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Original Article

A crucial role for the long non-coding RNA *CASC11* in the pathogenesis of human cancers

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Abstract: Long non-coding RNAs (lncRNAs) are non-coding RNAs more than 200 nucleotides in length. Although they do not encode proteins, lncRNAs can regulate gene expression at the transcriptional, post-transcriptional, and epigenetic levels. Emerging data show that lncRNAs are important for tumorigenesis and cancer progression. Cancer susceptibility candidate 11 (*CASC11*) is a prominent lncRNA that is upregulated in various types of cancers. Moreover, its overexpression correlates with larger tumor size, more advanced cancer stages, cancer metastasis, and poor overall survival for most types of cancer. Functionally, the knockdown of CASC11 can inhibit cell proliferation, invasion, and migration, while enhancing apoptosis through its regulation of gene expression and signaling pathways and its interactions with functional proteins. Here, we discuss the identification, expression, and function of *CASC11*. Additionally, we discuss the potential roles of *CASC11* as a diagnostic biomarker, prognostic biomarker, and therapeutic target in various cancers.

Keywords: Cancer, lncRNA, *CASC11*, prognosis, treatment

Introduction

According to 2015 estimates from the World Health Organization, cancer remains a leading cause of death worldwide [1, 2], and cancer incidence and mortality rates remain high [3]. In recent years, although the understanding of cancer-related molecular mechanisms has increased substantially, and the therapeutic methods for treating cancer have greatly improved [4-6], treatments for advanced-stage cancers still remain unsatisfactory, and early-stage cancers tend to go undiagnosed, in part, due to the lack of useful biomarkers for their detection. Therefore, it is urgent to identify biomarkers of early disease while continuing to investigate the mechanisms that contribute to cancer growth, invasion, and metastasis, to develop new cancer therapies.

In humans, although a large portion of the genome is transcribed, less than 2% of the genome encodes proteins [7]. The remaining transcripts represent various classes of non-coding RNAs (ncRNAs) [8, 9]. One class of ncRNAs is long non-coding RNAs (lncRNAs), which are defined as RNA transcripts exceeding 200 nucleotides in length [10, 11]. In recent years, lncRNAs have received much attention because they can regulate gene expression at the transcriptional, post-transcriptional, and epigenetic levels [12-14]. At the transcriptional level lncRNAs can affect the cofactors, transcription factors, and RNA polymerase II, at the post-transcriptional level they can influence protein interactions, alternative splicing, miRNA sponging, and mRNA stability and translation, and at the epigenetic level they can impact DNA methylation, histone modifications, and chromatin remodeling [10, 15-18].

The development of new genome sequencing technologies and bioinformatics tools has led to more and more lncRNAs being implicated as vital regulators of many physiological and pathological processes, including cancer occurrence and progression [19-21]. LncRNAs have been reported to affect multiple cellular behaviors, such as growth, differentiation, and apoptosis, which are generally dysregulated in cancer [22, 23]. Further, many lncRNAs are aberrantly expressed in cancer tissues and are

present at higher levels in cancer patient plasma compared with controls, suggesting lncRNAs might be promising diagnostic biomarkers for cancer [24-27].

A growing body of evidence shows that the lncRNA cancer susceptibility candidate 11 (*CASC11*) promotes oncogenesis and is upregulated in many cancers. CASC11 has attracted much attention, not only for its value in diagnosing cancer and predicting prognosis, but also for its potential as a therapeutic target in various cancers. Here, we summarize recent progress toward defining the molecular function of *CASC11* and how it relates to cancer. We also evaluate the potential prognostic, diagnostic, and therapeutic value of this lncRNA in various cancer types.

Approaches to detecting lncRNA *CASC11*

Unlike protein-coding genes, lncRNAs generally lack conserved sequence motifs that aid in their detection. At present, quantitative reverse-transcription polymerase chain reaction (qRT-PCR) is considered the gold standard for quantifying lncRNAs, and it is the most commonly used method for measuring the expressions of *CASC11* in tumor tissues, plasma, and cells. Liu et al. used qRT-PCR to show that *CASC11* is overexpressed in hepatocellular carcinoma (HCC) by comparing its expression in 69 HCC tumor samples to adjacent healthy tissue controls [28]. Likewise, Luo et al. used qRT-PCR to detect the presence of *CASC11* in the plasma of bladder cancer patients [29].

