Emerging Role of Enhancer RNAs in Cancer

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Contributor: Somayeh Panahi-Moghadam , Shokoufeh Hassani , Shirin Farivar , Faezeh Vakhshiteh

Enhancers are distal *cis*-acting elements that are commonly recognized to regulate gene expression via cooperation with promoters. Along with regulating gene expression, enhancers can be transcribed and generate a class of non-coding RNAs called enhancer RNAs (eRNAs).

enhancer RNA (eRNA) cancer prognosis diagnosis

1. Introduction

Enhancers are distal *cis*-acting elements that are known to regulate gene expression via spatial chromatin loops formation with target promoters [1][2]. They are short (50–1500 bp) regulatory elements of accessible DNA that assist in regulating the cell transcriptional machinery through increasing the transcription of target genes. Structurally, enhancers are open/accessible chromatin with low levels of DNA methylation, which are bound by RNA polymerase II (RNApol II), transcription factors (TFs), and cofactors, particularly transcription initiation factors, such as TBP, TFII, and P300/CBP. Enhancers are flanked by histones with permissive chromatin markers of histone H3 lysine 27 acetylation (H3K27ac) and histone H3 lysine 4 methylation (H3K4me) [3][4][5][6][7]. While promoters are *cis*-acting elements that recruit transcription in a position- and direction-dependent manner, enhancers perform freely of their position and orientation regarding their target gene; consequently, these elements can establish physical communication to interact distant promoters. Rather than contributing to gene expression, enhancers can be dynamically transcribed, forming a class of non-coding RNAs known as enhancer RNAs (eRNAs). It was initially anticipated that the product of enhancer transcription is the noisy outcome of the transcription procedure. Nevertheless, later studies suggest various roles for eRNA as a universal cellular mechanism involved in directing cell characteristics and function. In this research, researchers demonstrate recent understanding of eRNA structure along with function.

2. Biogenesis and Function of eRNA

Based on structure and transcription patterns, eRNAs (approximately from 0.1–9 Kb) [8] can be classified in two groups of short bidirectional, non-spliced, non-polyadenylated RNAs and long unidirectional, spliced, stable polyadenylated transcripts (**Figure 1**). Since eRNAs are mainly non-polyadenylated and unstable, they are predominantly localized in the nucleus and chromatin-enriched fractions [9][10][11][12]. Transcription of eRNAs generally occurs prior to mRNA expression from the target gene [13][14][15][16]. The tissue-specific transcription of enhancers has been shown in various diseases such as cancers. Enhancers typically contain specific DNA elements that are recognized by tissue-specific TFs. These factors often cooperate in their binding to enhancers

and frequently synergize to achieve the optimal activation of target genes [17]. Under extracellular stimuli and the activation of specific signaling pathways, TFs are recruited into the enhancer region, bind to particular DNA sequences, and stimulate the remodeling of nucleosome and histone modifications (regions enriched by H4K8ac, H3K27ac, and H3K4me are hallmarks of active enhancers) [18][19][20]. H3K27 and H4K8 are acetylated through CBP histone acetyltransferases, and p300 and chromatin is further opened in the enhancer region and, thus, RNApol II and BRD4 cofactor are recruited to the enhancer [20]. Integrator, a large complex associated with the carboxyl-terminal domain (CTD) of RNApol II, has an important role in transcriptional termination at the enhancers. The depletion of the integrator leads to the reduction in processed eRNAs and accumulation of primary eRNA transcripts [21].

