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Chapter 10

Jab1/Csn5 Signaling in Breast Cancer

Yunbao Pan and Francois X. Claret

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Abstract

c-Jun activation domain-binding protein1 (Jab1), also known as a monomer or the fifth component of the constitutive photomorphogenesis 9 signalosome (Csn5) complex, regulates cell proliferation, cell-cycle progression, and apoptosis and affects a series of pathways. Jab1/Csn5 also promotes cell transformation and tumorigenesis, and its overexpression in many tumor types suggests it is involved in cancer progression and closely associated with poor cancer prognosis. Jab1/Csn5 dysregulation contributes to oncogenesis by deactivating several tumor suppressors. Increasing evidence of the role of Jab1/Csn5 overexpression in breast and other cancers has spurred interest in Jab1/Csn5 inhibitors for cancer therapy. In this chapter, we summarize the evidence demonstrating the importance of Jab1/Csn5 expression in breast and other cancers and review recent advances in dissecting the Jab1/Csn5 signaling pathway along with its potential as a therapeutic target for cancer.

Keywords: breast cancer, Jab1/Csn5, biomarker, DNA damage, therapeutic approach

1. Introduction

c-Jun activation domain-binding protein 1 (Jab1), primarily identified as a c-Jun coactivator [1], is the fifth member of the constitutive photomorphogenesis 9 signalosome (Csn5) complex. Specifically, Jab1/Csn5 is an evolutionarily conserved multifunctional protein involved in developmental processes in eukaryotic organisms and primarily identified as an inhibitor of light-dependent growth and transcription in *Arabidopsis* [2, 3]. Jab1/Csn5 participates in deneddylation of neural precursor cell expressed developmentally downregulated gene 8 (NEDD8), transcription factor specificity, and binding of several key molecules. Increasing evidence indicates that dysregulation of Jab1/Csn5 activity contributes to tumorigenesis, which

is functionally inactivating several tumor suppressors and key negative regulatory proteins, including the cyclin-dependent kinase (CDK) inhibitor p27Kip1 (p27), p53, and SMAD4/7 [4]. Jab1/Csn5 is aberrantly expressed in different tumor types and lines of evidence support that it is a proto-oncogene. In this chapter, we describe some mechanisms by which Jab1/Csn5 is involved in cancer progression to provide perspective with the hope that these mechanisms will lay the foundation for future therapeutic intervention.

2. Structural features of Jab1/Csn5

CSN is a conserved protein complex that typically comprises eight subunits $^{1/m}$CSN1–CSN8$^{1/m}$ in descending order according to molecular weight [5]. Six of these subunits contain a proteasome, constitutive photomorphogenesis 9 signalosome, initiation factor 3 domain or PINT domain, that serves as a structural scaffold for the assembly of the constitutive photomorphogenesis 9 signalosome, and the other two subunits contain an MPR1 and PAD1 N-terminal (MPN) domain [5, 6]. Although both CSN5 and CSN6 have MPN domains; only the CSN5 MPN domain contains an embedded Jab1/MPN domain metalloenzyme motif (also named as an MPN + motif), which is the catalytic center for CSN isopeptidase activity [5]. Jab1/Csn5 contains 334 amino acids and assembles a nuclear export signal (NES) domain near the p27-binding domain at the end of the C-terminus [7]. This is a rich blend of leucine nuclear export signal sequences, which are highly conserved among different species. Through interaction with the NES domain, CRM1, which exports factors from the nucleus, combines with Jab1/Csn5 via an LMB-sensitive method and then carries the p27 protein out of the nucleus. When the leucine residues of Jab1/Csn5 are replaced by alanine residues, the NES can reduce Jab1 and CRM1 interaction, which impacts LMB-dependent nuclear cytoplasmic output process as well as the degradation of p27 in cells.

