George Sung[1]

Similar but Different: RBR E3 Ligases and their Domains that are Crucial for Function

Review Article

[1]Department of Biochemistry, McGill University, Montreal, QC, Canada

Email Correspondence

chin.sung@mail.mcgill.ca

Abstract

Background: The E3 ubiquitin ligases can be subdivided into four distinct types (RING, HECT, U-box, and RBR type) based on their domain architecture and ubiquitin transfer mechanism. Recent structures of different RBR E3 ligases have been solved showing enzymes in their autoinhibited state. The only exception is HOIP/HOIL-1L which was recently solved in its "active" conformation. This review discusses the structural and functional characteristics of three different members of the RBR E3 ubiquitin ligase family: Parkin, HOIP/HOIL-1L, and HHARI.

Methods: Searches were performed using PubMed. Search term includes "RBR E3 Ligase", "Parkin", "HOIP/HOIL-1L", "HHARI", "UbcH7", and "E2". In the end, 25 journal articles were selected as the foundation of this review. The structural coordinates of Parkin, HOIP, and HHARI were accessed from the PDB (www.rcsb.org) with the PDB IDs 4ZYN, 5EDV, and 4KBL, respectively.

Summary: Currently, most solved RBR E3 ligase structures are only in their inactive forms, except for HOIP/HOIL-1L, and these inactive forms provide valuable information on how these proteins are regulated in vivo. All the RBR E3 ligases have common domains, but their structures and functions are heavily dependent on their accessory domains, which serve as regulators that orchestrate certain ubiquitin chain syntheses and play a role in the autoinhibition of RBR E3 ligases. Although these domains are structurally different, they use distinct molecular interactions to achieve the same goal. While the regulation of most RBR E3 ligases has been extensively studied, more structural studies are required to further characterize the mechanism that these enzymes use to build different ubiquitin chains. Understanding the mechanisms underlying the formation of each type of ubiquitin chain could help elucidate their functions and related pathways.

Introduction

Protein turnover is an essential cellular process that allows non-functional or nonessential proteins to be degraded and new ones to be made. (1) One of the most prevalent degradation pathways is the protein ubiquitination pathway. (1,2) Protein ubiquitination is a key post-translational modification involved in the marking of cellular proteins for 26S proteosomal degradation.(1) The ubiquitin degradation pathway occurs via three steps: ubiquitin activation, conjugation, and the actual transfer of ubiquitin to the substrate. (1) The ubiquitin is activated by an E1 activation enzyme (E1) in an ATP-dependent reaction. (3) Ubiquitin is then transferred to an E2 conjugating enzyme (E2). (3) The E2 enzyme catalyzes the transfer of ubiquitin to either the E3 ligases (E3) or the substrate, depending on the type of E3 ligases used in the reaction. (4) These enzymes, particularly the RBR E3 ligases, accomplish the transfer of ubiquitin through the formation of thioester bonds. During the last step of the ubiquitination pathway, a stable isopeptide bond is formed between the substrate and the C-terminus of ubiquitin, as shown in Fig. 1. (3)

Ubiquitination can also occur multiple times on the same substrate, generating multiple ubiquitination sites. (1) Ubiquitination usually occurs on a lysine residue of the substrate, but can also occur on the N-terminus or more rarely on serine and threonine residues. Ubiquitination can also happen to ubiquitin to generate ubiquitin chains. (1) Different types of polyubiquitination chains lead to different signalling pathways, but often lead to protein degradation (Fig. 2). (1) For example, linear chains, which are generated by the HOIP/HOIL-1L complex or Linear Ubiquitin Assembly Complex (LUBAC), signal for the NF-kB pathway during an immune response. (1) In addition, K63 polyubiquitination often signals for DNA repair and lysosomal degradation, (1) whereas the K48 polyubiquitination signals for proteasomal or lysosomal degradation. (1, 5)

