

Cellular regulation by deubiquitinating enzymes

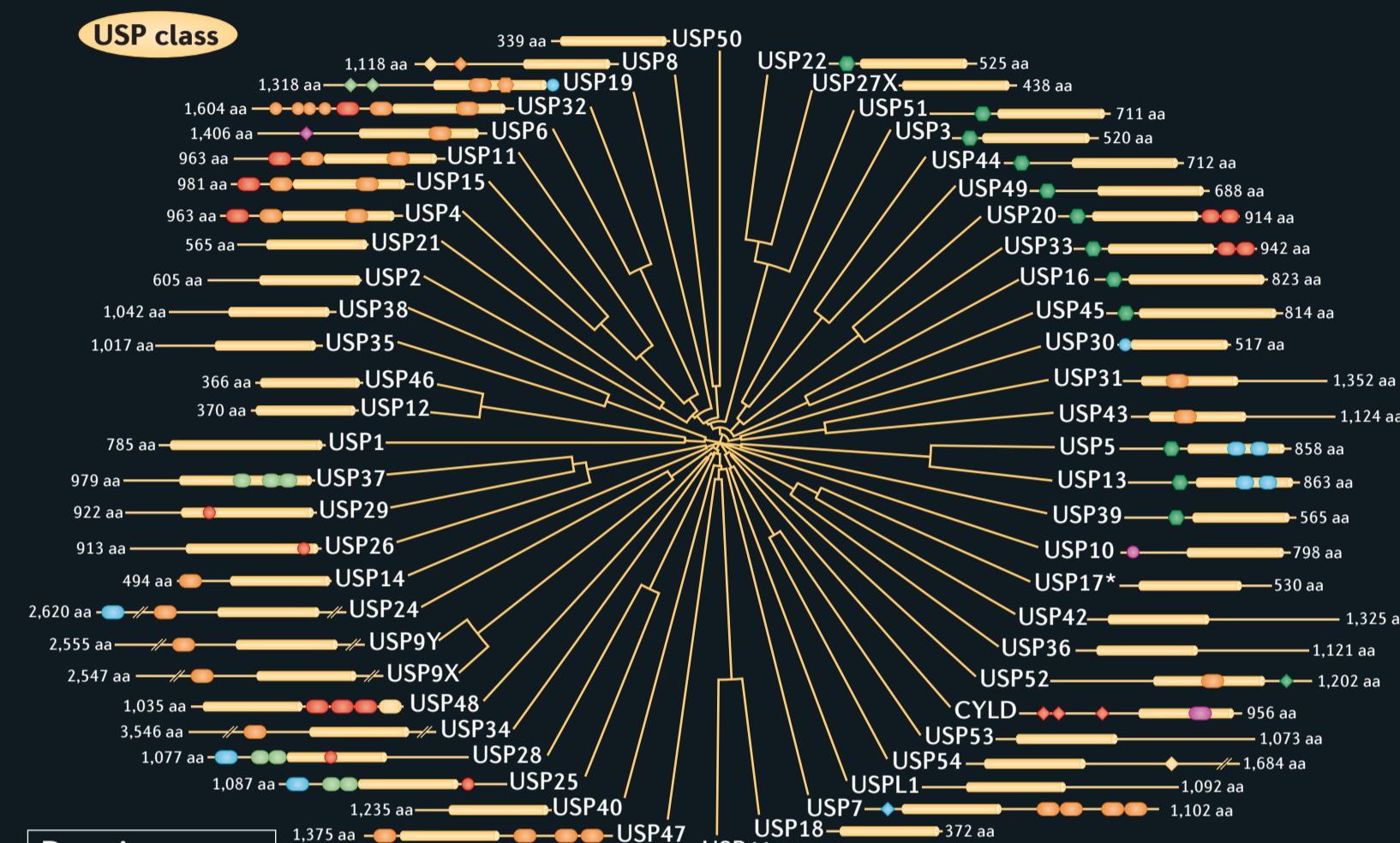
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Protein ubiquitination has emerged as a highly dynamic process that governs nearly every function in cells from endocytosis to mitosis. As such, the cellular machinery that both appends and removes ubiquitin from target proteins is highly regulated. 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

