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JAB1/CSN5: A Multifunctional Protein in Cancer

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Abstract

c-Jun activation domain-binding protein 1 (JAB1) was originally identified as a c-Jun co-activator and subsequently discovered to be a component of the COP9 signalosome (CSN) complex. JAB1, which is also known as CSN5, affects many partner proteins through protein-protein interaction, which leads to protein degradation and transcriptional activation. Thereby, JAB1/CSN5 functions as a multifunctional protein involved in the regulation of cell cycle, signal transduction, and DNA repair. In particular, JAB1/CSN5 plays an essential role in tumorigenesis by degrading tumor suppressor proteins and activating oncogenic transcription factors. JAB1/CSN5 overexpression has been observed in various types of cancer, and it has been multifunctionally involved in cancer progression.

In this review, we provide an overview of the roles of JAB1/CSN5 in tumorigenesis and summarize recent findings that highlight the novel roles of JAB1/CSN5 in this process.

Keywords: JAB1/CSN5; Tumorigenesis; Protein-protein interaction; Nuclear export; Protein degradation; Transcriptional activation

Introduction

Inactivation of oncogenic proteins and induction of tumor suppressor proteins have provided an effective avenue for treating cancer cells. However, targeting candidate oncogenic and tumor suppressor proteins exist so many. Therefore, the protein which positively regulates oncogenic proteins and negatively regulates tumor suppressor proteins is a potential target for novel and effective cancer therapy. In this study, we discuss c-Jun activation domain-binding protein 1 (JAB1), which has been implicated to be multifunctionally involved in tumorigenesis. JAB1 interacts with multiple proteins and affects many aspects of tumorigenesis, such as protein degradation of tumor suppressors and activation of oncogenic transcription factors. Therefore, JAB1 has the potential to be an effective target for cancer therapy.

JAB1 was originally identified as a c-Jun co-activator. JAB1 stabilizes c-Jun DNA-binding and potentiates its transcriptional activity [1]. JAB1 was subsequently discovered as the fifth integral component of the constitutive photomorphogenic-9 (COP9) signalosome (CSN) complex. For this reason, JAB1 is also referred to as CSN5 [2]. JAB1/CSN5 has many binding partners and affects their protein stability and transcriptional activity. Thereby, JAB1/CSN5 functions as a multifunctional protein involved in the regulation of cell cycle, signal transduction, and DNA repair [3].

JAB1/CSN5 plays an essential role in tumorigenesis by functionally inactivating several key tumor suppressor proteins including p53 [4,5], Smad7 [6], Runx3 [7], and the cyclin-dependent kinase inhibitor $p27^{Kip1}$ (p27) [8,9]. JAB1/CSN5 translocates these proteins from the nucleus to the cytoplasm and subsequently degrades them in the proteasome. In addition, JAB1/CSN5 is a transcriptional co-activator for c-Jun [1], MYC [10], HIF-1α [11,12] and STAT3 [13]. JAB1/CSN5 overexpression has been found in various types of cancer [14], and it has been multifunctionally involved in many aspects of tumorigenesis.

In this review, we provide an overview of the roles of JAB1/CSN5 in tumorigenesis and summarize recent research progress on cellular functions of JAB1/CSN5 in this process.

JAB1/CSN5 as a Member of the CSN

JAB1, which is also referred to as CSN5, is the fifth integral component of the CSN complex. Native-PAGE analyses have revealed that JAB1/CSN5 exists as a holocomplex, two smaller complexes (250 to 300 kDa and 100 kDa), and monomeric form. The CSN holocomplex and one smaller complex (250 to 300 kDa) are primarily located in the nucleus. On the other hand, the other smaller complex (100 kDa) and monomeric form are primarily located in the cytoplasm [9]. Furthermore, immunofluorescent staining and SDS-PAGE analyses also have revealed that JAB1/CSN5 is located in both the nucleus and the cytoplasm [9,13]. Interestingly, recent study has revealed that the transforming effects of JAB1/CSN5 require CSN subunits for assembly of the full COP9 signalosome and the isopeptidase activity of CSN5, which potentiates the transcriptional activity of MYC [15]. Furthermore, smaller complex-associated with JAB1/CSN5 (100 kDa), rather than the CSN holocomplex, drives p27 degradation in the cytoplasm [16]. These findings seem to be consistent with the cellular localization of the CSN holocomplex and smaller complex-associated with JAB1/CSN5. However, the detailed function of the CSN holocomplex, smaller complexes-associated with JAB1/CSN5, and monomeric form remains unclear. Further studies are needed to investigate the roles of the CSN holocomplex, smaller complex-associated with JAB1/CSN5, and monomeric form of JAB1/CSN5 in various cellular events such as cytoplasmic translocation, protein degradation, and activation of transcription factors.

