

# Ubiquitin signalling by ubiquitin-binding domains

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Ubiquitin is a post-translational modifier that forms multiple signals, or 'molecular barcodes', on cellular proteins to specify different functional outputs. Such barcodes range from single (monoubiquitylation) or multiple (multiple monoubiquitylation) ubiquitin moieties to ubiquitin chains (polyubiquitylation) of different type and length, covalently attached onto specific Lys residues in given protein substrates. Once formed, these signals are 'read' non-covalently by specialized ubiquitin-binding domains (UBDs) embedded in various proteins,

resulting in several possible functional outcomes. At present, more than 20 types of UBD have been recognized, which have been classified into 5 families. Ubiquitin-UBD interactions occur during many distinct cellular processes, in which they often have crucial roles, as shown by loss-of-function experiments. Therefore, increasing our knowledge of the landscape of ubiquitin-UBD interactions holds the potential to pave new avenues for targeting pathogenic processes in the development of human diseases.

Autophagy

**Proteasome-mediated** 

So-called ubiquitin receptors,

polyubiquitylated proteins and

transfer them to proteasomes. Proteasomes themselves carry

UBD-containing proteins, such

as RPN10 and RPN13, in their

regulatory 19S particle, which

recognize and trap proteins

destined for degradation.

such as RAD23, bind Lys48-linked

proteolysis

Multivesicular body

ESCRT-III

On severe oxidative stress, many proteins in

the cytoplasm become misfolded and prone

oligomers bridge misfolded proteins tagged

**Endocytosis** 

Activated transmembrane receptors are ubiquitylated and internalized in

endosomes by the concerted action of

several UBD-containing adaptors, such

ESCRT-0

as Sts proteins (which are inhibited by

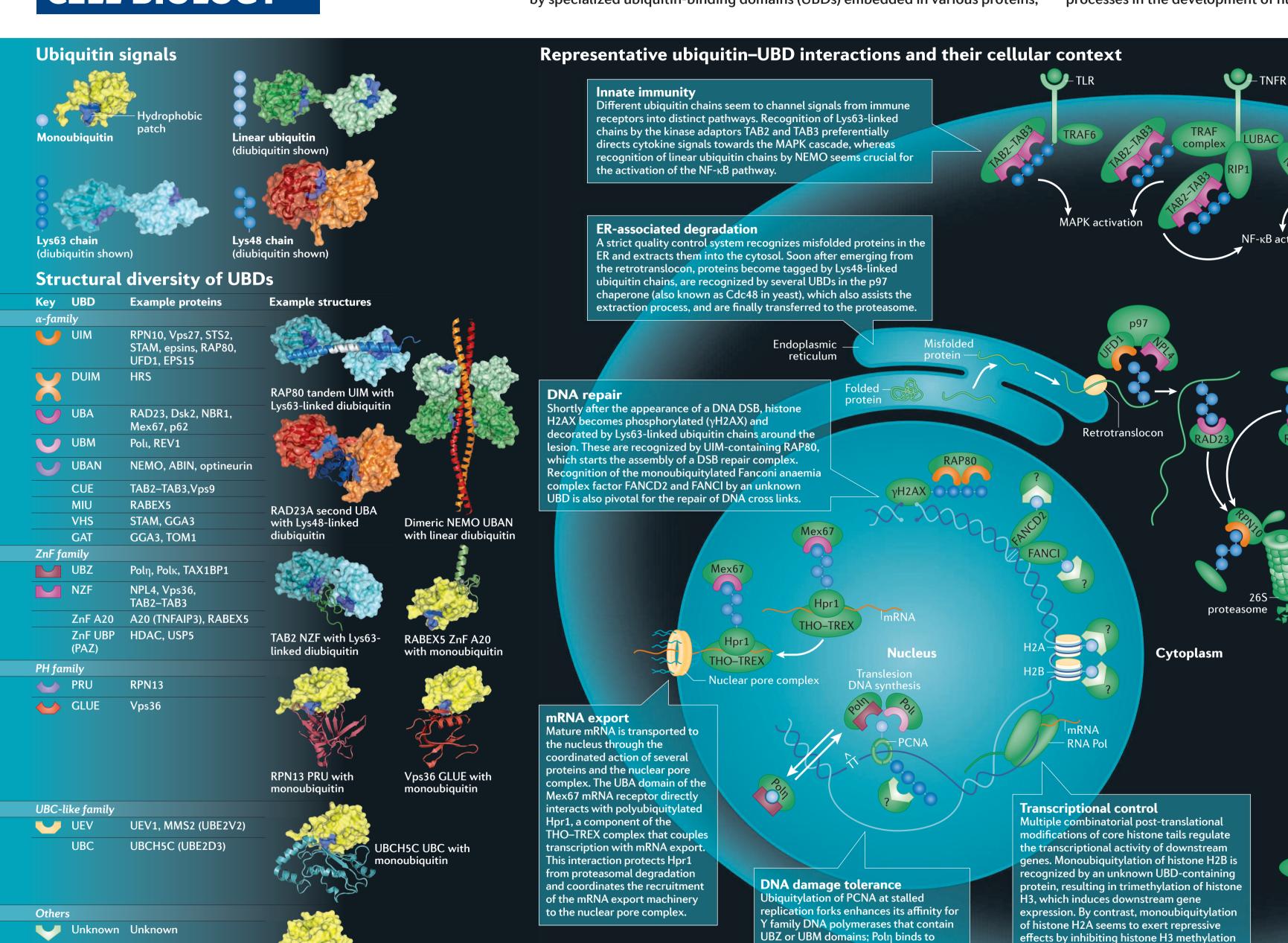
self-monoubiquitylation) and epsins.

to aggregate. UBA-containing p62-NBR1

with Lys48-linked ubiquitin chains and

initiate their degradation by autophagy.

