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Cancer Susceptibility Candidate 9 (CASC9): A Novel Targetable Long Noncoding RNA in Cancer Treatment

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ABSTRACT

Based on epidemiological data provided by the World Health Organization (2018), cancer is the second most prevalent cause of death worldwide. Several factors are thought to contribute to the high mortality rate in cancer patients, including less-than-optimal diagnostic and therapeutic strategies. Thus, there is an urgent need to identify accurate biomarkers with diagnostic, prognostic, and potential therapeutic applications. In this regard, long noncoding RNAs (lncRNAs) hold immense potential due to their regulatory roles in cancer development and associated cancer hallmarks. Recently, *CASC9* transcripts have attracted significant attention due to their altered expression during the pathogenesis of cancer and their apparent contributions to various cancer-associated phenotypes involving a broad spectrum of molecular mechanisms. Here, we have provided an in-depth review describing the known functions of the lncRNA *CASC9* in cancer development and progression.

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Introduction

Recent advances in cancer research have revealed several distinct cancer-associated "hallmarks" that allow tumor cells to migrate and invade secondary sites [1,2]. Recent studies have identified key molecules that, when dysregulated, can contribute to cancer development and progression. Of interest, recent studies have revealed that noncoding RNA molecules coordinate many biological functions, which correspond to ~98% of the human genome compared to ~2% of coding of RNA molecules [3–6].

Additionally, mounting evidence suggests that an essential class of noncoding RNA molecules, long noncoding RNAs (lncRNAs), defined based on their size of greater than 200 nucleotides, regulate various cellular processes. These include transcription, splicing, translation, protein localization, epigenetics, cell structure integrity, cell cycle, heat shock responses, imprinting, stem cell pluripotency, reprogramming, embryogenesis,

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immune response regulation, cell differentiation, cell fate determination, cell proliferation, and cell migration [3,7–15]. Previous studies have detected alterations of lncRNAs in virtually all human cancers [3,4,6,16]. Further, lncRNAs have been implicated in modulating various cancer-related hallmarks such as sustained proliferative signaling [17], evasion of growth suppressors [18], replicative immortality [18], induction of angiogenesis, activation of invasion and metastasis [19,20], resistance to cell death [21], avoiding immune destruction [22], tumor-promoting inflammation [23], deregulation of cellular energetics [23], and genome instability [23]. For instance, the lncRNA *H19* has been shown to regulate the proliferation of gastric cancer (GC) cells by binding with p53 [24], stimulation cell cycle progression through the G1/S transition in esophageal squamous cell carcinoma (ESCC) [25], and resistance of cell death in cholangiocarcinoma cells [26]. Similarly, the lncRNA *HOTAIR* has been implicated in promoting cellular proliferation, migration, and invasion in thyroid cancer cells [27]. Additionally, studies have demonstrated an association of lncRNA *MALAT1* with cellular proliferation and apoptosis in colon cancer [28].

This review aims to discuss the recently discovered "cancer susceptibility candidate 9" (*CASC9*) lncRNA (Ensemble ID: ENSG00000249395) and its potential roles in the pathogenesis of cancer. Additionally, we discuss the potential utility of *CASC9* as a prognostic marker and/or therapeutic target for cancer, as it was first identified in ESCC as an associated lncRNA having four transcriptional variants; [*CASC9*-201 (Ensemble ID: ENST00000504531.2), *CASC9*-202 (Ensembl ID: ENST00000521147.1), *CACS9*–203 (Ensembl ID: ENST00000522183.1), and *CASC9*-204 (Ensembl ID: ENST00000523313.1)]. Subsequently, these transcriptional variants were implicated in a variety of cancers, including breast, lung, and liver.

Here, we focus on the involvement of *CASC9* in the progression of tumorigenesis and the advancement of cancers via dysregulating the defining hallmarks of cancer. For each of the cancer hallmarks, we have presented significant protein-coding and non-coding molecules that are regulated by *CASC9*. We have also discussed the potential prognostic and diagnostic applications of *CASC9*, and its potential as a therapeutic target.