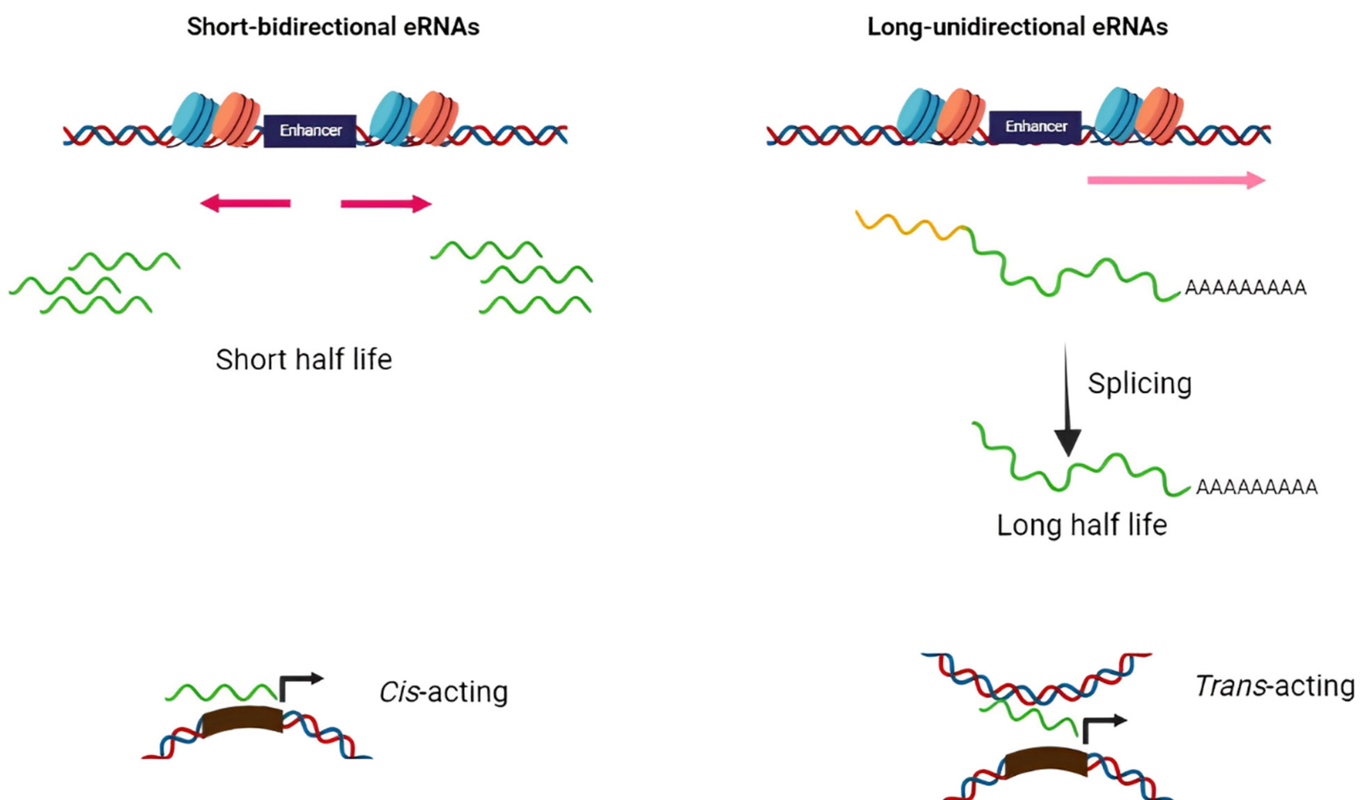

Figure 1. Schematic diagram of two distinct classes of eRNAs. The majority of eRNAs are short, bidirectional, non-polyadenylated, and unstable while others are long unidirectional, polyadenylated, and more stable. The former has *cis*-acting action while the latter perform as *trans*-acting elements.

