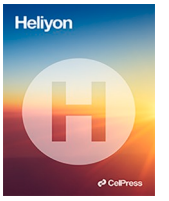
Heliyon 9 (2023) e20140

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Insights into the pleiotropic roles of ZNF703 in cancer

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ARTICLE INFO

Keywords:
ZNF703
Transcription factor
Carcinogenesis
Tumor progression

ABSTRACT

Zinc finger proteins (ZNFs) belong to the NET/NLZ protein family. In physiological functions, ZNF703 play significant roles in embryonic development, especially in the nervous system. As an transcription factors with zinc finger domains, abnormal regulation of the ZNF703 protein is associated with enhanced proliferation, invasion, and metastasis as well as drug resistance in many tumors, although mechanisms of action vary depending on the specific tumor microenvironment. ZNF703 lacks a nuclear localization sequence despite its function requiring nuclear DNA binding. The purpose of this review is to summarize the architecture of ZNF703, its roles in tumorigenesis, and tumor progression, as well as future oncology therapeutic prospects, which have implications for understanding tumor susceptibility and progression.

1. Introduction

Transcription factors (TFs) are *trans*-acting proteins that directly or indirectly recognize and bind specific DNA sequences near the transcriptional start site of a target gene, to regulate its transcription positively or negatively [1–3]. Over 1000 *trans*-acting factors regulate gene expression by affecting RNA polymerase II activity in human cells [4]. Multiple types of cancer are associated with abnormal TF expression [5,6].

Zinc finger proteins possess zinc 'finger' domains and perform a wide range of functions [7]. Zinc ions (Zn^{2+}) maintain the spatial conformation of ZNFs to recognize DNA, RNA, and proteins [8]. An assortment of ZNFs is generated through the utilization of various permutations of the conserved cysteine and histidine residues that are accountable for Zn^{2+} binding [9–12]. The largest zinc finger C2H2 motif (CX2CX3FX5LX2HX3H) folds to adopt a finger-like structure when interacting with Zn^{2+} [11],[13],[14]. As a result of this conformational change, the DNA binding domain forms a unique structure that complements the DNA double helix in order to facilitate recognition of specific DNA sequences and targeted regulation of gene transcription [11].

Chromosome 8p11.23 encodes the ZNF proteins, which have a molecular weight of 58 kDa and contain 590 amino acids. The zinc finger of ZNF703 is located between amino acids 456 and 484. Post-translational modifications including N-acetylation (Ser-2), phosphorylation (Ser-252), and omega-N-methylation (Arg-580) are known [15,16].The different styles of ZNF703 structure are indicated (Fig. S1). NET family proteins reveal three conserved domains (Sp, Btd box, and C2H2 zinc finger) typically [17], but there are six domains in ZNF703 (the conserved domains plus domains LP, PY, and YL) [18]. Furthermore, most ZNF proteins can translocate to the nucleus while ZNF703 lacks nuclear localization sequences.

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https://doi.org/10.1016/j.heliyon.2023.e20140
Received 15 May 2023; Received in revised form 5 September 2023; Accepted 12 September 2023
Available online 14 September 2023

Table 1
Expression of ZNF703 in various cancer types and cell proliferation.