Since the human proteome is quite large, it is reasonable for there to be many kinds of E3 ligases to accommodate the different substrates. Four different categories of E3s have been characterized based on their domains and ubiquitin transfer mechanism. (7) The first type is the RING type ligase, which allows the direct transfer of ubiquitin from the E2 enzyme to the substrate. (7) The second type of E3 is the HECT type ligase, in which the ubiquitin is first transferred to a cysteine in the E3 ligase and then to the substrate. (7) The third type of ligase is the U-box ligases, in which the transfer mechanism resembles RING type ligases using their U-Box

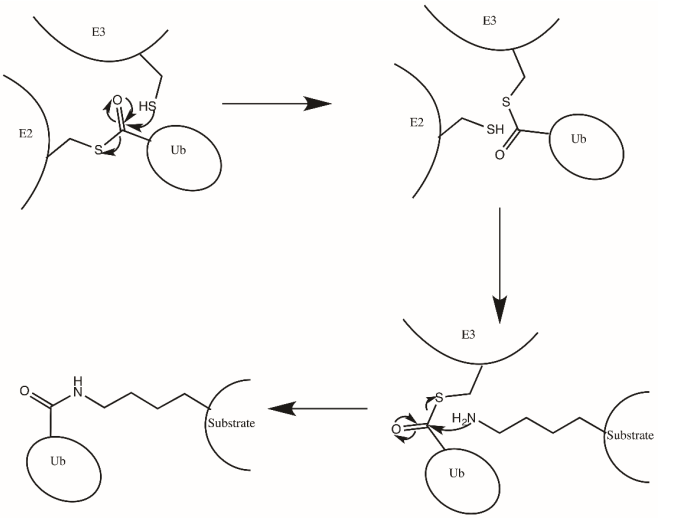

Figure 1: General ubiquitin transfer mechanism for RBR E3 ubiquitin ligases. Ubiquitin is transferred from E2 is transferred to the E3 via a conserved catalytic cysteine residue on the RING2 domain. Upon the binding the thiol from the E3 mediates a nucleophilic attack and facilitates trans-thiolation from the E2. The amine of the lysine on a substrate acts as a nucleophile to displace the E3 thiol and covalently attach the ubiquitin via an isopeptide bond.

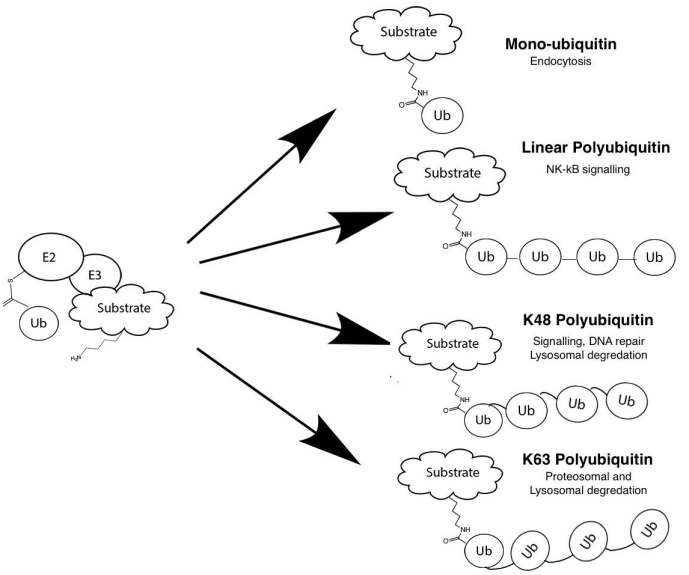

Figure 2: Different ubiquitin chains generated by various RBR E3 ligases. (1, 5, 6) The different ubiquitin chains shown have many different signalling pathways. Linear Chains could be generated by the LUBAC system by HOIP/HOIL-1L, K63 and K48 chains could be generated by either Parkin or the Ariadne Family.