Super-enhancers (SE) are described as a cluster of enhancers that have dense assemblies of RNApol II, TFs, and typical enhancer histone modifications (H4K8ac, H3K27ac, and H3K4me) that leads to a greater amount of super-enhancer RNA (seRNA) production (**Figure 2**) [22]. The difference between conventional enhancers and SEs is clearly displayed in the nature of the dependence of the transcription activity ensured by the regulatory element and the number of TFs and cofactors associated with it [23]. The transcription activity at an SE is typically higher than at a distinct enhancer. SEs have high potential to activate the transcription of their target genes and play significant roles in tissue-specific biological processes [24]. Most SE produce unidirectional polyadenylated seRNAs, which are more stable and have a longer half-life than non-polyadenylated eRNAs [25]. Production of

different isoforms by alternative splicing and *cis* and *trans* actions of seRNAs can orchestrate a precise pattern of gene expression [25][26]. As previously mentioned, eRNAs were initially considered as transcriptional noise of enhancers. Later, by using experimental methods, including global run-on sequencing (GRO-seq), Start-seq, and CRISPR/Cas9, several investigations have revealed that a subclass of eRNAs contribute to enhancer function, especially the regulation of gene expression [27][28][29]. As most eRNAs are unstable, their recognition is mainly proceeded via precision nuclear run-on sequencing (PRO-seq), GRO-seq, chromatin immunoprecipitation (ChIP-seq) [30][31][32], or cap analysis of gene expression (CAGE) sequencing [33] rather than the common RNA-seq. Using the CRISPR-Display method, eRNAs were demonstrated to bind to catalytically dead Cas9 (dCas9) for targeting a particular locus of a genome [34]. In another approach, single-molecule fluorescence in situ hybridization (smFISH) [35][36] and ChIRP-seq [37][38] were used as powerful methods for detection of eRNA loci in the genome. Overexpression and knockdown studies of eRNAs demonstrated that this group of non-coding RNAs have strong correlation with their target mRNAs [39]. This correlation is largely dependent on the proximity and correct interactions between the enhancer and promoter. Moreover, chromatin interaction studies revealed that enhancer–promoter looping structure induces higher expression of eRNAs in comparison with other enhancer regions [40][41]. Some studies suggested that eRNAs can act as a *cis* regulatory element and initiate or stabilize enhancer–promoter looping through association between TFs, mediators, cohesins, and RNApol II [42][43]. Moreover, eRNAs were shown to function in *trans* for modifying the chromatin structure and directing chromatin accessibility at protein-coding promoter regions [44]. The interaction of eRNAs with CBP and p300 histone acetyltransferases were shown to have a prominent impact on the modulation of H3K27 acetylation and methylation as eRNA knockdown led to decreased levels of H3K27ac and increased levels of H3K27me3 at target-promoter regions [45][46][47][48]. Upon interaction with enhancers, Polycomb repressive complex 1 and 2 (PRC1 and PRC2) have been shown to play regulatory roles in Polycomb-mediated gene transcription [49][50]. Although PRC1 and PRC2 have gene repression activities, in some cases it has been proposed that Polycomb chromatin domains can affect gene expression by forming chromatin topologies that support gene induction [51]. PRC2, for instance, composed of the EZH2 and SUZ12 subunits, which is responsible for establishing and maintaining histone H3K27 methylation during cell differentiation. The interaction of eRNAs and the EZH2 subunit of the PRC2 complex represses its methyltransferase activity and consequently leads to reduced H3K27me3 level and increased gene expression [1][39]. Direct interaction of eRNA with RNApol II, TFs, and general cofactors was shown to be required for initiation and elongation of transcription [14][52]. NELF and P-TEFb complexes are negative and positive elongation factors, respectively, which are released and recruited to RNApol II in the elongation phase. eRNA interacts with NELF and P-TEFb and further promotes the release of paused RNApol II and transition to active elongation by acting as decoys for these complexes [14][47].

