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c-Jun ACTIVATION DOMAIN-BINDING PROTEIN-1 (Jab1): ADVANCEMENTS TOWARDS ITS ROLE AS AN EMERGING THERAPEUTIC TARGET IN CANCER TREATMENT

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ABSTRACT

With an escalating side effect of chemotherapy and in depth knowledge of oncogenic signal transduction pathways, targeted therapies have emerged as an exciting advancement in the treatment of sepsis, and inflammatory and autoimmune diseases. Jab1-directed therapies might offer new treatment opportunities for cancer disease in the future with minimal side effects. Still, there are various hidden pockets resides in the cancer progression still which needs to be uncovered. Hence there is a strong need to reevaluate these mechanisms to elucidate new targets which could further aid in the development of targeted therapeutic approach. The present article concentrates on an upcoming therapeutic target, c-Jun activation domain-binding protein-1 (Jab1), a regulator of multiple protein interactions, integrin signaling, cell proliferation, apoptosis, genomic instability and DNA repair. Jab1 interacts with various nuclear receptors and activates transcription at the corresponding target genes which provide a firm basis for the link between the massive regulatory complexes containing nuclear receptor coactivators and the Jab1 containing signalosome. Our review may pave the way for targeting Jab1 for anti-cancer drug development and also provide an insight into the mechanisms for the development of inhibitory compounds against Jab1 which could be useful in the prevention of carcinogenesis with minimal side effects.

Keywords: Carcinogenesis, Chemotherapy, CSN complex, Jab1, Natural compounds, *In-silico*

INTRODUCTION

Cancer remains one of the most challenging human diseases and is leading cause of deaths due to boundless mechanisms in their progression. Chemotherapy is the most widely accepted treatment for the cure of cancer. Chemotherapy acts on active cells which may be either cancerous or non-cancerous cell. Chemotherapeutic drugs have the inevitable tendency to attack healthy cells which are responsible for severe side effects on the body. For a better knowledge of the molecular basis of the development and progression of carcinoma, there is a strong need to develop better treatment approaches. Oncogenic proteins inactivation and tumor suppressor proteins stimulation have emerged as an efficient manner for cancer treatment. Thus the protein which acts as a positive regulator of oncogenic proteins and negative regulator of tumor suppressor proteins could be considered as a potential target for novel and effective cancer therapy. This study would provide unique insight into the evolutionarily conserved transcriptional cofactor that plays a significant role in cell differentiation, proliferation, and apoptosis by modulating the activity of diverse factors and regulating the output of various signaling pathways. A multifunctional proto-oncoprotein that affect different stages of carcinogenesis by functionally inactivating several key negative regulatory proteins and tumor suppressors and has been involved in multiple protein interactions, integrin signaling, cell proliferation, apoptosis, and the regulation of genomic instability and DNA repair **(Shackleford *et al*. 2010).** The current treatment of cancer mainly relies on chemotherapy or surgery but has the limitation of various side effects on healthy cells hence there is a strong need to focus on a targeted therapeutic approach to combat with the side effects of chemotherapy. Therefore, there is a high need to elucidate inhibitors against Jab1/CSN5 due to the association of its overexpression with the initiation and outcome of various human cancers **(Hsu *et al*. 2008; Pan *et al*. 2012; Patil *et al*. 2005; Cope *et al*. 2003).**

Jab1/CSN5, a c-Jun coactivator, is a multifunctional protein complex that interacts with various tumor suppressor proteins including p27 **(Tomoda *et al*. 2002)**, p53, cyclin E, Smad 4/7, LHR and results in their inactivation either by translocating them from the nucleus to the cytoplasm or by modulating signal transduction.Various studies reported its interaction with different proteins and thereby resulting in increasing their stabilization and transcriptional activity. CSN5 inactivation results in restitution of

