Mini Review

Stem Cell INVESTIGATION

# Regulation of cancer stem cells by RING finger ubiquitin ligases

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**Abstract:** Like normal stem cells, cancer stem cells (CSCs) are capable of self-renewal, either by symmetric or asymmetric cell division. They have the exclusive ability to reproduce malignant tumors indefinitely, and to confer resistance in response to radiation or chemotherapy. The ubiquitin modification system plays various roles in physiology and pathology. The key component for the specificity of this system is ubiquitin ligases (E3s). Of these E3s, the majority are RING finger proteins. Many RING finger E3s, such as the Cullin1-Skp1-F-box protein (SCF) E3s, CBL, BRCA1, MDM2 and von Hippel-Lindau tumour suppressor (VHL), are crucial in the regulation of cell-cycle progression and cell differentiation. As a result, many RING finger E3s are implicated in the positive and negative regulation of CSC maintenance. This review summarizes current knowledge in this research field.

**Keywords:** Cancer stem cell (CSCs); ubiquitination; RING finger E3 ligase

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## Introduction

In the past several decades, cancer stem cells (CSCs, also known as cancer initiating cells) have been intensively investigated. Normal tissue stem cells give rise to transit-amplifying cells or progenitor cells by asymmetric cell division which in turn generates more differentiated cells in a given tissue. Similarly, CSCs are capable of self-renewal, either by symmetric or asymmetric cell division, and are able to reproduce malignant tumor cells indefinitely (1). Studies of the molecular mechanisms governing CSC maintenance and differentiation have mostly focused on the roles of signaling and transcriptional processes. However, it has recently been demonstrated that protein modification via the ubiquitin system is also crucial for the normal and abnormal stem cell functions, and the loss of such modifications can lead to tumorigenesis and progression. Thus, understanding the emerging field of how the ubiquitin modification system regulates CSC activity may lead to novel targeted cancer therapeutics.

## Cancer stem cell (CRC)

CSCs constitute a minority population in tumors and have low proliferative rate (2). They may originate from stem cells which have gained cancerous properties through genetic and epigenetic changes. Alternatively, they may arise from transformed progenitor cells that have acquired self-renewal capabilities (1).

CSCs reside in specialized microenvironments called niches, which play an important role in stem cell maintenance. The constituents of niche include fibroblasts, endothelial cells, perivascular cells, tissue macrophages, extracellular matrix, and soluble factors excreted from cells. There is cross talk between CSCs and the niche; CSCs instruct the formation of niche, whereas the niche governs the proliferation, differentiation, invasion and metastasis of CSCs or cancer cells (3). For example, the hypoxic locations in the tumor can function as niche for CSC, and induce stem-like characteristics of tumor cells through hypoxia inducible factor-1 (HIF-1) in many tumors. The stemness induction is achieved by activation of transcription factors involved in reprogramming of induced pleuripotent stem cells (i.e., Oct4, Sox2, Nanog and KLF4) (4).

Current cancer therapies frequently fail to eliminate advanced tumors, which may be due to their inability to effectively target CSC populations. The embryonic pathways such as Wnt, Hedgehog, and Notch control self-renewal and cell fate decisions of stem cells and progenitor

cells. And these evolutionary conserved pathways are also involved in CSC maintenance (5). Thus, targeting these pathways or the interactions between CSC and tumor microenvironment may be effective in eradicating CSCs and preventing radiation or chemotherapy resistance.

## The ubiquitin system

The attachment of ubiquitin polypeptides to intracellular proteins is a key mechanism in regulating many cellular processes. Ubiquitin is covalently attached to target proteins via an isopeptide bond between its C-terminal glycine and a lysine residue of the acceptor substrate. Assembly of a chain of at least four ubiquitins linked through their Lys48 residue marks cellular proteins for degradation by the 26S proteasome. In contrast, monoubiquitination or polyubiquitination with chains linked via Lys63 serve as nonproteolytic signals for intracellular trafficking, DNA repair, and signal transduction pathways. The ubiquitin modification of proteins occurs through an enzymatic cascade consisting of the ubiquitin-activating (E1), ubiquitin-conjugating (E2), and ubiquitin-ligating (E3) enzymes (6). E1 enzyme activates ubiquitin in an ATP-dependent manner, and subsequently transfers ubiquitin to E2. The E3 ligase binds to both the substrate and E2 conjugated with ubiquitin, and facilitates the ubiquitin transfer from E2 to substrates. The pairing of E2s and substrates by E3s determines the specificity in ubiquitination.

