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Cullin 7 in tumor development: a novel potential anti-cancer target

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As a core scaffold protein, Cullin 7 (Cul7) forms Skp1-Cullin-F-box (SCF) E3 ubiquitin ligase complexes with the regulator of cullins-1 (ROC1), S-phase kinase associated protein 1 (Skp1) and F-Box, and WD repeat domain containing 8 (Fbxw8). Alternatively, Cul7 can form a CRL7SMU1 complex with suppressor of Mec-8 and Unc-52 protein homolog (SMU1), damage-specific DNA binding protein 1 (DDB1), and ring finger protein 40 (RNF40), to promote cell growth. The mutations of Cul7 cause the 3-M dwarf syndrome, indicating Cul7 plays an important role in growth and development in humans and mice. Moreover, Cul7 regulates cell transformation, tumor protein p53 activity, cell senescence, and apoptosis, mutations in Cul7 are also involved in the development of tumors, indicating the characteristics of an oncogene. Cul7 is highly expressed in breast cancer, lung cancer, hepatocellular carcinoma, pancreatic cancer, ovarian cancer, and other malignant tumors where Cul7 promotes tumor development, cell transformation, and cell survival by regulating complex signaling pathways associated with protein degradation. In this review, we discuss the roles of Cul7 in malignant tumor development and its involvement in oncogenic signaling. We finally discuss the potential of Cul7 as a potential significant anti-cancer target.

Key words: Cullin 7, tumor, ubiquitin ligase, p53, apoptosis

Cullin 7 (Cul7), formerly known as KIAA0076, initially cloned from the cDNA library of human immature myeloid cell line KG-1, is a member of the Cullin protein family including Cul1, Cul2, Cul3, Cul4A, Cul4B, Cul5, Cul7, and Cul9 (parkin-like cytoplasmic protein, PARC) [1–5], which contains a region homologous and a more C-terminal region homologous to Cullins [6–9]. As a DOC domain-containing cullin, Cul7 is involved in assembling an SCF-ROC1-like E3 ubiquitin ligase complex including Skp1, Cul7, Fbx29, and ROC1 [6]. The coding region of Cul7 is located on the short arm of human chromosome 6 (6p21.1) [10]. Cul7 contains 1698 amino acids in length and is expressed in almost all human tissues. A high Cul7 expression level is detected in the human adult skeletal muscle, placenta, and fetal kidney [6]. Original studies have found that Cul7 is closely related to growth and development. The mutations of Cul7, obscurin-like protein 1 (OBSL1), or coiled-coil domain-containing protein 8 (CCDC8) cause 3-M dwarf syndrome, a primordial growth disorder characterized by developmental retardation before and after birth [10–13]. Cul7 plays an important role in the development of human and mouse embryos. The homozygote Cul7 gene knockout (Cul7–/–) in mice and human genetic disease models led to developmental defects in the placenta, slow fetus development, late pregnancy, and respiratory failure at birth [12, 14]. As the core scaffold protein of the Cullin-RING E3 ligase complex [15–18], Cul7 plays an important role in the cell transformation, cycle regulation, senescence, and apoptosis with its ubiquitin ligase activity [19–22]. E3 ubiquitin ligases play a key role in the recognition of target proteins [23, 24]. Cullin-RING E3 ligase regulates many important biological processes including cell cycle progression, DNA repair, signal transduction, autophagy, and apoptosis [25–30]. Abnormalities in ubiquitin-mediated protein degradation are closely related to tumorigenesis [16, 24,30]. In recent years, Cul7 has been found highly expressed in tumors and associated with a poor prognosis and malignant development. Bortezomib, a proteasome inhibitor, has been used to treat multiple myeloma and lymphoma. The clinical trials of Bortezomib in the treatment of other malignancies are underway [32–38]. There-

fore, it may be possible to treat tumors by using Bortezomib to inhibit the high expression of the Cul7-containing E3 ubiquitin ligase complex in tumors. Here, we focus on the relationship between Cul7 and tumors and other biological functions.

