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

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

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

Received February 18, 2023; Accepted July 7, 2023

DOI: 10.3892/mco.2023.2664

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.

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

Key words: cancer, E3 ligase, neural precursor cell expressed developmentally downregulated protein 4, post-translational modifications, ubiquitination

Contents

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

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_2) 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 cystine 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-β (TGF-β)-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 β-catenin, which decreased cellular β-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 tumorgenicity 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 PDL-1 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

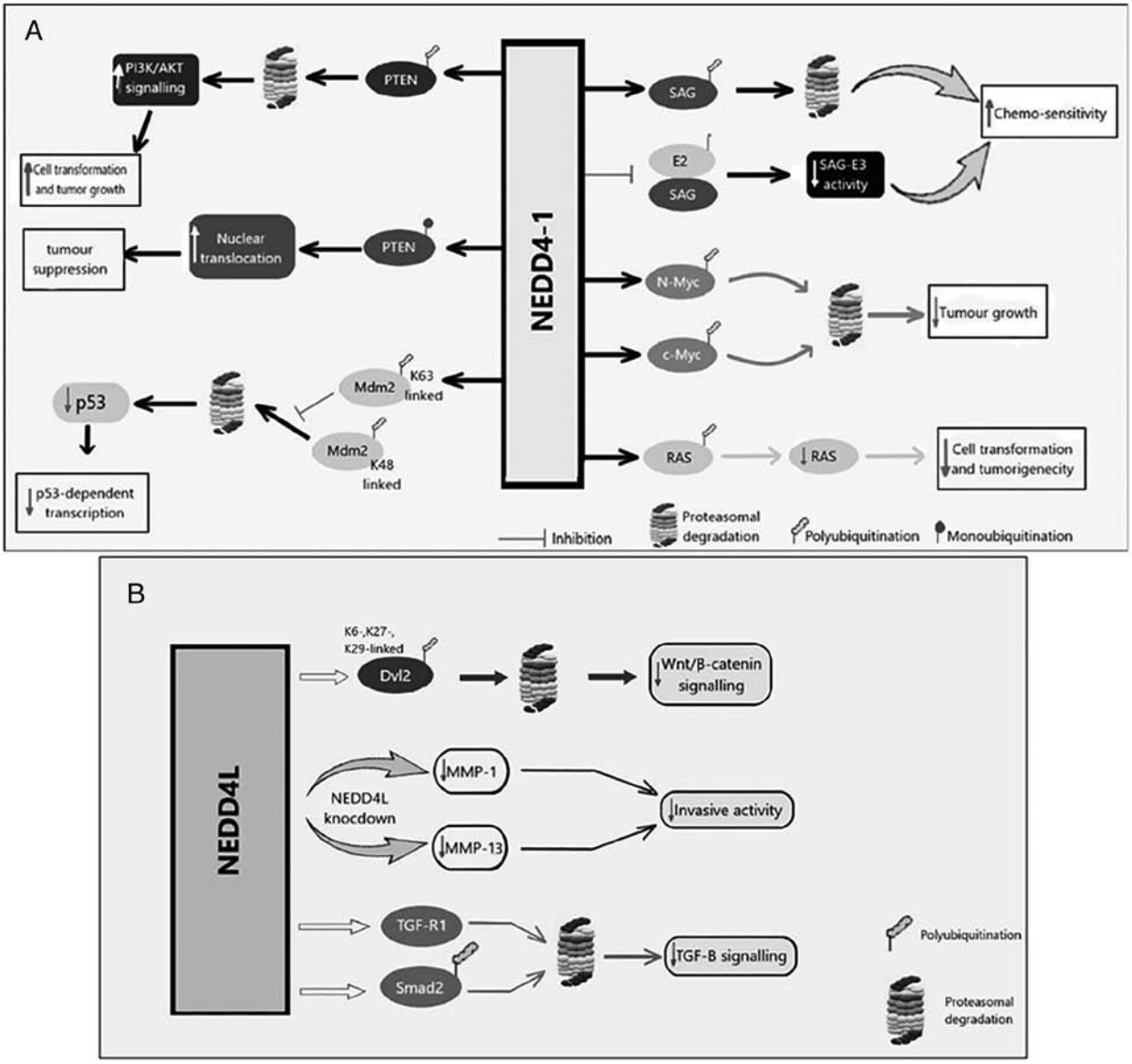

Figure 1. Molecular and signaling pathways of NEDD4-1 and NEDD4L in tumor development and drug resistance (93). (A) NEDD4-1 promotes the proteasomal degradation of PTEN, thereby enhancing PI3K/AKT signaling and tumor development (93). In addition, NEDD4-1 can monoubiquitinate PTEN, which facilitates 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 downregulated 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 β-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 NEED4L 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.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

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.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Cooper GM: The Cell: A Molecular Approach. 2nd edition. Sunderland (MA): Sinauer Associates. The Development and Causes of Cancer. https://www.ncbi.nlm.nih.gov/books/NBK9963/. 2000.
2. Hanahan D: Hallmarks of cancer: New dimensions. Cancer Discov 12: 31-46, 2022.
3. American Cancer Society. Cancer Statistics Center. http://cancerstatisticscenter.cancer.org. Accessed Dec 25, 2022.
4. World Health Organization (WHO): Editorial Style Manual WHO, Geneva, p83-91, 1993.
5. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
6. Siegel RL, Miller KD, Fuchs HE and Jemal A: Cancer statistics, 2022. CA Cancer J Clin 72: 7-33, 2022.
7. Bertram JS: The molecular biology of cancer. Mol Aspects Med 21: 167-223, 2000.
8. Kontomanolis EN, Koutras A, Syllaios A, Schizas D, Mastoraki A, Garmpis N, Diakosavvas M, Angelou K, Tsatsaris G, Pagkalos A, *et al*: Role of oncogenes and tumor-suppressor genes in carcinogenesis: A review. Anticancer Res 40: 6009-6015, 2020.
9. Welti J, Loges S, Dimmeler S and Carmeliet P: Recent molecular discoveries in angiogenesis and antiangiogenic therapies in cancer. J Clin Invest 123: 3190-3200, 2013.
10. Hanahan D and Weinberg RA: Hallmarks of cancer: The next generation. Cell 144: 646-674, 2011.