Association of the long non-coding RNA *CASC9* with Various Hallmarks of Cancer

CASC9 in Sustaining Proliferative Cell Signaling

Cellular proliferation in healthy cells is tightly regulated by growth signals and cell cycle regulators to maintain cellular homeostasis. Cancer cells often contain disrupted and/or dysfunctional biological regulators enhancing uncontrolled cellular proliferation [23]. The ability of cancer cells to sustain continuous proliferative signals can be attained in several ways, i.e., excessive production of growth ligands, disruption of feedback mechanisms, and evasion of growth suppressors, etc. [1]. Among multiple factors associated with the uncontrolled proliferation of cells in various cancer types, *CASC9* has been implicated as an essential factor for sustained cancer cell growth via distinct mechanisms. The deregulated expression of *CASC9* was first identified in ESCC, where gain and loss of function assays revealed roles for *CASC9* in promoting cell proliferation *in vitro* and tumor growth *in vivo* [29]. Subsequent studies found a direct correlation between *CASC9* expression and cancer progression, where depletion of *CASC9* reduced cell proliferation and colony formation of cancer cells compared to control cells, while overexpression had the reverse effect [30–34]. In biological systems, cellular proliferation and the cell cycle are tightly regulated by various checkpoints, tumor suppressor genes, oncogenes, and other downstream targets. In nasopharyngeal cancer (NPC), *CASC9* was found to interact with hypoxia-inducible factor-1 alpha (*HIF-1α*), enhancing its stability and further promoting glycolysis in NPC, thereby increasing cellular proliferation [35]. In ESCC cells, *CASC9* downregulated programmed cell death 4 (PDCD4) protein via reduction of associated mRNA levels. *PDCD4* is a highly conserved gene involved in inhibiting the translational initiation of multiple genes, including tumor suppressor *p53*, apoptosis-related *pro-caspase-3*, and autophagy-related *Atg5* (Figure 1) [36]. Studies on cell cycle regulators have identified a strong correlation between *PDCD4* and *CASC9*, where *PDCD4* rescued, in part, G1/S arrest caused by *CASC9* knockdown. Mechanistically, knockdown of *CASC9* reduced the expression of the S-phase cyclins *cyclin E2* (*CCNE2*) and *CDK6* while suppression of *PDCD4* rescued their expression (Figure 1). Furthermore, a series of investigations using microarray analysis, chromatin immunoprecipitation assays, western blot analysis, etc., have confirmed a regulatory role of *PDCD4* by recruiting enhancer like zeste homolog 2 (EZH2), which is associated with increased H3K27me3 methylation (Figure 1) [34]. Thus, these results suggested that *CASC9* may play an intrinsic role in association with sustained cell cycle progression in a *PDCD4*-dependent manner in ESCC cells.

Upregulation of *CASC9* was also found to regulate cell cycle progression in the G1 phase via cyclin D1 in lung adenocarcinoma (LAD) (Figure 1) [30,33–35,37]. Additionally, *in vitro* assays performed by Xi et al. (2020) demonstrated that the upregulation of *CASC9* resulted in overexpression of the glucose transporter 1 (*GLUT1*) gene in TU212 laryngeal carcinoma cells, thus contributing to cellular proliferation [38]. Further, potential interactions between *CASC9* and *cleavage polyadenylation specificity factor subunit 3* (*CPSF3*) (Figure 1) were observed in colorectal cancers (CRCs) via RNA immunoprecipitation and RNA-protein pull-down assays [39].

Studies have reported that *CASC9* modulated *TGFβ2* mRNA stability and thus upregulated the expression levels of *TGFβ* and *TERT*, which in turn resulted in the increased phosphorylation of mothers against decapentaplegic homolog 3 (SMAD3) and ultimately activated the TGFβ signaling pathways and TERT complex function in CRC cells (Figure 1) [39]. Thus, it may be concluded that *CASC9*, in association with CPSF3 and TGFβ, contributed to an elevated proliferation of CRC cells [39]. Additionally, enzyme-linked immunosorbent assay analysis demonstrated increased expression levels of TGFβ in serum, tissues, and cells of cervical cancer [40].

Regulatory roles of miRNAs in cell proliferation via modulation of target genes have been uncovered in the recent past. For example, *CASC9* has been shown to act as a competing endogenous RNA (ceRNA) by competitively binding to its target miRNAs at the 3′UTR region, inhibiting miRNA expression via a sponging effect [41–44]. In glioma cancer cells, *CASC9* was reported to exert a sponging effect on miR-519d, silencing its function and releasing its downstream target, the signal transducer and activator of transcription 3 (STAT3) transcription factor. The release of STAT3 further increased the transcription of *CASC9*, magnifying its oncogenic potential [43]. Furthermore, in MDA-MB-415 human breast cancer cells, *CASC9* positively regulated checkpoint kinase1 (CHK1) by binding to the miR-195/147 cluster (Figure 1) [44]. Silencing of *CASC9* resulted in increased levels of B-cell lymphoma 2 (BCL-2) (~2.0-fold), CCND1 (~2.5-fold), and CDK4 (~7.0-fold), as assessed by Western blot analysis, which facilitated breast cancer cell proliferation [44]. Suppression of *CASC9* was also found to suppress the expression of miR-758-3p, which in turn released its target gene, *LIN7A,* increasing its expression in SKOV3 and A2780 human ovarian cancer cells that ultimately lead to ovarian cancer cell proliferation (Figure 1). Thus, a defined regulatory pathway, *CASC9*/miR-758-3p/*LIN7A*, was identified in ovarian cancer progression [41].

