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Review

A review on the role of ADAMTS9-AS2 in different disorders

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ABSTRACT

Recent decade has seen a tremendous progress in identification of the role of different long non-coding RNAs (lncRNAs) in human pathologies. ADAMTS9-AS2 is an example of lncRNAs with different roles in human disorders. It is mostly acknowledged as a tumor suppressor lncRNA in different types of cancers. However, it has been reported to be up-regulated in tongue squamous cell carcinoma, salivary adenoid cystic carcinoma and glioblastoma. Moreover, ADAMTS9-AS2 is possibly involved in the pathoetiology of pulpitis, acute ischemic stroke, type 2 diabetes and its complications. This lncRNA sponges miR-196b-5p, miR-223–3p, miR-130a-5p, miR-600, miR-223–3p, miR-27a-3p, miR-32, miR-143–3p, miR-143–3p and miR-182–5p in order to regulate downstream mRNAs. This review aims at summarization of the role of ADAMTS9-AS2 in different disorders with a particular focus on its diagnostic and prognostic values.

1. Introduction

Long non-coding RNAs (lncRNAs) are a group of RNAs that do not contribute to protein production except for some rare cases. These types of RNA are transcribed by RNA polymerase II and are usually longer than 200 bp in length. Different kinds of mechanisms are employed by lncRNAs for regulation of gene expression. These mechanisms include sponging of microRNAs (miRNAs), genomic imprinting, histone modification, alternative splicing and transcriptional/translational regulation [44]. Based on these important functions, dysregulation of lncRNAs is considered as an important event in the pathogenesis of human disorders[10,11,13].

ADAMTS9 antisense RNA 2 (ADAMTS9-AS2) is an lncRNA with approved roles in the carcinogenesis [41]. In addition, abnormal expression of ADAMTS9-AS2 is associated with dysregulation of major signaling pathways like PI3K/AKT [12]. At least nine transcripts have been identified for this lncRNA (Fig. 1). According to NCBI gene database, it is mainly expressed in ovary (RPKM 6.7) and endometrium (RPKM 4.3). Because of significant number of functional studies on the role of ADAMTS9-AS2 in different disorders, especially cancers, this review tends to summarize the data related to these studies and disclose new insights on how this lncRNA is involved in different conditions.

2. Role of ADAMTS9-AS2 in cancers

2.1. Cell line studies

Different studies have investigated expression and function of ADAMTS9-AS2 in cell lines derived from tumoral cells. In triple-negative breast cancer cell lines (MDA-MB-231 and HCC1937), ADAMTS9-AS2 has been found to be downregulated. Upregulation of ADAMTS9-AS2 in the mentioned cell lines reverses malignant features of breast cancer, resulting in reduced viability and inhibition of Warburg effect through repression of TGF-β signaling pathway [26]. In another study in breast cancer, induced expression of ADAMTS9-AS2 in temozolomide (TMZ) resistant and non-resistant MCF-7 cells has resulted in adsorption of miR-130a-5p and reactivation of apoptosis inducer, PTEN, which in turn increases sensitivity to TMZ [42].

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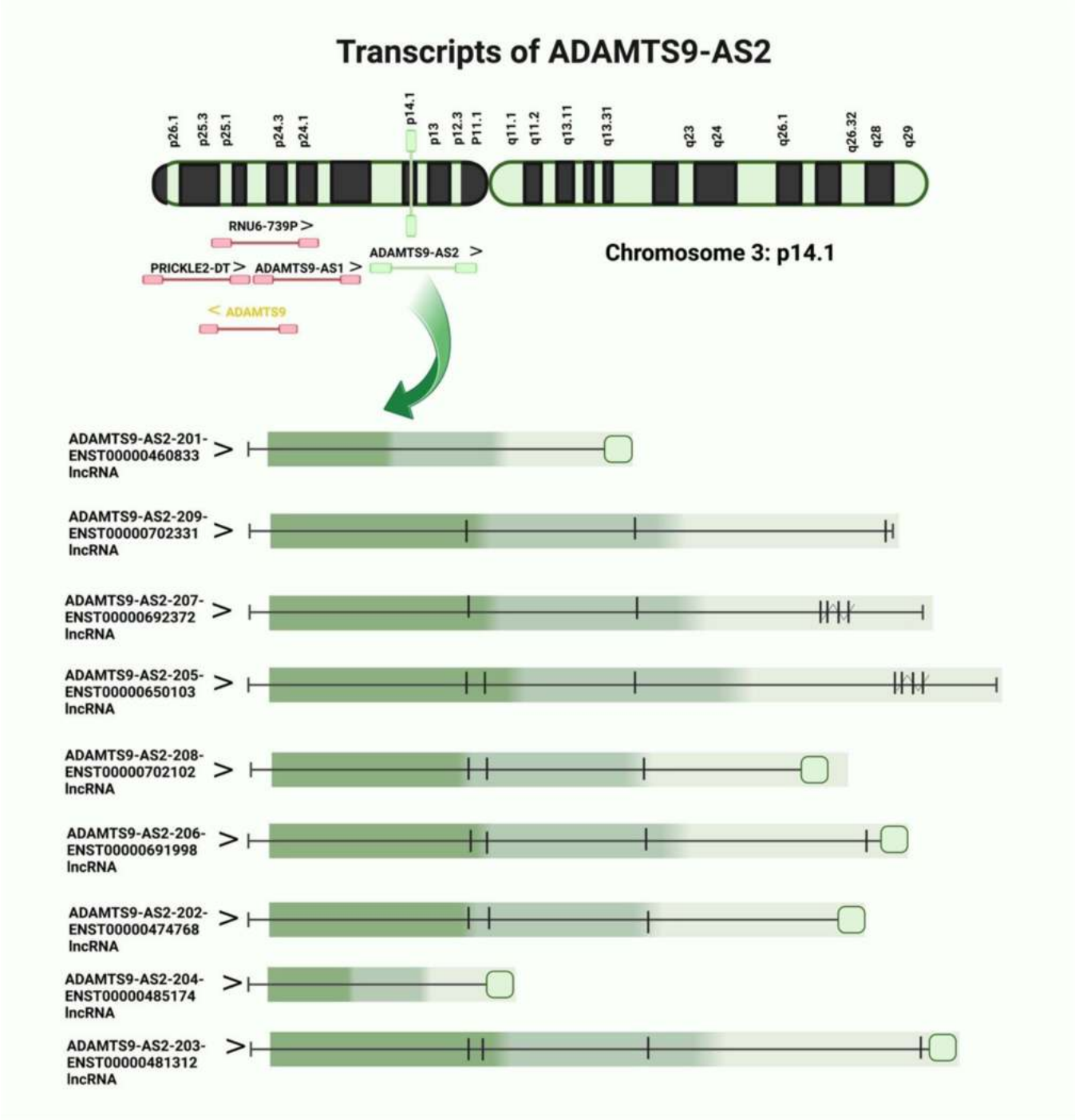