In addition to qRT-PCR, new methods are being developed for the detection of lncRNAs, such as, chemiluminescent, electrochemical techniques, next-generation sequencing, and third generation sequencing. Some studies have used microarray-based analyses to compare *CASC11* expression in tumors vs. controls. For example, microarrays were used in a study showing that *CASC11* is upregulated in gastric cancer tissues compared with normal adjacent tissues [30]. Others have used RNA-sequencing data downloaded from The Cancer Genome Atlas (TCGA) to examine *CASC11* expressions [31].

The expression of *CASC11* in cancer

Transcriptional profiling has revealed increased *CASC11* expressions in tumor tissues compared to adjacent non-tumor tissues in patients with various cancers, including colorectal cancer, hepatocellular carcinoma, bladder cancer, lung cancer, glioma, ovarian carcinomas including ovarian squamous cell carcinoma, cervical cancer, gastric cancer, neuroblastoma, and esophageal carcinoma. Cell lines representing these malignancies also show the trend of *CASC11* upregulation. Importantly, elevated *CASC11* expression is associated with increased tumor size, invasion, lymph metastasis, more advanced TNM stage, and decreased differentiation [30, 32-34]. Importantly, Kaplan-Meier survival analyses indicate that cancer patients with higher *CASC11* expression had poorer prognoses than those with lower *CASC 11* expression.

It remains unclear how *CASC11* is upregulated in tumors; however, transcriptional activation is a common mechanism used to upregulate lncRNA expression. Zhang et al. explored the promoter region of *CASC11* for potential transcription factor binding sites using the University of California Santa Cruz (UCSC) Genome Browser [33]. They identified an E-box region in the *CASC11* promoter that might be a potential c-Myc binding site. They performed in vitro experiments to demonstrate that the transfection of c-Myc into SW480 and HEK293T cells promotes luciferase expression from reporter constructs bearing the E-box region of the *CASC11* promoter. Additional chromatin immunoprecipitation (ChIP) assays and c-Myc gainays and c-Myc chromatin immunoprecipitation can directly bind to the E-box element and regulate the expression of *CASC11* [33]. The effects of c-Myc on transcription are likely due to the role of c-Myc in recruiting proteins important for histone H3 lysine acetylation. The UCSC Genome Browser was used to identify a region in the promoter of *CASC11* which was likely to bear the histone H3 lysine 27 acetylation (H3K27Ac) mark. The knockdown of c-Myc in SW620 cells combined with treatment with the histone deacetylase (HDAC) inhibitor trichostatin A demonstrated that preventing histone deacetylation facilitates the expression of *CASC11* in SW620 cells knocked-down for c-Myc. These results indicate that c-Myc enhances promoter histone acetylation to increase *CASC11* expression [33] (**Figure 1**). Another study showed that STAT3 can also upregulate *CASC11* expression in the context of HCC [35]. In this study, online bioinformatics tools from