CASC9 was also found to have a disrupted expression in benign tumors such as hemangioma (HA) [42], where higher levels of *CASC9* were detected in the tissues of proliferative-phase HA samples when compared to tissues in the involuting phase of HA and healthy tissue samples. Likewise, higher expression of *CASC9* correlated with a higher level of cyclin D1 in HA cells (Figure 1). Further investigation revealed that miR-125b was a direct target of *CASC9*, where the expression of miR-125b negatively correlated with *CASC9* expression in HA tissues. Additionally, *neuregulin-1* (NRG1) was found to be a direct downstream target of miR-125b, which together regulated cancer cell proliferation (Figure 1). *Neuregulin-1* is recognized as an oncogene in colon, lung, and gastric cancers, among others [45].

Taken together, the studies, as mentioned earlier, suggest that *CASC9* participates as one of the factors responsible for sustained proliferative

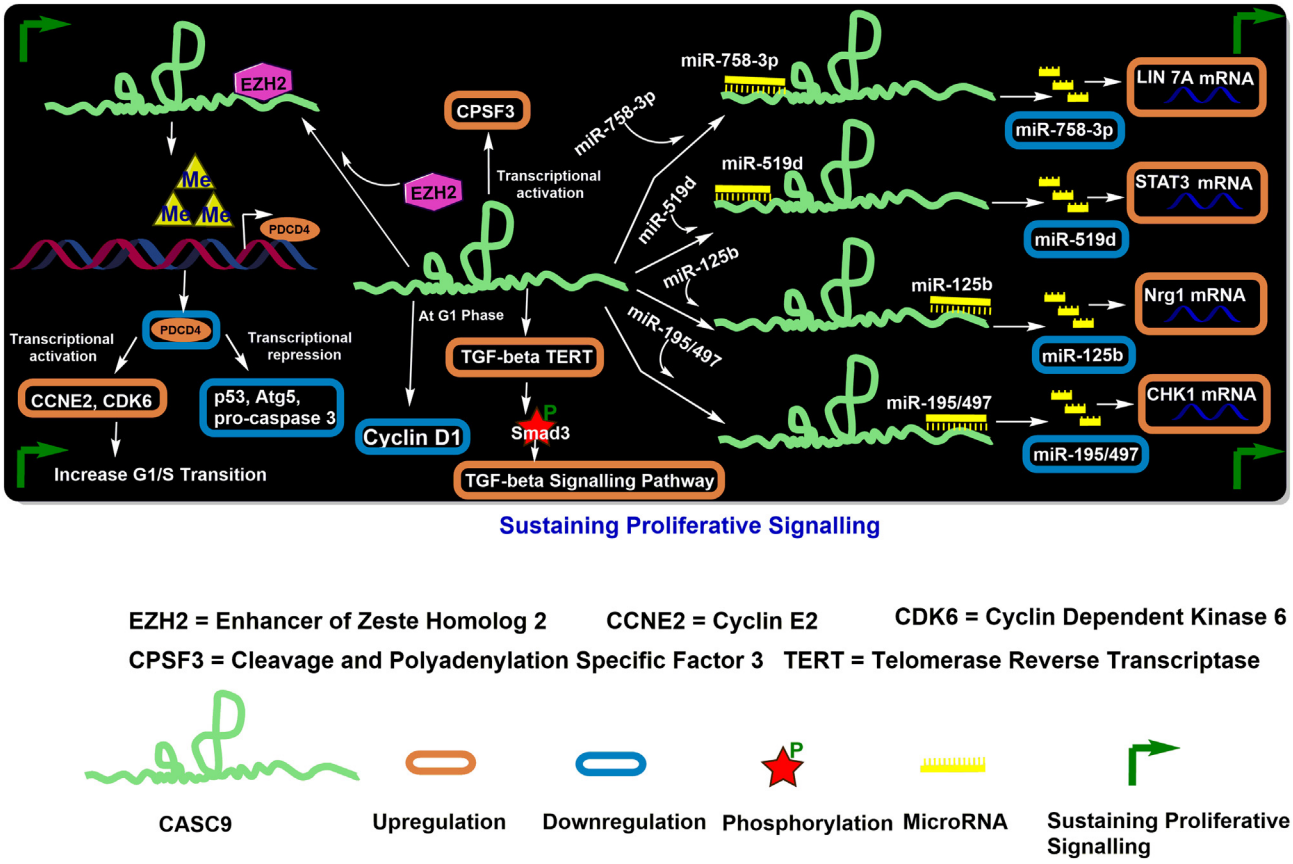

Figure 1. Regulatory mechanisms of *CASC9* in cancer cell proliferation.

signals in cancer cells through targeting various cell cycle proteins, miRNAs, and transcription factors.

CASC9 in Invasion and Metastasis

Invasion and metastasis are among several hallmarks of cancer that *CASC9* has been demonstrated to impact. Invasion and metastasis involve a cascade of discrete steps involving cellular changes, viz., local invasion, intravasation via lymphatic and blood vessels, extravasation through the hematogenous lymphatic system into the parenchyma of distant tissues, and the formation of micrometastases and/or secondary tumors. This cascade is, in turn, broadly regulated by the epithelial-mesenchymal transition (EMT) process, where the cancer cells acquire multiple attributes that enable them to invade barriers, resist apoptosis, and disseminate.

