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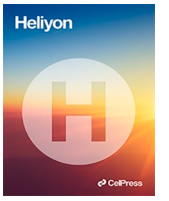

Review article

Biological functions and molecular mechanisms of LINC01116 in cancer

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ABSTRACT

LINC01116, a long non-coding RNA (lncRNA), serves as an important regulator in the progression of cancer cells and has attracted increased attention in biological fields. It is overexpressed in various cancer cells and is significantly correlated with cancer development and poor prognosis in cancer patients. Moreover, LINC01116 regulates the gene expression of various cancers through intricate pathways, such as sponging the microRNAs or other non-genic manners. These signaling pathways greatly affect the cancer's biological functions, including cell growth, migration, invasion, and chemoresistance. Hence, LINC01116 may serve as a prognostic biomarker and therapeutic target for human cancer. This paper summarizes the current evidence regarding the biological functions and molecular mechanisms of LINC01116 in the progression of cancer, providing theoretical references for LINC01116-related cancer treatment in the future.

1. Introduction

Cancer poses a grave threat to human health and is the leading cause of mortality worldwide, with rapidly increasing annual incidence and mortality rates [1–5]. Numerous effective therapeutics have been developed to combat cancer, including chemotherapy, radiotherapy, and targeted therapy. Traditional chemotherapy and radiotherapy have achieved short-term efficacy by directly killing tumor cells, but long-term treatment is limited by immune response suppression, tumor drug resistance, and toxicity to normal cells. In contrast, targeted therapy directly acts on disease-related biomarkers and molecular targets, thereby reducing the damage and side effects to normal tissues to achieve superior therapeutic efficacy [6–13]. In recent years, long non-coding RNAs (lncRNAs) have garnered attention for their crucial roles in regulating gene expression and their influence on cancer development and progression via multiple mechanisms. LncRNAs have been found to be closely associated with the occurrence, development, and prognosis of various cancer types [14–20]. For instance, lncRNA-SNHG16 is overexpressed in bladder cancer (BCa) tissues and cells and is closely related to

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poor prognosis in patients. LncRNA-SNHG16 directly binds to the enhancer of Zeste Homolog 2 (EZH2) and recruits it to the promoter region of p21, thereby inducing histone modifications that promote the proliferation of BCa cells [21]. Therefore, lncRNAs are regarded as potential biomarkers and therapeutic targets.

Long intergenic non-protein coding RNA 1116 (LINC01116), alternatively termed lncRNA TALNEC2, was initially identified in prostate cancer, residing on human chromosome 2q31.1, spanning 1058bp, and encompassing four transcripts [22]. Elevated expression of LINC01116 has been observed in various cancers, significantly influencing tumor initiation, proliferation, migration, and invasion [23,24]. The regulatory mechanisms of LINC01116 in cancer involve complex pathways, such as competitive endogenous RNAs (ceRNAs) or associations with crucial enzymes like enhancers of EZH2 or AGO1's 5′UTR [25,26]. These pathways directly or indirectly influence key oncogenic processes, including cell proliferation, metastasis, invasion, as well as chemoresistance. Hence, the upregulation of LINC01116 could predict poor prognosis. Understanding these mechanisms is essential for developing new cancer treatments involving LINC01116. This review summarizes the biological functions and molecular mechanisms of LINC01116 in the pathophysiology of cancer and discusses its prognostic value in future applications.

2. Mechanisms of LINC01116 in cancer

The expression level of LINC01116 has been identified as a critical factor in the onset and progression of cancer, resulting in unrestrained proliferation of cancer cells, resistance to apoptosis, and invasion of surrounding tissues and organs. This long non-coding RNA orchestrates cancer progression through complex molecular mechanisms that amplify fundamental biological processes. In this section, the mechanisms through which LINC01116 regulates cancer progression are discussed.

2.1. LINC01116-miRNAs

Generally, microRNAs (miRNAs) will bind to the 3′UTR of the target mRNA, resulting in reduced stability, promoted degradation, or inhibited translation of the mRNA. Similarly, the lncRNA can also recognize the miRNA elements through base pairing, which relieves the inhibitory effects and promotes the expression of the mRNAs by sponging miRNAs as ceRNAs, thereby regulating the expression of genes related to cell proliferation and progression in various cancers [27]. Furthermore, LINC01116 can competitively bind miRNAs to regulate downstream target gene expression (Table 1 and Fig. 1).

