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PDLIM4 negatively regulates Th17 cell differentiation by dephosphorylation of STAT3 transcription factor

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Abstract

The differentiation and activation of interleukin 17-producing T helper (Th17) cells is tightly regulated, otherwise exaggerated Th17 responses may cause autoimmune and inflammatory diseases, including rheumatoid arthritis. It, however, remains unclear how Th17 cell response is negatively controlled. PDLIM2 (PDZ and LIM domain protein-2) is a nuclear protein that belongs to a large family of LIM protein. We previously demonstrated that PDLIM2 negatively regulated Th17 cell differentiation as a ubiquitin E3 ligase targeting STAT3, the transcription factor critical for the commitment to the Th17 lineage, promoting its polyubiquitination and proteasomal degradation. We recently found that PDLIM4, another member of LIM protein, is also a negative regulator of STAT3 signaling and Th17 cell differentiation. In contrast to PDLIM2, PDLIM4 is located in the cytoplasm. Interestingly, PDLIM4 did not promote polyubiquitination and degradation of STAT3, but instead inhibited the phosphorylation of tyrosine residue essential for cytokine-induced STAT3 activation. PDLIM4 bound to and recruited PTP-BL, a protein tyrosine phosphatase, and facilitated dephosphorylation of STAT3, thereby terminating STAT3 activation. In $CD4^+$ T cells, PDLIM2-deficiency lead to increased STAT3 protein level and consequently enhanced Th17 differentiation, while PDLIM4-deficiency resulted in augmented tyrosine phosphorylation of STAT3 and enhanced Th17 cell differentiation. Our findings delineate an essential role of PDLIM4 in negatively regulating STAT3-mediated Th17 cell differentiation. Moreover, we also demonstrated that a single nucleotide polymorphism (SNP) of PDLIM4 is associated with rheumatoid arthritis susceptibility, suggesting that PDLIM4 may prevent the onset of human autoimmune diseases by negatively regulating Th17 responses.

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