

# Potential roles of NEDD4 and NEDD4L and their utility as therapeutic targets in high-incidence adult male cancers (Review)

AMJAD Z. ALROSAN<sup>1</sup>, KHALED ALROSAN<sup>1</sup>, GHAITH B. HEILAT<sup>2</sup>, RAWAN ALSHAREDEH<sup>3</sup>,  
RAWAN ABUDALO<sup>1</sup>, MUNA OQAL<sup>4</sup>, ABDELRAHIM ALQUDAH<sup>1</sup> and YASMIN A. ELMAGHRABI<sup>5</sup>

<sup>1</sup>Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmaceutical Sciences, The Hashemite University, Zarqa 13133; <sup>2</sup>Department of General Surgery and Urology, Faculty of Medicine, The Jordan University of Science and Technology, Irbid 22110; <sup>3</sup>Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, The Yarmouk University, Irbid 21163; <sup>4</sup>Department of Pharmaceutical Technology, Faculty of Pharmacy, The Hashemite University, Zarqa 13133, Jordan; <sup>5</sup>Wizard Pharmacy Willetton, Perth 6155, Western Australia

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**Abstract.** The term ‘cancer’ refers to >100 disorders that progressively manifest over time and are characterized by uncontrolled cell division. Although malignant growth can occur in virtually any human tissue, the underlying mechanisms underlying all forms of cancer are consistent. The International Agency for Research on Cancer's annual GLOBOCAN 2020 report provided an update on the global cancer incidence and mortality. Excluding non-melanoma skin cancer, the report predicts that there will be 19.3 million new cancer cases and >10 million cancer-related fatalities in 2023. Lung, prostate, and colon cancers are the most prevalent and lethal cancers in males. It was recognized that post-translational modifications (PTMs) of proteins are necessary for almost all cellular biological processes, as well as in cancer development and metastasis to other bodily organs. Thus, PTMs have a considerable impact on how proteins behave. Various PTMs may have harmful roles by affecting the hallmarks of cancer, metabolism and the regulation of the tumor microenvironment. PTMs and genetic changes/mutations are essential in carcinogenesis and cancer development. A pivotal PTM mechanism is protein ubiquitination. Of note, the rate-limiting stage of the protein ubiquitination cascade is hypothesized to be E3-ligase-mediated ubiquitination. Numerous studies revealed that the neural precursor cell expressed developmentally downregulated protein 4 (NEDD4) E3 ligase is among the E3 ubiquitin ligases that have essential

roles in cellular processes. It regulates protein degradation and substrate ubiquitination. In addition, it has been shown that NEDD4 primarily functions as an oncogene in various malignancies but can also act as a tumor suppressor in certain types of tumor. In the present review, the roles of NEDD4 as an anticancer protein in various high-incidence male malignancies and the significance of NEDD4 as a potential cancer therapeutic target are discussed. In addition, the targeting of NEDD4 as a therapeutic strategy for the treatment of human malignancies is explored.

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## 1. Introduction

Cells that manage to elude central endogenous regulatory mechanisms proliferate uncontrollably, which is how cancer is defined (1). Cancers may be categorized according to the organ or tissue from whence they originated, but the molecular properties of cancer cells are increasingly being studied and understood (2). Cancer is the second greatest cause of mortality and a significant public health issue globally, despite the notable advancements in tumor detection and therapy over the past few years, as noted by the World Health Organization and American Cancer Society (3,4). The GLOBOCAN 2020 update of the global cancer burden considers cancer incidence and mortality. It predicts that there will be 19.3 million new cases of cancer worldwide (excluding non-melanoma skin cancer) and >10 million cancer deaths (excluding non-melanoma skin cancer) in 2023 (5). There were 983,160 new cases of cancer in male patients and 322,090 fatalities in the United States in 2022 (6).

In males as a representative population, lung cancer is the most common type of cancer and the leading cause of

*Correspondence to:* Dr Amjad Z. Alrosan, Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmaceutical Sciences, The Hashemite University, 15 Damascus International Road, Zarqa 13133, Jordan  
E-mail: amjadz@hu.edu.jo

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cancer-associated death, followed by prostate cancer and colorectal cancers (5,6). Carcinogenesis is the process through which healthy normal cells develop into cancer cells, where oncogenes and tumor suppressor genes have a role in the development of cancer (7). In addition to acting as nuclear transcription factors and signal transducers, oncogenes may also act as growth factors (8,9). Various oncogenes in mammals regulate proper cell differentiation and proliferation (8,9).

