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Review

CSN6: a promising target for cancer prevention and therapy

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Summary. CSN6 has recently received increased attention as a multifunctional protein involved in protein stability. CSN6 plays an important role in controlling cellular proliferation, apoptosis and metastasis, modulating signal transduction, as well as regulating DNA damage and repair. Most studies have demonstrated that CSN6 is significantly upregulated in human malignant tumors such as cervical cancer, papillary thyroid cancer, colorectal cancer, breast cancer, lung adenocarcinoma, and glioblastoma, and its expression is usually correlated with poor prognosis. In this review, we summarize recent available findings regarding the oncogenic role of CSN6 in tumors, and provide a better understanding of CSN6 function at the molecular level and its potential therapeutic implications in combating human cancers.

Key words: CSN6, Ubiquitin, Signaling transduction, Targeted therapy

Introduction

CSN6 was discovered as the sixth subunit of the constitutive photomorphogenic 9 (COP9) signalsome (CSN), and confirmed to be conserved across diverse species including humans, mice, virus, and plants, which suggested that CSN6 was essential for cellular progression (Hoareau Alves et al., 2002; Gusmaroli et al., 2007; Leelatanawit et al., 2011; Rockel et al., 2014; Wang et al., 2014). Previous CSN6 knockout studies had demonstrated that CSN6 haplo-insufficiency blocked the development of cancer, suggesting that CSN6 was critical for tumor development (Zhao et al., 2011). Indeed, accumulating evidence has confirmed that CSN6 is important in regulating the degradation of cancer-related proteins such as c-Myc, p27, c-Jun, β-catenin, EGFR and p53 (Sanches et al., 2007; Birol and Echalier, 2014; Ma et al., 2014; Hou et al., 2017). Dysregulation of CSN6 was significantly associated with poor prognosis in several human cancers. However, the biological function and molecular mechanism by which CSN6 regulates the carcinogenesis/tumor progression remains poorly understood. In this review, we summarize recent available findings regarding the oncogenic role of CSN6 in carcinogenesis and progression as well as its potential therapeutic implications in combating human cancers.

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CSN6 is an integral component of the CSN complex

CSN complex is a multi-protein complex firstly identified in 1992 in Arabidopsis and discovered to be a repressor of light-mediated development (Wei et al., 1994; Karniol and Chamovitz, 2000). CSN complex is evolutionarily conserved and exists in all eukaryotes, consisting of 8 subunits (CSN1~CSN8) and the newly discovered ninth subunit CSNAP (Rozen et al., 2015; Fuzesi-Levi et al., 2019). These subunits are highly homologous with the 19S "cap" complex of the 26S

proteasome, and the 19S "cap" is believed to function to recognize ubiquitinated substrates and transfer them to the proteolytic core complex for degradation (Li and Deng, 2003). Thus, CSN complex has been postulated to function as the crucial modulator for protein degradation. Scientific evidence has reinforced that CSN complex is linked with the deneddylation activity of cullin-RING ligases (CRL), and coordinating CRL-mediated degradation of polyubiquitinated proteins (Bennett et al., 2010; Faull et al., 2019).

CSN complex consists of two symmetrical modules (CSN1/2/3/8 and CSN4/5/6/7) and CSNAP (Sharon et al., 2009; Fuzesi-Levi et al., 2019) (Fig. 1). CSN5 and CSN6 are the only two subunits that each share an MPN domain. The CSN-mediated deneddylation process is dependent on the JAMN (JAB1/MPN/Mov34) motif of the MPN domain of CSN5, whereas CSN5 alone has no deneddylation activity unless it is combined with other subunits of CSN (Fig. 2). CSN6 can interact with CSN4, CSN5, and CSN7, and these studies indicate that CSN6 as a core protein for CSN4/5/6/7 complex, suggesting its critical role for maintaining the integrity of the CSN complex (Kotiguda et al., 2012). Indeed, mounting evidence has indicated that depletion of CSN6 leads to the loss of CSN complex and the instability of several subunits (Gusmaroli et al., 2007; Zhang et al., 2013).

