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MOLECULAR CELL BIOLOGY

Cellular regulation by deubiquitinating enzymes

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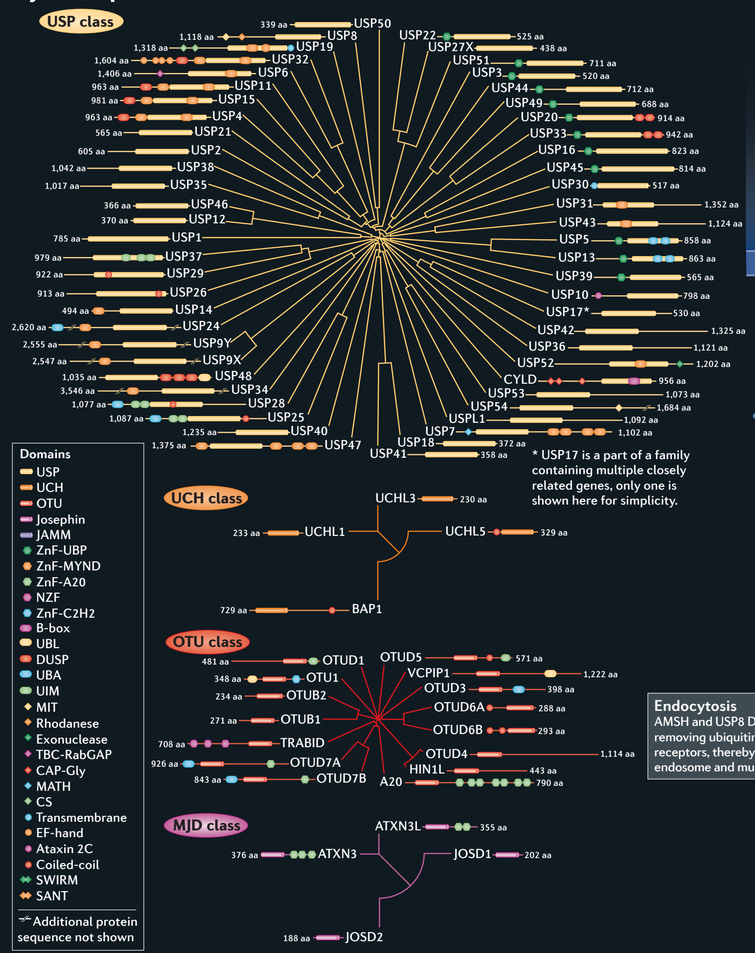
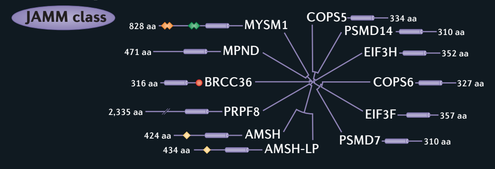
Protein ubiquitination has emerged as a highly dynamic process that governs nearly every function in cells from endocytosis to mitosis. As such, the cellular machinery that both appends and removes ubiquitin from target proteins is highly regulated. Evolving from our early understanding of the enzymes that remove ubiquitin from substrates (deubiquitinating enzymes (DUBs)) as enzymes that merely process ubiquitin precursors and scavenge ubiquitin from proteasome-targeted substrates, recent studies have revealed that DUBs are dynamic enzymes that partner with various interacting proteins to facilitate both substrate selection and DUB activity. Assembly of individual DUBs into distinct protein complexes has allowed for the diversification of DUB activity that is needed to process the increasingly diverse assemblages of monoubiquitin and polyubiquitin marks on substrates. This dynamic regulation in the ubiquitin proteasome system is underscored by the increasing evidence that many DUBs are part of ubiquitin ligase complexes, which enables DUBs to regulate the activity and abundance of both the ligase and the substrate. A subset of DUBs and their associated complexes are displayed below, along with the cellular pathways in which they act.

Cysteine protease DUBs

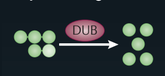


Zinc metalloprotease DUBs



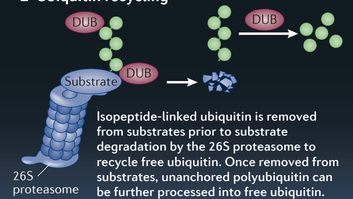
DUB activities

1 Ubiquitin precursor processing



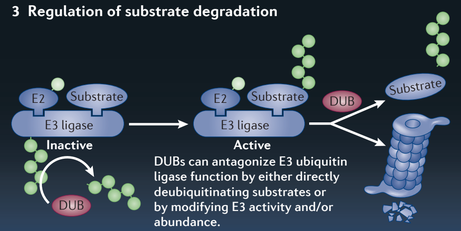
Ubiquitin is processed from its linear polyprotein precursor state into free ubiquitin by DUBs with ubiquitin hydrolase activity.