Cul7 is abnormally expressed in tumors. In many tumor tissues, Cul7 has been found abnormally expressed [38] and distributed in the nucleus and cytoplasm of cancer cells, with a higher level in the nucleus than in the cytoplasm [39, 40]. The expression level of Cul7 is increasing along with the tumor prognosis and stages. The latest cancer statistics have shown that lung cancer has the highest mortality rate in the world [41]. Using *in silico* microarray analysis, Cul7 is highly expressed in the nucleus of non-small cell lung cancer, which is positively correlated with the poor prognosis [42, 43]. Primary hepatocellular carcinoma (HCC) is a common malignant tumor. A large number of epidemiological studies have found that metabolic syndromes, including liver fibrosis and cirrhosis caused by non-alcoholic fatty liver disease, are associated with HCC occurrence. Cul7 is reportedly associated with HCC and metabolic syndrome upon the analysis of 20 patients by genomic hybridization [44]. The site of abnormal chromosomal amplification in HCC patients is 6p21.1 on chromosome 6, which is the site of the Cul7 gene. Cul7 is significantly overexpressed in HCC tissues. Immunohistochemical analysis has revealed that 11 of 20 HCC tissues are with high Cul7 expression in the nucleus, while PARC shows no significant changes [44]. Cul7 is highly expressed in the nucleus in the metastatic HCC tissues, which is positively correlated with the poor HCC prognosis [45]. Another study has shown that Cul7 is with 69.1% of the positive rate in 162 HCC tissues, but only 29% of the positive rate in the corresponding adjacent tissues. The abnormal expression of Cul7 is significantly correlated with lymph node metastasis, portal vein tumor thrombosis, and advanced clinical stages. Abnormal Cul7 expression promotes the proliferation, migration, and invasion of HepG2 cells [46]. Cul7 is also highly expressed in the nucleus of breast cancer tissues and significantly correlated with the pathological stage of breast cancer ($p=0.013$) and lymph node metastasis ($p=0.022$), but negatively correlated with patient prognosis [47]. In epithelial ovarian cancer, the Cul7 expression level is significantly higher in the epithelial ovarian cancer than that in the control tissues, indicating that the Cul7 expression is closely related to the clinical stages, lymph node metastasis, and poor prognosis [48]. Hematopoietic stem cell kinase 1 (HPK1) is expressed in normal pancreatic ducts, but absent in >95% of pancreatic cancer, which is rapidly degraded through the Cul7-Fbxw8 ubiquitin ligase complex in the ubiquitin-proteasome pathway [49]. The culmination of studies highlights the abnormally high expression of Cul7 in tumors, which correlates with the pathological stage, metastasis, and prognosis. On the other hand, the downregulation of Cul7 by miR-3940-5p suppresses developments of gliomas [50]. The association of Cul7 and tumors is summarized in Table 1. Therefore, Cul7 is an important clinical tumor marker, which is with the significance to explore the regulatory mechanisms of Cul7 in tumors.

Materials and methods

Cul7 interacts with tumor-related proteins. The molecular mechanisms of Cul7-associated tumorigenesis have been reported. As an oncogene [42], Cul7 is highly expressed in

Table1. Association of Cul7 with malignant tumors.