Fig. 1. Transcripts of ADAMTS9-AS2, located on chromosome 3. According to the *ensemble* genome database, ADAMTS9-AS2 has at least nine transcripts that are identified for this lncRNA.

Table 1
Role of ADAMTS9-AS2 in cancer cell lines (**Δ**: knock-down or deletion, ↑: overexpression, →: results in, EMT: Epithelial-mesenchymal transition, TMZ: Temozolomide, 5-FU: 5-Fluorouracil).

Tumor type	Targets/Regulators and signaling pathways	Cell line	Function	References
Esophageal cancer	miR-196b-5p/ PPP1R12B	EC109 and NEC	↑ ADAMTS9-AS2 (which adsorbs miR-196b-5p) → ↑ PPP1R12B: ↓ cell activity ↑ cell cycle arrest ↓ migration ↓ invasion	[5]
	DNMT1/ DNMT3 (A/B) /CDH3	OE21, OE19, OE33, and EC109	↑ ADAMTS9-AS2 (which recruits DNMT1/ DNMT3 (A/B) to the promoter region of CDH3) → ↓ CHD3: ↓ proliferation ↓ migration ↓ invasion	[23]
Lung adenocarcinoma/ Lung cancer	miR-150/ADAMTS9	PC9, NCI-H1975, NCI-H1299 and A549	↑ ADAMTS9-AS2 (which binds to miR-150) → ↑ ADAMTS9: ↓ proliferation ↓ migration ↓ invasion ↓ EMT process	[25]
	miR-223–3p/TGFBR3	A549, SPC-A1, H23 and NCI-H520	↑ ADAMTS9-AS2 (which sponges miR-223–3p) → ↑ TGFBR3: ↓ proliferation ↓ invasion ↑ apoptosis ↑ cell cycle arrest	[22]
Breast cancer/ Triple-negative breast cancer	RPL22/ TGF-β Signaling Pathway (Triple-negative breast cancer)	MDA-MB-231 and HCC1937	↑ ADAMTS9-AS2 → ↑ RPL22 → ↓ TGF-β Signaling Pathway: ↓ Warburg effect ↓ viability ↓ colony formation ↑ cell cycle arrest ↑ apoptosis ↓ invasion	[26]
	DNMT1 (breast cancer)	MDA-MB-231/ MCF07	Δ DNMT1 → promoter hypomethylation of ADAMTS9-AS2: ↑ ADAMTS9-AS2	[6]
	miR-130a-5p/PTEN (breast cancer)	MCF-7 (non-resistant) and MCF-7R (TAM resistant)	↑ ADAMTS9-AS2 (which sponges miR-130a-5p) → ↑ PTEN: ↑ sensitivity to TAM ↑ apoptosis ↑ proliferation of MCF-7R	[33]
Hepatocellular carcinoma	ADAMTS9/PI3K/AKT/mTOR signaling pathway	HepG2, MHCC97-H and Hep 3B2.1–7	↑ ADAMTS9-AS2 → ↑ ADAMTS9 (which inhibits PI3K/ AKT signaling pathway): ↓ proliferation ↓ migration ↓ invasion ↑ apoptosis	[18]
Bladder cancer	miR-182–5p	T24 and 5637	↑ ADAMTS9-AS2 → ↓ miR-182–5p: ↓ proliferation ↓ migration ↑ apoptosis	[14]
	ADAMTS9/ PI3K/AKT/mTOR	UC3, 5637, J82, T24, and EJ	↑ ADAMTS9-AS2 → ↑ ADAMTS9 → ↓ PI3K/AKT/mTOR ↓ proliferation ↓ migration ↓ invasion ↑ apoptosis	[45]
Oral squamous cell carcinoma	PI3K/AKT signaling pathway	CAL-27 and SCC-9	↑ exosomal ADAMTS9-AS2 → ↓ PI3K/AKT signaling pathway: ↓ viability ↓ colony formation ↓ metastasis ↓ EMT process	[47]
Tongue squamous cell carcinoma	miR-600/EZH2 axis	Cal27, SCC9, SCC15, SCC25 and SCC4	Δ ADAMTS9-AS2 (which sponges miR-600) → ↑ miR-600 → ↓ EZH2: ↓ proliferation ↓ EMT process ↓ migration ↓ invasion	[20]
Gastric cancer	miR-223–3p/NLRP3 axis	cisplatin-sensitive: SGC7901, MKN74, NUGC-4, HGC-27 and BGC-823/	↑ ADAMTS9-AS2 (which sponges miR-223–3p) → ↑ NLRP3: ↑ apoptosis in cisplatin-resistance cell	[30]