the many programs responsible for controlling cell proliferation and apoptosis and can be effective as an anti-cancer strategy. For this reason, Jab1 is also referred as a multifunctional protein involved in the regulation of cell cycle, signal transduction, and DNA repair **(Tian *et al.* 2010).** CSN5 over expression has been reported in breast, thyroid, skin, ovarian, lung, and liver cancers **(M.H. Lee. *et al.* 2011)**. SiRNA mediated knockdown of CSN5 cell-cycle progression and causes strong induction of apoptosis in hepatocellular carcinoma cells (**Y.H. Lee. *et al.* 2011**). CSN5 downregulation displayed significant role in impeding CSN function through an accumulation of neddylated cullin 1 (Cul1) which resulted in a decrease in the oncogenic F-box protein Skp2. Thus stabilization of the NEDD8–CRL complex through inhibition of CSN5 could represent a novel therapeutic approach for the treatment of CSN5-dependent cancers **(T. J. Shackleford *et al.* 2014)**. Through previous studies, CSN5 has been revealed as one of the early markers of malignant conversion through consistent upregulation of the fifth subunit of COP9 signalosome (CSN5) gene at the beginning of Hepatocellular carcinoma **(Kaposi-Novak *et al.* 2009)**. CSN5/Jab1 can be considered as the catalytic center of CSN complex which mediates the proteolysis via this pathway, transcription, protein phosphorylation and intracellular distribution. CSN5 is found to be responsible for the stability of various intracellular regulators such as MYC, TGFb1, MIF, c-Jun, HIF1a, p27, E2F1, RUNX3, and p53. Jab1 plays a pivotal role in the regulation of some pathways including integrin signaling, cell-cycle control, and apoptosis **(Bech-Otschir *et al.* 2001; Wan *et al.* 2002; Kim *et al.* 2009)**. CSN5 gene encoded protein is one of the eight subunits of a COP9 signalosome complex which serves as an important multiple signaling pathways regulator. Jab1 is responsible for the proteolysis of several intracellular molecules which play critical roles in tumorigenesis. It has been previously reported that Jab1 interacts with p27 and induces nuclear exportation and its subsequent degradation from the nucleus to the cytoplasm and also in triggering the proteolysis of the tumor suppressor p53 thus conferring tumor promoting activity in cells **(Fei *et al.* 2014)**. Besides, Jab1 also exhibited Smad4 degradation via the ubiquitin/proteasome pathway which leads to inhibition of TGF-b-induced gene transcription **(Wan *et al.* 2002)**. Since TGF-b shows anti-cancer activity in the early stages of tumorigenesis, inhibition of TGF-b signaling pathway by Jab1 may

promote tumor formation. Jab1 prevented degradation of hypoxia-inducible factor-1 by enhancing its transcriptional activity and in turn stimulates the VEGF expression, a major HIF-1 target, to increase tumor angiogenesis **(Bae *et al.* 2002).**

Jab1 as an integrative component of CSN complex

The constitutive photomorphogenesis 9 signalosome is an evolutionarily conserved nucleus-enriched multisubunit complex that comprises of 8 subunits which regulate CRL family and many cellular and developmental processes in plants and animals (Enchev et al. 2010; Wei et al. 2003; Cope e al. 2003; Wei et al. 1999) (Table 1). COP9 signalosome was first reported as a repressor of constitutive photomorphogenic seedling development in Arabidopsis thaliana (**Atias *et al.* 2009; Harari-Steinberg *et al.* 2004).** In humans, CSN is found to be responsible for the regulation of various cellular processes including cell-cycle progression, signal transduction, transcriptional regulation and protein degradation (**Von *et al.* 2003; Wolf *et al.* 2003; Peng *et al.* 2001; Schwechheimer *et al.* 2001**). In humans, COP9 signalosome complex consists of eight subunits (CSN1 to CSN8) in which six subunits with a PCI (proteasome, COP9, eIF3) domain and two subunits with an MPN (MOV34, PAD N-terminal) domain (Hofmann et al. 1998; Browning et al. 2001). Jab1 was first identified by **Claret *et al.*** which play an important part in the regulation of various cellular processes such as the cell cycle and apoptosis, as well as some oncogenic signal transduction pathways. Jab1 belongs to the constitutive photomorphogenesis 9 (COP9) signalosome complexes and is one of the most widely studied putative biological prognostic biomarker in various carcinomas. Jab1 is also known as the fifth component of the COP9 signalosome which is evolutionarily conserved among plants, fission yeast, mice and humans **(Seeger *et al.* 1998, Wei *et al.* 1999, Claret *et al.* 1996)**. Various studies have reported that Jab1 plays vital roles in different cellular mechanisms including development in Drosophila and mouse **(Tomoda *et al.* 2004)**, cell cycle control and signal transduction pathways. Jab1 is found to be critical to cell survival and proliferation since it has been evolutionarily conserved in plants, fission yeast, mice and human **(Wei et al. 1998)**. In Arabidopsis **(Kwok *et al.* 1999)**, Drosophila **(Oron *et al.* 2002)**, and mammalian cells Jab1 is present in the large CSN holo complex, smaller complexes, and as a monomer. Various studies stated the implication of Jab1 in the regulation of signal transduction pathways

