Review Article

EZH2: A Crucial Competing Endogenous RNA in Cancer Research-A Scoping Review

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Abstract

Recently, research on the competing endogenous RNAs (ceRNAs) in cancer has been in full swing, emphasizing their importance as critical RNAs in cancer progression. Enhancer of zeste 2 polycomb repressive complex 2 subunit (*EZH2*) is a ceRNA that has been introduced as a potential therapeutic target in many cancers. Due to EZH2's dual role as an oncogene and tumor suppressor in cancer, a more thorough exploration of its ceRNA functions may enhance clinical cancer treatment approaches. In the current scoping review, we searched several online databases to identify experimentally validated ceRNA axes, including *EZH2* in human cancers. We identified 66 unique axes consisting of 30 microRNAs (miRNAs), 32 long non-coding RNAs (lncRNAs), 9 messenger RNAs (mRNAs), and 14 circular RNAs (circRNAs). Notably, *SPRY4-IT1* - miR-101-3p - *EZH2* and *XIST* - miR-101-3p - *EZH2* were recurrent axes observed in multiple cancer types. Among the most frequent miRNAs were miR-101-3p, miR-144-3p and miR-124-3p, and ceRNAs including *SPRY4-IT1*, *XIST*, *SNHG6*, *HOXA11-AS*, *MALAT1*, and *TUG1* emerged as frequent competitors of *EZH2* for miRNA binding. This scoping review highlights the diversity of *EZH2*-containing ceRNA axes in cancer, suggesting their potential as therapeutic targets. Further studies are needed to clarify their roles and clinical utility.

Keywords: Enhancer of zeste 2 polycomb repressive complex 2 subunit; neoplasms; RNA, competitive endogenous; RNA, untranslated

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Introduction

EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) is the catalytic subunit of the polycomb repressive complex 2 (PRC2), which suppresses gene expression by methylation of lysine 27 of histone 3 (H3K27).[1] This epigenetic modification is thought to silence more than 200 tumor suppressor genes.[1] In addition, EZH2 can also methylate non-histone proteins and affect their transcriptional activity. For instance, EZH2 methylates the *GATA4* transcription factor and reduces its acetylation by p300, resulting in the inhibition of *GATA4*-mediated transcription.[2] Moreover, EZH2 can also activate downstream genes in a PRC2-independent way by methylation of non-histone proteins.[3] Through these mechanisms, EZH2 is involved in various cellular processes, such as cell cycle regulation, autophagy, apoptosis, DNA repair, and cellular senescence. EZH2 is also associated with many diseases, especially cancer.[4]

EZH2 is overexpressed in many types of cancer where it disturbs various cellular processes such as proliferation, apoptosis, migration, and invasion.[5] Moreover, EZH2 is subjected to post-translational modifications that modulate its function and activity in cancer. For example, the phosphorylation of EZH2 can either promote (pT350-EZH2) or inhibit (pT487-EZH2) cell invasion and metastasis. O-GlcNAcylation, acetylation, and methylation of EZH2 affect the proliferation, apoptosis, migration, and metabolism of cancer cells. Ubiquitination

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of EZH2 can target it for degradation, while deubiquitinases like ZRANB1 stabilize EZH2 and enhance its oncogenic effects.[6] However, EZH2 can also act as a tumor suppressor in some cancers, where its loss or inactivation facilitates cancer progression.[7] For instance, T-cell acute lymphoblastic leukemia (T-ALL) is to a large part driven by the oncogenic activation of NOTCH1 signaling, which reduces the activity of PRC2 and the histone H3K27me3 repressive mark in T-ALL cells.[8] Inactivation of EZH2 by phosphorylation at its Ser 21 subsequently induces anti-apoptotic genes, such as *IGF1*, *BCL2*, and *HIF1A*, and increases cell adhesion-mediated drug resistance in multiple myeloma cells.[9]

EZH2 expression is also regulated by many microRNAs (miRNAs), which are often deregulated in cancer. Examples of such miRNAs are miR-98 in nasopharyngeal carcinoma,[10] miR-101-3p in esophageal squamous cell carcinoma,[11] and miR-124 in gastric cancer.[12] The dysregulation of these miRNAs and their consequent effect on the *EZH2*'s expression contribute to the aggressive behaviors of these cancers. Therefore, the regulation and role of *EZH2* in cancer is a topic of significant interest to researchers in the field.

RNA molecules in the cells communicate with each other through shared miRNA response elements (MREs), which act as the building blocks of a novel language and are called competing endogenous RNAs (ceRNAs).[13] Many studies suggest that *EZH2* participates in cancer progression by acting as a member of a ceRNA axis.[14-17] As explained by these studies, the RNA of *EZH2*, as part of ceRNA axes, can engage in cancer progression as a subunit of PRC2 complex or in a PRC2-independent manner to both inhibit and activate gene transcription [Figure 1].

The current scoping review provides a comprehensive overview of the literature on ceRNA axes including *EZH2* in cancer. While previous studies have exclusively explored the roles of these ceRNA axes in different cancers,[14,15,18,19] this scoping review specifically maps the experimentally validated ceRNA axes containing *EZH2* in cancer and describes the gaps and opportunities regarding employing *EZH2*-related ceRNA axes as a promising therapeutic strategy in cancer therapy.

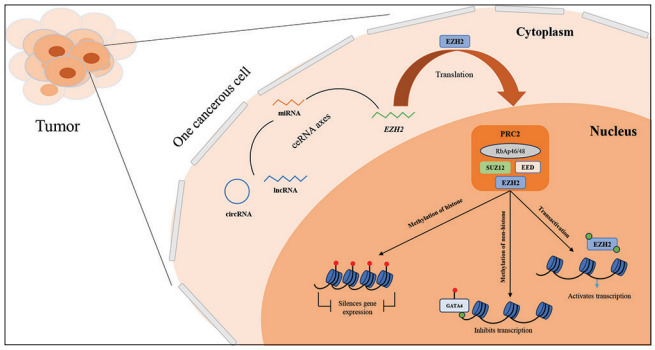

Figure 1: An Overview of EZH2 and its functions in cancerous cells. *EZH2* competes with competing endogenous RNAs (ceRNAs) like circular RNA (circRNA) and long non-coding RNA (lncRNA) for binding to the same microRNAs (miRNAs) and forms ceRNA axes. These interactions affect the expression of *EZH2*, in turn, the complex of EZH2 with EED, SUZ12, and RbAp46/48 as the polycomb repressive complex 2 (PRC2). This complex contributes to the control of transcription through the methylation of histone and non-histone proteins such as GATA4. EZH2 can also participate in the activation of transcription in a PRC2-independent way

Materials and Methods

Scoping reviews seek to map evidence regarding a potentially large and broad topic to recognize key concepts, theories, references, and areas lacking sufficient knowledge by following a systematic approach.[20,21] The current scoping review was performed according to the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist and explanation.[20] The methodology of the current scoping review included several steps: identification of the research question, identification of relevant studies, study selection based on the inclusion and exclusion criteria, charting and visualizing the data, and summarizing the findings.

Identifying the research question

This scoping review aims to map current knowledge about *EZH2* as an experimentally validated ceRNA in human cancers.

Identifying relevant studies

Systematic search was performed until 5th September 2024 in the PubMed, Web of Science, Scopus, Embase, Cochrane Library, and Google Scholar. For this aim, the following keywords were utilized: (cerna* OR "competing endogenous RNA*" OR "competitive endogenous RNA*" OR "microRNA response element*" OR "miRNA response element*" OR sponge OR axis) AND (EZH2 OR "Enhancer of Zeste Homologue 2") AND (cancer OR malignancy OR neoplasm* OR tumor OR tumour).

