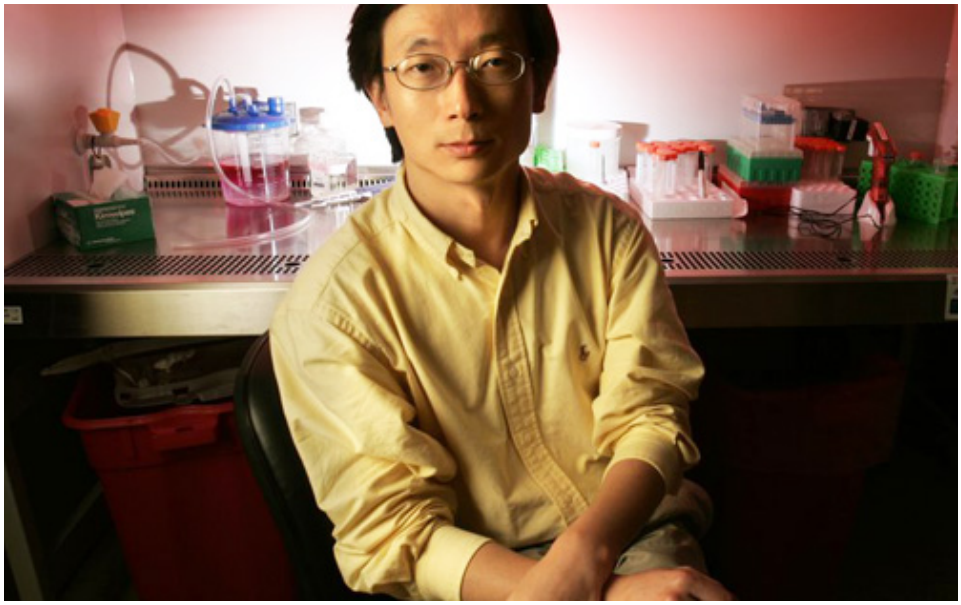
科学家找到重编程 T 细胞的小分子药物

Scientists Have Successfully discovered an epigenetic mechanism for Metabolic control of TH17 and induced Treg cell balance



丁胜教授

董晨教授

【Nature 系列】2017 年 8 月 10 日，清华大学药学院院长、加州大学旧金山分校 Gladstone 研究所丁胜教授和清华大学医学院董晨教授、Agios 制药公司的 Edward M. Driggers 合作，首次研发出重编程特定 T 细胞的方法。更确切地说，他们发现了如何将促炎细胞转化为抑制炎症的抗炎细胞，反之亦然。

他们的研究详细描述了一种代谢机制，有助于将一种细胞类型转化为另一种细胞：通过 GOT1 催化的转氨基作用的增加，导致在分化了的效应 Th17 细胞中戊二酸水平升高。2-羟戊二酸的积累导致的 Foxp3 基因超甲基化和抑制 Foxp3 转录，这是对形成效应 Th17 细胞必不可少。抑制谷氨酸转化成 α-酮戊二酸可以防止 2-羟戊二酸的生产，降低了 Foxp3 基因的甲基化，Foxp3 表达增加。这样可以拮抗转录因子 RORγ 的作用，阻断效应 Th17 细胞分化和促进极化形成调节性 iTreg 细胞功能。

这种新方法使 T 细胞可能有几个医疗应用。例如，在自身免疫性疾病中，效应 T 细胞过度激活，对机体造成损害。将这些细胞转化为调节性 T 细胞有助于减少多动症和恢复免疫系统的平衡，从而治疗疾病的根源。

许多癌症控制调节性 T 细胞来抑制免疫系统，创造一个肿瘤可以生长而不被检测到的环境。在这种情况下，研究小组的发现可用于将调节性 T 细胞转化为效应 T 细胞，增强免疫系统，从而更好地识别和摧毁癌细胞。

Metabolic control of TH17 and induced Treg cell balance by an epigenetic mechanism

表观遗传学机制重编程 T 细胞

清华大学药学院丁胜、医学院董晨

2017 年 8 月 10 日

doi:10.1038/nature23475

Metabolism has been shown to integrate with epigenetics and transcription to modulate cell fate and function1, 2, 3. Beyond meeting the bioenergetic and biosynthetic demands of T-cell differentiation4, 5, 6, 7, 8, whether metabolism might control T-cell fate by an epigenetic mechanism is unclear. Here, through the discovery and mechanistic characterization of a small molecule, (aminooxy)acetic acid, that reprograms the differentiation of T helper 17 (TH17) cells towards induced regulatory T (iTreg) cells, we show that increased transamination, mainly catalysed by GOT1, leads to increased levels of 2-hydroxyglutarate in differentiating TH17 cells. The accumulation of 2-hydroxyglutarate resulted in hypermethylation of the Foxp3 gene locus and inhibited Foxp3 transcription, which is essential for fate determination towards TH17 cells. Inhibition of the conversion of glutamate to α-ketoglutaric acid prevented the production of 2-hydroxyglutarate, reduced methylation of the Foxp3 gene locus, and increased Foxp3 expression. This consequently blocked the differentiation of TH17 cells by antagonizing the function of transcription factor RORγt and promoted polarization into iTreg cells. Selective inhibition of

GOT1 with (aminooxy)acetic acid ameliorated experimental autoimmune encephalomyelitis in a therapeutic mouse model by regulating the balance between TH17 and iTreg cells. Targeting a glutamate-dependent metabolic pathway thus represents a new strategy for developing therapeutic agents against TH17-mediated autoimmune diseases.