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REVIEW ARTICLE

lncRNA cytoskeleton regulator RNA (CYTOR): Diverse functions in metabolism, inflammation and tumorigenesis, and potential applications in precision oncology

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Abstract Long non-coding RNAs (lncRNAs) are a novel class of non-coding RNA (ncRNA), that have been studied extensively in the field of tumor research in recent years. In the case of tumor-associated lncRNAs, lncRNA cytoskeleton regulator RNA (*CYTOR*) displays extensive functions in tumorigenesis, including invasion, metastasis, malignant proliferation, glycolysis, and inflammatory response. Moreover, the dysregulation of *CYTOR* is closely related to clinicopathological characteristics, such as tumor stage, lymph node metastasis and infiltration, and

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Tumorigenesis

poor prognosis of tumor patients. In this review, we provide a novel strategy to summarize the biological functions and clinical value of *CYTOR* in tumors through an overview of the literature combined with gene set enrichment analysis. A deeper understanding of the role of *CYTOR* in tumorigenesis may provide new diagnostic, prognostic and therapeutic markers for human tumors.

Introduction

With the completion of the Human Genome Project and the arrival of the post-genome era, there is a new understanding of the status of non-coding sequences in the genome. More than 80% of these sequences do not contribute to protein-coding and were considered "junk DNAs",[1–3] which have now become "hot stars" in the areas of life science and technology. Numerous studies have shown that these "junk DNAs" can generate many non-coding RNAs (ncRNAs), most of which are long noncoding RNAs (lncRNAs) that play an important role in the biological activity of humans.[4,5] lncRNAs are a subset of RNAs first found in the eukaryotic cells. They are located in the nucleus or cytoplasm and have a transcription length of 200—100,000 nt without a complete functional open reading frame (ORF), and rarely encode a functional short peptide.[6–8] According to GENCODE analysis (www.gencodegenes.org) by the Ensembl Human Genome Browser (GRCh38, updated version, January 25, 2017), 27,908 transcripts generated by 15,778 genes were defined as lncRNAs. However, the lncRNA disease database (http://www.cuilab.cn/lncrnadisease) showed that only 2947 lncRNAs were related to disease. There are only a few hundred lncRNAs that have been identified as having biological functions because of limited research tools for analyzing lncRNA function and the cell type in which they are active. Therefore, lncRNAs remain a "gold mine" in the field of biological sciences, which researchers urgently need to excavate.

lncRNAs are widely found in prokaryotes and eukaryotes. As organisms increase in complexity, the proportion of lncRNAs in the genome increases accordingly, suggesting that lncRNAs play a pivotal role in biological evolution. In eukaryotes, lncRNAs are widely involved in the regulation of life activities in the form of tissue-specific expression, affecting the progression of disease.[9,10] lncRNAs perform multi-spatial, multi-stage, and specific regulation of important genes at epigenetic, transcriptional and post-transcriptional levels, as well as translation and protein modification in the form of initially transcribed RNA or spliced RNA.[11,12] They play an important role in basic physiological processes, including development, tissue differentiation, reproduction, and immunity.[13,14] Therefore, their dysfunction or abnormal expression is often associated with various human diseases, including tumors. Studies have shown that lncRNAs are closely related to the occurrence and development of tumors and participate in processes including malignant proliferation,[15] energy metabolism,[16] angiogenesis,[17] invasion and metastasis,[18,19] inflammatory response,[20] and immune escape.[21] Cytoskeleton regulator RNA (*CYTOR*) is a tumor-associated lncRNA molecule discovered in recent years,[22] which has been reported to be highly expressed in a variety of tumors.[23–54] Meanwhile, *CYTOR* also participates in the regulation of tumor invasion, metastasis, malignant proliferation, and inflammatory response via epigenetic modification (lncRNA-DNA), competing endogenous RNA (ceRNA) (lncRNA-miRNA), and lncRNA-protein interaction. Recently, a novel bioinformatic analysis software named Gene Set Enrichment Analysis (GSEA) (http://software.broadinstitute.org/gsea/index.jsp) was used to analyze whether a priori defined set of genes showed statistically significant, concordant differences between two biological phenotypes.[55] In this review, we provide a novel strategy to summarize the biological functions and clinical value of *CYTOR* in tumors via the overview of literature combined with GSEA analysis, thereby providing a comprehensive theoretical basis and evidence for *CYTOR* as a diagnostic marker and therapeutic target for tumors.

Biological characteristics and regulation of *CYTOR*

Biological characteristics of CYTOR

lncRNAs can be divided into five categories including sense lncRNAs, antisense lncRNAs, bidirectional lncRNAs, intragenic lncRNAs, and intergenic lncRNAs according to the relative locations of protein-encoding genes in the genome.[56] Based on lncRNA nomenclature,[57] the cytoskeleton regulator RNA (CYTOR) was named as long intergenic non-protein coding RNA 152 (LINC00152). *CYTOR* was homologous with MIR4435-2HG,[58] and was a large intergenic non-coding RNA (lincRNA) with a length of 852 bp, located on chromosome 2p11.2 (87455455—87521518) (Fig. 1A). Its nearest protein-coding gene, plasminogen-like B2 (PLGLB2), was more than 100 kb. The Human Genome (hg38) in the Genome Browser of USCS (http://www.genomaize.org/) annotates *CYTOR* with 14 transcripts, three of which can be transcribed into mature mRNAs (RefSeq: NR_024204, NR_024205, and NR_024206). According to the position and gene information on *CYTOR* (ID No. ENSG00000222041) from the Ensembl of USCS analysis of the genomic phylogenetic tree, the *CYTOR* gene sequence is well conserved only in human and macaque genomes, while that in other mammals (e.g., mice, dogs, and sheep) is not complete. The National Center for Biotechnology Information (NCBI) also does not