Cancer Type	Study type	Experimental model	NEL	Mechanism of action	Mode of modulation	References
Breast cancer	***In vitro***	MDA-MB-231 and 435S cell lines	↑	**siRNA**	**ZNF703 promoted cell proliferation regulated by lncRNA SPRY4-IT1.**	[36]
Lung adenocarcinoma	*In vivo*	SPCA-1 cell line	↑	**pcDNA3.1/ ZNF703**	ZNF703 promoted the tumor growth **regulated by** lncRNA WDFY3-AS2.	[48]
Gastric cancer	***In vitro***	MGC803 and BGC823 cell lines	↑	**pcDNA3.1/ ZNF703**	ZNF703 promoted cell proliferation and reduced the apoptosis by upregulated lncRNA LBX2-AS1.	[39]
Breast cancer	***In vitro***	MCF-7 cell line	↑	siRNA, GFP-ZNF703 vector	ZNF703 promoted cell proliferation and increased cancer stem cell population by acting as nuclear co-repressor to regulate E2F1 transcriptional activity.	[41]
Breast cancer	***In vitro***	MCF-7 cell line	↑	ZNF703 knockdown,	ZNF703 downregulated TGFβRII by directly binding its promoter regions to regulate cell proliferation.	[42]
Glioma	***In vitro***	LN229 and U87 cell lines	↑	pcDNA-ZNF703	ZNF703 alleviated the proliferative and invasive potentials by binding at the promoter regions of linc-UBC1.	[43]
Medullary thyroid cancer	MTC patients, ***In vitro,*** *in vivo*	MTC TT cell line	↑	**siRNA,** ZNF703 knockdown	ZNF703 promoted cell proliferation and tumor growth.	[46]

NEL: normal expression level.

Based on the deletion model of ZNF/NLZ1 specific domains, ZNF703 may gain access to the nucleus through its unique PY and YL domains by interacting with other proteins [18]. This is consistent with argument that the C-terminal residue of zebrafish Nlz1 is essential for nuclear localization [19,20]. Nuclear localization is crucial to ZNF703 activity [21], but the specific nuclear translocation mechanism remains to be elucidated. In physiological functions, ZNF703 is involved in the morphogenesis of cilia and various other tissues in zebrafish (*Danio rerio*) [22]. In the fruit fly (*Drosophila melanogaster*), NET family members Elbow and NocA are essential for