Study selection

Identified studies by the systematic search were reviewed by two authors (SSM and SMH). The studies were assessed based on the inclusion criteria, including (1) the *EZH2* RNA has been assessed in any type of cancer, (2) the ceRNA axis has been assessed in human samples, (3) *EZH2* has competition with at least one other ceRNA to sponge a miRNA, (4) the correlations of *EZH2* and other ceRNA (s) with the miRNA(s) have been validated based on the experimental analyses. The studies were excluded if they were (1) review studies, (2) not in English, (3) retracted, (4) not specified to cancer, (5) studies in which a specific condition (for example evaluating effects of a drug) have been examined, and (6) congresses abstract. After removing duplicated articles, titles and abstracts were assessed. Then, full texts were evaluated. Any disagreements were resolved through discussion with another reviewer (PN).

Charting the data

Extracted information contained the name of the first author, year of publication, country of origin (the country of the corresponding author), type of cancer, ceRNA axis, methods of interaction identification and validation, and the main role of the axis.

Visualization of the results

Cytoscape software (version 3.8.1)[22] was utilized to visualize ceRNA axes including *EZH2* which were identified through the previous steps.

Results

Characteristics of the included studies

2440 studies were initially identified through online search, among which, 1490 duplicates were omitted. By screening titles and abstracts, 862 studies were excluded, and 27 studies were removed via reading the full text [Supplementary file 1]. Finally, 61 studies were recruited in the current study based on the mentioned criteria. The number of studies at each step of the study selection process is indicated in a flow diagram [Figure 2]. The data extracted from the included studies has been shown in Table 1.

All of the included studies were from China and have been conducted between the years of 2014 to 2024. The identified studies have been performed in cancers consisting of colorectal cancer, gastric cancer, oral squamous cell carcinoma, lung cancer, bladder cancer, gallbladder cancer, glioma, hepatocellular carcinoma, prostate cancer, esophageal squamous cell carcinoma, pancreatic cancer, cholangiocarcinoma, ovarian cancer, tongue squamous cell carcinoma, cutaneous squamous cell carcinoma, endometrial cancer, papillary thyroid carcinoma, thyroid cancer, laryngeal squamous cell carcinoma, osteosarcoma, and breast cancer. Totally 66 unique axes were identified. There were 30 miRNAs, 32 long non-coding RNAs (lncRNAs), 9 messenger RNAs (mRNAs), and 14 circular RNAs (circRNAs) in the axes. A ceRNA network including these axes has been shown in Figure 3.

Both experimental and bioinformatic methods have been utilized in the included studies to identify and confirm the interactions among ceRNAs. Experimental methods were such as dual luciferase reporter assay, luciferase reporter, quantitative reverse transcriptase PCR (qRT-PCR), western blot, RNA

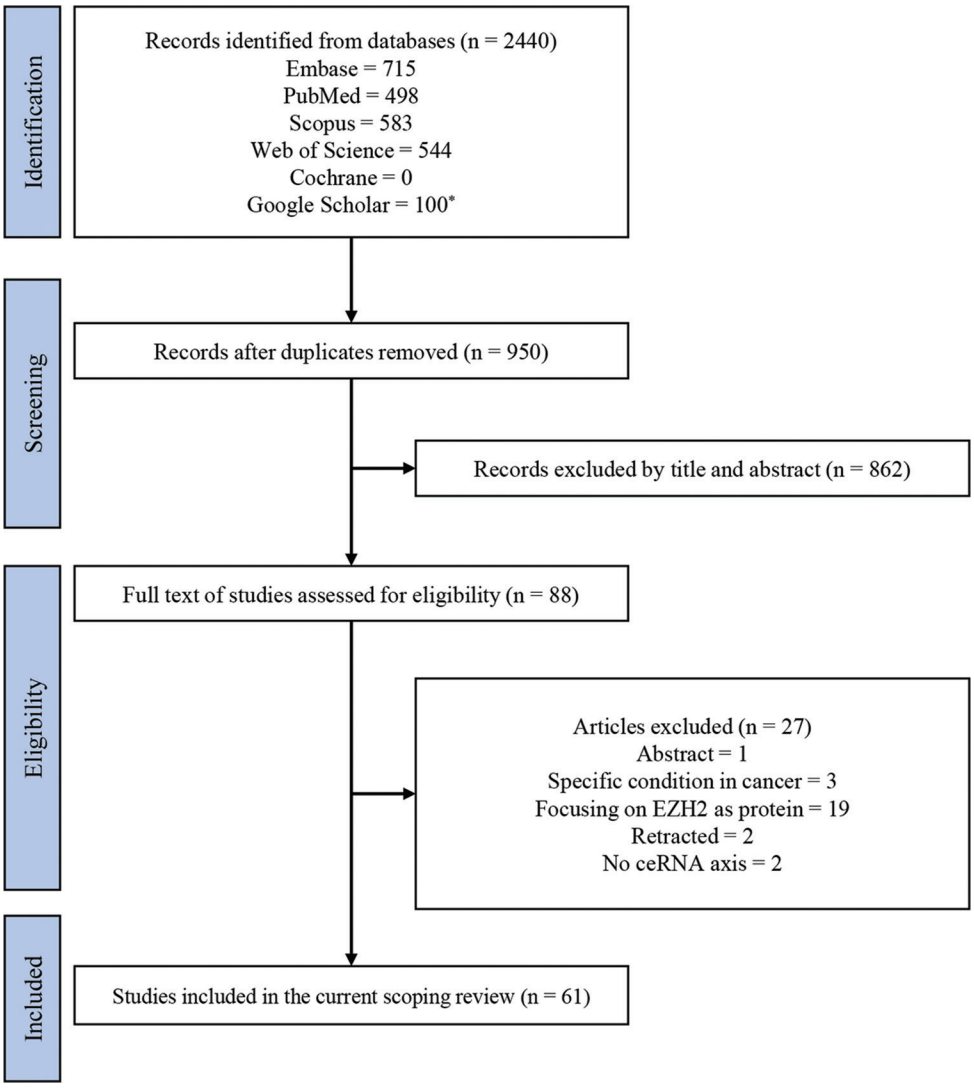

Figure 2: The flow diagram of the search results and number of records at each stage, ceRNA: competing endogenous RNA, EZH2: enhancer of zeste 2 polycomb repressive complex 2 subunit.* The first 100 hits, sorted by relevance, from Google Scholar were used in this study