Independent reports have revealed a correlation among *CASC9* overexpression and migration and invasion of ESCC tumor cells [32,46]. Consistent with these reports, the siRNA-mediated knockdown of *CASC9* decreased the migration and invasion potential of ESCC cells [32,46]. Besides, Western blot analysis confirmed that *CASC9* exerted its function by regulating the expression of genes involved in EMT, extracellular matrix (ECM) interactions, and focal adhesion, where it suppressed the expression of the EMT markers vimentin, Snail, and fibronectin [32] and ECM-interacting proteins laminin subunit gamma 2 (LAMC2) and integrin subunit beta 4 (ITGB4) [46]. In contrast, the levels of *E-cadherin* increased (Figure 2) [32]. Further analyses confirmed that *LAMC2* silencing attenuated the number of motile ESCC cells and inhibited the expression of matrix metallopeptidase (MMP) 10,13, focal adhesion kinase (pFAK), pPI3K, and pAKT (Figure 2). This indicated that *LAMC2* was the primary downstream target of *CASC9*-induced metastasis, which was modulated via the FAK-PI3K/AKT signaling pathway [46].

CASC9 has also been implicated in regulating the metastatic and invasive potential of tumor cells by sponging miRNAs. For example, CASC9 has shown to upregulate the expression of the *MT1E* gene encoding metallothionine 1E, which induced the inactivation of the matrix metallopeptidase 9 (*MMP9*) gene and downregulated the expression of other matrix metalloproteinase (*MMP1*, *MMP2*, *MMP11*, and *MMP14*) genes that break down the ECM. Further, it has been shown to regulate the genes encoding collagen subunits (*COL1A1*, *COL5A1*, and *COL6A1*) that constitute a part of the ECM, thereby collectively promoting tumorigenicity by increased invasion and metastasis (Figure 2) [47]. In glioma, miR-519d suppressed the expression of the *STAT3* gene, which was rescued by the sponging activity of *CASC9*. Since *CASC9* also harbors a binding site for STAT3 in its promoter region, increased STAT3 levels activated the transcriptional activity of *CASC9* by a positive feedback loop via the STAT3-*CASC9*-miR-519-STAT3 axis [43]. Similarly, *CASC9* upregulation resulted in increased migration and invasion of ovarian cancer cells (SKOV3 and A2780) using a transwell invasive assay [41]. *CASC9* acted as a competing endogenous RNA in ovarian cancer cells, where it suppressed miR-785-3p and increased the expression of *LIN7A*, as shown in Figure 2. The specific role(s) of *LIN7A* has yet to be determined in ovarian cancer; however, Hu et al. (2019) found that overexpression of *LIN7A* rescued the suppressive effects of *CASC9* silencing on cell migration and invasion [41].

In contrast, miR-145-5p was predicted as a putative target for *CASC9* in hepatocellular carcinoma cells (HCC), but due to its inappreciable expression levels, it was rendered inadequate for further analyses [48]. Also, increased *CASC9* expression in HCC cells resulted in no detectable difference in their proliferation rate, supporting the notion that lncRNAs were discordantly expressed in different tumor types and different subgroups of specific cancer types. Moreover, lncRNA *CASC9* positively correlated with epithelial phenotypes in HCC due to increased expression of *CDH1* (*E-cadherin*) and *CDH2* (*N-cadherin*), while it decreased the