Along with oncogenes, tumor-suppressor genes also have a significant role in the regulation of the growth and differentiation of normal cells and prevent the development of cancer (8,9). The vast majority of tumor-suppressor genes function together to prevent the development of neoplasia in an organism. A tumor-suppressor gene must be dormant in both copies inherited from each parental cell for a cancer cell to continue to grow or survive (7). Tumor-suppressor genes are present dispersed across the human genome and are involved in the development of the diverse forms of human neoplasia (7). A single cell that has developed malignant characteristics due to cellular DNA damage is the first step in the genesis of a malignant tumor in an otherwise healthy tissue (10). However, only a relatively small number of valuable cancer biomarkers are being identified and confirmed for diagnostic and therapeutically helpful screening. Given the increasing incidence and mortality of cancer worldwide, there is a growing demand for precise biomarkers for improved detection, diagnosis, prognosis and monitoring (11,12).

Protein post-translational modifications (PTMs) have a significant impact on how proteins function and are required for virtually all biological processes in cells (13). However, PTMs and genetic alterations are substantial in the onset and development of carcinogenesis and cancer, as evidenced by the detrimental effects of several PTMs (13). Protein ubiquitination is a post-translational alteration that controls several physiological processes (14). It involves binding of ubiquitin, a highly conserved 76-amino-acid polypeptide, to lysine residues of target substrates (15,16). The functions of protein ubiquitination are listed below, with the primary role of protein ubiquitination being the eventual breakdown of proteins (17). The two principal mechanisms that control the ubiquitination of proteins and, consequently, the size of protein pools, are proteasomal and lysosomal degradation (18). According to estimates, lysosomal-mediated degradation accounts for 20% of the total degradation of ubiquitinated proteins, with the proteasome contributing 80% (19,20).

Three necessary enzymes known as E1, E2 and E3 are responsible for tagging target proteins with ubiquitin chains (21,22). The E1 enzyme is a ubiquitin-activating enzyme that uses ATP to adenylate a lysine at the C-terminus of a ubiquitin molecule (23). The ubiquitin-conjugating enzyme (E2 enzyme) then transfers active ubiquitin to a cysteine residue, forming E2-S-ubiquitin intermediates (23). An E3 ubiquitin ligase enzyme then transfers the active ubiquitin to interact with an amino (NH<sub>2</sub>) group in the lysine residue of the target protein through the C-terminal domain of the ubiquitin signal that is attached to the E2 enzyme (24). Only two E1 enzymes, ~35 E2 enzymes and >600 E3 ubiquitin ligases are encoded in the human genome and they can target different compounds in different pathways (25). Of note, the protein ubiquitination cascade's rate-limiting stage is assumed to be E3-ligase-mediated ubiquitination.

As previously established, E3-ubiquitin ligases have a crucial role in the rate-limiting stage of protein ubiquitination before directing it to the proteasome or other minor routes for degradation. According to the method by which activated ubiquitin is transferred, the E3-ubiquitin families can be divided into subfamilies. The two most essential subfamilies are known as really interesting new gene (RING)-type E3 ubiquitin ligases and homologous to E6Ap C-terminus (HECT)-domain E3 ubiquitin ligases (23,26,27). Direct ubiquitin transfer is made possible by RING E3s building bridges across the ring finger motif between E2 enzymes and the target protein (23,26-28).

HECT E3 ligases, on the other hand, have a HECT domain that joins with the E2 and forms a thioester bond with the target protein, transferring ubiquitin from the cysteine residue to the protein (29). Nearly 95% of all E3-ubiquitin ligases belong to the largest subfamily, the RING E3s. With only 30 members described thus far, the HECT-domain subfamily is substantially smaller. There are further subfamilies, such as the recently identified RING/HECT hybrid subfamily and UFD2 (or U-box) homologous proteins (30). In addition, there are three other subcategories under the HECT domain subfamily, including neural precursor cell expressed developmentally downregulated protein 4 (NEDD4), HECT and RLD domain containing E3 ubiquitin protein ligase and other residual HECTs (23,31). From yeast to humans, NEDD4 is a highly conserved HECT-domain E3 ligase subfamily (32-35). A lipid-binding N-terminal C2 domain, an auto-ubiquitination HECT ligase domain and 2-4 tryptophan-tryptophan (WW) fields are necessary for interaction with adaptors or substrates, making up its conserved structure (36-38). A total of 9 NEDD4 E3 ligases are present in the human genome and have been demonstrated to be crucial for viral budding, protein trafficking and target protein degradation (37).

