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Authors: Daqi Xu, Marissa L. Matsumoto, Brent S McKenzie, Ali A. Zarrin

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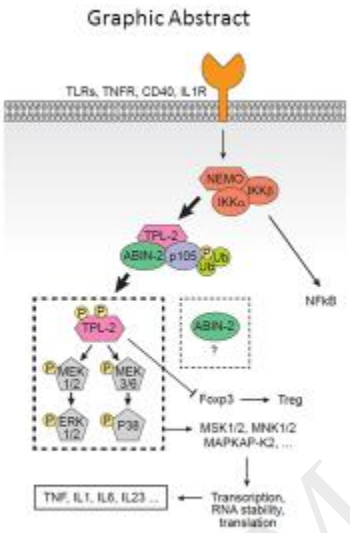
TPL2 positively regulates MAPK signaling in inflammation

Daqi Xu, Marissa L. Matsumoto, Brent S McKenzie, Ali A. Zarrin
Genentech Research, Genentech Inc., 1 DNA Way, South San Francisco, CA 94080, USA.

Graphical abstract



Abstract

Tumor progression locus 2 (TPL2, also known as COT or MAP3K8) is a mitogen-activated protein kinase kinase kinase (MAP3K) activated downstream of TNFαR, IL1R, TLR, CD40, IL17R, and some GPCRs. TPL2 regulates the MEK1/2 and ERK1/2 pathways to regulate a cascade of inflammatory responses. In parallel to this, TPL2 also activates p38α and p38?? to drive the production of various inflammatory mediators in neutrophils. We discuss the implications of this finding in the context of various inflammatory diseases.

Keywords

TPL2, COT, MAP3K8, phosphorylation, MAPK, ERK, p38, TLRs, TNFα, macrophage, neutrophil, inflammation, autoimmune disease, psoriasis, IBD, rheumatoid arthritis, multiple sclerosis, COPD

1. Introduction

Tumor progression locus 2 (TPL2, also called COT and MAP3K8) is a mitogen-activated protein kinase kinase kinase (MAP3K) downstream of TNFαR, IL1R and TLR receptors[1-3]. MAPKs function in a hierarchical fashion, in which MAP3Ks activates MAP2Ks by phosphorylation of a serine and/or threonine, and MAP2Ks activate MAPKs by dual phosphorylation of a Thr-X-Tyr motif[1,2]. TPL2 was first discovered as an oncogene in a human thyroid carcinoma cell line[4].