LINC01116 was found to be highly expressed in colorectal cancer cells and could directly interact with the 3′UTR binding site of miR-9-5p, which effectively relieved the inhibitory effect of miR-9-5p on stathmin 1 (STMN1) and increased the related expression, thereby promoting colorectal cancer (CRC) cell proliferation and migration [28]. Moreover, previous studies investigating gliomas found that LINC01116 promotes glioma growth and migration by sponging miRNA-744-5p, miR-774-5p, miR-31, miR-31-5p, and miR-10b to regulate their downstream target genes, including murine double minute 2 (MDM2) [29], transforming growth factor-β (TGF-β) [30], vascular endothelial growth factor A (VEGF-A) [31], matrix metalloproteinase 9 (MMP-9), and vimentin [32], respectively. Additionally, overexpression of LINC01116 was found to activate the miR-10b/HOXD signaling pathway, thereby promoting glioma growth, increasing the number and metabolic activity of astrocytes, and triggering the transformation of astrocytes towards tumor formation [33]. In non-small cell lung cancer (NSCLC), LINC01116 acts as a molecular sponge for miR-744-5p and increases the expression of cell division cycle-associated protein 4 (CDCA4) to mediate cell proliferation, migration, and invasion [35]. Similarly, a study on breast cancer (BC) also revealed high LINC01116 expression, with an enhanced expression of estrogen receptor 1 (ESR1) owing to the competitive binding with miR-145, hence promoting BC progression [40]. In melanoma, LINC01116 was found to competitively bind with miR-3612 to enhance the expression of growth differentiation factor 11 (GDF11) and syndecan 3 (SDC3),

Table 1
The pathways of LINC01116 in cancer.

Cancer	Signaling pathway and gene expression	Refs
CRC	EZH2/TPM1; miR-9-5p/STMN1	[25,28]
Glioma	miR-744-5p/MDM2/p53; miR-774-5p/TGF-β1; miR-31-5p/VEGFA; miR-31/MMP-9; HOXD/miR-10b; DDX5/IL-1β	[29–34]
NSCLC	miR-744-5p/CDCA4; p-AKT; IFI44	[35–37]
PCa	miR-744-5p/UBE2L3	[38]
ESCC	AGO1	[26]
Chordoma	miR-9-5p/Pkg1	[39]
BC	miR-145/ESR1	[40]
Melanoma	miR-3612/GDF11/SDC3	[41]
PA	miR-744-5p/HOXB8	[42]
Osteosarcoma	miR-424-5p/EZH2/HMGA2; EZH2/PTEN/p53	[43,44]
NPC	MYC	[45]
GC	miR-145/CASC11	[46,47]
HCC	EWSR1/PPARA/FABP1	[48]
BCa	miR-3612/ELK3; DKC11/HOXD8	[49]
SCLC	miR-93-5p/STAT3	[50]

Note. CRC, colorectal cancer; GC, gastric cancer; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; BC, breast cancer; NPC, nasopharyngeal cancer; ESCC, esophageal squamous cell carcinoma; PCa, prostate cancer; HCC, hepatocellular carcinoma; BCa, bladder cancer; PA, pituitary adenoma.