There are two major types of E3s in eukaryotes, defined by the presence of either a HECT or a RING domain (6). The HECT family comprises large proteins, each with the ability to interact directly with E2 enzymes and their specific substrates. By contrast, RING finger E3 ligases are multi-subunit complexes that bind the E2 ligase via a catalytic ring finger protein and interact with substrates via a separate receptor protein. RING finger ubiquitin ligases, which are the focus of this review, are conserved from yeast to humans, with about 616 different RING finger proteins potentially expressed in human cells (7). However, many aspects of these enzymes remain poorly understood.

It has become evident that many RING finger E3 ligases are implicated in malignancy. Oncogenic transformation is characterized by dysregulated cell growth signals, insensitivity to anti-growth or pro-apoptotic signals, dysregulation of the cell cycle and genomic instability. Solid tumors also acquire the ability to induce angiogenesis and metastasis (8). RING finger proteins are implicated in all of these steps. We will focus below on specific RING finger ubiquitin ligases that regulate different properties of CSCs (*Figure 1*), which might provide potential therapy targets for the treatment of various types of malignancies.

## SCF RING finger E3 ligase

The SCF complex represents one of the largest classes of RING finger ubiquitin ligases. It consists of three invariable components: Rbx1 (RING finger protein, binding with E2 enzyme), Cullin1 (scaffold protein), and Skp1 (adaptor protein). It also has one variable component, known as F-box protein, that binds to Skp1 through its F-box motif and recognizes substrates through different substrate-interacting motifs (SIMs) (9). Up to 69 F-box proteins (in humans) can potentially serve as substrate recognition elements. Among them, there are several well-studied F-box proteins involved in the control of cell-cycle progression, and the self-renewal and differentiation of stem cells.

### *S phase kinase-associated protein 2 (Skp2)*

Skp2 is an F-box protein of SCF E3 ligase complex, and recognizes substrates through the leucine-rich repeats (LRR) motif. In addition to forming the canonical SCF E3 complex, Skp2 also binds with ankyrin-repeat SOCS box-containing protein 2 (Asb2), and facilitate the formation of a non-canonical dimeric E3 ligase complexes containing not only Cullin1-Skp1, but also Cullin5-ElonginB/C E3 ligases, which promotes the degradation of substrates of both Cullin1 and Cullin5 (10).

Although Skp2 targets numerous proteins involved in various biological processes, such as cyclins, E2F1, Foxo1 and E47 (9), G1/S cyclin-dependent kinase inhibitor (p27) seems to be the best-studied target of Skp2 (11). p27 is a tumor suppressor, and Skp2 regulates apoptosis, cell-cycle progression, and proliferation through promoting the ubiquitination and degradation of p27 (12). Skp2 knock-out mice are viable, but the cells contain markedly enlarged nuclei with polyploidy and multiple centrosomes, show a reduced growth rate and increased apoptosis. Skp2 deficient cells exhibit increased accumulation of p27 (11). Over-expression of Skp2 is frequently observed in human cancers. The ectopic expression of Skp2 promotes tumorigenesis and metastasis in prostate tumor models (13), and induces T cell lymphomas in mice cooperating with activated N-Ras (14). Furthermore, it is recently reported that Skp2 triggers the nonproteolytic K63-linked ubiquitination of Akt, and

 