(*continued on next page*)

Table 1 (*continued*)

Tumor type	Targets/Regulators and signaling pathways	Cell line	Function	References
		cisplatin-resistant: SGC7901/DDP and BGC-823/DDP	↓ proliferation ↓ migration ↓ viability ↓ EMT process	
	SPOP	MKN45	↑ ADAMTS9-AS2 → ↑ SPOP: ↓ proliferation ↑ apoptosis ↓ spheroid formation	[37]
	miR-372/CADM2 axis	MKN-45 and HGC-27	↑ ADAMTS9-AS2 → ↑ miR-372 and ↑ CADM2	[27]
Glioblastoma (GBM)/ Glioma	FUS/MDM2 axis	T98G and U118	Δ ADAMTS9-AS2 → ↑ MDM2/FUS interaction (which results in FUS K48-ubiquitination and degradation): ↑ sensitivity to TMZ ↓ migration ↓ invasion	[42]
	DNMT1	T98G, A172, SNB-19, U87, and U251	Δ DNMT1→ ↑ ADAMTS9–2: ↓ migration ↓ invasion	[43]
Clear cell renal cell carcinoma	miR-27a-3p/FOXO1 axis	786-O, caki-1 and 769-P	↑ ADAMTS9-AS2 (which sponges miR-27a-3p) → ↑ FOXO1: ↓ proliferation ↓ colony formation ↓ resistance to 5-FU	[34]
Colorectal cancer (CRC)	miR-32/PHLPP2 axis	HT29, SW480 and SW620	↑ ADAMTS9-AS2 (which sponges miR-32) → ↑ PHLPP2: molecular regulation of CRC	[28]
Salivary adenoid cystic carcinoma	miR-143–3p/ ITGA6 /PI3K/Akt and MEK/Erk Signaling pathways	SACC-83 and SACC-LM	c-Myc activates ADAMTS9-AS2 Δ ADAMTS9-AS2 (which sponges miR-143–3p) → ↑ miR-143–3p → ↓ ITGA6 → ↓ PI3K/Akt and MEK/Erk: ↓ migration ↓ invasion	[40]
Ovarian cancer	miR-182–5p/FOXF2 axis	SKOV3, HO8910, A2780, OVCAR, and HOSEpiC	↑ ADAMTS9-AS2 (which sponges miR-182–5p) → ↑ FOXF2 ↓ proliferation ↓ invasion ↓ EMT process ↓ colony formation	[36]

One of the main signaling pathways regulated by ADAMTS9-AS2 is PI3K/AKT pathway, a pathway with important functions in the regulation of cell cycle [12]. For instance, in hepatocellular carcinoma cell lines (HepG2, MHCC97-H and Hep 3B2.1–7), upregulation of ADAMTS9-AS2 results in increased ADAMTS9 transcription, which inhibits PI3K/AKT signaling pathway and hampers proliferation, migration and invasion in aforesaid cell lines [18]. Equivalent to hepatocellular carcinoma, the mentioned molecular pathway applies for bladder cancer cell lines (UC3, 5637, J82, T24, and EJ) [45].

In two different cancers, it has been approved that promoter hypermethylation of ADAMTS9-AS2 downregulates its expression and contributes to malignant properties of cells. The first study conducted on breast cancer cell lines (MDA-MB-231/ MCF07) revealed that silencing DNA methyltransferase 1 (DNMT1) upregulates ADAMTS9-AS2 expression [6]. Similarly, in glioma cell lines T98G, A172, SNB-19, U87 and UC251, knockdown of DNMT1 reactivated ADAMTS9-AS2 expression and reduced migration and invasion of mentioned cell lines [43].

Interestingly, DNMT1 and DNMT3 can be recruited by ADAMTS9-AS2 in esophageal cancer [23]. Upregulated ADAMTS9-AS2 in OE21, OE19, OE33, and EC109 cell lines recruits DNMT1/DNMT3. This results in hypermethylation of CDH3, resulting in reduced proliferation, migration and invasion.

In gastric cancer, upregulating ADAMTS9-AS2 has anti-tumor effects. For example, upregulation of ADAMTS9-AS2 in MKN-45 cell line causes Speckle Type BTB/POZ Protein (SPOP) elevation and reduces proliferation and induces apoptosis [37]. Table 1 and Fig. 2 summarize the role of ADAMTS9-AS2 in different cancer cell lines.

