的重要细胞因子，但其经典下游信号分子Smad3可负性调节Th17细胞分化与功能，诱导Th17细胞转分化，提示TGF-β信号对Th17细胞分化具有复杂的作用。本文综述Smad3对Th17细胞分化及转分化的调控作用与机制，为构建靶向Th17细胞的新型治疗策略和药物开发提供参考。

关键词

Th17细胞，Smad3，分化，转分化

The Role and Mechanism of Smad3 in the Regulation of Th17 Cell Differentiation and Transdifferentiation

Siyuan Liu, Yue Dai*

School of Traditional Chinese Medicine, China Pharmaceutical University, Nanjing jiangsu

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Abstract

Th17 cells belong to a subset of effector T cells that protect the body from foreign pathogens and maintain tissue integrity, but their increased numbers or over-activation can cause and exacerbate

*通讯作者。

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autoimmune diseases. Transforming growth factor *β* (TGF-*β*) is an important cytokine that induces Th17 cell differentiation; however, its classical downstream signaling molecule Smad3 negatively regulates Th17 cell differentiation, inhibits Th17 cell function, and induces Th17 cell transdifferentiation, suggesting a complex role of TGF-*β* signaling on Th17 cell differentiation. This paper reviews the regulatory roles and mechanisms of Smad3 on Th17 cell differentiation and transdifferentiation, and provides a reference for the construction of novel therapeutic strategies targeting Th17 cells.

Keywords

Th17 Cell, Smad3, Differentiation, Transdifferentiation

1. 引言

Th17 细胞是继 Th1 和 Th2 细胞后发现的第三种 T 辅助细胞，其特征细胞因子为 IL-17。靶向 IL-17A 的单克隆抗体在银屑病和类风湿性关节炎中，均取得较好的临床实验结果[1]。靶向 Th17 细胞分化的核心转录因子 RORγt 的小分子抑制剂，如 JTE-151、JTE-451、ARN-6039、PF-06763809、ABBV-157 和 SAR-441169 被报道用于银屑病等自身免疫性疾病的临床研究[2]；IL-23 对于 Th17 细胞的致病性至关重要，靶向 IL-23 p40 亚基的单抗 Stelara® (ustekinumab)临床上表现出极佳的抗结肠炎效果[3]，是治疗溃疡性结肠炎的一线药物。

Th17 细胞分化需要 TGF-*β* 的参与[4] [5]。TGF-*β* 通过与受体结合并使其活化，招募并磷酸化下游的 Smad2/3 蛋白复合物，磷酸化的 Smad2/3 与 Smad4 结合形成三聚体复合物，然后转移到细胞核中介导靶基因转录，此过程为经典的 TGF-*β* 信号传导(图 1)。另一方面，其受体具有丝氨酸－苏氨酸激酶活性，可以激活 ERK [6]、JNK [7]、MAPKs [8]、PI3K/AKT5 和 RhoA/ROCK [9] [10]等信号通路，这些称为非经典的 TGF-*β* 信号通路。

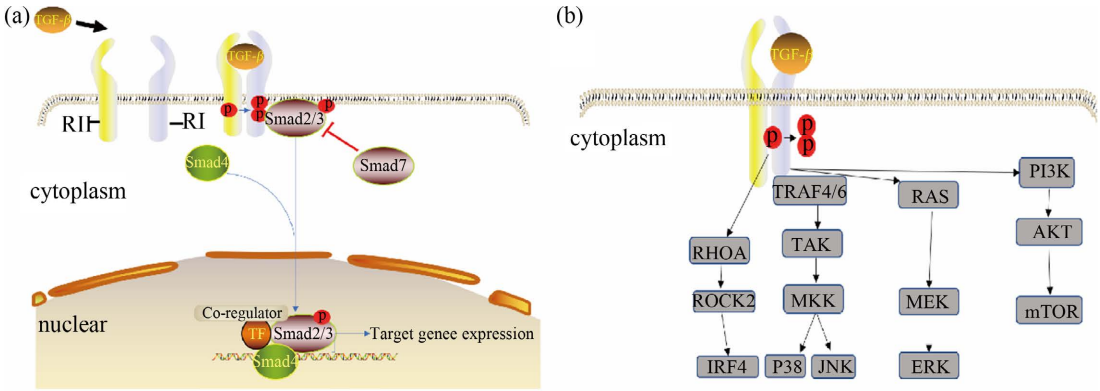

Figure 1. TGF-*β* signals via canonical Smad and non-Smad signaling pathways to regulate cell fate: (a) Classic TGF-*β* signaling transduction; (b) TGF-*β*/non-Smad signaling pathway
图 1. TGF-*β* 通过典型 Smad 和非 Smad 信号通路调节细胞命运：(a)经典的 TGF-*β* 信号通路示意图；(b)非经典的 TGF-*β* 信号通路示意图

