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PI3K-Akt-mTORC1 pathway regulates Th17 differentiation by controlling Gfi1 expression and nuclear translocation of ROR γ t

Shigenori NAGAI[1], Yutaka KUREBAYASHI[1], Yukiko BABA, Shigeo KOYASU[1,2] Akihiko YOSHIMURA[1]

1 Keio University School of Medicine, Shinjuku, Tokyo
2 RIKEN RCAI, Yokohama, Kanagawa

Abstract

IL-17 secreting helper T (Th17) cells are known to be involved in neutrophil-mediated inflammation and combat microbes attacking epithelial layers. Furthermore, Th17 cells also play major roles in the pathogenesis of chronic diseases such as rheumatoid arthritis or inflammatory bowel disease. Therefore, it is very important to clarify the mechanisms of Th17 differentiation for the cure of these autoimmune diseases. Members of the phosphoinositide 3-kinase (PI3K) are important for the differentiation, proliferation, and survival of a variety of cells, including immune cells. In $CD4^+$ T cells. it has been reported that PI3K-Akt axis augments the clonal expansion of Th1 and Th2 cells. In this time, we demonstrated that the suppression of PI3K or mTOR complex 1 (mTORC1) activity impaired Th17 differentiation in a $p70^{S6K1}$ (S6K1) / $p70^{S6K2}$ (S6K2)-dependent fashion. PI3K-Akt-mTORC1-S6K1 axis impaired the downregulation of Gfi1, which is a negative regulator of Th17 differentiation. In addition, we demonstrated that S6K2 induced by PI3K-Akt-mTORC1 activation bound RORγt, and carried RORγt to the nucleus. These results suggest that a pivotal role of PI3K-Akt-mTORC1-S6K1/2 axis in Th17 differentiation.