2.2. Animal studies

Different in vivo studies mainly in mice support anti-tumor effects of ADAMTS9-AS2 (Fig. 3). These studies have been conducted in animal models of esophageal cancer [5], triple negative breast cancer [26], gastric cancer [30], ovarian cancer [36] and lung cancer [22] (Table 2). In general, forced upregulation of ADAMTS9-AS2 results in a decreased tumor volume and tumor weight. One exemption is in salivary adenoid cystic carcinoma, in which downregulation of ADAMTS9-AS2 yields reduced tumor growth and metastasis inhibition [40].

Mechansitical aspects of ADAMTS9-AS2 down-/up-regulation have not been fully studied in animal models. A single study in gastric cancer has shown that upregulation of ADAMTS9-AS2 in nude mice results in increased pyroptotic cell death. This phenomenon is regulated by the elevation of lactate dehydrogenase, and different kinds of chemokines [30].

2.3. Studies in clinical samples

In most cancer cases, downregulation of ADAMTS9-AS2 in clinical specimens (tumor samples in comparison to normal samples) is associated with an adverse effect on patients' overall survival. For instance, studies conducted in esophageal cancer using both clinical specimens and expression databases, revealed that downregulation of ADAMTS9-AS2 is an inevitable event in this disease being associated with adverse outcomes [4,5,9,23,32].

Moreover, studies on lung adenocarcinoma (LUAD) show that downregulation of ADAMTS9-AS2 is associated with shorter overall survival. In LUAD, this lncRNA acts as a molecular sponge for miR-223–3p, and if downregulated, levels of miR-223–3p increases.

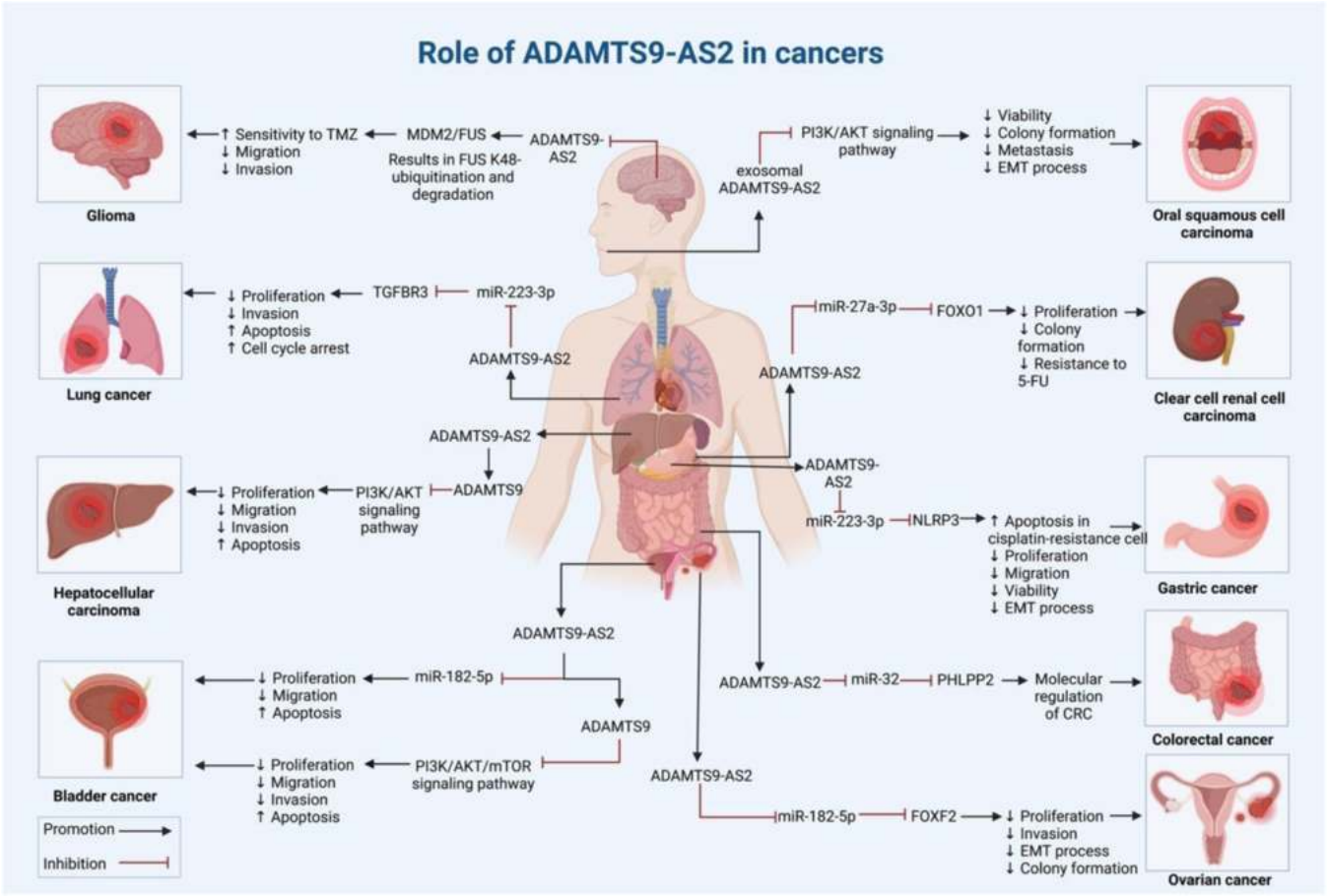

Fig. 2. ADAMTS9-AS2-relatedc signaling pathways in different types of cancer. The lncRNA ADAMTS9-AS2 has tumor-suppressing properties via sponging several oncomiRs. In addition, ADAMTS9-AS2 directly targets oncogenic signaling pathways in order to inhibit proliferation, migration, and invasion of cancer cells and increase the apoptosis process.