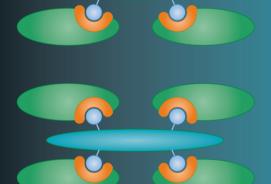




# Molecular outputs of ubiquitin-UBD interactions Affinity enhancement A single molecule of ubiquitin is reversibly attached onto a given substrate, thus providing an additional interaction surface for a protein that carries the corresponding UBD. Examples include the interaction of PCNA with Y family DNA polymerases during translesion DNA synthesis and the recognition of ubiquitylated cargos by ESCRTs during endocytosis of transmembrane proteins.

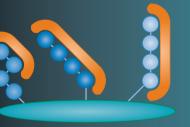
## Molecular bonding

A ubiquitylated protein can be recognized by two or more proteins carrying specific UBDs, leading to the formation of protein clusters. This can result in specific outputs. Examples include the interaction of HRS with monoubiquitylated receptors, such as EGFR.



# Chain selectivity

Different types of ubiquitin chain coexist in a cell, but are selectively read and interpreted at the molecular level by chain-selective UBDs. For example, in the NF-κB signalling pathways, TAB2-TAB3 selectively bind Lys63linked chains through their NZF domain, whereas NEMO binds linear ubiquitin chains through its UBAN domain in response to the same signal.



Self-ubiquitylation and intramolecular binding Certain UBD-containing proteins use their UBD to mediate self-monoubiquitylation. This can result in ubiquitin-UBD in cis interactions, leading to protein inhibition. For example, STS1 and STS2 self-interact during the internalization of EGFRs.



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monoubiquitin

CIN85 (SH3KBP1)

Doa1

PRP8

PFU

JAMM

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### **Abbreviations**

monoubiquitylated PCNA. DNA is then

by translesion DNA synthesis.

synthesized across damaged nucleotides

ABIN, A20-binding inhibitor of NF-κB activation 2; CLN85, Cbl-interacting protein of 85 kDa; CUE, coupling of ubiquitin conjugation to ERAD; DSB, double-strand break; Dsk2, dominant suppressor of Kar1; EGFR, epidermal growth factor receptor; EPS15, EGFR substrate 15; ER, endoplasmic reticulum; ESCRT, endosomal sorting complex required for transport; GAT, GGA and TOM; GGA, Golgi-localized y-ear-containing, ARF-binding protein; GLUE, GRAM-like ubiquitin-binding in EAP45: HDAC, histone deacetylase: HRS, hepatocyte growth factorregulated Tyr kinase substrate; Hpr1, hyperrecombination 1; JAMM, JAB1/MPN/MOV33; LUBAC, linear ubiquitin chain assembly complex; MAPK, mitogen-activated protein kinase; MIU, motif interacting with ubiquitin; MMS2, methyl methanesulphonate sensitive 2; NBR1, neighbour of BRCA1 1; NEMO, NF-κB essential modulator; NF-κB, nuclear factor-κB; NPL4, nuclear protein localization protein 4 homologue; NZF, NPL4 ZnF; PCNA, proliferating cell nuclear antigen;

and by affecting local chromatin structure.

PFU, PLAA family ubiquitin-binding domain; PH, pleckstrin homology; Pol, polymerase; PRP8, pre-mRNA-processing splicing factor 8; PRU, pleckstrin-like receptor for ubiquitin; RABEX5, RAB5 GDP/GTP exchange factor; RAP80, receptor-associated protein 80; REV1, reversionless 1; RIP1, receptor-interacting Ser/Thr protein kinase 1; RPN, regulatory particle, non-ATPase-like; SH3, Src homology 3; STAM, signal transducing adaptor molecule; Sts, suppressor of T cell receptor signalling; TAB; TAK1-binding protein; TAX1BP1, TAX1-binding protein 1; TLR, Toll-like receptor; TNFR, tumour necrosis factor receptor; TOM1, target of Myb protein 1; TRAF, TNFR-associated factor; TREX, 3' repair exonuclease; UBA, ubiquitin associated; UBAN, ubiquitin binding in ABINs; UBC, ubiquitin conjugating; UBM, ubiquitin-binding motif; UBZ, ubiquitin-binding ZnF; UEV, ubiquitin-conjugating enzyme E2 variant; UFD1, ubiquitin fusion degradation 1; UIM, ubiquitin interaction motif; USP5, ubiquitin-specific processing protease 5; VHS, Vps27, HRS and STAM; Vps, vacuolar protein sorting-associated protein; ZnF, zinc finger.

Cargo sorting

Sorting of receptors in early endosomes

orchestrated by the sequential action of specialized escorting complexes

(ESCRT-0-ESCRT-III), the components

of which harbour various types of UBD.

and in the multivesicular body is

#### Further reading

Dikic, I., Wakatsuki, S. & Walters, K. J. Ubiquitin-binding domains — from structures to functions. Nature Reviews Mol. Cell Biol. 10, 659–671 (2009).

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