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Anticancer Target Molecules Against the SCF Ubiquitin E3 Ligase in RCC: Potential Approaches to the NEDD8 Pathway

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1. Introduction

Several alternative treatments have recently been developed for metastatic renal cell carcinoma (RCC). Vascular endothelial growth factor (VEGF) is a potent pro-angiogenic protein, which is responsible for increased vasculature and tumor-growth in RCC. Fundamentally, a mutation in the von Hippel-Lindau (VHL) tumor suppressor gene induces overexpression of VEGF via accumulation of hypoxia-inducible factor (HIF)-1 in RCC. Several agents inhibiting the VEGF signaling cascade, such as sorafenib, sunitinib and bevacizumab, have been found to exert significant anti-tumor effects and provide meaningful clinical benefits. Furthermore, temsirolimus and everolimus, inhibitors of the mammalian target of rapamycin (mTOR), which block the phosphoinositide 3-kinase (PI3K)/AKT signaling pathway involved in numerous cellular functions including cell proliferation, survival and angiogenesis, have been found to be effective agents against advanced RCC in the clinical setting. Although molecular targeting therapies against the VEGF or mTOR signaling pathway have revolutionized the treatment of advanced RCC, no curative therapy has yet been established.

In this chapter, we focus on potent molecules and agents possibly suppressing the tumor growth of RCC via regulation of the ubiquitination-proteasome system. NEDD8, one of the ubiquitin-like proteins, reportedly forms conjugates with cullin family proteins and thereby activates the Skp1-Cullin-F-box (SCF) ubiquitin protein ligase complex that catalyzes the ubiquitination of many cell-cycle regulators, e.g. cyclin E, p21, p73 and p27. It is possible that negative regulation of NEDD8 and its conjugation system induces an antiproliferative action on RCC, secondary to inhibition of ubiqitin-proteasome activity. We previously showed that these negative regulator proteins, such as NEDD8 ultimate buster 1 (NUB1) and a dominant negative form (Ubc12 C111S) of NEDD8 E2 ligase, exhibited remarkable antitumor effects against some tumors, including RCC. Moreover, MLN4924, a potent and selective inhibitor of NEDD8-activating enzyme (NAE), was recently reported to disrupt SCF ubiquitin E3 ligase-induced protein turnover leading to apoptosis in tumor cells via deregulation of the cell cycle. This compound has already been applied in the clinical setting, e.g., malignant lymphoma. Thus, negative regulation of NEDD8 and its conjugation is an attractive anti-cancer strategy based on evidence obtained by basic research. We have

developed a hypoxia-inducible factor-1 (HIF-1)-triggered expression vector for the purpose of selective gene therapy using NEDD8 negative regulator molecules, including NUB1 and the Ubc12 dominant negative form.

In this chapter, we summarize the data on potent molecules associated with the ubiquitin-proteasome system as anti-cancer targets on the basis of our reseach and discuss future perspectives in the treatment of RCC.