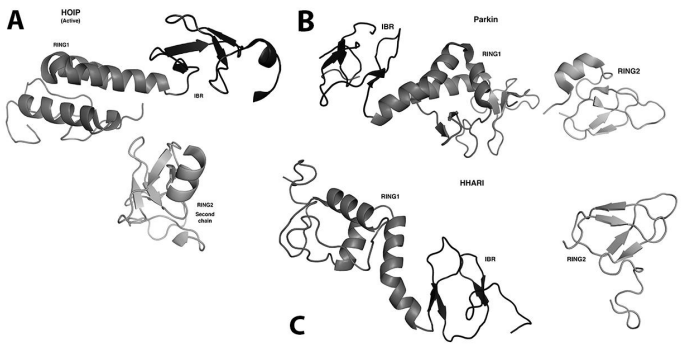

Figure 3: Comparison of the common domains of RBR E3 ligases. (9-11) The structural difference of the RING1, IBR, and RING2 domains among these proteins are shown. A) In the active form, two HOIP molecules interacts with two UbcH5B (an E2). The RING1 and IBR domain interacts with the E2 with another HOIP's RING2 domain. The different arrangement of these domains give rise to different regulation and activation mechanisms. (Structure coordinate from Lechtenberg et al. Nature 2016, Trempe et al. Science 2013, and Duda et al. Structure 2013)

domains rather than the RING domain. (8) The fourth type of ligase, and the focus of this review, is the RBR E3 ligase which uses a unique mechanism incorporating elements from the RING and HECT E3 ligases. (7) The different adjacent domains and ligands of RBR E3 ligases dictate their different functions in the cell. In this paper, the structural and functional characteristics of RBR E3 ligases will be discussed to analyze the common and distinct features between Parkin and other RBR counterparts, with particular focus on the Ariadne family and HOIP/HOIL-1L complex.

Structural Characterists of the RBR E3 Ligase Family

The RBR E3 ubiquitin ligases have three characteristic Zn2+-binding domains known as the RING1, in-between RING (IBR), and RING2 domains (Fig 3). In all of these domains, the coordination with Zn2+ ions occurs through seven cysteines and one histidine. (10) The RING1 domain is structurally similar and exhibits the same functional role for binding an E2 enzyme as typically observed for the RING domains of RING-type E3 ligases. (10) The RING1 domain, which is highly conserved among the RBR E3 ligases in sequence and structure, is important for the binding of an E2 enzyme. (10) For example, the RING1 domain displays the characteristic cross-brace motif structure observed in RING ligases (Fig 4). (10) The RING2 domain in the RBR ligases, despite bearing the same name, is not a true RING domain. Indeed, it is not able to bind to E2 conjugating enzymes and has a different structure. (10) In the RBR E3 ligases, the transfer of ubiquitin is done between the E2 enzyme and the RING2 domain through trans-thiolation (Fig 1) (3) The role of the IBR domain remains unclear, but the IBR domain is required for function and displays flexibility in known structures. (10, 12)

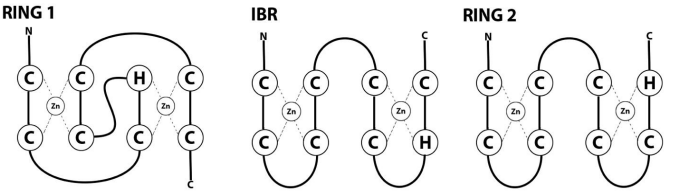

Figure 4: The topology of zinc fingers of each RING and RING-like domain in RBR E3 Ligases. The residues that coordinate structural zinc ions are shown in blue circles labeled as C, cysteine, and H, Histidine. The RING1 domain displays a topology that is characteristic of the RING domain in RING-type E3 ligases. The IBR and RING2 domains show similar topology. Upon studying the structure coordinate for various E3 ligases, the fold observed for the RING1 domain of Parkin is similar across the RBR E3 ligases.