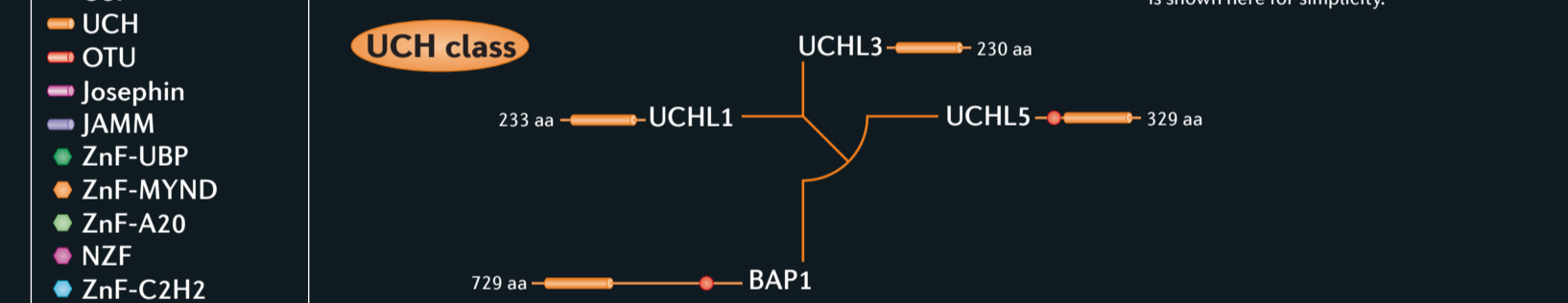
and DUB activity. Assembly of individual DUBs into distinct protein complexes has allowed for the diversification of DUB activity that is needed to process the increasingly diverse assemblages of monoubiquitin and polyubiquitin marks on substrates. This dynamic regulation in the ubiquitin proteasome 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.