NEDD4 (also known as NEDD4-1), NEDD4 like E3 ubiquitin protein ligase (NEDD4L; also known as NEDD4-2), WW domain-containing E3 ubiquitin-protein ligase 1 (WWP1), WWP2, itchy E3 ubiquitin protein ligase, SMAD-specific E3 ubiquitin-protein ligases (Smurf1), Smurf2, HECT, C2 and WW domain containing E3 ubiquitin protein ligase 1 [NEDL1 (HECW1)] and NEDL2 (HECW2) are the 9 ligases that constitute the NEDD4 family (39). Although the structures of these ligases are similar, they have different roles due to their unique WW domains, which are crucial for binding to target proteins through their proline-rich sequence domains or phospho-serine/threonine domains (38). Previous studies have indicated a strong association between NEDD4L expression and tumor progression in various malignancies, including prostate cancer, gastric cancer, hepatoma and gallbladder carcinoma (40-42). In addition, it controls several cellular functions by degrading certain proteins. It has been acknowledged that ubiquitination is a crucial stage in the development and progression of various diseases in humans (39,43). To find new therapeutic targets for a variety of illnesses, including atherosclerosis, cancer and neurodegenerative disorders (44-46), the ubiquitin proteasomal system has become increasingly studied (47). This has led to the development of treatments for various pathological conditions with proteasomal inhibitors. For instance, the proteasomal inhibitor bortezomib (Velcade®) is used to treat multiple myeloma (48).

## 2. NEDD4 and NEDD4L in cancer

**Lung cancer.** Lung cancer is one of the most globally prevalent cancers and the leading cause of cancer-related death in both men and women worldwide, given its often rapidly occurring metastasis and its aggressiveness (49,50). In recent years, there has been a sharp rise in the incidence of lung cancer and patients only have a 19% 5-year survival rate, despite the extensive research and improved understanding of the disease (51). Lung cancer is categorized into small cell lung cancer (SCLC) and non-SCLC (NSCLC). NSCLC includes three major histological subtypes: Adenocarcinoma (ADC), extensive cell lung cancer and squamous cell carcinoma (51-54). Around 85% of all lung cancer cases are of the NSCLC subtype and 60% of these are of the ADC subtype (55). NEDD4 and NEDD4L play a part in the proliferation, apoptosis, migration and medication resistance of lung cancer cells (56). In-depth research is therefore urgently required to increase the survival rate of lung cancer patients.

The role of NEDD4 in lung cancer has received increasing attention recently. It has been proposed that NEDD4 contributes to the development and spread of lung cancer tumors and is overexpressed in a sizeable fraction of NSCLCs (57). A previous study has indicated that lung cancer tissues have higher levels of NEDD4 and its silencing was linked to a reduction in lung cancer cell proliferation *in vitro* and tumor growth *in vivo* (56). NEDD4 augments the malignant features of lung epithelial cells and promotes cell proliferation, migration and invasion through phosphatase and tensin homolog (PTEN) degradation (56). The PTEN gene is a tumor suppressor that produces a lipid phosphatase and counteracts the effects of PI3K/Akt. Lung cancer cells frequently exhibit PTEN and PI3K/Akt signaling pathway loss and this is associated with malignant transformation of lung cells and resistance to chemotherapeutic drugs. In 55-74% of NSCLC cases, PTEN expression is decreased or has been lost (57). NEDD4 negatively impacts PTEN levels by polyubiquitination and proteolysis, although its impact on lung cancer has remained elusive (52,57).

It has been found that the HER receptor tyrosine kinase family member, epidermal growth factor receptor (EGFR) and NEDD4 are able to interact. This signaling system is essential for processes including lung cancer cell growth, migration, invasion and apoptosis, as well as relapse (58). In addition, NEDD4 is activated by EGFR signaling in NSCLC tumor tissues. NEDD4 knockdown significantly inhibits the migration of NSCLC cells in response to EGF and NEDD4 promotes EGF-induced cathepsin B lysosomal secretion, indicating that NEDD4 mediates a novel EGFR migration signaling pathway in lung cancer. Another study found that NEDD4 is more readily degraded when prostate transmembrane protein, androgen induced 1 (TMEAI) interacts with NEDD4 and binds to the transforming growth factor- $\beta$  (TGF- $\beta$ )-type I receptor.