Table 1: The main characteristics of included studies

Type of cancer	First author, Year (Refa)	Country	Axis	Methods	Functions
Colorectal cancer (CRC)	Ma X, 2021[15]	China	circ_0115744 - miR-144-3p - *EZH2*	Bioinformatic tools, qRT-PCRb, RIPc assay, western blot, correlation analysis, dual luciferase reporter assay, and RNA pull-down assay, microarray	circ_0115744 is associated with CRC metastasis and invasion and its increased levels promotes the expression of *EZH2*.
	Kong WQ, 2021[23]	China	*DLX6-AS1* - miR-26a-5p - *EZH2*	qRT-PCR, correlation analysis, western blot, and dual luciferase reporter assay	*DLX6-AS1* - miR-26a - *EZH2* axis affects the cell cycle, metastasis, and proliferation of CRC cells.
	Xie JJ, 2019[24]	China	*MALAT1* - miR-363-3p - *EZH2*	qRT-PCR, western blot, and dual luciferase reporter assay	*MALAT1* is upregulated in colorectal cancer and promotes the cancer through this axis.
	Zhang M, 2019[25]	China	*SNHG6* - miR-26a-5p - *EZH2*	qRT-PCR, western blot, dual luciferase reporter assay, and RIP assay	*SNHG6* is highly expressed in CRC cells and its knockdown results in decreased migration, invasion and EMT* through this axis.
	Xu M, 2019[26]	China	*SNHG6* - miR-26a-5p - *EZH2* *SNHG6* - miR-26b-5p - *EZH2* *SNHG6* - miR-214-3p - *EZH2*	Bioinformatic tools, qRT-PCR, luciferase reporter assay, RNA pull-down assay, and RIP assay	The increased expression of *SNHG6* may be a crucial factor in the advancement and growth of colorectal cancer and inhibition of apoptosis. *SNHG6* functions as a molecular sponge, binding to miR-26a, miR-26b and miR-214 in CRC, thereby releasing *EZH2*, which is accountable for the tumor-promoting effects of *SNHG6*.
	Shi L, 2019[27]	China	*ZNFX1-AS1* - miR-144-3p - *EZH2*	Bioinformatic tools, qRT-PCR, RIP assay, correlation analysis, western blot, and dual luciferase reporter assay, microarray	The lncRNA *ZNFX1-AS1* sponges miR-144 to regulate *EZH2* expression, thereby promoting CRC cells proliferation, invasion, tumorigenesis, and metastasis.
	Yong W, 2018[28]	China	hsa_circ_0071589 - miR-600 - *EZH2*	Bioinformatic tools, qRT-PCR, correlation analysis, RIP assay, western blot, and dual luciferase reporter assay	This axis contributes to the development of CRC. The upregulation of hsa_circ_0071589 in CRC tissue and its correlation with shorter overall survival time, along with its targeting by miR-600, suggests that this axis could be a promising target for CRC treatment.
Oral squamous cell carcinoma (OSCC)	Xu J, 2023[29]	China	circ_0000311 – miR-876-5p – *EZH2*	Bioinformatic tools, qRT-PCR, western blot, RNA pull-down assay, and dual luciferase reporter assay	circ_0000311 is overexpressed in OSCC and promotes the progression of this cancer through the axis.
	Zhang Y, 2022[18]	China	*DSCAM-AS1* - miR-138-5p - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, RIP assay, and dual luciferase reporter assay	Expressions of *DSCAM-AS1* and *EZH2* are increased in both OSCC cell lines and tissues. Silencing of *DSCAM-AS1* significantly inhibits cell migration and invasion of HSC-3 and CAL-27 cells, indicating that *DSCAM-AS1* promotes OSCC progression by suppressing miR-138-5p expression, which in turn directly inhibits *EZH2* and thus the progression of OSCC.
	Yao Y, 2021[30]	China	*LINC*00662 - miR-144-3p – *EZH2*	Bioinformatic tools, qRT-PCR, western blot, correlation analysis, dual-luciferase reporter assay, and RIP assay	*LINC*00662 correlates with TNM† stage, lymph node metastasis, proliferation, migration, and invasion of OSCC cells. It exerts its oncogenic role through the axis.
	Xiao L, 2020[31]	China	*MALAT1* - miR-101-3p - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, correlation analysis, and dual-luciferase reporter assay	*MALAT1* is overexpressed in OSCC tissues and cell lines and promotes cell proliferation and invasion via this axis.

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Table 1: Contd...

Type of cancer	First author, Year (Refa)	Country	Axis	Methods	Functions
	Wu K, 2020[32]	China	*RC3H2* - miR-101-3p - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, RNA pull-down assay, and dual luciferase reporter assay, microarray	The axis facilitates the malignant behavior of OSCC. Overexpression of *RC3H2* in OSCC cells leads to increased cell proliferation, migration, and invasion.
	Hong Y, 2018[33]	China	*H19* - miR138-5p - *EZH2*	Bioinformatic tools, qRTPCR, western blot, and dual luciferase reporter assay	By sponging miR-138, over-expressed *H19* promotes *EZH2* expression and thus, contributes to the induction of the EMT process, migration, invasion, and metastasis of OSCC cells. Suppression of H19 induces cell apoptosis, arrests the cells in the G0/G1 phase, and decreases the tumor volume.
	Zheng M, 2015[34]	China	*Snail* - miR-101 - *EZH2* *Slug* - miR-101 - *EZH2*	miRNA array, qRT-PCR, western blot, and dual luciferase reporter assay	Co-overexpression of *Snail* and *Slug*, correlates with migration, invasion and EMT as well as generating stem cell-like cells. These effects are regulated via this axis.
Gastric cancer (GC)	Zheng Y, 2022[14]	China	circ_0038138 - miR-198 - *EZH2*	Bioinformatic tools, western blot, dual luciferase reporter assay, and RNA pull-down assay	Exosomal circ_0038138 can promote malignant phenotype by regulating and activating the Wnt/β-catenin pathway through this axis.
	Yan H, 2022[35]	China	circKIF4A - miR-144-3p – *EZH2*	Bioinformatic tools, qRT-PCR, correlation analysis, western blot, and dual luciferase reporter assay	circKIF4A is overexpressed and enhances the progression of GC by the axis. It contributes to the EMT, migration, and proliferation of GC cells and its high expression correlates with poor prognosis.
	Huang HG, 2020[12]	China	*LINC*00511 - miR-124-3p - *EZH2*	Correlation analysis, qRT-PCR, western blot, and dual-luciferase reporter assay	*LINC*00511 is overexpressed in GC and induces proliferation and invasion of GC cells via this axis.
	Cao C, 2019[36]	China	*LINC*01303 - miR-101-3p - *EZH2*	qRT-PCR, western blot, and luciferase reporter assay	*LINC*01303 is overexpressed in GC and facilitates cancer progression through the modulation of cell migration and invasion via the *LINC*01303 - miR-101-3p - *EZH2* axis.
	Chen DL, 2016[37]	China	*XIST* - miR-101-3p - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, correlation analysis, and dual luciferase reporter assay	Up-regulation of lncRNA *XIST* expression correlates with GC progression and unfavorable prognosis in GC patients, and it modulates *EZH2* expression through sponging miR-101 in GC cells.
	Sun M, 2016[38]	China	HOXA11-AS - miR-1297 - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, correlation analysis, dual luciferase reporter assay, and RIP assay	The lncRNA *HOXA11-AS* is upregulated in GC and associates with disease progression and poor survival. *HOXA11-AS* acts as a ceRNA by sponging miR-1297, and thus regulating *EZH2*, participating in promoting GC cell proliferation, migration, and invasion and inhibition of apoptosis.
Glioma	Wang J, 2023[19]	China	*SPRY4-IT1* – miR-101-3p – *EZH2*	Bioinformatic tools, qRT-PCR, western blot, RNA-sequencing, immunoblot analysis, and correlation analysis	*SPRY4-IT1* is upregulated in glioma and induces angiogenesis and proliferation of glioma cells through this axis. *SPRY4-IT1* through this axis increases VEGFA expression. VEGFA then via VEGFR2/AKT/ERK1/2 signaling pathway induces cancer progression.
	Pan T, 2021[39]	China	*NNT-AS1* - miR-582-5p - *EZH2*	Bioinformatic tools, western blot, qRT-PCR, and dual luciferase reporter assay	*NNT-AS1* is overexpressed in glioma. *NNT-AS1* promotes metastasis of glioma cells by targeting miR-582-5p - *EZH2* axis, which leads to aggravation of the malignant behaviors of glioma.

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Table 1: Contd...