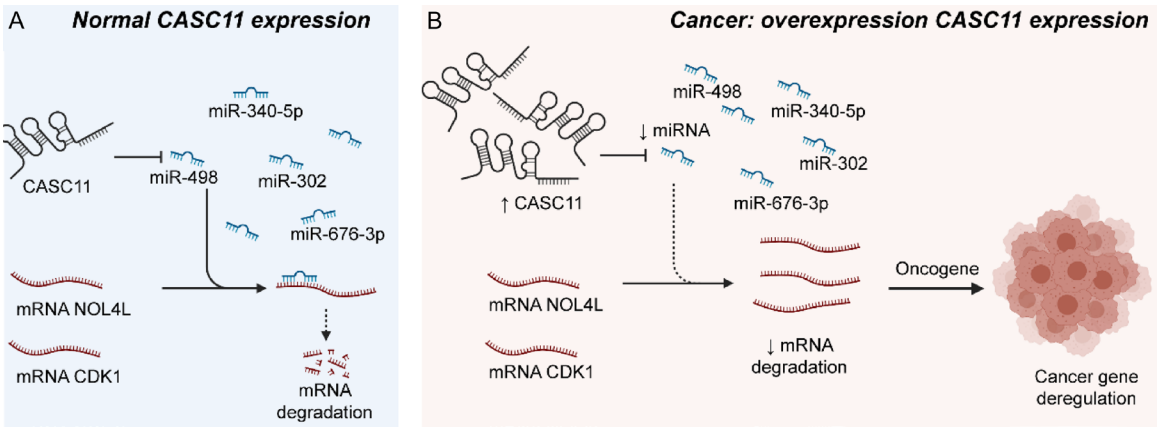

Figure 1. Transcriptional activation mechanisms leading to the elevated expression of *CASC11*. A. The E-box region of the *CASC11* promoter might serve as a c-Myc binding site. Once bound, c-Myc can recruit other proteins to enhance promoter histone acetylation and increase *CASC11* expression. B. *CASC11* expression can be increased in the presence of the transcriptional activator STAT3, and the transcription factors FOXO3 and SP1 have both been shown to bind to the CASC11 promoter region to promote *CASC11* expression.

Table 1. The expression patterns of CASC11 in cancers

Cancer types	Expression	Detecting method	Sample types	Prognostic relevance	Refs
colorectal cancer	upregulated	RT-qPCR	tissues and cells	/	27012187
hepatocellular carcinoma	upregulated	RT-qPCR and IHC	Serum and tissues	poor survival	33252856
	upregulated	RT-qPCR	tissues	/	32194694
	upregulated	RT-qPCR	tissues and cell lines	poor survival	30503497
	upregulated	RT-qPCR	tissues	poor survival	30910841
bladder cancer	upregulated	RT-qPCR	tissues	/	30916832
lung cancer	upregulated	RT-qPCR	tissues and cell lines	/	31378894
	upregulated	RT-qPCR	tissues	poor survival	31537383
	upregulated/plasma	RT-qPCR	plasma	poor survival	30965130
glioma	upregulated	RT-qPCR	tissues and cell lines	poor survival	31121483
ovarian carcinoma	upregulated	RT-qPCR	plasma	poor survival	32158258
	upregulated	RT-qPCR	plasma		31181314
cervical cancer	upregulated	RT-qPCR	tissues and cell lines	poor survival	31255182
gastric cancer	upregulated	RT-qPCR	tissues	/	30200804
	upregulated	RT-qPCR	tissues	/	31632064
neuroblastoma	upregulated	RT-qPCR	tissues and cell lines	poor survival	31645055
esophageal carcinoma	upregulated	RT-qPCR	tissues	poor survival	31696474

JASPAR (http://jaspar.genereg.net) and UCSC (http://genome.ucsc.edu/) were used to predict that STAT3 is a transcriptional activator of *CASC11*. Luciferase reporter assays and ChIP assays confirmed that STAT3 occupies the *CASC11* promoter [35]. Other transcription factors also reported to promote *CASC11* expression include FOXO3 and SP1 [32, 36] (**Figure 1**). Taken together, it is clear that transcription factors regulate the expression of CASC11, but the contributions of each of these factors in different contexts is not yet clear.

Functional activities of *CASC11* in cancer

Emerging data show that many lncRNAs have important roles in tumorigenesis and cancer progression [37-40]. LncRNAs can promote malignant features, such as sustaining growth, inducing invasion and metastasis, inhibiting death, and enhancing chemotherapeutic resistance [19, 41, 42]. Strikingly, *CASC11* expression is consistently elevated in most cancer types and generally enhances malignant cell characteristics (**Table 1**).

CASC11 in cell proliferation

Increasing evidence indicates that *CASC11* overexpression promotes cancer cell growth in vitro and vivo. Colony formation and cell proliferation assays show that the knockdown of *CASC11* in HCC cells significantly inhibits cell proliferative potential compared with control cells [31, 43]. *CASC11* also promotes tumor cell growth in other tumor cell lines, including colorectal cancer [33], bladder cancer [29], lung cancer [32, 44], glioma [36], ovarian carcinoma [45], cervical cancer [46], gastric cancer [30, 47], neuroblastoma [48] and esophageal carcinoma [49], suggesting it may act as an oncogene. Consistently, the effects of silencing and overexpressing *CASC11* in xenograft animal models also indicate that *CASC11* plays a role in oncogenesis [33, 46].