NEDD4 is required to deliver TMEPAI to the lysosome (59). However, it is unclear exactly how NEDD4 affects EGFR-dependent lung cancer cell migration (58). In addition to controlling the expression of NEDD4, EGFR signaling also regulates the expression of NEDD4L (60). As a crucial player in the development of lung cancer, NEDD4L may serve as

a prognostic indicator due to its association with aggressive clinicopathological tumors and poor overall survival (60). It is recommended to use NEDD4L to build a bridge between the EGFR and the mammalian target of rapamycin (mTOR) pathways, where mTOR is another important oncogene in solid tumors, the signaling of which regulates protein synthesis, cell proliferation and survival (61). Thus, the EGFR-NEDD4L-mTOR pathway is crucial for determining the outcome of NSCLC.

NEDD4 is implicated in the control of cancer cell drug resistance, which may be a significant impediment to effective treatment. According to a study on HCC827/ER lung cells, NEDD4 may increase acquired resistance to erlotinib in NSCLC cells by suppressing the expression of PTEN (62). Furthermore, in nude mice with xenografted HCC827/ER cells, suppression of NEDD4 reduced tumor development and tumor weight (62). Another *in vitro* study revealed that NEDD4L expression was downregulated in NSCLC, where it functions as a tumor suppressor, and NEDD4L knockdown increased cell proliferation, invasion and migration (63,64). In another study, NEDD4L expression was inhibited to demonstrate the oncogenic role of microRNA (miR)-93 in lung cancer (65). miR-93 is a member of the miR-106b-25 cluster, whose expression increases in NSCLC, and upregulation of miR-93 was observed to be associated with poor survival in patients with lung cancer (65). When miR-93 directly binds to the 3'-UTR of the NEDD4L mRNA, NEDD4L expression is downregulated. Consequently, miR-93 overexpression may be a useful technique in the pathogenesis of lung cancer (65). Reduced NEDD4L accelerated TGF-induced epithelial-mesenchymal transition, decreased SMAD2/SMAD3 degradation and enhanced TGF signal transmission (63,64). Conversely, A549 cancer cells exhibited NEDD4 expression, a specific E3 ligase for serine/threonine-protein kinase (GCN2), which increases the aggressiveness of tumors (58,59). Through the action of arrestin, a GCN2-arrestin-NEDD4L axis facilitated ubiquitin-mediated GCN2 degradation and thus protects cells from cancer (58,59).

Another crucial factor in the role of NEDD4 in lung cancer is the serine/threonine kinase mitogen-activated protein kinase (MAPK) kinase kinase 5 (MEKK5), also known as apoptosis signal-regulating kinase 1 and a member of the MAPK kinase family apoptosis signal-regulating kinase (63,66). It has been shown that NEDD4 is able to interact with MEKK5 through its WW domain and overexpression and downregulation of MEKK5 had opposite effects on NEDD4 ubiquitination (63,67). This suggests that the MEKK5 and NEDD4 interaction may serve as a possible inhibitory mechanism for NEDD4 migration signaling. In addition, NEDD4 is associated with the action of nitidine chloride (NC), an antioxidant and anti-cancer phytochemical alkaloid, and the downregulation of NEDD4 increased NC-induced antitumor effects (50). Although NC targets multiple signaling pathways in different types of cancer to have a tumor-suppressing impact, its significance in lung cancer is has remained elusive (50). In addition, NEDD4L is associated with the action of dimethyl-acryl-alkannin (ALCAP2), a naturally occurring substance and traditional Chinese medicine obtained from the roots of the plant *Lithospermum erythrorhizon* (53). ALCAP2 has been shown to play a role in cell cycle arrest and

apoptosis promotion. ADC was prevented from proliferating, migrating and invading by NEDD4L-stimulated ubiquitination of  $\beta$ -catenin, which decreased cellular  $\beta$ -catenin and activated the transcription of survivin, cyclin D1 and matrix metalloproteinase-9 (53). Thus, NEDD4 and NEDD4L inhibitors may serve as novel therapeutics for treating lung cancer, since NEDD4 and NEDD4L both have critical roles in lung carcinogenesis and tumor progression.

**Bladder cancer (BCa).** According to GLOBOCAN 2020, BCa is one of the most common urogenital malignancies and accounts for 3% of all cancer diagnoses worldwide (68). Muscle-invasive BCa (MIBC) is a metastatic type of cancer with recurrence-related characteristics. Although it is possible to recover from non-MIBC (NMIBC), various NMIBC patients may exhibit recurrence of NMIBC (69). Therefore, identifying the mechanism of BCa tumorigenicity is crucial.