CSN6 is a proto-oncoprotein

CSN6 is mapped to 7q22.1, where amplification is frequently observed in many cancers, including glioblastoma, breast cancer, and esophageal squamous cell carcinoma (Forozan et al., 2000; Tang et al., 2001; Du et al., 2019). Thus, CSN6 might have a substantial role in modulating the carcinogenesis/tumor progression. Indeed, increasing studies have demonstrated that CSN6 is upregulated in varieties of cancers, including lung adenocarcinoma, papillary thyroid carcinoma, glioblastoma, cervical cancer, breast cancer, pancreatic cancer, colorectal cancer, and many others, indicated that CSN6 may be a prognostic marker for multiple carcinomas (Table 1) (Yang et al., 2016; Wen et al., 2018). For example, overexpression of CSN6 was significantly related to tumor size, tumor aggressiveness, and TNM stage of papillary thyroid carcinoma and glioma, leading to poor prognosis for these cancers. Additionally, the high level of CSN6 was correlated with lymph node metastasis of breast cancer (Wang et al., 2013; Hou et al., 2017). In colorectal cancer and glioblastoma, CSN6 expression was related to cell proliferation and metastasis (Fang et al., 2015; Hou et al., 2017). Interestingly, recent studies showed that CSN6 mediated drug sensitivity of papillary thyroid carcinoma cell lines to FH535 therapy. And Choi et al. (2015a-c) found that CSN6 regulated DNA damage-associated apoptosis by γ-irradiation (IR) in breast cancer (Choi and Lee, 2015). Therefore, CSN6 is considered a strong biomarker of poor survival of tumor patients, and believed to be a proto-oncoprotein.

Deregulation of CSN6 exerts dramatic effects on diverse cellular functions

As mentioned above, CSN6 is indispensable for the integrity of CSN complexes, and many studies have indicated that CSN6 acts as an important modulator of the degradation of cancer-related proteins such as c-Myc, p27, c-Jun, β-catenin, EGFR and p53, suggesting its importance in cancerogenesis. Indeed, more and more studies of CSN6 concentrate on the biological function and molecular mechanism by which CSN6 facilitates carcinogenesis/tumor progression. Thus, we summarize some recent advances and describe the role of CSN6 in tumor progression of cancer cells.

Role of CSN6 in cell proliferation

Infinite proliferation is a unique feature of neoplasms and may cause immense damage to the human body. Several studies have indicated that CSN6 promotes the proliferation of different tumors by modulating the protein stability of key regulators governing cell-cycle progression. The tumor suppressor p53 is a critical inhibitor involved in cell-cycle arrest. Increasing evidence has indicated the inverse correlation between CSN6 and p53 expression in many human cancers, including colon cancer, glioblastoma, cervical cancer, breast cancer, and lung adenocarcinoma (Choi et al., 2011; Zhao et al., 2011; Xue et al., 2012; Wang et al.,