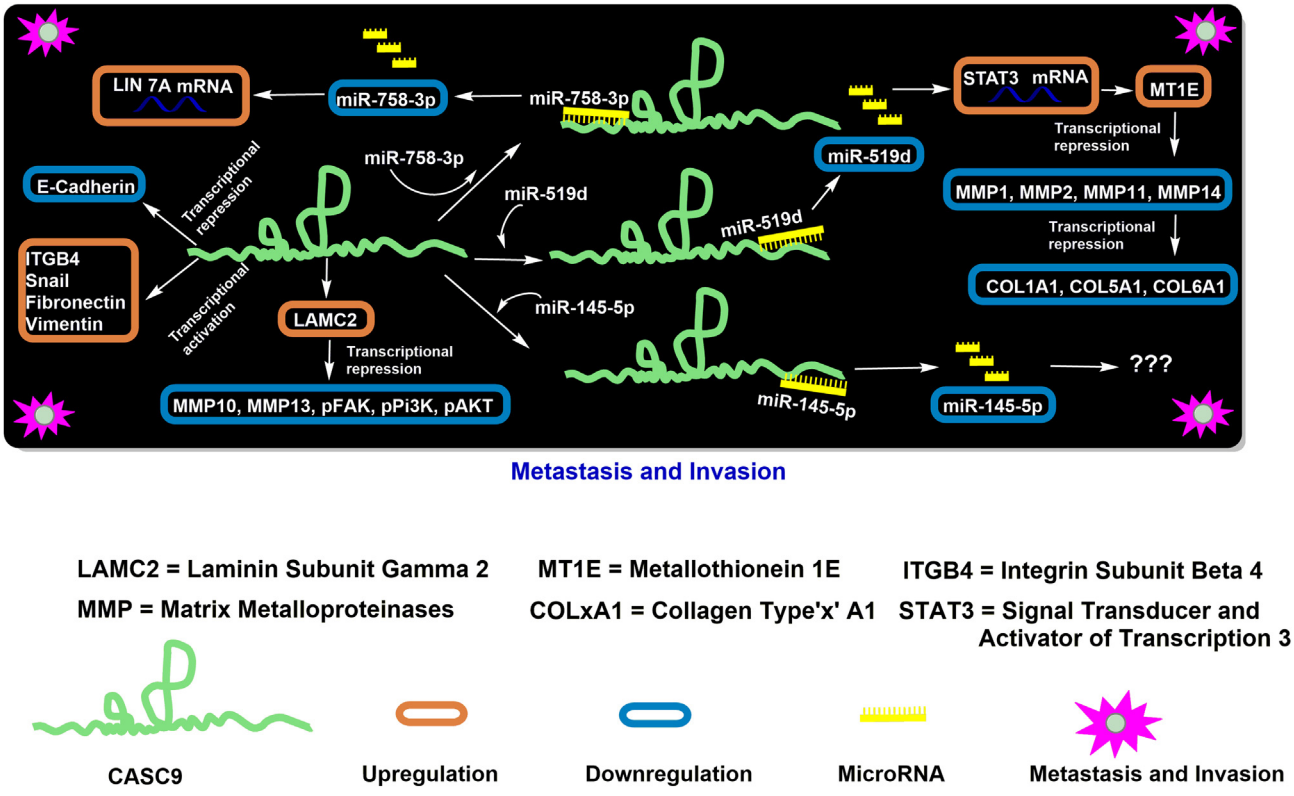

Figure 2. Regulatory mechanisms of *CASC9* in cancer cell migration and invasion.

expression of *MMP9* and the migration potential of the cells [48]. However, Yu et al. (2017) demonstrated that *CASC9* significantly promoted the invasion potential of the pancreatic cell lines SW190 and BxPC compared to control cells [49].

CASC9 promotes the invasion and metastasis through modulating the expression of miR-519, miR-145-5p, EMT-associated proteins, and matrix metallopeptidases in various cancers. Thus, CASC9 may be used as a diagnostic marker for the advanced stages of certain cancers.

CASC9 in Resisting Cell Death

Apart from the regulatory role of *CASC9*, it is also associated with cellular proliferation, cellular invasion, and cellular metastasis, and it also plays an essential role in resisting cell death or apoptosis in various cancer cells. Moreover, it is well established that the ratio of BCL-2 and BCL-2-associated X protein (BAX) in the cell acts as an indicator for cellular apoptosis [50], where BCL-2 is antiapoptotic and BAX is proapoptotic. Cancer cells have the potential to tolerate both environmental and genomic stresses and thus exhibit resistance to apoptosis [23]. However, several studies have suggested that dysregulation of *CASC9* expression may result in resistance to the death of cancer cells.

Recent evidence suggested that the upregulated expression of *CASC9* in breast cancer tissues and cell lines correlated with various clinicopathological characteristics, as shown in Table 1 [44,51]. Silencing of *CASC9* in MDA-MB-415 and MCF-7/DOX human breast cancer cells promoted their apoptotic potential [44,51], whereas silencing of *CASC9* in MDA-MB-231 cells showed an opposite effect, as assessed by flow cytometry [44]. Moreover, investigation of apoptosis-associated proteins in the si-*CASC9*–treated MCF-7/DOX cells showed decreased levels of BCL-2, pro-caspase-3, and pro-caspase-9. On the other hand, BAX, cleaved caspase-3, and cleaved caspase-9 showed increased expression levels in breast cancer cells (Figure 3) [51]. However, another study suggested higher expression levels of *BCL-2* and lower expression of *caspase-3* in si-*CASC9*–treated MDA-MB-415 cell lines compared to untreated cells [44]. Shao et al. (2019) found a negative correlation of *CASC9* expression with *miR-197* and *miR-497* expression in breast cancer tissues and a positive correlation with *CHK1* levels, presumably by the sponging of *miR-197* and *miR-497* [44]. Another study has reported an upregulated expression of *CASC9* in GC cells and tissues that correlated with various clinicopathological characteristics, as shown in Table 1 [52,53]. To investigate the role of *CASC9* in apoptosis, two independent groups performed knockdown of *CASC9* in the GC cell lines BGC823/DR, SGC7901/DR, SGC7901, and MKN-45 and showed increased apoptosis in these cells. Furthermore, Fang et al. (2019) reported that apoptosis in GC cells was regulated by downregulation of the B cell–specific Moloney murine leukemia virus integration site 1 (BMI1) protein in conjunction with other apoptosis-associated proteins (e.g., BCL-2) and cleaved caspase-3 [53]. Lo et al. (2019) showed an upregulated expression of *CASC9* in CRC cell lines and tissues and found an association with various clinicopathological characteristics, as shown in Table 1. *CASC9* possesses four transcript variants, and of these, *CASC9*-202 and *CASC9*-204 were the most abundant and dysregulated in HCT-116, SW620, and SW480 CRC cell lines. Knockdown of the dysregulated transcripts of *CASC9* (*CASC9*-202, *CASC9*-204) led to a disruption of the cell cycle in the G2/M phase and thus increased the apoptotic potential of the cancer cells [41]. Another group reported that *CASC9* was overexpressed in lung squamous cell carcinoma and correlated with various clinicopathological characteristics (as shown in Table 1). However, its expression was not associated with the apoptotic status of the cells [54]. Similarly, *CASC9* was found to be dysregulated in hepatocellular carcinoma and ESCC cells [32,34,35,46,48], but no significant role in apoptosis in these cells has yet been established.