CASC11 in cell apoptosis

Apoptosis is a finely-balanced, ordered, orchestrated mechanism of cellular death, and tumor formation and cancer progression can result from too little apoptosis [50, 51]. Several studies have revealed that *CASC11* suppresses apoptosis in multiple types of cancer tumor cells. For example, the overexpression of *CASC11* inhibits apoptosis in ovarian carcinoma cells [45], but the silencing of *CASC11* enhances apoptosis in HCC cells [31]. Additionally, in cervical cancer [46], gastric cancer [30], and esophageal carcinoma [49], the knockdown of *CASC11* was reported to remarkably increase tumor cell apoptosis and inhibit cancer progression.

CASC11 in cell invasion and migration

The invasion and migration of cancer cells into surrounding tissue and vasculature is an essential step in cancer metastasis [52, 53], which greatly contributes to cancer-related death. Transwell experiments using HeLa cervical cancer cells showed that silencing *CASC11* decreases cell migration and invasion compared to controls, but the overexpression of *CASC11* increases cell migration and invasion [46]. Similar results were demonstrated in other cancer cell lines [29-31, 33, 36]. Consistent with these in vitro findings, *CASC11* also promotes tumor metastasis in vivo [33]. Together, these findings indicate *CASC11* may have an important role in cancer cell invasion and migration.

CASC11 in chemotherapeutic resistance

Chemotherapeutic resistance is one of the major hindrances in the fight against cancer, and *CASC11* expression may contribute to this resistance [54]. The *CASC11* plasma levels were significantly increased at both 3 and 6 months following the initiation of chemotherapy in ovarian squamous cell carcinoma patients [55]. Similarly, ovarian carcinoma cells treated with either cisplatin, oxaliplatin, tetraplatin or carboplatin displayed higher *CASC11* expressions than the untreated controls, and when *CASC11* was overexpressed in treated cells, it led to increased cell proliferation, but when *CASC11* was silenced, it inhibited proliferation [55]. Consistent with these observations, the plasma levels of *CASC11* were also increased in HCC patients at 3 and 6 months after the initiation of chemotherapy, and the knockdown of *CASC11* decreased the viability of carboplatin-treated HCC cells [28]. Together, these findings are consistent with a model in which elevated levels of *CASC11* contribute to chemotherapy resistance.

Mechanisms of *CASC11* action in cancer

Although most lncRNAs have not been functionally annotated, and lncRNAs remain challenging to characterize [56], accumulating evidence indicates that lncRNAs interact with other RNAs, DNA, and proteins to participate in processes ranging from transcription and intracellular trafficking to chromosome remodeling [57]. Although it is clear that *CASC11* has important functions related to cancer, the specific mechanisms and pathways involved are extremely complex, multifactorial, and poorly understood (**Table 2**).

One mechanism, the regulation of target gene expression via competing endogenous RNA (ceRNA) interplay, might be the major mechanism underling the oncogenic functions of *CASC11*. CeRNAs are non-coding RNAs that compete with messenger RNAs (mRNAs) for their microRNA (miRNAs) regulators, to modulate gene expression post-transcriptionally [58]. Many RNA species can act as ceRNAs, including other miRNAs, lncRNAs, circular RNAs, and pseudogenic RNAs [59, 60]. As a ceRNA, *CASC11* might inhibit related miRNAs to promote the translation of their miRNA-targeted mRNAs by

Table 2. The regulatory mechanisms of lncRNA CASC11 in various cancers

Cancer types	Interacting proteins or genes	Related signaling pathways	Refs
colorectal cancer	hnRNP-K	WNT/P-Ktal ca	27012187
hepatocellular carcinoma	EIF4A3	NF-κF signaling and PI3K/AKT/mTOR pathway	33252856
hepatocellular carcinoma	EZH2	PI3K/AKT signaling pathway	30503497
hepatocellular carcinoma	miRNA-188-5p	/	30910841
bladder cancer	miRNAer c	/	30916832
lung cancer	microRNA-302/CDK1	/	31378894
non-small cell lung cancer	miR-498	/	31537383
glioma	miR-498/FOXK1	/	31121483
cervical cancer	/	Wnt/β-catenin	31255182
gastric cancer	miR-340-5p/CDK1	cell cycle pathway	30200804
neuroblastoma	microRNA-676-3p/nucleolar protein 4like (NOL4L)	/	31645055
esophageal carcinoma	KLF6	/	31696474