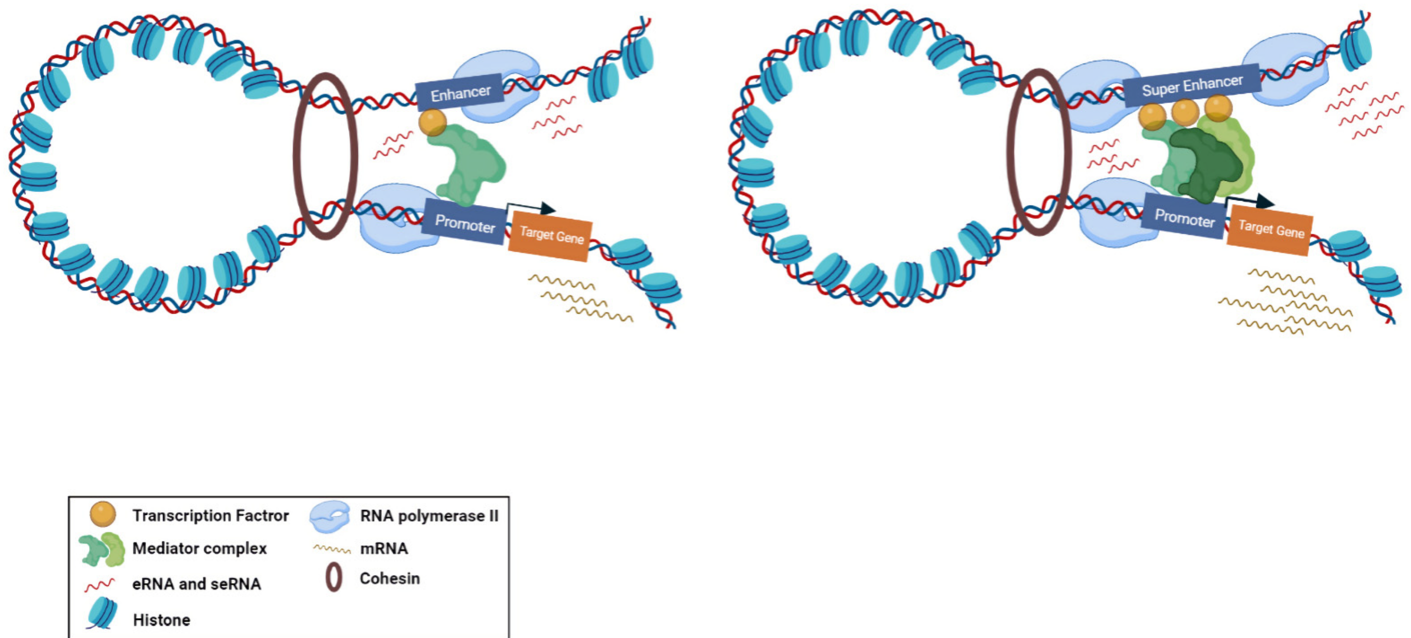

Figure 2. Biogenesis of typical eRNA and seRNA and their corresponding function. Active enhancers are bidirectionally transcribed to produce eRNAs and seRNAs. Super enhancers are augmented with higher amount of transcription factors, mediators, and RNApol II compared to enhancers. Therefore, the transcription activity at a super enhancer is typically higher than at a distinct enhancer. From the functional perspective, super enhancers have a greater potential to stimulate target gene transcription.

3. Functional Roles of eRNAs in Cancer

Given that enhancers are recognized to influence the maintenance of different types of cells, it is not unexpected that their malfunction has emerged as a powerful factor behind numerous types of malignancies. Translocation, duplication, insertion, deletion, or point mutation at enhancer regions, and especially transcription factor binding elements [53][54], are frequently observed in cancers [55][56]. One interesting possibility is that these types of mutations make a difference in eRNA expression that eventually drives cancer development. For instance, specific three-stranded nucleic acid organization of the DNA:RNA hybrid and the related non-template single-stranded DNA, known as R-loop, can be shaped at enhancer regions with exceeded eRNA expression levels. Particularly, R-loops are correlated with genomic instability and DNA injury, proposing an association in the initiation and progression of cancer [57]. Moreover, single-stranded DNA (ssDNA) in R-loops may be an off-target for the action of the activation-induced cytidine deaminase (AID) enzyme [58]. Intrinsically, this enzyme is responsible for initiating somatic hypermutation on ssDNA at immunoglobulin (Ig) loci and preferentially alters cytosine to uridine by deamination [59]. AID off-target positions correlate with extremely transcribed enhancers, which promotes genome instability and tumorigenesis [60].