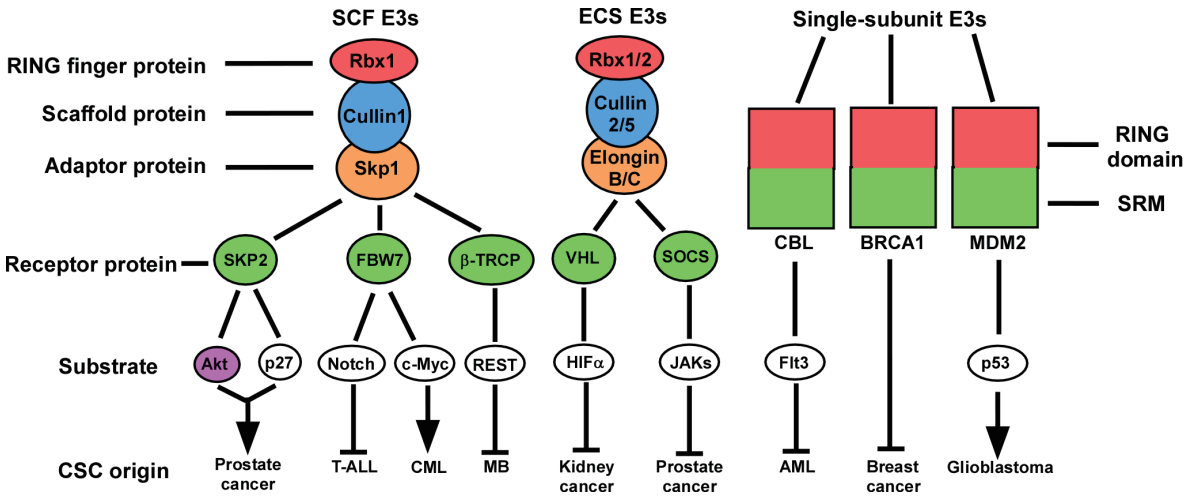


**Figure 1** The structures and functions of RING finger ubiquitin E3 ligases. RING domain containing E3 ligases are multi-subunit complexes or single-subunit large proteins. The multi-subunit complex binds the E2 enzyme through a RING finger protein, and interacts with substrates via a separate receptor protein. The single-subunit E3 ligase contains RING domain and SRM, and is able to bind E2 enzyme and substrate at the same time. The receptor subunit or the SRM of RING finger E3 ligases are variable and key components for the substrate specificity and functions in the tumor progression and maintenance of CSC. The substrate in pink circle is modified by the ubiquitin chain linked through Lys63, and is activated by the ubiquitin signal. In contrast, the substrate in white circle is modified by the ubiquitin chain linked through Lys48, which triggers the degradation of substrate. The arrow indicates that the function of E3 ligase is to promote the maintenance of CSC with specific origin. In contrast, the block line indicates that the function of E3 ligase is to inhibit the maintenance of CSC. T-ALL, T-cell acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; MB, medulloblastoma; AML, acute myelogenous leukemia; CSC, cancer stem cell; SRM, substrate recognition motif.

promotes Akt-mediated glycolysis and tumorigenesis (15).

The dysregulation of cell-cycle and aerobic glycolysis contribute to the self-renewal and proliferation of CSC. Knock-down and pharmacological inhibition of Skp2 significantly reduce the ALDH$^+$ CSC population of prostate cancer, and down-regulate the sphere formation capability of prostate cancer CSC (16). Thus, targeting Skp2 is a promising strategy for cancer treatment.

### *F-box and WD repeat-containing protein 7 (Fbw7)*

Fbw7 is another F-box protein of the SCF complex that targets several oncoproteins, including cyclin E, c-Myc, and Notch, for ubiquitination and degradation through its WD-40 motif. It is thus thought to function as a tumor suppressor (9). Germ-line deletion of Fbw7 results in embryonic lethality at around E10.5 due to vascular defects, which are attributed to the stabilization of Notch4 in the embryo (17). Conditional deletion of Fbw7 in the hematopoietic system leads to an increase in the frequency of actively cycling LSK (Lin$^-$, c-Kit$^+$, Sca-1$^+$) population, with eventual exhaustion of hematopoietic stem cells (HSCs) (18). Furthermore, *Fbw7*$^{-/-}$ LSK cells down-regulate genes involved in HSC quiescence, implying a global loss of quiescence characteristics (19).