JAB1/CSN5 Structure and its Structural Function

JAB1/CSN5 gene is highly conserved in humans, mouse, Drosophila, fission yeast, and Arabidopsis, suggesting that JAB1/CSN5 is critical for development and survival. Indeed, *JAB1/CSN5*-deficient mice had an embryonical lethality [17]. Human *JAB1/CSN5*

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gene is located on chromosome 8q13. JAB1/CSN5 protein consists of 334 amino acids and has a molecular mass of 38 kDa. JAB1/CSN5 protein is localized in both the nucleus and the cytoplasm. JAB1/CSN5 has two structural characteristics. One is nuclear export signal (NES)-like sequence, and the other is Mpr1-Pad1-N-terminal (MPN) domain containing metalloenzyme (JAMM) motif. JAB1/CSN5 directly binds to p27 and mediates cytoplasmic shuttling of p27 from the nucleus in a nuclear export inducer, CRM1-dependent manner through a NES-like sequence [9]. Furthermore, JAB1/CSN5 has a MPN domain that contains a JAMM motif. The JAMM motif in JAB1/CSN5 cleaves the ubiquitin-like protein, Nedd8 from the Cul1 subunit and catalytically regulates the enzymatic activity of SCF E3 ubiquitin ligases [18]. Interestingly, all components of the CSN resemble to all subunits of the lid complex of the proteasome in terms of subunit composition and the amino acid sequence of each subunit [19,20]. Indeed, the JAB1/CSN5 MPN domain containing a JAMM motif resembles to the amino acid sequence of 26S proteasome lid component, RPN11, which is responsible for the ubiquitin cleavage from the ubiquitinated proteins in the proteasome [18,21]. These similarities suggest that these proteins originate from a common ancestor and share similar molecular properties. There are some evidences that the CSN interacts with the proteasome and competes with the lid of the proteasome [22,23]. Among the effects of JAB1/CSN5 on its binding partner proteins, cytoplasmic shuttling and protein degradation can be substantially explained by NES-like sequence, JAMM motif, and the similarity between the CSN holocomplex and the lid of the proteasome. Compared with such effects of JAB1/CSN5, the mechanism by which transcription factors are activated can't be substantially explained. Some studies have reported that JAB1/CSN5 is located on chromatin DNA [24,25]. However, it still remains unclear how JAB1/CSN5 exists on chromatin DNA, its binding to chromatin DNA is direct or indirect, and whether other partner proteins exist or not. Further studies are needed to elucidate the mechanism by which JAB1/CSN5 binds to chromatin DNA.

Multifunction of JAB1/CSN5

JAB1/CSN5 interacts with many proteins, and affects many activities, such as the regulation of protein degradation and stability, cytoplasmic shuttling from the nucleus, the DNA-binding activity of transcription factors, and their transcriptional activity.