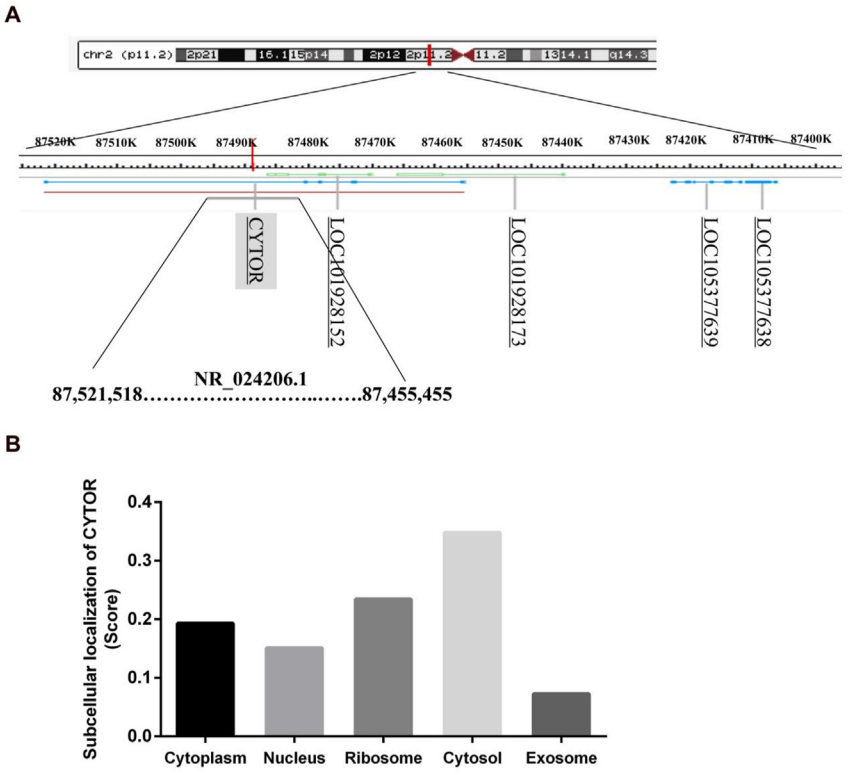

Figure 1 Biological characteristics of *CYTOR*. **(A)** Representative location of *CYTOR* on chromosome 2p11.2 (87455455—87521518). **(B)** The subcellular localization of CYTOR was predicted by lncLocator.

include the corresponding genetic information on human *CYTOR* gene sequences and other species. In addition, *CYTOR* belongs to a class of lncRNAs with short half-life. The half-life of *CYTOR* in neural stem cells (NSCs) is 2.1 h, which affects the expression of surrounding genes.[59] *CYTOR* has the characteristics of most disease-associated lncRNAs and can be stably present in the form of mRNA in tissues, cells, serum, and exosomes.[41,60] *CYTOR* is closely related to physiological processes such as cell differentiation,[59] stress response,[61] and cell stress.[62] For example, Tani et al found that *CYTOR* was highly expressed in NSCs that were differentiated from human-induced pluripotent stem cells (hiPSCs).[59] Moreover, Tani et aldemonstrated that the expression level of *CYTOR* was responded to the chemical stresses (hydrogen peroxide, cycloheximide, cadmium, or arsenic) in hiPSCs.[61] Thus, it results in a series of diseases, including gastritis,[63] vascular disease,[64] tuberculosis,[65] oral diseases,[66] tumors,[67] and other diseases.

lncRNAs exert biological functions mainly in the cells. Therefore, it is helpful to understand and detect the molecular mechanism of the regulatory machinery of *CYTOR* by analyzing and speculating its location and function at the cellular level. Unlike mRNAs, lncRNAs are widely distributed in the nucleus and cytoplasm,[4] and the subcellular localization of lncRNAs is often closely related to their biological functions.[68,69] Nötzold et al detected the cellular localization of multiple *CYTOR* isoforms in HeLa cells and found that more than 70% of *CYTOR* transcripts were detected in the cytoplasm.[22] The distribution of *CYTOR* in cells was predicted by the lncLocator website of lncRNA localization analysis (www.csbio.sjtu.edu.cn/bioinf/lncLocator) (Fig. 1B).[70] *CYTOR* is distributed in the form of mRNA uniformly in various subcellular locations, including the cytoplasm, nucleus, ribosome, cytosol, and exosomes. Furthermore, *CYTOR* is mainly distributed in the cytoplasm, especially in the cytosol. Interestingly, the cytoskeleton in the cytosol is an important subcellular structure, which is closely related to cell movement and morphological changes, and provides a favorable framework structure for enzyme reactions in the cytoplasm. In recent years, researchers have found that *CYTOR* is closely related to cytoskeleton changes, and renamed it based on LINC00152; this is consistent with the fact that *CYTOR* is mainly located in cytosol. Notably, the distribution ratio of *CYTOR* from the nucleus to cytoplasm changed with different stimulating factors. Nishizawa et al showed that hypoxia can induce an increase in cytoplasmic localization of *CYTOR* in colorectal cancer (CRC) cells.[33] Moreover, our research group demonstrated that cancer cell density can induce an increase in cytoplasmic expression of *CYTOR* in CRC cells.[71] Therefore, when the cells are under different stress conditions, the subcellular localization of *CYTOR* also changes, thereby regulating specific biological functions of cells.

Regulatory mechanism of CYTOR

lncRNAs function differently depending on their subcellular location. When lncRNAs are located in the nucleus, they often play a role in regulating epigenetic modification,

regulating the expression of downstream target genes through histone modification, and by binding the gene enhancer region.[72] When lncRNAs nucleate to the cytoplasm, the expression of the corresponding miRNA target genes and their downstream genes are mainly regulated by the action of ceRNA at the post-transcriptional level or blocking the phosphorylation sites of certain proteins, thereby affecting downstream molecules or signaling pathways.[73] However, when lncRNAs are secreted extracellularly in the form of exosomes, they can be transported to target cells in a "cell-to-cell" way, thereby exerting their biological function.[74] According to the different functions of lncRNAs, the molecular mechanisms involved can be divided into four categories: 1) Signal archetype: a molecular signal or indicator for transcriptional activity; 2) Scaffold archetype: provides a platform for related molecular components, such as functional proteins or RNAs; 3) Guide archetype: directs the ribonucleoprotein complex to specific targets; 4) Decoy archetype: binds to other regulatory RNAs or proteins and isolates them.[75] Therefore, clarifying the subcellular localization of lncRNAs is an important step in the analysis and study of their biological functions.