2. Mechanisms of ubiquitination pathway

Programmed destruction of regulatory proteins is crucial for homeostasis of cellular biological functions. The ubiquitination-proteasome pathway is a major scavenger system associated with regulated proteolysis inside cells. The pathway of protein destruction begins by conjugating a chain of polyubiquitin to a target molecule (Hershko & Ciechanover, 1998). The first step in the production of this chain is to connect a monoubiquitin molecule to E1(ubiquitin-activating enzyme) through a thioester bond in an ATP-dependent manner. Next, E2 (ubiquitin-conjugating enzyme) receives an activated ubiquitin from E1 and transfers a ubiquitin to a lysine residue in a target protein with the assistance of an E3 ubiquitin ligase. Repeated cycles via the E1-E2-E3 cascade generate a polyubiquitin chain, namely a death signal, which is subsequently recognized by the regulatory subunit of the 26S proteasome machinery (Fig. 1).
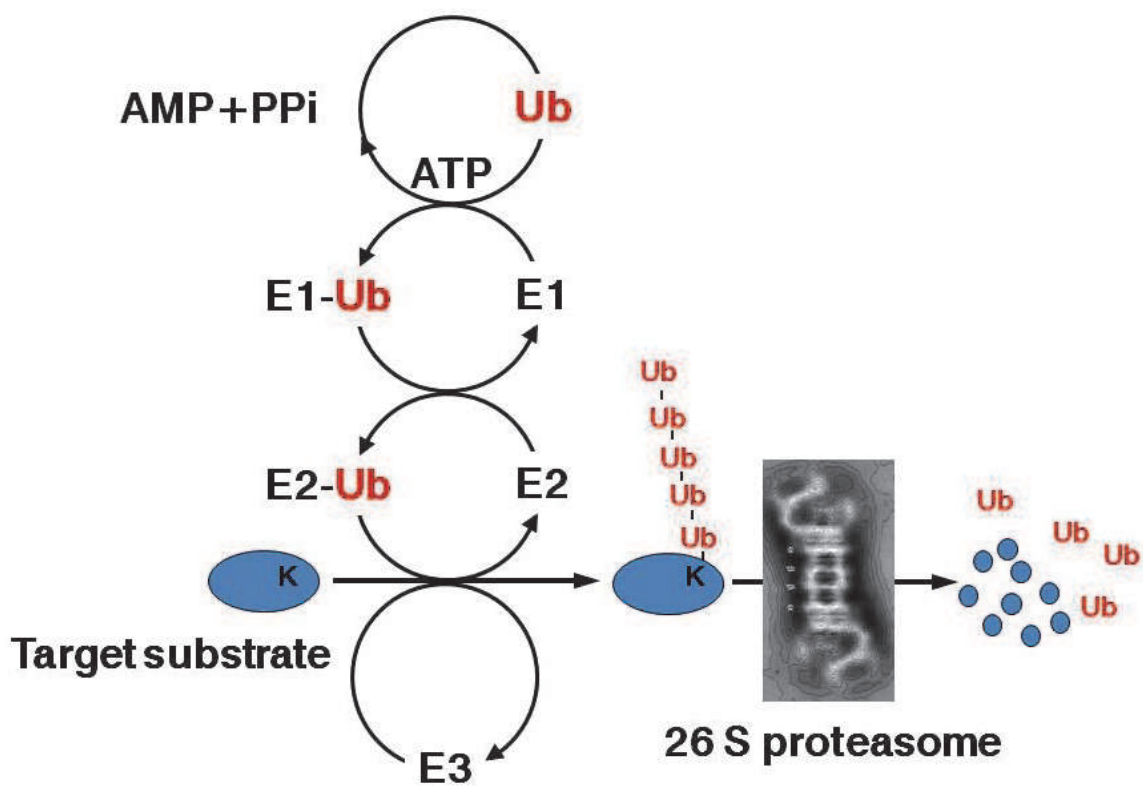

Fig. 1. Overview of the ubiquitination-proteasome pathway. Lysine residue (K) of the substrate is conjugated to ubiquitin (Ub).

2.1 Multiplicity of SCF (Skp-1, Cullins, F-box proteins) complex E3 ubiquitin ligases and their target proteins

The SCF complex E3 ligases or CRLs (Cullin-RING ubiquitin ligases), which are mainly comprised of Skp-1, Cullins, F-box proteins and Rbx/Roc RING finger proteins, are predominate among members of the E3 ubiquitin ligase family that promotes the ubiquitination of target proteins regulating various biological processes, including cell-cycle progression, signal transduction, and differentiation. The substrate specificity of SCF ligase depends on the combination pattern of its components, particularly the F-box binding domain. Numerous regulatory proteins targeted by SCF ligases have just recently been reported, as shown in Table 1. Therefore, deregulation of SCF E3 ligases may reinforce the instability of cellular functions; cell-cycle arrest, apoptosis, tumorigenesis, etc.

