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PIP4Ks impact on PI3K, FOXP3, and UHRF1 signaling and modulate human regulatory T cell proliferation and immunosuppressive activity

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Abstract

Regulatory T cells (Tregs) play fundamental roles in maintaining peripheral tolerance to prevent autoimmunity and limit legitimate immune responses, a feature hijacked in tumor microenvironments in which the recruitment of Tregs often extinguishes immune surveillance through suppression of T-effector cell signaling and tumor cell killing. The pharmacological tuning of Treg activity without impacting on T conventional (Tconv) cell activity would likely be beneficial in the treatment of various human pathologies. PIP4K2A, 2B, and 2C constitute a family of lipid kinases that phosphorylate PtdIns5P to PtdIns(4,5)P2. They are involved in stress signaling, act as synthetic lethal targets in p53-null tumors, and in mice, the loss of PIP4K2C leads to late onset hyperinflammation. Accordingly, a human single

nucleotide polymorphism (SNP) near the PIP4K2C gene is linkedwith susceptibility to autoimmune diseases. How PIP4Ks impact on human T cell signaling is not known. Using ex vivo human primary T cells, we found that PIP4K activity is required for Treg cell signaling and immunosuppressive activity . Genetic and pharmacological inhibition of PIP4K in Tregs reduces signaling through the PI3K , mTORC1/S6, and MAPK pathways, impairs cell proliferation , and increases activation-induced cell death while sparing Tconv. PIP4K and PI3K signaling regulate the expression of the Treg master transcriptional activator FOXP3 and the epigenetic signaling protein Ubiquitin-like containing PHD and RING finger domains 1 (UHRF1). Our studies suggest that the pharmacological inhibition of PIP4K can reprogram human Treg identity while leaving Tconv cell signaling and T -helper differentiation to largely intact potentially enhancing overall immunological activity .

Author keywords

Immunosuppression; Phosphatidylinositol 5-phosphate 4-kinase; Phosphoinositide kinases; T - regulatory cells; UHRF1

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