The regulation of *CYTOR* can occur in different ways, including epigenetic modifications, ceRNAs, and protein interactions, because of its complex subcellular distribution. Epigenetic modification refers to the heritable change in gene expression caused by a mechanism that does not affect the DNA sequence and is usually related to the regulation of acetylation and methylation of transcription factors. *CYTOR* is not only regulated by the transcription factors SP1[48] and β-catenin/TCF4,[30] but also by the epigenetic modification of these transcription factors that can affect the expression of *CYTOR*. *CYTOR* also transcriptionally regulates a series of downstream genes via binding with other transcription factors, cyclin-dependent kinase inhibitor 1A (CDKN1A, also named p21) and cyclin dependent kinase inhibitor 2B (CDKN2B, also named p15),[76] cell cyclin dependent kinase inhibitor 2A (CDKN2A, also named p16),[44] IL-24,[34] and E-cadherin,[76] in the nucleus by recruiting enhancer of zeste homolog 2 (EZH2), thereby affecting their transcription and expression levels.

The ceRNA mechanism involves lncRNAs competitively binding to miRNA by ceRNA, thereby reversing the protein expression level of miRNA target genes and that of their downstream molecules.[77,78] Recent studies have shown that the ceRNA mechanism of lncRNAs is involved in the development of various tumors, such as breast cancer,[79] CRC,[80] gastric cancer (GC),[81,82] hepatocellular carcinoma (HCC),[83,84] non-small cell lung cancer (NSCLC),[85,86] and kidney cancer.[87] Since *CYTOR* is mainly located in the cytoplasm, the important regulatory mechanism of *CYTOR* is the interaction of ceRNA with miRNAs. *CYTOR* can also interact with a range of miRNAs, such as miR-139-5p,[28,32] miR-103a-3p,[35] miR-205,[44] miR-4775,[45] miR-138,[48] miR-125b,[54] miR-4767,[64] miR-193a-3p,[31,88] miR-107,[89] miR-612,[90] miR-376c-3p,[91] miR-632 and miR-185-3p,[71] regulating a series of tumor processes.

Aside from regulating epigenetic modification-related proteins, lncRNAs can regulate transcriptional, post-transcriptional, and translational levels of certain proteins through various means of interaction, such as through guide, decoy, or scaffold molecules, thus affecting the expression and activation or silencing of downstream signaling pathways.[92,93] Many studies have shown that *CYTOR* may participate in the regulation of multiple signaling pathways, such as the Wnt/β-catenin,[27,30] Notch,[32] hypoxia-inducible factor-1 (HIF-1) signaling pathway,[33] mTOR,[37] MAPK,[45] PI3K/AKT,[45,48] and epidermal growth factor receptor (EGFR)[64,94] in tumorigenesis. However, few studies have demonstrated the specific molecular mechanisms of the interaction between cytoplasmic *CYTOR* and pathway proteins. Yue et al reported that *CYTOR* can block β-catenin phosphorylation induced by casein kinase 1 (CK1) by binding to cytoplasmic β-catenin, thereby inducing β-catenin expression in the nucleus to promote invasion and metastasis of CRC.[30] Shan et al also found that *CYTOR* binds to β-catenin and methyltransferase SMYD2, promoting the methylation of β-catenin to maintain its stability, consequently activating the Wnt/β-catenin signaling pathway in GC.[27] In addition, Zhou et al showed that *CYTOR* directly binds to EGFR in GC cells, activating the PI3K/AKT signaling pathway and accelerating cell cycle progression, thereby promoting the proliferation of GC cells.[25] Currently, lncRNA-binding proteins are screened mainly by RNA pull-down and CHIRP-seq techniques. However, these have persistent high false-positive rates. Therefore, further studies on targeted drugs that improve the success rate of screening lncRNA-binding proteins are immediately warranted.

Role of *CYTOR* in the development and progression of tumors

Hanahan and Weinberg published "Hallmarks of cancer: the next generation" in the journal *Cell*,[95] which summarized and clarified 10 characteristics of tumors. lncRNAs are closely associated with the occurrence and development of tumors, and are involved in processes, such as malignant proliferation, angiogenesis, abnormal energy metabolism, invasion, metastasis, radiotherapy and chemotherapy, and immune escape.[96,97] *CYTOR* plays a pivotal role in the occurrence and development of tumors (Fig. 2); however, the comprehensive function of *CYTOR* remains unknown. In this study,[49] the GSE77491 of GEO database was used to identify gene set differences between the two groups (si-*CYTOR* group *vs.* si-*Ctrl* group) in a cancer cell line (Fig. 3). We further revealed the biological role of *CYTOR* in tumorigenesis, including malignant proliferation, invasion, metastasis, glycolysis, and inflammatory response.

CYTOR and malignant proliferation of tumor cells

The malignant proliferation of tumors is the most common malignant process in tumor development. Tumor cells usually exhibit contact inhibition and proliferation[98,99]; thus, tumors are also classified as a type of progressive hyperplastic disease.[100] Although surgery of a malignant proliferation of tumor is considered effective to begin cancer treatment, the current results regarding its efficacy remain unsatisfactory. Finding key, effective, and broad-spectrum targets for malignant tumor proliferation remain a challenge for scientists.[101,102] In recent years, lncRNAs, including *CYTOR*, have attracted wide attention as targets

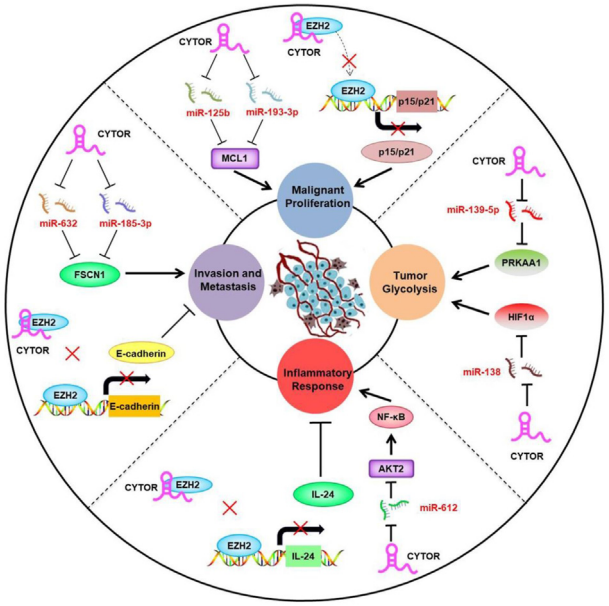

Figure 2 lncRNA *CYTOR* in cancer phenotypes. *CYTOR* contributes to a series of hallmarks of cancer. Selected examples of *CYTOR* and their molecular partners or genomic targets are shown for malignant proliferation, invasion and metastasis, tumor glycolysis, and inflammatory response.