2.2 NEDD8, one of the ubiquitin-like proteins (UBLs), conjugation pathway

Several ubiquitin-like proteins (UBLs), including NEDD8, Sentrin/SUMO, ISG15, FAT10, Atg8 and Atg12, have been demonstrated to conjugate to a target molecule in a manner similar to ubiquitin. NEDD8 (neural precursor cell-expressed developmentally downregulated) was originally reported as a novel gene highly enriched in fetal mouse brain (Kumar et al., 1992). NEDD8 encodes a small protein of 81 amino acids, which is 60% identical and 80% homologous to ubiquitin, and equivalently conjugates to substrates (Kamitani et al., 1997). The crystal structure of NEDD8 is quite analogous to that of ubiquitin with the exception of two surface regions which are different (Fig. 2).
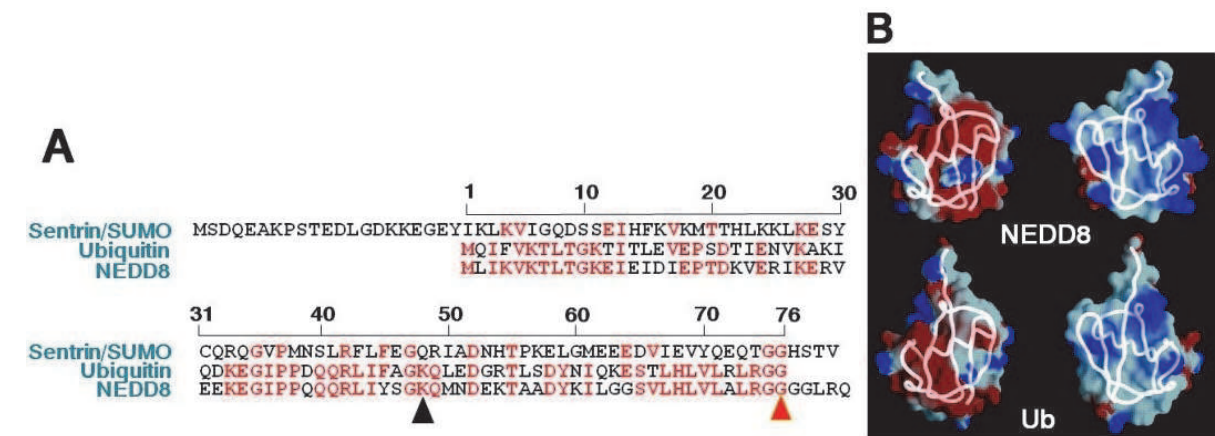

Fig. 2. (A) Alignment of amino acid sequences of human SUMO/Sentrin, Ubiquitin, and NEDD8. Black triangle; site of conjugation with lysine. Red triangle; active cleavage site for glycine. (B). 3D-structures of Ubiquitin and NEDD8.

The NEDD8 conjugation cascade, also known as neddylation, is mediated by E1 NEDD8-activating enzyme (NAE), E2 NEDD8 conjugating enzyme (Ubc12), and E3 NEDD8 ligase, which successively activate and transfer NEDD8 to a target molecule. First, the C-terminal glycine of NEDD8 is adenylated by an E1 NAE, which is composed of APP-BP1 and Uba3 heterodimer, in an ATP-dependent manner and transferred to E1 via a thiolester linkage. Second, activated NEDD8 is consecutively transferred to an E2 NEDD8 conjugation enzyme (Ubc12, Ube2f). Third, an E3 NEDD8 ligase transfers NEDD8 to a substrate lysine residue via an isopeptide bond. On the contrary, covalent neddylation of a substrate is reversibly