The suppression of PTEN expression and the activation of Notch-1 signaling has shown that overexpression of the NEDD4 protein increased RT4 BCa cell proliferation and invasion. In addition, NEDD4 inhibition suppressed Notch-1 while activating PTEN. Therefore, the downregulation of NEDD4 in BCa cells resulted in increased apoptosis, decreased cell migration and decreased cell proliferation (70,71). This emphasizes the significance of NEDD4 inhibitor research for managing human BCa. Another proposed mechanism is that NEDD4 stabilizes Kruppel-like factor 8 expression, which reduces the inhibitory effect of miR-132 on nuclear respiratory factor 1 and boosts BCa cell survival, tumor development and migratory capacity (72). Jing *et al* (73) hypothesized that NEDD4 caused BCa by upregulating PD-L1 expression, which attenuates the action of antitumor T-lymphocytes, allowing cancer cells to evade immune monitoring more readily and enhancing their capacity for proliferation and invasion. Fibroblast growth factor receptor 3 (FGFR3) activation enhanced NEDD4, which then regulated PD-L1 ubiquitination (73). Mutations that activate the FGFR3 gene are highly prevalent in BCa. Jing *et al* (73) sought to elucidate the relationship between FGFR3, NEDD4 and PD-L1 during immune surveillance. It was found that when FGFR3 was activated, PD-L1 was downregulated in BCa cells and FGFR3 phosphorylated the E3 ubiquitin ligase NEDD4. This accelerated NEDD4 ubiquitination and degradation, thereby decreasing the amount of PD-L1 present at the cell membrane. NEDD4 activity is also required for FGFR3 to regulate the stability of PD-L1, and the stabilizing effect of FGFR3 on PD-L1 was lost when NEDD4 was silenced or inhibited, resulting in increased PD-L1 levels (73). Thus, NEDD4 is required for FGFR3 to modulate the expression of PD-L1.

Furthermore, NEDD4L has a tumor-suppressing function; downregulation of NEDD4L is observed in clear-cell renal cell carcinoma (ccRCC), where it may have an anticancer effect by inhibiting TGF1 signaling (74). The modulation of tumor energy metabolism is another proposed anticancer mechanism of NEDD4L in ccRCC (74).

**Prostate cancer.** Prostate cancer is the second leading cause of cancer-associated male deaths worldwide (5). Given the improved therapeutic options and early detection of prostate cancer utilizing prostate-specific antigen testing, the 5-year

survival rate of patients with prostate cancer has increased significantly (74-77). The three main types of treatment currently available for prostate cancer are surgery, radiation and hormonal ablation therapy (78). However, androgen deprivation therapy resistance has led to the development of metastatic castrate-resistant prostate cancer, which has resulted in poor survival rates among patients with prostate cancer (79,80). Consequently, identifying novel therapeutic methods to treat prostate cancer is essential.

Numerous studies have supported the carcinogenic function of NEDD4 and its overexpression in prostate cancer and other human malignancies (75,81). Of note, the fact that NEDD4 overexpression promotes cell growth, migration and invasion while NEDD4 downregulation inhibits cell growth and motility of prostate cancer cells supports the notion that NEDD4 functions as an oncoprotein in this disease (75). It has been found that the downregulation of androgenic receptors and PTEN causes NEDD4 to have an oncogenic effect (82). As a result, NEDD4 may be targeted for the treatment of prostate cancer using a variety of inhibitors, including natural substances such as diosgenin, a potential NEDD4 inhibitor in prostate cancer cells, by inhibiting cell proliferation (83). In addition, aggressive prostate tumors have lower levels of NEDD4L than benign prostatic hyperplasia (75).

**Colorectal cancer.** Colorectal cancer is the third most common type of cancer worldwide and one of the most common malignancies in both men and women (84). Colon cancer affects 1.2 million individuals worldwide and accounts for >600,000 deaths annually (85). Both hereditary and environmental factors have a significant impact on the genesis of colorectal cancer (86). Compared to other types of cancer, the etiology of colorectal cancer involves genetic and epigenetic changes resulting in tumor cell growth (87). Even though 80% of patients with colon cancer are diagnosed at an early stage, the high mortality and recurrence rates in those with advanced-stage colorectal cancer still pose a challenge for scientists and clinicians (88). It should be emphasized that surgery and chemotherapy are the primary methods of treatment for colon cancer (89). Despite the advances in colon cancer treatment over the past few years, which have included the adoption of cutting-edge drugs, such as immunotherapeutics and targeted therapies, the prognosis for the disease remains bleak (90). Thus, there is an urgent need to develop novel individualized medications.