Downstream gene of this miRNA is TGFBR3, therefor dysregulated ADAMTS9-AS2/miR-223–3p/ TGFBR3 axis is related to aggravated condition of LUAD patients [22]. In addition, according to the cancer genome atlas (TCGA), ADAMTS9-AS2 downregulation is associated with shorter disease specific survival, N stage, gender, and smoking [21].

In glioma, there are two conflicting studies. One study conducted on high-grade and low-grade gliomas shows that ADAMTS9-AS2 increases alongside with the tumor grade [7]. In contrasts to this study, another study has revealed that as the tumor progresses, level of ADMATS9-AS2 is decreased and this event is associated with shorter overall survival, WHO grade, KPS and tumor size [43].

As mentioned in animal studies, expression of ADAMTS9-AS2 in salivary adenoid cystic carcinoma (SACC) is an exemption in comparison to other conditions. Expression analysis in SACC unveiled that there is an upregulation in tumor samples compared to adjacent normal tissues, and upregulation has a negative correlation with overall survival and a positive one with tumor metastasis.

ADAMTS9-AS2 has been shown to act as a tumor-suppressor in breast cancer and is reported to be downregulated in two different studies [6,33]. ADAMTS9-AS2 downregulation results in miR-130a-5p activation and reduced rate of apoptosis via inhibition of PTEN [33].

In another study of TCGA data in bladder urothelial carcinoma, ADAMTS9-AS2 has been among differentially expressed lncRNAs which have related to overall survival of patients [38]. Moreover, Kaplan–Meier curve analysis has shown negative correlation between ADAMTS9-AS2 and overall survival [38]. Assessment of GEPIA data has confirmed that lower expression of ADAMTS9-AS2 is associated with a good prognosis in patients with bladder urothelial carcinoma [38].

Overall, except for salivary adenoid cystic carcinoma and tongue squamous cell carcinoma, ADAMTS9-AS2 is poorly expressed in tumor tissues compared to paired adjacent normal tissues, and ultimately results in a poor prognosis (Table 3).

Diagnostic value of ADAMTS9-AS2 has been assessed in samples obtained from patients with lung cancer where its expression could differentiate between affected and unaffected tissues with AUC value of 0.985 and between patients' plasma samples and control plasma samples with AUC value of 0.957 [1]. Three other studies in prostate cancer [16], lung adenocarcinoma [17] and esophageal cancer [4] have reported high accuracy of this lncRNA in separation of affected tissues from unaffected ones (Table 4).

2.4. Non-malignant disorders

ADAMTS9-AS2 has a possible role in the pathogenesis of endothelial cell dysfunction after ischemic stroke. Expression of this lncRNA has been found to be reduced in the plasma samples of patients with acute ischemic stroke and in the brain tissues and plasma samples of animal models of ischemic stroke. Notably, down-regulation of ADAMTS9-AS2 has been associated with higher infarct size. Moreover, intraluminal middle cerebral artery occlusion has marginally induced angiogenesis, which has been further increased by up-regulation of ADAMTS9-AS2. Mechanistically, ADAMTS9-AS2 acts as a sponge for miR-185–5p to affect expression of its target IGFBP-2. Taken together, ADAMTS9-AS2 promotes angiogenesis via regulation of miR-185–5p/IGFBP-2 axis [8].

A systematic examination of microarray and sequencing data of pulpitis samples has led to identification of 280 RRA_DEmRNAs and 90