deconjugated by the action of proteins (e.g. COP9 signalosome, NEDP1/DEN1, USP21) involved in deneddylation (Gong et al., 2000; Lyapina et al., 2001; Rabut & Peter, 2008) or inhibited by Cullin binding to CAND1 (Cullin-associated and neddylation-dissociate 1)(Goldenberg et al., 2004), or negatively down-regulated by NUB1 (NEDD8 ultimate buster 1) linked to the 26S proteasome (Kamitani et al., 2001; Kito et al., 2001) (Fig. 3).
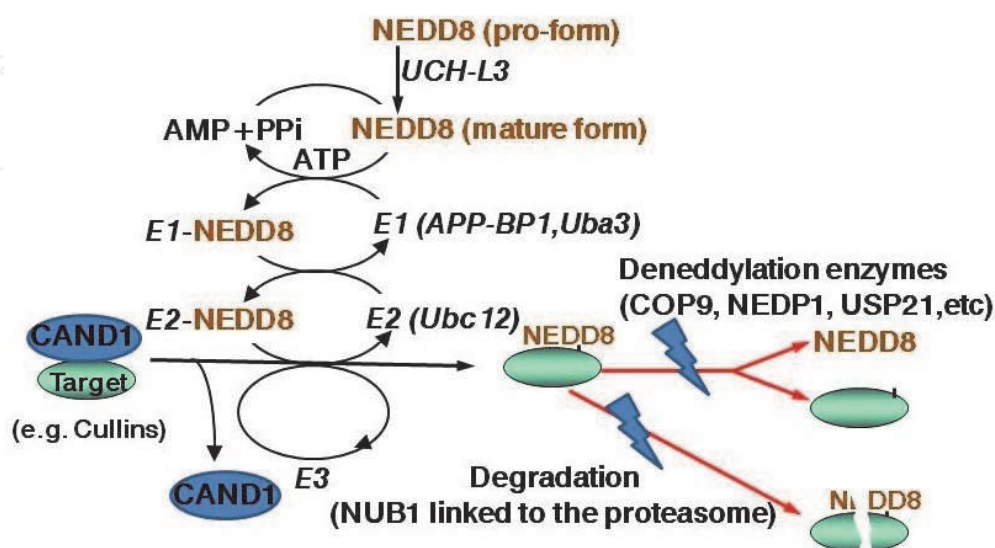

Fig. 3. Overview of the NEDD8 conjugation and deconjugation pathway.

2.2.1 Substrates conjugated by NEDD8; Cullins and other target molecules

Cullins, scaffold proteins assembling other components of an E3 SCF complex, are the substrates usually targeted by NEDD8 (Table 1). To date, seven Cullin family members (Cul-1, -2, -3, -4A, -4B, -5, -7) have been identified. Cul-1-based SCF complexes (CRL1), such as SCF^{Skp2}, SCF$^{\beta-Trcp}$ and SCF^{Fbw7}, are the most studied in terms of their cancer-related actions. SCF^{Skp2} is involved in the degradation of several cell-cycle regulators (e.g. cyclin D, p27^{Kip1}, p21^{Cip1}, p73, p130, etc) (Guardavaccaro & Pagano, 2004). SCF$^{\beta-Trcp}$ promotes degradation of IκBα of the NFκB inhibitor and β-catenin (Skaar et al., 2009). Moreover, SCF^{Fbw7} has been reported to promote degradation of cyclin E, c-myc oncoproteins and Notch (Guardavaccaro & Pagano, 2004). A recent study identified more than 350 possible CRL1 substrates by employing global protein stability profiling (Yen & Elledge, 2008). Cul-2 properly generates a CRL2 complex (also known as VBC) with the von Hippel-Lindau gene product (pVHL) through elongin B and elongin C. This complex induces degradation of the hypoxia-inducible factor-1 α subunit (HIF-1α), of which proline residues are hydroxylated by prolyl hydroxylase in an oxygen-dependent manner and then targeted to pVHL for ubiquitination (Kaelin & Ratcliffe, 2008). Bialleic deletion of the VHL gene mainly results in the stability of HIF-1α and thereby ultimately contributes to tumorigenesis of sporadic clear-cell type RCC. The Cul-3-based SCF complex (CRL3), which is produced with Rbx1 and BTB-domain protein, promotes degradation of cyclin E, Mei-1 (a component of mitotic spindle), Dsh (a regulator of Wnt-β-catenin pathway) and NRF2 (a transcriptional factor associated with an anti-oxidant response) (Angers et al., 2006; Furukawa et al., 2003; Furukawa & Xiong, 2005). The CRL4 complex, including Cul-4 (A or B), a damaged DNA