Interaction between E2 and RBR E3 ligases

The RBR E3 ligases all contain a RING1 domain, which is involved in the binding of the E2 conjugating enzyme. (3) There are many E2 conjugating enzymes that have the ability to bind different E3s, and some E2s have the ability to either use the RING-type transfer mechanism (ubiquitin transferred directly onto the lysine residue of a substrate) or HECT-type mechanism (where ubiquitin is first transferred to the cysteine on the HECT E3, then to the lysine on substrate). (4) Moreover, the discovery of UbcH7 (E2) that could not transfer ubiquitin directly to a lysine residue indicated that the RBR E3 ligases behaved like HECT-type ligases. (13) However, since RBR E3s behave like the HECT-type and use the RING1 domain to bind to E2s, there are E2s that can interact with both types. (4) Some of the most common types of E2s that have been shown to interact with most RBR E3s are UbcH7 and UBCH5b. (13) These E2s have been shown to have some preference for the types of ubiquitin chains they make, but it has been demonstrated that E2s might not be as specific as we previously thought. For example, it has been documented that E2s such as Ube2K, which normally produce Lys 48 chains, produce a linear chain in conjunction with the HOIP/HOIL-1L complex. (14-16) Generally, researchers have suggested that the E2 might influence the type of ubiquitin chains it makes, but the HECT and RBR E3 ligases should presumably dictate the types of ubiquitin chains made.

What sets these RBR E3 ligases apart?

In addition to their three core domains, each RBR E3 ligase has other different domains that have similar functions. Parkin activity is modulated by its Ubl (ubiquitin-like) domain, a unique RING0 domain, and the Repressed Element of Parkin (REP) linker. Indeed, the Ubl domain and the REP linker of Parkin affect its binding to E2. (10) The Ubl domain is crucial for Parkin as it contains a site for phosphorylation by PINK1, a kinase localized at the mitochondria, during the mitophagy pathway. (17) PINK1 phosphorylation of Parkin is required for the activation of Parkin ubiquitination activity when mitochondria are depolarized. (17,18) Parkin will then ubiquitinate mitochondrial protein to promote mitophagy. (17) In addition, Parkin's unique RING0 domain contributes to the maintainencemaintenance of the Parkin autoinhibited conformation in the context of healthy mitochondria. (19)

HOIP and HOIL-1L are other types of RBR E3 ligases. Unlike other RBR E3 ligases, they both ligases form a complex to carry out polyubiquiti-

nation reactions. (20) Moreover, HOIP also includes a Ubiquitin Associated (UBA) domain, which is involved in autoinhibition; however,, but the binding site for the UBA domain on HOIP is still unknown. (9) Like Parkin, HOIL-1L contains a Ubl domain, but ; however, it acts as an trans-activating agent for the HOIP ligase instead of an autoinhibiting domain. (21) In addition, both HOIP and HOIL-1L contain NZF domains that are involved in the stabilization of linear ubiquitin chains. (21) The linear ubiquitin chain formed by the HOIP/HOIL-1L complex could then activate the NF-kB pathway by conjugating the ubiquitin chain to NF-κB essential modulator (NEMO). (22)

Another class of RBR E3 ligases is the Ariadne family, which has a signature Ariadne domain at their C-terminus. (23) The Ariadne domain in the HHARI ligase has been shown to interact with its RING2 domain, similarly to the RING0 domain of Parkin, to produce its own autoinhibition. (11). Despite having completely different structures, both Ariadne and RING0 domains restrict the access to the catalytic cysteine. (10, 11) HHARI have been shown to be activated by binding to neddylated Cullin-RING Ligases (CRL) complex, potentially allowing the regulation ofe the activity of HHARI activity. (24) HHARI activation leads to cellular proliferation due to the formation of nuclear bodies. (25)

How do cells regulate the ubiquitination activity of Parkin, A?