Several studies uncover roles for individual eRNAs in tumorigenesis of many cancer types, including ovarian, breast, prostate, colorectal, and lung adenocarcinomas, showing that their ectopic expression is strongly linked to enhancer dysfunction [61][62][63]. In tumor cells, eRNAs regulate target genes by both *cis*- and *trans*-regulatory

activities and, hence, play a crucial role in a variety of important signaling cascades [37][64]. For instance, in colorectal cancer, it has been stated that the presence of Colon Cancer-associated Transcript 1 (*CCAT1*) eRNA was highly correlated with *c-Myc* overexpression [63]. MYC is accepted as a crucial regulator of cell proliferation and deregulation of this proto-oncogene associated with the development of many cancer types [65]. In a separate study, the knockdown of oncogenic *CCAT1* eRNA in squamous cell carcinomas suppressed the SE-associated genes expression required for the propagation and migration of cancer cells [66]. *Net1e* eRNA, which is located downstream of *NET1* proto-oncogene, is a breast cancer specific eRNA and its knockdown by LNA (locked nucleic acids) antisense RNA was shown to strongly reduce cell proliferation in the MCF7 breast cancer cell line [67]. *ARIEL* in leukemia [68], *HPSE* in different cancer types [69], and *P2RY2* in bladder cancer [70] are other examples of eRNAs targeted by knockdown approaches that may serve as new therapeutic targets for cancer treatment. In breast cancer, 17b-oestradiol (E2)-bound estrogen receptor α (ER- α) could raise the expression of enhancers close to E2-induced coding genes. These differentially expressed eRNAs were demonstrated to elevate the strength of ER-α activated looping of the enhancer–promoter by direct interaction with cohesin. Targeted knockdown of eRNA from corresponding enhancers attenuated cohesion attachment to the ER-α enhancer and consequently reduced enhancer–promoter looping [37]. Wang et al. indicated that *WAKMAR2* can be a new candidate eRNA in modulating the microenvironment of invasive breast cancer cells and its downregulation might influence the immune-related genes expression in favor of tumor progression. eRNAs are implicated in various cancer signaling pathways by potentially modifying their target genes, such as immune checkpoints and clinically actionable genes [71]. By successful delineation of basic eRNA mechanisms, including RNA–RNA, RNA–DNA, and RNA–protein interactions, these eRNAs can be considered as new therapeutic targets and will pave the way for eRNA-based cancer diagnostic and therapeutic approaches [72].

4. Data Resources to Explore eRNA in Cancer

As mentioned before, most eRNAs are unstable and non-polyadenylated with low abundance [2]. Thus, they are not easily detectable in routine RNA-sequencing methods, which are based on polyadenylated RNAs. Alternative techniques rely on measuring promising transcripts, such as global run-on sequencing (GRO-Seq) [7], precision run-on nuclear sequencing (PRO-Seq) [73], and cap analysis gene expression (CAGE) [33] to certify that no eRNA is missed. These methodologies are instrumental for the detection of formerly undiscovered eRNAs and active enhancers. For example, the CAGE technique was applied by the FANTOM consortium for profiling the large amounts of transcriptomes of different types of cells, from which 43,011 enhancer elements were revealed to be transcribed to eRNAs [74]. Since the number of detected eRNA transcripts are increased exponentially, comprehensive databases and computational pipelines are highly required to illustrate and consolidate the eRNA expression profiles in normal and cancerous samples. Currently, two types of eRNA data resources were generated. While datasets such as Ensemble (https://www.ensembl.org, accessed on 1 January 2002), ENCODE (https://www.encodeproject.org, accessed on 5 September 2012), FANTOM (http://fantom.gsc.riken.jp/index.html, accessed on 26 March 2014), and the Roadmap Epigenomics Project (http://www.roadmapepigenomics.org, accessed on 13 October 2010) include numerous annotated regulatory elements containing enhancers, other datasets such as The Cancer Genome Atlas (TCGA) (https://portal.gdc.cancer.gov, accessed on 26 September