11. Hanahan D and Weinberg RA: The hallmarks of cancer. Cell 100: 57-70, 2000.
12. Kamali H, Golmohammadzadeh S, Zare H, Nosrati R, Fereidouni M and Safarpour H: The recent advancements in the early detection of cancer biomarkers by DNAzyme-assisted aptasensors. J Nanobiotechnology 20: 438, 2022.
13. Pan S and Chen R: Pathological implication of protein post-translational modifications in cancer. Mol Aspects Med 86: 101097, 2022.
14. Hershko A and Ciechanover A: The ubiquitin system. Annu Rev Biochem 67: 425-479, 1998.
15. Weissman AM: Themes and variations on ubiquitylation. Nat Rev Mol Cell Biol 2: 169-178, 2001.
16. Komander D and Rape M: The ubiquitin code. Annu Rev Biochem 81: 203-229, 2012.
17. Salas-Lloret D and González-Prieto R: Insights in post-translational modifications: Ubiquitin and SUMO. Int J Mol Sci 23: 3281, 2022.
18. Liebl MP and Hoppe T: It's all about talking: Two-way communication between proteasomal and lysosomal degradation pathways via ubiquitin. Am J Physiol Cell Physiol 311: C166-C178, 2016.
19. Tu Y, Chen C, Pan J, Xu J, Zhou ZG and Wang CY: The Ubiquitin Proteasome Pathway (UPP) in the regulation of cell cycle control and DNA damage repair and its implication in tumorigenesis. Int J Clin Exp Pathol 5: 726-738, 2012.
20. Klionsky DJ and Schulman BA: Dynamic regulation of macroautophagy by distinctive ubiquitin-like proteins. Nat Struct Mol Biol 21: 336-345, 2014.
21. Kerscher O, Felberbaum R and Hochstrasser M: Modification of proteins by ubiquitin and ubiquitin-like proteins. Annu Rev Cell Dev Biol 22: 159-180, 2006.
22. Ciechanover A and Kwon YT: Degradation of misfolded proteins in neurodegenerative diseases: Therapeutic targets and strategies. Exp Mol Med 47: e147, 2015.
23. Berndsen CE and Wolberger C: New insights into ubiquitin E3 ligase mechanism. Nat Struct Mol Biol 21: 301-307, 2014.
24. Kravtsova-Ivantsiv Y and Ciechanover A: Non-canonical ubiquitin-based signals for proteasomal degradation. J Cell Sci 125(Pt 3): 539-548, 2012.
25. Buetow L and Huang DT: Structural insights into the catalysis and regulation of E3 ubiquitin ligases. Nat Rev Mol Cell Biol 17: 626-642, 2016.
26. Rotin D and Kumar S: Physiological functions of the HECT family of ubiquitin ligases. Nat Rev Mol Cell Biol 10: 398-409, 2009.
27. Metzger MB, Hristova VA and Weissman AM: HECT and RING finger families of E3 ubiquitin ligases at a glance. J Cell Sci 125(Pt 3): 531-537, 2012.
28. Joazeiro CA and Weissman AM: RING finger proteins: Mediators of ubiquitin ligase activity. Cell 102: 549-552, 2000.
29. Bernassola F, Karin M, Ciechanover A and Melino G: The HECT family of E3 ubiquitin ligases: Multiple players in cancer development. Cancer Cell 14: 10-21, 2008.
30. Dove KK, Stieglitz B, Duncan ED, Rittinger K and Klevit RE: Molecular insights into RBR E3 ligase ubiquitin transfer mechanisms. EMBO Rep 17: 1221-1235, 2016.
31. Li W and Ye Y: Polyubiquitin chains: Functions, structures, and mechanisms. Cell Mol Life Sci 65: 2397-2406, 2008.