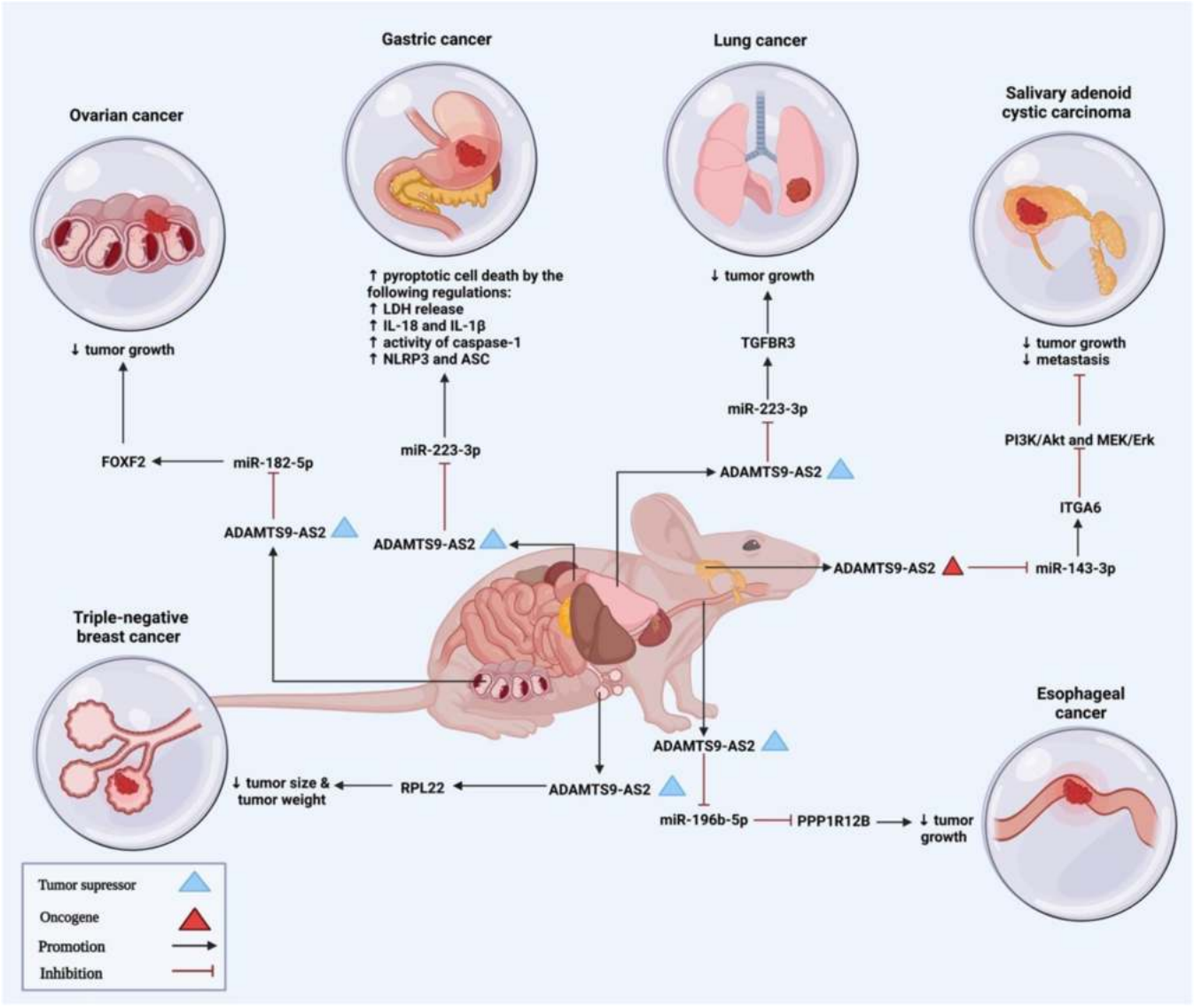

Fig. 3. The impacts of ADAMTS9-AS2 in carcinogenesis based on studies in animal models.

Table 2
Impact of ADAMTS9-AS2 in carcinogenesis based on investigations in animal models (Δ: knock-down or deletion, LDH: lactate dehydrogenase).

Tumor type	Animal models	Results	References
Esophageal cancer	Nude mice	↑ ADAMTS9-AS2: ↓ tumor growth	[5]
	BABL/c- nude mice	↑ ADAMTS9-AS2: ↓ tumor volume & tumor weight	[23]
Triple-negative breast cancer	BALB/c-nude mice	↑ ADAMTS9-AS2: ↓ tumor size & tumor weight	[26]
Gastric cancer	Nude mice	↑ ADAMTS9-AS2 → ↑ pyroptotic cell death by the following regulations: ↑ LDH release ↑ IL-18 and IL-1β ↑ activity of caspase-1 ↑ NLRP3 and ASC	[30]
Salivary adenoid cystic carcinoma	BALB/c mice	Δ ADAMTS9-AS2: ↓ tumor growth ↓ metastasis	[40]
Ovarian cancer	BALB/c-nude mice	↑ ADAMTS9-AS2: ↓ tumor growth	[36]
Lung cancer	Nude mice	↑ ADAMTS9-AS2: ↓ tumor growth	[22]

Table 3
Dysregulation of ADAMTS9-AS2 in clinical specimens (ANT: adjacent normal tissue, OS: overall survival, DFS: disease-free survival, DSS: disease-specific survival, RFS: relapse-free survival, BM: bone marrow, PFS: progression-free survival, TMZ: Temozolomide, GEPIA: Gene Expression Profiling Interactive Analysis, GEO: Gene Expression Omnibus(includes GSE), TCGA: the cancer genome atlas OSF: Oral submucous fibrosis, IDC: invasive ductal carcinoma, DCIS: noninvasive ductal carcinoma in situ).