The catalytic activity of the CSN complex resides in the deneddylation of the CRLs, that is, the hydrolysis of the cullin-neural precursor cell expressed developmentally downregulated gene 8 (Nedd8) isopeptide bond. Although CSN-dependent Jab1/Csn5 has isopeptidase activity, it is intrinsically inactive in other physiologically conditions. Although the Jab1/Csn5 active site is catalytically competent and compatible with di-isopeptide binding, the Ins-1 segment obstructs access to its substrate-binding site, and structural rearrangements are necessary for the Nedd8-binding pocket formation. Detailed study of Jab1/Csn5 by molecular dynamics discovered the flexibility and plasticity of the Ins-1 segment [8]. These studies resulted in the identification of a molecular trigger implicated in the active/inactive switch that is sufficient to impose on Jab1/Csn5 an active isopeptidase state. Additionally, a dynamic monomer-dimer equilibrium exists both in vitro and in vivo and may be functionally relevant [8].

3. Jab1/Csn5 overexpression in breast cancer and other cancer types

Jab1/Csn5 regulates the transcriptional activity of activator protein 1 (AP-1) and also modulates cell signal transduction, regulating genetic transcription and the stability of the

protein [1]. Importantly, Jab1/Csn5, alongside with Myc, was found to act as a master regulator of a wound gene expression signature in breast cancer cells. This study suggests that Jab1/CSN5 plays an important role in translating the cell stress response to transcription of response genes that are involved in proliferation and matrix invasiveness [9]. Aberrant overexpression of Jab1/Csn5 is implicated to play a role in the pathogenesis of several types of human malignancies and tends to correlate with poor cancer prognosis. Adler et al. [10] provided the first evidence that Jab1/Csn5 isopeptidase activity is essential for human and murine mammary epithelial transformation and progression. In another study, Jab1/Csn5 expression was low in or absent from normal breast tissue, but it was aberrantly expressed in 57% (125 of 220) of node-negative breast tumors and 90% (9 of 10) of metastatic lesions [11]. Importantly, breast cancer patients with Jab1/Csn5-negative tumors had neither relapse nor disease progression at a median follow-up time of 70 months [12]. Additionally, Jab1/Csn5 was overexpressed in 33% (11 of 33) of benign ovarian tumors and 68% (32 of 47) of malignant ovarian tumors and correlated with poor overall survival of ovarian cancer [13]. Additionally, aberrant expression of Jab1/Csn5 has been positively associated with hepatitis C virus infection and negatively correlated with hepatitis B virus infection in hepatocellular carcinoma patients, indicating a possible mechanism that promotes hepatocarcinogenesis [14]. In a study of non-small cell lung cancer patients, those with elevated Jab1/Csn5 expression had a poorer overall survival rate (44%) after 5 years than did patients with lower Jab1 expression levels (63%) [15]. Jab1/Csn5 expression also is closely linked with histological differentiation, clinical stage, and lymph node metastasis in oral squamous cell carcinoma cases [16]. Patients with oral squamous cell carcinoma, nasopharyngeal carcinoma, and laryngeal squamous cell carcinomas, as well as those with thyroid carcinomas and Jab1/Csn5 overexpression, tend to have poor overall survival, indicating a critical role in cancer progression [16–19]. Furthermore, Jab1/Csn5 plays a role in cancer therapy. In particular, depletion of Jab1/Csn5 enhanced the antitumor effects of cisplatin and ionizing radiation in NPC cells [20, 21].

Researchers have made substantial progress in deciphering the critical role of Jab1/Csn5 in diverse cellular and developmental processes. However, little is known about the underlying regulatory principles that promote Jab1/CSN5 overexpression in cancer. Jab1/Csn5 overexpression may result from *Jab1/Csn5* gene amplification. The *Jab1/Csn5* locus is located on 8q13.1, which is always amplified in breast cancer and other cancer patients [9, 22]. As we described above, several other signaling pathways may also contribute to overexpression of Jab1/Csn5, such as interleukin 6/signal transducer and activator of transcription 3 (Stat 3), human epidermal growth factor receptor 2 (EGFR) (HER–2)/AKT, and Bcr/Abl. For example, the protein psoriasin (S100A7) enhances Jab1/Csn5 as well as activator protein 1 activity and promotes tumorigenesis [23]. Moreover, expression of Jab1/Csn5 is related to degradation of p57 protein [24] and contributes to tumor recurrence [19]. These findings provided a new opportunity to make Jab1/Csn5 a tumor target. Identifying the underlying mechanisms of Jab1/Csn5 in cancer still requires further exploration, but Jab1/Csn5 has proven to be a useful diagnostic and prognostic marker for cancer.