and Jab1-interacting proteins including components of cell signaling pathways **(Calandra *et al.* 2000)**. MIF, a pleiotropic cytokine, is a critical mediator of many immune and inflammatory conditions including bacterial septic shock rheumatoid arthritis, atherosclerosis, and tumorigenesis **(Bernhagen *et al.* 1993; Burger-Kentischer *et al.* 2002; Mitchell *et al.* 2000)**. MIF inhibits the increased Jab1 mediated phosphorylation level of c-Jun and activities of several transcription factors **(Morand *et al.* 2003)**. Jab1 exhibits a wide variety of functions independently or as a member of a CSN complex through interaction with a variety of proteins in a wide array of eukaryotes from plants to humans.

Functional domains of Jab1

In humans, the Jab1 gene is located on chromosome 8 and constitutes 334 amino acids with molecular mass of 38kDa **(Shackleford *et al.* 2010)**. Jab1 is either found in free form or CSN-associated form. Free Jab1 is located in both cytoplasm and nucleus whereas CSN associated Jab1 present in the nucleus. Jab1, located in both nucleus and cytoplasm, consists of nuclear export signal (NES) - like sequence and Mpr1-Pad1-N-terminal (MPN) domain containing metalloenzyme (JAMM) motif.

Jab1 mediated degradation of several tumor suppressor genes through the Ubiquitin- dependent proteasome pathway

Autophagy and the ubiquitin-proteasome system are two mechanisms responsible for intracellular protein degradation and replacement. CSN is the major component involved in regulating degradation of proteins by the UPS. The potential involvement of Jab1 in degradation of several tumor suppressor genes could be linked to its role in ubiquitin-meditated protein degradation activity **(Hershko *et al.* 1998)**. Ubiquitin (Ub)-proteasome pathway (UPP) involves activation, conjugation, ligation, and elongation and utilizes action of three different enzymes for attachment of Ub with the target protein and its degradation by an ATP-dependent process **(Glickman MH *et al.* 2002)**. Firstly Ub-activating enzyme E1 uses ATP to activate the Ub *via* the thiol ester linkage needed for its conjugation with proteins. Upon activation, Ub gets transferred to the sulfhydryl group of one of the E2 enzymes. The E2s are small Ub-carrier or conjugating proteins having a conserved 16-kD core which contains the cysteine that helps in forming a thiolester linkage with the activated Ub. These E2s are present in larger number and found to be helpful in generating the specificity of the ubiquitination system and can conjugate

with various E3enzymes. E3 enzymes are found to be either homologous to HECT domain or RING fingers. These E3 enzymes are Ub-protein ligase which plays a significant role in the catalytic transfer of activated Ub from E2 to a lysine residue of specific protein substrate and then subsequently to lysines of Ubiquitin which subsequently leads to the formation of a substrate-anchored chain of Ub molecules. 26S proteasome recognizes the attached Ub molecules. The 26s proteasome complex comprises of a 20S proteolytic core and two 19S regulatory caps on either side of the complex. Ub tagged protein gets recognized by the 19S caps which subsequently leads to the deubiquitinylation and unfolding of the target protein. 20S catalytic core pulls the unfolded protein and along with peptides degrade into amino acids components. This highly sophisticated ubiquitin-proteasomal pathway results in the aberrations in the protein degradation systems leading to various serious human diseases **(Seeger *et al.* 1998)**.