Tumor type	Samples	Expression (tumor vs normal)	Kaplan-Meier Analysis (ADAMTS9-AS2 dysregulation impact)	Univariate/ Multivariate cox regression	Association of ADAMTS9-AS2 expression with clinicopathologic characteristics	References
Esophageal cancer (EC)/Esophagus Squamous Cell Carcinoma (ESCC)	50 EC + paired ANT + TCGA	Downregulated	-	-	-	[5]
	9 ESCC para-cancer + 2 ESCC (grade 3) + 7 ESCC (grade 2)	Upregulated in grade 2	-	-	-	[9]
	GSE120356 and GSE33810 datasets	Downregulated	Shorter OS	Independent prognosis indicator	-	[32]
	126 ESCC + paired ANT + GSE45670 dataset	Downregulated	-	-	-	[23]
	TCGA (162 EC + 11 normal samples) + GSE89102 (5 EC + paired ANT)	Downregulated	-	-	-	[4]
Oral squamous cell carcinoma (OSCC)	10 normal mucous + 10 OSF + 20 OSCC	High expression in normal mucous, moderated expression in OSF and downregulated in OSCC	Shorter OS	-	-	[47]
Tongue squamous cell carcinoma (TSCC)	76 TSCC + paired ANT	Upregulated	Shorter OS	-	Associated with tumor size, clinical stage and lymph node metastasis	[20]
Non-small cell lung cancer (NSCLC)	92 NSCLC + paired ANT	Downregulated	-	-	-	[35]
	80 NSCLC (tissue and plasma) + 80 patients with benign lesions (tissue and plasma)	Downregulated in tissues and plasma	-	-	-	[1]
	Array set: 44 NSCLC + paired ANT Validation set: 38 NSCLC + paired ANT + TCGA	Downregulated	-	-	-	[2]
Lung adenocarcinoma (LUAD)/ Lung cancer (LC)	TCGA dataset	Downregulated	Shorter OS and DSS	-	Associated with N stage, gender, and smoking	[21]
	GSE130779 dataset (8 LUAD + paired ANT)	Downregulated	-	-	-	[25]
	15 LUAD + 15 normal tissues + 10 LUAD bone metastasis tissues	Downregulated in LUAD and bone metastasis	-	-	-	[15]
	GSE85716, GSE113852 and GSE130779 (a Total of 41 LUAD samples + 41 healthy controls samples)	Downregulated	-	-	-	[46]
	GSE70880 and GSE113852 datasets (a total of 47 LUAD +48 normal samples) + TCGA (497 tumor samples + 54 normal samples)	Downregulated	Shorter OS	-	-	[17]
	68 LC + paired ANT + GSE70880 dataset (19 LC + paired ANT)	Downregulated	Shorter OS	-	-	[22]
Glioma	50 high-grade + 50 low-grade	Upregulated in high-grade tumors	-	-	-	[7]
	70 glioma tissues + paired ANT (including 46 low-grade + 24 high grade)	Downregulated (especially in high-grade tumors)	Shorter OS	Independent predictor of poor survival	Associated with WHO grade, KPS and tumor size	[43]
Glioblastoma (GBM)	59 TMZ non-responsive GBM + 85 TMZ responsive GBM	Upregulated in TMZ non-responsive GBM	Shorter PFS	-	-	[42]
Prostate cancer (PCa)	110 PCa + paired ANT	Downregulated	Shorter OS	Independent prognosis factor for survival	Associated with tumor size and tumor stage	[16]
Breast cancer (BC)	Initial phase: 24 samples including 6 IDC + paired ANT, 7 DCIS, 5 apparently normal tissues Validation phase: 52 IDC + paired ANT	Downregulated in IDC compared to normal and apparently normal tissues (methylation levels increased in IDC)	-	-	-	[6]
	52 BCE + paired ANT	Downregulated	-	-	-	[33]
Triple-negative breast cancer (TNBC)	62 TNBC + paired ANT	Downregulated	Shorter OS	-	Associated with TNM stage and tumor size	[26]

(*continued on next page*)

Table 3 (*continued*)

Tumor type	Samples	Expression (tumor vs normal)	Kaplan-Meier Analysis (ADAMTS9-AS2 dysregulation impact)	Univariate/ Multivariate cox regression	Association of ADAMTS9-AS2 expression with clinicopathologic characteristics	References
Gastric cancer (GC)	54 GC + paired ANT + TCGA	Downregulated	Higher expression is associated with poor prognosis (according to TCGA)	-	-	[39]
	45 GC + paired ANT	Downregulated	Shorter OS	-	Associated with tumor size, TNM stage and lymphatic invasion	[30]
	54 GC + paired ANT	Downregulated	Shorter OS	-	Associated with poor histologic and advanced TNM stage	[27]
Bladder urothelial carcinoma (BUC)	GEPIA (a total of 404 tumor samples + 28 normal samples)	Downregulated	Better OS	-	-	[38]
Clear cell renal cell carcinoma (ccRCC)	76 ccRCC + paired ANT + GEPIA	Downregulated	Shorter OS	-	Associated with tumor stage and tumor diameter	[34]
Colorectal cancer (CRC)	54 CRC + paired ANT + TCGA dataset	Downregulated	-	-	Associated with advanced TNM stage and poor histologic differentiation	[28]
	30 CRC + paired ANT	Downregulated	Shorter OS	-	-	[19]
Salivary adenoid cystic carcinoma (SACC)	102 SACC + paired ANT	Upregulated	Shorter OS	-	Associated with metastasis	[40]
Ovarian cancer (OC)	47 OC tissues + paired ANT	Downregulated	Shorter OS	-	Associated with FIGO stage and lymph node metastasis	[36]

Table 4
Diagnostic value of ADAMTS9-AS2 in diseases (ANT: adjacent normal tissue).

Disease type	Samples	Distinguish between	Area under curve	Sensitivity (%)	Specificity (%)	References
Non-small cell lung cancer (NSCLC)	80 NSCLC (tissue and plasma) + 80 patients with benign lesions (tissue and plasma)	NSCLC vs. benign lesions	Tissue: 0.985	98.7	99.1	[1]
			Plasma: 0.957	95	99.1	[1]
Prostate cancer (PCa)	110 PCa + paired ANT	Tumor vs. normal	0.902	90	79.09	[16]
Lung adenocarcinoma	TCGA (497 tumor samples + 54 normal samples)	Tumor vs. normal	0.9116	81.49	96.30	[17]
Esophageal cancer (EC)	162 EC + 11 normal samples	Tumor vs. normal	0.851	-	-	[4]

Table 5
Summary of cell line/animal studies on the role of ADAMTS9-AS2 in non-malignant conditions (Δ: knock-down or deletion, OGD/R: oxygen–glucose deprivation, MCAO: middle cerebral artery occlusion).