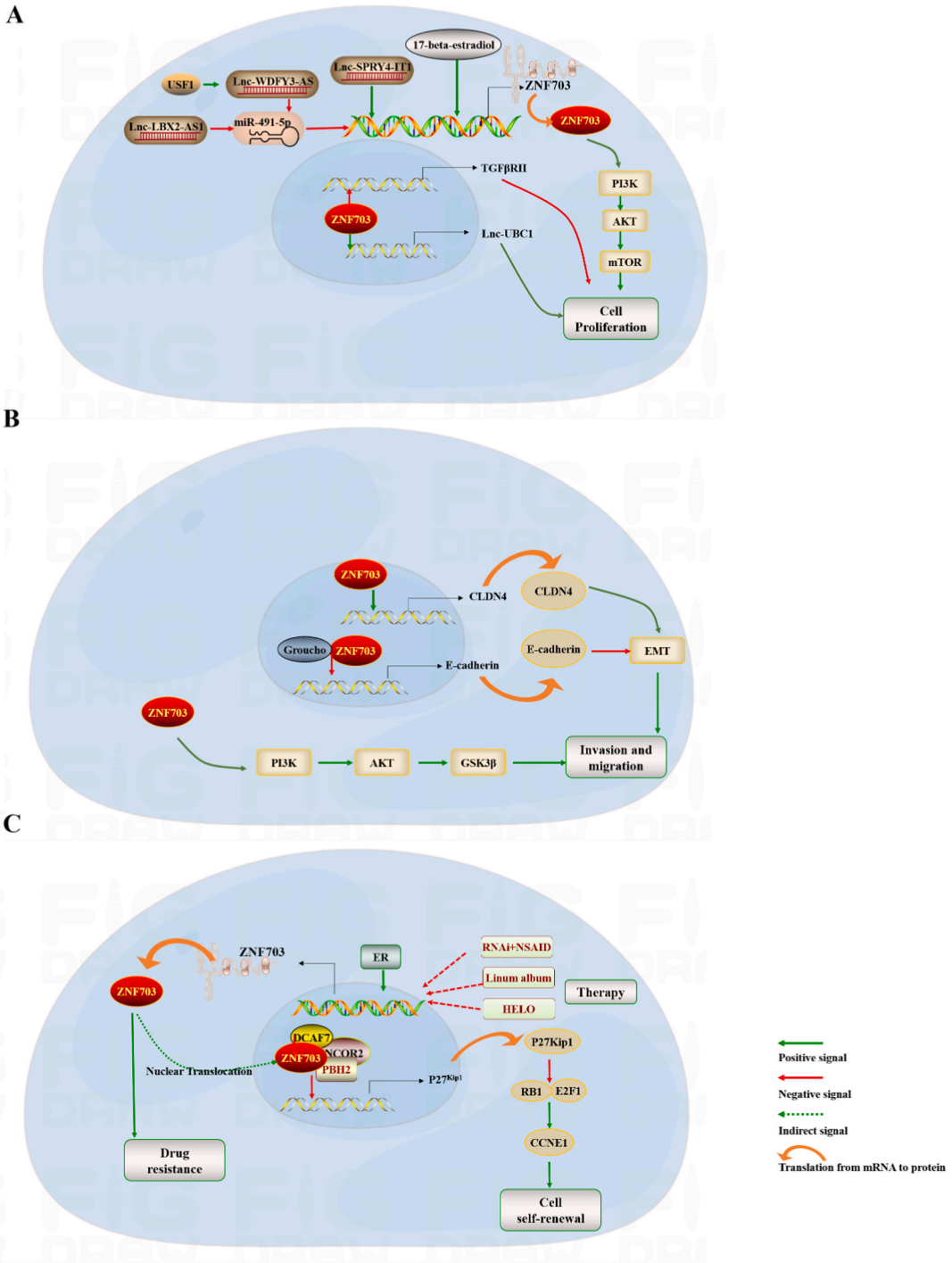

Fig. 1. The mechanism involved in ZNF703 including the signaling pathway, upstream regulation network and downstream targets. **A**:The mechanism of ZNF703 in cancer cell proliferation. **B**: The mechanism of ZNF703 in cancer cell invasion and migration. **C**: The mechanism of ZNF703 in cancer cell self-renew, drug resistance and therapy.

trachea, eye, wing, and leg development [23]. In non-human vertebrates, Nlz1 and Nlz2 participate in various developmental processes, including brain development, limb formation, and visual fissure closure [17,20,23–28]. Moreover, abnormal regulation of ZNF703 plays an important role in the occurrence and development of human tumors. A review is presented here for the first time summarizing ZNF703's malignant biological behaviors and potential significance in tumors, and proposing directions for future clinical research.

2. Roles in oncogenesis and tumor progression

Globally, cancer is a major public health concern associated with high mortality rates. Among the hallmarks of malignancy are sustained proliferation of cells, evasion of growth suppressors, resistance to cell death, indefinite replication potential, angiogenesis, invasive and metastatic capacity, metabolic reprogramming, and immune evasion [29]. Genome rearrangement is a complex process with functional consequences. As the only full-length gene within the smallest amplified part in the 8p12 chromosomal region [30,31], ZNF703 is widely considered to be evolutionarily conserved. It is common to exhibit simultaneous amplification of 11q12-11q14 and 8p11-8p12 chromosomal regions for breast tumors [32]. Chr8-chr11 translocation may be a critical event in the early stages of tumorigenesis [33,34], especially in squamous lung cancer, breast cancer, squamous esophageal cancer, and urothelial cancer [35].