Smad3 和 Smad2 同属于经典的 TGF-*β* 信号通路的胞内信号分子，但对 Th17 细胞分化的贡献截然相

反[11]-[17]。Smad2 激活与 IL-17A 的产生密切相关[18]。不仅如此，Smad2 还可上调 IL-6R 表达[15]，也可作为 STAT3 的共激活因子诱导 Th17 谱系基因的表达[11]。当 T 细胞中 Smad2 激活缺陷时，Th17 细胞体外分化受损[19]。而 Smad3 可整合多种受体信号，控制早期分化信号网络，调控 $CD4^+$ T 细胞的命运[20]。Smad3 能与 STAT3 相互作用并招募激活 STAT3 蛋白抑制因子(protein inhibitor of activated STAT3, PIAS3)，介导 STAT3 的转录活性抑制，阻遏 Th17 细胞分化[18]。此外，Smad3 密切参与 Th17 细胞的转分化，能作用于 Th17 细胞的 IL-10 基因启动子，促进其转录，使 Th17 细胞转变为抗炎表型。Smad3 可能是 TGF-β 信号发挥免疫抑制的关键信号蛋白。鉴于 TGF-β 在 Th17 细胞分化与转分化中的参与和作用，本文综述 Smad3 对 Th17 分化及转分化的作用和机制，深入了解 TGF-β 信号通路对 Th17 细胞命运的调控，为自身免疫病的细胞治疗提供参考。

2. Smad3 的结构与功能

Smad3 蛋白，类似于果蝇“mothers against decapentaplegic (Mad)”基因和秀丽隐杆线虫 Sma 基因的产物，是 TGF-β 信号的胞内信号传导分子，将信号从细胞表面传递到细胞核，从而调节相关靶基因的转录，介导 TGF-β 的生物学效应。一方面 Smad3 可与其他 Smad 蛋白形成复合物并结合于靶基因启动子上，调节基因转录；另一方面 Smad3 又可作为转录因子单独发挥作用。人和鼠 Smad3 蛋白均由 425 个氨基酸构成，氨基酸序列高度同源，仅 269 位不同(图 2(a))。根据其氨基酸序列序列，Smad3 蛋白可分为三个功能域，从 N 端到 C 端分别为 MH1、linker 和 MH2 domain，每个结构域都有其特有的功能(图 2(b)，表 1)。各种 Smads 蛋白 MH1 和 MH2 结构域高度保守，各结构域中含有不同的微型结构，这使得各种 Smads 结构产生区别，确保其发挥准确的生物学功能。Smad3 和 Smad2 最显著的区别在 N 末端 MH1 结构域上，Smad2 的 MH1 结构域独特插入外显子 3 编译的蛋白，从而阻止其与核输入受体蛋白之间相互作用，Smad3 无此氨基酸序列，从而使得 Smad3 能与 TGF-β 响应序列结合而充当转录因子[21]；所有 Smad 家族蛋白其 MH2 结构域中均含有与I型受体相互作用的 L3 环结构，但 I-Smad MH2 结构域末端不含 SSXS 基序，无法被受体磷酸化激活[22]。Smad3 除被I型受体在特定的位点上磷酸化外，还可被多种激酶磷酸化(表 2)，介导信号网络之间的交互。Smad3 作为转录因子，其一方面可通过与 Smad4 合作，共同完成核易位，这也是经典的 TGF-β/Smad3 信号传导模式，另一方面 Smad3 的 MH1 结构域中含有核定位序列(NLS)，能与核输入受体蛋白 β1 (importin-β1)相互作用，介导核易位[23]。MH2 结构域中含有核输出序列(NES)，能与核输出受体蛋白 4 (exportin-4)相互作用，介导核转位，从而完成 Smad3 的胞质胞核之间的穿梭。

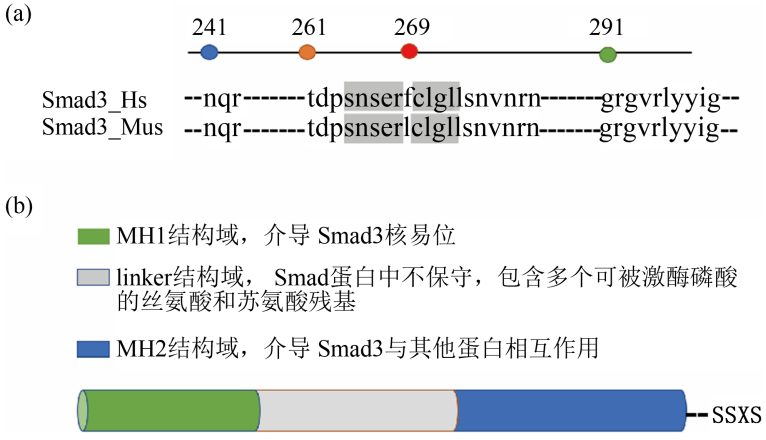

Figure 2. Structure and function of Smad3 protein: (a) Amino acid sequence difference of Smad3 protein in human and mouse; (b) Smad3 protein domain and its function