2 Ubiquitin recycling



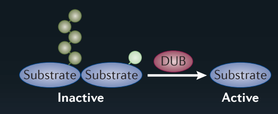
Isopeptide-linked ubiquitin is removed from substrates prior to substrate degradation by the 26S proteasome to recycle free ubiquitin. Once removed from substrates, unanchored polyubiquitin can be further processed into free ubiquitin.

3 Regulation of substrate degradation



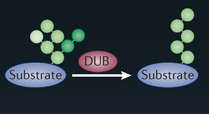
DUBs can antagonize E3 ubiquitin ligase function by either directly deubiquitinating substrates or by modifying E3 activity and/or abundance.

4 Regulation of substrate activity



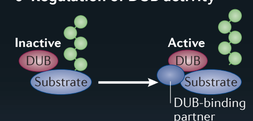
DUBs can regulate substrate activity by removing monoubiquitin or non-degradative polyubiquitin from substrates.

5 Ubiquitin chain editing

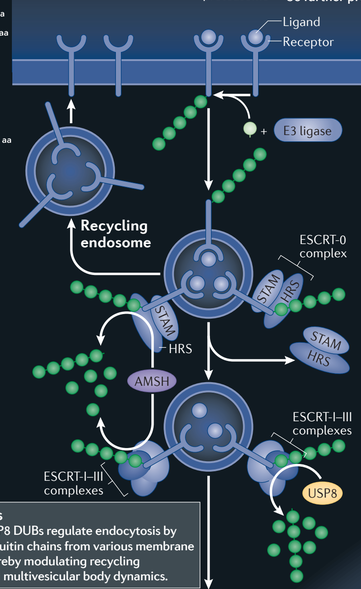


Mixed polyubiquitin chains can be edited by DUBs, or DUBs can remove one chain linkage type prior to elongation of a second chain.