2013) and Genotype-Tissue Expression (GTEx) (https://gtexportal.org/home, accessed on 29 May 2013) have multi-omic data including RNA-seq and survival data from patient samples and the Cancer Cell Line Encyclopedia (CCLE) (https://portals.broadinstitute.org/ccle/about, accessed on 8 May 2019) that apply genomics and sequencing data in ~1000 cancer cell lines for pan-cancer and tumor-specific analysis of eRNAs. These omics data can be downloaded via Xena platform. UCSC Xena cancer browser (https://xena.ucsc.edu, accessed on 22 May 2020) allows biologists to correlate between genomic and/or phenotypic variables with visualizations and analyses. To facilitate research on eRNA, many enhancer pipelines such as SEdb, HACER, RAEdb, HEDD, DiseaseEnhancer, TiED, SEA, and DENdb [75][76][77][78][79][80][81] have been generated. GeneHancer [82] is one of the most common pipelines, which integrates the enhancer annotations from four altered enhancer resources, including Ensembl, FANTOM, VISTA, and ENCODE [10][83][84][85]. Human enhancer RNA Atlas (HeRA) is another data portal that accommodates data from the ENCODE, FANTOM, and GTEx that presents an expression profile and regulatory network of eRNAs in normal human samples [86]. On the contrary, the eRic (eRNA in cancer) database (https://hanlab.uth.edu/eRic, accessed on 8 October 2019) can predict eRNA functions in cancer via collecting eRNA expression profiles, clinical features, target genes, and drug response [67]. By using RNA-seq data from TCGA and GTEx and using CAGE-defined enhancers annotated by FANTOM, Chen et al. developed The Cancer eRNA Atlas (TCeA) data portal, which provides a high-resolution map of eRNA loci. In this map, SE showed discrete loci with sharp eRNA expression peaks. The annotation of SE activities can be used for a broad range of biomedical investigations, such as immunotherapy response and enhanced explanations of cancer phenotypes by resolving intratumoral heterogeneity [87].

5. eRNAs as Prognostic and Diagnostic Biomarker in Cancer

Even though remarkable progress has been made in the field of cancer research, there are still a number of issues that need to be improved, such as delayed diagnosis and poor prognosis. Non-coding RNAs have gained wide consideration in recent years because of their specific expression and functional diversity in a variety of cancers [88]. They play critical roles in various biological pathways and hold great promise in cancer diagnosis and therapy. Clinical trials have also initiated investigating non-coding RNA-based medications as adjuncts to traditional chemotherapeutics [89]. Regarding eRNAs, an increasing number of studies have reported that these non-coding RNAs have amenable prognostic and diagnostic values due to their tumor-specific expression patterns [90][91]. In this section, researchers will review the present findings on eRNAs and their potential prognostic and diagnostic values in cancers. **Table 1** summarizes eRNAs and seRNAs as diagnostic and/or prognostic biomarkers in different cancers.

5.1. Head and Neck Squamous Cell Carcinoma

Head and neck cancer is considered one of the most common malignancies in the world, with ~870,000 new cases and ~440,000 deaths in 2020 [92] in which the most common histological subtype of head and neck cancer is head and neck squamous cell carcinoma (HNSCC). Feng et al. showed the role of certified eRNAs as an innovative biomarker in HNSCC. The group indicated the role of eRNA in 500 HNSCC cases by means of an eRNA expression matrix annotated from the TCGA database. Functional enrichment analyses were carried out using