Tumor	Method	Cul7 expression	Regulatory mechanism	References
Breast cancer	WB, IHC	No or weak Cul7 expression in 26 normal tissues and Cul7 expression in the nucleus of 39 breast cancer tissues.	Cul7 promotes the proliferation and invasion of breast cancer cells by down-regulating the expression of p53.	[89]
Lung cancer	IHC	No or weak expression of Cul7 in the cytoplasm of normal lung mucosa and epithelial cells. Cul7 is expressed in lung cancer tissues, with a stronger expression in the nucleus than that in the cytoplasm.	Cul7 promotes the proliferation and invasion of lung cancer cells by down-regulating p53.	[42, 43]
HCC	qRT-PCR	Cul7 is expressed in 91% of 34 HCC tissues, which is significantly higher than that in adjacent normal tissues.	Cul7 up-regulates N-cadherin and Vimentin and down-regulates E-cadherin and α-cadherin promoting EMT transformation of cells.	[45]
HCC/MS	IHC	Cul7 overexpression in 11 of 20 HCC patients with metabolic syndrome.	Cul7 promotes cell proliferation and reduces apoptosis by targeting the degradation of Cyclin D1.	[90]
Epithelial ovarian cancer	qRT-PCR	The positive expression rate of Cul7 in ovarian cancer tissues is 2.1-8.4 times higher than that in normal ovarian epithelial tissues.	Downregulation of Cul7 inhibits the migration and invasion of cancer cells.	[48]
Glioma	TCGA, CGGA, WB, IHC	Cul7 is highly expressed in gliomas with high grade and poor prognosis.	Cul7 is associated and ubiquitin-mediated MST1 degradation, which promotes the NF-κB signaling pathway for glioma development.	[50]

Abbreviations: WB-Western blots; IHC-Immunohistochemistry; HCC-Hepatocellular carcinoma; HCC with metabolic syndrome; TCGA-the Cancer Genome Atlas database; CGGA-the Chinese Glioma Genome Atlas database; MST1-mammalian sterile 20 like kinase 1; NF-κB-nuclear factor- κB

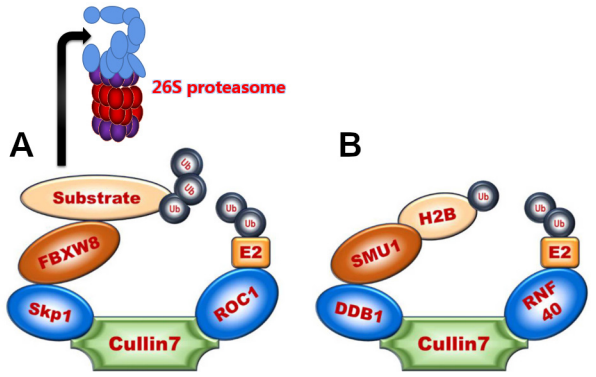

Figure 1. Cullin7 acts as a scaffold protein. A) Cul7 interacts with ROC1 and SKp1-Fbxw8 complex to form the SCF E3 ubiquitin ligase complexes, permitting the degradation of protein substrates; B) Cul7 forms a HECT-type E3 ligase complex with SMU1-DDB1 complex and RNF40 regulating the monoubiquitination of H2B.

Table 2. Substrates of Cul7 assembled SCF-ROC1-like E3 ubiquitin ligase complex.

Subtract	Function	Reference
Cyclin D1	A cellular proto-oncogene, as allosteric regulators of cyclin-dependent kinase 4 (CDK4) and CDK6 to regulate cell cycle transition from G1 to S phase	[22, 44, 54, 55]
IRS-1	A signaling adaptor to promotes tumor growth	[22, 56, 57]
HPK1	A critical negative regulator in the activation of T lymphocytes and dendritic cells	[49, 58]
GRASP65	A marker of malignant cancer cells for the ability of cancer cells to invade the extracellular matrix	[59, 60]
rEga1	Eag1 (Kv10.1) potassium (K+) channels associated with congenital neurodevelopmental anomalies and tumorigenesis	[9, 10, 61]
TBC1D3	An oncogene to stimulate the intrinsic GTPase activity of RAB5A, an essential actor in early endosome trafficking	[62-64]