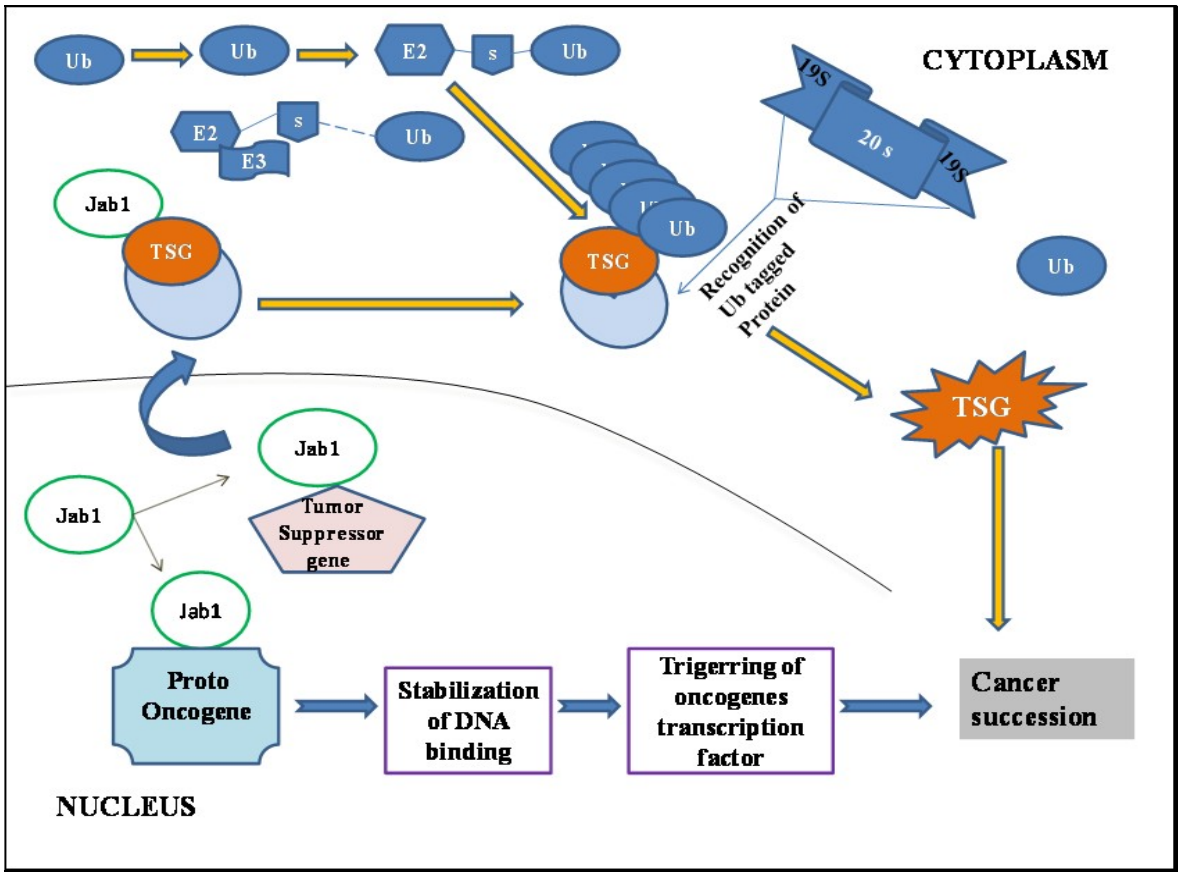

Fig: Pictorial representation of Ubiquitin-mediated degradation of tumor suppressor gene by Jab1. Ub=ubiquitin;TSG=Tumor suppressor gene;E2=Ub-carrier or conjugating proteins;E3=Ub-protein ligase.

Strategies employing Jab1 as a therapeutic target

Various molecular factors have been found to be involved in the chemotherapeutic resistance of cancer tumors. Commonly used treatment available for cancer includes Radiotherapy and chemotherapy. One of the possible causes of the limited success of chemotherapy is the acquirement of drug resistance by tumors, reduced target drug delivery, and its toxicity. Thus, seeking new treatment strategies aiming to reduce the side effects of chemotherapy is urgent in clinical practice to increase the therapeutic efficacy and inhibit metastasis of various carcinomas. It has led to the identification of novel molecule as a target for the development of therapeutic agents. This review provides a detailed insight into the various therapeutic approaches utilizing Jab1 for cancer treatment. A study recently demonstrated that Jab1 is a major contributor to the resistance of Nasopharyngeal carcinoma to UV radiation, IR, and cisplatin and used as a biomarker for predicting outcomes of cisplatin- and irradiation-based therapy in these patients. **(Pan *et al.* 2012)**.