Type of cancer	First author, Year (Refa)	Country	Axis	Methods	Functions
	Deng Y, 2021[40]	China	*SNHG7* - miR1385p - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, correlation analysis, dual luciferase reporter assay, and RIP assay	The upregulation of lncRNA *SNHG7* in glioma cells promotes cell proliferation by sponging miR-138-5p and upregulating *EZH2* expression.
	Liu L, 2021[41]	China	*DLGAP1-AS1* - miR-1297 - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, correlation analysis, dual luciferase reporter assay, and RNA pull-down assay	*DLGAP1-AS1* is involved in regulating the invasive, migratory, and proliferative abilities of glioma cells by manipulating miR-1297 to regulate *EZH2*.
	Yuan DH, 2019[42]	China	circ-TTBK2 - miR-520b - *EZH2*	qRT-PCR, western blot, and dual luciferase reporter assay	circ-TTBK2 and *EZH2* are upregulated and have significant roles in the pathogenesis and progression of glioma. circ-TTBK2 induces carcinogenesis through sponging miR-520b and subsequently targeting *EZH2* in glioma. Downregulation of *EZH2* enhances cell apoptosis.
	Xu C, 2017[43]	China	*HOXA11-AS* - miR-214-3p – *EZH2*	Bioinformatic tools, qRT-PCR, correlation analysis, western blot, and dual luciferase reporter assay	*HOXA11-AS* is upregulated and contributes to the promotion of growth and metastasis of glioma cells via this axis.
Lung cancer	Huang M, 2024[44]	China	*LOC107986454* – miR-143-3p – *EZH2*	Bioinformatic tools, qRT-PCR, western blot, and dual-luciferase reporter assay, and RNA pull-down assay	This axis contributes to the radiosensitivity of cancerous cells through the regulation of (-)-epicatechin. Downregulation of *LOC107986454* and *EZH2* suppress cell migration and induces Apoptosis.
	Liu Y, 2022[45]	China	circPVT1 - miR-124-3p - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, and dual-luciferase reporter assay	Exosomal circPVT1 originating from lung cancer prompts M2 macrophage polarization and boosts lung cancer cell malignancy. It may increase *EZH2* expression through miR-124-3p sponging.
	Wang Y, 2019[46]	China	circ-PRMT5 - miR-377 – *EZH2* circ-PRMT5 – miR-382-5p – *EZH2* circ-PRMT5 – miR-498 - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, luciferase assay, and RNA pull-down assay	circ-PRMT5 promotes the growth of NSCLC‡ by upregulating oncogenic *EZH2* expression through sponging miR-377, miR-382, and miR-498.
	Qiu C, 2019[47]	China	PVT1 - miR526b - *EZH2*	Bioinformatic tools, qRTPCR, correlation analysis, and dual luciferase reporter assay	*PVT1* - miRNA-526b - *EZH2* regulatory loop participates in NSCLC malignant progression by influencing tumor cell proliferation and migration, thus offering new clinical treatment directions.
	Qu D, 2018[48]	China	hsa_circ_0020123 - miR-144-3p - *EZH2* *ZEB1* – miR-144-3p – *EZH2*	qRT-PCR, western blot, correlation analysis, dual luciferase reporter assay, RNA pull-down assay, RIP assay, and microarray	The upregulation of hsa_circ_0020123 is associated with unfavorable prognosis in NSCLC patients because it enhances cell proliferation and migration, while suppressing apoptosis through its interaction with miR-144, resulting in increased expression of ZEB1 and *EZH2*.
Prostate cancer	Xu W, 2024[49]	China	*NEAT1* – miR-582-5p – *EZH2*	Bioinformatic tools, qRT-PCR, western blot, dual luciferase reporter assay	Expression of *NEAT1* through this axis is correlated to tumor progression, invasion, metastasis, apoptosis and EMT.
	Dong Q, 2023[50]	China	*SNHG4* - let-7a - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, dual luciferase reporter assay, and RIP assay	lncRNA *SNHG4*, through this axis, plays a significant role in driving prostate cancer progression and enzalutamide resistance, making it a potential therapeutic target.

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Type of cancer	First author, Year (Refa)	Country	Axis	Methods	Functions
	Sha J, 2020[51]	China	*circ-TRPS1* - *miR-124-3p* - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, dual luciferase reporter assay, and RNA sequencing	circ-*TRPS1* functions as a miR-124-3p sponge, stimulating increased *EZH2* levels, and amplifying the differentiation of cancer stem-like cells during the progression of prostate cancer.
	Chen Y, 2019[52]	China	*FOXC2-AS1* - miR-1253 - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, correlation analysis, and dual luciferase reporter assay	*FOXC2-AS1*, which is overexpressed in prostate cancer, promotes cancer progression through the *FOXC2-AS1* - miR-1253 - *EZH2* pathway.
	Yang X, 2018[53]	China	*PCSEAT* - miR-143-3p – *EZH2* *PCSEAT* - miR-24-2-5p – *EZH2*	Bioinformatic tools, qRT-PCR, western blot, correlation analysis, and dual luciferase reporter assay	*PCSEAT* exhibits increased expression in prostate cancer and facilitates cell proliferation and motility through this axis, potentially promoting the proliferation of other cells via exosome transport.
Hepatocellular carcinoma (HCC)	Lei D, 2022[54]	China	circ*SYPL1* - miR-506-3p - *EZH2*	qRT-PCR, correlation analysis, dual luciferase reporter assay and RNA pull-down assay	Progression of HCC is promoted by this axis and upregulation of *EZH2* expression and inhibition of apoptosis.
	Zhang Y, 2019[55]	China	lnc-*PDZD7* - miR-101-3p - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, correlation analysis, dual luciferase reporter assay, RNA pull-down assay, and microarray	Upregulation of *lnc-PDZD7* in HCC leads to the inhibition of HCC cell sensitivity to anticancer drugs and the promotion of stemness features in these cells through the *lnc-PDZD7* - miR-101 - *EZH2* axis. Suppresion of lnc-*PDZD7* causes increased chemosiensitivity to 5-fluorouracil (5-Fu) and sorafenib.
	Lin T, 2019[56]	China	hsa_circ_0008450 - miR-214-3p - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, correlation analysis, and dual luciferase reporter assay	Overexpression of hsa_circ_0008450 leads to the promotion of invasion, proliferation, and migration and apoptosis inhibition of HCC cells through the axis.
	Shi Y, 2018[57]	China	*HANR* – miR-214-3p – *EZH2*	Bioinformatic tools, qRT-PCR, and dual luciferase reporter assay	Modulation of TGF-β signaling by the *HANR* - miR-214 - *EZH2* axis can impact tumor phenotypes in HCC.
Esophageal squamous cell carcinoma (ESCC)	Wang J, 2020[11]	China	*SNHG6* - miR-101-3p - *EZH2*	qRT-PCR, western blot, correlation analysis, and dual luciferase reporter assay	Expression of *EZH2* is regulated by *SNHG6*-miR-101-3p, which in turn affects apoptosis in ESCC cells.
	Qiu BQ, 2020[58]	China	*PSMA3-AS1* - miR-101-3p – *EZH2*	qRT-PCR, western blot, correlation analysis, dual luciferase reporter assay, RIP assay, and RNA pull-down assay	Upregulation of *PSMA3-AS1* participates in the progression of ESCC.
	Wu X, 2017[59]	China	*XIST* - miR-101-3p - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, correlation analysis, and dual luciferase reporter assay	*XIST* is upregulated and via this axis facilitates ESCC progression and modulates EMT in ESCC cells.
Gallbladder cancer	Wang S, 2021[60]	China	circTP63 - miR-217-5p – *EZH2*	qRT-PCR, western blot, correlation analysis, dual luciferase reporter assay, and RNA pull-down assay	The growth and EMT processes of gallbladder cancer cells were inhibited by the downregulation of circTP63, which occurs through sponging miR-217 and subsequently up-regulating *EZH2*.
	Li Y, 2021[61]	China	*MYLK-AS1* - miR-217-5p - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, and dual luciferase reporting assay, microarray	The upregulation of *MYLK-AS1* in gallbladder cancer cells through the axis and the subsequent upregulation of *EZH2* leads to increased cell proliferation and resistance to gemcitabine.