There are several hypotheses explaining how NEDD4 and colon cancer are related. In 80% of colorectal cancers, NEDD4 is present and induces the ubiquitination of PTEN, which results in the degradation of PTEN and thus increased tumor growth (91). PTEN serves as an essential negative regulator of the PI3K/AKT signaling pathway and suppresses AKT activation by dephosphorylating PIP3 (91). Phosphoinositide 3-kinase (PI3K) is a protein kinase that promotes cell development by phosphorylating PIP2 to create PIP3 by activating receptor tyrosine kinases (91). In colorectal cancer, PTEN is frequently deleted, changed, or even hypermethylated, which results in the PI3K/AKT signaling pathway becoming activated (91). One study, which used HCT-15 and LoVo colon cancer cells, revealed that PTEN and PI3K/AKT signaling was not required for NEDD4 to increase colon cancer cell growth (91). In their investigation into the relationship between NEDD4 and colon cancer, it was established that NEDD4/forkhead box A1 (FOXA1)/miR-340-5p/activating

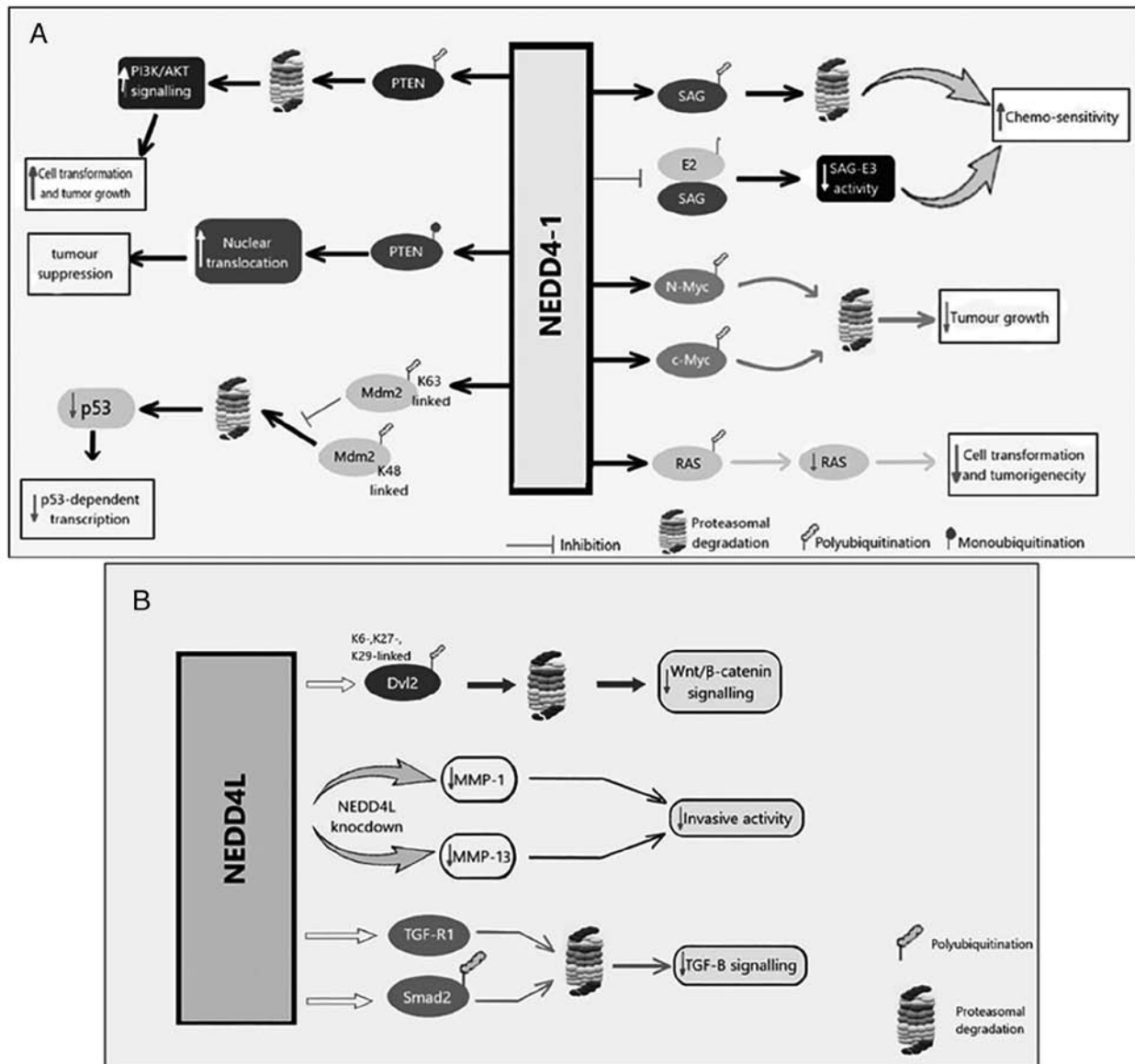


Figure 1. Molecular and signaling pathways of NEDD4-1 and NEDD4L in tumor development and drug resistance (93). (A) NEDD4-1 promotes the proteasomal degradation of PTEN, thereby enhancing PI3K/AKT signalling and tumor development (93). In addition, NEDD4-1 can monoubiquitinate PTEN, which facilitates PTEN nuclear translocation, possibly protects PTEN from degradation and boosts the tumor-suppressive effects of PTEN (93). By interfering with RAS, NEDD4-1 has an essential function in normal cells, inhibiting the transformation and tumorigenicity (93). By increasing Mdm2-mediated K63-linked polyubiquitination, NEDD4-1 inhibits Mdm2 autoubiquitination and reduces p53-dependent transcription (93). NEDD4-1 also enhances chemosensitivity by inhibiting SAG, another E3, by promoting its degradation and preventing its binding to ubiquitin-bound E2. Oncoproteins n-Myc and c-Myc are also destabilized by the tumor-suppressing NEDD4-1. (B) NEDD4L downregulates TGF signaling by ubiquitinating TGF-β-R1 and Smad2 and directing them toward degradation. Depletion of NEDD4L can decrease MMP-1 and MMP-13 levels and, consequently, the invasiveness of gallbladder cancer (93). Negative regulation of Wnt/β-catenin signaling is observed when NEDD4L promotes the K6, K27 and K29-linked polyubiquitination of Dvl2, resulting in its degradation (93). PTEN, phosphatase and tensin homolog; NEDD4-1, neural precursor cell expressed developmentally downregulated protein 4; NEDD4L, NEDD4-like E3 ubiquitin protein ligase; TGF-β-R1, transforming growth factor-β-receptor 1; SAG, sensitive to apoptosis; Dvl2, dishevelled segment polarity protein 2.