Although all the RBR E3 ligases have the three core domains, they are regulated very differently. Generally, the E3 ligases are autoinhibited due to the other domains within the ligase. (23) Different RBR E3 ligases have been found to inhibit themselves via various mechanisms involving different accessory domains. While these accessory domains may have similar functions, they have different structures as isn the case with the of Parkin and the Ariadne Family.

The autoinhibition of Parkin

Parkin has two structural features, the Ubl domain and REP linker, which regulate its activity by modulating the access of its E2 binding site. It has been shown that the Ubl domain interacts with the RING1 domain, acting as a switch between inactive and active Parkin. (26, 27) Lysine 48 (K48) is required for the Ubl to interact with Parkin, with any mutations to K48 resulting in the loss of Ubl-dependent autoinhibition. (10). Furthermore, binding of phospho-ubiquitin and the phosphorylated Ubl domain induce a structural change in Parkin which increases Parkin activity. (12, 27-29) The phosphorylation of Parkin on serine 65 (S65) is performed by PINK1. (17) Phosphorylation of the Ubl domain decreases its affinity to RING1 which results in the activation of the protein. (10, 17)

In addition to the Ubl domain, the REP linker has been shown to occlude the E2 binding site. However, after the phosphorylation of the Ubl domain, a change in its conformation makes the E2 binding site accessible. (26) In the REP linker, tryptophan 403 (W403) is involved in the binding of RING1 domain. Mutations on W403 have been associated with higher Parkin activity because the hydrophobic residue fits in the RING1 domain. (10) Despite the the crucial the tryptophan residue being crucial , a hydrophobic residue, is crucial for the interaction between the REP linker and the RING1 domain, not all hydrophobic residues have the same effect. (10) A mutation to alanine, also a hydrophobic residue, has been shown to increase Parkin's activity, possibly because alanine is not long enough to bind to the groove that would otherwise be occupied by tryptophan. (10)
Aside from the E2 binding site, Parkin has another regulation site located at the RING2 -RING0 interface. (10) The active cysteine (C431) required for the trans-thiolation is buried between the hydrophobic interfaces of the RING2 and RING0 domain. (10) Mutations in the hydrophobic residues involved in the interaction between RING2 and RING0, such as phenylalanine 146, have been shown to increase Parkin's activity. (10) Without this hydrophobic interaction, the RING2 domain can easily dissociate from the RING0 domain, thus exposing the active cysteine to the surrounding environment.

HOIP/HOIL-1L regulation mechanism

Similar to Parkin, an interaction between the third ubiquitin binding region (UBR3) and ubiquitin is important for HOIP's activity. (9) However, the difference between Parkin and HOIP is that Parkin is activated upon the binding by phosphorylated ubiquitin, whereas HOIP is activated by non-phosphorylated ubiquitin. (9) In HOIP, the autoinhibitory function is carried out by its UBA domain, however, upon interaction with HOIL-1L, HOIP becomes activated. (9) Furthermore, linear di-ubiquitin could also remove HOIP-UBA autoinhibition. (9) It has been shown that residues such as Ile807 and Glu809 in the Ubiquitin-Binding Region 3 (UBR3) of HOIP are important in order to bind to ubiquitin or ubiquitin chains. (9) These interaction between the UBR3 and ubiquitin allows HOIP/HOIL-1L to form linear ubiquitin chains. (9)

Ariadne family is also autoinhibited like Parkin

Similar to Parkin, the Ariadne family also has accessory domains that aid in its autoinhibition. These domains are structurally different as Ariadne domains exist as four alpha helices in HHARI, while Parkin's RING0 contains two beta sheets and one alpha helix, as shown in Fig 5. (10, 11) The Ariadne domain behaves functionally like the RING0 domain in Parkin; however, the way that these interactions occur is completely different. The Ariadne domain interacts with its RING2 domain via hydrogen bonds. (11) Consequently, the active cysteine in HHARI (C357) is occluded from interacting with the E2-bound ubiquitin. Not only is the Ariadne domain occluding the RING2 active site, but it also intercalates between the IBR and RING2 domain. (11) The intercalation between IBR and the RING2 domain separates the active site from the RING1-bound E2. (11)

