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REVIEW

WWP2: A Multifunctional Ubiquitin Ligase Gene

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Abstract The ubiquitin-proteasome system plays an important role in various celluar processes. WWP2, a recently identified ubiquitin E3 ligase, has been proved a multifunctional gene by degradation a series of targets via ubiquitin-dependent proteasome system, including PETN, Smads, Oct4, EGR2, TIRF and so. Hereafter, we reviewed the recent research process about the function of WWP2.

Keywords WWP2 (AIP2) · Ubiquitylation · Cancer;

Human WWP2 (WW domain containing E3 Ub-protein ligase 2), also known as AIP2 (atrophin-1 interacting protein 2), is a C2-WW-HECT (homologous to E6-AP COOH terminus)-type ubiquitin E3 ligase. Within the HECT-domain E3 ligases are a small sub-group known as the NEDD4 family. The NEDD4 sub-group of HECT E3 ligases share three functional domains: an Nterminal Ca2+/phospholipid-binding C2 domain for membrane binding, a central region containing up to four WW (double-tryptophan) domains, and a C-terminal HECT domain for ubiquitin protein ligation [1]. The NEDD4 family is involved in numberous cellular processes, including membrane protein trafficking, protein degradation, signaling, transcription, and apoptosis [2–5]. Increasing evidence indicates that WWP2 plays important roles in cancers, thus we attempt to comprehensively summarize the recent processes of WWP2 investigation especially related to cancer.

Protein ubiquitination is a posttranslational modification regulating a variety of cellular processes including protein degradation, endocytosis of membrane proteins, protein-protein interactions in signal transduction, to cell-cycle progression, apoptosis, gene transcription and immune responses [6–11]. Ubiquitin is a 76 amino acid protein and covalently attaches to target proteins via an isopeptide bond between the C-terminal Gly76 carboxyl group on ubiquitin and the free amino group on internal lysine's within the substrate. Ubiquitin conjugation includes a series of events catalyzed sequentially by E1 (ubiquitin-activating), E2 (ubiquitin-conjugating) and E3 (ubiquitin ligase) enzymes. There are approximately 600 E3 ubiquitin ligases in the mammalian genome [12], and they are key to provide target substrate specificity. E3 ubiquitin ligases can be segregated primarily into RING-type and HECT-domain ligases. The RING type E3s have no intrinsic ligase activity, and act as scaffolds that recruit specific substrates to an associated E2 ligase that is then responsible for ubiquitin transfer. In contrast, the HECT E3s have intrinsic ligase activity, and they lock onto specific substrates as well as directly mediating ubiquitination.

Biochemistry of WWP2

WWP2 Gene Expression

Human WWP2 (WW domain containing E3 Ub-protein ligase 2) was originally identified by Pirozzi in screening for WW

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domain-containing proteins [13]. With yeast two-hybrid and in vitro binding assays, Wood demonstrated that WWP2 bound to atrophin-1 [14]. Wood also reported that WWP2 was ubiquitously expressed in several human organs, including heart, placenta, lung, liver, muscle, kidney, pancreas and brain [14]. In the same study, radiation hybrid mapping localized WWP2 to chromosome 16q21.1. With northern bolt analysis, Huiming Xu et al. identified two WWP2 transcripts, 4.4 and 2.4 kb in length, respectively. The 4.4-kb transcript was the predominant form. Their group found the WWP2 transcript level was the highest in the skeletal muscle, peripheral leukocytes, placenta, heart, and kidney; higher in the brain, spleen, and lung; and lower in the thymus, liver, colon, and intestine [15]. Scrutiny of Mammalian Gene Collection (MGC) databases containing sequence-validated full-length protein-coding complementary DNA clones identified a unique and interesting feature of WWP2:there were three WWP2 isoforms arising from the same gene locus: full-length WWP2 (WWP2-FL, 870aa), an N-terminal isoform (WWP2-N, 336aa) presumably generated by failure to splice-out intron 9–10, and a C-terminal isoform (WWP2-C, 440aa) possibly generated from a second promoter within intron10–11. Recently, by using isoform-specific primers and reverse transcriptase–PCR (RT–PCR) methods, SM Soond and A Chantry detected these three transcripts in Colo-357 pancreatic carcinoma cells, subsequently confirmed by western bolt [16]. However, until now there are no reports about the specific distribution of WWP2 isoforms.