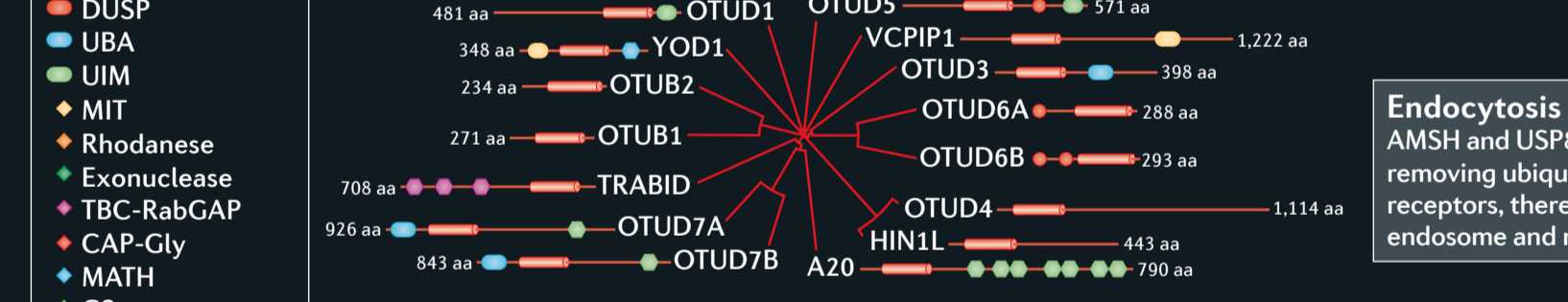
Cysteine protease DUBs



UCH class



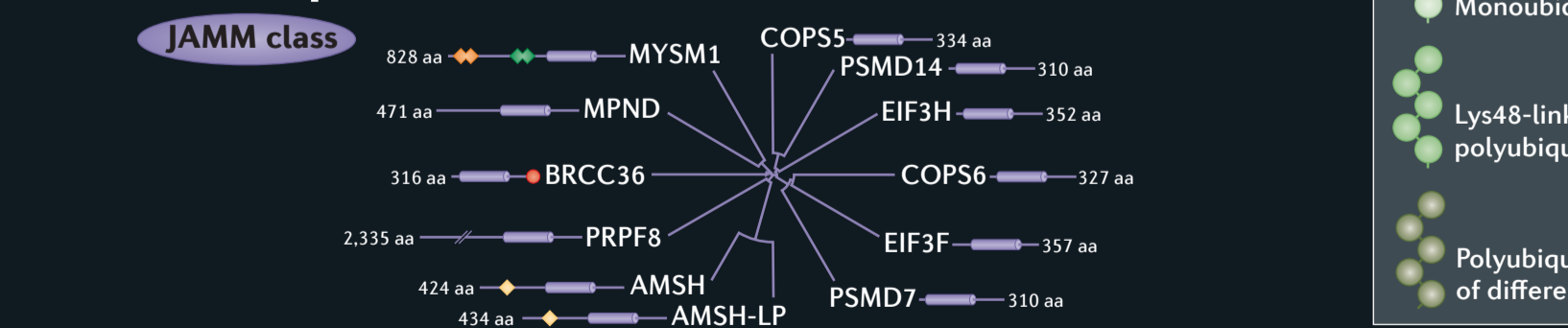
OTU class



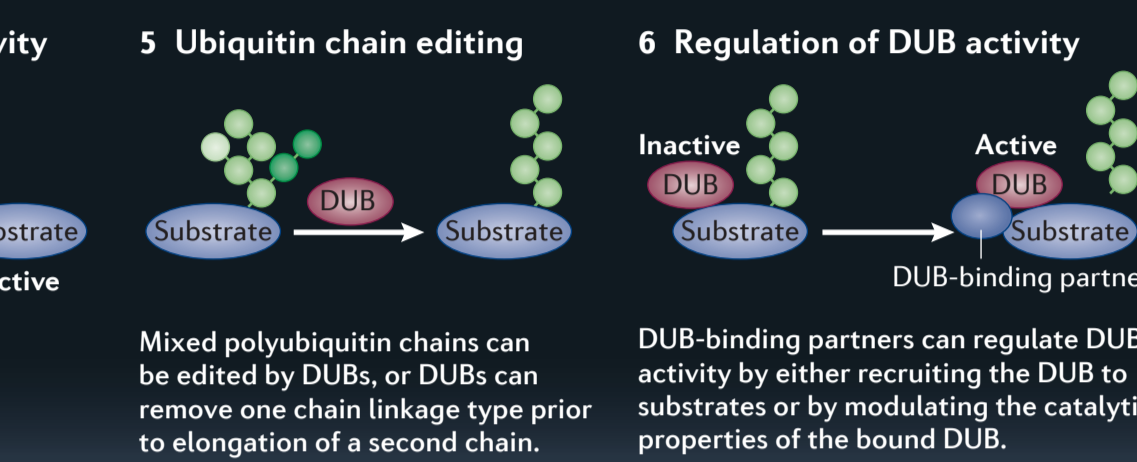
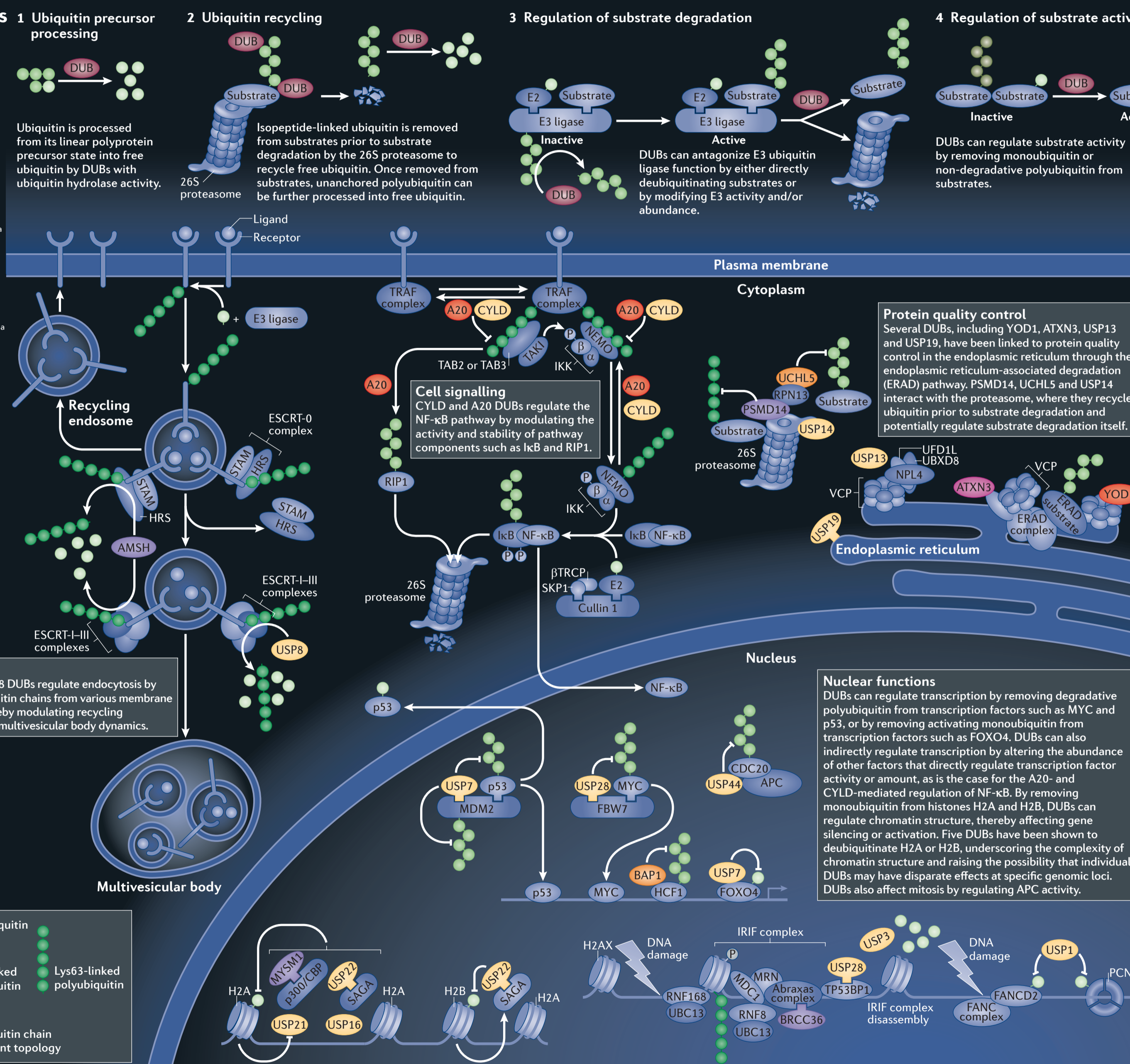
MJD class