The RING2 domain of HHARI contains 14% aromatic residues. (30) Trends between HHARI and other RBR E3 ligases were compared, and a sequence alignment suggests that the tryptophan and histidine observed in both HHARI and Parkin might play a role in maintaining their protein fold. (30, 31) In Parkin, these aromatics, such as His 433, are involved in the transfer of ubiquitin to its target. (10) Therefore, iIt is possible that these aromatics on HHARI also play an important role in the transfer of ubiquitin.

Types of ubiquitin chains formed by RBR E3 ligases

The ubiquitination signaling pathway is vital in the elimination of misfolded or unwanted proteins. (1) The only way for these different chains to form is through E3 ligases. These chains could be linear, K48, K63, or branched polyubiquitin. (1) Ubiquitin has seven lysine residues and the amino group of its N-terminus can be used to form isopeptide bonds. It is suggested that the type of E2 utilized will affect the types of chains that are made. However, in some cases, the rules might not be as rigid.

It has been previously suggested that Parkin is able to form branched ubiquitin chains such as the formation of Lys 63, Lys 48, and Lys 27 branched polyubiquitin chains. (32) Recently, it was discovered that Parkin has a preference to form Lys 6 chains, although its signalling pathway is poorly understood. (32) Structurally, the crucial residue that has been implicated to aid the transfer of ubiquitin is the histidine residue that is two residues away from the catalytic cysteine. (10) Although the preference for a certain type of chain has been discovered, the mechanisms in which they are transferred are still unclear. It should be expected that the structural difference between these RBR E3 ligases will contribute more to the formation of different ubiquitin chains. Since these E3s use different E2s, it is most likely that the structural difference between these E2s and the structural difference between the E3s contributes to the different chain formations.

In contrast to other RBR ligases, HOIP/HOIL-1L are complexed in the LUBAC (linear ubiquitin chain assembly complex) pathway. (15) It has been shown that HOIL-1L contains a UBL domain, however, in contrast to Parkin, this UBL domain does not participate in the autoinhibitory mechanism, but is used to activate the HOIP once in complex with HOIL-1L and SHARPIN. Furthermore, both HOIL-1L and SHARPIN have the

NZF domain that coordinates one zinc ion with four conserved cysteine residues. (21) These NZF domains facilitate the binding to ubiquitin via a conserved TF/Φ motif. (21) Furthermore, HOIL-1L has been shown to bind linear chains via hydrophobic interaction between the NZF domains and certain ubiquitin residues. (21) It has been shown that Phe4 and Ile44 have been shown to interact with the NZF core and its tail. (21) It is possible that the NZF domain of HOIL-1L or SHARPIN is used to stabilize the di-ubiquitin that could facilitate the linear conjugation of further linear polymerization. (21) Although both proteins have an NZF domain, the NZF domain of SHARPIN is also involved in programmed cell death. (21) Although the mechanism for the formation of different ubiquitin chains is not clear, using the model of the HOIP/HOIL-1L system might shed some light onto the structural variance that can give rise to different types of chains made by the LUBAC complex.

Conclusion

Due to the recentness of its discovery, a lot of ambiguity still surrounds the Hect-type mechanism used by RBR ED ligases. Although all RBR E3 ligases have common domains, their functions are heavily dependent on the accessory domains. In the case of HOIP/HOIL-1L, the NZF domain from HOIL-1L serves as an aid to form linear ubiquitin chains. For the Parkin and Ariadne family, there are accessory domains dedicated to autoinhibition. Their structural differences provide different interactions between these accessory domains and the RING2 domain. In contrast to the Ariadne family and Parkin, the HOIP/HOIL-1L system activation requires another RBR E3 ligase (HOIL-1L). Since the regulation of most RBR E3 ligases has been extensively studied, more structural studies are required to characterize the mechanism in which different ubiquitin chains are formed. Understanding the mechanisms underlying the formation of each type of ubiquitin chain could help to elucidate their functions and related signaling pathways.

