

m6A mRNA modification potentiates Th17 functions to inflame autoimmunity



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 (m⁶A) is the most extensive studied RNA modification across various species, and the important effect of m⁶A



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 m⁶A methyltransferase METTL3 control T cells homeostasis and sustain the suppressive function of regulatory T cells (Tregs). However, the role of m⁶A 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 <u>cell differentiation</u>, 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.

m⁶A modification has been reported to participate in RNA metabolism, predominantly affecting RNA stability. SOCS gene mRNAs have been documented as m⁶A 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 m⁶A 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.



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