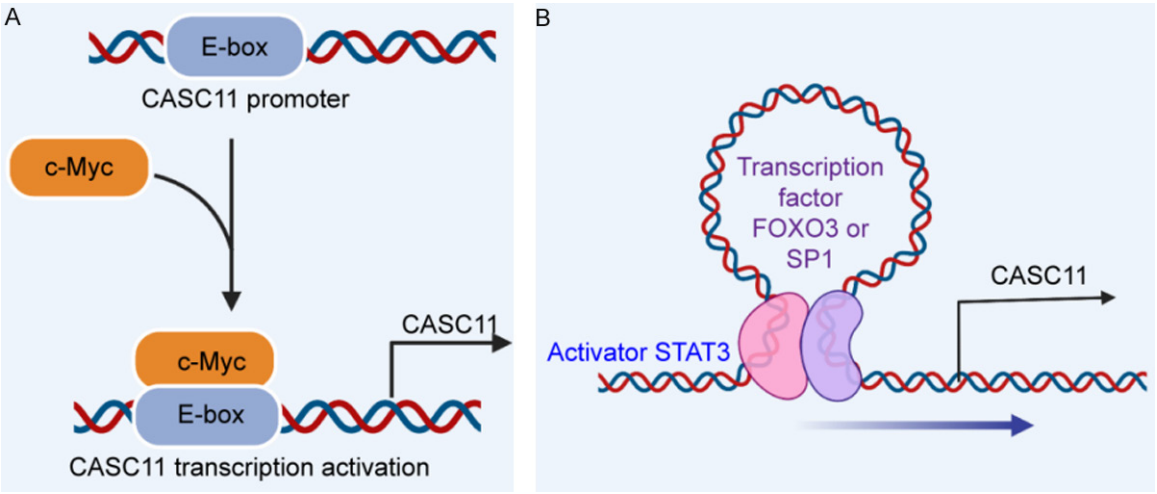

Figure 2. *CASC11* may act as a ceRNA in cancer. *CASC11* can inhibit specific miRNAs to promote protein expression by regulating the level of the miRNA's target gene's mRNA degradation. A. When *CASC11* is normally expressed, the *CASC11* levels are insufficient to compete with mRNA for binding to specific miRNAs, permitting the miRNA to promote degradation of its mRNA target. B. When *CASC11* is overexpressed, it can compete with mRNA for binding to specific miRNAs, thus inhibiting the ability of the miRNA to promote the degradation of its mRNA target as has been shown for MIR302, MIR498, MIR340-5p, and MIR676-3p.

modulating the miRNA-mediated mRNA degradation level. Indeed, *CASC11* has been reported to act as a ceRNA for several miRNA/mRNA combinations: MIR302/*CDK1* [44], MIR498/*FOXO3* [32], MIR340-5p/*CDK1* [30], and MIR-676-3p/*NOL4L* [48]. Dual-luciferase reporter gene data combined with other experimental data show that *CASC11* binds MIR302, which targets cyclin dependent kinase 1 (*CDK1*) mRNA in lung cancer cells [44]. Additional functional assays indicate that high expressions of *CASC11* may accelerate lung cancer progression through a MIR302/*CDK1* axis. Similarly, *CASC11*, promotes tumor cell proliferation in non-small cell lung cancer through targeting MIR498/forkhead box O3 (*FOXO3*), and Zhang et al. linked the *CASC11*/MIR340-5p/*CDK1* network to gastric cancer [30, 32]. In addition, *CASC11* was found to serve as a molecular sponge for MIR676-3p, relieving its inhibition of nucleolar protein 4-like mRNA (*NOL4L*) in neuroblastoma cells [48] (**Figure 2**).

