

# The Role of Dub3-Snail1 in Metastasis of Breast Cancer

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## ABSTRACT

Nowadays, oncogenic proteins have been widely discovered and identified, scarcely ever oncogenic proteins can be well applied as drug targets, which is a difficult problem for translational medicine of breast cancer. Dub3, overexpressed in breast cancer, is a Snail1 deubiquitination enzyme that can interact with Snail1 and stabilize it. Snail1 is a key transcription factor in epithelial-mesenchymal transformation (EMT) and breast cancer metastasis and is prone to ubiquitination and degradation. Dysregulation of Dub3 can lead to Snail1 instability and inhibit the process of EMT, thereby reducing the migration, invasion and metastasis of tumor cells. Dub3 will provide potential of targeted therapies for breast cancer patients. This review expounds expression and mechanism of Dub3 and Snail1 in breast cancer and reviews the playing role of Dub3-Snail1 signaling axis in breast cancer.

**KEYWORDS:** Breast cancer; Deubiquitinase; Dub3; Snail1

**ABBREVIATIONS:** EMT: Epithelial-mesenchymal transformation; PTM: Protein Post-Translational Modification; UPS: Ubiquitin-Proteasome System; Ub: Ubiquitin; DUBs: Deubiquitinase; The Bromine Domain and Extra Terminal Domain

## INTRODUCTION

Breast cancer is one of the most important killers threatening women's lives. According to the latest statistics, the American Cancer Society estimates that the incidence of breast cancer will far exceed that of lung cancer reaching 30% and mortality rate by 15% in 2021 [1]. There are many risk factors for the increase of breast cancer incidence, such as genetic factors, weight, hormone replacement therapy, reproductive factors, and family history [2]. At present, the treatments of breast cancer include surgery, chemotherapy, radiotherapy, hormone therapy, and targeted therapy. Chemotherapy is still a very important treatment for breast cancer [3]. However, there are still many shortcomings in the treatment of breast cancer. Chemotherapy resistance, response

difference and high recurrence, especially triple negative breast cancer has high invasion and metastasis, poor clinical prognosis, and even about 40% of patients are prone to metastasis and recurrence [4]. However, in recent years, with the continuous development of tumor molecular biology, molecular targeted therapy of breast cancer has made breakthrough progress in clinical treatment, so it is imperative to continue to find new specific new targets.

Protein post-translational modification (PTM) controls the function of a variety of cellular transcription factors and participates in a variety of signal transduction pathways in cancer [5]. Ubiquitination, as a common post-translational modification, alters protein activity, localization, interaction, and stability, and regulates key cellular processes such as protein degradation,

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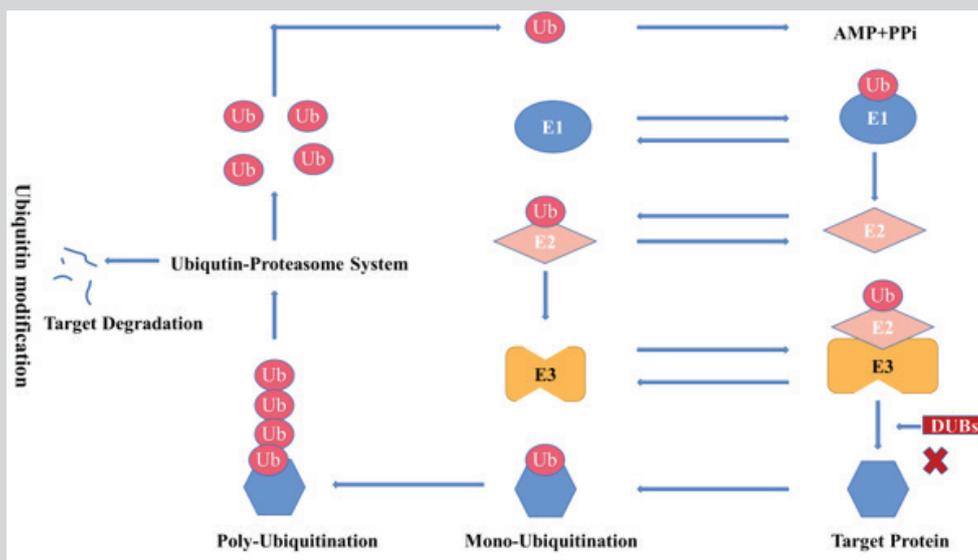
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transport, signaling pathways, immune response, and apoptosis [6]. Ubiquitin, composed of 76 amino acids, is a highly conserved small molecule protein. Ubiquitin-activating enzymes (E1s), ubiquitin-conjugating enzymes (E2s), and ubiquitin ligase enzymes (E3s) are responsible for adding ubiquitin to target proteins [7], so that the protein is labeled and activated. Finally, the proteasome specifically recognizes the ubiquitin-labeled protein and degrades it. Ubiquitination is a reversible process. Deubiquitination is an inverse process mediated by deubiquitinase (DUBs). In the process of deubiquitination, ubiquitin can be removed from the substrate