transcription factor-1 (ATF1) has a novel function in the emergence of colon cancer. FOXA1 is known to be necessary for the growth and development of specific endoderm-derived organs, but its significance in the genesis of cancer remains unclear. FOXA1 may, however, contribute to the growth of cancer and the repression of critical cellular functions (92,93). They proposed that NEDD4 resulted in the ubiquitination and degradation of FOXA1, which alters the expression of miR-340-5p and ATF1 and inhibits the progression of colon cancer. Thus, this may shed light on the pathophysiology of colon cancer and aid in creating novel gene-based treatments.

N-myc downstream regulated 1 (NDRG1) was down-regulated in CRC tissues, and both *in vitro* and *in vivo* studies revealed a beneficial relationship between NDRG1 and p21 (94). Zhang *et al* (94) proposed that E3 ligase NEDD4 may directly bind with and degrade p21, a cyclin-dependent kinase inhibitor; however, NDRG1 could oppose the NEDD4-mediated ubiquitylation of p21, increasing the effective p21 expression and thus reducing tumor growth. Although NDRG1 is a cytoplasmic and nuclear protein, it has been discovered to be intricately involved in cell adhesion, differentiation, tumor growth and metastasis. Furthermore, it is involved in autophagy and cell

Table I. Clinical studies on the regulation of NEDD4 in lung cancer and CRC.

A, Lung cancer		
Tissue type	NEDD4/NEDD4L expression levels	(Refs.)
NSCLC	NEDD4 high	(52)
Lung adenocarcinoma	NEDD4 high	(54)
NSCLC	NEDD4L low	(101)
B, Colorectal cancer		
Tissue type	NEDD4/NEDD4L expression levels	(Refs.)
CRC	NEDD4 high	(102,103)
CRC	NEDD4 high and NEDD4L low	(95)

NEDD4, neural precursor cell expressed developmentally downregulated protein 4; NEDD4L, NEDD4-like E3 ubiquitin protein ligase; CRC, colorectal cancer; NSCLC, non-small cell lung cancer.

cycle regulation, as it has been shown to cause cancer cell cycle arrest at G0/G1 (94). In addition, NDRG1 was associated with improved survival rates in several malignancies, including breast, colon, prostate and pancreatic cancer (94). Thus, this may be a target mechanism for treating colorectal cancer.

Lu *et al* (95) also investigated the relationship between NEDD4 and the WNT signaling pathway, which has various roles in several physiological and cellular processes, including cellular proliferation, fate and embryonic development. For instance, it has been demonstrated that NEDD4 blocks the transcription factors lymphoid enhancer binding factor 1 and YY1 to at least partially limit colonic WNT signaling and tumor growth (95).