Collectively, CASC9 hinders the apoptotic potential of the healthy cells, thus assisting in the transformation of healthy cells into a cancerous phenotype through regulating the expression of proapoptotic and antiapoptotic proteins and various miRNAs such as miR-197 and miR-497.

Table 1
Implications of CASC9 with Various Hallmarks of Cancer Through Targeting Genes/Proteins/Pathways

Hallmarks of Cancer	Cancer Types	Regulation of CASC9	Clinicopathological Characteristics	Targets of CASC9	References
Sustaining proliferative signaling	Esophageal squamous cell carcinoma	Up	Gender, age, tumor size, differentiation, tumor invasion, lymph node metastasis, TNM stage, smoking, drinking	*PDCD4*, *EZH2*, Cyclin D1 *CCNE2, CDK6*, *p53,*	[29,32,34,36,46]
	Ovarian cancer	Up	Age, tumor size, lymph node metastasis, FIGO stage	Pro-caspase-3, *Atg5*	[41]
	Breast cancer	Up	Age, tumor size, histological grade, lymph node metastasis, AJCC status, lymphovascular invasion, ER expression	*LIN7A*, miR-758-3p	[44,51]
	Lung cancer	Up	Gender, age, tissue type, tumor location, stage, distant metastasis, lymph node metastasis, primary tumor stage, anatomical classification	*CHK1*, miR-195/147, *BCL-2*, Cyclin D1, *CDK4*	[37,54]
	Colorectal cancer	Up	Gender, age, tumor size, differentiation grade, tumor location, lymph node metastasis, TNM stage	*CPSF3*, *TGFβ, TERT,* p- SMAD3	[39]
	Glioma	Up	-	miR-519d, STAT3	[43]
	Hemangioma	Up	-	Cyclin D1, miR-125b, *Nrg1*	[42]
	Laryngeal carcinoma	Up	-	*GLUT-1*	[38]
	Nasopharyngeal carcinoma	Up	-	*HIF-1α*, Cyclin D1	[35]
Metastasis and invasion	Esophageal squamous cell carcinoma	Up	Gender, age, tumor size, differentiation, tumor invasion, lymph node metastasis, TNM stage, smoking, drinking	Vimentin, Snail, fibronectin, *LAMC2, ITGB4*, E-cadherin, *MMP10, MMP13*, pFAK, pPI3K, pAKT	[29,32,34,36,46]
	Lung cancer	Up	Gender, age, tissue type, tumor location, stage, distant metastasis, lymph node metastasis, primary tumor stage, anatomical classification	-	[37,54]
	Hepatocellular carcinoma	Up	-	miR-145-5p, E-cadherin, N-cadherin, *MMP9*	[48]
	Pancreatic ductal adenocarcinoma	Up	-	-	[49]
	Ovarian cancer	Up	Age, tumor size, lymph node metastasis, FIGO stage	miR-785-3p, *LIN7A*	[41]
	Breast cancer	Up	Age, tumor size, histological grade, lymph node metastasis, AJCC status, lymphovascular invasion, ER expression	-	[44,51]
	Glioma	Up	-	STAT3, *MT1E, MMP9,*	[47]
	Hemangioma	Up	-	*MMP1, MMP2, MMP11, MMP14, COL1A1, COL5A1, COL6A1*, miR- 519d	[42]
Resisting cell death	Esophageal squamous cell carcinoma	Up	Gender, age, tumor size, differentiation, tumor invasion, lymph node metastasis, TNM stage, smoking, drinking	No significant role in apoptosis has been reported.	[29,32,34,36,46]
	Hepatocellular carcinoma	Up	-	-	[48]
	Gastric cancer	Up	Gender, age, tumor size, histology, tumor stage, lymph node metastasis,, site, Bormann type, depth of invasion, infiltrating pattern, lymphatic/venous invasion	BMI1, BCL-2, cleaved caspase-3	[52,53]
	Lung cancer	Up	Gender, age, tissue type, tumor location, stage, distant metastasis, lymph node metastasis, primary tumor stage, anatomical classification	-	[37,54]
	Breast cancer	Up	Age, histological grade, tumor size, lymph node metastasis, AJCC status, Lymphovascular invasion, ER expression	Bax, cleaved caspase-3, cleaved caspase-9, BCL-2, pro-caspase-3 and pro-caspase-9, miR-197, miR-497, *CHK1*	[44,51]
	Colorectal cancer	Up	Gender, age, tumor size, differentiation grade, tumor location, lymph node metastasis, TNM stage	-	[39]
Deregulation of cellular energetics	Nasopharyngeal cancer	Up	-	*HIF-1α*	[35]