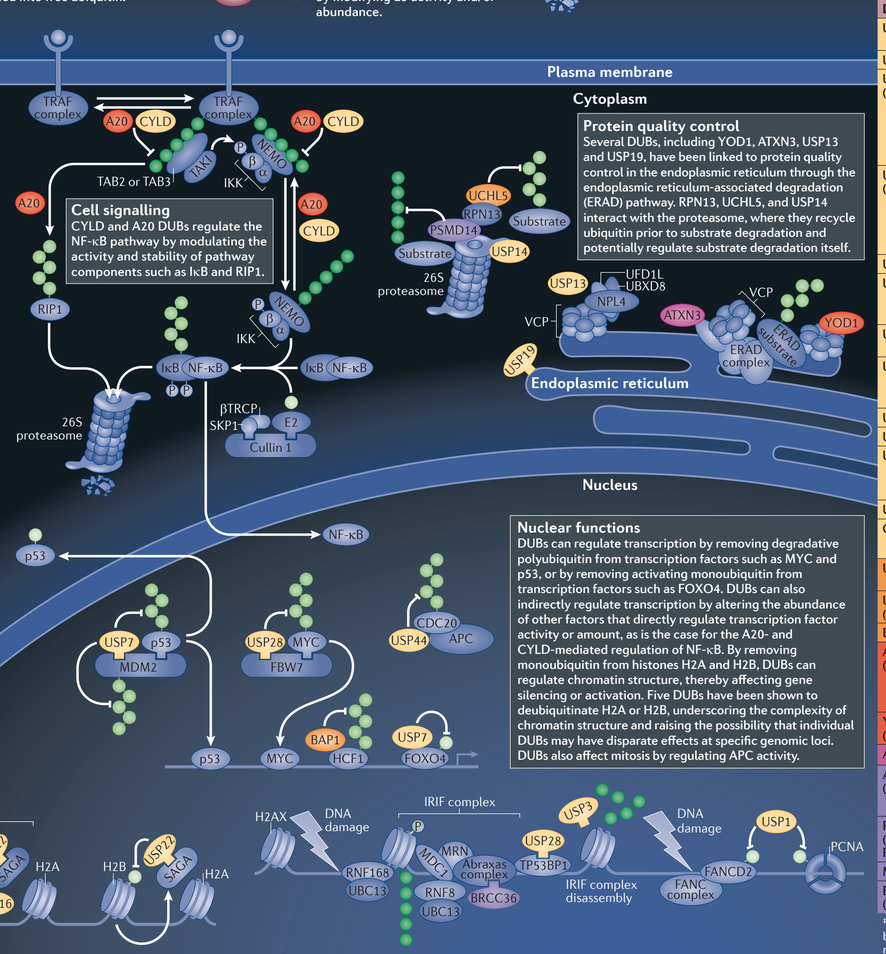
6 Regulation of DUB activity



DUB-binding partners can regulate DUB activity by either recruiting the DUB to substrates or by modulating the catalytic properties of the bound DUB.



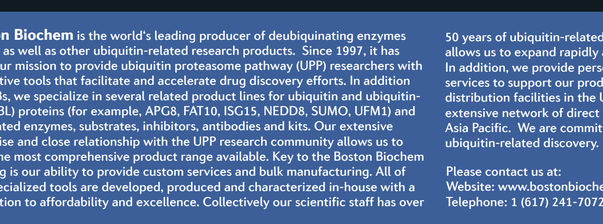
Endocytosis
AMSH and USP8 DUBs regulate endocytosis by removing ubiquitin chains from various membrane receptors, thereby modulating recycling endosome and multivesicular body dynamics.



Cell signalling
CYLD and A20 DUBs regulate the NF-κB pathway by modulating the activity and stability of pathway components such as IκB and RIP1.

Protein quality control
Several DUBs, including YOD1, ATXN3, USP13 and USP19, have been linked to protein quality control in the endoplasmic reticulum through the endoplasmic reticulum-associated degradation (ERAD) pathway. RPN13, UCHL5, and USP14 interact with the proteasome, where they recycle ubiquitin prior to substrate degradation and potentially regulate substrate degradation itself.

Nuclear functions
DUBs can regulate transcription by removing degradative polyubiquitin from transcription factors such as MYC and p53, or by removing activating monoubiquitin from transcription factors such as FOXO4. DUBs can also indirectly regulate transcription by altering the abundance of other factors that directly regulate transcription factor activity or amount, as is the case for the A20- and CYLD-mediated regulation of NF-κB. By removing monoubiquitin from histones H2A and H2B, DUBs can regulate chromatin structure, thereby affecting gene silencing or activation. Five DUBs have been shown to deubiquitinate H2A or H2B, underscoring the complexity of chromatin structure and raising the possibility that individual DUBs may have disparate effects at specific genomic loci. DUBs also affect mitosis by regulating APC activity.



DUB[‡]	Biological process	Substrates[‡]	Binding partners[‡§]	Activity
USP1	DNA damage response	FANCD2, PCNA	WDR48	4, 6
USP3	DNA damage response	H2A, H2B	Unknown	4
USP7 (HAUSP)	Apoptosis, cell proliferation	p53	Unknown	3
	Apoptosis, cell proliferation	MDM2	Unknown	4
	Chromatin remodelling	H2B	GMPS	4, 6
	Viral replication	EBNA1	Unknown	4
	Oxidative stress signalling	FOXO4	Unknown	4
USP8 (UBPY)	Endocytosis, growth factor signalling	Membrane receptors	STAM2	4, 6
			CHMP1A, 1B, 7	4
	Regulation of cell signalling	RNF41 (NRDP1)	Unknown	3
	Cytokinesis	BRUCE	Unknown	4
USP13	ERAD	Unknown	VCP	3
USP14	Proteasomal degradation	Proteasome substrates	26S proteasome	2, 3, 6
	Regulation of cell signalling	CXCR4	Unknown	4
USP16	Chromatin remodelling, cell proliferation	H2A	Unknown	4
USP19	Cell proliferation	RNF123 (KPC1)	Unknown	3
	ERAD	CFTRΔF508, TCRA	Unknown	3
USP21	Chromatin remodelling	H2A	Unknown	4
USP22	Chromatin remodelling	H2A, H2B	SAGA complex	4
USP28	Cell proliferation	MYC	FBW7A	4
	DNA damage response	TP53BP1, claspin	Unknown	3
USP44	Cell cycle regulation	CDC20	Unknown	3
CYLD	NF-κB signalling	TRAF2, TRAF6	NEMO (IKBKG)	4
	Cell proliferation	BCL3	Unknown	4
UCHL1	Ubiquitin processing	Ubiquitin precursors	Unknown	1
UCHL5 (UCH37)	Proteasomal degradation	NFRKB	ADRM1 (RPN13)	2, 3, 6
BAP1	Cell cycle regulation	HCF1	Unknown	4
A20 (TNFAIP3)	NF-κB signalling	RIP1	Unknown	3, 4
		TRAF6	Unknown	4
			TAX1BP1, ABIN (TNIP1)	4
YOD1 (OTUD2)	ERAD	RI_{1-7}, TCRA, α1-antitrypsin	VCP	3
ATXN3	ERAD	CD3Δ, TCRA	VCP	3
AMSH (STAMBP)	Endocytosis, growth factor signalling	Membrane receptors	STAM2	4, 6
			CHMP1A, 1B, 3, SMAD6, 7	4
PSMD14 (POH1, RPN11)	Proteasomal degradation	Proteasome substrates	26S proteasome	2, 3
MYSM1	Chromatin remodelling	H2A	p300/CBP (CREBBP)	4
BRCC36 (BRCC3)	Chromatin remodelling	Unknown	RAP80 (UIMC1), abraxas (FAM175A)	4