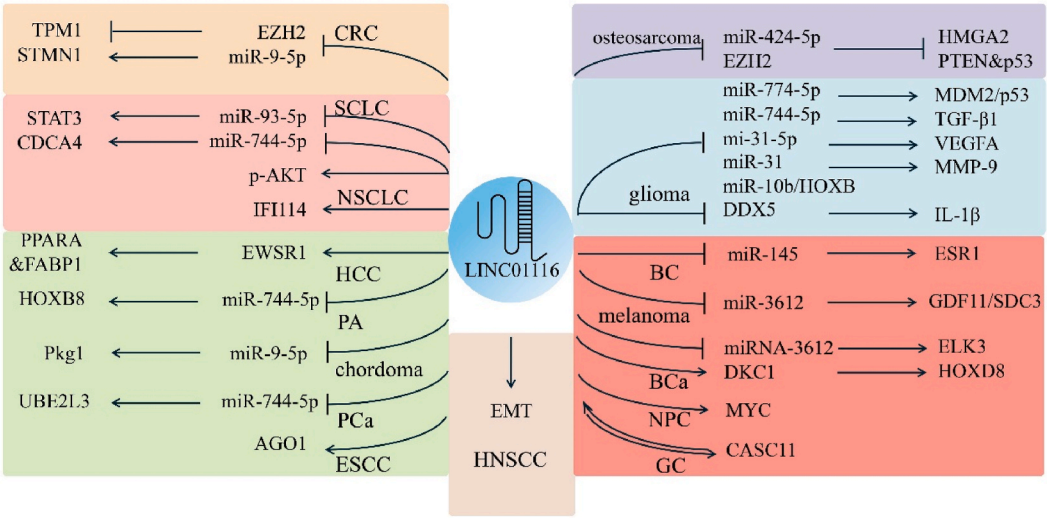

Fig. 1. The mechanisms of LINC01116 in cancer. **Note.** CRC, colorectal cancer; GC, gastric cancer; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; BC, breast cancer; NPC, nasopharyngeal cancer; ESCC, esophageal squamous cell carcinoma; PCa, prostate cancer; HCC: hepatocellular carcinoma; BCa, bladder cancer; PA, pituitary adenoma; EOC, epithelial ovarian cancer; HNSCC, head and neck squamous cell carcinoma.

promoting melanoma cell proliferation, migration, and invasion [41]. In pituitary adenoma (PA) and prostate cancer (PCa), LINC01116 has been found to bind to miR-744-5p, upregulating HOXB8 expression [42] and increasing ubiquitin-conjugating enzyme E2L3 (UBE2L3) expression, thereby promoting the proliferation, migration, invasion, and epithelial-mesenchymal transition (EMT) of pituitary tumors and PCa [38]. In chordomas, LINC01116 could bind with miR-9-5p to upregulate the expression of phosphoglycerate kinase 1 (Pkg1) and promote chordoma cell proliferation and invasion [39].

2.2. *Other signaling mechanisms*

LINC01116 also regulates cancer occurrence and development via other pathways. For instance, LINC01116 enhances the methylation of the tropomyosin 1 (TPM1) promoter region by recruiting enhancer of EZH2 to suppress TPM1 transcription, downregulating TPM1 expression, and promoting proliferation and angiogenesis of CRC cells [25]. Meanwhile, LINC01116 was found to downregulate PTEN and p53 expression by binding to EZH2, promoting osteosarcoma development [44]. In nasopharyngeal cancer, LINC01116 directly regulates myelocytomatosis viral oncogene MYC to accelerate its translation, increase MYC protein expression, and promote cancer progression [45]. A previous study reported that LINC01116 also mediates NSCLC occurrence and development by activating the AKT pathway [36]. In esophageal squamous cell carcinoma (ESCC), LINC01116 binds to 5′UTR of argonaute 1 (AGO1), accelerates its translation, and increases its expression to promote EMT, migration, invasion, and tumorigenesis [26]. In hepatocellular carcinoma (HCC), LINC01116 increases the expression of EWS RNA-binding protein 1 (EWSR1) by inhibiting ubiquitination mediated by RAD18 E3 ubiquitin-protein ligase (RAD18). Subsequently, the enhanced EWSR1 upregulates peroxisome proliferator-activated receptor alpha (PPARA) and fatty acid binding protein1 (FABP1). FABP1 is a long-chain fatty acid (LCFA) transporter that competes with T cells for LCFA, promoting its own growth, and leading to T cell dysfunction, enhanced cancer cell proliferation, and reduced tumor sensitivity to immunotherapy [48]. In BCa, LINC01116 bound to dyskerin pseudouridine synthase 1, upregulated its own expression, and enhanced HOXD8 expression and stability, forming a positive feedback loop to promote BCa migration and invasion [49]. LINC01116 has been confirmed to interact with lncRNA CASC11, which upregulate each other's expression in gastric cancer (GC) [46]. Additionally, LINC01116 accelerates the EMT process to promote cancer development. LINC01116 in head and neck squamous cell carcinoma (HNSCC) reduced the expression levels of N-cadherin, Slug, and snail, while increasing *E*-cadherin and ZO-1 expression, proving that EMT is a downstream effector of LINC01116 that accelerates the migration and invasion of HNSCC [54].

