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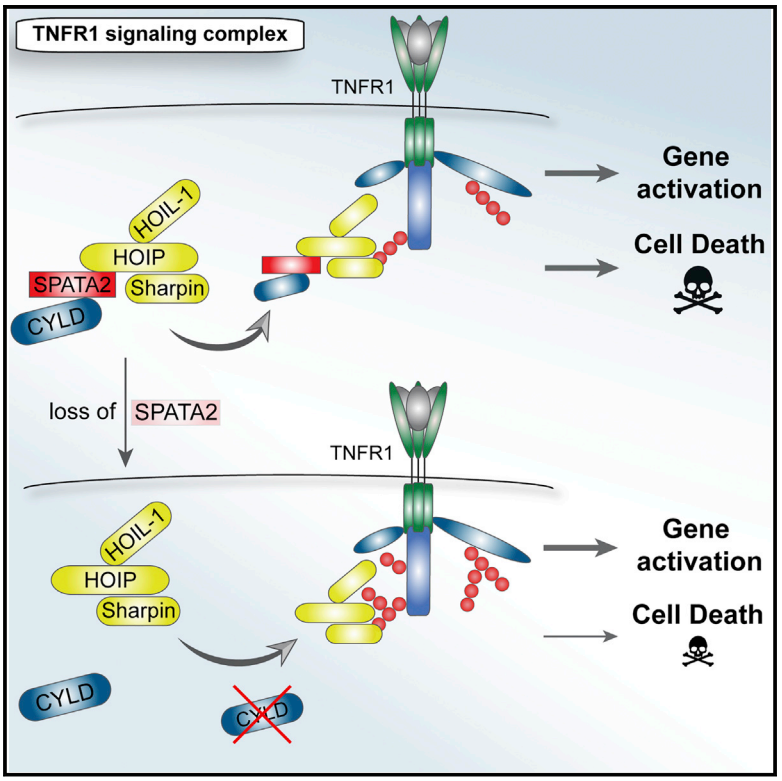
# SPATA2-Mediated Binding of CYLD to HOIP Enables CYLD Recruitment to Signaling Complexes

## Graphical Abstract




## Highlights

- SPATA2 bridges the interaction between HOIP and CYLD
- CYLD recruitment to the TNFR1-signaling complex requires SPATA2
- Loss of SPATA2 phenocopies absence of CYLD in TNFR1 signaling

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## In Brief

Kupka et al. show that the previously demonstrated interaction of CYLD with HOIP, which is required for recruitment of CYLD into signaling complexes, is indirect and mediated by SPATA2. Loss of SPATA2 abrogates recruitment of CYLD to signaling complexes and consequently mimics CYLD deficiency with regards to gene activation and necroptosis induced by TNF.

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# SPATA2-Mediated Binding of CYLD to HOIP Enables CYLD Recruitment to Signaling Complexes

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## SUMMARY

**Recruitment of the deubiquitinase CYLD to signaling complexes is mediated by its interaction with HOIP, the catalytically active component of the linear ubiquitin chain assembly complex (LUBAC). Here, we identify SPATA2 as a constitutive direct binding partner of HOIP that bridges the interaction between CYLD and HOIP. SPATA2 recruitment to TNFR1- and NOD2-signaling complexes is dependent on HOIP, and loss of SPATA2 abolishes CYLD recruitment. Deficiency in SPATA2 exerts limited effects on gene activation pathways but diminishes necroptosis induced by tumor necrosis factor (TNF), resembling loss of CYLD. In summary, we describe SPATA2 as a previously unrecognized factor in LUBAC-dependent signaling pathways that serves as an adaptor between HOIP and CYLD, thereby enabling recruitment of CYLD to signaling complexes.**

## INTRODUCTION

Over the past few years, the balancing roles of E3 ubiquitin ligases (E3s) and deubiquitinases (DUBs) in creating and degrading ubiquitin chains, respectively, have emerged as crucial at regulating innate and adaptive immune responses (Fiil and Gyrd-Hansen, 2014; Zinngrebe et al., 2014). There are eight different kinds of ubiquitin chains that accomplish different physiological outcomes (Yau and Rape, 2016). For example, lysine 48 (K48)-linked chains target proteins for degradation by the proteasome, whereas K63- and methionine 1 (M1)-linked chains (the latter also referred to as linear ubiquitin chains) are involved in the regulation of gene activation pathways and cell death (Chen and Sun, 2009; Iwai et al., 2014). The differently linked types of ubiquitin chains are generated by specific E3s and are degraded by specialized DUBs. Hence, precise timing of the respective activities of these enzymes is paramount for fine regulation of the signaling output generated by ubiquitin-involving signaling complexes (SCs) (Chen and Sun, 2009; Kupka et al., 2016; Zinngrebe et al., 2014).

Tumor necrosis factor (TNF) binding to TNF receptor 1 (TNFR1) triggers formation of the TNFR1 signaling complex (TNFR1-SC) (Walczak et al., 2012). Signals initiated from this complex result in two very different outcomes: (1) induction of gene activation via NF-κB and mitogen-activated protein (MAP) kinases and (2) induction of cell death, which can either be apoptotic or necroptotic. Linear ubiquitination, mediated by the linear ubiquitin chain assembly complex (LUBAC), is crucial in deciding the fate of cells upon TNF stimulation. In the absence of LUBAC, the lack of linear ubiquitin chains in the TNFR1-SC results in defective recruitment of various components and complex destabilization (Haas et al., 2009). This shifts the signaling toward enhanced formation of a secondary SC, which induces cell death (Peltzer et al., 2014), also referred to as complex II of TNFR1 signaling (Newton and Manning, 2016). In addition, linear and other ubiquitin linkages are removed by the DUB CYLD, a process that is crucial to enable the formation of complex II, as CYLD- deficient cells are resistant to TNF-induced cell death (Draber et al., 2015; Moquin et al., 2013).

LUBAC targets within the TNFR1-SC include RIP1, NEMO, TNFR1, and TRADD (Draber et al., 2015; Gerlach et al., 2011; Tokunaga et al., 2011). Furthermore, LUBAC regulates signaling through various other receptors, including CD40, NOD2, and IL-1R (Damgaard et al., 2012; Emmerich et al., 2013; Gerlach et al., 2011). LUBAC is composed of three subunits: SHARPIN, HOIL-1, and the catalytic component HOIL-1 interacting protein (HOIP) (Draber et al., 2015; Haas et al., 2009; Ikeda et al., 2011; Kirisako et al., 2006; Tokunaga et al., 2011). Additionally, LUBAC is associated with two DUBs: CYLD and OTULIN (Draber et al., 2015; Elliott et al., 2014; Takiuchi et al., 2014). Interaction of OTULIN and CYLD with HOIP is mutually exclusive (Draber et al., 2015). Although CYLD is co-recruited into signaling complexes via HOIP, OTULIN is not (Draber et al., 2015). The mechanistic explanation for this observation remains elusive, yet together, these findings point toward specific and distinct functions for OTULIN versus CYLD in regulating LUBAC.

Intriguingly, although the interaction of OTULIN with HOIP has been shown to be direct and was structurally characterized (Elliott et al., 2014; Schaeffer et al., 2014), we were not able to detect direct binding of CYLD to HOIP. This suggested the existence of


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