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Table 1: Contd...

Type of cancer	First author, Year (Refa)	Country	Axis	Methods	Functions
	Wang SH, 2016[62]	China	*MINCR* - miR-26a-5p - *EZH2*	qRT-qPCR, dual luciferase reporter assay, and RIP assay	*MINCR* is overexpressed in gallbladder cancer, and its activation promotes cancer advancement by influencing cell proliferation, cell cycle regulation, and apoptosis.
Bladder cancer	Min J, 2022[63]	China	SNHG1 - miR-137-3p – *EZH2*	Bioinformatic tools, qRT-PCR, western blot, dual-luciferase reporter assay, and RIP assay	*SNHG1* facilitates the proliferation, migration, invasion, and EMT of BC cells by sponging miR-137-3p and engaging in the transcriptional inhibition of KLF2 through its interaction with *EZH2*, while also competitively binding to miR-137-3p in the cytoplasm to boost *EZH2* expression and contributing to the epigenetic suppression of *KLF2* in the nucleus through recruitment of *EZH2*.
	Liu D, 2017[64]	China	*SPRY4-IT1* - miR-101-3p - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, dual luciferase reporter assay, RNA pull-down assay	*SPRY4-IT1* functions as an oncogene by positively controlling *EZH2* expression via miRNA sponging, thereby promoting the growth and spread of bladder cancer and suppressing apoptosis.
Cholangiocarcinoma (CCA)	Xie Y, 2018[65]	China	*DVL3* - let-7c – *EZH2*	Bioinformatic tools, qRT-PCR, western blot, dual luciferase reporter assay, and microarray	This axis contributes to various functions of the Wnt/β-catenin pathway, including migration, invasion, metastasis, and self-renewal capacity in CCA cells. let-7c expression is lower in CCA tissues but higher in serum samples and its downregulation facilitates invasion and targets *EZH2* and DVL3/β-catenin, which plays a role in the malignant behavior of CCA.
	Xu Y, 2018[66]	China	*SPRY4-IT1* - miR-101-3p – *EZH2*	qRT-PCR, western blot, correlation analysis, luciferase reporter assay, and RIP assay	Overexpression of *SPRY4-IT1* in CCA is linked to aggressive tumor characteristics and poor prognosis, as well as its role as a molecular sponge for miR-101-3p in inhibiting *EZH2* protein synthesis, indicating the possibility of discovering new predictive or therapeutic targets for CCA. Suppression of *SPRY4-IT1* promotes apoptosis and reverses EMT.
Endometrial cancer (EC)	Wang W, 2019[67]	China	*NEAT1* - miR-144-3p - *EZH2*	qRT-PCR, western blot, and dual luciferase reporter assay	*NEAT1*, extensively expressed in EC tissues and cells, enhances EC cell proliferation, migration, and invasion by functioning as a molecular sponge of miR-144-3p and enhancing the expression of *EZH2* through miR-144-3p.
	Konno Y, 2014[68]	China	MCL-1 – miR-101-3p – *EZH2* FOS – miR-101-3p – *EZH2*	qRT-PCR, western blot, immunoblot analysis, correlation analysis, luciferase activity assay, and microarray	miR-101 participates in suppressing cell proliferation and EMT, induction of apoptosis as well as increasing sensitivity to paclitaxel in aggressive EC cells and shows an inverse correlation with the expression of *EZH2*, *MCL*-1, and *FOS* in EC specimens.
Pancreatic cancer	Zhao L, 2017[69]	China	*TUG1* - miR-382-5p - *EZH2*	qRT-PCR, western blot, correlation analysis, dual luciferase reporter assay, RIP assay, RNA pull-down assay, and microarray	*TUG1* enhances the growth, migration and EMT of pancreatic cancer cells by acting as a ceRNA and sponging miR-382, resulting in the increased expression of *EZH2*, thus playing a role in the observed phenomena.
Ovarian cancer	Yang X, 2021[70]	China	hsa_circ_0026123 - miR1243p - *EZH2*	Bioinformatic tools, qRT-PCR, western blot and dual luciferase reporter assay	Increased level of hsa_circ_0026123 in ovarian cancer cells and tissues results in the upregulation of *EZH2* expression by capturing miR-124-3p, thus impacting migration, proliferation, and CSC differentiation.

Contd...

Table 1: Contd...

Type of cancer	First author, Year (Refa)	Country	Axis	Methods	Functions
Cutaneous squamous cell carcinoma (CSCC)	Zou S, 2021[71]	China	*HCP5* - miR1385p – *EZH2*	Bioinformatic tools, qRT-PCR, western blot, dual luciferase reporter assay, and RNA pulldown assay	Expression levels of *HCP5* and *EZH2* are increased in CSCC, while the expression of miR-138-5p is decreased, and these molecules can influence autophagy and apoptosis in CSCC cells through the STAT3/*VEGFR2* pathway.
Papillary thyroid carcinoma (PTC)	Guo K, 2021[17]	China	MIAT - miR-150-5p - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, dual luciferase reporter assay, and microarray	Upregulation of MIAT may play a role in promoting the movement and growth of PTC cells through the ceRNA network and inhibition of apoptosis.
Thyroid cancer	Ma X, 2021[72]	China	C*CDC26* - miR-422a – *EZH2*	Bioinformatic tools, qRT-PCR, western blot, correlation analysis, dual luciferase reporter assay, and RIP assay	*CDC26* acts as a sponge for miR-422a, leading to increased expression of *EZH2* and Sirt6 in thyroid cancer cells, thereby promoting the progression and inhibiting apoptosis of thyroid cancer through the miR-422a - *EZH2* axis.
Breast cancer	Lin Y, 2020[73]	China	*FERRE* - miR-19a-5p – *EZH2*	Bioinformatic tools, qRT-PCR, western blot, correlation analysis, and dual luciferase reporter assay	Upregulation of *FERRE* can promote migration, proliferation, and invasion of the breast cancer cells through this axis.
Tongue squamous cell carcinoma (TSCC)	Li Y, 2019[74]	China	*ADAMTS9-AS2* - miR-600 – *EZH2*	qRT-PCR, western blot, correlation analysis, luciferase reporter assay, RIP assay, and microarray	Upregulation of *ADAMTS9-AS2* in TSCC specimens, especially in those with lymphoid metastasis, was found to inhibit TSCC cell migration and invasion by reversing TGF-β1-induced EMT through miR-600 sponge activity and *EZH2* targeting.
Laryngeal squamous cell carcinoma (LSCC)	Xiao D, 2019[75]	China	*XIST* - miR-124-3p - *EZH2*	Bioinformatic tools, qRT-PCR, western blot, correlation analysis, and dual luciferase reporter assay	*XIST* is overexpressed and through this axis enhances the malignant behavior of LSCC.
Osteosarcoma	Cao J, 2017[76]	China	*TUG1* - miR-144-3p - *EZH2*	qRT-PCR, western blot, correlation analysis, dual luciferase reporter assay, RIP assay, and RNA pull-down assay	*TUG1* upregulation plays a significant role in osteosarcoma development and EMT due to the involvement in the miRNA-144-3p - *EZH2* axis and the Wnt/β-catenin pathway.