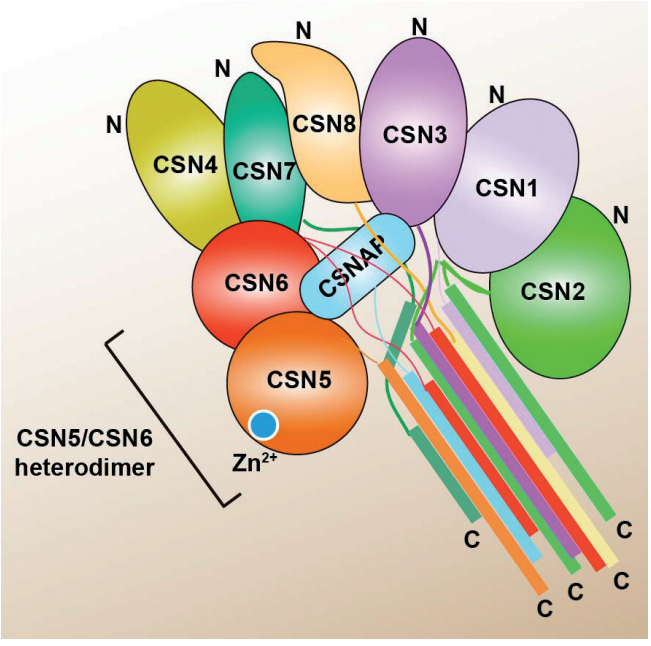

Fig. 1. The CSN complex Structure. CSN complex contains 8 subunits (CSN1~CSN8) and the newly discovered ninth subunit CSNAP. The N-terminal repeat domains radiate out from the winged-helix of the PCI ring. The C-terminal helical regions form a helical bundle that stabilizes the complex.

Table 1. The impact of CSN6 on different types of cancer.

Type of cancer	CSN6 status	Possible mechanism	Clinical effect	Reference
Breast cancer	Overexpression	1. CSN6 overexpression diminishes MEKK1-mediated c-Jun ubiquitination 2. CSN6-mediated ROS production and DNA damage by affecting COP1-p27-Aurora A axis 3. CSN6 protein expression and correlation with mutant-type P53 protein in breast cancer. 4. CSN6 promotes Skp2-mediated protein ubiquitination of p57Kip2 5. Expression of CSN6 appeared to prevent MDM2 autoubiquitination at lysine 364, resulting in stabilization of MDM2 and degradation of p53	1.CSN6 overexpression correlates with poor survival in breast cancer patients 2. CSN6 promotes breast cancer development by influencing genome integrity 3. CSN6 was positively related to tumor size, histological type and lymph node metastasis of breast cancer 4. Overexpression of CSN6 was related to cancer cell growth. 5. Overexpression of CSN6 promotes tumorigenesis	Shin et al., 2015; Choi et al., 2015a-c; Wang et al., 2013; Chen et al., 2012; Zhao et al., 2011
Colon cancer	Overexpression	CSN6 attenuated the effect of quercetin-induced apoptosis by positively regulating Myc on colon cancer cells.	Overexpression of CSN6 reduced the effect of quercetin induced apoptosis on colon cancer cells.	Yang et al., 2016
Papillary thyroid cancer	Overexpression	CSN6 positively regulated β-catenin expression in a β-Trcp-dependent manner	Downregulation of CSN6 attenuates papillary thyroid carcinoma progression and sensitizes cancer cells to FH535 therapy	Wen et al., 2018
Glioblastoma	Overexpression	CSN6 positively regulated EGFR stability by increasing CHIP ubiquitination	Overexpression of CSN6 promotes glioblastoma cell proliferation, migration, invasion and tumorigenesis	Hou et al., 2017
Cervical cancer	Overexpression	CSN6 associated with E6AP and stabilized E6AP expression by reducing E6AP poly-ubiquitination, thereby regulating p53 activity.	Overexpression of CSN6 promotes cervical cancer development	Gao et al., 2015
Colorectal cancer	Overexpression	1.CSN6 regulated β-Trcp and stabilized β-catenin expression by blocking the ubiquitin-proteasome pathway 2. CSN6 specifically interacts with p27 protein and accelerates its degradation; 3. CSN6 associates with COP1 and is involved in 14-3-3σ ubiquitin-mediated degradation.	1.Overexpression of CSN6 promotes cell proliferation and tumor growth 2. Overexpression of Jab1/CSN5 associates with poor overall survival in Colorectal cancer 3. CSN6 overexpression leads to increased cell growth, transformation and promotes tumorigenicity	Fang et al., 2015; Hyun et al., 2012, 2015
Pancreatic cancer	Overexpression	CSN6-enhanced Cullin neddylation facilitates auto-ubiquitination and degradation of Myc E3 ligase Fbxw7, thereby stabilizing Myc	CSN6 overexpression is frequent in human cancers	Chen et al., 2014
Lung adenocarcinoma	Overexpression	HER2-Akt axis positively affect CSN6 expression during carcinogenesis and cancer progression	Overexpression of CSN6 increases DNA damage and promotes cancer cell growth	Xue et al., 2012