for tumor proliferation.[103] Several studies have reported that *CYTOR* can participate in multiple gene and signaling pathways related to tumor cell proliferation, thus promoting tumor progression. In the study of GC, Huang et al reported that *CYTOR* competitively binds to miR-193a-3p in GC cells, thereby promoting the expression of its target gene *MCL1* and the proliferation of GC cells.[29] In addition, Zhao et al found that knocking out *CYTOR* in GC cells can block the cell cycle of those cells in the G1 phase.[24] Furthermore, Chen et al showed that *CYTOR* inhibits the expression of the cyclin-dependent kinase inhibitor p15/p21 in the progression from G1 to S phase by recruiting EZH2, thereby promoting the proliferation of GC cells.[76] Zhang et al demonstrated that knockdown of *CYTOR* in lung cancer cells significantly reduced the protein expression of PI3K and AKT and increased p21 expression.[94] Cai et al confirmed that *CYTOR* activates the PI3K/AKT signaling pathway *in vitro*, ultimately accelerating the cell cycle process and promoting the malignant proliferation of gallbladder cancer cells.[48] In addition, Chen et al showed that *CYTOR* acts as a ceRNA of miR-125b in ovarian cancer to regulate the expression of MCL-1 and MCL-1-mediated mitochondrial apoptosis pathways.[54] Wu et al reported that *CYTOR* promotes tumor growth of triple-negative breast cancer and inhibits apoptosis by inducing the activation of BRCA1/PTEN by promoting the expression of DNA methyltransferases.[50]

CYTOR, tumor invasion, and metastasis

Tumor invasion and metastasis refer to the process of malignant tumor cells disengaging from the primary tumor site and transferring to secondary tissues or organs via the

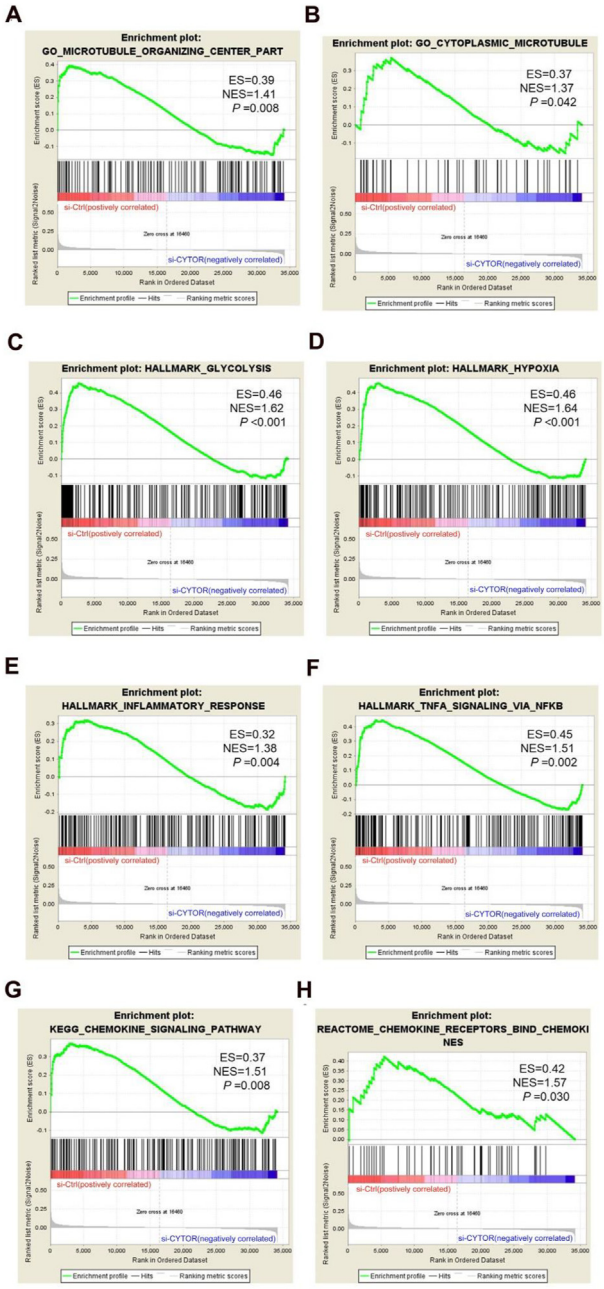

Figure 3 Correlation analysis between *CYTOR* and cytoskeleton-associated gene sets. Gene sets involved with the microtubule-organizing center **(A)**, cytoplasmic microtubule **(B)**, glycolysis **(C)**, hypoxia **(D)**, inflammatory response **(E)**, TNFA signaling **(F)**, chemokine signaling **(G)**, and chemokine binding to receptors **(H)** as demonstrated by GSEA (analyzing si-*CYTOR vs.* si-*Ctrl* MDA-MB-231 cells). ES, enrichment score; NES, normalized enrichment score.

circulatory system, where they colonize and grow to form secondary tumors. Tumor invasion and metastasis is a complex cascade of dynamic processes, involving epithelial—mesenchymal transition (EMT), hypoxia, angiogenesis, tumor microenvironment, and other mechanisms, as well as changes in cells, including cell adhesion, cytoskeletal reconstruction, extracellular matrix degradation,

and formation of cell components and pseudopods.[104] Tumor invasion and metastasis is a major problem in the clinical treatment of tumors, affecting the prognosis and survival of patients, and is a major cause of tumor-related death. According to epidemiological statistics, 90% of deaths in cancer patients are due to tumor metastasis, but only approximately 0.02% of tumor cells form distant metastases.[105] Therefore, the study of the mechanism of tumor cell invasion and metastasis for better treatment and prevention of tumors is of great significance. lncRNAs are a class of molecules that play an important role in tumor invasion and metastasis,[106] and *CYTOR* is naturally involved as a tumor-associated lncRNA molecule. Deng et al showed that the key protein X of hepatitis B virus (HBV) infection induces the expression of *CYTOR*, while the high expression of *CYTOR* inhibits the expression of the epithelial cell marker E-cadherin by binding to EZH2 and promoting the EMT process in liver cancer cells.[39]