*EMT: epithelial-mesenchymal transition, †TNM: tumor, node, metastasis, ‡NSCLC: non-small cell lung cancer

immunoprecipitation (RIP), and RNA pull-down assays. For bioinformatic analyses, studies used online databases such as TargetScan[77] and CircInteractome.[78] In all of the included studies, a ceRNA axis including *EZH2*, as a critical ceRNA, as well as the role of this axis on the studied cancer were disclosed. Three of the included studies examined the ceRNA axes in the context of exosomes.[14,45,53] Three of the included studies[14,65,76] experimentally validated that *EZH2*-related ceRNA axes influence the Wnt/β-catenin pathway in various ways. Furthermore, STAT3/VEGFR2 and VEGFR2/AKT/ERK1/2 signaling pathways were reported in cutaneous squamous cell carcinoma[71] and glioma,[19] respectively, by which the axes participate in cancer progression.

Of note, most of the included studies demonstrated a correlation between these axes with cancer-related mechanisms such as cellular proliferation, epithelial-mesenchymal transition (EMT), and cellular metastasis of cancerous cells. These findings are summarized in Figure 4. Several studies investigated the association of these axes with drug resistance in cancer. They included enzalutamide resistance in prostate cancer,[50] 5-fluorouracil (5-Fu) and sorafenib resistance in hepatocellular carcinoma,[55] paclitaxel resistance in endometrial cancer,[68] and gemcitabine resistance in gallbladder cancer.[61]

Common EZH2-related axes, miRNAs and ceRNAs

Among the ceRNA axes identified in this review, two axes stood out as they were reported in more than one cancer type, highlighting their potential significance across different malignancies. These axes are particularly noteworthy because their repeated identification suggests they may play a more universal role in cancer biology.

SPRY4-IT1* - miR-101-3p - *EZH2 axis was reported in glioma,[19] bladder cancer[64] and cholangiocarcinoma.[66] *SPRY4-IT1* is upregulated in all of these cancers and its high expression leads to an increase of *EZH2* by sponging miR-101-3p.[19,64,66]

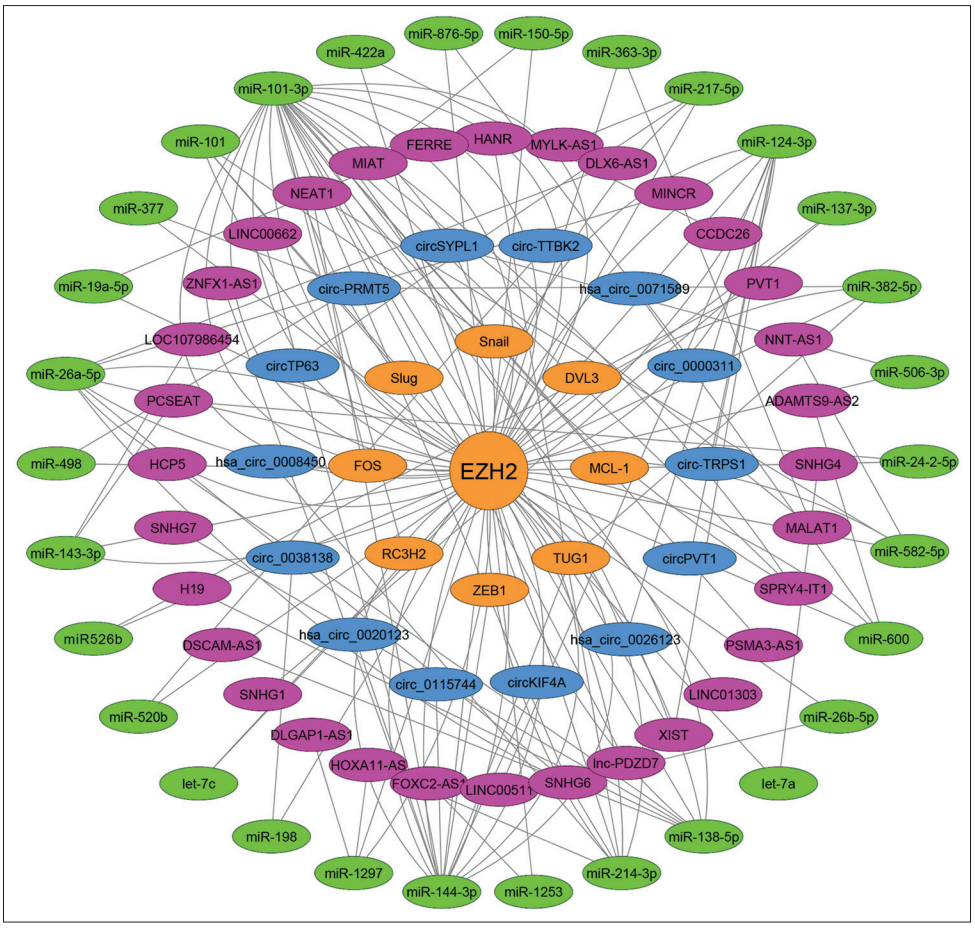

Figure 3: *EZH2*-related ceRNA network in cancer. Orange, blue, purple, and green colors represent mRNAs, circRNAs, lncRNAs, and miRNAs, respectively

This affects proliferation,[19,66,66] metastasis,[64,66] apoptosis,[64,66] EMT[64,66] and angiogenesis[19] of tumoral cells.

XIST* - miR-101-3p - *EZH2 axis was another axis reported in two cancer types including gastric cancer[37] and esophageal squamous cell carcinoma.[59] Overexpression of *XIST* exerts an oncogenic role and aggressive tumor phenotypes in these cancers through the sponging of miR-101-3p and increased expression of *EZH2*.[37,59]

Among the miRNAs identified in this review, twelve miRNAs were reported in more than one cancer type or study, highlighting their potential broader roles in cancer biology and their frequent association with *EZH2*-related ceRNA axes. These miRNAs stand out due to their recurrence, which may reflect conserved mechanisms of oncogenesis across multiple malignancies. The twelve miRNAs include miR-101-3p,[11,19,31,32,36,37,55,58,59,64,66,68] miR-144-3p,[15,27,30,35,48,67,76] miR-124-3p,[12,45,51,70,75] miR-138-5p,[18,71,33,40] miR-214-3p,[26,43,56,57] miR-26a-5p,[23,25,26,62] miR-1297,[38,41] miR-217-5p,[61,60] miR-382-5p,[46,69] miR-143-3p,[53,44] miR-582-5p,[39,49] and miR-600.[28,74] Notably, one study[34] did not specify whether they examined miR-101-3p or other variants of miR-101, so we excluded this study when counting recurrent miRNAs.

Recurrent ceRNAs, including *SPRY4-IT1,*[19,64,66] *XIST,*[37,59,75] *SNHG6,*[11,26,25] *HOXA11-AS,*[43,38] *MALAT1,*[31,24] *NEAT1,*[67,49] and *TUG1*[69,76] were ceRNAs repeated in several *EZH2*-related ceRNA axes studies. These ceRNAs compete with *EZH2* for binding to the miRNAs, affecting the abundance of *EZH2* and impacting key cancer-related processes such as cellular proliferation, metastasis, migration, apoptosis, EMT, signaling pathways, and chemotherapy resistance. The recurrence of these ceRNAs across multiple cancer types and studies emphasize their potential as critical modulators of EZH2-related pathways in cancer biology. The main functions of these ceRNAs and their associated miRNAs in cancer progression are summarized in Table 1.