Regulation of protein degradation and stability

JAB1/CSN5 promotes the degradation of its binding partner proteins including p27 [8,9], p53 [4,5], SMAD7 [6], Runx3 [7], Rad9-Rad1-Hus1 (9-1-1) complex [26], MYC [10], estrogen receptor α [27] misfolded cystic fibrosis transmembrane conductance regulator (CFTR) [28], West Nile virus capsid protein [29], and endothelin type A and B receptors [30]. JAB1/CSN5 degrades various proteins localized in the nucleus, the cytoplasm, and the cell membrane through protein-protein interaction. Interestingly, JAB1/CSN5 induces nuclear export and subsequent degradation of its binding partner proteins in the nucleus (e.g. p27, p53, 9-1-1 complex, SMAD7, and Runx3). JAB1/CSN5 induces nuclear export and subsequent degradation of p27, leading to exit from G1 phase and entry into S phase [9]. JAB1/CSN5 enhances nuclear export and cytoplasmic degradation of p53 through MDM2-mediated p53 ubiquitination [4,5]. JAB1/CSN5 also mediates translocation of 9-1-1 complex from the nucleus to the cytoplasm and subsequent degradation of 9-1-1 complex [26]. Nuclear export and subsequent degradation of p53 and 9-1-1 complex caused by JAB1/CSN5 leads to the impairment of DNA damage checkpoint. Furthermore, JAB1/CSN5 enhances nuclear export and cytoplasmic degradation of SMAD7 [6], and Runx3 [7] which function as tumor suppressors. On the other hand, JAB1/CSN5 stabilizes several JAB1/CSN5-interacting proteins including HIF-1α [11,12], c-Jun [31], and transformed mouse 3T3 cell double minute 2 (Mdm2) [5]. JAB1/CSN5 may determine to degrade or stabilize its interacting proteins depending on their ubiquitination status. Further studies are needed to elucidate the mechanism to determine degradation or stabilization of JAB1/CSN5-interacting proteins.

Regulation of cytoplasmic shuttling from the nucleus

JAB1/CSN5 controls nuclear export of p27, p53, 9-1-1 complex, Runx3, and SMAD7. These JAB1/CSN5-interacting proteins translocate from the nucleus to the cytoplasm, and are subsequently degraded in the proteasome. As JAB1/CSN5 contains a nuclear export signal (NES) sequence and translocates from the nucleus to the cytoplasm through the interaction with CRM1, which can transport its interacting proteins to the cytoplasm, JAB1/CSN5-interacting proteins in the nucleus may translocate to the cytoplasm as a consequence of JAB1/CSN5 translocation to the cytoplasm.

Regulation of the DNA-binding activity of transcription factors and their transcriptional activity

JAB1/CSN5 was initially identified as a co-activator of c-Jun, a member of the activating protein-1 (AP-1) complex [1]. JAB1/CSN5 can specifically stabilize c-Jun protein binding to its DNA binding site and potentiate c-Jun-induced transcriptional activity. However, JAB1/CSN5 does not affect JunB or v-Jun DNA-binding [1]. The involvement of JAB1/CSN5 as a co-activator has been demonstrated for several transcription factors in addition to c-Jun. JAB1/CSN5 is a transcriptional co-activator for heart and neural crest derivatives expressed 2 (HAND2) [32], MYC [10], and HIF-1α [11,12]. Furthermore, our finding shows that JAB1 knockdown decreased STAT3 DNA-binding activity and the expression levels of its target genes [13]. These results suggest that JAB1/CSN5 positively regulates STAT3 DNA-binding activity and the expression levels of its target genes. Recent studies have suggested that JAB1/CSN5 associates with chromatin DNA. Chromatin immunoprecipitation (ChIP) experiments showed that JAB1/CSN5 and its interactor, SMYD3 exist in the *INK4a* promoter [24]. Furthermore, JAB1/CSN5 as a Cockayne syndorome group A protein-binding partner was detected in the solubilized chromatin fraction in response to UV irradiation [25]. However, it still remains unclear how JAB1/CSN5 exists on chromatin DNA. Further studies to identify the protein complex-associated with JAB1/CSN5 on chromatin DNA are needed.

JAB1/CSN5 in Cancer

As described above, the functions of JAB1/CSN5 have contributed to oncogenesis. JAB1/CSN5 transports the tumor suppressor proteins including p27, p53, 9-1-1 complex, Runx3, and SMAD7 to the cytoplasm, and subsequently degrades these proteins in the proteasome. Furthermore, JAB1/CSN5 activates oncogenic transcription factors including c-Jun, MYC, HIF-1α, and STAT3.