The invasion and metastasis of tumor cells is closely related to the spatial and temporal coordination of the cytoskeleton.[107,108] Dynamic reconstruction of the cytoskeleton provides plate-like pseudopods, filopodia, invasive pseudopods, and other special structures for cell invasion,[109,110] which enable tumor cells to enter the blood circulation. There is a certain relationship between *CYTOR* and the skeleton reconstruction of tumor cells. Interestingly, our research group identified that *CYTOR* is highly expressed in CRC and acts as a competing endogenous RNA sponging with miR-632 and miR-185-3p to regulate the expression of fascin actin-bundling protein 1 (FSCN1), which is an important cell skeleton-associated gene.[71] Moreover, we found positive associations between *CYTOR* and multiple cytoskeleton-associated gene sets, including gene sets involved in the microtubule-organizing center and cytoplasmic microtubule, by analyzing GSE77491 of the GEO database using GSEA software (Fig. 3A, B). This suggests that *CYTOR* may participate in the regulation of tumor cell invasion and metastasis by regulating the cytoskeleton.

CYTOR and tumor glycolysis

In most solid tumors, hypoxic conditions appear as the tumor volume increases; however, the tumor cells do not stop their malignant biological behavior because of a specific cellular metabolism, called glycolysis-based cellular metabolism.[111–113] Under hypoxic conditions, the glycolytic enzyme activity of tumor cells is strengthened, including hexokinase 2 (HKII), 6-phosphofructokinase subunit alpha (PFK1), pyruvate kinase (PK), and lactate dehydrogenase (LDH),[114] while the activity of ATP-producing enzymes in mitochondria is weakened, as is oxidative phosphorylation. Tumor cells maintain the energy supply for biological activities (e.g., cell proliferation, invasion, metastasis, and angiogenesis) by anaerobic glycolysis. However, tumor cells use glycolysis as the primary means of producing ATP even under aerobic conditions, which is known as the Crabtree effect or the anti-Paste effect.[115] The expression of HIF-1 in tumor cells was induced in a hypoxic environment,[116] which inhibited the oxidative phosphorylation pathway and enhanced the glycolytic pathway in cells.[117,118] Effective drugs for targeting tumor cell metabolism are currently lacking; therefore, finding a molecular diagnosis and treatment target related to tumor glycolysis is one strategy for inhibiting tumor growth and controlling tumor progression. There is increasing evidence that lncRNAs play an important role in the process of tumor glycolysis.[119–121] As a key molecule in tumor progression, *CYTOR* is also closely related to tumor glycolysis. Sun et al reported that *CYTOR* regulates the expression of miR-139-5p and its downstream target gene protein kinase AMP-activated catalytic subunit alpha 1 (PRKAA1) in GC cells, thus promoting their glycolytic process.[28] In addition, Nishizawa et al showed that the expression of *CYTOR* in CRC cells was significantly increased in a hypoxic environment.[33] Cai et al found that *CYTOR* regulates the expression of miR-138 and its downstream target gene HIF-1α as ceRNA, promoting EMT transformation of gallbladder cancer cells.[48] HIF-1α is an important molecule regulating tumor glycolysis,[116–118] which implies that there is a relationship between *CYTOR*, HIF-1α, and tumor glycolysis. Moreover, we found positive associations between *CYTOR* and multiple energy metabolism-associated gene sets, including gene sets involved in glycolysis and hypoxia, by analyzing GSE77491 of the GEO database using GSEA software (Fig. 3C, D). Thus, the regulatory network between *CYTOR*, HIF-1α, and tumor glycolysis may provide a theoretical basis for the development of novel tumor-targeted drugs in the future.

CYTOR and inflammatory response

In recent years, tumors and inflammation have been a major focus of research. Tumors affect approximately 25% of humans because of non-resolving inflammation. These studies clarified that non-resolving inflammation accelerates the 'inflammation–tumor' reaction chain and eventually leads to the formation of tumors referred to as "non-resolving inflammation-associated tumors". Non-resolving inflammation is an important biological malignancy and is known as the "seventh characteristic of tumors".[122–124] In recent years, an increasing amount of evidence has shown that lncRNAs regulate the microenvironment, immune escape, invasion, and metastasis of non-resolving inflammation-associated tumors by affecting important factors related to the occurrence of non-resolving inflammation, such as inflammatory cells, inflammatory factors, and chemokines.[125–127] Recent studies have reported that *CYTOR* is associated with gastric inflammation,[63] hepatitis,[39] retinitis pigmentosa,[128] and other uncontrollable inflammatory diseases; however, the correlation between *CYTOR* and uncontrollable inflammatory responses has not been explored via molecular mechanisms. Zhu et al demonstrated that the expression of *CYTOR* in gastritis tissues infected by *Helicobacter pylori* increased dramatically in comparison with normal gastric tissue by microarray.[63] Deng et al reported that *CYTOR* expression in patients with HCC with HBV positivity increased and the high expression of *CYTOR* was associated with HBx, an essential protein of HBV infection.[39] In addition, Chen et al found that in lung adenocarcinoma cells, *CYTOR* inhibits the expression level of interleukin 24 (IL24) by binding to EZH2.[34] IL24 is a molecule related to uncontrollable

inflammation.[129,130] It is worth exploring whether *CYTOR* can establish a connection with the inflammatory response through IL24. Cai et al reported that *CYTOR* regulates the AKT2/NF-κB pathway in glioblastoma by competitively binding endogenous miR-612.[90] Moreover, while analyzing GSE77491 of the GEO database using GSEA software, we found positive associations between *CYTOR* and multiple inflammation-associated gene sets, including gene sets involved in inflammatory response, TNFA signaling, chemokine signaling, and chemokine binding to receptors (Fig. 3E–H). In summary, inconspicuous evidences indicate that *CYTOR* plays an important role in the progression of non-resolving inflammation-associated tumors.