2.1. Roles of ZNF703 in proliferation

One of the most common features of tumors is the dysregulated proliferation of cells. ZNF703 promotes tumor cell proliferation through diverse mechanisms. A breast cancer study found that lncRNA SPRY4-IT1 up-regulates ZNF703, thereby promoting proliferation, opposing apoptosis, and arresting the G1 phase [36]**. This mechanism was confirmed in esophageal squamous cell carcinoma** [37]**. USF1 activated lncRNA WDFY3-AS2 via targeting miR-491-5p to upregulate ZNF703 and promoted cell proliferation in lung adenocarcinomas** [38]. In gastric cancer, miR-491-5p also upregulated ZNF703, although the upstream regulator in this case was LBX2-AS1 [39]. The similar mechanism was also detected in a breast cancer study [40]. Most of them was the ceRNA mechanism. Additionally, 17-β-oestradiol increased ZNF703 levels, which decreased transforming growth factor-β receptor II (TGF-βRII) expression [41]**,** thereby preventing TGF-β from inhibiting proliferation of breast cancer cell [42]. Notably, this was associated with binding of ZNF703 to the TGF-βRII promoter and transcription-suppressive chromatin modification. In glioma, ZNF703 targeted the promoter of the lncRNA linc-UBC1 to enhance glioma cell proliferation [43]. It may be that copy number variation and/or activation of the PI3K/AKT pathway led to the overexpression of ZNF703 in head and neck squamous cell carcinomas [44,45]. ZNF703 facilitated proliferation of medullary thyroid carcinoma cells by activating the AKT/mTOR pathway *in vitro* and *in vivo* [46], ZNF703 and was also involved in the progression of non-small cell lung cancer by activating the AKT/mTOR pathway [47]. Most of all, ZNF703 was acting as a transcription factor. Literature (Table 1) and mechanisms (Fig. 1A) were summarised.

2.2. Roles of ZNF703 in invasion and metastasis

ZNF703 transactivated claudin 4 (CLDN4) expression to induce epithelial mesenchymal transition (EMT) via directly binding to the

Table 2
Expression of ZNF703 in various cancer types and migration and invasion.

Cancer Type	Study type	Experimental model	NEL	Mechanism of action	Mode of modulation	References
Hepatocellular carcinoma	HCC patients, *in vitro, in vivo*	HCCLM3 and SMMC7721 cell lines	↑	ZNF703 knockdown	ZNF703 induced EMT via directly binding to the CLDN4 promoter and transactivating CLDN4 expression.	[49]
Colorectal cancer	CRC patients, *in vitro*	LoVo and cell lines	↑	RNA interference	Knockdown of ZNF703 expression inhibited CRC cell proliferation and migration.	[50]
Cholangiocarcinoma	CAA patients, *in vitro, in vivo*	QBC939 and RBE cell lines	↑	**siRNA,** ZNF703 knockdown	ZNF703 could potently promote the progression of CCA.	[53]
Oral squamous cell carcinoma	OSCC patients, *in vitro, in vivo*	Tca-8113 and KB cell line	↑	pGCFU-ZNF703-GFP vector, ZNF703 knockdown	ZNF703 activated the PI3K/AKT/GSK-3β signaling pathway and its downstream effectors to regulat the cell cycle and EMT.	[54]
Gastric cancer	GC patients, *in vitro*	SGC7901 cell line	↑	RNA interference	ZNF703 acting as a oncogene promoted cell proliferation and migration significantly to be considered a therapeutic target for metastatic gastric cancer.	[55]
Papillary thyroid cancer	PTC patients, *in vitro*	K1 cell line	↑	ZNF703 siRNA	ZNF703-siRNA down-regulated E2F1 and MMP9 protein expression and enhanced the expression of p27 protein to inhibit the proliferation and invasion of K1 cells.	[57]

NEL: normal expression level.

CLDN4 promoter [49]. It is confirmed that ZNF703 promoted colorectal cancer cell invasive ability *in vitro* experiments [50]. In breast cancer, ZNF703 overexpression also promoted EMT, thereby inhibiting cell adhesion and enhancing cell invasion [51]. Mechanistically, ZNF703 complexed with Groucho prevented E-cadherin transcriptional activation to accelerate the tumor progression and metastasis [51]. ZNF703 also participate in the progression from carcinoma *in situ* to infiltrating lobular breast cancer [52]. ZNF703 played a crucial role in cholangiocarcinoma emergence and progression [53], and ZNF703 also facilitated growth and metastasis via the PI3K/AKT/GSK-3β pathway in oral squamous carcinoma [54]. Furthermore, ZNF703 was highly expressed in infiltrated gastric cancer tissues (with *in vitro* findings consistent with those of the above studies) [55], and the lncRNA TYMSOS interacted with miR-4739 to regulate its target gene ZNF703 in gastric cancer [56]. ZNF703 expression was associated with the tumor size, lymph node metastasis, and advanced disease stage in papillary thyroid carcinoma [57]. ZNF703 could be detected in circulating tumor DNA from patients with advanced ovarian cancer [58]. ZNF703 regulated by miRNA-651-3p affected EMT in ovarian cancer cells [59]. Literature (Table 2) and mechanisms (Fig. 1B) are summarised.