4. Jab1/Csn5-associated signaling

A number of studies have demonstrated that Jab1 lies at the intersection of several important signal transduction pathways that are believed to be important in the progression of breast cancer (**Figure 1**). Elucidating the regulatory mechanism of Jab1/Csn5 expression in these pathways will enhance our understanding of breast tumorigenesis.

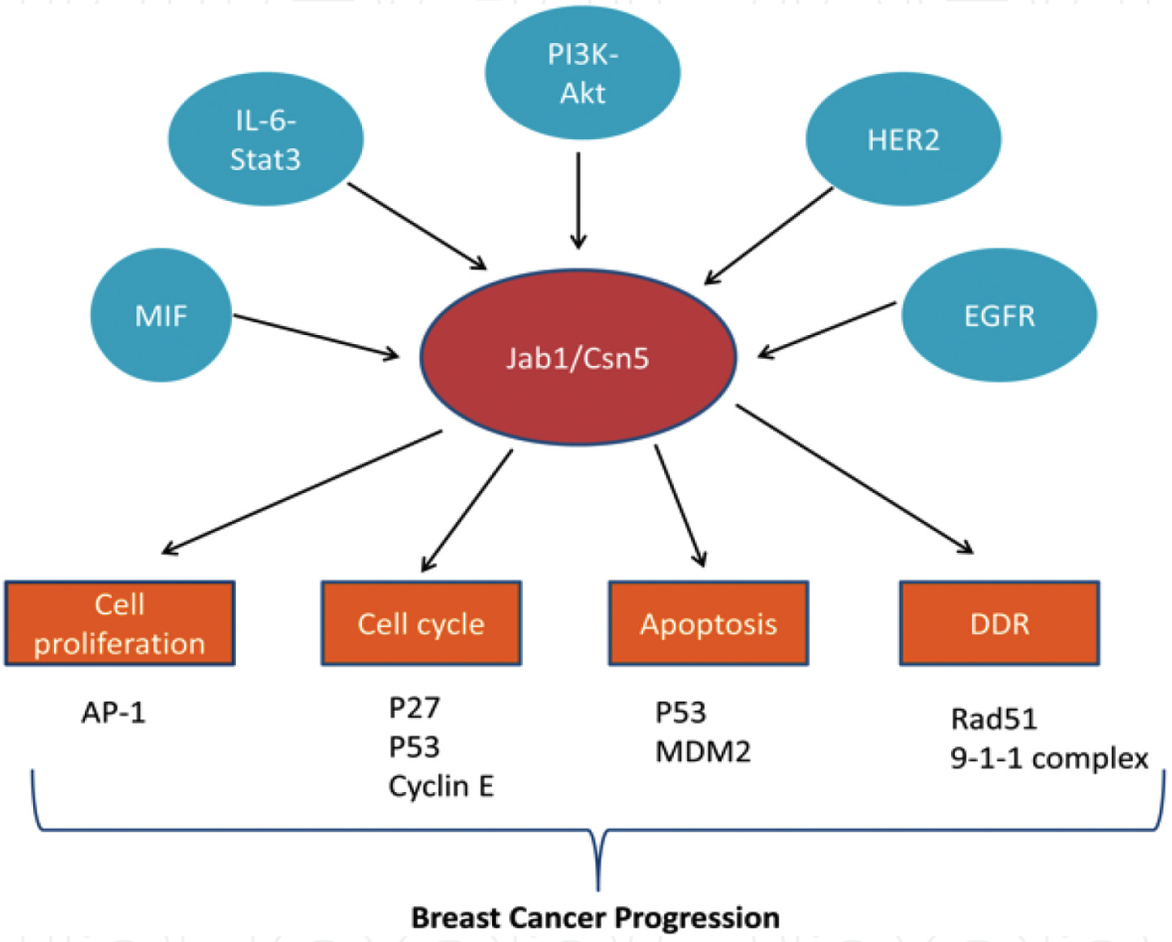

Figure 1. Jab1/Csn5 regulatory network in breast cancer cases. Jab1/Csn5 plays an essential role in breast cancer progression. On the one hand, Jab1/Csn5 activity and expression can be regulated by several typical oncogenic signaling pathways, such as MIF, phosphoinositide 3-kinase/AKT, interleukin-6/Stat3, HER-2/AKT, and EGFR. On the other hand, Jab1/Csn5 regulates a myriad of proteins involved in cell proliferation, cell cycle, apoptosis, and DDR.

4.1. Jab1/p27 signaling

Increasingly, studies have demonstrated that Jab1/Csn5 overexpression is negatively associated with p27 expression and poor prognosis [25] for many human cancers. p27 is a member of the cell-cycle inhibitor family of proteins, which is a primary driving force for cell-cycle progression through ubiquitination of G1 cyclins and CDK inhibitors, such as cyclinE-CDK2 and cyclinD1-CDK4 [25]. Eventually, p27 causes cell-cycle arrest during G1 phase and inhibits

cell proliferation. Jab1/Csn5 directly binds to p27 and mediates its shuttling from the nucleus to cytoplasm in a CRM1-dependent manner via the NES sequence [7]. Furthermore, researchers have observed cytoplasmic translocalization of p27 in human cancers and that it correlates with poor survival [26]. Many studies have demonstrated that Jab1/Csn5 expression increases along with p27 nuclear translocation, thereby accelerating p27 degradation via the ubiquitin-proteasome pathway [27]. Also, depletion of Jab1/Csn5 by small interfering RNA substantially increases