to prevent the stability or degradation of the substrate, which depends on the specific deubiquitination sites [8].

Overall, in the regulation of ubiquitination, E3 ubiquitin ligases and deubiquitination enzymes have the role of substrate recognition and control the selective specificity of protein ubiquitination and deubiquitination process [9-11]. On this basis, the study of Dub3-Snail1 signaling axis provides a theoretical basis for deubiquitinase as a therapeutic target.

## Ubiquitination and Deubiquitination



**Figure 1:** E1 activates ubiquitin using ATP; E2 recognizes the activated ubiquitin molecules and transfers the activated ubiquitin to E2 through the thioester bond to form E2-ubiquitin complex. E3 is a key factor in UPS, which has two different E2-substrate binding sites. It recognizes and binds the associated E2 and predegraded marker proteins. E3 promotes the transfer of ubiquitin from E2 to lysine, forming an ISO peptide bond between the C-terminal Gly of ubiquitin and substrate lysine residues. DUBs destroys the normal ubiquitination process by inhibiting E3 ligase mediated USP, removing the ubiquitin chain in protein posttranslational modification, leading to the reversal of ubiquitin signal, or by saving the degradation of proteasomes (such as cytoplasmic proteins) or lysosomes (such as internalization receptors) to achieve protein stability and ensure their functional level.

In eukaryotic cells, there are mainly two systems responsible for protein conversion: ubiquitin-proteasome system (UPS) and lysosome system. UPS has four main components: proteasome, ubiquitin (Ub), ubiquitinase and DUBs [12]. Ubiquitination is a reversible but dynamic process catalyzed by a series of enzymes. With the participation of ATP, ubiquitin-activated enzyme (E1) transfers Ub to the carrier ubiquitin-binding enzyme (E2), which, with the assistance of ubiquitin ligase (E3), marks Ub to the anchored substrate in turn, thus realizing the modification of polyubiquitination [13] (Figure 1). In addition, another polyubiquitin ligase E4 was identified as a ubiquitin chain elongation factor family for polyubiquitin chain assembly of some monoubiquitinated proteins [14]. During ubiquitination, seven lysine residues in ubiquitin provide different types of connections, including monoubiquitination, multiubiquitination and branched ubiquitination, to regulate different functions of target proteins [15]. The exact role of ubiquitin signal transduction regulation will provide new insights into the mechanisms and treatment of various human diseases related to ubiquitination, including neurodegenerative diseases, cancer, infection, and immune diseases [16].