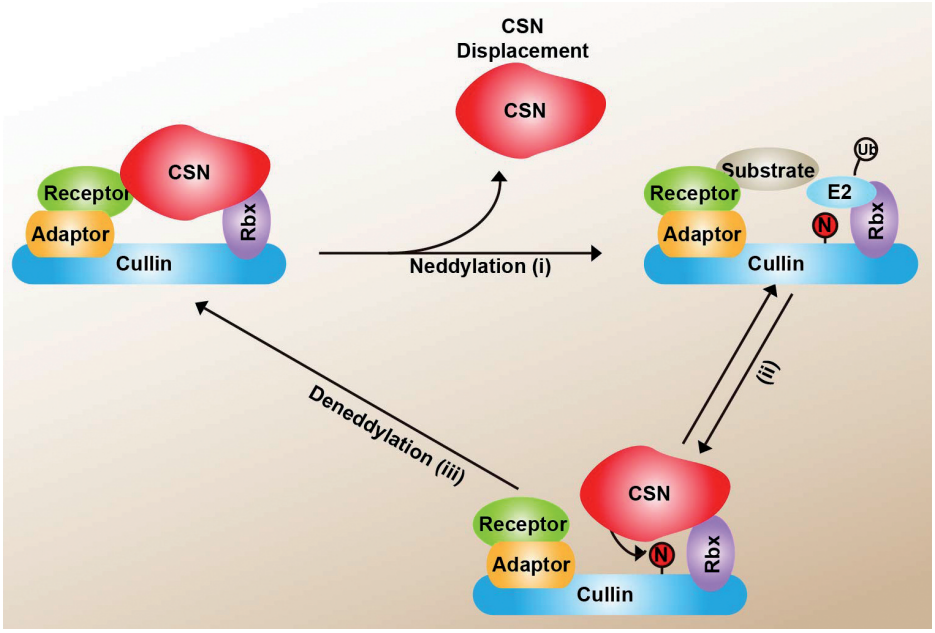

Fig. 2. A schematic model for the neddylation-dependent regulation of CRLs by the CSN complex. The CSN complex can bind and inhibit substrate ubiquitylation in a neddylation dependent manner. (i) Deneddylated CRLs can be activated through neddylation and CSN displacement to promote substrate and E2 binding and subsequent substrate ubiquitylation. (ii) Interaction between the CRL to the CSN positions and activates CSN5 to allow deneddylation to occur (iii).

2013; Gao et al., 2015; Yang et al., 2016; Hou et al., 2017). CSN6 negatively regulated p53 expression by accelerating MDM2-mediated p53 degradation (Iyer and Iwakuma, 2012; Xue et al., 2012). Loss of CSN6 increased p53 protein stability and inhibited cell proliferation. Moreover, expression of many cell-cycle regulators, such as p57, p27, and c-Myc were also regulated by CSN6. For example, CSN6 interacted with p57 and Skp2, and facilitated Skp2-mediated degradation of p57 (Chen et al., 2012) . Another study identified that CSN6 as a COP1-associated protein, was involved in the cytoplasmic distribution and protein degradation of p27 (Choi et al., 2015a). Besides, CSN6 enhanced the autoubiquitination/degradation of Fbxw7, a known E3 ubiquitin ligase involved in c-Myc ubiquitination, thereby stabilizing c-Myc (Chen et al., 2014). Taken together, these results indicate that CSN6 enhances the degradation of cell-cycle regulators and thus regulates cell proliferation in cancer cells.