Disease type	Interactions	Cell line	Function	Animal	References
Acute ischemic stroke (AIS)	miR-185–5p/ IGFBP-2	bEnd.3 (Mouse brain endothelial cell)	bEnd.3 subjected to OGD/R: ↓ ADAMTS9-AS2 in a time-dependent manner * ↑ ADAMTS9-AS2 (which downregulates miR-185–5p) → ↑ IGFBP-2: ↑ angiogenesis ↑ migration	**Model**: C57BL/6 mice (sham operation group and MACO group) **Result of studies** First: ↑ ADAMTS9-AS2: ↓ Cerebral Infarction in MACO group Second: ↑ ADAMTS9-AS2: ↑ angiogenesis in MACO group	[8]

differentially expressed lncRNAs among them being ADAMTS9-AS2 [24]. Tables 5 and 6 summarize the results of studies that assessed ADAMTS9-AS2 in non-malignant conditions.

There are a number of polymorphims near or within ADAMTS9-AS2, namely rs4607103, rs6795735 and s4607103. A replication study of GWAS-validated risk variants for type 2 diabetes in the Lebanese population has identified rs4607103 as a risk locus for this disorder at initial phase, yet the association has been lost after multiple testing correction [3]. Moreover, rs6795735 has been identified as a risk locus for this disorder among Pakistanis [31]. Finally, rs4607103 has been recognized as a risk locus for diabetic retinopathy among Chinese population [29]. Table 7 summarizes the results of these studies.

3. Discussion

ADAMTS9-AS2 is mostly acknowledged as a tumor suppressor lncRNA in different types of cancers. However, it has been reported to be up-regulated in tongue squamous cell carcinoma [20], salivary adenoid

Table 6
Summary of human studies on the role of ADAMTS9-AS2 in non-malignant conditions.

Disease type	Number of clinical samples	Expression (case vs. control)	References
Pulpitis	11 inflamed pulp samples + 10 normal pulp samples + GSE77459 and GSE92681 datasets (13 inflamed pupls + 11 normal pupls)	Downregulated in inflamed pupls	[24]
Acute ischemic stroke (AIS)	43 AIS plasma + 68 healthy controls plasma	Downregulated	[8]

Table 7
Variants within ADAMTS9-AS2 which are associated with increased risk of type 2 diabetes and diabetic retinopathy (DKD: diabetic kidney disease).

Disease type	Number of samples	Variant	Effect allele	References
Type 2 diabetes (T2D)	995 T2D + 1076 controls	rs4607103	T	[3]
	1057 T2D + 626 controls	rs6795735	C	[31]
Diabetic retinopathy (DR)	1251 participants (238 controls + 313 DR + 419 DKD + 281 with both DR & DKD)	rs4607103	C	[29]

cystic carcinoma [40] and glioblastoma [42]. It is worth mentioning that controversy exists about the role of ADAMTS9-AS2 in glioma/glioblastoma.

Mechanistically, ADAMTS9-AS2 can influence activity of several miRNA/mRNA axes such as miR-196b-5p/PPP1R12B, miR-150/ADAMTS9, miR-223–3p/TGFBR3, miR-130a-5p/PTEN, miR-600/EZH2, miR-223–3p/NLRP3, miR-372/CADM2, miR-27a-3p/FOXO1, miR-32/PHLPP2, miR-143–3p/ITGA6 and miR-182–5p/FOXF2. These effects are exerted throughsponging the mentioned miRNAs. Moreover, ADAMTS9-AS2 can affect activity of ADAMTS9/PI3K/AKT/mTOR and MEK/Erk signaling pathways.

ADAMTS9-AS2 has been found to have appropriate diagnostic power in differentiation of tissues or plasma samples obtained from patients with lung cancer, prostate cancer and esophageal cancer from those retrieved from normal subjects. In fact, expression levels of this lncRNA can differentiate malignant samples from non-malignant ones with suitable diagnostic power. This application has been verified in lung cancer [1], prostate cancer [16], lung adenocarcinoma [17] and esophageal cancer [4]. These findings are promising since they can be used in design of novel non-invasive routes of cancer diagnosis. Moreover, dysregulation of ADAMTS9-AS2 has been associated with poor clinical outcomes in a variety of cancers.

Among different SNPs, association between human disorders and three SNPs, namely rs4607103, rs6795735 and rs4607103 have been assessed in the context of non-malignant disorders. However, contribution of these SNPS in the pathogenesis of cancers has not been evaluated yet.

In brief, ADAMTS9-AS2 is a newly identified lncRNA that is involved in the pathogenesis of several types of cancer and possibly in the pathoetiology of pulpitis, acute ischemic stroke, type 2 diabetes and its complications. Future functional studies are needed to find the most important signaling pathways being involved in these processes.

Moreover, contribution of functional SNPs within this lncRNA in the pathogenesis of human disorders, particularly cancers should be assessed in future.

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CRediT authorship contribution statement

SGF wrote the draft and revised it. AB and MT designed and supervised the study. MM, BMH and AK collected the data and designed the figures and tables. All the authors read the submitted version and approved it.

Competing interest

The authors declare they have no conflict of interest.

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Declarations

Ethics approval and consent to Participant

Not applicable.

Consent of publication

Not applicable.

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