2.3. Roles of ZNF703 in cancer stem cells

Cancer stem cells (CSCs) exist in various types of tumors [60–66]. Self-renewing populations of these cells are highly tumorigenic and resistant to conventional radiation and chemotherapy [67–69]. During asymmetric division, stem cells maintain their own population while producing functionally mature progeny [70,71]. The role of ZNF703 in CSCs had received very little research. Although some studies suggested that ZNF703 may not bind directly to DNA due to its single zinc finger domain [17,72,73]. In response to oestrogen receptor signalling, it complexed with DCAF7, PHB2 and NCOR2 to inhibit E2F1 transcription and inactivate RB1 and P27Kip1, thereby shortening the G1 phase and switching the cellular balance from differentiation to self-renewal) [41]. Mechanisms are summarised (Fig. 1C). Future studies could target ZNF703 in CSCs to explore mechanisms and therapeutic prospects.

2.4. Roles of ZNF703 in resistance to chemotherapy and other antineoplastic drugs

Cancer recurrence and poorer outcome are associated with drug resistance. Chemotherapeutic resistance include intrinsic and acquired, which is caused and sustained by intracellular detoxification and reduced effective intracellular drug concentration, alterations in drug targets and signalling transduction molecules, abnormal repair of DNA damage, and evasion of cell apoptosis [74]. There was an increase in sorafenib sensitivity in cells with *ZNF703* knockout, suggesting that ZNF703 may serve as a biomarker or therapeutic target for sorafenib resistance [49]. A next-generation sequencing for the evaluation of breast cancer responsiveness to neoadjuvant chemotherapy revealed that there was 30.1% *ZNF703* amplification [75]. Allele loss or amplification within the 8p11-12 chromosomal region predicts a poorer response to radiation and chemotherapy, as well as poorer survival [76] (Fig. 1C). Based on above all, there was insufficient evidence to demonstrate the relationship and mechanism between ZNF703 and chemotherapy resistance. According to the published literatures, tumor cells overexpressing ZNF703 were more likely to develop resistance to chemotherapy drugs by affecting signal transduction pathways or cell apoptosis.

2.5. Therapeutic targeting of ZNF703

MCF7 cell proliferation was effectively inhibited by small interfering RNA (siRNA) targeting ZNF703 combined with ibuprofen-mediated COX-2 inhibition [77]. *Linum album* extracts induced apoptosis of the gastric cancer cell line AGS, possibly via down-regulating ZNF703 expression, and may therefore have therapeutic potential in gastric cancer [78]. Similarly, a hydroalcoholic extract of *Levisticum officinale*, a Chinese medicinal herb, induces apoptosis of breast cancer cells by decreasing the level of ZNF703-encoding mRNA [79] (Fig. 1C).

2.6. The signalling pathways involving in ZNF703

Several transcription factors are involved in the development and occurrence of tumors by regulating multiple signalling pathways [80]. The cellular signalling pathways themselves are intricately interconnected. ZNF703 was involved in the Wnt signalling pathway in embryonic development [22,51,81]. In tumor related research, most studies involving ZNF703 and signalling pathways had shown abnormal activation of the PI3K/AKT pathway, respectively, in oral squamous cell carcinoma [54], ovarian cancer [82], Luminal breast cancer [83], non-small cell lung cancer [47] and medullary thyroid carcinoma cell [46]. However, they were only phosphorylation changes, and the mechanism has not yet been fully elucidated. About MAPK signalling pathway, there was only one study in which ZNF703 affected the MEK/ERK pathway in ovarian cancer without further investigation [59]. Research on ZNF703 and signalling pathways is still superficial and needs to be further explored.