Application of *CYTOR* in the clinical treatment of tumors

CYTOR and clinicopathological features

Tumor markers are substances present in malignant tumor tissues or cells, or are produced or secreted by abnormal reactions of malignant tumor cells. They can be used to determine the progress of tumors and monitor the therapeutic effects of drugs.[131–133] Tumor markers play an important role in the early diagnosis of tumors,[134] monitoring high-risk populations,[135] assessing severity, developing a personalized treatment plan,[136] and assessing treatment and prognosis.[137] Although lncRNAs are not expressed as high as protein-encoding genes, the former are present in abundance in cells, tissues, blood, and feces, and have a certain stability, specificity, and sensitivity. Therefore, lncRNAs have received considerable attention from researchers as a new tumor marker.[138,139] Similar to most tumor-related lncRNA molecules, *CYTOR* exists stably in tissues, cells, serum,[41,60] and exosomes[60] in the form of their target mRNA. *CYTOR* has been reported to be highly expressed in various tumors, such as GC,[23–29] CRC,[30–33] NSCLC,[34–36] HCC,[37–39] pancreatic cancer,[40] esophageal cancer,[41,42] clear cell renal cell carcinoma,[43,44] glioma,[45,46] hemangioma,[47] gallbladder cancer,[48] breast cancer,[49,50] tongue squamous cell carcinoma (TSCC),[51] head and neck squamous cell carcinoma,[52] retinoblastoma,[53] and ovarian cancer.[54] Interestingly, by analyzing The Cancer Genome Atlas (TCGA) database using the Gene Expression Profiling Interactive Analysis (GEPIA), we also found that *CYTOR* has abundant expression in various types of tumors (Fig. 4).

CYTOR is not only highly expressed in tumors, but is also closely related to the clinicopathological features, such as tumor stage, malignancy, infiltration, and poor prognosis of various tumors (Table 1), and has potential tumor marker characteristics. By analyzing TCGA database using the Kaplan–Meier Plotter (http://kmplot.com/analysis/index.php?p=service&cancer=pancancer_rnaseq), we found that high expression of *CYTOR* was positively correlated with poor survival (Fig. 5). Moreover, Xiong et al constructed the lncRNA expression profile in TSCC using gene chip technology and screened and verified the expression of *CYTOR* in tongue squamous cell carcinoma, followed by in situ hybridization (ISH) detection of *CYTOR* expression in paraffin-embedded specimens of tongue squamous cell carcinoma,[51] further confirming that high expression of

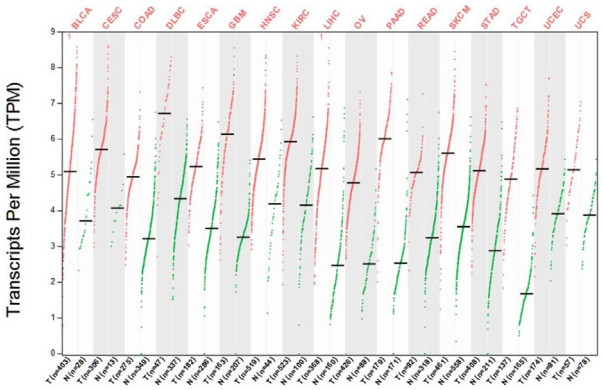

Figure 4 Expression aberration of *CYTOR* in multiple types of tumors using the GEPIA2 database. Red, tumor samples; grey, normal control samples. BLCA, bladder urothelial carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KIRC, kidney renal clear cell carcinoma; LIHC, liver hepatocellular carcinoma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; READ, rectum adenocarcinoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TGCT, testicular germ cell tumors; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma.

CYTOR is closely related to infiltration, lymph node metastasis, tumor stage, and poor prognosis of TSCC patients. The overall survival time and disease-free survival time of patients with high *CYTOR* expression were shorter than that of patients with low *CYTOR* expression. This is similar to the findings of other research teams testing *CYTOR* on other types of tumors. For example, in GC, increased expression of *CYTOR* is positively correlated with tumor size, depth of tumor invasion, lymph node metastasis, TNM stage, and adverse survival rate.[24,76] Cai et al reported that high levels of *CYTOR* were positively associated with lymph node invasion and progression of TNM staging in gallbladder carcinoma.[9] In addition to *CYTOR* pathological detection, it can be detected in blood and exosomes as a test indicator.[26,60] Yang et al found that people with high *CYTOR* expression in serum and *H. pylori* infection were more likely to develop GC.[26] In addition, Li et al showed that *CYTOR* levels in plasma and exosomes of GC patients were significantly higher than those of normal controls, and the expression level of *CYTOR* in plasma after surgery was significantly lower than that in plasma before surgery.[60] *CYTOR* is an lncRNA molecule with tumor characteristics involved in tumor progression and can be used for early detection and prognosis monitoring of tumors.

Prospects for CYTOR in tumor therapy

Although tumor treatment has made great progress and the 5-year survival rate of many cancer patients has been significantly improved, the incidence and mortality of tumors increase annually. Therefore, studies on suitable drug targets for the clinical treatment of tumors remain the

Table 1 Correlation between *CYTOR* and clinicopathological features of tumors.