Discussion

EZH2 is a prominent target for cancer therapy

Targeting the protein of EZH2 as a critical factor in cancer progression has gained a lot of attention in recent years. There are two main groups of EZH2 inhibitors: inhibitors of EZH2 methyltransferase activity and those damaging the structure of PRC2.[79]

There are many introduced EZH2 inhibitors for cancers. Tazemetostat is a member of the first group that was approved

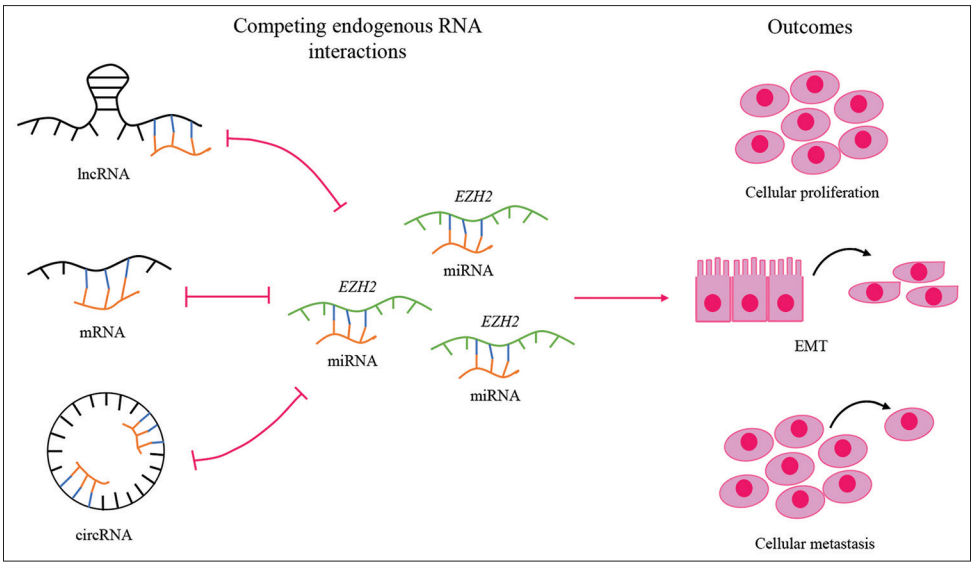

Figure 4: *EZH2*-related competing endogenous RNA (ceRNA) axes and their primary outcomes in cancer. Various types of RNAs, including long non-coding RNAs (lncRNAs), messenger RNAs (mRNAs), and circular RNAs (circRNAs), can compete with *EZH2* for binding to the same microRNAs (miRNAs). These interactions form ceRNA axes that contribute to cancer progression through mechanisms such as cellular proliferation, epithelial-mesenchymal transition (EMT), and metastasis

by the FDA for advanced epithelioid sarcoma.[80] UNC1999, an autophagy inducer with a high level of oral bioavailability, inhibits H3K27me3/2 and specifically kills diffuse large B-cell lymphoma cells.[81] As a member of the PRC2 complex, EZH2 interacts with EED and SUZ12. Thus, targeting PRC2 or the two mentioned elements can indirectly lead to the inhibition of EZH2.[79] Astemizole targets EZH2 by disrupting the interaction between EZH2 and EED and suppresses the proliferation of cancer cells.[82] UNC6852 as a degrading factor of PRC2, decreases H3K27me3 in HeLa cells and targets diffuse large B-cell lymphoma carrying the *EZH2* mutations.[83]

Although these drugs have important advantages in the treatment of some hematological tumors, they are not effective for some solid tumors.[79] These drugs primarily target the methyl transferase activity and domain of EZH2. EZH2 has different functions and because of that, these inhibitors have some defects.[79] It should be taken into account that utilizing these inhibitors might cause an increase in tumor growth instead of prevention.[79] Therefore, studying the RNA form of *EZH2* along with its protein, may provide a deeper understanding of the molecular mechanisms of EZH2 and facilitate the development of more effective therapeutic options.

EZH2's ceRNA axes in cancer

EZH2 has been identified as an important ceRNA in various types of cancer. In the current scoping review, we systematically searched and collected the studies in which *EZH2* has been reported as a ceRNA, in the context of axis, by utilizing experimental approaches. Based on Table 1, in some types of cancer, the role of *EZH2* as a ceRNA has not been well investigated. However, in some others such as colorectal, gastric, and lung cancers, a considerable number of studies have dealt with *EZH2* as a significant ceRNA. In these *EZH2*-related ceRNA axes, *EZH2* not only exerts a pivotal influence on the cancer progression but the ceRNA(s) that compete with *EZH2*, along with the miRNAs present in these axes, play a fundamental role. The whole axis should be considered as a critical unit.

Although most of the included studies have been performed on tissues and cell lines, few of them have investigated ceRNA axes within exosomes.[14,45,53] Exosomal ceRNAs are important for cellular communication in cancer. Dysregulation of ceRNAs within exosomes affects the proliferation, differentiation, and apoptosis of cancerous cells.[84]

What do we know of *EZH2*'s ceRNA axes?

The influence of RNAs within these axes on EZH2 expression highlights their significance in cancer therapy. Two commonly observed ceRNA axes (*SPRY4-IT1* - miR-101-3p - *EZH2* and *XIST* - miR-101-3p - *EZH2*) across various types of cancer serve as intricate regulatory networks, orchestrating gene expression patterns that drive tumorigenesis and progression. The fact that they are found in different cancer types suggests a consistent mechanism of disruption in cancer cells, which presents promising opportunities for targeted interventions. Utilizing these ceRNA axes as diagnostic biomarkers or therapeutic targets has great potential for enhancing precision oncology strategies. Further investigation into their mechanistic underpinnings and clinical implications is warranted to harness their full therapeutic utility in combating cancer. Among the axes reviewed in the current study, there were common ceRNAs and miRNAs. Due to the abundance of these RNAs, we focus on those most frequently reported.

SPRY4-IT1

SPRY4-IT1 was reported in three of the included studies[19,64,66]

and in all of them, it competes with *EZH2* for binding to the miR-101-3p. lncRNA *SPRY4-IT1* is overexpressed in prostate cancer and through the PI3K/AKT signaling pathway, promotes the proliferation of cancerous cells.[85] In breast cancer, upregulation of *SPRY4-IT1* induces the NF-κB signaling pathway, which promotes cell proliferation and inhibits apoptosis.[86] *SPRY4-IT1* acts as a sponge for miR-101-3p in different types of cancer, for example, it promotes cell proliferation and angiogenesis by inducing VEGFA in glioma,[19] and EMT in colorectal[87] and osteosarcoma.[88] In line with these results, short hairpin RNA targeting *SPRY4-IT1* also inhibits the growth of tumors and modifies the levels of miR-101, ZEB1/2, and E-cadherin.[88]

XIST

XIST is a crucial RNA and studies have identified its impacts on cancer development. The alteration of *XIST* expression in cancer has significant implications for cell growth, invasion, response to chemotherapy, and metastasis. The mechanisms by which it exerts these roles have been reviewed,[89,90] showing *XIST* promotes malignant behaviors in cancer by sponging different types of miRNAs. For example, in breast cancer, *XIST* sponges let-7a-2-3p and induces the production of IL-6 from the cancerous cells. This leads to increased surface IL-6 receptors and the promotion of cancer stem cell self-renewal.[91]