WWP2 Protein Structure

WWP2-N isoform contains C2 domain and only a single WW domain (WW1), WWP2-C isoform harbors WW4 domain and the HECT E3 ligase domain, and WWP2-FL includes C2 domain, WW4 domain and the HECT E3 ligase domain [16]. The N terminal Ca2t/phospholipid-binding C2 domain is required for membrane binding, and C-terminal HECT domain is responsibled for ubiquitin protein ligation [1]. The WW domains are essential for target specificity and they interact with PPXY (also known as–PY) motifs, phospho-Ser-Pro and Pro-Arg containing sequences in target substrates [1, 13, 17].

Regulation of WWP2

The molecular mechanisms regulating the catalytic activity and turnover of WWP2 protein are largely unknown until now. Bing Liao et al. first reported that when in high dosages, Wwp2 molecules could represse its own ubiquitin ligase activity both in vitro and in vivo through form homodimers, which might explain why Wwp2 represses its own Ub ligase activity [18]. Results from other E3 ligases may sheet light on this question. Increasing evidences have shown that autoinhibition is a common way regulating the activity of E3 ubiquitin ligase, and thus many ubiquitin (Ub) protein ligases (E3s) can target themselves for degradation [19–23]. Therefore, it is appropriate to speculate that these mechanisms may apply to WWP2, but it required to be verified in future research. Recently, with luciferase reporter assay, Dong Lu et al. reported that miR-25 may bind to 3'-UTR of Wwp2, thus it can regulate the expression of this gene [16].

Functional Roles of WWP2

Roles of WWP2 Involved in Cancer

WWP2 belongs to HECT-domain-containing E3 ligases which regulate ubiquitin-dependent degradation of their substrates. Recently, the role of WWP2 in carcinogenesis has attacked much interest. Recent research has demonstrated that WWP2 interacted with PTEN, Smads and Oct4, and mediated their degradation through an ubiquition-depend manner. These three proteins are involved in key oncogenic signaling pathways linked to cancer cell growth, survival and tumor spread. PTEN is a lipid phosphatase frequently mutated in human cancer, and Maddika and coworkers recently reported that WWP2 physically interacted with PTEN, and PETN underwent polubiquitin-mediated proteasomal turnover [24]. WWP2-mediated depletion of PTEN, which is also an important negative regulator of the PI3K-AKT pathway, consequently elevated AKT signaling activity and rendered prostate cancer cell lines resistant to stress-induced cell death. Following on from this, stable expression of WWP2 enhanced transformation of prostate cancer cells based soft-agar colony formation assays and enhanced tumorigenicity was observed using in vivo xenograft experiments.

The oncogenic function of WWP2 is further supported by the research from Soond and Chantry [16]. In their study, WWP2 was found to interact with Smad proteins that are responsible for canonical signaling activity through the transforming growth factor-β(TGFβ) signaling pathway. TGFβ, functioning through transcription factors Smad, has a multifunctional role in cancer and in latestage tumors responsible for driving a differentiation program known as epithelial–mesenchymal transition (EMT) that converts static epithelial cells into highly invasive mesenchymal cells, a necessary event for neoplasm metastasis. Furthermore, these isoforms displayed differential binding activity towards individual Smad proteins. The full-length WWP2 (WWP2-FL) bound to TGFβ receptor regulated R-Smads (Smads 2/3) and also to inhibitory I-Smad7, although it preferentially bound to I-Smad7 which is polyubiquitinated and rapidly degraded. However, the truncated isoforms displayed differential binding activities and WWP2-N bound onto Smads 2/3 selectively,