32. Dinudom A, Harvey KF, Komwatana P, Young JA, Kumar S and Cook DI: Nedd4 mediates control of an epithelial Na+ channel in salivary duct cells by cytosolic Na+. Proc Natl Acad Sci USA 95: 7169-7173, 1998.
33. Goulet CC, Volk KA, Adams CM, Prince LS, Stokes JB and Snyder PM: Inhibition of the epithelial Na+ channel by interaction of Nedd4 with a PY motif deleted in Liddle's syndrome. J Biol Chem 273: 30012-30017, 1998.
34. Harvey KF, Dinudom A, Komwatana P, Jolliffe CN, Day ML, Parasivam G, Cook DI and Kumar S: All three WW domains of murine Nedd4 are involved in the regulation of epithelial sodium channels by intracellular Na+. J Biol Chem 274: 12525-12530, 1999.
35. Harvey KF, Dinudom A, Cook DI and Kumar S: The Nedd4-like protein KIAA0439 is a potential regulator of the epithelial sodium channel. J Biol Chem 276: 8597-8601, 2001.
36. Kanelis V, Farrow NA, Kay LE, Rotin D and Forman-Kay JD: NMR studies of tandem WW domains of Nedd4 in complex with a PY motif-containing region of the epithelial sodium channel. Biochem Cell Biol 76: 341-350, 1998.
37. Ingham RJ, Gish G and Pawson T: The Nedd4 family of E3 ubiquitin ligases: Functional diversity within a common modular architecture. Oncogene 23: 1972-1984, 2004.
38. Dodson EJ, Fishbain-Yoskovitz V, Rotem-Bamberger S and Schueler-Furman O: Versatile communication strategies among tandem WW domain repeats. Exp Biol Med (Maywood) 240: 351-360, 2015.
39. Scheffner M and Kumar S: Mammalian HECT ubiquitin-protein ligases: Biological and pathophysiological aspects. Biochim Biophys Acta 1843: 61-74, 2014.
40. Lee IH, Dinudom A, Sanchez-Perez A, Kumar S and Cook DI: Akt mediates the effect of insulin on epithelial sodium channels by inhibiting Nedd4-2. J Biol Chem 282: 29866-29873, 2007.
41. Goel P, Manning JA and Kumar S: NEDD4-2 (NEDD4L): The ubiquitin ligase for multiple membrane proteins. Gene 557: 1-10, 2015.
42. Lu X, Xu H, Xu J, Lu S, You S, Huang X, Zhang N and Zhang L: The regulatory roles of the E3 ubiquitin ligase NEDD4 family in DNA damage response. Front Physiol 13: 968927, 2022.
43. Chaugule VK and Walden H: Specificity and disease in the ubiquitin system. Biochem Soc Trans 44: 212-227, 2016.
44. Herrmann J, Soares SM, Lerman LO and Lerman A: Potential role of the ubiquitin-proteasome system in atherosclerosis: Aspects of a protein quality disease. J Am Coll Cardiol 51: 2003-2010, 2008.
45. Potjewyd FM and Axtman AD: Exploration of Aberrant E3 ligases implicated in Alzheimer's disease and development of chemical tools to modulate their function. Front Cell Neurosci 15: 768655, 2021.
46. Sun T, Liu Z and Yang Q: The role of ubiquitination and deubiquitination in cancer metabolism. Mol Cancer 19: 146, 2020.
47. Petroski MD: The ubiquitin system, disease, and drug discovery. BMC Biochem 9 (Suppl 1): S7, 2008.