3. Biological functions of LINC01116 in cancer

Cell growth and apoptosis play essential roles in cell proliferation [55]. In addition, metastasis and invasion are closely related to tumor progression and poor prognosis. Down-regulation of LINC01116 expression could inhibit the proliferation, invasion, migration, and chemotherapeutic resistance of tumor cells, thereby inhibiting the progression of cancer. Therefore, the biological functions of LINC01116 in cancer were summarized.

3.1. *Cell growth*

LINC01116 has been confirmed to play a major role in tumor cell growth, including promoting cell proliferation, affecting the cell

cycle, and inhibiting apoptosis (Table 2). Cell cycle disruption is one of the main features of cancer. Evidence suggests that tumors are a type of cyclical disease, and analyzing tumor cell staging is essential for controlling tumor progression and treatment. In glioma, NSCLC, chordoma, osteosarcoma, and HCC, LINC01116 overexpression results in a significant accumulation of cells at the S-phase, with a decreased proportion of cells at the G0/G1 phase [34,39,44,51,52]. Conversely, down-regulated LINC01116 expression could decrease the proportion of cells in the S-phase of the cell cycle, while increasing the number of cells at the G0/G1 phase. Previous studies have employed the ratio of S-phase cells as an indicator of tumor proliferation status. Down-regulation of LINC01116 led to a decrease in the proportion of cells in the S-phase, inhibited tumor cell proliferation, and controlled cancer progression. Moreover, cancer typically exhibits resistance to apoptosis. Decreased or inactivated expression of tumor suppressor genes in normal cells could prevent apoptosis in cancer cells, thereby granting unlimited proliferation. Therefore, analyzing the anti-apoptotic ability of tumor cells is crucial for controlling cancer progression. In ESCC, CRC, NSCLC, PA, chordoma, osteosarcoma, GC, BCa, HCC, and epithelial ovarian cancer (EOC), the overexpression of LINC01116 was significantly correlated with the apoptosis of tumor cells [26,28,39,42,44,47,49,51–53]. LINC01116 could inhibit tumor cell apoptosis by suppressing the expression of tumor suppressor genes such as p53 and TGF-β1. Down-regulation of LINC01116 could increase the apoptosis rate of tumor cells and inhibit cancer development. Therefore, downregulating the expression of LINC01116 could interfere with the metabolic process of tumor cells, preventing tumor cells from entering the S-phase, inhibiting proliferation, and inducing apoptosis.

3.2. Cancer metastasis and invasion

LINC01116 mediates cell migration and invasion by accelerating the process of EMT (Table 2). Specifically, in the EMT process, cells lose their epithelial characteristics and acquire mesenchymal characteristics, leading to decreased expression of *E*-cadherin and increased expression of N-cadherin and vimentin, which effectively disrupts tight cell-cell connections and confers cells the ability to invade and migrate [56]. Elevated expression of LINC01116 has been shown to facilitate the invasive and migratory capacities of cells in CRC [25,28], glioma [29–32,34], NSCLC [35,36,51], BC [40], GC [46], and SCLC [50]. In contrast, decreased LINC01116 expression can impede both the rate and the ability of migration and invasion in cells affected by osteosarcoma, PCa, BCa, and melanoma. Hence, LINC01116 shows promising potential in impeding cellular migration, and invasion, as well as in enhancing the prognosis of patients.

3.3. Chemotherapeutic resistance

Studies have shown that overexpression of LINC01116 is closely associated with the chemoresistance of various tumor cells. For instance, LINC01116 is highly expressed in NSCLC cells and tissues, which causes a gefitinib-resistant cellular behavior [37]. Additionally, overexpressed LINC01116 could also contribute to doxorubicin resistance in osteosarcoma, as evidenced by increased resistance in MG-63/Dox cells [43]. Chemoresistance remains a significant challenge in chemotherapy, and further research on LINC01116 may reveal its potential in mitigating treatment resistance and enhance efficacy.