Gene Ontology and the Kyoto Encyclopedia of Genes and Genomes (KEGG). Global expression of eRNAs was increased in tumor tissues compared to normal cases; out 369 differentially expressed eRNAs, 330 were upregulated and 39 were downregulated. According to the eRNA expression matrix and survival information, 5 eRNAs were identified with a correlation with the prognosis value in HNSCC cases, which represent an innovative finding in the molecular mechanisms of HNSCC [93]. Gu et al. demonstrated the role of prognosis-related *AP001056.1* eRNA in HNSCC. In this research, an incorporated data analysis methodology was developed to recognize major eRNAs in HNSCC. To discover the RNA levels and clinical data from the TCGA project, the interactive web servers, TANRIC (the Atlas of Noncoding RNAs in Cancer) and cBioPortal were applied. From the obtained 5 significant eRNA candidates, *AP001056.1* was the most significant survival-associated eRNA in HNSCC with immune-related *ICOSLG* as its target gene. While strong associations between *AP001056.1* and *ICOSLG* expression were demonstrated in a number of cancers, the most significant effect on overall survival (OS) was observed in HNSCC [94].

Table 1. eRNAs and seRNAs as diagnostic and/or prognostic biomarkers.

Cancer Type	eRNAs/seRNAs	Deregulation in Cancer	Target Gene/Pathways	Clinical Sample/Number of TCGA Cases	Sample/Model Information	Application	Ref.
HNSCC	*ENSR00000188847* *ENSR00000250663* *ENSR00000313345* *ENSR00000317887* *ENSR00000336429*	Up	-	500 TCGA HNSCC samples	Patient sample	Prognosis	[93]
	AP001056.1	Down	*ICOSLG*	426 TCGA HNSCC samples	Patient sample	Prognosis	[94]
LUAD	*TBX5-AS1*	Down	*TBX5*	10 LUAD samples	Patient sample	Prognosis/Diagnosis	[95]
	188 functional eRNAs	129 Up/59 Down	Cell cycle and immune system-related pathways	80 LUAD samples/481 TCGA LUAD samples	Patient sample	Prognosis	[62]
CRC	*CCAT1* *CCAT2*	Up	*c-Myc*	150 CRC samples	Patient sample	Prognosis	[96]
	RP11-569A11.1	Down	*IFIT2*	39 CRC samples	Patient sample/cell line	Diagnosis	[97]
	PVT1	Down (epigenetic regulation mediated	*Myc*	698 TCGA CRC dataset	Patient sample	Prognosis	[98]

Cancer Type	eRNAs/seRNAs	Deregulation in Cancer	Target Gene/Pathways	Clinical Sample/Number of TCGA Cases	Sample/Model Information	Application	Ref.
		through aberrant methylation in CRC)					
GC	*EMX2OS*	Up	*EMX2*	375 TCGA GC samples	Patient sample	Prognosis	[99]
	FALEC	Up	*ECM1*	60 GC samples	Patient sample/cell line	Prognosis	[100]
	HPSE	Up	hnRNPU/p300/EGR1/HPSE axis	90 GC samples	Patient sample/cell line	Prognosis	[69]
	CDK6-AS1	UP (in patients below 60 years)	*CDK6*	407 TCGA GC samples	Patient sample	Prognosis	[101]
	WAKMAR2	Down	*TNFAIP3*	371 TCGA GC samples	Patient sample	Prognosis	[102]
Breast Cancer	*SLIT2*	Down	MAPK/c-Fos signaling pathway	1211 TCGA breast cancer and 12 bone metastases samples	Patient sample/cell line	Prognosis/Bone metastasis	[103]
	WAKMAR2	Down	*IL27RA* *RAC2* *FABP7* *IGLV1-51* *IGHA1* *IGHD*	1104 TCGA invasive breast cancer samples	Patient sample	Prognosis	[71]
HCC	*DCP1A*	Up	*PRKCD*	1580 TCGA samples together with 1791 target genes	Patient sample	Prognosis	[104]
	SPRY4-AS1	Up	*SPRY4*	124 TCGA samples	Patient sample	Prognosis	[105]
	AL445524.1	Up	*CD4-CLTA4* related genes	371 TCGA HCC tumor samples and	Patient sample	Prognosis	[106]