48. Orlowski RZ and Kuhn DJ: Proteasome inhibitors in cancer therapy: Lessons from the first decade. Clin Cancer Res 14: 1649-1657, 2008.
49. Thandra KC, Barsouk A, Saginala K, Aluru JS and Barsouk A: Epidemiology of lung cancer. Contemp Oncol (Pozn) 25: 45-52, 2021.
50. Zhang J, Cao R, Lian C, Cao T, Shi Y, Ma J, Wang P and Xia J: Nitidine chloride suppresses NEDD4 expression in lung cancer cells. Aging (Albany NY) 13: 782-793, 2020.
51. Rajdev K, Siddiqui AH, Ibrahim U, Patibandla P, Khan T and El-Sayegh D: An unusually aggressive large cell carcinoma of the lung: Undiagnosed until autopsy. Cureus 10: e2202, 2018.
52. Amodio N, Scrima M, Palaia L, Salman AN, Quintiero A, Franco R, Botti G, Pirozzi P, Rocco G, De Rosa N and Viglietto G: Oncogenic role of the E3 ubiquitin ligase NEDD4-1, a PTEN negative regulator, in non-small-cell lung carcinomas. Am J Pathol 177: 2622-2634, 2010.
53. Zhang W, Zhang R, Zeng Y, Li Y, Chen Y, Zhou J, Zhang Y, Wang A, Zhu J, Liu Z, *et al*: ALCAP2 inhibits lung adenocarcinoma cell proliferation, migration and invasion via the ubiquitination of β-catenin by upregulating the E3 ligase NEDD4L. Cell Death Dis 12: 755, 2021.
54. Song YH, Zhang CQ, Chen FF and Lin XY: Upregulation of neural precursor cell expressed developmentally downregulated 4-1 is associated with poor prognosis and chemoresistance in lung adenocarcinoma. Chin Med J (Engl) 131: 16-24, 2018.
55. Chen Z, Fillmore CM, Hammerman PS, Kim CF and Wong KK: Non-small-cell lung cancers: A heterogeneous set of diseases. Nat Rev Cancer 14: 535-546, 2014.
56. He H, Huang C, Chen Z, Huang H, Wang X and Chen J: An outlined review for the role of Nedd4-1 and Nedd4-2 in lung disorders. Biomed Pharmacother 125: 109983, 2020.
57. Georgescu MM: PTEN tumor suppressor network in PI3K-Akt pathway control. Genes Cancer 1: 1170-1177, 2010.
58. Wei C, Lin M, Jinjun B, Su F, Dan C, Yan C, Jie Y, Jin Z, Zi-Chun H and Wu Y: Involvement of general control nonderepressible kinase 2 in cancer cell apoptosis by posttranslational mechanisms. Mol Biol Cell 26: 1044-1057, 2015.
59. Shao G, Wang R, Sun A, Wei J, Peng K, Dai Q, Yang W and Lin Q: The E3 ubiquitin ligase NEDD4 mediates cell migration signaling of EGFR in lung cancer cells. Mol Cancer 17: 24, 2018.
60. Sakashita H, Inoue H, Akamine S, Ishida T, Inase N, Shirao K, Mori M and Mimori K: Identification of the NEDD4L gene as a prognostic marker by integrated microarray analysis of copy number and gene expression profiling in non-small cell lung cancer. Ann Surg Oncol 20 (Suppl 3): S590-S598, 2013.
61. Li G, Song Z, Wu C, Li X, Zhao L, Tong B, Guo Z, Sun M, Zhao J, Zhang H, *et al*: Downregulation of NEDD4L by EGFR signaling promotes the development of lung adenocarcinoma. J Transl Med 20: 47, 2022.
62. Li R, Hu Z, Sun SY, Chen ZG, Owonikoko TK, Sica GL, Ramalingam SS, Curran WJ, Khuri FR and Deng X: Niclosamide overcomes acquired resistance to erlotinib through suppression of STAT3 in non-small cell lung cancer. Mol Cancer Ther 12: 2200-2212, 2013.