4. Prognosis

Elevated LINC01116 expression is correlated with poor prognosis across various cancers, including CRC [25,28], glioma [29–32,34], NSCLC [36,51], BC [40], and GC [46,47] (Table 3). LINC01116 upregulation has been linked to reduced overall survival in BC, ESCC [26], HCC [52], EOC [53], and HNSCC [53]. It is also associated with poorer progression-free survival in HCC and EOC, shorter

Table 2
Functional characterization of lncRNA LINC01116 in cancer metastasis.

Cancer	Types on cell growths	Types on cell metastasis	Roles	Refs
CRC	Proliferation, apoptosis	Angiogenesis, invasion, migration	Promotion	[25,28]
Glioma	Proliferation, cell cycle, apoptosis	Invasion, migration	Promotion	[29–34]
NSCLC	Proliferation, cell cycle, apoptosis, chemotherapeutic resistance	Invasion, migration	Promotion	[35–37,51]
PCa	Proliferation	Invasion, migration	Promotion	[38]
ESCC	Proliferation, apoptosis	Invasion, migration	Promotion	[26]
Chordoma	Proliferation, cell cycle, apoptosis	Invasion	Promotion	[39]
BC	Proliferation	Migration	Promotion	[40]
Melanoma	Proliferation	Invasion, migration	Promotion	[41]
PA	Proliferation, apoptosis	Migration	Promotion	[42]
Osteosarcoma	Proliferation, cell cycle, apoptosis, chemotherapeutic resistance	Invasion, migration	Promotion	[43,44]
NPC	Proliferation	Migration	Promotion	[45]
GC	Proliferation, cell cycle, apoptosis	Invasion, migration	Promotion	[46,47]
HCC	Proliferation, cell cycle	Migration	Promotion	[48,52]
BCa	Proliferation, apoptosis	Invasion, migration	Promotion	[49]
SCLC	/	Invasion, migration	Promotion	[50]
EOC	Proliferation, anti-apoptotic	Migration	Promotion	[53]
HNSCC	/	Invasion, migration	Promotion	[54]

Note. CRC, colorectal cancer; GC, gastric cancer; SCLC, small cell lung cancer; BC, breast cancer; NPC, nasopharyngeal cancer; ESCC, esophageal squamous cell carcinoma; PCa, prostate cancer; HCC, hepatocellular carcinoma; BCa, bladder cancer; PA, pituitary adenoma; EOC, epithelial ovarian cancer; HNSCC, head and neck squamous cell carcinoma.

time to recurrence in HNSCC, and lower postoperative survival rates in CRC, indicating its potential as an independent prognostic marker. In addition, LINC01116 expression was found to be correlated with clinical and pathological features such as TNM staging, tumor progression, and lymph node metastasis. For example, its upregulation in CRC, GC, BC, ESCC, and HCC was associated with advanced TNM staging. In CRC, glioma, NSCLC, BC, and ESCC, LINC01116 overexpression has been associated with larger tumor size and altered differentiation status. Previous studies in CRC, GC, and osteosarcoma demonstrated that LINC01116 was linked to increased lymph node metastasis, particularly lung metastasis in osteosarcoma. Furthermore, LINC01116 expression patterns have diagnostic significance, effectively differentiating ER+ from ER- BC subtypes [57]. Overall, high LINC01116 expression suggests its potential as a diagnostic biomarker and therapeutic target in most cancers, reflecting poor prognosis and low survival rates.