binding (DDB1) protein, and a DDB1 and Cul-4-associated factor (DCAF), controls DNA replication and nucleotide excision repair through ubiquitination of CDT1, p21, Histone H2A/H3/H4, XPC, etc (Hu et al., 2004; Jackson & Xiong, 2009; Kapetanaki et al., 2006). Interestingly, knockdown or a specific inhibitor of Cul-4A has attracted research attention as a strategy for treating Cul-4-amplified breast cancer (Chen et al., 1998) and UV-induced skin cancer (Liu et al., 2009). The CRL5 complex, comprised of Cul-5, a suppressor of cytokine signaling (SOCS) family proteins, Elongin B and C, and Rbx1, suppresses JAK-STAT signaling via degradation of JAK family proteins (Hilton, 1999). On the contrary, Cul-5 has been identified as a possible tumor suppressor, overexpression of which induces growth-inhibition of breast cancer cells (Johnson et al., 2007). As regards Cul-7, to date, there have been no reported observations indicating that it is neddylated in the formation of a CRL7 complex.

Scaffold	Adaptor	Receptor	Ring box	Substrates
Cul-1	Skp1	Skp2	Rbx1	p21, p27, p73, p130, Cyclin A/ D
Cul-1	Skp1	β-TrCP	Rbx1	Iκβα, β-catenin, Bim EL, Wee1, p53
Cul-1	Skp1	Fbxw7	Rbx1	Cyclin E, c-Myc, c-Jun, Notch
Cul-2	Elongin BC	VHL	Rbx1	HIF1α
Cul-3		BTB-domain proteins	Rbx1	Cyclin E, Mei-1, Dsh, NRF2
Cul-4	DDB1	DCAF	Rbx1	CDT1, p21, Histone H2A/H3/H4, XPC
Cul-5	Elongin BC	SOCS	Rbx1	TEL-JAK2, JAK-STAT family proteins
Cul-7	Skp1	Fbxw8	Rbx1	IRS-1, Cyclin D

Table 1. SCF E3 ligases and their substrates.

As to NEDD8-target molecules other than Cullins, p53 is modified with NEDD8 via the function of MDM2, a RING finger E3 ligase, to facilitate its transactivation activity (Xirodimas et al., 2004). MDM2 also neddylates the proapoptotic protein, TAp73, and thereby enhances the localization of NEDD8-conjugated TAp73 in the cytoplasm to suppress its transactivation action (Watson et al., 2006). Moreover, MDM2 itself is also involved in NEDD8 modification, which contributes to its protein stability (Watson et al., 2010; Xirodimas et al., 2004). In addition, breast cancer-associated protein 3 (BCA3), which is highly expressed in breast and prostate cancers, was identified as a NEDD8 substrate (Gao et al., 2006). BCA3 inhibits NFκB-dependent transcription through its ability to bind to NFκB subunit p65 and the cyclin D1 promoter in a neddylation-dependent manner.

3. Focusing on the SCF E3 ligases for anticancer strategy

The SCF ubiquitin E3 ligases have been found to be dysregulated in a wide range of cancers, resulting in unlimited cell-proliferation and carcinogenesis via accumulation of their target-substrates. Consequently, the control of these E3 ligases is attracting attention as a possible strategy for treating cancers. The components (e.g. cullins, Skp-1/2, F-box proteins, Rbx1/2) and the molecules associated with modification by a SCF-activator protein, NEDD8, are potential candidates to be targeted in this approach.

3.1 Potent molecules involved in inhibition of SCF E3 ligases through deneddylation

As mentioned in section **2.2**, neddylation, i.e. conjugation of NEDD8 to target substrates, is catalyzed by certain known enzymes (E1, E2, E3) in a multistep fashion. Recently, MLN4924, a specific inhibitor of E1 NAE, was identified as an adenosine sulfamate derivative based on

the results of a high throughput screen (HTS) study designed to identify NAE inhibitors (Soucy et al., 2009). Pharmaceutically, MLN4924 irreversibly forms a covalent adduct with NEDD8 via the NAE involved in the first NEDD8 adenylation step. MLN4924 is a potent ATP-competitive inhibitor that disrupts the thiolester bond between NEDD8 and Uba3, a subunit of NAE. Fundamentally, MLN4924-mediated suppression of cullin neddylation has been shown to increase expression levels of CRL-targeting substrates (Fig. 4). Moreover, MLN4924 was revealed to have antitumor effects against acute myeloid leukemia (AML) cells both in vitro and in xenograft models, simultaneously leading to increases in the amounts of CRL-specific substrates including IκβΑ (Milhollen et al., 2010; Swords et al., 2010). Clinical trials using this agent are currently ongoing in AML patients.