The regulation of cell-cycle by Fbw7 is mainly through targeting cyclin E and Notch for degradation. Cyclin E is involved in driving cells in the G0 or G1 phase into the S phase and, as predicted, is frequently dysregulated in cancer (20). Notch is important for directing lymphoid lineage cell fate determination and has also been implicated in HSC self-renewal (21,22). Notch is expressed by HSCs while its ligand, Jagged, is expressed by the HSC niche, and increased Jagged/Notch activation results in increased HSC number and niche expansion (23). Notch is a potent oncogene in T-cell acute lymphoblastic leukemia (T-ALL), and the aberrant activation of Notch promotes the self-renewal of leukemia stem cell and drives the leukemic phenotype (24). And over 10% of these malignancies exhibit either a mutation or homozygous deletion of *Fbw7* gene. The loss of Fbw7 function promotes the development of T-ALL through stabilization of Notch proteins (25).

In contrast with T-ALL, Fbw7 has an important function for the initiation and the progression of chronic

 

myelogenous leukemia (CML). Deletion of Fbw7 leads to c-Myc over-expression in leukemic initiating cells (LICs). Although c-Myc is able to promote tumor progression, unphysiological over-expression of oncogenic c-Myc inhibits tumor growth through inducing p53-dependent apoptosis. Thus, the ablation of Fbw7 results in the apoptosis in LICs, and eventually the inhibition of CML progression (26).

### *β-TrCP*

F-box and WD repeat-containing protein 1A (β-TrCP) is a versatile F-box protein of the SCF E3 ligase complex that targets various substrates for degradation. β-catenin and IκBα are well-established targets of β-TrCP for ubiquitylation and degradation (27). The role of β-TrCP in tumor progression is paradoxical. On one hand, it promotes the degradation of β-catenin and thus inactivates the Wnt pathway, which stimulates the proliferation of cancer cells (28). The genetic alterations of *β-TrCP* gene and accumulation of β-catenin have been shown in several studies on human gastric cancer and prostate cancer (29). On the other hand, it also accelerates the turnover of IκBα and activates the NFκB pathway, which antagonizes the pro-apoptotic signals and enhances the chemo-resistance of cancer cells (30).

Recent report indicates that β-TrCP is involved in the normal differentiation of neural stem cell (NSC) through promoting the degradation of a transcriptional repressor REST (31). REST is found to be over-expressed in human medulloblastoma (MB), which represents one of the most malignant brain tumors in children and is believed to arise from undifferentiated NSC present in the cerebellum. The ectopic expression of REST in v-myc-immortalized NSC promotes MB formation in mice (32). Thus, up-regulation of β-TrCP could be a promising therapy for this deadly disease by promoting the terminal differentiation of MB stem cell.

## ECS RING finger E3 ligase

ECS complex is another major class of RING finger E3 ligases, and includes three invariable subunits: Elongin B/C (adaptor protein), Cullin2/5 (scaffold protein) and Rbx1/2 (RING finger protein, binding with E2). It also has one variable element for substrate recognition, known as BC-box protein since it binds with Elongin B/C through BC-box domain (33). Among the BC-box proteins there are two major populations, SOCS-box proteins and VHL-box proteins. The SOCS-box containing proteins specifically interact with Cullin5 and Rbx2, whereas the VHL-box proteins form a complex with Cullin2 and Rbx1. SOCS-box protein population are mainly composed of four families, SOCS, WSB, SSB and ASB, which respectively contain SH2 domain, WD-40 repeats, SPRY domain and Ankyrin repeats N-terminal to the SOCS box (34). They target various components of cytokine signaling for degradation, and negatively regulates cellular proliferation signal (10,33-36). While the VHL-box proteins, including von Hippel-Lindau tumour suppressor (VHL), LRR-1 and FEM1B, facilitate the degradation of proteins involved in the stress response and cellular metabolism (33,37).