图 2. Smad3 蛋白结构域和功能：(a)人和鼠 Smad3 蛋白氨基酸序列的不同；(b) Smad3 蛋白结构域与其对应的功能

Table 1. Smad3 domain and its corresponding amino acid sequence
表 1. Smad3 结构域及其所对应的氨基酸序列

Region_name	Origin
N-terminal Mad Homology 1 (MH1)	8...132
Linker	137..231
Disordered	165..208
C-terminal Mad Homology 2 (MH2)	224..414
Sufficient for interaction with XPO4 (NES)	271..324
SSXS motif	422..425

Table 2. Smad3 phosphorylated site
表 2. Smad3 磷酸化位点

Phosphorylation		Site
TGF-β Signalling pathway	TGF-βRI	S422, S423 and S425 [54] [55]
MAPK Signalling pathway	ERK	T179, S204, S213 [55] S207, S203 and t178 [56]
	P38	S204, S208 and S213 [55]
	JNK	S208 and S213 [55]
Cyclin-dependent kinase (CDK) family	CDK4 and CDK2	T8, T178 and S212 [56] [57]
	CDK8/9	T179, S208 and S213 [57]
Glycogen synthase kinase-3β (GSK-3β)	GSK-3β	T66 and T179 [55] [57]
Cyclin guanosine monophosphate/Protein Kinase G	cGMP/PKG	S309 and T368 [58]

3. Smad3 在 Th17 细胞反应中的参与和作用

Th17 细胞活化是多种自身免疫性疾病的致病因素[2]，转录调节因子 Smad3 是 TGF-β 介导的免疫抑制的重要介质，Smad3 对抗炎及自身免疫耐受很重要：人全基因组研究发现 Smad3 是 IBD (炎症性肠病)的易感基因[24]，遗传学研究已经揭示，Smad3 与 IBD 的发病密切相关[25]，Smad3 信号缺陷引起的炎症性疾病在胃肠道中尤为突出，IBD 患者肠道固有层细胞中可以观察到 TGF-β/Smad3 信号是缺陷的，表现为 Smad3 磷酸化水平降低，Smad7 的水平显著上调[26]，尽管他们体内有较于正常人更高的 TGF-β 水平[27]。Smad3 敲除鼠会自发细菌性结肠炎，是一种常用的 IBD 模型[28]小鼠表现出大肠 T 细胞浸润和黏膜愈合受损[19]。事实上，增强 TGF-β/Smad3 信号的 Smad7 siRNA 是治疗 IBD 的潜在候选药物[29]。除此之外在多种自身免疫病模型中均伴随着 Smad3 激活的受损。在鼻窦炎模型小鼠的淋巴细胞中，可以观察到 Smad3 激活的抑制，改善 Smad3 的激活能够调节免疫细胞亚型治疗疾病[30]。同样的，在急性移植物抗宿主病(aGVHD)模型小鼠的皮肤、肠、肺和肝脏中可观察到 Smad3 的磷酸化水平的降低[31]。恢复模型小鼠 Smad3 磷酸化能改善炎症[29] [31]。Smad3 基因突变会影响自身耐受性，造成自身免疫失调。50%的 Smad3 突变携带者患有过敏性疾病，尤其是哮喘(23%)和过敏性结膜炎(23%) [32]。综上所述，Smad3

可能是自身免疫病治疗的潜在可行的靶点。

4. Smad3 对 Th17 分化的作用

在 CD3/CD28 共刺激条件下，naïve $CD4^+$ T 细胞在 IL-6 和 TGF-β 存在下，分化产生 Th17 细胞。IL-6 驱动 STAT3 磷酸化易位到细胞核中，诱导 T17 细胞转录因子 RORα 和 RORγt 的表达[33] [34]。TGF-β 通过抑制 IL-6 诱导的 SOCS3 表达，从而延长 STAT3 活化。STAT3 和 RORγt 协同诱导 Th17 细胞特征基因 IL-17A，IL-17F，IL-22 和 IL-23R 的转录。IL-23 能稳定 Th17 细胞谱系和诱导 GM-CSF 的产生，使这些细胞具有致病性[35]。