5. Conclusions

In conclusion, LINC01116 is correlated with various malignancies and plays pivotal roles in biological processes. Mechanistically, LINC01116 mainly functions as ceRNAs by binding to miRNAs as molecular sponges to regulate the expression of downstream target genes, thereby exerting oncogenic effects. Additionally, biological functions could also be regulated via other enzyme-mediated pathways to indirectly modulate cancer development. On the one hand, overexpression of LINC01116 has a profound impact on cellular growth, migration, invasion as well as drug resistance, suggesting the potential of LINC01116 as a prognostic marker and a therapeutic target. On the other hand, LINC01116 is significantly associated with adverse prognostic elements in cancer such as high-grade pathology, advanced clinical staging, increased lymph node metastasis rate, shortened overall survival, and reduced survival rate. This potential establishes LINC01116 as a novel cancer biomarker with great clinical value in early cancer diagnosis, targeted therapy, and prognosis assessment. However, several challenges remain to be addressed. Firstly, the signaling mechanisms of LINC01116 are intricate and may vary in different types of cancer, which greatly increases the difficulty in identifying potent treatments targeting LINC01116. Secondly, the current data on LINC01116 in cancer mainly comes from basic experiments, and future research should integrate basic research with clinical studies. Additionally, the availability of effective therapeutics targeting LINC01116 is currently limited. Considering the intricate regulatory mechanisms associated with LINC01116, further research is urgently needed to develop novel therapeutic strategies. Nanomedicine features a good safety profile, excellent therapeutic efficacy, and targeted treatment; vehicles can be used to deliver specific drugs aimed at directly or indirectly regulating the expression level of LINC01116 on demand in the future. Collectively, a better understanding of the biological effects and regulatory mechanisms of LINC01116 in cancer will contribute to the refinement of its regulatory network. This serves as a solid foundation for the development of practical diagnostic and therapeutic applications for LINC01116 in clinical treatment.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Table 3
The roles of lncRNA LINC01116 in various cancers and its clinical features.

Cancer	Expression	Role	Clinical features	Refs
CRC	up	oncogene	Postoperative survival, tumor size, tumor stage, lymph node metastasis, TNM stage	[25,28]
Glioma	up	oncogene	OS, tumor diameter, WHO grade	[29–32,34]
NSCLC	up	oncogene	OS, the volume of tumor, lymph node metastasis,	[36,51]
ESCC	up	oncogene	tumor stage, TNM stage	[26]
BC	up	oncogene	OS, tumor size, TNM stage, diagnosis	[40,57]
Osteosarcoma	up	oncogene	OS, tumor size, WHO grade, pulmonary metastasis	[44]
GC	up	oncogene	OS, TNM stage, lymph node metastasis, invasion, grade	[46,47]
HCC	up	oncogene	OS, free-event survival, TNM stage, diagnosis	[52,58]
BCa	up	oncogene	OS	[49]
SCLC	up	oncogene	OS	[50]
EOC	up	oncogene	OS, free-event survival, DFS	[53]
HNSCC	up	oncogene	OS, DFS	[54]

Note. CRC, colorectal cancer; GC, gastric cancer; SCLC, small cell lung cancer; BC, breast cancer; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; BCa, bladder cancer; EOC, epithelial ovarian cancer; HNSCC, head and neck squamous cell carcinoma; OS, overall survival; DFS, disease-free survival.

CRediT authorship contribution statement

Ke Shi: Writing – original draft, Visualization, Validation, Conceptualization. **Xue-Ying Wang:** Writing – original draft. **Li-De Huang:** Writing – original draft, Validation, Formal analysis. **Qiang Guo:** Writing – review & editing. **Wei Yuan:** Writing – review & editing, Validation, Data curation. **Yan Lv:** Writing – review & editing, Validation, Data curation, Conceptualization. **Dan Li:** Writing – review & editing, Validation, Data curation, Conceptualization.

Declaration of competing interest

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

Abbreviations

DDX11	DEAD/H-box helicase 11
EZH2	zeste homolog 2
TPM1	tropomyosin 1
STMN1	stathmin 1
MDM2	murine double minute 2
TGF-β	transforming growth factor-β
VEGFA	vascular endothelial growth factor A
MMP-9	matrix metalloproteinase 9
CDCA4	cycle-associated protein 4
ESR1	estrogen receptor 1
GDF11	growth differentiation factor 11
SDC3	syndecan 3
HOXB8	homeobox protein Hox-D8
UBE2L3	ubiquitin conjugating enzyme E2L3
Pkg1	phosphoglycerate kinase 1
PTEN	phosphatase and tensin homolog deleted on chromosome ten
EWSR1	EWS RNA-binding protein 1
RAD18	RAD18 E3 ubiquitin protein ligase
PPARA	peroxisome proliferator activated receptor alpha
FABP1	fatty acid binding protein1
LCFA	long-chain fatty acid
DKC1	dyskerin pseudouridine synthase 1
EMT	epithelial-mesenchymal transition
OS	Overall Survival

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