Ubc12, an E2 NEDD8-conjugation enzyme, is also a key molecule in the neddylation cascade. Activated NEDD8 is transferred to the active site cystein residue of Ubc12 via a thiolester bond. Finally, Ubc12 conjugates NEDD8 to a single lysine residue of target substrates. Artificial Ubc12-C111S with mutant substitution of Cys-to-Ser in the active site (cys-111) was shown to have a dominant negative effect on the internal function of wild-type Ubc12, attributable to its covalent binding to NEDD8 (Wada et al., 2000) (Fig. 4). This mutant Ubc12-C111S has a forceful anti-proliferative action on cancer cells, concomitant with the instability of cellular morphology due to an actin cytoskeleton irregularity (Leck et al., 2010; Wada et al., 2000).
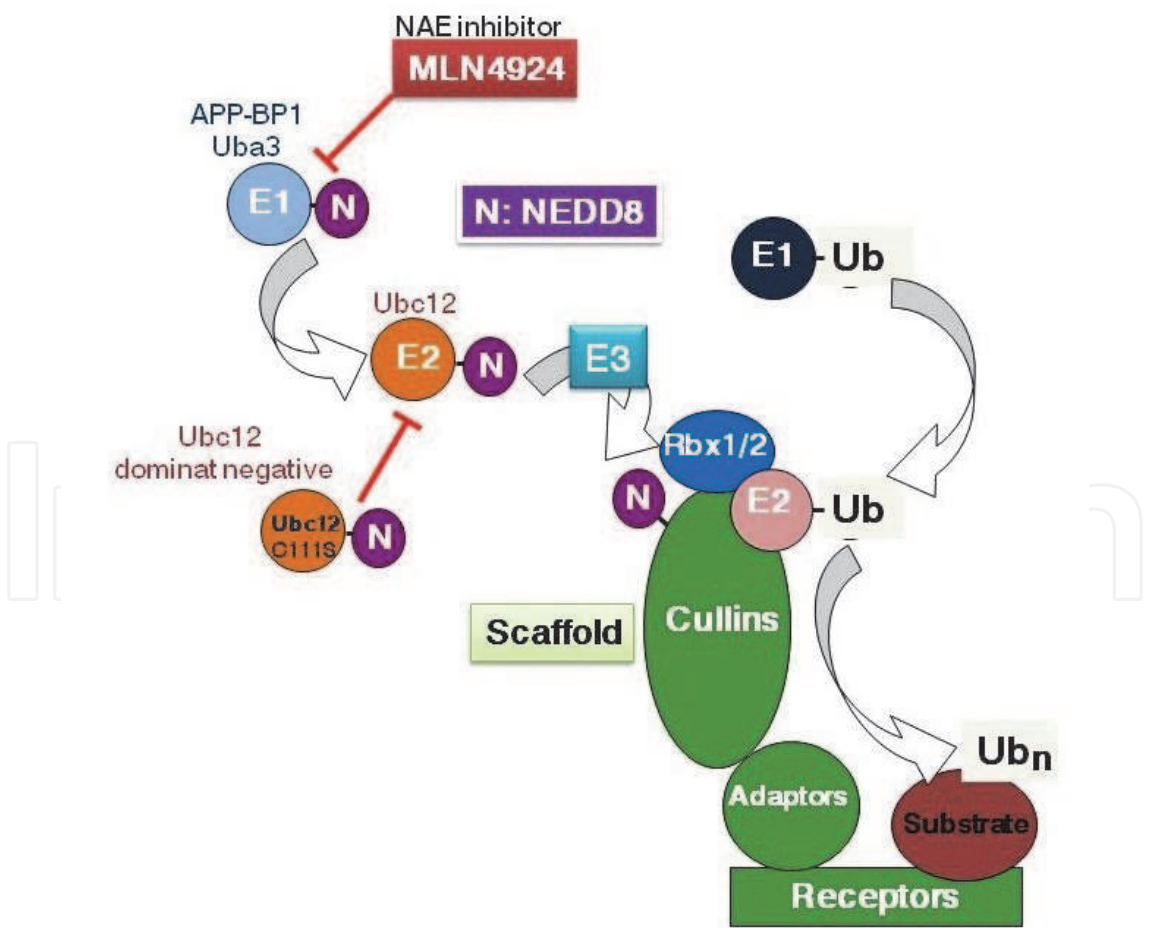