Jab1 Knockdown by employing siRNA technology

Different types of small synthetic RNA including siRNA, shRNA, and bi-shRNA have gained a lot of interest in various therapies such as treatment of single-gene disorders and development of potent drugs for cancer treatment with reduced side-effects. RNA interference is a gene silencing mechanism which involves Knock downing of gene products involved in tumorigenesis. RNAi therapy has been emerged as the most significant player as compared to the other methods used in cancer treatment having low cost, high specificity in the induction of silencing in the advanced stages of growth and transmission of the silenced gene to the next generation **(Mansoori *et al.* 2014)**. The involvement of multiple siRNAs targeting various oncogenes from different cellular pathways would simultaneously result in the development of more potent and effective therapies for cancer. RNA interference strategy involves the use of siRNA of 21 to 23 nucleotides in length to silences a target gene by binding to its complementary mRNA and thereby resulting in its degradation. Jab1 overexpression has led to increased pancreatic cancer cell growth and protein degradation, whereas Jab1 gene silencing by siRNA suppressed various cancer cell proliferation. siRNA knockdown of CSN5/Jab1 showed that Jab1 controls autocrine MIF-mediated Akt signaling by inhibition of MIF secretion **(Kleemann *et al.* 2000)**.

***In silico* approach employing Jab1/CSN5 Protein as a target and Discovery of Small Potent inhibitory compound against Jab1 in cancer treatment**

In the current scenario, the criteria used to choose best possible anticancer drug candidates include inhibitors of cell proliferation and pathways in cancerous cells. Drug discovery is a very complicated and time-consuming procedure with a numerous limitation including lack of effectiveness, side effects, poor pharmacokinetics. Hence, Intervention of in silico approach employing software is imperative to bring down the cost and time required in the drug designing. *In silico* approach helps in designing the suitable inhibitors against a target protein via bioinformatics tools **(Altschul *et al*. 1990)**. Cancer can be considered to be one of the leading causes of death in India and around the world. The introduction of new drug-targeted therapies has indubitably increased the cancer survival rate. However, advanced metastasized carcinoma remains incurable. Use of phytocompounds as an anti cancerous agent is a promising approach to treat various diseases including cancer. Plants are a tremendous source of bioactive compounds with their various health valuable effects and their anti-cancer activities. Experimental knowledge based on the medicinal benefits of plants pave us the way to identify novel anti-cancerous phytocompounds against cancer. A study recently reported that natural compounds in dietary food could also target small molecules in cancer cells and could activate or deactivate molecular signaling cascades **(Chen *et al*. 2012; Malik *et al*. 2007)**. Since there is a strong correlation between Jab1 overexpression and cancer progression, therefore, this review could be very insightful in understanding the significance of elucidating specific inhibitory compounds against Jab1 to combat the side effects of chemotherapeutic drugs. This study summarizes the latest research in the cancer treatment targeting Jab1 using various inhibitory compounds such as azaindoles as a new class of CSN5 inhibitors, which led to Skp2 degradation in cells, and reduced the viability of HCT116 cells **(Altmann, E. *et al*, 2017)**. Two Phytocompounds namely Curcumin and emodin have also been identified as the potential Jab1/CSN inhibitors which enhance the stability of the p27 and p53 protein **(Uhle *et al*. 2003; Desai *et al*. 2008; Aggarwal *et al*. 2003; Shao *et al*. 2002))**. PEGylated curcumin conjugate has also shown more potent effects on pancreatic cancer cell growth inhibition than free curcumin **(Li *et al*. 2009; Li *et al*. 2015)**. Turmeric also strongly inhibits the activity of a c-Jun N

terminal kinase, protein tyrosine kinases and protein serine/threonine kinases **(Leu *et al*., 2002)**. A derivative of the thermoquinone compound such as 5-methyl-2-(propan-2-yl)-3-(prop-2-en-1-yl) cyclohexa-2,5-diene-1,4-dione also plays a significant role in Jab1/CSN5 down-regulation in pancreatic cancer. These findings showed a link between Jab1 overexpression and carcinogenesis, suggesting that JAB1/CSN5 is intimately involved in cancer progression.

CONCLUSION

The high correlation between Jab1/CSN5 overexpression and cancer progression in humans gave us the way to elucidate its role as a strong prognostic biomarker further to aid in the development of targeted therapeutic approach. In this review, we provide concise information on the functions of Jab1 in cancer progression. Phytocompounds have been widely used to arrest the initiation and progression of carcinogenesis. Through this study, we have observed sound chemopreventive effects by various compounds against Jab1 in different carcinomas. Further investigation of inhibitory compounds against Jab1 would provide a reliable alternative to the use of chemotherapy or surgery for the treatment of cancer. Thus the goal of this review is not just to focus on the significance of Jab1 in cancer progression but to impend thrust to determine Jab1 specific inhibitors that may result in the discovery of potent anticancer agents. To the best part of my knowledge, very few significant research has been done to identify inhibitory compounds against Jab1 hence there is a broad scope of exploring Jab1 specific inhibitors to combat the side effects of chemotherapeutic drugs.