DUBs are a group of enzymes that remove ubiquitin from ubiquitinated proteins [17]. The ubiquitin in the target protein is removed and the stability increased by inhibiting E3 ligase-mediated protein degradation. Deubiquitinating enzymes can be divided into seven families. Each family presents unique structural folding: ubiquitin-specific protease (USP), ubiquitin C-terminal hydrolase (UCH), ovarian tumor protease (OTU), Machado-Joseph disease protease family (MJDs), MINDY protease family (DUB family containing MIU), JAMM family (metalloenzyme containing Jad1/Pad/MPN domain), and the newly discovered ZUFSP/Mug105 family (zinc finger with UFM1-specific peptidase domain protein/C6orf113/ZUP1) [18]. Most of these enzymes play functions by reversing the polyubiquitination or monoubiquitination of target proteins. The USP family is expected to have about 56 members with similar catalytic domains for cysteine protease activity, making it the largest DUB family [19]. Each USP contains a catalytic domain consisting of a catalytic triplet of cysteine, histidine, and aspartic acid residues [20,21]. Among them, Dub3 belongs to the USPs group and is a 58kDa protein. Its catalytic domain is located near the N-terminal, and there are also three highly conserved residues (Cys89, His334 and Asp350) that form a catalytic triad.

The two-acetyl hyaluronic acid binding motifs are located in the C-terminal region [22]. Studies have shown that Dub3 has the ability to stabilize Snail, Geminin, MCL1, Cdc25A, NRF2, BRD4 and Cyclin A [23-27], and Dub3 dysfunction can lead to dysfunction of the ubiquitin system, increasing the role of oncogenes or reducing the activity of tumor suppressor genes. In recent years, the research on Dub3 - Snail1 signal axis has been deepening, providing a new and promising treatment strategy for breast cancer.

### The Role of Dub3 and Snail1

Breast cancer is the most common malignant tumor in women. Compared with normal subjects, breast cancer patients with higher Dub3 expression and lower overall survival rate. Breast cancer patients with higher Dub3 expression have poorer overall survival rate, but there is no significant difference. It suggests that Dub3 may play an important role in breast cancer and is associated with survival rate. Studies have shown that Dub3 can play a role in different aspects of breast cancer. Pristimerin is a naturally occurring quinone methyl triterpenoid, which can inhibit the activity, migration, and cell cycle of breast cancer cells, and induce apoptosis. Overexpression of miR-542-5p in breast cancer cells treated with pristimerin leads to a decrease in Dub3 level, which inhibits breast cancer progression by inhibiting Dub3 expression through a typical miRNA-mediated mechanism [28]. Geminin is a key inhibitor of DNA replication licenser Cdt1. In order to correctly realize its function, the level of Geminin is strictly regulated in the cell cycle through ubiquitin-dependent proteasome degradation. Dub3 and USP7, as regulators of Geminin stability, overexpression of any Dub3 or Dub7 can increase its expression, especially in invasive breast cancer. In conclusion, Dub3 and USP7 regulate DNA replication by controlling Geminin levels and point out the new role of Dub3 in breast cancer progression [25]. BRD4 is a member of the bromine domain and extra terminal domain (BET) protein family, which can interact physically and/or functionally with transcription factors through cancer type-specific ways, such as TWIST in breast cancer. The drug resistance of BET inhibitors often occurs, which is related to the abnormal degradation of BRD4 protein in cancer. However, BRD4 can induce the downregulation of Dub3 by up regulating the nuclear receptor co-repressor protein (NCOR2), thus overcoming the drug resistance of BET inhibitors in cancer becomes a feasible therapeutic target [23].