Fig. 4. Targeting the NEDD8 conjugation cascade to obtain antitumor activity.

3.1.1 Potent tumor-suppressor proteins of RCC, NUB1 (NEDD8 ultimate buster 1)/NUB1L

NUB1 is a NEDD8-interacting protein composed of 601 amino acid residues with a calculated molecular mass of 69.1 kDa. It is an interferon (IFN)-inducible protein and predominantly localizes in the nucleus. Moreover, NUB1L, a splicing variant of NUB1, possesses an insertion of 14 amino acids that codes for an additional ubiquitin-associated (UBA) domain, corresponding to a NEDD8-binding site (Fig. 5). Biologically, NUB1/NUB1L recruits NEDD8 and its conjugates to the proteasome for degradation and negatively regulates the NEDD8 conjugation system (Kamitani et al., 2001; Kito et al., 2001; Tanaka et al., 2003).
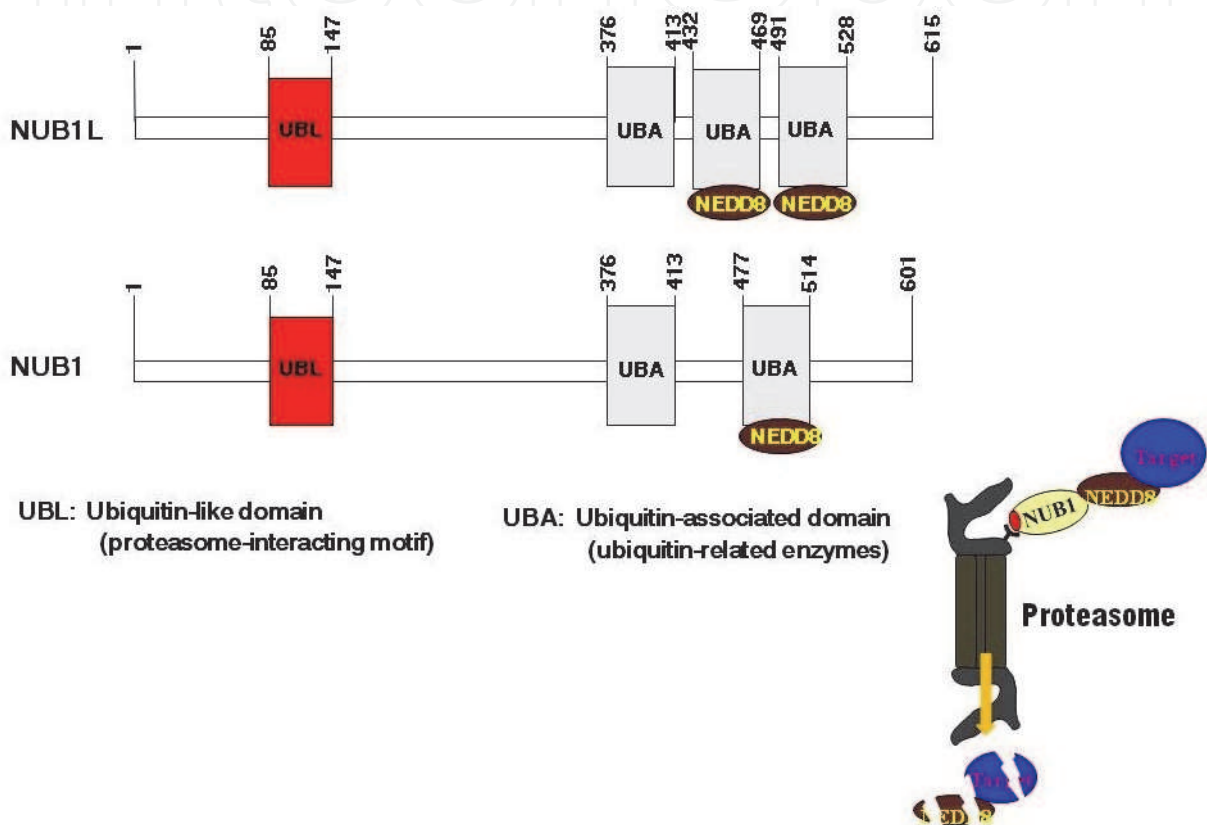