63. Xie S, Xia L, Song Y, Liu H, Wang ZW and Zhu X: Insights into the biological role of NEDD4L E3 ubiquitin ligase in human cancers. Front Oncol 11: 774648, 2021.
64. Lai XN, Li J, Tang LB, Chen WT, Zhang L and Xiong LX: MiRNAs and LncRNAs: Dual roles in TGF-β signaling-regulated metastasis in lung cancer. Int J Mol Sci 21: 1193, 2020.
65. Qu MH, Han C, Srivastava AK, Cui T, Zou N, Gao ZQ and Wang QE: miR-93 promotes TGF-β-induced epithelial-to-mesenchymal transition through downregulation of NEDD4L in lung cancer cells. Tumour Biol 37: 5645-5651, 2016.
66. Bai X, Jing L, Li Y, Li Y, Luo S, Wang S, Zhou J, Liu Z and Diao A: TMEPAI inhibits TGF-β signaling by promoting lysosome degradation of TGF-β receptor and contributes to lung cancer development. Cell Signal 26: 2030-2039, 2014.
67. Sun A, Zhu J, Xia S, Li Y, Wu T, Shao G, Yang W and Lin Q: MEKK5 interacts with and negatively regulates the E3 ubiquitin ligase NEDD4 for mediating lung cancer cell migration. Life (Basel) 11: 1153, 2021.
68. Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA and Barsouk A: Epidemiology of bladder cancer. Med Sci (Basel) 8: 15, 2020.
69. Sanli O, Dobruch J, Knowles MA, Burger M, Alemozaffar M, Nielsen ME and Lotan Y: Bladder cancer. Nat Rev Dis Primers 3: 17022, 2017.
70. Wen W, Li J, Wang L, Xing Y, Li X, Ruan H, Xi X, Xiong J and Kuang R: Inhibition of NEDD4 inhibits cell growth and invasion and induces cell apoptosis in bladder cancer cells. Cell Cycle 16: 1509-1514, 2017.
71. Wang X, Trotman LC, Koppie T, Alimonti A, Chen Z, Gao Z, Wang J, Erdjument-Bromage H, Tempst P, Cordon-Cardo C, *et al*: NEDD4-1 is a proto-oncogenic ubiquitin ligase for PTEN. Cell 128: 129-139, 2007.
72. Mao M, Yang L, Hu J, Liu B, Zhang X, Liu Y, Wang P and Li H: Oncogenic E3 ubiquitin ligase NEDD4 binds to KLF8 and regulates the microRNA-132/NRF2 axis in bladder cancer. Exp Mol Med 54: 47-60, 2022.
73. Jing W, Wang G, Cui Z, Xiong G, Jiang X, Li Y, Li W, Han B, Chen S and Shi B: FGFR3 Destabilizes PD-L1 via NEDD4 to Control T-cell-mediated bladder cancer immune surveillance. Cancer Res 82: 114-129, 2022.
74. Zhao H, Zhang J, Fu X, Mao D, Qi X, Liang S, Meng G, Song Z, Yang R, Guo Z, *et al*: Integrated bioinformatics analysis of the NEDD4 family reveals a prognostic value of *NEDD4L* in clear-cell renal cell cancer. PeerJ 9: e11880, 2021.
75. Hu XY, Xu YM, Fu Q, Yu JJ and Huang J: Nedd4L expression is downregulated in prostate cancer compared to benign prostatic hyperplasia. Eur J Surg Oncol 35: 527-531, 2009.
76. Negoita S, Feuer EJ, Mariotto A, Cronin KA, Petkov VI, Hussey SK, Benard V, Henley SJ, Anderson RN, Fedewa S, *et al*: Annual report to the nation on the status of cancer, part II: Recent changes in prostate cancer trends and disease characteristics. Cancer 124: 2801-2814, 2018.