Snail1 is one of the most important and characteristic transcription factors in EMT process. EMT represents the process of cell dedifferentiation, which regulates embryonic development, tissue remodeling, wound healing, and metastasis. The classic EMT transcription factor (EMT-TF) is divided into three groups. Snail/Snail1 belongs to the zinc finger protein family of Snail family and participates in the regulation of tumor metastasis [29]. It has been reported that Snail1 can be used as an independent negative diagnostic indicator of breast cancer, which is closely related to poor differentiation, strong invasiveness, easy metastasis and short survival period of breast cancer [30]. TGF- $\beta$  superfamily signal is the main inducer of EMT, which can promote the invasion and metastasis of cancer cells. SMAD4 encodes the classic TGF- $\beta$  signal, which makes a crucial contribution to the subsequent gene regulatory events during the execution of EMT. SMAD4 mutation makes TGF- $\beta$  signal inactivated, but the EMT in SMAD4 mut cells induced by Snail1 is completely independent of TGF $\beta$ /BMP receptor activity to promote tumor metastasis [31]. The effects of miR-205 on proliferation, differentiation and invasion of tumor cells have been confirmed. miR-205 can target HOXD9-Snail1 axis to inhibit

the proliferation and chemical resistance of triple negative breast cancer cells [32].

A large number of studies have shown that the degradation of Snail is controlled by the E3 ligase [33], and Dub3 can stabilize Snail1 by deubiquitination. The interaction between Snail and Dub3 is mediated in the N-terminal region of Snail (SNAG domain), which is the most common binding site of E3 [34]. On the one hand, the deubiquitinating enzyme Dub3 can counteract the degradation process of Snail to maintain a high level of Snail protein in cancer cells [35]; on the other hand, Dub3 is highly expressed in basal-like breast cancer (BLBC) cells containing high levels of Snail1 and the steady state level of Snail1 is enhanced by increasing Dub3 expression in a dose-dependent manner [34]. How does the regulation of Dub3-Snail1 occur?

### Dub3-Snail1 Signal Axis

Dub3 has become an important deubiquitinating enzyme in DNA repair, cell proliferation, transcription factor regulation and tumor metastasis. Dub3 promotes EMT by stabilizing Snail through deubiquitination. The whole process involves the activation of Dub3 and the stability of SNAIL1. Bioinformatics analysis showed that the expression of Dub3 JAK/STAT3 signaling pathway was highly correlated with cyclin and was involved in TGF- $\beta$  signaling pathway (Figure 2). At the same time, it was reported in the literature that the activation of Dub3 could be regulated by IL-6-JAK/STAT3 signaling pathway [36] and CDK4/6-Dub3 signaling axis [37]. IL-6 is a central pro-inflammatory cytokine in tumor microenvironment. High level of IL-6 is correlated with poor prognosis of tumor [38]. The activity and expression of Dub3 can be rapidly induced by IL-6. CDK4/6 signal can become overactive in cancer cells through genetic or epigenetic mechanisms [39] and can promote its activation by phosphorylation of Ser41 site in Dub3 *in vitro* [37]. CDK4/6 inhibitors palbociclib, ribociclib and abemaciclib can be directly combined with CDK4 and CDK6 to inhibit their activities [40]. As an unstable protein, several E3 ubiquitin ligases, including  $\beta$ -TRCP1, FBXL14 and FBXO11, have been proved to induce ubiquitination and degradation of Snail1. The catalytic activity of Dub3 makes Snail1 avoid ubiquitination and degradation, and then Snail1 can trigger EMT by inhibiting the expression of E-cadherin [41]. Therefore, WP1130 reduces the migration and metastasis of cancer by inhibiting the catalytic activity of Dub3, thereby restoring the ubiquitin-mediated snail degradation [42]; (Figure 3).

### Long-Term Effects of Dub3-Snail1 on Breast Cancer Treatment

Tumor-related deaths are mostly caused by tumor metastasis. EMT is an important mechanism of tumor metastasis, which enhances the migration and invasion ability of tumor cells, is more likely to infiltrate into surrounding tissues, and form metastatic foci with blood flow running to distant sites. Snail1 is one of the most important and characteristic transcription factors in the process of EMT, which encodes Snail1 [43]. A large number of studies have shown that Snail1 can promote one of the key transcription factors of tumor invasion and metastasis by mediating EMT. Snail1 plays the role of the initiation step of inducing EMT, leading to invasion processes such as breast cancer [44], colon cancer [45], and liver cancer [46]. Snail1 plays a key role in human breast cancer metastasis [47]. Dub3 stabilizes Snail1 by deubiquitinating Snail1, so Dub3 may also promote breast cancer metastasis. The expression of Dub3 and Snail1 in breast cancer tissue samples was detected by breast cancer tissue microarray. The results showed

