

Soluble TNF- α binds TNFR1

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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

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Reactome database release: 88

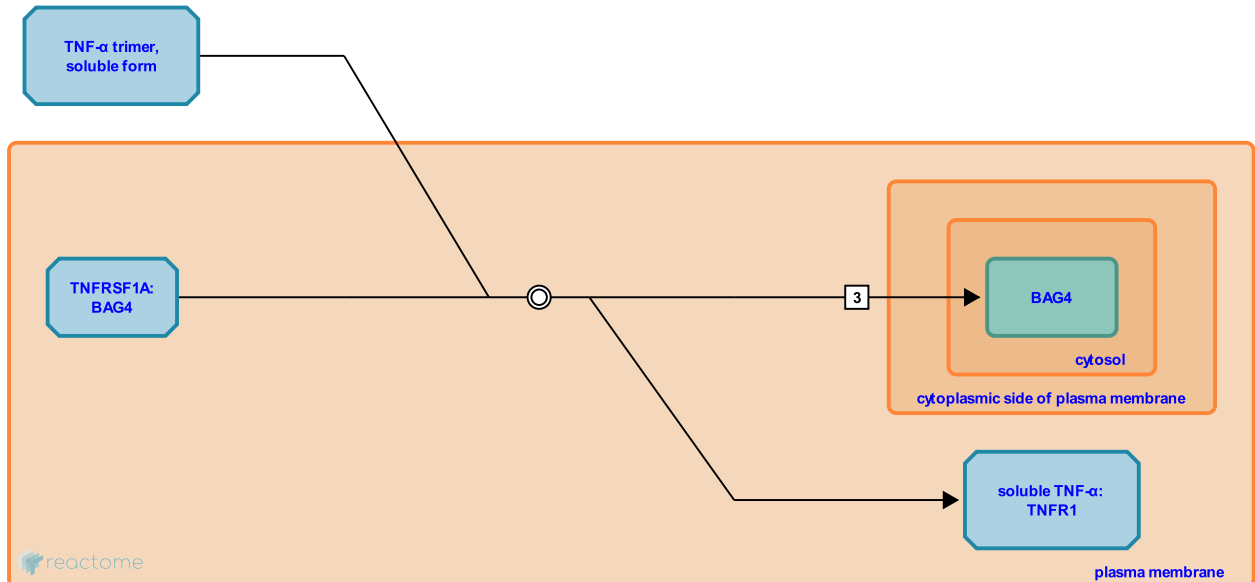
This document contains 1 reaction ([see Table of Contents](#))

Soluble TNF- α binds TNFR1 [↗](#)

Stable identifier: R-HSA-3371353

Type: dissociation

Compartments: plasma membrane, extracellular region, cytosol



The soluble form of TNF- α is cleaved from membrane-anchored TNF- α and retains the ability to bind to TNF receptor 1 (TNFR1) and TNFR2.

BAG4, also known as silencer of death domain (SODD), belongs to the BAG family of anti-apoptotic proteins. Mammalian BAG4 was found to associate with TNFR1 preventing receptor signaling in the absence of ligand (Jiang Y et al. 1999; Miki K and Eddy EM 2002). Furthermore, crystallographic data and biochemical analysis showed that TNFR1 forms inactive homodimers or homotrimers in the absence of TNF by the N-terminal domain, the pre ligand assembly domain (PLAD) (Chan FK et al. 2000; Wang YL et al. 2011). Upon TNF- α binding BAG4 is quickly released from TNFR1 and three receptor molecules form a complex with the TNF trimer. The TNF- α homologue ligand, lymphotoxin-alpha (LTA, also known as TNF- β), which as homotrimer only occurs as a soluble ligand, also interacts with TNFR1. LTA binds three receptor molecules and triggers the same effects as soluble TNF-alpha (Banner DW et al. 1993; Etemadi N et al. 2013).

The TNF- α :TNFR1 receptor complex then transmits the signal leading to cell death or survival. However, it remains unclear whether BAG4 binds to death domain of monomeric TNFR1 to prevent receptor oligomerization or recognizes receptor trimers to facilitate ATP-dependent TNFR1 trimer disassembly (Jiang Y et al. 1999; Miki K and Eddy EM 2002). Additionally, BAG4 is known to interact with HSP70, death receptor 3, and the anti-apoptotic protein Bcl-2 (Antoku et al. 2001; Brockmann et al. 2004; Jiang et al. 1999).

BAG4-overexpressing HeLa cells showed reduced cellular sensitivity to treatment with extracellular TNF α and CD95 ligand (Eichholtz-Wirth H et al. 2003). In addition, increased expression level of BAG4 in tumor cells leads to resistance of TNF- α -induced cell death and is associated with pancreatic cancer, some types of melanoma, acute lymphoblastic leukemia etc. (Ozawa et al. 2000; Tao H et al. 2007; Reuland SN et al. 2013). The physiological relevance of BAG4 for TNFR1 signaling, however, is difficult to judge because BAG4 knockout mice have no or only a mild effect on pro-inflammatory TNF signaling and give no evidence for an inhibitory role of BAG4 in TNFR1-induced cell death (Takada H et al. 2003; Endres R et al. 2003).

Literature references

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Editions

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