Abbreviations: IRS-1-insulin receptor substrate 1; HPK1-hematopoietic progenitor kinase 1; GRASP65-Golgi peripheral membrane protein p65; rEga1-rat ether à go-go 1; TBC1D3-Tre-2/Bub2/Cdc16 (TBC1) domain family member 3

different types of tumors [51]. Cul7 promotes tumorigenesis through complex signaling pathways [1, 52]. Cul7 contains unique domains including CH, CPH, DOC, and BH3, and interacts with the complex of ROC1 and SKp1-Fbxw8 through the CH domain to form the SCF class of E3 ubiquitin ligase complex [5, 14, 19, 37, 53]. The Cul7 assembled SCF-ROC1-like E3 ubiquitin ligase complex permits the degradation of protein substrates (Figure 1A), including cyclin D1 that is a cellular proto-oncogene [22, 44, 54, 55], insulin receptor substrate 1 (IRS-1) that supports tumor growth [22, 56, 57], HPK1 that is a critical negative regulator in the activation of T lymphocytes and dendritic cells [49, 58], Golgi peripheral membrane protein p65 (GRASP65) that is associated with tumor growth and cell apoptosis [59, 60], rat ether à go-go 1 (rEga1) that is associated with tumorigenesis [9, 10, 61], and Tre-2/Bub2/Cdc16 (TBC1) domain family member 3 (TBC1D3) that is an oncogene [62–64] (Table 2). Cul7, as a core scaffold protein, assembles a novel HECT-type E3 ligase complex with suppressor of mec-8 and unc-52 homolog (SMU1), damage-specific DNA Binding Protein 1 (DDB1), and ring finger protein 40 (RNF40), which regulates the monoubiquitination of H2B (Figure 1B), thereby affecting cell mitosis and genome stability [65]. An array assay has identified Cul7 binding partners, including p53 [66], SV40 large T antigen [67], Cul9 (PARC) [68], obscurin-like protein 1 (OBSL1), coiled-coil domain containing 8 (CCDC8) [69], DDB 1, and RNF40 [65]. Mutations and/or abnormal expression have shown that these proteins are often associated with tumor development.

Cul7 inhibits apoptosis and promotes cell growth. As an anti-apoptotic oncogene [42], Cul7 promotes cell proliferation by antagonizing p53 functions [66, 69]. p53, as a tumor suppressor protein, is regulated its stability, translation, localization, and transcriptional activity through the extensive post-translational modifications (PTMs) [70–72]. Nuclear magnetic resonance (NMR) spectroscopy has shown that p53 directly binds to the conserved CPH domain of Cul7, which inhibits p53 transcriptional activity [53, 73, 74]. Mutations in the CPH domain of Cul7 inhibit the binding of Cul7 to p53, leading to a recovery of p53 activity. To date, there has been no direct evidence that Cul7 E3 ubiquitin ligase could degrade p53 through polyubiquitination [66, 75]. In the cytoplasm, Cul7 binds directly to p53 to inhibit p53 transcriptional activity, although another E3 ligase, mouse double minute 2 (MDM2) promotes cell survival, proliferation, invasion, and therapeutic resistance by binding to p53 to promotes its degradation through ubiquitination [66, 76]. However, the Cul7-p53 interaction is cell line dependent [21]. The accumulation of p53 does not occur in either Cul7-suppressed or Cul7-knockout in mouse embryonic fibroblasts (MEFs) [42], but p53 is upregulated in SHEP neuroblastoma cells [21]. In breast cancer and lung cancer cells, the silencing of Cul7 by RNAi increases the p53 expression [77]. The experimental evidence is lacking whether the degradation of Cul7 is induced through the direct polyubiquitination of p53. Therefore, the specific reasons for Cul7 degradation remain unclear. The overexpression of Cul7 inhibits C-Myc and N-Myc-induced apoptosis of neuroblastoma SHEP cells in a p53-dependent manner [42]. During etoposide-induced DNA damage, the increase in the Cul7 mRNA expression inhibits apoptosis in a p53-dependent manner [42, 66, 78, 79]. However, the overexpression of Cul7 promotes apoptosis of NIH3T3 cells through the effect of Cul7 on the integrity of the BH3 domain. The transfection of mutant Cul7 (1152 stop) in human osteosarcoma U2OS cells reduces the apoptosis induced by MG-132 and etoposides [79].