JAB1/CSN5 is found to be overexpressed in a number of human tumors, and it is important to clarify whether this overexpression is sufficient in tumorigenic process. To investigate more directly how JAB1/CSN5 overexpression leads to tumorigenesis, a stable form of JAB1/CSN5 was ectopically expressed in mice. Consequently, the transgenic mice developed myeloproliferative disorders [24]. However, the tumorigenic phenotype was less severe, suggesting that JAB1/CSN5 collaborates with other oncogenic proteins. Interestingly, JAB1/

CSN5 was found to act as a master regulator of wound gene expression signature in breast cancer cells in cooperation with MYC [10]. Wound gene expression signature seems to reflect the gene expression signature of metastasis and invasion. Therefore, this result suggests that JAB1/CSN5 acquires metastatic ability to cancer cells in cooperation with MYC. *JAB1/CSN5* gene is located on 8q13, and *MYC* gene is located on 8q24. These regions are frequently amplified in breast, prostate, and ovarian cancers [33-35]. It suggests that the amplification of 8q region leads to the acquisition of metastatic ability of cancer cells. Further studies are needed to investigate whether the combination of JAB1/CSN5 and MYC has effects on the other phenotypes of cancer cells, such as drug resistance, cancer stemness, and cell survival. Furthermore, JAB1/CSN5 is involved in DNA repair. In JAB1/CSN5-deficient cells, *RAD51* expression level was reduced by the accumulated p53 binding to the *RAD51* promoter [36]. Recent studies showed that the combination of JAB1/CSN5 knockdown and cisplatin-induced DNA damage increased apoptosis compared with JAB1/CSN5 knockdown alone [37]. Furthermore, JAB1/CSN5 knockdown increased UV radiation- and ionizing radiation-induced apoptosis. In contrast, JAB1/CSN5 overexpression blocked UV radiation-, ionizing radiation-, and cisplatin-induced apoptosis [38]. These results suggest that JAB1/CSN5 knockdown reduces RAD51 expression level, leading to the decrease in the ability to repair the DNA lesions.

JAB1/CSN5 and Prognosis

A number of studies have implicated that JAB1/CSN5 overexpression correlated with reduced p27 expression and poor prognosis [3]. Furthermore, the combination of JAB1/CSN5 overexpression and reduced p27 expression more highly correlated with poor prognosis [39]. While the connection between JAB1/CSN5 overexpression and reduced p27 expression is evident in human tumors, the correlation between JAB1/CSN5 overexpression and the activation of transcription factors, such as c-Jun, MYC, HIF-1α and STAT3 remains to be validated in human specimens. These transcription factors are well-characterized oncogenes that have been demonstrated to promote cellular proliferation, metastasis, and drug resistance. Furthermore, these transcription factors have been proven to have prognostic value in a number of tumor types and to contribute to carcinogenesis. As the activated transcription factors translocate to the nucleus, we should focus on the expression level of nuclear JAB1/CSN5 but not total JAB1/CSN5. Further studies are needed to investigate whether the combination of nuclear JAB1/CSN5 overexpression and the activation of oncogenic transcription factor or nuclear JAB1/CSN5 overexpression alone more highly correlates with poor prognosis.

Regulation of JAB1 Expression, Nuclear Localization, and its Activity

JAB1/CSN5 gene is located on 8q13, which is frequently amplified during cancer progression. DNA copy number gain of JAB1/CSN5 was confirmed in a study of hepatocellular carcinoma with amplification of 8q region [40]. Besides JAB1/CSN5 amplification, several proteins have been shown to regulate JAB1/CSN5 expression level. The oncogenic tyrosine kinase Bcr-Abl regulates the formation of JAB1/CSN5 subcomplex, which is required for p27 down-regulation [16]. Furthermore, the human epidermal growth factor receptor 2 (HER2) oncogene increases *JAB1/CSN5* expression through the binding of β-catenin and transcription factor 4 (TCF-4) to the *JAB1/CSN5* promoter [41]. Interestingly, epidermal growth factor (EGF) treatment increases nuclear JAB1/CSN5 expression level but not its total expression level, leading to the reduction of p27 expression level [42]. Psoriasin/S100A7 also increases nuclear JAB1/CSN5 expression level but not its total expression level, resulting in the increase of AP-1 activity and the reduction of p27 expression level [43]. These results suggest that EGF treatment or psoriasin/S100A7 overexpression increases nuclear import of JAB1/CSN5, leading to an increase in nuclear JAB1/CSN5 activity. Further studies are needed to elucidate the mechanism by which JAB1/CSN5 translocates into the nucleus. Recent study has revealed that *JAB1/CSN5* is transcriptionally activated through the binding of STAT3 to the *JAB1/CSN5* promoter in breast cancer cells [44]. Combined with our finding that JAB1/CSN5 positively regulates STAT3 DNA-binding

