m6A mRNA modification potentiates Th17 functions to inflame autoimmunity

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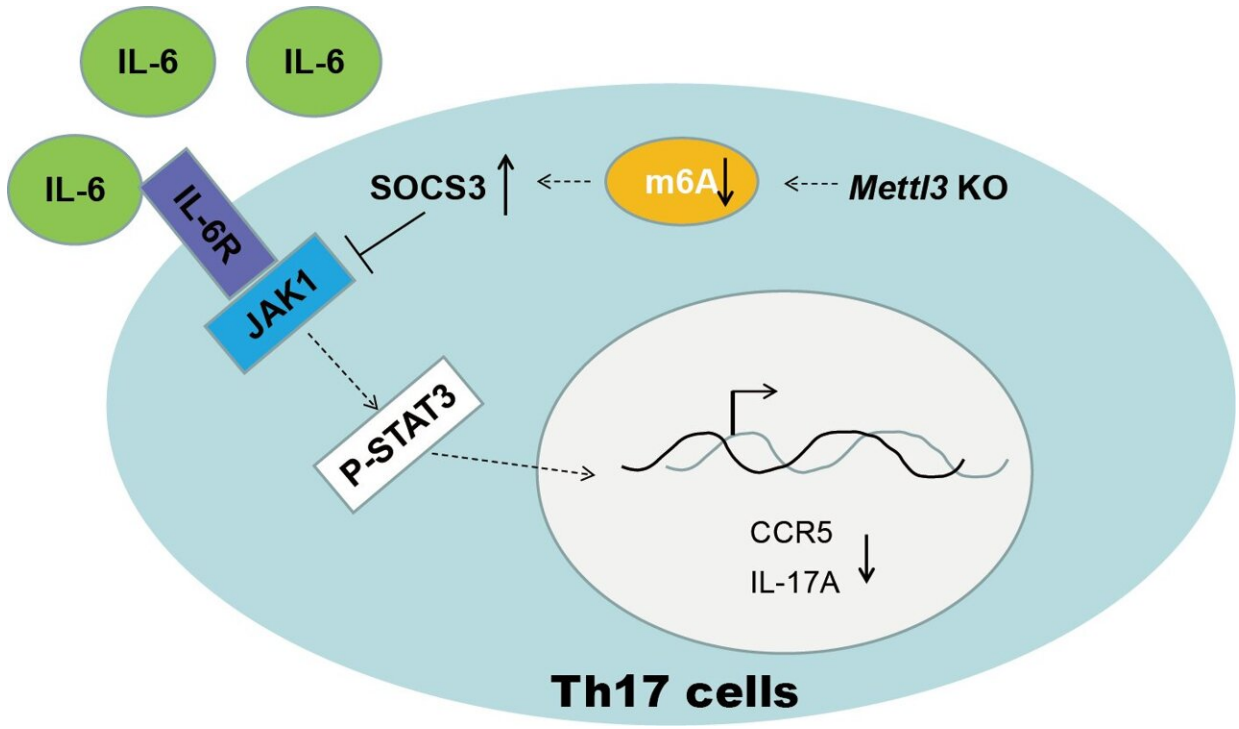

Loss of METTL3 in Th17 cells facilitated SOCS family RNA stability, inhibited IL-6/STAT3 mediated IL-17A and CCR5 expression, which in turn impeding Th17 cells differentiation and infiltration, eventually attenuating the process of EAE. Credit: Science China Press

N^6-methyladenosine (m^6A) is the most extensive studied RNA modification across various species, and the important effect of m^6A

modification in immune systems has been revealed in distinct contexts, including mRNA metabolism, cell differentiation, proliferation and response to stimulation.

Previous studies from the Hua-Bing Li group demonstrated that m^6A methyltransferase METTL3 control T cells homeostasis and sustain the suppressive function of regulatory T cells (Tregs). However, the role of m^6A methyltransferase in other subtype of T cells remains unknown.

T helper cells 17 (Th17) play a pivotal role in host defense and autoimmunity. In this study, the scientists found that the loss of METTL3 in T cells caused serious defect of Th17 cell differentiation, and impeded the development of experimental autoimmune encephalomyelitis (EAE). They generated $Mettl3^{f/f}Il17a^{Cre}$ mice and observed that METTL3 deficiency in Th17 cells significantly suppressed the development of EAE and displayed less Th17 cells infiltration into CNS.

m^6A modification has been reported to participate in RNA metabolism, predominantly affecting RNA stability. SOCS gene mRNAs have been documented as m^6A targets in $CD4^+$ T cells, and deletion of METTL3 led to attenuation of SOCS mRNA decay. In this work, they verified that depletion of METTL3 facilitated SOCS3 RNA stability, then further attenuated IL-17A and CCR5 expression, disrupted Th17 cells differentiation and infiltration, and eventually attenuated the process of EAE.

Collectively, the scientists highlight that m^6A modification sustains Th17 cell function, which provides new insights into the regulatory network of Th17 cells, and also implies a potential therapeutic target for Th17 cell mediated autoimmune disease.

The work is published in the journal *Science China Life Sciences*.

More information: Xuefei Wang et al, m6A mRNA modification potentiates Th17 functions to inflame autoimmunity, *Science China Life Sciences* (2023). DOI: 10.1007/s11427-022-2323-4