Abstract

MyD88 plays a crucial role in connecting the signaling pathways of Toll-like receptors (TLRs) and interleukin-1 receptors (IL-1Rs). Its importance lies in its essential function in coordinating host defense against invading pathogens and responding to tissue damage. MyD88-mediated signaling initiates a cascade of events leading to the activation of pro-inflammatory genes and the production of cytokines necessary for an effective immune response. Infections or injuries are often considered as triggers of autoimmune disorders. However, the regulators of MyD88 signaling in disease remain elusive. Here we identified the kinase TBK1 and associated adaptors TANK and AZI2 as new components of the IL-1R-SC. Mechanistically, TANK and AZI2 recruit TBK1 to the signaling complex to inhibit MyD88-dependent signaling and subsequent production of pro-inflammatory cytokines. Moreover, we showed that TBK1-mediated inhibition of MyD88-dependent production of TNF is essential for reducing the severity of TNF-mediated inflammation *in vivo*. Lastly, we propose that MyD88 or its downstream kinase IRAK4 can serve as potential targets in the treatment of inflammatory diseases.