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REFERENCES

[1] Aggarwal BB, Kumar A, Bharti AC (2003). Anticancer potential of curcumin: preclinical and clinical studies. Anticancer research 23: 363-398.

[2] Altmann, E., Erbel, P., Renatus, M., Schaefer, M., Schlierf, A., Druet, A., & Jones, M. (2017). Azaindoles as Zinc-Binding Small-Molecule Inhibitors of the JAMM Protease CSN5. *Angewandte Chemie*, *129*(5), 1314-1317.

[3] Altschul SF, Gish W, Miller W, Myers EW, Lipman DJ (1990). Basic local alignment search tool. Journal of molecular biology 215: 403-410.

[4] Atias O, Chor B, Chamovitz DA (2009). Large-scale analysis of Arabidopsis transcription reveals a basal co-regulation network. BMC systems biology 3: 86.

[5] Bae MK, Ahn MY, Jeong JW, Bae MH, Lee YM, Bae SK, Kim KW (2002). Jab1 interacts directly with HIF-1α and regulates its stability. Journal of Biological Chemistry 277: 9-12.

[6] Bech-Otschir D, Kraft R, Huang X, Henklein P, Kapelari B, Pollmann C, Dubiel W (2001). COP9 signalosome-specific phosphorylation targets p53 to degradation by the ubiquitin system. The EMBO journal 20: 1630-1639.

[7] Bernhagen, J, Calandra T, Mitchell RA, Martin SB, Tracey KJ, Voelter W, Bucala R (1993). MIF is a pituitary-derived cytokine that potentiates lethal endotoxaemia. Nature 365: 756-759.

[8] Burger-Kentischer A, Goebel H, Seiler R, Fraedrich G, Schaefer HE, Dimmeler S, Ihling C (2002). Expression of macrophage migration inhibitory factor in different stages of human atherosclerosis. Circulation 105: 1561-1566.

[9] Calandra T, Echtenacher B, Le Roy D, Pugin J, Metz CN, Hültner L, Glauser MP (2000). Protection from septic shock by neutralization of macrophage migration inhibitory factor. Nature medicine 6: 34-38.

[10] Chen H, Yao K, Nadas J, Bode AM, Malakhova M, Oi N, Dong Z (2012). Prediction of molecular targets of cancer preventing flavonoid compounds using computational methods. PloS one 7: e38261.

[11] Claret FX, Hibi M, Dhut S, Toda T, Karin M (1996). A new group of conserved coactivators that increase the specificity of AP-1 transcription factors. Nature 1996. 383: 453–457.

[12] Cope GA, Deshaies RJ (2003). COP9 signalosome: a multifunctional regulator of SCF and other cullin-based ubiquitin ligases. Cell 114: 663-671.

[13] Desai AG, Qazi GN, Ganju RK, El-Tamer M, Singh J, Saxena AK, Bhat HK (2008). Medicinal plants

and cancer chemoprevention. Current drug metabolism 9: 581-591.

[14] Fei, M., Hang, Q., Hou, S., He, S., & Ruan, C. (2014). Adhesion to fibronectin induces p27Kip1 nuclear accumulation through down-regulation of Jab1 and contributes to cell adhesion-mediated drug resistance (CAM-DR) in RPMI 8,226 cells. Molecular and cellular biochemistry 386: 177-187.

[15] Glickman MH, Ciechanover A (2002). The ubiquitin-proteasome proteolytic pathway: destruction for the sake of construction. Physiological reviews 82: 373-428.

[16] Harari-Steinberg O, Chamovitz DA (2004). The COP9 signalosome: mediating between kinase signaling and protein degradation. Current Protein and Peptide Science 5: 185-189.

[17] Hershko A, Ciechanover A (1998). The ubiquitin system. Annual review of biochemistry 67: 425-479.

[18] Hsu MC, Huang CC, Chang HC, Hu TH, Hung WC (2008). Overexpression of Jab1 in hepatocellular carcinoma and its inhibition by peroxisome proliferator-activated receptorγ ligands in vitro and in vivo. Clinical cancer research 14: 4045-4052.