Several studies suggest that in addition to acting as a ceRNA that influences protein levels, *CASC11* can exert its function by interacting with proteins directly. For example, the histone methyltransferase enhancer of zeste homolog 2 (EZH2) epigenetically represses the expression of the tumor suppressor phosphatase and tensin homolog deleted on chromosome ten (PTEN) [35]. *CASC11* binds to EZH2 to enhan-

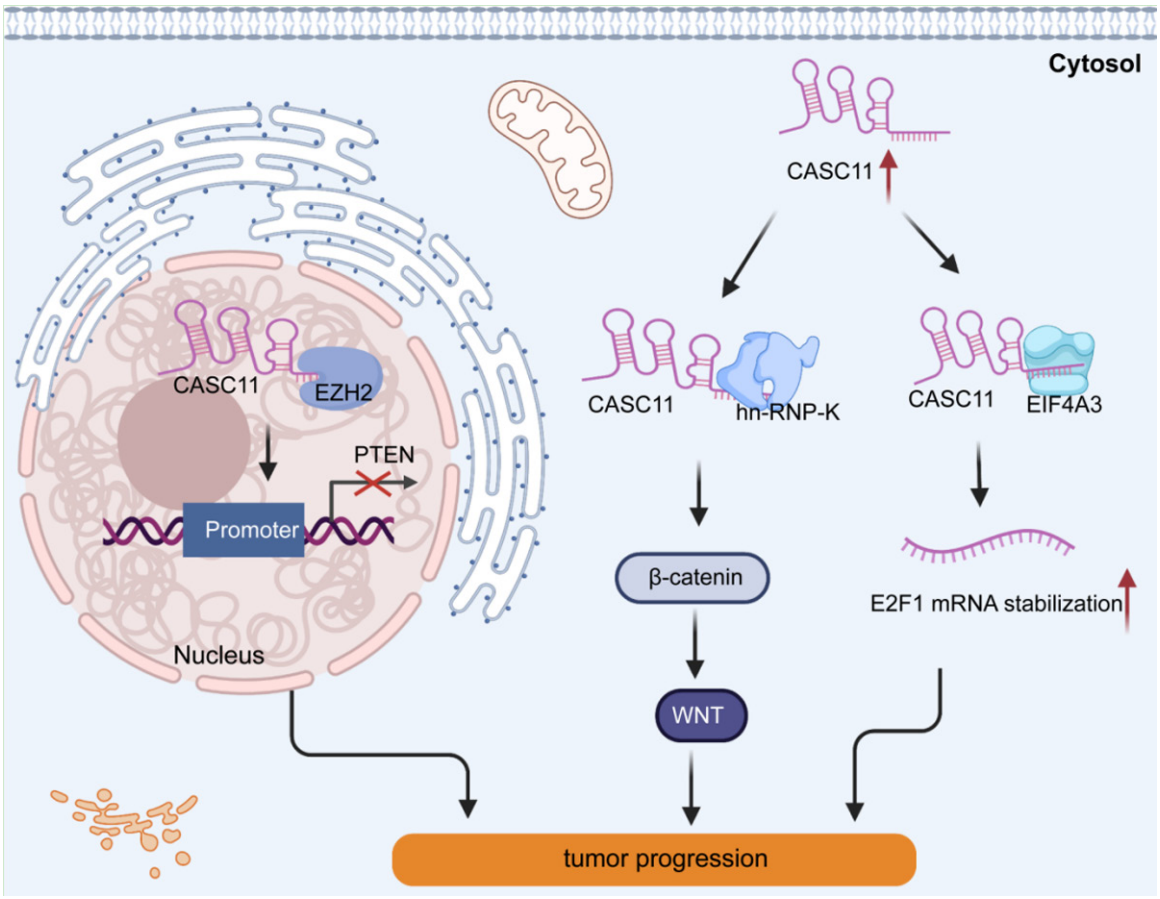

Figure 3. *CASC11* exerts some of its functions through protein interactions. *CASC11* directly binds to EZH2 to enhance the epigenetic silencing of the PTEN promoter region and suppress PTEN expression. The overexpression of *CASC11* activates the WNT signaling pathway in colorectal cancer cells by increasing β-catenin nuclear accumulation through its interaction with hnRNP-K. Additionally, the upregulation of *CASC11* promotes tumor progression by enhancing the stability of *E2F1* mRNA by recruiting eukaryotic translation initiation factor 4A3 (EIF4A3).

ce epigenetic silencing in the PTEN promoter region. *CASC11* also interacts with heterogeneous nuclear riboprotein K (hnRNP-K), a protein that shuttles between the nucleus and cytoplasm and interacts with RNA and DNA [61, 62]. The overexpression of *CASC11* activates WNT signaling in colorectal cancer cells by increasing the nuclear accumulation of β-catenin by interacting with hnRNP-K [33]. Additionally, another recent study demonstrated that *CASC11* promotes HCC progression by enhancing the stability of E2F transcription factor 1 (*E2F1*) mRNA by binding to and recruiting eukaryotic translation initiation factor 4A3 (EIF4A3) [31] (**Figure 3**). Given these many examples of functional *CASC11*-protein interactions, it will be important to determine, whether *CASC11* has other regulatory functions mediated by direct interactions with other proteins.