p27 expression, including that of the p27/cyclin E/Cdk2 complex, and nuclear accumulation of p27 and inhibits the cell-cycle transition from G1 to S phase [27]. In addition, Jab1/Csn5 may degrade p27 through a Skp2-independent mechanism [28]. Investigators found that Skp2-mediated degradation of p27 mainly occurred in cells undergoing DNA replication [29]. Interestingly, evidence suggests that elevated AKT (a protein kinase B) expression leads to decreased p27 expression in the nucleus. AKT-mediated phosphorylation of p27 at Thr187 is known to inactivate p27 and restrain the translocation of p27 into the nucleus. Subsequently, degradation of p27 by the ubiquitin-proteasome system is associated with dysregulation of the cell cycle and promotes tumor formation [30]. Hsu et al. [31] provided the first evidence that Jab1/Csn5 expression may be regulated by HER-2/neu via the AKT signaling pathway. Whether Jab1 is directly related to AKT or the underlying mechanism of action between them is currently unknown.

4.2. HER-2 and EGFR signaling

Jab1/Csn5 is linked with EGFR and HER-2/neu receptor signaling in breast tumorigenesis. Jab1/Csn5 is a downstream target of HER-2/neu, and Jab1/Csn5 overexpression is correlated with HER-2/neu in breast cancer [32]. HER-2/neu directly activates Jab1/Csn5 promoter activity and upregulates Jab1/Csn5 mRNA expression via AKT/β-catenin signaling [31]. Suppression of HER-2/neu by treatment with trastuzumab (Herceptin) decreases Jab1/Csn5 expression in different types of cancer cells [33]. Furthermore, Jab1/Csn5 is a target of EGFR signaling, and its expression correlates with EGFR expression in estrogen receptor-alpha-negative breast cancer cell lines. EGFR activation increases the translocation of Jab1/Csn5 to the nucleus and regulates p27 downstream from Jab1 [34]. These findings suggested that Jab1/Csn5 is involved in the development and progression of breast cancer.