Fig. 5. Functional domains of both NUB1 and NUB1L, which are linked to the proteasome.

Furthermore, NUB1 is expressed in some cancer cell lines, including rectal adenocarcinoma, neuroblastoma, malignant lymphoma, cervical adenocarcinoma and RCC (Kito et al., 2001). Recently, NUB1 was shown to not only correlate with IFNα-induced antimitogenic action, but also exert anticancer effects against RCC cells, concomitant with S-phase transition during the cell cycle and apoptosis via accumulation of p27 and cyclin E (Hosono et al., 2010). Interestingly, overexpression of NUB1 strongly inhibits tumor proliferation in IFNα-resistant RCC cells (Hosono et al., 2010).

In general, tumorigenesis of RCCs, particularly clear cell carcinoma, is mainly attributed to HIF-1α-VEGF-mediated angiogenesis. HIF-1α is stabilized by loss of the function of a CRL2 complex via inactivation of VHL protein and of the hydroxylated oxygen-dependent degradation (ODD) domain of HIF-1α in a state of hypoxia inside RCC cells. For the purpose of developing tumor-specific gene therapy for RCCs, our laboratory constructed a

potent delivery plasmid, composed of HIF-1-dependent reporter genes, in which 5 copies of the hypoxia-response element (5HRE) enhanced expression of the ODD domain and target gene under hypoxic conditions. Thus, these novel vectors including 5HRE-ODD-NUB1 or 5HRE-ODD-Ubc12 C111S may be useful for targeting advanced RCCs, even RCCs resistant to IFN, tyrosine kinase inhibitors, or mTOR inhibitors.

4. Conclusion

Potent agents (tyrosine kinase inhibitors, mTOR inhibitors), targeting VEGF and mTOR signal cascades, have recently been used worldwide for the purpose of treating metastatic RCC (mRCC) patients. Although these drugs have produced significant benefits in terms of overall survival and progression-free survival, as compared to traditional immunotherapy with IFN, there is no definitive strategy for the progressive-disease state of mRCC resistant to these target therapies. Alternative molecular targets (e.g. mTORC2, angiopoetin family proteins) complementary to the HIF-VEGF or PI3K-Akt-mTOR signal cascade are anticipated from future research. However, another approach distinct from conventional molecular targeting therapies is needed to prolong the survival of mRCC patients. Targeting neddylation as a procedure for inactivation of SCF E3 ligases was revealed to have a strong potential to suppress cancer cell growth.

Thus, a novel strategy for regulating NEDD8-dependent signal pathways may yield a breakthrough in the field of mRCC treatments, if it meets the criteria of showing high selectivity for cancer cells and being minimally toxic to normal cells.

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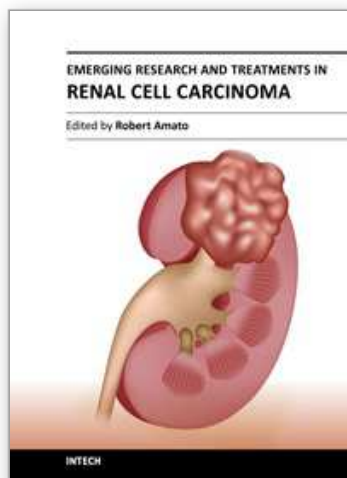
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