MST1 negatively regulates TNFα-induced NF-κB signaling through modulating LUBAC activity

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Summary

The nuclear factor (NF)-κB pathway plays a central role in inflammatory and immune responses, with aberrant activation of NF-κB signaling being implicated in various human disorders. Here we show that mammalian ste20-like kinase 1 (MST1) is a previously unrecognized component of the tumor necrosis factor α (TNFα) receptor 1 signaling complex (TNF-RSC) and attenuates TNFα-induced NF-κB signaling. Genetic ablation of MST1 in mouse embryonic fibroblasts and bone marrow-derived macrophages potentiated the TNFα-induced increase in IκB kinase (IKK) activity as well as the expression of NF-κB target genes. TNFα induced the recruitment of MST1 to TNF-RSC and its interaction with HOIP, the catalytic component of the E3 ligase LUBAC (linear ubiquitin assembly complex). Furthermore, MST1 activated in response to TNFα stimulation mediates the phosphorylation of HOIP and thereby inhibited LUBAC-dependent linear ubiquitination of NEMO/IKKγ. Together, our findings suggest that MST1 negatively regulates TNFα-induced NF-κB signaling by targeting LUBAC.