The ubiquitin system and A20: implications in health and disease

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Appendix Table 1. Structure and function of ubiquitin-editing enzymes in the regulation of NF-κB signaling.

Ubiquitin-editing enzymes	Structure	Targeted Substrates	Function	Related human diseases	Refs.
cIAP1	Possesses baculoviral IAP repeat domains which facilitate protein-protein interactions and a RING-IBR-RING domain which promotes its E3 ligase function.	NEMO, TRAF2, RIP1, itself	Regulator of NF-κB pathway.	Inflammatory bowel disease, autoinflammation and lymphoid malignancies.	(Hrdinka and Yabal 2019; Mace et al. 2010)
PARKIN (Park2)	Contains an ubiquitin-like domain at the N-terminus and 4 zinc-coordinating RING domains which mediate E3 ligase activity.	NEMO, TRAF2, RIP1	Promotes the activation of NF-κB signaling.	Early-onset Parkinson's disease, glioblastoma multiforme, cancers.	(Seirafi et al. 2015; Swatek and Komander 2016; Veeriah et al. 2010; Wang et al. 2018)
HOIL-1 (heme-oxidized IRP2 ubiquitin ligase-1)	Contains a N-terminal ubiquitin-binding domain, Npl4-ypte zinc finger domain for M1 polyubiquitin binding and a C-terminal RING-IBR-RING (RBR) domain.	In a complex with SHARPIN and HOIP (HOIL-1 interacting protein) mediates M1-linked polyubiquitination	Facilitates the activation of NF-κB dependent gene expression.	Autoinflammatory syndrome, cardiomyopathy, amylopectinosis and increased risk of bacterial infections.	(Boisson et al. 2012; Elton et al. 2015)

		of NEMO and RIP1			
HOIP (HOIL-1-interacting protein)	Contains a N-terminal ubiquitin associated domain and a C-terminal RBR domain with a unique linear ubiquitin chain determining region (LDD) .	In a complex with SHARPIN and HOIL-1 mediates M1-linked polyubiquitination of NEMO and RIP1.	Facilitates the activation of NF-κB dependent gene expression.	Diffuse autoinflammation, common variable immunodeficiency, amylopectinosis, and lymphangiectasia.	(Boisson et al. 2012; Lechtenberg et al. 2016; Oda et al. 2019)
SHARPIN (SHANK-associated RH domain-interacting protein)	Contains a N-terminal pleckstrin homology (PH) domain and a C-terminal ubiquitin-like domain and Np14-zinc finger domain that mediates interaction with HOIP and ubiquitin	In a complex with HOIL-1 and HOIP mediates M1-linked polyubiquitination of NEMO and RIP1.	Regulates NF-κB dependent gene expression.	Mycosis Fungoides, Cancers.	(Chen et al. 2019; Oda et al. 2019; Stieglitz et al. 2012; Tanaka et al. 2016)
OTULIN (also known as FAM105B or Gumby)	Consists of a catalytic OTU domain responsible for deubiquinating activity and a highly conserved PUB-interacting motif which mediates its ubiquitin binding activity	Linear ubiquitin chain assembly complex (LUBAC) comprised of HOIP, HOIL-1 and SHARPIN. Directly interacts with HOIP.	Restricts NF-κB signaling in response to TNF and NOD2 stimulation	Potentially fatal autoinflammatory disorder termed OTULIN-related autoinflammatory syndrome (ORAS).	(Damgaard et al. 2016; Stangl et al. 2019)

USP7	Contains an N-terminal poly-glutamine stretch and a highly conserved ubiquitin-specific protease (USP) domain responsibly for its catalytic and ubiquitin-interacting sites.	TRAF6, Nek2, NEMO	Regulates NF-κB signaling.	Neurodevelopmental disorders.	(Bhattacharya et al. 2018; Fountain et al. 2019)
MYSM1 (myb-like SWIRM and MPN domains 1)	Consists of a central SWIRM domain and C-terminal metalloproteinase domain responsible for its deubiquitinating activity.	TRAF3, TRAF6, RIP2	Restricts NF-κB signaling.	Bone-marrow failure syndromes and developmental aberrations.	(Bahrami et al. 2017; Panda and Gekara 2018; Panda et al. 2015)

References for Appendix Table 1

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Supplemental References for Figure 1

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