Acknowledgement

I would like to thank Dr. Kalle Gehring for giving me the opportunity to work in his lab and learn about the laboratory practices, equipment, and special techniques for X-ray crystallization. I would also like to thank Dr. Véronique Sauvé for supervising me and providing me with the expertise on the protein studied. Moreover, I would like to thank the other lab members for making our lab a vibrant and productive work space.

References

1. Komander D, Rape M. The ubiquitin code. Annual review of biochemistry. 2012;81:203-29.
2. Swatek KN, Komander D. Ubiquitin modifications. Cell Research. 2016;26(4):399-422.
3. Dove KK, Stieglitz B, Duncan ED, Rittinger K, Klevit RE. Molecular insights into RBR E3 ligase ubiquitin transfer mechanisms. EMBO reports. 2016;17(8):1221.
4. Ye Y, Rape M. Building ubiquitin chains: E2 enzymes at work. Nat Rev Mol Cell Biol. 2009;10(11):755-64.
5. Chau V, Tobias JW, Bachmair A, Marriott D, Ecker DJ, Gonda DK, et al. A multiubiquitin chain is confined to specific lysine in a targeted short-lived protein. Science (New York, NY). 1989;243(4898):1576.
6. Seirafi M, Kozlov G, Gehring K. Parkin structure and function. The Febs Journal. 2015;282(11):2076-88.
7. Berndsen CE, Wolberger C. New insights into ubiquitin E3 ligase mechanism. Nature structural & molecular biology. 2014;21(4):301-7.
8. Robinson PA, Ardley HC. Ubiquitin-protein ligases. J Cell Sci. 2004;117(Pt 22):5191-4.
9. Lechtenberg BC, Rajput A, Sanishvili R, Dobaczewska MK, Ware CF, Mace PD, et al. Structure of a HOIP/E2~ubiquitin complex reveals RBR E3 ligase mechanism and regulation. Nature. 2016;529(7587):546-50.
10. Trempe JF, Sauve V, Grenier K, Seirafi M, Tang MY, Menade M, et al. Structure of parkin reveals mechanisms for ubiquitin ligase activation. Science (New York, NY). 2013;340(6139):1451-5.
11. Duda DM, Olszewski JL, Schuermann JP, Kurinov I, Miller DJ, Nourse A, et al. Structure of HHARI, a RING-IBR-RING ubiquitin ligase: autoinhibition of an Ariadne-family E3 and insights into ligation mechanism. Structure (London, England : 1993). 2013;21(6):1030-41.
12. Sauvé V, Lilov A, Seirafi M, Vranas M, Rasool S, Kozlov G, et al. A Ubl/ubiquitin switch in the activation of Parkin. The EMBO Journal. 2015;34(20):2492-505.
13. Wenzel DM, Lissounov A, Brzovic PS, Klevit RE. UbcH7 reactivity profile reveals Parkin and HHARI to be RING/HECT hybrids. Nature. 2011;474(7349):105-8.
14. Chen ZJ, Niles EG, Pickart CM. Isolation of a cDNA encoding a mammalian multiubiquitinating enzyme (E225K) and overexpression of the functional enzyme in Escherichia coli. The Journal of biological chemistry. 1991;266(24):15698-704.
15. Kirisako T, Kamei K, Murata S, Kato M, Fukumoto H, Kanie M, et al. A ubiquitin ligase complex assembles linear polyubiquitin chains. Embo j. 2006;25(20):4877-87.
16. Smit JJ, Monteferrario D, Noordermeer SM, van Dijk WJ, van der Reijden BA, Sixma TK. The E3 ligase HOIP specifies linear ubiquitin chain assembly through its RING-IBR-RING domain and the unique LDD extension. The EMBO Journal. 2012;31(19):3833-44.