4.3. Migration inhibitory factor/phosphoinositide 3-kinase/AKT signaling

Jab1/Csn5 controls autocrine macrophage migration inhibitory factor (MIF)-mediated activation of phosphoinositide 3-kinase/AKT signaling, a novel, indirect mechanism between the Jab1/Csn5 and phosphoinositide 3-kinase/AKT pathways, by inhibiting MIF secretion and its autocrine prosurvival activities [35]. In turn, MIF negatively regulates Jab1/Csn5, as MIF can specifically interact with Jab1/Csn5 and inhibit Jab1/Csn5-enhanced activator protein 1 and c-Jun N-terminal kinase activity [36].

4.4. Interleukin-6/STAT3 signaling

Jab1/Csn5 interacts with protein to regulate unphosphorylated Stat3 DNA-binding activity. Loss of Jab1/Csn5 expression markedly decreases unphosphorylated Stat3 DNA-binding

activity as well as expression of Stat3 target genes but tends to increase nuclear Stat3 in human colon cancer cells [37]. This interesting phenomenon must be studied further to elucidate how Jab1/Csn5 determines the fate of transcription factors as its binding partners. Does it do so by binding to target DNA or via protein degradation? In contrast, another study demonstrated that Stat3 binds to the Jab1/Csn5 promoter, enhances its promoter activity, and increases Jab1/Csn5 transcription in breast cancer cells. Depletion of Stat3 dramatically decreases Jab1/Csn5 promoter activity and Jab1/Csn5 mRNA and protein expression [38]. Moreover, upstream activators of Stat3, such as interleukin-6 and Src, also contribute to activation of Jab1/Csn5 transcription and expression via Stat3.

4.5. Jab1/Csn5 in DNA damage response

In recent years, owing to rapid advances in knowledge of DNA damage repair signal mechanisms and the study of epigenetic molecular mechanisms, researchers have made great progress in understanding the principle and mechanism of tumorigenesis after DNA damage response (DDR). Inactivation of DDR genes increases the risk of accumulating genetic mutations, which may greatly promote cancer development [4]. Increasing evidence supports that Jab1/Csn5 affects both the activity and stability of DDR proteins [20]. Jab1/Csn5 is essential for tumor survival and enhances tumor resistance to chemotherapy and radiotherapy [20]. Importantly, Jab1/Csn5 can mediate the nuclear export and degradation of several nuclear proteins, including those involved in DDR [4]. Study results have demonstrated that Jab1/Csn5 deletion during meiosis can activate the DNA damage checkpoint in *Drosophila melanogaster* [39]. CSNs regulate the ubiquitin ligase activity of the damage DNA-binding protein 1 or DNA-binding protein 2 and Cockayne syndrome group A complexes in response to exposure to DNA-damaging agents. The authors report that Jab1/Csn5 deficiency decreased the repair vitality of DNA-binding protein 2 by 50% [40]. Additionally, Cdc10-dependent transcript 1, a licensing factor for the prereplication complex, is regulated by Jab1/Csn5. Cdc10-dependent transcript 1 is degraded after DNA damage, and Jab1/Csn5 deficiency may lead to accumulation of Cdc10-dependent transcript 1 [41]. Also, the Rad9/Rad1/Hus1 complex is a DNA damage sensor that transduces DNA damage and plays an important role in initiation of cellular responses to DNA damage. This complex promotes ATR-mediated phosphorylation and activation of Chk1, a protein kinase that regulates progression to S phase, cell-cycle arrest at G2/M, and replication fork stabilization [42]. Because Jab1/Csn5 is involved in regulating the stability and translocation of the Rad9/Rad1/Hus1 complex in cells, it likely provides information about Jab1/Csn5 in checkpoint and DDR [4].

In eukaryotes, Rad51, a key DNA-repair protein, plays a primary role in DNA damage repair using emerging nucleoprotein filaments and mediation of strand conversion among DNA duplexes [43]. Rad51 is vital for embryo survival in response to exogenous DNA-damaging stimulation for the repair of spontaneous chromosome breaks during cell development [44]. In accordance with these findings, Jab1/Csn5 has been discovered the function with Rad51 in the homologous recombination repair pathway [43]. Furthermore, Jab1/Csn5 deficiency has not only decreased Rad51 expression but also affected its activity, and the

absence of Rad51 has caused a large number of chromosome breaks, leading to increased apoptosis. Decreased Rad51 expression in Jab1/Csn5 knockdown cells is at least partly dependent on p53 expression [20].