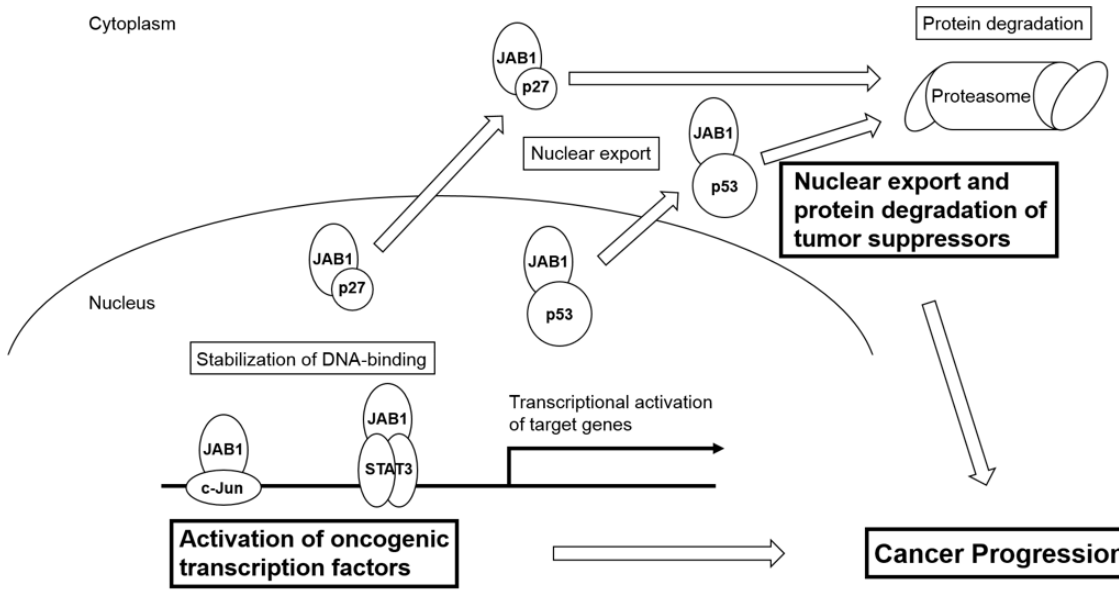

Figure 1: Overview of the roles of JAB1/CSN5 in cancer progression. In the nucleus, JAB1/CSN5 positively regulates oncogenic transcription factors through stabilization of their DNA-binding, leading to transcriptional activation of target genes. JAB1/CSN5 also negatively regulates tumor suppressor proteins through their nuclear export and protein degradation in the cytoplasm.

activity [13], a positive feedback loop between JAB1/CSN5 and STAT3 may exist. Taken together, these studies showed a link between JAB1/CSN5 expression and the activity of well-known oncogenes, suggesting that JAB1/CSN5 is closely involved in cancer progression.

Conclusions and future Perspective

In this review article, we provide succinct information on the roles of JAB1/CSN5 in tumorigenesis. JAB1/CSN5 interacts with multiple proteins and affects many aspects of tumorigenesis in both the nucleus and the cytoplasm. In the nucleus, JAB1/CSN5 positively regulates oncogenic transcription factors through stabilization of their DNA-binding, which leads to transcriptional activation of target genes. JAB1/CSN5 also negatively regulates tumor suppressor proteins through their nuclear export and protein degradation in the cytoplasm (Figure 1). Consequently, JAB1/CSN5 leads to an increase in cell proliferation, cell viability, DNA repair, metastasis, and drug resistance. JAB1/CSN5 functions as a member of the CSN holocomplex, smaller complex consisting of some CSN subunits, and monomeric form. Further studies are needed to elucidate which form-associated with JAB1/CSN5 regulates protein degradation of tumor suppressors and activation of oncogenic transcription factors. Answering these unknown things will provide a novel and effective strategy for the prevention of tumor progression and lead to a successful treatment of human malignant tumors.

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Conflicts of interest

The authors confirm that there are no conflicts of interest.

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