TRAF6 oligomerizes within the ALPK1:ADP-heptose:TIFA oligomer complex

Gillespie, ME., Shamovsky, V., Shao, F.
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 71

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Tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) is a RING domain Ub ligase (E3), which, in conjunction with Ubc13-Uev1A, catalyzes K63-linked polyubiquitination that is required for activation of transforming growth factor β-activated kinase (TAK1 or MAP3K7) and IκB kinase (IKK). TRAF6 is activated downstream of alpha-protein kinase 1 (ALPK1) by binding to TRAF-interacting protein with FHA domain (TIFA) (Milivojevic M et al. 2017; Zhou P et al. 2018). TIFA recruits TRAF6 via a consensus TRAF6-binding motif of TIFA. Glycerol-gradient ultracentrifugation showed that only the high-molecular-weight forms of TIFA co-sedimented with TRAF6, suggesting that oligomerization of TIFA greatly enhanced its ability to bind to TRAF6 (Ea CK et al. 2004). In vitro ubiquitination assay in the presence of E1, Ubc13-Uev1A, purified endogenous TRAF6, Ub, and ATP showed that TIFA enhanced the Ub ligase activity of TRAF6 (Ea CK et al. 2004). Incubation of TRAF6 with wild-type or mutant TIFA proteins followed by gel-filtration chromatography showed that TIFA protein led to oligomerization of TRAF6, which eluted from the gel filtration column in the void volume (>700 kDa) (Ea CK et al. 2004). Importantly, these high-molecular-weight forms of TRAF6 displayed greatly increased Ub ligase activity as compared with TRAF6 of lower-molecular-weight species, despite a similar amount of TRAF6 protein in these fractions. Moreover, only the fraction with significantly higher Ub ligase activity of TRAF6 was able to activate IKK (Ea CK et al. 2004). The TIFA mutant that did not bind to TRAF6 was also unable to induce TRAF6 oligomerization (Ea CK et al. 2004). Cell fractionation and immunoblot analysis also suggest that TRAF6 forms oligomers in a TIFA-dependent manner in HEK293T cells in response to Shigella flexneri infection (Gaudet RG et al. 2017). Thus, upon bacterial infection such as Yersinia pseudotuberculosis, Shigella flexneri, Salmonella typhimurium or Neisseria meningitidis ALPK1 kinase activity induces TIFA oligomerization (Milivojevic M et al. 2017; Zhou P et al. 2018). The oligomerized forms of TIFA bind to TRAF6 and promote TRAF6 oligomerization (Ea CK et al. 2004). As a result, the TRAF6 Ub-ligase is activated to catalyze K63-linked polyubiquitination in conjunction with the Ubc13-Uev1A E2 complex (Ea CK et al. 2004). Activated TRAF6 promotes polyubiquitin-mediated activation the protein kinase TAK1 (MAP3K7) complex (Ea CK et al. 2004). Activated TAK1 (MAP3K7) in turn phosphorylates IκB kinase (IKK) at key serine residues within the activation loop, thereby activating IKK complex (Israël A 2010).

### Literature references

## Editions

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