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The roles of Linc-ROR in the regulation of cancer stem cells

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ABSTRACT

Cancer stem cells (CSCs) are considered to be a kind of tumor cell population characterized by self-renewal, easy to metastasize and drug resistance, which play an indispensable role in the occurrence, development, metastasis and drug resistance of tumors, and their existence is an important reason for high metastasis and recurrence of tumors. Long non-coding RNAs (LncRNAs), which are more than 200 nucleotides in length, have a close relationship with the malignant progression of cancer.In recent years, abundant studies have reavling that LncRNAs are beneficial to the regulation of various cancer stem cells. Linc-ROR, as a newly discovered intergenic non-protein-coding RNA in recent years, is considered to be a key regulator affecting the development of human tumors. Dysregulation of Linc-ROR is related to stemness phenotype and functional regulation of cancer stem cells. For that, Linc-ROR has the potential to be used as a diagnostic biomarker for cancer patients and can serve as a clinically meaningful potential therapeutic target. In this review, we generalize the existing research results on the important role of Linc-ROR in regulation of CSCs.

Introduction

After treatment of malignant tumors, patients often die due to recurrence and high rates of metastasis, which has been a major clinical treatment problem. The part of reason that cancer is difficult to cure can be attributed to the emergence of invasive cell populations such as CSCs. As a subset of self-renewing malignant cells, cancer stem cells(CSCs) can enable to self-renew and evade the effects that many drugs inhibit cancer cell proliferation [1]. Additionally, they can differentiate into non-stem cancer cells, causing the heterogeneity of some malignant tumor [2]. CSCs are located in a specific "cancer stem cell niche", which is a specific microenvironment in tumors tissues, including stromal cells, immune cells, networks of cytokines and growth factors,and extracellular matrix.

These niches are involved in maintaining CSCs plasticity by regulating pathways or transcription factors during self-renewal or epithelial-mesenchymal transformation (EMT) processes through paracrine factors or direct cell-cell contact [3]. In turn, some of these niche components can be actively recruited by CSCs to create a appropriate microenvironment for their survival. It is critical for CSCs to have an interaction with these regulators for maintaining CSC populations.

LncRNAs, as a class of non-coding RNAs with a length of more than 200 nucleotides, have no potential to encode proteins and are found to be commonly expressed in specific tissues [4]. Due to the different subcellular localization, lncRNAs can play different regulatory roles, so there are lots of biological processes that can be regulated by lncRNAs, such as regulating gene expression, maintaining genome integrity, chromatin remodeling and genome silencing, transcriptional activation as well as interference, nuclear transport, cell differentiation and development [5].As molecules involved in the regulation of stemness or stemness phenotypes, Long non-coding RNAs (LncRNAs) can regulate a variety of biological processes through multiple mechanisms, including acting as scaffolds for protein complexes, baits for RNAs, sponges for microRNAs, and guiding transcription factors [6], such as cell proliferation, cell death, differentiation, and cell homeostasis. Linc-ROR, one of the recently identified LncRNAs, has been shown to positively impact the maintenance of stemness properties of CSC by directly targeting major CSC-related transcription factors (e.g., Sox2, Oct-4, and Nanog) as well as other tissue-specific transcription factors, and is required for the maintenance of pluripotent stem cell phenotypes and their local proliferation [7,8]. In this review, we describe the relationship between Linc-ROR and the acquisition of stem phenotypes in cancer cells, and the biological significant meaning of this relationship.

Origin and characteristics of CSCs

Cancer stem cells (CSCs) are functional tumor cell subsets with stemness,which can promote the malignant occurrence and

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development of cancer. In 1994, the Lapidot team successfully authenticated and extractd tumorigenic stem cell populations in acute myeloid leukemia and fully confirmed their tumorigenicity through animal experiments [9]. Subsequently, it has been successively demonstrated that CSCs are prevalent in many solid tumors, including breast cancer, glioblastoma, etc. Scholars have successively carried out researchs on solid tumor stem cells [10]. It's verited by mounting studies that CSCs are derived from normal cancer cells differentiated from progenitor cells or normal stem cells [11], or from stem cells obtained through the epithelial-mesenchymal transition (EMT) process [12]. Now, the EMT process is deemed as a continuum from a fully epithelial/proliferative to a fully mesenchymal/invasive phenotype, including a series of intermediate mixed states.CSCs can represent any of these phenotypic states and exhibit excellent plasticity. By reducing the polarity and adhesion of common cancer cells and cancer stem cells, the activation of the EMT program causes these cells to increase their mobility and aggressiveness, which are critical steps in cancer development as well as treatment resistance [13]. Although there are different opinions on the origin of cancer stem cells, numerous studies have proven that CSCs populations can be identified by the stemness-related transcription factors(such as Nanog, Oct4, Sox2, and CD133). In the process of tumor development, CSCs perform an increasingly vital role in various stages of tumor initiation, progression, distant metastasis, and treatment resistance. It's said that maintaining the CSCs population give tumors more opportunities to resist the chemotherapy and radiotherapy, thereby increasing the chances of cancer recurrence.

