IMMUNOLOGY

Hippo signalling influences T cell fate

“TAZ...is required for the differentiation of ... T_H17 cells, but inhibits the differentiation of ... T_{reg} cells”

The Hippo signalling pathway is primarily known for its roles in tissue homeostasis, organ size regulation and tumour suppression. However, emerging evidence implicates key components of this pathway in T cell development and function. New research published in *Nature Immunology* now reveals that Hippo signalling is an important regulator of the reciprocal differentiation of T helper 17 (T_H17) cells and regulatory T (T_{reg}) cells, two T cell subsets with prominent roles in autoimmunity. Geng *et al.* show that a downstream effector of the Hippo

signalling pathway, the transcriptional coactivator TAZ (also known as WW domain-containing transcription regulator protein 1), is required for the differentiation of inflammatory T_H17 cells, but inhibits the differentiation of immunosuppressive T_{reg} cells.

TAZ expression was substantially enriched in T_H17 cells, and expression of the gene encoding TAZ was higher in memory CD4⁺ T cells isolated from patients with rheumatoid arthritis, Sjögren syndrome or inflammatory bowel disease than in cells from healthy individuals. Conversely, TAZ deficiency protected mice from T_H17 cell-driven autoimmune diseases (experimental autoimmune encephalomyelitis and a T cell transfer model of colitis). Mechanistically, TAZ promoted T_H17 differentiation and function by directly binding to and activating RORγt (considered to be the master transcriptional regulator of T_H17 cells) and blocking the activity of FOXP3 (the T_{reg} cell master regulator, which has an inhibitory effect on RORγt). TAZ also impaired T_{reg} cell development by disrupting the acetylation of FOXP3 by the histone

acetyltransferase Tip60 (also known as KAT5), thus targeting FOXP3 for proteasomal degradation.

When Hippo signalling is inactivated, TAZ translocates to the nucleus, where it binds to and activates TEAD family transcription factors, leading to transcription of genes related to cell proliferation. Geng *et al.* demonstrated that T_{reg} cell-polarizing conditions induced high levels of expression of the transcription factor TEAD1, which disrupted the interaction of TAZ with RORγt, FOXP3 and Tip60 by binding TAZ with higher affinity, thereby promoting T_{reg} cell differentiation.

Notably, knockout of TAZ or overexpression of TEAD1 induced T_{reg} cell differentiation, whereas expression of a transgene encoding TAZ or disruption of Hippo signalling promoted T_H17 cell differentiation. Together, the findings highlight the critical role of Hippo signalling in T cell homeostasis.

Sarah Onuora

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