[19] Kim JH, Choi JK, Cinghu S, Jang JW, Lee YS, Li Y, Bae SC (2009). Jab1/CSN5 induces the cytoplasmic localization and degradation of RUNX3. Journal of cellular biochemistry 107: 557-565.

[20] Kleemann R, Hausser A, Geiger G, Mischke R (2000). Intracellular action of the cytokine MIF to modulate AP-1 activity and the cell cycle through Jab1. Nature 408: 211-216.

[21] Kwok SF, Staub JM, Deng XW (1999). Characterization of two subunits of Arabidopsis 19S proteasome regulatory complex and its possible interaction with the COP9 complex. J Mol Biol 285: 85-95.

[22] Leu TH, Maa MC (2002). The molecular mechanisms for the antitumorigenic effect of curcumin. Current Medicinal Chemistry-Anti-Cancer Agents 2: 357-370.

[23] Li GQ, Xie J, Lei XY, Zhang L (2009). Macrophage migration

inhibitory factor regulates proliferation of gastric cancer cells via the PI3K/Akt pathway. World Journal of Gastroenterology, 15: 5541.

[24] Li J, Gu Z, Li S, Xiao Z, Sun K (2015). Reverse correlation of Jab1 and Smad4 in PANC-1 cells involved in the pathogenesis of pancreatic cancer. International journal of clinical and experimental pathology 8: 9279.

[25] Li J, Wang Y, Yang C, Wang P, Oelschlager DK, Zheng Y, Wan M (2009). Polyethylene glycosylated curcumin conjugate inhibits pancreatic cancer cell growth through inactivation of Jab1. Molecular pharmacology 76: 81-90.

[26] M.-H. Lee, R. Zhao, L. Phan, S.-C. J. Yeung, Cell Cycle 2011,10, 30576.

[27] Malik F, Kumar A, Bhushan S, Khan S, Bhatia A, Suri KA, Singh J (2007). Reactive oxygen species generation and mitochondrial dysfunction in the apoptotic cell death of human myeloid leukemia HL-60 cells by a dietary compound withaferin A with concomitant protection by N-acetyl cysteine. Apoptosis 12: 2115-2133.

[28] Mansoori B, Shotorbani SS, Baradaran B (2014). RNA interference and its role in cancer therapy. Advanced pharmaceutical bulletin 4: 313.

[29] Mitchell RA, Bucala R (2000). Tumor growth-promoting properties of macrophage migration inhibitory factor (MIF). Academic Press, In Seminars in cancer biology, pp. 359-366.

[30] Morand EF, Bucala R, Leech M (2003). Macrophage migration inhibitory factor: an emerging therapeutic target in rheumatoid arthritis. Arthritis & Rheumatology 48: 291-299.

[31] Oron E, Mannervik M, Rencus S, Harari-Steinberg O, Neuman-Silberberg S, Segal D, Chamovitz, DA (2002). COP9 signalosome subunits 4 and 5 regulate multiple pleiotropic pathways in Drosophila melanogaster. Development 129: 4399-4409.

[32] Pan Y, Zhang Q, Tian L, Wang X, Fan X, Zhang H, Yang H (2012). Jab1/CSN5 negatively regulates p27 and plays a role in the pathogenesis of nasopharyngeal

carcinoma. Cancer research 72: 1890-1900.

[33] Patil MA, Gütgemann I, Zhang J, Ho C, Cheung ST, Ginzinger D, Kakar S (2005). Array-based comparative genomic hybridization reveals recurrent chromosomal aberrations and Jab1 as a potential target for 8q gain in hepatocellular carcinoma. Carcinogenesis 26: 2050-2057.

[34] Peng Z, Serino G, Deng XW (2001). Molecular characterization of subunit 6 of the COP9 signalosome and its role in multifaceted developmental processes in Arabidopsis. The Plant Cell : 2393-2407.

[35] Schwechheimer C, Serino G, Callis J, Crosby WL, Lyapina S, Deshaies RJ, Deng XW (2001). Interactions of the COP9 signalosome with the E3 ubiquitin ligase SCFTIR1 in mediating auxin response. Science 292: 1379-1382.

[36] Seeger M, Kraft R, Ferrell K, Bech-Otschir D, Dumdey R, Schade R, Dubiel W (1998). A novel protein complex involved in signal transduction possessing similarities to 26S proteasome subunits. The FASEB Journal 12: 469-478.