SNHG6

A meta-analysis, published in 2020, has reported the correlation of *SNHG6* expression with advanced tumor, node, metastasis (TNM) stage, tumor invasion depth, lymph node, and distance metastasis in human cancers.[92] Silencing of *SNHG6* can have therapeutic effects. For example, inhibition of *SNHG6* increases the sensitivity of esophageal cancer cells to 5-FU.[93] In contrast, *SNHG6* is down-regulated in gemcitabine-resistant pancreas cancer and up-regulation of *SNHG6* increases the response of gemcitabine-resistant pancreatic cancer cell lines to gemcitabine via *SNHG6* – miR-944 - *KPNA5* axis.[94]

miR-101-3p

miR-101-3p acts as a tumor suppressor in lung cancer through targeting *MALAT-1* and PI3K/AKT signaling pathways.[95] In gastric cancer, miR-101-3p exhibits tumor suppressor properties by inhibiting cell proliferation and inducing apoptosis via regulation of *PIM-1* expression.[96] However, there are also some studies suggesting that miR-101 functions as an oncogene, particularly *in vivo*, and increased levels of miR-101-3p are associated with poorer survival outcomes in ovarian cancer patients.[97] miR-101-3p participates in determining cellular sensitivity to the methods of cancer treatment. For patients with bladder urothelial carcinoma, miR-101-3p increases the sensitivity of cancerous cells to cisplatin by targeting and silencing of *EZH2*.[98] miR-101-3p also promotes the sensitivity of lung cancer cells to irradiation through suppression of the mTOR-signaling pathway.[99]

miR-144-3p

miR-144-3p is dysregulated in cancers and can have both tumor suppressive and oncogenic roles depending on its target genes.[100] miR-144-3p inhibits the proliferation and metastasis of lung cancer cells via targeting *HGF*.[101] In multiple myelomas, miR-144-3p by suppressing *MEF2A* expression, inhibits proliferation, angiogenesis, and migration.[102] miR-144-3p induces ferroptosis, thereby suppressing the development of osteosarcoma cells via regulation of *ZEB1* expression.[103] In a study conducted by Lou *et al*.,[104] it was indicated that miR-144-3p is a potential diagnostic biomarker in clear cell renal cell carcinoma. They revealed that miR-144-3p expression is significantly higher in the tissue and plasma of these patients compared to their normal counterparts. Furthermore, the plasma level of this miRNA is reduced after the surgery treatment.

miR-124-3p

miR-124-3p is associated with the initiation, progression, and survival of cancer.[105] In hepatocellular carcinoma, miR-124-3p suppresses cell proliferation and EMT through modulating *ARRDC1* expression.[106] It also inhibits the progression of these cancerous cells via targeting *CRKL* and thereby suppressing the ERK pathway and EMT.[107] miR-124-3p along with miR-194-5p influence ROR2/PI3K/Akt pathway by inhibition of *ROR2* expression in medulloblastoma. This regulation results in medulloblastoma suppression.[108] In glioblastoma multiforme, miR-124-3p induces apoptosis as well as inhibits cellular proliferation and migration by affecting RhoG expression.[109]

Signaling pathways related to the EZH2's ceRNA axes

Based on the included studies, Wnt/β-catenin is one of the major signaling pathways that *EZH2*-related axes contribute to regulate. Wnt/β-catenin signaling regulates various cell signaling pathways, including EGFR, Hippo/YAP, NF-κB, Notch, Sonic Hedgehog, and PI3K/Akt, which are integral to the molecular mechanisms underlying cancer development.[110] EZH2 can have regulatory effects on this signaling pathway in multiple ways. For example, EZH2 can contribute to the activation of the Wnt/β-catenin pathway by reducing the expression of antagonists, such as growth-suppressive SFRP5, NKD1, PRICKLE1, PPP2R2B, and AXIN2 in hepatocellular carcinoma.[111] In contrast, in a study by Ren *et al*.,[112] they demonstrated that SALL4 can activate the Wnt/β-catenin pathway in gastric cancer. SALL4 can be down-regulated by the H3K27me3 effect of EZH2. Thus, it is suspected that EZH2 can negatively regulate the Wnt/β-catenin pathway in gastric cancer. However, it has been demonstrated that in colorectal cancer, phosphorylated EZH2 at serine 21 by the active AKT, enhances its interaction and methylation of β-catenin at lysine 49, promoting β-catenin's chromatin binding; furthermore, EZH2-mediated trimethylation of β-catenin facilitates its association with TCF1 and RNA polymerase II, leading to significant amplification of genomic regions with β-catenin occupancy.[113] These studies show that the effects of EZH2 on the Wnt/β-catenin pathway are context-dependent and might be the result of complex interactions with various regulatory factors. This should be carefully considered in future therapeutic approaches aimed at inhibiting EZH2.

VEGFR2 signaling pathway is another pathway related to *EZH2*-related axes. This pathway contributes to physiological and pathological angiogenesis as well as different aspects of tumor microenvironment during cancer progression.[114] For instance, In gastric cancer, the VEGFR2 signaling pathway induces tumor progression leading to poor survival in patients.[115] In breast cancer, blocking VEGFR1 and VEGFR2 by suppression of various signaling pathways inhibits tumor progression and metastasis.[116] Studying these axes can help us to unveil the importance of these signaling pathways underlying the development of cancer.

Chemosensitivity-related role of the EZH2's ceRNA axes

Although targeted therapies for the treatment of cancer are widely studied and may be selected as the most effective ones in the future, chemotherapy remains a widely utilized method.[117] Unfortunately, many side effects have been reported for chemotherapy such as arrhythmia, neutropenia, cardiovascular disorders, and neuropathy which have been reviewed elsewhere.[117] Significant roles of *EZH2* axes in response to the commonly used chemotherapy drugs such as paclitaxel, 5-FU, and gemcitabine were revealed among the included studies. For example, in endometrial cancer cells, miR-101-3p reduces chemotherapy resistance to paclitaxel by inhibiting the expression of *EZH2*.[68] In gallbladder carcinoma, upregulation of *MYLK-AS1* sponges miR-217 causes increased expression of *EZH2* and resistance to gemcitabine.[61] Understanding the molecular mechanisms that regulate cancerous cells' responses to these drugs, can help us reduce the side effects and improve the efficiency of chemotherapy in cancer treatment.

Strengths, limitations, and suggestions for the future studies

The current scoping review study has several strengths. First, different databases were searched, systematically. Furthermore, we focused on experimentally validated ceRNA axes rather than those only predicted through prediction algorithms. Finally, we searched ceRNA axes in all types of cancers and provided a comprehensive view of *EZH2* as a ceRNA in cancer.

As for the limitation of the current scoping review, there are various constraints that need to be considered when interpreting the findings, including the absence of relevant articles in certain types of cancers like melanoma and kidney cancer, as well as the potential publication bias regarding studies with null or negative results.

This scoping review presents recommendations for future research. An imperative exists for the thorough exploration of common ceRNA axes, miRNAs, and ceRNAs, given their considerable significance in cancer biology. It is essential to delve deeper into their underlying mechanisms to fully exploit their therapeutic potential in the management of cancer. On the other hand, while *EZH2* has been identified as a crucial ceRNA in certain cancers, its role remains insufficiently studied in others, thus necessitating further investigation to gain insights into the molecular characteristics of *EZH2* in other cancer types.

Conclusions

Multiple lines of evidence have reported vital functions of *EZH2* in cancers. In this scoping review, we summarized the emerging insights on ceRNA axes including *EZH2* in cancer which have been experimentally validated. These axes contain competition of *EZH2* with other important ceRNAs for binding to the miRNAs, thereby influencing cancer progression. The current study provides a comprehensive perspective of these ceRNA axes in cancer focusing on *EZH2*. More studies are needed to further investigate these axes and assess their clinical utilities.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary File 1

Excluded Studies Based on the full Text Examination

Reason of exclusion	References
Abstract	[1]
A specific condition in cancer	[2-4]
Focusing on the EZH2 as a protein (epigenetic regulator)	[5-23]
Retracted	[24,25]
No ceRNA axis	[26,27]

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