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TAB2, an important upstream adaptor of interleukin-1 signaling pathway, is subject to SUMOylation

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Abstract SUMOylation has been considered as an important mechanism to regulate multiple cellular processes, including inflammation. TAB2 (TAK1-binding protein 2) is an upstream adaptor protein in the IL-1 signaling pathway. Covalent modifications of TAB2 have not been well studied. In this study, we demonstrated that TAB2 could be modified by SUMO. Using Ubc9 (SUMO-conjugating enzyme) fusion and mutation analysis, we identified evolutionarily conserved lysine 329 as the major SUMOylation site of TAB2. PIAS3, a SUMO E3 ligase, preferentially interacted with and promoted its SUMOylation. Interestingly, block of SUMOylation by mutation of lysine 329 enhanced the activity of TAB2, as reflected by AP-1 luciferase reporter assays. Taken together, these results suggest that SUMOylation may serve as a novel mechanism for the regulation of TAB2.

Keywords TAB2 · SUMOylation · PIAS3 · JNK

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Introduction

The inflammation characterized by activation of c-Jun N-terminal kinase (JNK) and nuclear transcription factor κB (NF-κB) is widely involved in pathophysiological processes, such as tumorigenesis, metabolic disorders, neurodegenerative diseases, and so on. In the cascade of JNK and NF-κB activation, TRAF6 (TNF receptor–associated factor 6) and TAK1 (transforming growth factor-activated protein kinase) are key components. In mammalian cells, activation of TAK1 requires an upstream kinase complex consisting of TAK1 and two specific TAK1-binding proteins, TAB1 and TAB2 [1]. TAB1 acts as an activator of TAK1 while TAB2 as an adaptor protein that links TAK1 to the upstream TRAF6 in the IL-1 signaling pathway [1, 2]. TRAF6 functions as an ubiquitin ligase that associates with a dimeric Ub-conjugating enzyme complex and is self-ubiquitinated to form a unique polyubiquitinated chain linked through lysine-63 (K63) of ubiquitin [5]. TAB2 is an important adaptor protein in the IL-1 signaling pathway. Upon IL-1 stimulation, TAB2 binds to the polyubiquitinated TRAF6 via the zinc finger (ZnF) domain at the C-terminal, and TAB2 binds to TAK1 via a Coiled Coil (CC) domain beside the ZnF domain, resulting in the formation of a TRAF6-TAB2-TAK1 complex, which is critical for the signaling pathways leading to the activation of JNK and NF-κB [2–4, 6]. In mammals, TAB2 deficiency is embryonic lethal due to liver degeneration and apoptosis, which is similar to the phenotypes of NF-κB, IKKβ, and NEMO/IKKγ deficiencies [7]. TAB2 could also directly interact with NLK and form a TAK1.TAB2.NLK complex, which is involved in the inhibition of canonical Wnt signaling. [28].

Post-translational modification of proteins by the small ubiquitin-like modifiers (SUMO) plays an important role in