### *The suppressor of cytokine signaling (SOCS)*

SOCS proteins are well-studied substrate recognition subunits of Cullin5 ECS complex. They recognize the phosphorylated tyrosine residues of substrates through SH2 domains, and promote the ubiquitination and degradation of those proteins. The reported targets of SOCS proteins include the p65 subunit of NFκB, myeloid differentiation primary-response gene 88 (MyD88)-adaptor-like protein (MAL) and Janus protein kinases (JAKs), which play pivotal roles in inflammation, as well as in the progression of cancers (38,39).

JAK/STAT pathways are important intracellular signaling cascades to transduce the differentiation and proliferation signals from cytokines, growth factors, and hormonal factors. Once activated by the receptors of above molecules, JAKs promote the dimerization and activation of downstream transcription factors, such as members of the signal transduction and activators of transcription (STAT) family. STAT dimers then translocate to the nucleus where they bind IFN-γ-activated (GAS)-like elements, leading to the transcriptional activation of multiple genes (40). Persistent JAK/STAT activation is observed in many cancer cells, including colorectal cancer, prostate cancer, breast cancer, and leukemia (41). Consistently, promoter hypermethylation and decreased expression of SOCS1 and SOCS3 are detected in various cancers (42,43). Mice with SOCS3 deletion in gastrointestinal epithelial cell (T3b-SOCS3 cKO mice) display the aberrant JAK-STAT signaling and severe phenotype of gastric cancer (44). According to a recent report, the elevated activation of IL-6/JAK/STAT3 pathway is observed in the stem-like cells of prostate cancer patients, and the abnormal activation

 

promotes the clonogenicity of stem-like cancer cells and the outgrowth of castration-resistant tumor (45). Therefore, up-regulation of SOCS proteins, especially SOCS3 could be a promising treatment for advanced prostate cancer.

### *VHL*

*VHL* was first discovered as a tumor suppressor gene that is inactivated in the familial kidney cancer syndrome VHL disease (46). Approximately 57% of sporadic clear cell cancers of the kidney contain inactivating mutations of VHL, and 98% of these have loss of heterozygosity (LOH) at the VHL locus (47). As the substrate recognition subunit of Cullin2 ECS complex, VHL targets Hypoxia inducible factor α (HIFα), an important transcription factor promoting cell survival under hypoxic conditions. Under normoxic conditions, VHL recognizes the hydroxylated proline of HIFα protein, and facilitates its degradation (48).

The loss of VHL protein stabilizes HIFα protein and induces HSC quiescence, which is determined by an increase in LSK (Lin–, c-Kit+, Sca-1+) cell number in G0 phase and the attenuated differentiation status in peripheral blood (49). Furthermore, the hypoxia environment and stabilized HIF expand the sub-population of cancer cells positive for CSC markers, and promote a stem-like phenotype in cancer cells. This phenotype of CSC may contribute to the recurrence after radiation or chemotherapy by reducing ROS and enhancing the activity of DNA checkpoint kinases to prevent DNA damage (5). Thus, introduction of VHL to cancer cells could be a promising method to reduce the therapeutic resistance.

## Single-subunit RING finger E3 ligase

There are also a large number of RING finger proteins mediating substrate ubiquitination individually. They contain RING finger domain binding to E2 enzymes, and various SIMs, and are involved in different stages of cancer progression.

### *CBL*

Casitas B cell lymphoma (C-Cbl), the cellular homolog of the v-Cbl oncogene, encodes a single-subunit RING finger E3 ligase, and contains a highly conserved N-terminal tyrosine kinase-binding (TKB) domain that mediates interactions between c-Cbl and phosphorylated tyrosine residues on its substrates (50). It can regulate the protein levels of c-Kit, STAT5 and Flt3, all of which contribute to HSC maintenance (51,52).