17. Greene AW, Grenier K, Aguileta MA, Muise S, Farazifard R, Haque ME, et al. Mitochondrial processing peptidase regulates PINK1 processing, import and Parkin recruitment. EMBO Reports. 2012;13(4):378-85.
18. Vives-Bauza C, Przedborski S. Mitophagy: the latest problem for Parkinson's disease. Trends in molecular medicine. 2011;17(3):158-65.
19. Hristova VA, Beasley SA, Rylett RJ, Shaw GS. Identification of a novel Zn2+-binding domain in the autosomal recessive juvenile Parkinson-related E3 ligase parkin. The Journal of biological chemistry. 2009;284(22):14978-86.
20. Spratt Donald E, Walden H, Shaw Gary S. RBR E3 ubiquitin ligases: new structures, new insights, new questions. Biochemical Journal. 2014;458(Pt 3):421-37.
21. Sato Y, Fujita H, Yoshikawa A, Yamashita M, Yamagata A, Kaiser SE, et al. Specific recognition of linear ubiquitin chains by the Npl4 zinc finger (NZF) domain of the HOIL-1L subunit of the linear ubiquitin chain assembly complex. Proceedings of the National Academy of Sciences of the United States of America. 2011;108(51):20520-5.
22. Tokunaga F, Iwai K. LUBAC, a novel ubiquitin ligase for linear ubiquitination, is crucial for inflammation and immune responses. Microbes and Infection. 2012;14(7–8):563-72.
23. Smit JJ, Sixma TK. "Ubiquitylation: mechanism and functions" Review series: RBR E3-ligases at work. EMBO Reports. 2014;15(2):142-54.
24. Kelsall IR, Duda DM, Olszewski JL, Hofmann K, Knebel A, Langevin F, et al. TRIAD1 and HHARI bind to and are activated by distinct neddylated Cullin-RING ligase complexes. The EMBO Journal. 2013;32(21):2848-60.
25. Elmehdawi F, Wheway G, Szymanska K, Adams M, High AS, Johnson CA, et al. Human Homolog of Drosophila Ariadne (HHARI) is a marker of cellular proliferation associated with nuclear bodies. Experimental cell research. 2013;319(3):161-72.
26. Caulfield TR, Fiesel FC, Moussaud-Lamodière EL, Dourado DFAR, Flores SC, Springer W. Phosphorylation by PINK1 Releases the UBL Domain and Initializes the Conformational Opening of the E3 Ubiquitin Ligase Parkin. PLoS Computational Biology. 2014;10(11):e1003935.
27. Wauer T, Komander D. Structure of the human Parkin ligase domain in an autoinhibited state. The EMBO Journal. 2013;32(15):2099-112.
28. Kazlauskaite A, Martínez-Torres RJ, Wilkie S, Kumar A, Peltier J, Gonzalez A, et al. Binding to serine 65-phosphorylated ubiquitin primes Parkin for optimal PINK1-dependent phosphorylation and activation. EMBO Reports. 2015;16(8):939-54.
29. Wauer T, Simicek M, Schubert A, Komander D. Mechanism of phospho-ubiquitin-induced PARKIN activation. Nature. 2015;524(7565):370-4.
30. Spratt DE, Mercier P, Shaw GS. Structure of the HHARI Catalytic Domain Shows Glimpses of a HECT E3 Ligase. PLoS ONE. 2013;8(8):e74047.
31. Riley BE, Lougheed JC, Callaway K, Velasquez M, Brecht E, Nguyen L, et al. Structure and function of Parkin E3 ubiquitin ligase reveals aspects of RING and HECT ligases. Nature Communications. 2013;4:1982.
32. Cunningham CN, Baughman JM, Phu L, Tea JS, Yu C, Coons M, et al. USP30 and parkin homeostatically regulate atypical ubiquitin chains on mitochondria. Nat Cell Biol. 2015;17(2):160-9.