Role of CSN6 in apoptosis

The development of neoplasms is regarded as a consequence of imbalanced apoptosis versus proliferation. Some studies have demonstrated that CSN6 was important to the regulation of the protein stability of p53 for cell proliferation and anti-apoptosis (Chen et al., 2012). Indeed, Zhao et al. (2011) found that CSN6-deficient mice died early in embryogenesis owing to accelerated p53-dependent apoptosis (Zhao et al., 2011). Moreover, CSN6 was also involved in the quercetin-induced apoptosis of colon cancer cells, and overexpression of CSN6 could reduce the effect of quercetin treatment on tumor cells (Yang et al., 2016). Interestingly, several studies indicated that CSN6 expression was altered in response to apoptotic stimuli. For example, da Silva Correia et al. (2007) reported that Nod1, a cytoplasmic protein involved in apoptotic pathways, was responsible for the recruitment of caspases 8 to the CSN complex and then facilitated cleavage of CSN6 during apoptosis (da Silva Correia et al., 2007). Another study demonstrated that apoptotic stimuli induced the caspase-dependent cleavage of CSN6, which was followed by the cleavage of CSN6-associated partner, ROC1/Rbx1 (Hetfeld et al., 2008). Collectively, these studies indicate that CSN6 executes an important function during the apoptotic process.

Role of CSN6 in metastasis

An interesting correlation between CSN6 and β-catenin expression highlights the biological function of CSN6 in metastasis. β-catenin, a multitasking and evolutionary conserved protein, acts as a critical signal transducer of Wnt signaling, which is important during embryonic development and drives carcinogenesis and promotes metastasis (Wang et al., 2019). CSN6 positively modulated β-catenin expression and promoted the epidermal-to-mesenchymal transition (EMT) in papillary thyroid carcinoma, glioblastoma, and colorectal cancer via decreasing β-trcp-mediated degradation of β-catenin (Fang et al., 2015; Wen et al., 2018). In addition, we recently found that CSN6 facilitated cell migration and invasion by modulating the EGFR pathway in glioblastoma. Another study also reported that CSN6 promoted the migration and invasion of cervical cancer cells by inhibiting autophagic degradation of Cathepsin L (Mao et al., 2019). Furthermore, Chen et al. reported that CSN6 was related to lymph node metastasis (Wang et al., 2013). Therefore, these results demonstrate that CSN6 is involved in metastasis.

Role of CSN6 in DNA damage repair

Recent studies pointed out that CSN6 might participate in DNA damage repair progression and link to the maintenance of genome integrity (Choi et al., 2015c). Over-expression of CSN6 leads to mitotic defects and ROS production by regulating the COP1-p27-Aurora axis, suggesting that CSN6 may be related to the initial steps of developing oncogenic mutations in cells leading to cancer initiation. Importantly, loss of CSN6 also affects DNA damage repair progression and sensitizes to DNA damage inducer. For example, silencing of CSN6 increased the drug sensitivity of papillary thyroid carcinoma cells for FH535 therapy (Wen et al., 2018). Moreover, mice haplo-insufficiency for CSN6 was sensitized to γ-irradiation–induced, DNA damage-associated apoptosis (Zhao et al., 2011). Thus, CSN6 may play different roles in tumorigenesis and malignant progression during DNA damage repair. More in-depth studies of the function, role and molecular mechanism of CSN6 in terms of DNA damage repair are essential for the better understanding of malignant tumor.

CSN6 cross-talk with major signaling pathways in cancer

CSN6 was previously reported to modulate cell cycle and cell proliferation by interacting with the hVIP (human immunodeficiency virus 1 accessory protein Vpr). Recently, more and more studies have demonstrated that CSN6 is involved in several crucial signaling pathways that are critical in carcinogenesis/tumor progression, such as MDM2-p53 signaling, E6-E6AP-p53 signaling, COP1-14-3-3σ-Akt signaling, COP1-p27 signaling, HER2-Akt-CSN6-p57 signaling, Fbxw7-c-Myc signaling, Wnt-β-catenin signaling and CHIP-EGFR signaling (Fig. 3). Interpreting the molecular mechanism of CSN6 in these pathways may provide a better understanding of carcinogenesis/tumor progression.