The main characteristics of stemness

Expression of main marker

As a member of homeodomain transcription factors in the Pit-Oct-Unc family, Oct-4 is regarded as one of the most critical core transcription factors, which has become a major regulator in the control of stem cell pluripotency, self-renewal and maintenance [14]. Studies have demonstrated that Oct-4 can maintain lung cancer stem cell (CSC) -like properties, and its presence is strongly linked with poor prognosis in lung adenocarcinoma and colorectal cancer [15,16]. Besides, Oct-4 was found to promote the polarization of M2 macrophage by upregulating macrophage colony-stimulating factor in lung cancer, leading to growth and metastasis of lung cancer, which suggests that the axis in M2 macrophage polarization may be a promising therapeutic target for lung cancer [17]. Similarly, the high expression of Oct-4 was observed in CD44+/CD24- breast CSC-like cells, and chemotherapy induction of KDM6A induced by S100A10 promoted the formation of Oct-4-mediated breast cancer stem cell [18]. In addition, YTHDF2 promotes the phenotype of hepatoma stem cell and the metastasis of HCC by modulating the m6A methylation of Oct-4 mRNA [19]. Thus, these studies were able to demonstrate that Oct-4 is a pluripotent factor in CSCs.

The transcription factor Sox2, belonging to the SRY-associated HMG-box (Sox) family, is a marker of undifferentiated cells and is involved in maintaining the phenotype of undifferentiated cell, and its abnormal expression in cancer can lead to increased chemoresistance and asymmetric division [20]. As one of the key transcription factors in CSCs, it has been used as a surface marker for the identification of CSCs in a variety of tumors, and can be regulated by self-renewal related genes to regulate stemness characteristics [21]. High expression level of Sox2 can be found in a variety of cancers with poor prognosis [22], and is key to characterizing a stem-like phenotype in more than a dozen tumors [23]. Besides, through targeting β-catenin and Beclin1 / autophagy signaling, Sox2 can promote chemoresistance in CRC, the characteristics of stem cells and EMT process [24]. Sox2 is essential for the development of osteosarcoma. It can maintain CSCs self-renewal in osteosarcoma,but the loss of Sox2 abolishes the ability of OS cells to proliferate and sphere-form [25]. Sox2 can also promote the dedifferentiation of cancer cell and confer stem-like characteristics to pancreatic cancer cells [26]. On the whole,these curent conclusions suggest that Sox2 plays an significant role in regulating CSC self-renewal as well as proliferation ability.

Nanog, as a transcription factor, has pleiotropic effects in the tumourigenic cascade, including resistance to chemotherapy and radiation, promotion of EMT, and modulation of CSCs populations [27]. Relevant studies have shown that Nanog is silent in normal human cells, but aberrantly expresses in tumors (e.g., liver cancer) and is connected with advanced stages of cancer (tumor node metastasis ((e.g.,TNM) stage III/IV) [28]. Moreover, Nanog has tumorigenic potential, but its inactivation weakens the tumorigenic potential of cancer cells in vitro and in vivo [29]. In contrast, forced overexpression of Nanog in established cancer cell lines can enhance stemness as well as EMT in cancer stem cells, resulting in promoting tumorigenicity [30]. Recently, studies on immune refractory tumor cells have shown that LC3B promotes immune resistance and CSC-like phenotypes by overactivating the EGFR-AKT functional axis, and therefore can counteract Nanog + immune refractory tumors by inhibiting LC3B expression [31]. This has significant implications for immunotherapy of tumors. It's proven that Nanog is irreplaceable in regulating the stemness properties of CSCs.

Self-renewal and proliferation

Self-renewal, as an important feature of cancer stem cells, refers to the biological process by which stem cells generate at least one daughter cell that retains stem cell characteristics through symmetrical or asymmetric division [32]. Self-renewal not only increases the number of stem cells, but also maintains the potential of stem cells to differentiate into multiple types in the meantime. For some tissue-specific stem cells, self-renewal is the basis for maintaining their lifelong differentiation potential. A key step in tumorigenesis is that mutations in some genes involved in regulating self-renewal lead to self-renewal ability of tumor cells [33].CSCs have unlimited proliferation of malignant clones, symmetrical(to increase in number)or asymmetric(to generate more differentiated descendant) sphere-forming division and growth. Asymmetric self-renewal division is to produce a offspring retained in the stem cell lineage, while the other undergoes limited rounds of transport expansion and differentiation [34]. In melanoma, the persistence of CSC demonstrated the ability of stem cells to self-renew in melanoma following serial cloning in vitro and transplantation of pluripotent melanoma stem cells in vivo [35]. Among malignant proliferating cells in tumors, CD133 $^{+}$stem cells show stronger colony-forming ability, higher proliferation efficiency, and the stronger ability of successive passages to form tumors in vivo [36]. Increasing evidence supports the idea that the self-renewal of CSCs can be guided by activation of multiple pathways, including Wnt, Notch, and Hedgehog. CSCs can autonomously trigger appropriate signaling cascades to maintain self-renewal and provide minimal niche support.Some CSCs may even require an appropriate microenvironment to provide stimulation for uncontrolled self-renewal.