5. Predictive and therapeutic roles of Jab1 in cancer cases

Increasingly, studies have demonstrated that overexpressed Jab1/Csn5 is involved in cancer pathogenesis and correlates with poor cancer prognosis [25]. The authors reported that Jab1+/p27− patients had poor overall survival of many cancers [13, 25]. Lin Guo's group recently provided the first evidence that NCoR is a target of Jab1/Csn5 and mediates endocrine resistance in breast cancer [45]. Jab1/Csn5 might involve in multiple stages of breast cancer progression by regulating different protein targets. Further identification and elucidation of the E3 ligase that connects Jab1/Csn5 and NCoR are of importance to understand the precise mechanisms underlying endocrine resistance and identify additional druggable molecular targets. Thus, Jab1/Csn5 is an attractive therapeutic target for cancer given its multiple prominent functions in many stages of tumorigenesis.

Downregulation of Jab1/Csn5 expression has inhibited growth of and induced apoptosis in breast cancer [31] and nasopharyngeal carcinoma cells [27]. Furthermore, researchers found that Jab1/Csn5-deficient mice had an embryonically lethal phenotype, indicating that Jab1/Csn5 is critical for fetal development and survival [46]. In that study, Jab1/Csn5-null embryos were smaller than wild-type embryos and displayed delayed growth [46].

Also, the development of Jab1/Csn5-specific inhibitors has had major effects on cancer treatment. For example, curcumin is a yellow plant pigment that directly inhibits the activity of Jab1/Csn5-associated kinases, causing cell-cycle arrest in tumor cells during the mitotic phase and making them more prone to apoptosis by inhibiting Jab1/Csn5 [47]. A recent study demonstrated that PEGylated curcumin, a water-soluble compound, inhibited the growth of pancreatic cancer cells and sensitized them to gemcitabine-induced apoptosis [48]. Another study demonstrated that the curcumin analog T83 markedly induced cell-cycle arrest and apoptosis in nasopharyngeal carcinoma cells. In addition, T83 effectively inhibited Jab1/Csn5 expression in these cells and sensitized them to radiotherapy [49].

Another potential Jab1/Csn5-targeted drug is troglitazone, a peroxisome proliferator-activated receptor γ ligand that directly suppresses Jab1/Csn5 promoter activity by inhibiting Sp1- and Tcf4-mediated transcription [32]. A number of in vitro and in vivo studies have demonstrated that treatment with troglitazone effectively attenuated tumor growth and upregulated p27 expression in tumor cells in a time- and dose-dependent manner [50]. Animal studies verified that intratumoral or intraperitoneal injection of troglitazone attenuated hepatocellular carcinoma cell growth and reduced Jab1/Csn5 expression in hepatocellular tumors [14].

Although increasing evidence demonstrates that Jab1/Csn5 can be used as a therapeutic target for cancer, much work is still needed to develop a Jab1/Csn5-specific inhibitor for cancer

treatment. The degree, duration, and cell specificity required for Jab1/Csn5 blockade to attenuate tumor growth should be studied further.

6. Conclusion and perspective

Jab1/Csn5 is a master regulator of a myriad of protein interactions involved in signaling pathways, cell survival, apoptosis, and DNA damage repair via ubiquitin-dependent proteolysis (**Figure 1**). Although Jab1/Csn5 function has a different role in each tumor type, overexpressed Jab1/Csn5 is associated with the whole process of carcinogenesis and cancer progression, and further studies of Jab1/Csn5 as a therapeutic target will provide new insight into cancer treatment. Considering the pivotal role of Jab1/Csn5 signaling, a reasonable assumption is that Jab1/Csn5 is a promising diagnostic, prognostic, and therapeutic biomarker for cancer.

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Conflict of interest

None.

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