Cancer Type	eRNAs/seRNAs	Deregulation in Cancer	Target Gene/Pathways	Clinical Sample/Number of TCGA Cases	Sample/Model Information	Application	Ref.
				54 adjacent normal specimens			
Brain Cancer	*AC003092.1*	Up	*TFPI2*	161 TCGA GBM patients	Patient sample	Prognosis	[107]
	CYP1B1-AS1	Up	*CYP1B1*	10,000 TCGA cancer sufferers covering 33 diverse cancer types	Patient sample	Prognosis	[108]
	LINC00844 *MRPS31P5* *CRNDE*	Down Down Up	*PHYHIPL* *ATP7B and NEK3* *IRX5*	693 TCGA cohorts and 325 cohort in Chinese Glioma Genome Atlas (CGGA)/40 glioma samples	Patient sample	Prognosis/Diagnosis	[109]
	ENSR00000210436 *ENSR00000249159* *ENSR00000195717* *ENSR00000195824* *ENSR00000094845* *ENSR00000283518* *ENSR00000094854* *ENSR00000031043* *ENSR00000031044* *ENSR00000260651* *ENSR00000146066* *ENSR00000301859* *ENSR00000213692* *ENSR00000326719* *ENSR00000134110* *ENSR00000134111* *ENSR00000134112* *ENSR00000013533* *ENSR00000013524* *ENSR00000082228* *ENSR00000048324* *ENSR00000082228* *ENSR00000048324*	Association with immune-related dysfunctions in the TME	*ADCYAP1R1* *FGF13* *PSMB8* *MAPT* *BMPR1A* *DDX17* *ELN* *BMP2* *SEMA6C* *PDIA2* *PTPN6* *SSTR5* *CD4*	TCGA and CGGA samples	Patient sample/cell line	prognosis	[110]
Prostate Cancer	*K-KLK3*	Up	*KLK3*	45 patient samples	Patient sample/cell line	Diagnosis	[111]

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Cancer Type	eRNAs/seRNAs	Deregulation in Cancer	Target Gene/Pathways	Clinical Sample/Number of TCGA Cases	Sample/Model Information	Application	Ref.
	PARGP1	Up	AGAP4	TCGA database	Patient sample	Prognosis	[112]
Bladder Cancer	*MARC1*	Up	–	37 tissues	Patient sample/cell line	Diagnosis	[113]
	EMP1	UP	APOLD1 and GPRC5A/ KRAS signaling, etc.	411 TCGA bladder urothelial carcinoma samples	Patient sample	Prognosis/Bone metastasis prediction	[114]
ESCA	*AC007255.1*	Up	*PRR15*	162 ESCA TANRIC database/12 pairs of ESCA tissues and normal tissues	Patient sample	Prognosis	[115]
Colon Adenocarcinoma	*LINC02257*	Up	*DUSP10*	521 TCGA samples	Patient sample	Prognosis	[116]
Ovarian Cancer	*FOXP4-AS1*	Down	*FOXP4*	379 TCGA samples/42 patient samples	Patient sample	Prognosis	[117]
Thyroid Cancer	*NBDY* *MEG3* *AP002358.1* *AC141930.1*	Relation to the prognosis of thyroid cancer patients	-	510 TCGA samples	Patient sample	Prognosis/Diagnosis	[90]
PAAD	*LINC00242*	Down	*PHF10*	177 PAAD data set from UCSC	Patient sample/cell line	Prognosis	[91]

Abbreviations: HNSCC, head and neck squamous cell carcinoma; LUAD, lung adenocarcinoma; CRC, colorectal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; ESCA, esophageal cancer; PAAD, pancreatic adenocarcinoma.

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