whereas WWP2-C interacted with I-Smad7. Unexpectedly, WWP2-N, which lacks a functional HECT ligase domain was also found to complex with WWP2-FL in a TGFβ-regulated manner and activate WWP2-FL ligase activity causing degradation of unstimulated Smads 2/3. Consequently, it was suggested that WWP2-FL has a role to play in TGFβ-induced cancer cell metastasis based on its substrate preference for inhibitory Smad7, and this was supported by cell based EMT experiments in which expression of an isolated Smad7- binding WW4 domain caused selective disruption of the Smad7: WWP2 complex, and stabilized Smad7 protein levels to thereby prevent TGFβ-induced EMT. Furthermore, it was suggested that one role of WWP2-N might in fact be to suppress TGFβ-induced EMT, by virtue of its unique ability to limit the levels of receptor regulated R-Smads 2/3. Remarkably, this study also highlighted for the first time an interdependent role for distinct WWP2 isoforms, that could impact on both the in vivo and cell based studies of WWP2-FL function highlighted above.

Besides direct evidence demonstrating its oncogenic role of WWP2, there is also some indirect evidence confers that WWP2 may plays a vital role in the process of carcinogenesis. It has been suggested that neoplasm can be seen as a disease of unregulated self-renewal in which mutations convert normal stem cell self-renewal pathways into engines for neoplastic proliferation [25–27]. Recent studies have demonstrated that transcription factor Oct4 plays critical roles in maintaining pluripotency and controlling lineage commitment of embryonic stem cells (ESCs). Expression of Oct4 is downregulated during differentiation. However, recently it has been demonstrated that some malignant cells regained the ability to express Oct4 [28]. Recent research has well established the role of Oct4 in the process of tumorigenesis [28]. Recent study from Youwen Qiang showed that by competitively interacted with WWP2, p28GANK could inhibited the interaction between WWP2 and Oct4, resulting in a decrease of ubiquitination and degradation of Oct4 mediated by WWP2, ultimately promoted the expansion of tumor initiating cells [29].

As WWP2 and WWP1 share some common functional domain, it is reasonable to speculate that they may share some common substrates, regrettably no such substrate has been found yet. WWP1 is also one member of the HECT family of ubiquitin ligases, its role in cancer development has been well documented (reviewed in [1, 30].

The Role of WWP2 in Stem Cells

Oct-4 is a key transcription factor regulating the fate of pluripotent embryonic stem cells. But, how Oct4 is regulated still remains to be elucidated. Huiming Xu et al. firstly reported that a novel murine ubiquitin ligaseWwp2 specifically interacted with Oct-4 and promotes its ubiquitination both in vivo and in vitro [31]. Subsequent research reported that human ubiquitin ligase WWP2, also can interact with OCT4 specifically through its WW domain and enhance Ub modification of OCT4 both in vitro and in vivo. They also found that WWP2 promoted degradation of OCT4 via 26S proteasome in a dosage-dependent manner. Remarkably, our data show that the endogenous OCT4 protein level was significantly elevated whenWWP2 expression was downregulated by specific RNA interference (RNAi), suggesting that WWP2 is an important regulator for maintaining a proper OCT4 protein level in human ES cells. [15].Further research from the same group reported that Wwp2 played an important role in ubiquitination and degradation of Oct4 during differentiation of embryonal carcinoma cells (ECCs), however, Wwp2 did not affect Oct4 protein levels in the undifferentiated ECCs and ESCs. Mechanistically, Wwp2 catalyzes Oct4 polyubiquitination via the lysine 63 linkage in a dosage-dependent manner. Interestingly, Wwp2 also regulates its own ligase activity in a similar manner. Moreover, autoubiquitination of Wwp2 occurs through an intra-molecular mechanism. Taken together, these results collectively demonstrated a crucial role of WWP2 (Wwp2 in murine)in controlling endogenous Oct4 protein levels during differentiation processes of embryonal carcinoma cells (ECCs) and suggested an interesting dosage-dependent mechanism for regulating the catalytic activity of the E3 ubiquitin ligase, Wwp2 [18]. More recently, Dong Lu and colleagues showed that overexpressed miR-25 or introducing its mimics enhanced induced pluripotent stem cells (iPSCs), Wwp2 is one of miR-25 target gene. [32]. Since Wwp2 plays a important role in regulating one crucial transcription factor in maintaining the pluripotent and self-renewing state of embryonic stem (ES) cells [15, 31], thus it is reasonable to speculate that miR-25 may participate in iPSCs through regulation Wwp2 mediated Oct4 degradation.