CASC9 in Cellular Energetics

Past studies have documented the dependence of cancer cells on specific metabolic pathways. Metabolism in healthy cells often involves the conversion of glucose to pyruvate via a multistep process of glycolysis [23]. During aerobic respiration, pyruvate enters the mitochondria where it is oxidized to generate ATP to fulfill cellular energy demands. On the contrary, in cancerous cells, pyruvate is often directed away from the mitochondria to create lactate via the action of the enzyme lactate dehydrogenase (LDH/LDHA), which is characteristic of a hypoxic environment; this phenomenon is known as aerobic glycolysis or the "Warburg effect" [23].

Su et al. (2017) found that *CASC9* was highly overexpressed (by ~12-fold) in the nasopharyngeal carcinoma (NPC) cell line CNE-1 when compared to a normal control cell line, NP-69. Additionally, similar results were observed in NPC tissues compared to their healthy counterparts [35]. The authors found that higher expression of *CASC9* resulted in higher levels of *HIF-1α* in CNE-1 cells. They also demonstrated the binding of *CASC9* to HIF-1α via immunoprecipitation assays [35]. *HIF-1α* is a known transcriptional regulator of oxygen homeostasis that regulates the expression of some critical genes such as glucose transporters (e.g., *GLUT-1*) that are responsible for controlling glycolysis in cancer cells. (Figure 4). Su et al. (2017) also performed a glucose uptake assay to validate the reprogramming of glycolysis by *CASC9*.

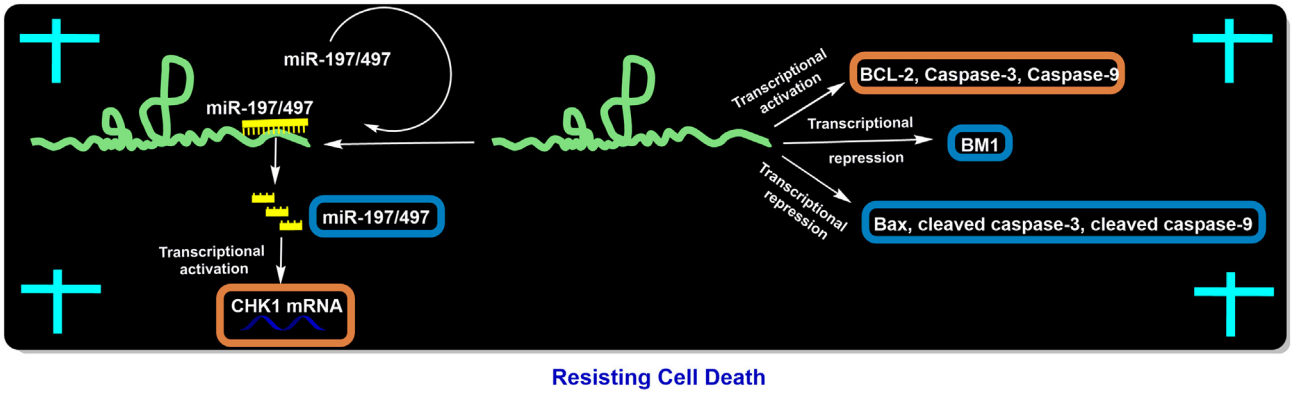

Figure 3. Regulatory mechanisms of *CASC9* in resisting cancer cell death.