CSN6-MDM2-p53 signaling

Inactivation of p53 and overexpression of the

oncogene MDM2 (Murine Double Minute 2), the major negative modulator of p53, frequently occur in human cancers, and are related to poor prognosis, advanced forms of the disease, and chemoresistance. Zhao et al. (2011) found that CSN6 expression was positively associated with MDM2 expression in human cancers. CSN6 directly interacted with MDM2, and prevented MDM2 auto-ubiquitination at lysine 364, resulting in stabilization of MDM2 and degradation of p53 (Zhao et al., 2011). Moreover, Xue et al. (2012) reported that HER2-Akt axis was crucial in regulating CSN6 expression and then destabilizing p53 (Xue et al., 2012). Thus, CSN6 is crucial in regulating p53-mediated tumor suppression through control of the stability of MDM2.

CSN6-COP1 signaling

The constitutively photomorphogenic 1 (COP1) protein which acts as an E3 ubiquitin ligase, contains RING-finger, WD40-repeat and coiled-coil domains, is evolutionarily conserved in both plants and mammalians (Yi and Deng, 2005). In plants, COP1 is associated with CSN complex, and functions as an important regulator to repress photomorphogenesis in the dark by targeting light-induced transcription factor HY5 for ubiquitination and degradation (Osterlund et al., 2000). In mammalian cells, COP1 is highly expressed in many human cancers, and is associated with tumorigenesis through ubiquitin-mediated degradation of the tumor suppressor, such as p53, 14-3-3σ, and p27 (Dornan et al., 2004; Wertz et al., 2004; Choi et al., 2011, 2015b). Several studies have indicated that CSN6 directly interacts with COP1, and stabilizes COP1 expression by reducing its auto-ubiquitination (Choi et al., 2015a; Choi and Lee, 2015). 14-3-3σ, a tumor suppressor induced by p53 in response to DNA damage, was involved in signal transduction, apoptosis, cell cycle, and metabolic reprogramming (Fu et al., 2000; Laronga et al., 2000). Choi et al. (2011) found that CSN6-COP1 axis was involved in 14-3-3σ degradation (Choi et al., 2015c). Interestingly, 14-3-3σ could inhibit the expression of COP1 in response to DNA damage (Choi et al., 2015c). Taken together, these studies demonstrate that COP1 is important in CSN6-mediated tumorigenesis, metabolic reprogramming, genome integrity, and others, conferring impacts on the stability of p53, p27, and 14-3-3σ.

HER2-Akt-CSN6-Skp2-p57 signaling

p57, a cyclin-dependent kinase inhibitor, is primarily involved in the progression of cell cycle and differention (Rossi et al., 2018). p57 expression was frequently