3. Interaction with other proteins

The transcription factor's activity is controlled by phosphorylation, ubiquitination, acetylation/deacetylation, and interactions between two or more proteins, including occasional switching from one to the opposite function [84,85]. Many interaction partners of ZNF703 have been identified. For example, it binds HDAC deacetylases directly to act as a transcriptional repressor, specifically, the domain of ZNF703 required for binding appeared to reside between the 'buttonhead box' (Btd) and the C2H2 zinc finger (ZF) [86]. However, ZNF703 could regulate breast CSC self-renewal activity by directly interacting with DCAF7, PBH2, and NCOR2 [41]. We also

found that ZNF703 as an oncogene played an important role in the epigenetic modification of ovarian cancer proliferation by interacting with HE4 and epigenetically regulating PEA15 [82]. Most of the functions of ZNF703 are performed in the nucleus, but it is not clear how ZNF703 enters the nucleus and may be related to interacting proteins. The online software String was also used to retrieve the interacting protein of ZNF703 (Fig. S2). A list of ZNF703-interacting proteins is provided (Table 3). The results of the database might not be exactly the same as reported in the literatures.

4. Discussion and conclusions

Morbidity and mortality caused by cancer are among the highest in the world [102]. Although targeted therapy has made significant progress in treating a few cancers, many cancers still pose a difficult diagnosis and treatment challenge. Angiogenesis is also necessary for cancer cell survival and metastasis [103]. Angiogenesis-targeting drugs such as anti-VEGF monoclonal antibodies are already under investigation and in clinical use [104]. There have been few studies investigating the role of ZNF proteins in angiogenesis, which could be explored further. Compared to normal tissue, cancer cells maintain a high rate of glycolysis, rapidly converting glucose into lactic acid even in the presence of oxygen ('oxygen glycolysis'); this preference for energy generation by converting pyruvate to lactic acid is also known as the 'Warburg effect' [105]. Many studies have examined the roles of ZNF proteins in tumor cell glucose metabolism. A ZBTB7A ZNF mutation significantly up-regulated expression of glycolytic genes resulting in enhancing glycolysis and supporting tumor cell proliferation [106]. However, there are currently no reports regarding the effect of ZNF703 on tumor cell glucose metabolism. In response to insulin, growth factors, and cytokines, the PI3K-AKT pathway is activated and regulates key metabolic processes, such as glucose metabolism, molecules biosynthesis to support both systemic metabolic homeostasis metabolism of cells [107]. In tumor cells, oncogenic activation of the PI3K-AKT pathway reprograms cellular metabolism by augmenting the activity of metabolic enzymes through the key downstream substrates: TSC2, GSK3, and the FOXO transcription factors [108]. As noted above, however, several studies have reported that ZNF703 activated the PI3K/AKT pathway [44,45,54], which played a major role in tumor metabolism [109]. We therefore speculate that ZNF703 affects tumor metabolism, and encourage studies exploring associated mechanisms and therapeutic prospects. Imaging combined with serological marker detection has been applied to tumor screening. And it was also reported that ZNF703 could be detected in circulating tumor DNA (ctDNA) in patients with ovarian cancer by hybrid capture-NGS based on liquid biopsy [58]. Actually, liquid biopsy markers include circulating tumor cells, circulating tumor DNA, extracellular vesicles, and exosomes [110,111]. Liquid biopsy has many limitations, including low abundance, specialized equipment and instruments, high fragmentation of ctDNA, spatial differences, sensitivity and specificity of detection methods [112,113]. These limitations will affect the detection of ZNF703 expression. The clinical application of ZNF703 as a potential biomarker for liquid biopsy needs further investigation. Tumor progression and metastasis also require metabolic changes [114]. Many ZNF protein post-translational modifications (e.g. phosphorylation, ubiquitination, acetylation, methylation, glycosylation, and hydroxylation)

Table 3
The interaction proteins of ZNF703.