[‡]Alternative protein names are provided in brackets. [§]'Unknown' means that no binding partner has been shown to modulate activity of the DUB. For an expanded version of this table and a list of references, see: http://www.nature.com/nrm/posters/dubs

Abbreviations

AMSH, associated molecule with the SRC homology 3 domain of STAM; AMSH-LP, AMSH-like protein; APC, anaphase promoting complex; ATXN, ataxin; BAP1, BRCA1-associated protein 1; BRCC36, BRCA1- and BRCA2-containing complex subunit 36; βTRCP, β-transducin repeat-containing protein; CDC20, cell division control protein 20; CYLD, cylindromatosis tumour suppressor; EIF3, eukaryotic translation initiation factor 3; ESCRT, endosomal sorting complex required for transport; FANC, Fanconi anaemia; FBW, F-box- and WD repeat-containing protein; FOXO4, forkhead box O4; HCF1, host cell factor 1; HIN1L, HIN1-like; HRS, hepatocyte growth factor-regulated Tyr kinase substrate; IκB, inhibitor of NF-κB; IKK, IκB kinase; IRIF, ionizing radiation-induced foci; JAMM, JAB1/MPN/MOV34 metalloenzyme; JOSD, josephin domain; MDC1, mediator of DNA damage checkpoint protein 1; MDM2, mouse double minute 2; MJD, Machado-Joseph disease; MYSM1, Myb-like, SWIRM and MPN domain-containing protein 1; NEMO, NF-κB essential modifier; NF-κB, nuclear factor-κB; NPL4, nuclear protein localization 4; OTUD, OTU domain; PCNA, proliferating cell nuclear antigen; PRPF8, pre-mRNA-processing splicing factor 8; PSMD, 26S proteasome non-ATPase regulatory subunit; RIP1, REV-interacting protein 1; RNF, RING finger; SAGA, Spt–Ada–Gcn5 acetyltransferase; SKP1, S phase kinase-associated protein 1; STAM, signal-transducing adaptor molecule; TAB, TAK1-binding; TP53BP1, p53-binding protein 1; TRABID, TRAF-binding protein domain; TRAF, TNF receptor-associated factor; UBC13, ubiquitin-conjugating enzyme 13; UBXD8, UBX domain-containing protein 8; UCH, ubiquitin carboxy-terminal hydrolase; UFD1L, ubiquitin fusion degradation protein 1 homologue; USP, ubiquitin-specific protease; VCP, valosin-containing protein.
For abbreviations that only appear in the table, see the online version. Domains have not been defined owing to space limitations.

Further reading

Komander, D., Clague, M. J. & Urbé, S. Breaking the chains: structure and function of the deubiquitinases. *Nature Rev. Mol. Cell Biol.* **10**, 550–563 (2009) |
Sowa, M. E., Bennett, E. J., Gygi, S. P. & Harper, J. W. Defining the human deubiquitinating enzyme interaction landscape. *Cell* **138**, 389–403 (2009)

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