[37] Shackleford TJ, Claret FX (2010). JAB1/CSN5: a new player in cell cycle control and cancer. Cell division 5: 26.

[38] Shao ZM, Shen ZZ, Liu CH, Sartippour MR, Go VL, Heber D, Nguyen M (2002). Curcumin exerts multiple suppressive effects on human breast carcinoma cells. International Journal of Cancer 98: 234-240.

[39] T. J. Shackleford, F. X. Claret, Cell Div. 2010, 5, 26. [9] J. R. Skaar, J. K. Pagan, M. Pagano, Nat. Rev. Drug Discovery 2014, 13, 88.

[40] Tian L, Peng G, Parant JM, Leventaki V, Drakos I, Zha Q, Lozano G (2010). Essential roles of Jab1 in cell survival, spontaneous DNA damage, and DNA repair. Oncogene 29: 6125.

[41] Tomoda K, Kubota Y, Arata Y, Mori S, Maeda M, Tanaka T, Kato JY (2002). The cytoplasmic shuttling and subsequent degradation of p27Kip1 mediated by Jab1/CSN5 and the COP9 signalosome complex. Journal of Biological Chemistry 277: 2302-2310.

[42] Tomoda K, Yoneda-Kato N, Fukumot A, Yamanaka S, Kato JY (2004). Multiple functions of Jab1 are required for early embryonic development and growth potential in mice. Journal of Biological Chemistry 279: 43013-43018.

[43] Uhle S, Medalia O, Waldron R, Dumdey R, Henklei P, Bech-Otschir D, Dubiel W (2003). Protein kinase CK2 and protein kinase D are associated with the COP9 signalosome. The EMBO journal 22: 1302-1312.

[44] Von Arnim, AG (2003). On again–off again: COP9 signalosome turns the key on protein degradation. Current opinion in plant biology 6: 520-529.

[45] Wan M, Cao X, Wu Y, Bai S, Wu L, Shi X, Cao X (2002). Jab1 antagonizes TGF-β signaling by inducing Smad4 degradation. EMBO reports 3: 171-176.

[46] Wei N, Deng XW (1999). Making sense of the COP9 signalosome: a regulatory protein complex conserved from Arabidopsis to human. Trends in Genetics 15: 98-103.

[47] Wei N, Tsuge T, Serino G, Dohmae N, Takio K, Matsui M, Deng XW (1998). The COP9 complex is conserved between plants and mammals and is related to the 26S proteasome regulatory complex. Current Biology 8: 919-924.

[48] Wolf, DA, Zhou C, Wee S (2003). The COP9 signalosome: an assembly and maintenance platform for cullin ubiquitin ligases?. Nature cell biology 5: 1029-1033.

[49] Y.-H. Lee, A. D. Judge, D. Seo, M. Kitade, L. E. Gomez-Quiroz, T. Ishikawa, J. B. Andersen, B.-K. Kim, J. U. Marquardt, C.Raggi, I. Avital, E. A. Conner, I. MacLachlan, V. M. Factor, S. S.Thorgeirsson, Oncogene 2011, 30, 4175.

Appendix

List of abbreviations

53BP1	**p53-binding protein 1**
BM2	**Influenza B virus BM2 protein**
COP9	**Constitutive photomorphogenesis 9**
CRL	**Cullin-RING ubiquitin ligases**
CSN	**COP9 signalosome complex**
ER	**Endoplasmic Reticulum**
HIF	**Hypoxia inducible factor-1**
IRE1alpha	**Inositol-requiring protein 1**
Jab1	**c-Jun activation domain-binding protein-1**
JAMM J	**Jab1 MPN domain metalloenzyme**
LHR	**Luteinizing hormone receptor protein**
MIF	**Macrophage Migration Inhibitory Factor**
MPN	**Mpr1-Pad1-N-terminal domain**
NES	**Nuclear export signal**
PBD	**p27 binding domain**
PCI	**Proteasome component domain**
PI3K	**Phosphatidylinositol-4,5-bisphosphate 3-kinase**
SCF	**Skp, Cullin, F-box containing complex**
SRC	**Proto-oncogene tyrosine-protein kinase**
STAT3	**Signal transducer and activator of transcription 3 Factor**
TGF	**Transforming growth factor**
TSG	**Tumor suppressor gene**
UPP	**Ubiquitin (Ub)-proteasome pathway**
VEGF	**Vascular endothelial growth factor**