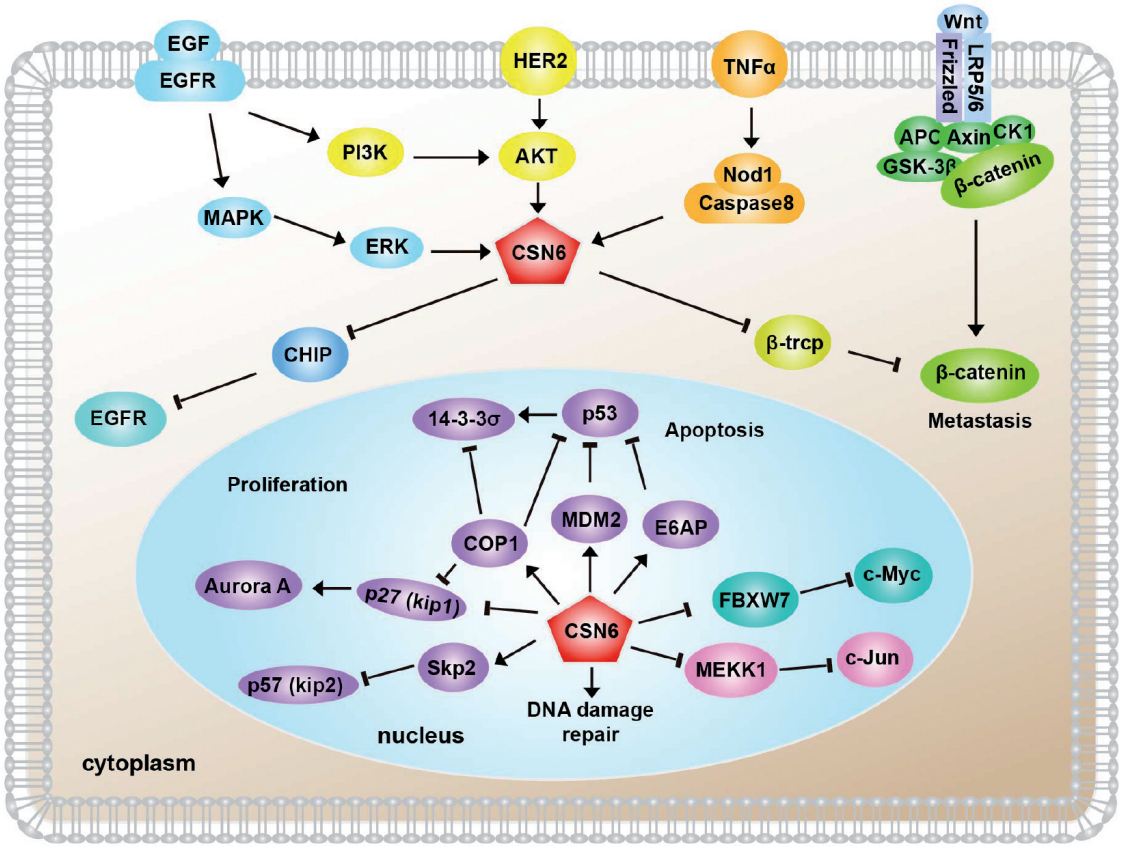

Fig. 3. Overview of the CSN6 molecular mechanisms involved in cancer progress. CSN6 is a multifunctional protein that is involved in several critical oncogenic signal transduction pathways in tumorigenesis, such as MDM2-p53 signaling, E6-E6AP-p53 signaling, COP1-14-3-3σ-Akt signaling, COP1-p27 signaling, HER2-Akt-CSN6-p57 signaling, Fbxw7-c-Myc signaling, Wnt-β-catenin signaling and CHIP-EGFR signaling. Deregulation of CSN6 can exert dramatic effects on diverse cellular functions, including cell proliferation, metastasis, apoptosis, and DNA damage repair.

downregulated in some human cancers as a consequence of epigenetic changes such as DNA methylation and repressive histone marks at the promoter (Kavanagh and Joseph, 2011). Chen et al. (2012) found that CSN6 interacted with p57 and Skp2, and promoted Skp2-mediated ubiquitination and degradation of p57. Overexpression of CSN6 in cancers can lead to the decreasing of p57 and alleviate the p57-mediated G1 arrest (Chen et al., 2012). Another study demonstrated that Akt was a crucial positive modulator of the stabilization of CSN6, Akt bound to CSN6, and phosphorylated CSN6 at Ser60, reducing ubiquitin-mediated degradation of CSN6 (Xue et al., 2012). Thus, CSN6-mediated p57 degradation is an extension of the HER2-Akt-CSN6 axis. Therefore, the HER2-Akt-CSN6-Skp2-p57 signaling pathway will be a promising molecular target for cancer therapy and intervention.

CSN6- E6-E6AP-p53 signaling

It has been established that high-risk human papillomavirus (HR-HPV) is a major risk factor for the cervical cancers. HPV E6 and cellular E6-Associating Protein (E6AP/UBE3A) can target p53 for proteasome-mediated degradation (Beaudenon and Huibregtse, 2008; Fuentes-Mattei et al., 2014). Gao et al. (2015) found that CSN6 interacted with E6AP and regulated the auto-ubiquitination and degradation of E6AP, thereby modulating p53 stability in cell cycle, apoptosis and stress response (Gao et al., 2015). Taken together, CSN6-E6AP-p53 axis will be a promising therapeutic target.