Types of cancer	Sample sources	Dysregulation	Relationship with clinicopathology	Ref.
Glioblastoma malignancy	tissue	up	WHO classification	90
Laryngeal cancer	tissue	up	Lymph node metastasis or an advanced clinical stage	140
	tissue	up	Clinical stage and pathological differentiation degree	141
Tongue squamous cell carcinoma	tissue	up	T stage, N stage andTNM stage	51
Oral squamous cell carcinoma	tissue	up	TNM stage and lymph node metastasis	142
Esophageal carcinoma	tissue	up	Lymphatic metastasis and advanced pTNM classification	143
	tissue	up	TNM stage and lymph node metastasis	144
Papillary thyroid carcinoma	tissue	up	Tumor size, LNM, clinical stage and extrathyroidal extension	145
Non-small cell lung cancer	tissues, plasma	up	Tumor size and pathological grades	146
	tissue	up	Lymph node metastasis station, remote metastasis and TNM staging	36
	tissue	up	Tumor volume and lymph node metastases	147
	tissue	up	TNM stage, larger tumor size and lymph node metastasis	34
Hepatocellular carcinoma	tissue	up	Tumor size, HBV infection and tumor number	39
	tissue	up	Tumor size and Edmondson grade	37
	tissue	up	Differentiation grade, tumor size, TNM stage and tumor capsular	148
Gallbladder cancer	tissue	up	Tumor status progression and lymph node invasion	
	tissue	up	Tumor status progression, lymph node invasion and TNM stage advancement	48
Gastric cancer	tissue	up	Clinical stage and lymphatic metastasis	149
	tissue	up	Tumor size	25
	tissue	up	Tumor invasion depth, lymph node metastasis and TNM stage	76
	tissue	up	Tumor size	24
	tissue	up	Invasion	150
Colorectal cancer	tissue	up	Pathological grade and lymph node metastases	151
	tissue	up	Tumor stage	32
	Tissue	Up	Tumor size, tumor grade, tumor node metastasis (TNM) stage and distant metastasis	71
Renal cell carcinoma	tissue	up	Lymph node metastasis and higher TNM stage	44
	tissue	up	TNM stage	43
Cervical cancer	tissue	up	Histologic grade	152
Ovarian cancer	tissue	up	Histological grade and clinical stage	54
Bladder Cancer	tissue	up	Lymph node metastasis and histological grade	153
Osteosarcoma	tissue	up	Tumor size, TNM stage and clinical stage	154

main means that improve the therapeutic effect of tumors, delaying the progression of tumors, and improving the survival rate of patients. In recent years, non-coding RNA has played a pivotal role in the study of tumor therapy,[155–157] and several miRNA-related tumor therapeutic drugs have entered clinical trials. The tumor drug MRX34 (NCT01829971), developed by Mirna that targets miR-34, has entered phase I clinical trials of various solid and hematological tumors.[158,159] The miR-122-targeted oncology drug Miravirsen (SPC3649) developed by Roche has entered phase II clinical trials for hepatitis C.[160–162] MRG-106, a tumor drug targeting miR-155 developed by miRagen, has entered phase I clinical trials for hematological tumors. The process from basic research to clinical application is a lengthy one. Although miRNA-targeted tumor drugs have entered phase I and phase II clinical trials, it would still take a long way to be considered in clinical treatment. The study of tumor drugs targeting lncRNAs is still at the initial stage. Most of the drugs are currently in animal testing. For example, Arun et al demonstrated that MALAT1 antisense oligonucleotides slow tumor growth and metastasis in a breast cancer mouse model induced by mouse mammary tumor virus-PyMT, and inhibit breast cancer progression in mice.[163] In addition, Claes Wahlestedt et al proposed that antagoNAT [antago (natural antisense transcript) oligonucleotides, antagoNAT oligonucleotides] targeting antisense lncRNA is expected to become a new technology to promote the development of

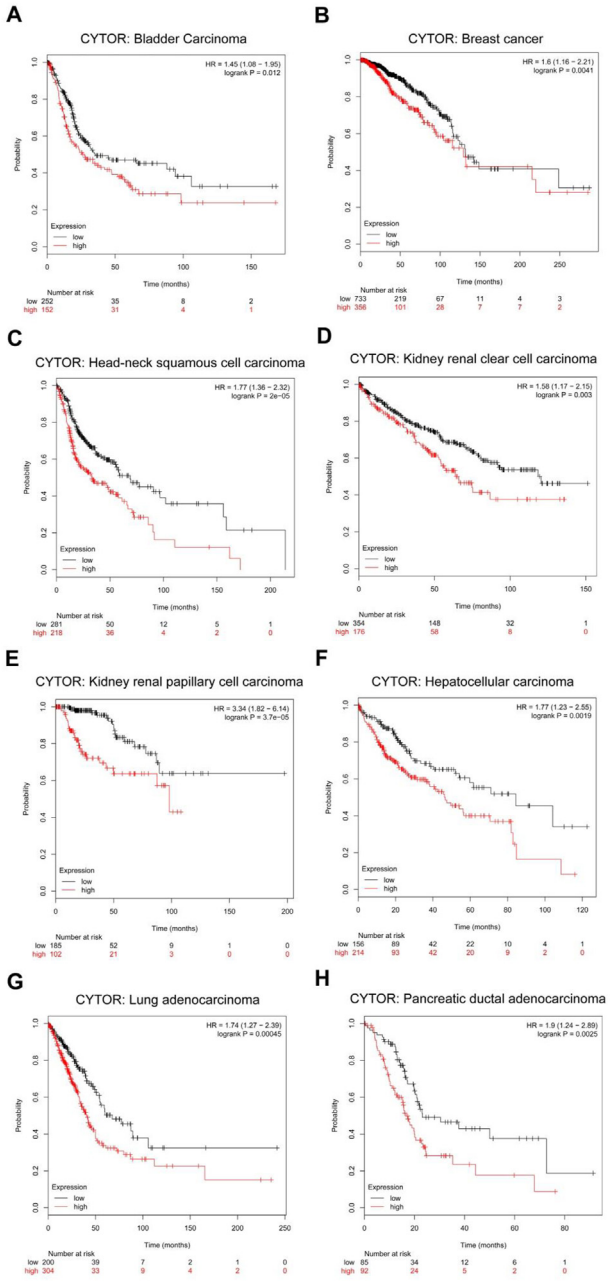

Figure 5 Kaplan—Meier analysis showing overall survival (OS) curves of multiple types of tumors patients with different expression of *CYTOR*. Black graphic lines are representative of tumor patients with low expression of *CYTOR*; Red graphic lines are representative of tumor patients with high expression of *CYTOR*.

tumor-targeted therapeutic drugs.[164] There are many lncRNAs with tumor characteristics similar to *CYTOR*, such as HOTAIR, MALAT1, and AFAP1-AS1. Building a bridge connecting non-coding RNA and tumor therapy to maximize its application value in tumor therapy is a challenge that needs further clinical research.