Protein	Combined Score	Function	Evidences	References
DCAF7	0.641	Involved in craniofacial development. Acts upstream of the EDN1 pathway and is required for formation of the upper jaw equivalent, the palatoquadrate.	Experimental/ Biochemical Data	[41]
TRIM28	0.900	Mediates gene silencing by recruiting CHD3, a subunit of the nucleosome remodeling and deacetylation (NuRD) complex, and SETDB1 (which specifically methylates histone H3 at 'Lys-9' (H3K9me)) to the promoter regions of KRAB target genes.	Association in Curated Databases	None
FIGN	0.632	Severs microtubules along their length and depolymerizes their ends, primarily the minus-end, that may lead to the suppression of microtubule growth from and attachment to centrosomes.	Co-Mentioned in Pubmed Abstracts	[87,88]
TEP1	0.587	Component of the telomerase ribonucleoprotein complex that is essential for the replication of chromosome termini. Also component of the ribonucleoprotein vaults particle, a multi- subunit structure involved in nucleo-cytoplasmic transport.	Co-Mentioned in Pubmed Abstracts	[[53,86,89,90]]
PPAPDC1B	0.627	Displays magnesium-independent phosphatidate phosphatase activity *in vitro*. Catalyzes the conversion of phosphatidic acid to diacylglycerol. May be a metastatic suppressor for hepatocellular carcinoma.	Co-Mentioned in Pubmed Abstracts	[91–94]
PROSC	0.819	Pyridoxal 5′-phosphate (PLP)-binding protein, which may be involved in intracellular homeostatic regulation of pyridoxal 5′-phosphate (PLP), the active form of vitamin B6.	Co-Mentioned in Pubmed Abstracts	[[47,93]]
ERLN2	0.794	Component of the ERLIN1/ERLIN2 complex which mediates the endoplasmic reticulum-associated degradation (ERAD) of inositol 1,4,5-trisphosphate receptors (IP3Rs) such as ITPR1.	Co-Mentioned in Pubmed Abstracts	[94,95]
CCND1	0.650	Regulatory component of the cyclin D1-CDK4 (DC) complex that phosphorylates and inhibits members of the retinoblastoma (RB) protein family including RB1 and regulates the cell-cycle during G(1)/S transition.	Co-Mentioned in Pubmed Abstracts	[96–98]
CTNND1	0.582	Binds to and inhibits the transcriptional repressor ZBTB33, which may lead to activation of target genes of the Wnt signalling pathway (By similarity). Associates with and regulates the cell adhesion properties of both C-, E– and N-cadherins, being critical for their surface stability.	Co-Mentioned in Pubmed Abstracts	[99,100]
ZNF142	0.637	May be involved in transcriptional regulation; Zinc fingers C2H2-type	Co-Mentioned in Pubmed Abstracts	[101]

alter protein function. No reports currently exist regarding the effects of post-translational modification on ZNF703 function, but it is known to be modified by various enzymes at multiple natural modification sites (as mentioned above). It is worth investigating, for example, whether modified ZNF703 can compete with unmodified ZNF703 to interfere with its carcinogenic activities.

ZNF703 plays a pivotal role in embryonic development and tumor emergence and progression, including acquisition of resistance to chemotherapy and other antineoplastic drugs. Oncogenic mechanisms of ZNF703 depend on the specific tumor microenvironment. It is still unknown how ZNF703 is translocated to the nucleus and how it regulates gene expression, as well as what its potential utility as a tumor biomarker. Research on therapeutic targeting of ZNF703 is lacking. In summary, multiple studies implicate ZNF703 in carcinogenesis, but mechanisms remain incomplete understood, which has impeded translation of findings into clinical practice. Future research could focus on: clarifying the mechanisms highlighted above, the potential utility of ZNF703 as a precision medicine biomarker and therapeutic target, and the simplest and most sensitive methods for detecting and therapeutically targeting ZNF703.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

No data was used for the research described in the article.

Funding

This review was supported by grant from the National Natural Science Foundation of China (82203702) and the Open Fund of Tianjin Central Hospital of Gynecology Obstetrics/Tianjin Key Laboratory of human development and reproductive regulation (2022XH08).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Acknowledgements for all the members who help with this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20140.

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