The Role of WWP2 in Immune System

Besides the important part of WWP2 involved in cancer and stem cells, accumulating evidence has indicated that WWP2 play a vital role in the regulation of immune system. WWP2 can positively regulate T cell activation [33]. In mouse primary T cells, ectopic expression of WWP2 enhances their proliferation and interleukin-2 production by suppressing the apoptosis of T cells. WWP2 interacts with and promotes ubiquitin-mediated degradation of early growth response (EGR), a zinc finger transcription factor that has been found to regulate Fas ligand (FasL) expression during activation-induced T-cell death. Small RNA interference suppresses the expression of WWP2 leads to upregulation of EGR2, inhibition of EGR2 ubiquitination and FasL expression, and enhancement of the apoptosis of T cells [33]. More recently, Yan Yang and coworkers suggested that upon TLR3 activation

WWP2 was associated with TRIF and target it for K48-linked ubiquitination and degradation. Knockdown of WWP2 resulted in compromised TRIF ubiquitination, elevated TRIF protein level and enhanced expression of IFNB after TLR3 activation. Furthermore, deletion of Wwp2 in mice lead to increased expression of proinflammatory cytokines and type I IFNs in macrophages and susceptibility to poly (I:C)-induced death in vivo, these results further highlighting the significant position of WWP2 in immune system [34].

Other Roles of WWP2

WWP2 are also implicated in regulating the turnover of the epithelial sodium channel (ENaC) [35], divalent metal-ion transporter (DMT1) [36], the large subunit of RNA polymerase II (Rpb1) [37] and ADAR2 [38]. ENaC is a critical component of the pathway maintaining salt and water balance. McDonald reported WWP2 is a candidate to regulate ENaC-mediated Na^+ transport in epithelia [35]. Moreover, WWP2 can also regulate the divalent metal ion transporter DMT1 and iron homeostasis by an ubiquitin-dependent mechanism [36]. And Li Hui found that Wwp2 specifically interacted with mouse Rpb1 and targeted it for ubiquitination both in vitro and in vivo [37]. Ubiquitination and the degradation of the large subunit of RNA polymerase II, Rpb1, are involved in DNA damage-induced arrest. Wwp2 interacts specifically with Rpb1, independent of DNA damage and phosphorylation state, resulting in its ubiquitination and degradation through 26S proteasome. Furthermore, they showed that Wwp2 is essential for the maintenance of Rpb1 steady-state protein levels in embryonic pluripotent stem cells. Their findings suggest that Wwp2 play a significant role in the regulating of expression of Rpb1 in normal physiological conditions [37]. WWP2 also binds to ADAR2 and catalyze its ubiquitination and subsequent degradation, whicn may affecting the catalytic activity of ADAR2 (ADAR2 catalyses the deamination of adenosine to inosine at the GluR2 Q/R site in the pre-mRNA encoding the critical subunit of AMPA receptors) [38]. Therefore, WWP2 may regulate other key cellular proteins.

All these findings are observed in normal cells, however, how the modification of these protein influence the physiological function and signal transduction remains to be elucidated.

Conclusions and Perspectives

In summary, as a WW domain-containing HECT type ubiquitin E3 ligase. WWP2 targets a number of PY motif containing substrate proteins, including Smad2, PTEN, Oct4, EGR2, TIRF, for ubiquitination-dependent degradation. However, whether WWP2 can regulate other substrate without PY motif through adaptor still remains to be explored. In addition, recent research mainly focus the role of WWP2 involved in cancers, considered WWP2 being a multifunctional protein, whether WWP2 participate in other kind of diseases warrants further investigation.

In the future, the specific distribution and function of WWP2 isoforms need to be detected ugently. Additionally, WWP2 knock-out animal models will be urgently required to elucidate the physiological and pathological functions of WWP2 in human diseases. Xenograft animal models will also be of significance and importance to determine the role of exact WWP2 in cancer biology. Whether the genetic and expression alterations of WWP2 can be used as biomarkers in cancers and other diseases should be studied in large cohorts of patients. Finally, the mechanism of regulation of WWP2 still remains to be elucidated.

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