CSN6-Cullin-Fbxw7-c-Myc signaling

The c-Myc oncoprotein, a transcription factor frequently amplified in a multitude of cancers, is related to various physiological progressions such as cell proliferation, apoptosis, and metastasis (Carroll et al., 2018). Owing to the critical role of c-Myc in modulating cellular pathways, its expression is tightly regulated. Chen et al. (2014) found that CSN6 could enhance the neddylation of Cullin-1 and promote auto-ubiquitination and degradation of Fbxw7, thereby stabilizing the expression of c-Myc and promoting tumorigenesis (Chen et al., 2014). Therefore, CSN6 functions as a positive modulator of c-Myc through increasing the autocatalytic degradation of Fbxw7, and this signaling axis may be a promising therapeutic target in c-Myc-overexpressing cancers.

CSN6-Wnt-β-catenin signaling

Wnt/β-catenin signaling pathway is crucial to modulate carcinogenesis/tumor progression, such as cell cycle, cell migration and invasion, differentiation, and apoptosis. Fang et al. (2015) found that expression of CSN6 was upregulated in colon cancer, and was positively correlated with β-catenin (Fang et al., 2015). CNS6 increased the expression of β-catenin by blocking β-trcp-mediated degradation of β-catenin, thereby promoting the development of colon cancer. In addition, Wen et al. (2018) also demonstrated that CSN6 could induce EMT in thyroid cancer via the Wnt/β-catenin pathway (Wen et al., 2018). These studies indicate that CSN6-Wnt-β-catenin axis may be a promising therapeutic target.

CSN6-CHIP-EGFR signaling

EGFR is a transmembrane glycoprotein that is highly expressed in a variety of malignancies (Libermann et al., 1985). EGFR phosphorylation activates several important downstream signaling pathways, such as MAPK, Akt, and Src pathways, which are responsible for cell survival and metastasis of cancer cells (Yarden and Sliwkowski, 2001). Our recent studies have demonstrated that CSN6 positively modulates the stability of EGFR and promotes the tumorigenesis and metastasis of glioblastoma cells. And CSN6 interacts with CHIP (carboxyl terminus of heat-shock protein 70-interacting protein), a known E3 ubiquitin ligase for inducing the degradation of EGFR, and down-regulation of CHIP expression by facilitating the ubiquitination of CHIP (Hou et al., 2017). These studies suggest that the CSN6-CHIP-EGFR axis may serve as a promising therapeutic target for combatting tumors.

Clinical strategy of CSN6 in cancers

Given the important role of CSN6 as an oncoprotein in human tumors, development of a therapy to inhibit CSN6 would be an efficient way to retard proliferation, metastasis, and tumorigenesis, and improve the radiotherapy and chemotherapy of malignant tumors. Directly targeted inactivation of CSN6 through structure disruption mechanisms and gene-silencing strategies, such as short interfering RNAs (siRNA), short hairpin RNAs (shRNA), and clustered regularly interspaced short palindromic repeat-associated nuclease 9 (CRISPR/Cas9) systems may be a novel strategy for the prevention of progression of tumors. In addition, several studies have demonstrated that several signaling pathways, including EGFR/ERK pathway and HER2/AKT pathway can activate CSN6 expression (Xue et al., 2012; Fang et al., 2015). Thus, the combined treatment of inhibitors of these pathways with radiotherapy/chemotherapy may be a good strategy for improving the cancer patients' outcomes.

Conclusion

CSN6, a critical subunit of the CSN complex, plays a crucial role in the assembly and integrity of CSN complex, which is related to cell survival, DNA damage response and signaling pathways. CSN6 is overexpressed in many malignant tumors, and has been confirmed to be a master regulator of a variety of

proteins such as p53, p27, p57, 14-3-3σ, β-catenin, EGFR and c-Myc via ubiquitin-dependent proteolysis. Therefore, CSN6 exerts its oncogene activity by taking an active part in carcinogenesis/tumor development. Considering the pivotal role of CSN6 and its promising therapeutic implications in human cancers, more in-depth investigation of CSN6 will promote the development of molecular-targeted therapy for various types of cancers.

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