CASC11 as a diagnostic and prognostic biomarker in cancer

Molecular biomarkers for cancer have improved dramatically in recent years [63-65]. The primacy of specificity as a requirement for diagnostic and prognostic biomarkers points to lncRNAs, because the expression of most lncRNAs is strikingly tissue-specific compared with protein-coding genes [66]. *CASC11* is upregulated in the sera and tissues of HCC patients, and HCC patients with higher *CASC11* expressions exhibit larger tumors and have poorer prognoses than those with lower *CASC11* expressions. Receiver operating characteristic (ROC) curve analyses show that *CASC11* may be a good candidate as a prognostic biomarker for HCC (AUC=0.8) [31]. The diagnostic potential of *CASC11* has also been evaluated

using ROC curve analyses in patients with bladder cancer vs. healthy controls (AUC=0.899) indicating *CASC11* expression might be a predictor for this cancer [29]. *CASC11* plasma levels are also upregulated in ovarian carcinoma patients compared with healthy controls and ROC curve analyses show that *CASC11* levels can predict early-stage ovarian carcinoma [45]. The results of a survival curve analysis demonstrated that *CASC11* overexpression predicts poor prognosis in ovarian carcinoma and ovarian squamous cell carcinoma [45, 55]. Taken together, these studies strongly indicate the potential of *CASC11* expression as a biomarker that can be detected in less-invasive blood tests.

CASC11 as a therapeutic target in cancer

Accumulating evidence indicates that lncRNAs might be promising therapeutic targets [67-70]. *CASC11* has attracted much attention, not only for its value in diagnosing cancer and predicting prognosis, but also for its potential as a therapeutic target. Several studies show that the expression of *CASC11* is altered in tumor tissues, plasma from cancer patients, and in cancer cell lines, indicating it has a regulatory role in cancer. The overexpression of *CASC11* is closely associated with tumor size, stage, and prognosis [31, 32, 35]. Gain- and loss-of-function experiments with *CASC11* indicate that *CASC11* may function as an oncogene to promote tumor cell proliferation, invasion, migration, and chemotherapeutic resistance, while suppressing tumor cell apoptosis through the modulation of the WNT/β-catenin, NF-κB signaling, and PI3K/AKT/mTOR pathways [31, 33, 35]. Thus, these findings suggest that *CASC11* plays an oncogenic role in a variety of cancer types and that targeting this lncRNA may provide a novel approach toward improved cancer therapy.

Conclusions and perspectives

A growing amount of evidence supports lncRNAs as biomarkers for the diagnosis and prognosis of patients with cancer [71-74]. *CASC11* is a novel lncRNA that acts as an oncogene in several different types of cancer. Most studies indicate that *CASC11* is overexpressed in multiple cancers, and its overexpression correlates with larger tumor size, more advanced cancer stages, cancer metastasis, and poor overall survival for most types of cancer. Functionally, the knockdown of *CASC11* can inhibit cell proliferation, invasion and migration, while promoting apoptosis through its regulation of gene expression and signaling pathways, and its interactions with functional proteins. Overall, there is substantial evidence that *CASC11* may have immediate clinical potential for diagnosing cancer and predicting patient prognosis, as well as future potential as a therapeutic target. Although the wide diversity of molecular interactions that contribute to cancer tumorigenesis and progression complicate the development of optimal cancer treatments, CASC11 may provide a new target for cancer therapy. Currently, the development of methods to inhibit *CASC11* to target cancer is in the early stages [30, 32, 35], and further in-depth studies of *CASC11* and the molecular mechanisms it affects are both needed and worthy of attention.

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Disclosure of conflict of interest

None.

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