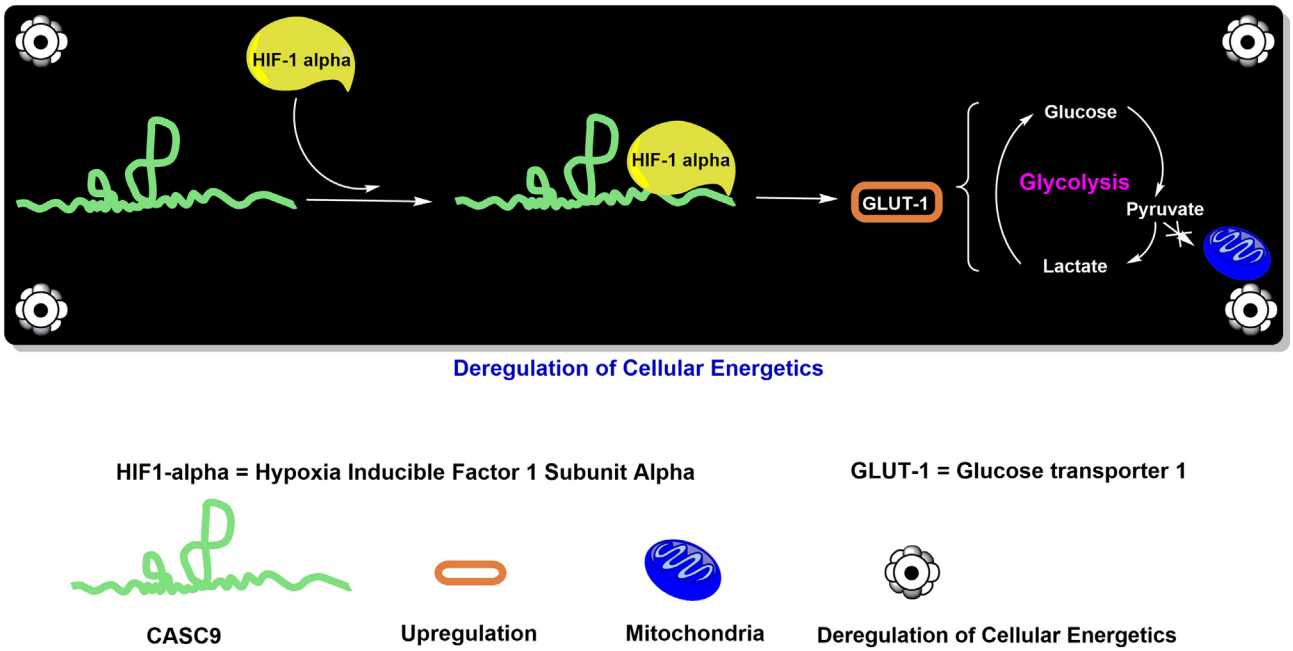

Figure 4. Regulatory mechanisms of *CASC9* in cancer cell metabolism.

The results demonstrated that the upregulation of *CASC9* induced significantly higher glucose uptake and lactate production in CNE-1 cells compared to control cells [35].

Furthermore, knockdown of *CASC9* in CNE-1 cells led to a decreased level of lactate production compared to untreated cells, and its depletion in *HIF-1α*–deficient CNE-1 cells showed no significant increase in glucose uptake compared to control cells [35]. The results of this study suggested that *CASC9* promoted glycolysis in cancer cells by increasing the levels of *HIF-1α* (Figure 4). Taken together, these results provided evidence that *CASC9* was associated with *HIF-1α* reprogramming of glycolytic metabolism in cancer cells. Thus, *CASC9* may prove to be a useful target to exploit for cancer therapy, though more studies are required on its mechanistic role (s) in NPC and other cancer types.

Closing Remarks and Future Directions

Despite recent advances involving novel diagnostic and prognostic strategies for cancer treatment, unfortunately, the global incidence of cancer is increasing worldwide with no significant decrease in cancer incidence and cancer-related mortality. To restrain cancer-related mortality, there is a critical need to develop novel prognostic and diagnostic strategies for cancer treatment. Recent studies involving new

high-throughput RNA sequencing techniques have demonstrated the potential application of novel lncRNAs with potential applications as a biomarkers or therapeutic targets for personalized cancer treatment. In this review, we have discussed one such lncRNA, *CASC9*, and its potential roles in promoting various hallmarks of cancer. *CASC9* can influence the expression of various transcription factors, oncogenes, and associated cancer signaling pathways involving cancer etiology and progression, such as metastasis and invasion, cell metabolism, resistance to cell death, and cellular proliferation.

Additionally, we have discussed the roles of *CASC9* as a sponging RNA and its regulatory association with critical noncoding RNAs, i.e., miRNAs. Recently, several studies have focused on the roles of lncRNAs in cancer; however, studies focusing on lncRNA-based therapeutics and diagnostics are still in their infancy. We were not able to find relevant scientific data regarding the delivery-associated toxicity and potential stimulation of immune responses of lncRNA-based therapeutics.

Though many lncRNAs, including *CASC9*, have been discovered in the recent past, scientific knowledge stating the effects of lncRNA on targeted therapeutics is limited. Therefore, future investigation in regard to crucial cellular signaling molecules and specific pathways altered by specific lncRNAs in cancer may provide new insights toward the development of personalized biomarkers/targets for cancer diagnosis and prognosis. In conclusion, we are hopeful that this review will stimulate future research to expand our knowledge of cancer pathogenesis and assist in the discovery of new biological markers for personalized cancer therapies.

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Author Contributions

U. S., V. A., S. T., and A. J. conceived the idea. U. S., T. S. B., V. A., and S. T. wrote the majority of the manuscript. U. S. composed the figures and table. K. M. V. and A. J. made critical revisions. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of Interest

The authors declare no conflict of interest.

Ethical Approval

This review article does not contain studies with human participants or animals performed by any of the authors.

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