Cbl knock-out mice exhibit aberrant hematopoiesis. $Cbl^{-/-}$ HSCs show enhanced reconstitution capacity in competitive bone marrow transplantation (BMT) assays and more proliferation in BrdU incorporation experiments. $Cbl^{-/-}$ LSKs have increased levels of phospho-STAT5 and c-Myc mRNA (STAT5 is an activator of Myc transcription) suggesting Cbl deficiency stabilizes active STAT5 and promotes the hyperproliferative phenotype (24).

Cbl is mutated in 5-15% of human myeloid leukemia. Mice containing loss-of-function mutations of the *c-Cbl* gene develop aggressive myeloid leukemia, and the leukemic stem cells from those mice exhibit augmented signaling from Flt3, which is a receptor tyrosine kinase (RTK) and a substrate of c-Cbl E3 ubiqutin ligase (53). Thus, the ubiquitination and degradation of RTK signaling components by c-Cbl might also contribute to its effect on CSC proliferation.

### *BRCA1*

BRCA1 is a tumor suppressor that is frequently mutated in familial breast and ovarian cancer (54). Similar to c-Cbl, BRCA1 is a single-subunit RING finger E3 ligase, and contains two BRCA1 C-terminal (BRCT) domains, which recognize the phosphorylation sites of substrates (55). The role of BRCA1 in DNA repair was well established. BRCA1 deficiency leads to a defect in the repair of double-stranded breaks by homologous recombination (HR), which is responsible for the genomic instability and tumorigenesis (56). A key ubiquitination substrate of BRCA1 is CTBP interacting protein (CTIP), which is the binding partner of the transcriptional repressor CTBP, and is involved in the checkpoint arrest in response to DNA damage (57).

Recently a role of BRCA1 in stem cell regulation and the control of mammary gland differentiation have been suggested. BRCA1 expression is required for the differentiation of ER-negative stem/progenitor cells to ER-positive mature luminal cells (58). Loss of BRCA1 may result in the accumulation of genetically unstable breast stem cells or luminal progenitor cells, providing prime targets for further transformation.

### *MDM2*

MDM2 is a single subunit RING finger E3 ligase that

 

targets p53 for degradation, as well as inhibits the transcriptional activity of p53 by binding to its N-terminus (59). Loss of MDM2 activity in HSC leads to stabilized p53, which impedes hematopoiesis via induction of cell cycle arrest, senescence and ultimately cell death of HSCs and progenitors (60).

MDM2 acts as an oncoprotein, and is up-regulated in glioblastoma stem cells through MEK-ERK signaling. MDM2 prevents p53 function and maintains the expression of $O^6$-methylguanine DNA methyltransferase (MGMT), which is a key factor in conferring the Temozolomide (TMZ) resistance to glioma stem cells (61).

## Targeted therapy towards RING fingers

Since the RING finger E3 ligases play important roles in regulating the self-renewal, differentiation and therapeutic resistance of CSCs, specific inhibition on certain RING finger proteins may provide promising strategies for cancer treatment. RING finger proteins facilitate ubiquitin transfer from E2 directly to the substrate, but they are not catalysts with active sites. Thus, inhibitor development would probably have to be focused on disrupting the RING structure or the RING-E2 interface. Some specific inhibitors of RING finger E3 ligases have been developed. For example, Nutlin-3 is a novel small-molecule antagonist of MDM2 that binds MDM2 in the p53-binding pocket, thereby interfering with MDM2-directed p53 degradation. The p53 stabilization results in apoptosis in cancer cells (62). Another promising chemical inhibitor can bind with Trp97 of Skp2 and prevents the interaction between Skp2 and its adaptor protein Skp1. This inhibitor can effectively reduce the CSC population in prostate cancer, and overcome chemo-resistance (16). Therefore, with the accumulation of structural and functional data and the elucidation of the pathways that are controlled by RING finger E3s, there is great potential to apply this knowledge to the development of novel targeted therapeutics.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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