that the high expression of Dub3 protein was positively correlated with metastasis. High Snail1 protein expression is also positively correlated with metastatic cancer. Importantly, the expression of Dub3 was positively correlated with Snail1 protein in metastatic carcinoma [34]. The study found that in breast cancer patients, the expression of Snail1 was also positively correlated with metastasis progress, indicating that Dub3 and Snail1 were positively correlated

in metastatic breast cancer. Dub3, as a deubiquitination enzyme, can be used to reduce the ubiquitination level of Snail1 in breast cancer, increase the stability of Snail1 *in vivo* and promote the occurrence of EMT. Based on the dual role of Dub3 in regulating tumor growth and metastasis, future clinical and drug research will guide this specific interaction of Dub3-Snail1.

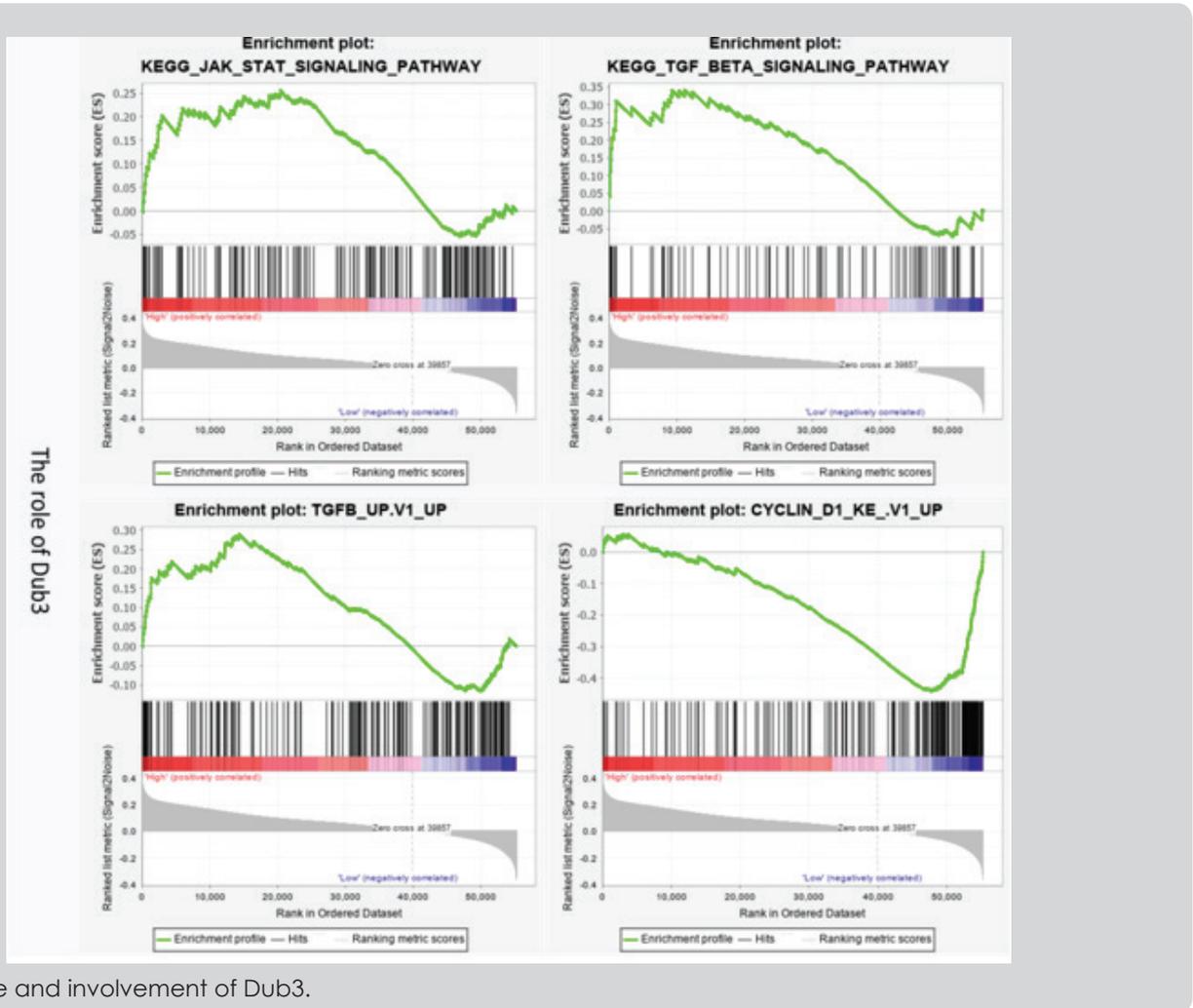


Figure 2: Role and involvement of Dub3.

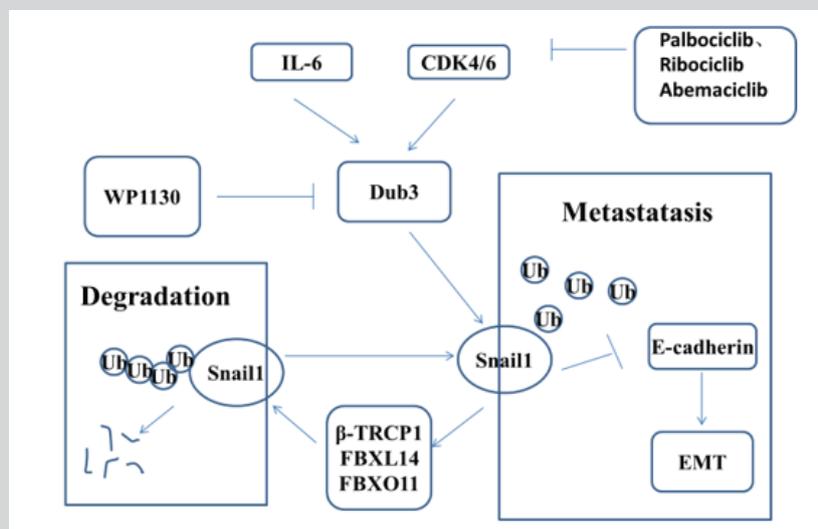


Figure 3: Dub3-snail1 and E3 ligase-mediated EMT and metastasis model.

## CONCLUSION

In summary, various evidence show that Dub3 inhibits the degradation of Snail1 protein in breast cancer cells by deubiquitination and promotes the occurrence of EMT. Dub3 has the effect of stabilizing the expression of Snail1. This finding is expected to provide new targets for precise treatment of breast cancer. Dub3 therapeutic inhibitors can inactivate some key cancer-promoting proteins or destroy the stability of these proteins to destroy the driving process, so as to achieve therapeutic purposes. In conclusion, although a variety of Dub3 specific inhibitors are still in the research stage, it is believed that selective Dub3 small molecule inhibitors will have a far-reaching impact on improving the treatment of breast cancer in the near future. In order to better understand the role of Dub3-SNAIL1 in cancer progression and metastasis, especially the mechanism related to signaling pathways, more studies are needed. It may provide new schemes of mechanisms related to cancer development and provide the basis for innovative treatment of metastatic breast cancer.

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### Authors' Contributions

XiaoChen Hou, Fei Ge and Qianxi Yang searched the literature and wrote the manuscript. LinLin Liu and Wenlin Chen conceived the idea and critically revised the manuscript and gave the final approval. All authors have read and approved the final manuscript.

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