77. Butler SS, Muralidhar V, Zhao SG, Sanford NN, Franco I, Fullerton ZH, Chavez J, D'Amico AV, Feng FY, Rebbeck TR, *et al*: Prostate cancer incidence across stage, NCCN risk groups, and age before and after USPSTF Grade D recommendations against prostate-specific antigen screening in 2012. Cancer 126: 717-724, 2020.
78. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, Stein KD, Alteri R and Jemal A: Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 66: 271-289, 2016.
79. McCrea E, Sissung TM, Price DK, Chau CH and Figg WD: Androgen receptor variation affects prostate cancer progression and drug resistance. Pharmacol Res 114: 152-162, 2016.
80. Zhang Y, Duan H, Zhao H, Qi L, Liu Y, Zhang Z, Liu C, Chen L, Jin M, Guan Y, *et al*: Development and evaluation of a PSMA-targeted nanosystem co-packaging docetaxel and androgen receptor siRNA for castration-resistant prostate cancer treatment. Pharmaceutics 14: 964, 2022.
81. Zhao Y, Li J, Chen J, Ye M and Jin X: Functional roles of E3 ubiquitin ligases in prostate cancer. J Mol Med (Berl) 100: 1125-1144, 2022.
82. Li H, Xu LL, Masuda K, Raymundo E, McLeod DG, Dobi A and Srivastava S: A feedback loop between the androgen receptor and a NEDD4-binding protein, PMEPA1, in prostate cancer cells. J Biol Chem 283: 28988-28995, 2008.
83. Zhang J, Xie JJ, Zhou SJ, Chen J, Hu Q, Pu JX and Lu JL: Diosgenin inhibits the expression of NEDD4 in prostate cancer cells. Am J Transl Res 11: 3461-3471, 2019.
84. Kim SE, Paik HY, Yoon H, Lee JE, Kim N and Sung MK: Sex- and gender-specific disparities in colorectal cancer risk. World J Gastroenterol 21: 5167-5175, 2015.
85. Xi Y and Xu P: Global colorectal cancer burden in 2020 and projections to 2040. Transl Oncol 14: 101174, 2021.
86. Rattray NJW, Charkoftaki G, Rattray Z, Hansen JE, Vasiliou V and Johnson CH: Environmental influences in the etiology of colorectal cancer: The premise of metabolomics. Curr Pharmacol Rep 3: 114-125, 2017.
87. Parmar S and Easwaran H: Genetic and epigenetic dependencies in colorectal cancer development. Gastroenterol Rep (Oxf) 10: goac035, 2022.
88. Hsieh MH, Kung PT, Kuo WY, Ke TW and Tsai WC: Recurrence, death risk, and related factors in patients with stage 0 colorectal cancer: A nationwide population-based study. Medicine (Baltimore) 99: e21688, 2020.
89. Mishra J, Drummond J, Quazi SH, Karanki SS, Shaw JJ, Chen B and Kumar N: Prospective of colon cancer treatments and scope for combinatorial approach to enhanced cancer cell apoptosis. Crit Rev Oncol Hematol 86: 232-250, 2013.