Results

The overexpression of Cul7 in the breast cancer cell line HCC1937 enhances cell proliferation, migration, and invasion, but decreases the expression of p53 and downstream p21 and p27 [46]. In contrast, Cul7 knockdown in BT474 cells inhibits proliferation, migration, and invasion [47]. Cul7 also promotes the proliferation, migration, and invasion of lung cancer cells [43]. When Cul7 is silenced, the expression of p53 and downstream p27 and p21 is increased [43]. Cyclin D1 regulates G1 to S phase of the cell cycle by PTMs. Fbxw8 mediates the ubiquitination of Cyclin D1 through the MAPK kinase-mediated phosphorylation of Thr286 [80]. The conversion of Thr286 to Ala286 or Fbxw8/ Cul1/Cul7 silence stabilizes Cyclin D1 and inhibits the cell cycle progression [80–82]. Cul7 degrades Cyclin D1 in HCC cell lines, HepG2 and SKHep-1, which may contribute to the effect of Cul7 on hepatocarcinogenesis and hepatic metabolic syndrome [44]. In Hela and MDA-MB-231 cells, Cul7 inhibits apoptosis induced by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) through the ubiquitination of Caspase 8 [51]. Whether Cul7 is an anti- or pro-apoptotic factor requires further clarification in a range of cellular systems. The consensus to-date is that Cul7 inhibits apoptosis, promotes proliferation, and regulates tumor development.

Cul7 contributes to genome stability. DNA damage repair is key to the maintenance of genome stability. Cul7, OBSL1, CCDC8 and Fbxw8 constitute the 3M complex and mutations in these genes are the main cause of 3M and other growth retardation syndromes [69]. OBSL1 regulates the transcriptional expression of Cul7, while CCDC8 affects the centrosome localization of Cul7. Cul7 and/or OBSL1 silencing results in abnormal microtubule dynamics. In lung cancer NCI-H1155 cells treated with low dose paclitaxel/taxol (10 nM), an anti-tumor agent that stabilizes microtubules, both Cul7 and OBSL1 depletion greatly delayed chromosome alignment and increased the transit time between prometaphase and metaphase. Therefore, the deletion of Cul7 leads to disorders in mitosis and cytokinesis through microtubule defects [69]. Cul9 is a tumor suppressor that is downstream of the 3M complex and highly homologous to Cul7 regarding Cul9 structure and ability to bind to p53. When Cul9 is silenced, the microtubule dynamics and mitotic disorders caused by the knockdown of Cul7 and OBSL1 can be reversed. Survivin is the strongest apoptotic suppressor gene discovered to date. Cul9 ubiquitinates and degrades Survivin, which is reversed by Cul7 [68]. Cul7 silencing reduces Survivin expression. The exogenous overexpression of Survivin reverses the impairment in microtubule dynamics and mitotic dysfunction caused inhibition. In addition, the deletion of Cul7 in the newly discovered $CRL7^{SMU1}$ complex leads to chromosomal lagging, the formation of anaphase/ nuclear bridges and multipolar spindles, affecting mitotic processes and genome stability [65]. Based on these results, Cul7 plays an important role in microtubule maintenance, mitosis, and genomic integrity, in addition to tumorigenesis and development. However, the specific mechanism(s) of these effects require further exploration.