Tanksley *et al* (96) reported that NEDD4L was considerably downregulated, whereas NEDD4 was significantly upregulated in all stages of colorectal cancer. According to the hypothesized mechanism of action, NEDD4L acted as a tumor suppressor in colorectal cancer by inhibiting WNT signaling at or downstream of  $\beta$ -catenin (96). Unexpectedly, patients with high NEDD4L expression have been demonstrated to exhibit prolonged disease-specific survival. However, NEDD4L was discovered to be highly upregulated in colon cancer (91).

Another study by Eide *et al* (91) linking NEDD4 to colon cancer did not focus on how NEDD4 affected signaling mechanisms but instead showed that NEDD4 has a significant role in regulating the actin cytoskeleton in colon cancer cells. It was observed that the actin cytoskeleton and changes in cell shape were brought about by NEDD4 knockdown (91). Considering all available research, more work is necessary to fully determine the role of NEDD4 in CRC.

Fig. 1 illustrates the general molecular and signaling pathways of NEDD4-1 and NEDD4L in tumor development and drug resistance.

*Clinical studies on the regulation of NEDD4 and NEDD4L in lung and colorectal cancers.* In preclinical studies, targeting NEDD4 and NEDD4L as a method of cancer treatment demonstrated promise. NEDD4 and NEDD4L may function as therapeutic targets for the treatment of various types of

cancer as well as a biomarker for poor prognosis (73,97-99). NEDD4 may function as a tumor suppressor and an oncogene, and NEDD4L may also function as a tumor suppressor and an oncogene, in both cases depending on the type of cancer being assessed (97-102), necessitating the use of NEDD4 and/or NEDD4L inhibitors or activators in cancer therapy.

It was discovered that NEDD4 is an oncogene as it inhibits PTEN, a known tumor suppressor; thus, PTEN levels are decreased and NEDD4 levels are elevated in a variety of human cancer cell lines (100). PTEN is a phosphatase that inhibits the PI3K/Akt signaling pathway, which is essential for cancer cell survival, to prevent the development of tumors by cancer cells. It has been demonstrated that NEDD4 is a PTEN-specific E3 ligase, which decreases PTEN protein levels, and thus increases Akt signaling. Therefore, NEDD4 has been suggested as a potential oncoprotein and tumor suppressor.

In various cancer models, inhibiting NEDD4 has been shown to reduce tumor growth and make cancer cells more responsive to therapy (97). Targeting NEDD4 can be accomplished by a variety of mechanisms. These include using small chemical inhibitors and RNA interference technology (101). To prevent the degradation of tumor suppressor proteins or to interfere with the activation of oncogenic pathways, small molecule inhibitors may be developed to bind to NEDD4 and limit its activity.

Although numerous preclinical studies indicate that the NEDD4 protein possesses both oncogenic and antitumor properties, only a small number of clinical studies support this assertion. These clinical studies (52,54,101-103), summarized in Table I, demonstrate that the NEDD4 and NEDD4L proteins can be potential therapeutic targets for preventing and treating lung and colorectal cancer. There are currently no clinical outcomes for prostate and BCa, and additional clinical research and trials are required.

### 3. Conclusions and future perspective

It is evident from combining studies that NEDD4 and NEDD4L ligases are essential to the signaling pathways



that enhance the development of various types of cancer. However, their importance in certain types of cancers remains to be determined. In most cancer types, both of NEDD4 and NEDD4L slow carcinogenesis by increasing the ubiquitination and degradation of their substrates, which play vital oncogenic and tumor-suppressing roles in a range of malignancies. Given their functions in carcinogenesis, NEDD4 and NEDD4L are therefore potential targets for developing novel treatments for the management of anti-cancer agents. Treatment strategies that interfere with NEDD4 and NEDD4L interacting with their substrates with no/few adverse effects may be preferable to those that directly target NEDD4 and NEDD4L activity, given the wide range of targets and the duality of their roles. However, additional research is required to fully determine the significance of NEDD4 in carcinogenesis.

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AZA designed and performed the narrative review, and drafted and proofread the article critically. KA helped in writing the section on colorectal cancer and critically revised the manuscript. GBH helped in writing the conclusion section and revised the article critically for intellectual content. RAS contributed to writing the section on lung cancer. Rawan AD helped in writing the section on BCa. MO helped in writing the section on prostate cancer. AA and YAE assisted in reviewing the manuscript critically. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

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### Patient consent for publication

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### Competing interests

The authors declare that they have no competing interests.

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