Smad2 和 Smad3 同属于经典的 TGF-β 下游胞内信号分子，但是对 Th17 细胞分化的作用两者相反，Smad2 正向调节 Th17 细胞分化[15]，而 Smad3 负向调节 Th17 细胞分化。较 Treg 细胞相比 Th17 细胞 Smad3 显著低表达[36]，敲除 Smad3 能够促进 Th17 细胞分化[13]。Smad3 激活缺陷的 Th17 细胞，IFN 和 IL-17 表达显著增加，致病性增强[16]。Smad3 过渡激活的 T 细胞，在初始刺激后分化成 Th17 细胞受阻[14]，MAP3K2 和 MAP3K3 所介导的 Smad3 接头区域磷酸化能抑制 Th17 细胞的体外分化，突变 Smad3 接头区域磷酸化位点能显著促进 Th17 细胞分化[37]。磷酸酶 PP2A 能选择性降低 Smad3 磷酸化，这对于 Th17 细胞分化至关重要，当敲除/抑制 PP2A，Smad3 的 C 端磷酸化显著增加，导致 Il17a 基因的转录减少，Th17 细胞分化显著抑制[14]。随着研究的深入，Smad3 抑制 Th17 细胞分化的作用机制已有相关论述，有报道表明 C 端未磷酸化的 Smad3 能与 STAT3 相互作用并招募 PIAS3 介导 STAT3 的转录活性抑制，造成 Th17 分化显著抑制[11]。也有研究表明，Smad3 能直接与 RORγt 结合，并抑制其转录活性[13]。除此之外，激活 Smad3 能通过抑制 Tiam1 的表达[38]，促进 Th17 细胞表达 Foxp3 [39]，抑制 Th17 细胞分化。

5. Smad3 对 Th17 细胞转分化的作用

从一种细胞类型转化到另一种细胞类型的过程被称为转分化，此过程伴随着谱系基因表达的改变和细胞功能的变化，这种转分化的潜力通常被称为可塑性。T 细胞的可塑性是一种细胞应对微环境刺激，而适应性的改变发育程序的内在能力。Th17 细胞存在广泛的可塑性，目前已有相关报道表明，Th17 细胞不仅可转分化为经典的 Treg [40]和 Th1 [41]细胞，还可转分化为 TR1 细胞(一型调节性 T 细胞) [42]，后者是一种新的具有免疫抑制功能的 $CD4^+$ T 细胞亚群。Th17 细胞转分化为调节性细胞，有助于炎症反应的消退[42]，其不稳定性和可塑性是是治疗类风湿性关节炎等自身免疫病的潜在靶点[43]，Th17 细胞的这种可塑性可以避免机体过度炎症和自身免疫性疾病的发生发展[44]。

目前，治疗自身免疫性疾病的方法旨在针对 Th17 细胞的分化和功能，但鉴于 IL-17A 的抗感染和促黏膜愈合作用[45]，以及 IL-17A 单抗对 IBD 临床试验失败无效的事实[46]，基于 Th17 细胞的可塑性，调节其转分化有望成为自身免疫病治疗的新方向[47]。Nanduri R 等[31]发现维生素 D 受体活化通过增加 Smad3 表达介导 Th17 细胞中 IL-10 的产生增加。Xu H 等[48]发现在 Th17 细胞中 Smad3 的激活能协同 Smad4 共定位于 IL-10 基因的启动子区域，诱导 IL-10 基因转录的增加，使炎性 Th17 细胞转变为抗炎表型，有利于炎症的消退和疾病的治疗。mTOR 缺陷型 naïve T 细胞在 Th17 分化条件下，分化为 Treg 细胞，这与过度活化激活的 Smad3 相关[14]。激活 Smad3 通过降低 NF-κB 的磷酸化促进 Th17 细胞转分化为 Treg 细胞，从而调节 Th17/Treg 细胞平衡[49]。TGF-β 通过 Smad3 诱导 Th17 细胞向 TR1 细胞的转分化[42]。Th17 细胞的可塑性是炎症性疾病的潜在治疗靶点，Samd3 在其中扮演着关键角色。

6. 总结与展望

综上，Smad3 密切参与 Th17 细胞的分化和转分化过程，并对 Th17 细胞所致的自身免疫病的发生发展具有积极的改善作用。但目前仍有很多尚未解决的问题，Th17 细胞分化和转化详细的具体的开关和触

发事件是什么？这些信号网络随环境和时间的具体变化是什么？以及 Smad3 具体的参与是什么？相信随着研究的深入，这些空白将会得到有效的填充和完善。越来越多的证据表明 Samd3 的激活在 Th17 细胞分化过程中显著受到抑制[50] [51] [52]，促进 Smad3 的激活是包括 UC 在内的自身免疫病的有效治疗策略，其相关药物已经进入 UC 三期临床试验[53]，虽然没能成功走出临床，我们认为可能的原因与 Smad2 的激活有关。因此，尽管 Smad3 在 Th17 分化和转分化以及自身免疫病治疗等相关研究中已经取得了可喜的进展，但该领域急切地需要靶向 Smad3 的相关研究的深入，机体的复杂性和 TGF-β 信号网络的多效性的背景下。从而为靶向 Smad3 治疗自身免疫病的药物开发提供良策。

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