Zinc metalloprotease DUBs



DUB activities



DUB ¹	Biological process	Substrates ²	Binding partners ³	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
USP8 (UBPY)	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, CHMP1A, 1B, 7	4, 6
	Regulation of cell signalling	RNF41 (NRDP1)	Unknown	3
USP13	Cytokinesis	BRUCE	Unknown	4
	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
	ERAD	CTRA1, TRAF508, TRCA	Unknown	3
USP19	Cell proliferation	RNF123 (KPC1)	Unknown	3
	ERAD	CTRA1, TRAF508, TRCA	Unknown	3
USP21	Chromatin remodelling	H2A	Unknown	4
USP22	Chromatin remodelling	H2A, H2B	SAGA complex	4
USP28	Cell proliferation	MYC	FBW7A	3, 4
	DNA damage response	TP53BP1, claspin	Unknown	3
USP44	Cell cycle regulation	CDC20	Unknown	3
CYLD	NF-κB signalling	TRAF2, TRAF6	NEMO (IKKγ)	4
	Cell proliferation	BCL3	Unknown	4
UCHL1	Ubiquitin processing	Ubiquitin precursors	Unknown	1
UCHL5 (UCH37)	Proteasomal degradation	NFKB	ADRM1 (RPN13)	2, 3, 6
BAP1	Cell cycle regulation	HCF1	Unknown	4
	NF-κB signalling	RIP1 (KRR1)	Unknown	3, 4
A20 (TNFAIP3)	NF-κB signalling	TRAF2, 6	Unknown	4
	NF-κB signalling	RIP1, TRAF6	TAX1BP1, ABIN (TNIP1)	4
	NF-κB signalling	RIP1, TRAF6	TAX1BP1, ABIN (TNIP1)	4
YOD1 (OTUD2)	ERAD	RIP1, TRAF6, α1-antitrypsin	VCP	3
ATXN3	ERAD	CD3Δ, TRCA	VCP	3
AMSH (STAMB)	Endocytosis, growth factor signalling	Membrane receptors	STAM2, CHMP1A, 1B, 3, SMAD6, 7	4, 6
PSMD14 (POH1, RPN11)	Proteasomal degradation	Proteasome substrates	26S proteasome	2, 3
MYSM1	Chromatin remodelling	H2A	p300/CBP (CREBBP)	4
BRCC36 (BRCC3)	DNA damage response	Unknown	RAP80 (UIMC1), abraxas (FAM175A)	4

¹Alternative protein names are provided in brackets. ²Unknown* means that no binding partner has been shown to modulate activity of the DUB. For an expanded version of this table, a list of references and some representative structures, see: <http://www.nature.com/nrm/posters/dubs>

Boston Biochem is the world's leading producer of deubiquitinating enzymes (DUBs) as well as other ubiquitin-related research products. Since 1997, it has been our mission to provide ubiquitin proteasome pathway (UPP) researchers with innovative tools that facilitate and accelerate drug discovery efforts. In addition to DUBs, we specialize in several related product lines for ubiquitin and ubiquitin-like (UBL) proteins (for example, APC8, FAT10, ISG15, NEDD8, SUMO, UFM1) and associated enzymes, substrates, inhibitors, antibodies and kits. Our extensive expertise and close relationship with the UPP research community allows us to offer the most comprehensive product range available. Key to the Boston Biochem offering is our ability to provide custom services and bulk manufacturing. All of our specialized tools are developed, produced and characterized in-house with a dedication to affordability and excellence. Collectively our scientific staff has over

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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; FANCD2, 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 Tyrosine 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, RNF-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; TRAFID, 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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