Cul7 promotes tumor metastasis. Metastasis is an important characteristic of malignant tumors, which reduces the anticancer therapeutic efficiency and promotes cancer-related death. The expression of Cul7 is closely related to tumor metastasis. Scratch and invasion assays have shown that the Cul7 silencing inhibits the invasion and migration of choriocarcinoma, ovarian cancer, liver cancer, breast cancer, glioma, and other cancer cell lines, while the Cul7 overexpression promotes cancer cell invasion and migration [50]. Cul7 induces epithelial-mesenchymal transition (EMT), an important mechanism of tumor metastasis and progression, in choriocarcinoma JEG3 cells [83, 84]. The overexpression of Cul7 increases the expression of zinc finger E-box binding homeobox 1 (ZEB1) and Slug, inhibits the expression of E-cadherin, and enhances the migration and invasion of cancer cells. Cul7 also promotes the invasion and migration of HCC cells through inducing EMT [45]. The expression of Cul7 in HCC cell lines, HCCLM3, SUN886, and SNU423, is stronger than that in non-invasive cell lines, HepG2 and Huh7. The Cul7 silencing in SUN886 cells increases the expression of E-cadherin and catenin but decreases the expression of N-cadherin and Vimentin. The overexpression of Cul7 in HepG2 cells leads to the reverse phenotype. Cul7 promotes the invasion of breast cancer cells through the inhibition of p53. The Cul7 silencing inhibits the invasion and migration of BT474 breast cancer cells, while the down-regulation of p53 simultaneously reverses these effects [47]. Therefore, Cul7 promotes tumor invasion and metastasis, but the specific pathways that regulate its ability to ubiquitinate and degrade new substrates require further investigation.

Discussion

Cul7 is involved in cell senescence. Insulin receptor substrate-1 (IRS-1) mediates the signal transduction through its ability to bind insulin receptors and insulin-like growth factor-1 (IGF-1) receptors, which regulate the glucose metabolism for growth and development. The degradation of IRS-1 is dependent on Cul7 ubiquitin ligase [53, 85]. Following the receptor activation, IRS-1 is phosphorylated on an array of tyrosine residues and recruited by Src homology 2 (SH2) adaptor proteins to activate downstream Akt and RAS/MEK/ERK pathways through PI3K and Grb2/SOS, respectively. The inactivation or deletion of Fbxw8 and Cul7 promotes the accumulation of IRS-1 [85, 86]. Cul7 E3 ligase mediates IRS-1 degradation in an mTOR-dependent manner, suggesting that Cul7 is an important regulator of the negative feedback loop of mTOR/IRS-1 and stably regulates the activity of PI3K and other continuously activated mTOR/S6K targets [21, 87]. The accumulation of IRS-1 and the persistent activation of Akt, MEK/ERK, and downstream IRS-1 pathways are observed in Cul7−/− MEFs [22]. Although these mitogenic signaling

pathways are activated, Cul7–/–mice fibroblasts grow slowly and the number of cells arrested in the G1 phase increases. In addition, Cul7–/– fibroblasts exhibit the characteristics of the cell senescence, including the upregulation of the tumor suppressor p16, the low phosphorylation level of pRb, and the increased level of β-galactosidase [44]. SV40 large T-antigen binds to a 1391–1698 amino acid stretch at the C-terminal of Cul7, which inhibits Cul7 ubiquitination-mediated degradation of IRS-1, enhancing IRS-1 signaling [88].

In summary, Cul7 is highly expressed in multiple malignant tumors, including lung cancer, liver cancer, breast cancer, ovarian cancer, and the expression of Cul7 closely correlates with the clinical staging and prognosis [43, 45, 47, 48]. Cul7 inhibits the activity of apoptotic proteins, promotes the invasion and metastasis of cancer cells, maintains the microtubule and genome stability, and degrades IRS-1 through mTOR to participate in the cell senescence. However, the mechanisms that regulate Cul7 during tumorigenesis are still not fully understood. Cul7 is expressed in the cytoplasm of many non-cancerous tissues, while the immunohistochemistry suggests that Cul7 is overexpressed in the nucleus of tumor cells. The biological role of Cul7 in the nucleus remains unclear. Whether Cul7 could degrade p53 through ubiquitination is also controversial. Cul7 silencing increases the sensitivity of cancer cells to paclitaxel drugs, however, the specific mechanisms of this effect require further investigation. Revealing the in-depth molecular mechanisms of Cul7 in cancer therapy may open new avenues for tumor diagnosis, prognosis, and molecular targeted therapy.

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