90. Golshani G and Zhang Y: Advances in immunotherapy for colorectal cancer: A review. Therap Adv Gastroenterol 13: 1756284820917527, 2020.
91. Eide PW, Cekaite L, Danielsen SA, Eilertsen IA, Kjenseth A, Fykerud TA, Ågesen TH, Bruun J, Rivedal E, Lothe RA and Leithe E: NEDD4 is overexpressed in colorectal cancer and promotes colonic cell growth independently of the PI3K/PTEN/AKT pathway. Cell Signal 25: 12-18, 2013.
92. Aikemu B, Shao Y, Yang G, Ma J, Zhang S, Yang X, Hong H, Yesseyeva G, Huang L, Jia H, *et al*: NDRG1 regulates Filopodia-induced Colorectal Cancer invasiveness via modulating CDC42 activity. Int J Biol Sci 17: 1716-1730, 2021.
93. Zou X, Levy-Cohen G and Blank M: Molecular functions of NEDD4 E3 ubiquitin ligases in cancer. Biochim Biophys Acta 1856: 91-106, 2015.
94. Zhang S, Yu C, Yang X, Hong H, Lu J, Hu W, Hao X, Li S, Aikemu B, Yang G, *et al*: N-myc downstream-regulated gene 1 inhibits the proliferation of colorectal cancer through emulative antagonizing NEDD4-mediated ubiquitylation of p21. J Exp Clin Cancer Res 38: 490, 2019.
95. Lu C, Thoeni C, Connor A, Kawabe H, Gallinger S and Rotin D: Intestinal knockout of Nedd4 enhances growth of Apc^{min} tumors. Oncogene 35: 5839-5849, 2016.
96. Tanksley JP, Chen X and Coffey RJ: NEDD4L is downregulated in colorectal cancer and inhibits canonical WNT signaling. PLoS One 8: e81514, 2013.
97. Liu J, Shaik S, Dai X, Wu Q, Zhou X, Wang Z and Wei W: Targeting the ubiquitin pathway for cancer treatment. Biochim Biophys Acta 1855: 50-60, 2015.
98. Wang K, Yu Y, Wang W, Jiang Y, Li Y, Jiang X, Qiao Y, Chen L, Zhao X, Liu J, *et al*: Targeting the E3 ligase NEDD4 as a novel therapeutic strategy for IGF1 signal pathway-driven gastric cancer. Oncogene 42: 1072-1087, 2023.
99. Ahn Y, Hwang CY, Lee SR, Kwon KS and Lee C: The tumour suppressor PTEN mediates a negative regulation of the E3 ubiquitin-protein ligase Nedd4. Biochem J 412: 331-338, 2008.
100. Ao N, Chen Q and Liu G: The small molecules targeting ubiquitin-proteasome system for cancer therapy. Comb Chem High Throughput Screen 20: 403-413, 2017.
101. Wang X, Duan J, Fu W, Yin Z, Sheng J, Lei Z and Wang H: Decreased expression of NEDD4L contributes to NSCLC progression and metastasis. Biochem Biophys Res Commun 513: 398-404, 2019.
102. Yue M, Yun Z, Li S, Yan G and Kang Z: NEDD4 triggers FOXA1 ubiquitination and promotes colon cancer progression under microRNA-340-5p suppression and ATF1 upregulation. RNA Biol 18: 1981-1995, 2021.
103. Kim SS, Yoo NJ, Jeong EG, Kim MS and Lee SH: Expression of NEDD4-1, a PTEN regulator, in gastric and colorectal carcinomas. APMIS 116: 779-784, 2008.