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Ubiquitin ligase Itch regulates p38α and skin inflammation via ubiquitination of Tab1

Deficiency of the ubiquitin ligase Itch causes a scratching 'Itchy' phenotype. However, the precise molecular mechanisms by which Itch regulates skin inflammation remain unclear. We have found elevated activation of the kinase p38α in the spontaneous and experimentally induced skin lesions of Itch-/- mice. Mechanistically, we demonstrate that Itch binds directly to Tab1 via the conserved PPXY motif and negatively regulates p38α. ShRNA-mediated inhibition of Tab1 attenuated the prolonged p38α phosphorylation seen in Itch-/- cells. Similarly, reconstitution of WT Itch but not the Itch-C830A mutant (which lacks the ligase activity) inhibited p38α phosphorylation in Itch-/- cells. Since Itch-deficient mice are unable to regulate Tab1 and p38α, elevated levels of pro-inflammatory cytokines including TNF, IL-6, IL-1β, IL-11 and IL-19 were observed in the skin. Inhibition of p38 or blocking the interaction of p38α with Tab1 using a cell-permeable peptide dramatically attenuated skin inflammation in Itch-/- mice. These results provide new insights into how Itch-mediated regulatory mechanisms prevent chronic skin inflammation, which could be exploited therapeutically in chronic inflammatory skin diseases.

Biography

Venuprasad Poojary has completed his PhD in Immunology at the National Center for Cell Science, Pune, India and Postdoctoral studies from La Jolla Institute for Allergy Immunology in San Diego, CA. He is an Associate Investigator at the Baylor Institute for Immunology Research in Dallas, TX. He has published more than 25 papers in reputed journals.

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