TLR Crosstalk Activates LRP1 to Recruit Rab8a and PI3K gamma for Suppression of Inflammatory Responses

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Abstract

The multi-ligand endocytic receptor, low-density lipoprotein-receptor-related protein 1 (LRP1), has anti-inflammatory roles in disease. Here, we reveal that pathogen-activated Toll-like receptors (TLRs) activate LRP1 in human and mouse primary macrophages, resulting in phosphorylation of LRP1 at Y4507. In turn, this allows LRP1 to activate and recruit the guanosine triphosphatase (GTPase), Rab8a, with p110γ/p101 as its phosphatidylinositol 3-kinase (PI3K) effector complex. PI3Kγ is a known regulator of TLR signaling and macrophage reprogramming. LRP1 coincides with Rab8a at signaling sites on macropinosomal membranes. In LRP1-deficient cells, TLR-induced Rab8 activation is abolished. CRISPR-mediated knockout of LRP1 in macrophages alters Akt/mTOR signaling and produces a pro-inflammatory bias in cytokine outputs, mimicking the Rab8a knockout and PI3Kγ-null phenotype. Thus, TLR-LRP1 crosstalk activates the Rab8a/PI3Kγ complex for reprogramming macrophages, revealing this as a key mechanism through which LRP1 helps to suppress inflammation.

KEYWORDS

Akt; LRP1; PI3Kγ; Rab8a; Toll-like receptor; crosstalk; inflammation; mTOR; macrophage; polarization