The development of drugs or inhibitors targeting *CYTOR* remains unelucidated; however, with the continuous optimization of detection methods, Soares et al used different ISH methods to detect the expression of *CYTOR* in multiple cell lines.[165] It was found that the branched-DNA probe method can detect stronger *CYTOR* signals. Further clinical verification by this probe may be more conducive to the detection of *CYTOR* signals in tissues or blood, which may improve the specificity, sensitivity, and accuracy. With the deepening of basic research on *CYTOR*, the value of its clinical application has attracted increasing attention from researchers. In our laboratory, Xiong et al tested the expression of *CYTOR* in tissues and serum of patients with TSCC and acquired three Chinese patents (CN106480196A, CN106511368A, and CN106381339A).[61] Thus, *CYTOR* has displayed potential for clinical conversion in various tumor studies. It is believed that in the near future, detection kits and therapeutic drugs targeting *CYTOR* can be put into clinical research.

Conclusions and future perspectives

Researchers reported approximately 25 years ago that the lncRNA molecule H19 is associated with cancer and fetal growth[166,167] and the lncRNA molecule Xist silences the second X chromosome.[168] Moreover, these lncRNAs were thought to function only in specific cells. It was not until 2005 that Siepel et al discovered 35,000 ncRNAs through the large-scale project FANTOM,[169] after which lncRNAs received renewed attention. However, there has been a disagreement about the function and role of lncRNAs in humans. Bassett et al pointed out that important genetic material should be highly conserved, whereas lncRNA sequences are not highly conserved between species.[170] Cabili et al identified lncRNAs in cells using a new fluorescent probe method and performed single-cell imaging of lncRNAs in different human tissues.[171] They found that many lncRNAs were not randomly distributed: some were present in the cytoplasm, while some were present in the nucleus, which is contrary to the expectation that lncRNA was a "junk" molecule. Regardless of the final conclusion of the debate, lncRNAs are still a hot "star" in the field of cancer research. With the continuous update and optimization of bioinformatics analysis software as well as the continuous development of high-throughput sequencing technology and molecular experimental technology (especially CRISPR technology[172,173]), several new lncRNAs have been discovered and identified, especially tumor-associated lncRNAs. These lncRNAs can regulate the expression levels of a series of molecules by interacting with proteins, adsorbing miRNAs, and inducing epigenetic modifications to DNA sequences, thereby participating in the occurrence and development of tumors. The pathogenesis of tumor-associated lncRNAs could be targeted by gene knockout, RNA interference, gene complementation, etc. Thus, the study of lncRNAs can provide new strategies for early tumor detection and treatment. At present, there are two difficulties in research related to lncRNAs: 1) identifying whether the predicted lncRNAs are functional; 2) verifying whether functional lncRNAs are related to the course of disease. Therefore, maximizing the research and application of new tumor-associated lncRNAs is the need of the hour for cancer researchers.

CYTOR, an intergenic lncRNA molecule with a total length of 852 bp, short half-life, and evident tumor characteristics, can be expressed in tissues, cells, serum, and exosomes. It is

also involved in tumor invasion and metastasis, malignant proliferation, immune escape, radiotherapy and chemotherapy resistance, formation of microenvironments, and other malignant processes of various tumors. High expression of this molecule is also closely related to clinicopathological features such as staging, infiltration, and poor prognosis, so it is a potential tumor marker and molecular therapeutic target. However, because of the limitations of research methods and strategies, there is still a long way to go from basic research to clinical application for targeted inhibitors of *CYTOR*. The reasons are as follows: 1) because the sequence of *CYTOR* is not well conserved among other species; compared with the human genome, the mouse genome does not have a complete *CYTOR* gene sequence; therefore, it is difficult to construct a *CYTOR* knockout mouse for corresponding research and drug clinical research; 2) *CYTOR* has multiple transcripts; therefore, transcript or transcripts that play a regulatory role in the environment remain unclear; 3) *CYTOR* is located in the nucleus, cytoplasm, cytosol, ribosome, vesicle, and other subcellular locations and organelles, and the distribution of *CYTOR* changes under different conditions, raising the question of the effect of cellular localization of *CYTOR* on its biological function 4) The molecular mechanism of *CYTOR* remains unelucidated, and upstream signal stimulation (such as hypoxia, cell density, and TGFβ stimulating factor) can be accepted, and downstream molecular mechanisms (e. g., interaction with EZH2 for epigenetic modification or adsorption of miRNA to form ceRNA for regulation) can be regulated by *CYTOR*. Despite these limitations, the etiology and clinical value of *CYTOR* have been analyzed from both basic and clinical research perspectives. This provides a theoretical basis for *CYTOR* as a marker in the early diagnosis, prognosis, and treatment of cancer and further promotes the development of basic biological research in clinical settings.

Conflict of interests

The authors declare no competing financial interest.

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Abbreviations

BLCA bladder urothelial carcinoma
CDKN1A cell cyclin dependent kinase inhibitor 1A
CDKN2B cyclin dependent kinase inhibitor 2B
ceRNA competing endogenous RNA
CESC cervical squamous cell carcinoma and endocervical adenocarcinoma
COAD colon adenocarcinoma
CRC colorectal cancer
CYTOR cytoskeleton regulator RNA
DLBC lymphoid neoplasm diffuse large B-cell lymphoma
DNMTs DNA methyltransferases
EGFR epidermal growth factor receptor
EMT epithelial—mesenchymal transition
ESCA esophageal carcinoma
EZH2 enhancer of zeste homolog 2
FSCN1 fascin actin-bundling protein 1
GBM glioblastoma multiforme
GC gastric cancer
GSEA gene set enrichment analysis
HBV hepatitis B virus
HCC hepatocellular carcinoma
HIF-1 hypoxia-inducible factor-1
HNSC head and neck squamous cell carcinoma
ISH in situ hybridization
KIRC kidney renal clear cell carcinoma
LIHC liver hepatocellular carcinoma
lincRNA large intergenic noncoding RNA
lncRNAs long non-coding RNAs
NCBI national center for biotechnology information
ncRNA non-coding RNA
NSCLC non-small cell lung cancer
ORF open reading frame
OS overall survival
OV ovarian serous cystadenocarcinoma
PAAD pancreatic adenocarcinoma
PLGLB2 plasminogen-like B2
PRKAA1 protein kinase AMP-activated catalytic subunit alpha 1
READ rectum adenocarcinoma
SKCM skin cutaneous melanoma
STAD stomach adenocarcinoma
TGCT testicular germ cell tumors
TNBC triple-negative breast cancer
TSCC tongue squamous cell carcinoma
UCEC uterine corpus endometrial carcinoma
UCS uterine carcinosarcoma

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