Metastasis

Metastasis refers to a biological process in which cancer cells spread from the primary tumor and migrate to other areas of the body to form new malignant tumors. Epithelial-mesenchymal transition (EMT) can enhance the metastatic ability of cancer cells, which can stimulate many biological special characteristics of MCSC, including remodeling the cytoskeleton, reduced adhesion, etc., allowing them to escape the primary site and spread throughout the body [37]. During cancer metastasis, CSCs undergo epithelial-mesenchymal transition (EMT) thereby acquiring mesenchymal features, migrating to adjacent stromal tissues, and invading blood vessels or lymphatic vessels, thereby enhancing cancer recurrence and metastasis [38,39]. The role of the microenvironment is also non-negligible in transferring CSC.

Tumorigenic ability

In terms of animal experiments, the tumorigenic capacity of CSC is defined as the ability of a subset of cells with stem cell properties to induce phenotypic copies of the original tumor after continuous transplantation into NOD/SCID mice and to continue to grow into tumors that can be continuously transplanted [40]. The number of CSC is very small, and the tumorigenic ability is more than hundreds of times larger than that of common tumor cells, which is an indispensable factor for tumor development, progression and maintenance. Animal experiments clearly verified that cancer stem cells have strong tumorigenic ability in vivo. In 1994, the Lapidot team successfully isolated the tumorigenic stem cell population of acute myeloid leukemia for the first time, and its tumorigenicity was fully confirmed by animal experiments [9]. Subsequently, its tumorigenicity has been continuously explored through animal experiments in various solid cancers, including breast cancer, brain cancer, ovarian cancer, and pancreatic cancer

Drug resistance

Cancer stem cells (CSCs) are an important cause of tumor recurrence and drug resistance. Cancer cells develop tolerance for many reasons, one of which is the ability to actively excrete therapeutic agents through ABC-family transporters and induce overexpression of the metabolic enzyme aldehyde dehydrogenase (ALDH) [41], while interestingly, a feature of cancer stem cells in the context of drug resistance is the high level of expression of ABC transporters as well as aldehyde dehydrogenase (ALDH) expression [42]. In addition to this, increasing evidence suggests that CSC can also protect against chemotherapeutic agents through multiple mechanisms, such as excessive activation of the DNA damage response (DDR), apoptosis evasion, activation of Notch, Hedgehog, and Wnt pathways [43], and cell cycle promotion and/or altered cellular metabolism (e.g., mitochondrial metabolism) [44].

Dysregulated signaling pathways in CSC and their effect on cancer cell stemness

It is clear that all signaling pathways function as a coordinated network rather than operating in isolation.The phenotype of CSCs relies on the output of the entire signaling network.Currently, the main stem cell signaling pathways are Wnt/β-catenin, Notch, and Hedgehog (Hh) [45].In the case of cumulative mutations or absence of regulatory mechanisms, the above signaling cascade network may be aberrantly activated or dysregulated, leading to some changes in the cellular characteristics of CSCs. This aberrant activation may be beneficial to enhance the self-renewal ability, the cell proliferation and differentiation in CSCs. Here we briefly introduce one of these signaling cascades, Wnt/β-catenin pathway.The Wnt/β-catenin pathway has been verified to can be activated by β-catenin, leading to the expression of target genes regulating stem cell self-renewal and playing an essential role in normal and pathological cell stemness.In lung cancer, inhibition of the Wnt/β-catenin pathway significantly downregulated Oct-4/Nanog expression, restored susceptibility to clinically relevant anticancer drugs and reversed EMT process [46]. LncRNAs can also regulate cancer stem cells by regulating Wnt/β-catenin signaling channels, thereby regulating malignant proliferation of tumors. For example, LncRNA-p21, as a tumor suppressor in colorectal cancer, can suppress CSC-like characteristics (such as self-renewal ability) in colorectal cancer by inhibiting the activation of β-catenin signaling [47].As mentioned above, dysregulated signaling pathways in CSCs do play an integral role in the maintenance of cancer cell stemness.

The concept of Linc-ROR and its regulatory mechanisms in CSCs

The reprogramming regulator (Linc-ROR), located on chromosome 18 and composed of four exons, is a novel and important oncogenic LncRNA with the length of 2.6 kb, participating in the regulation of cellular reprogramming processes [48]. Researches in this field have been extensively expanded owing to its discovery, showing the important functions of Linc-ROR in tumorigenesis.Initially, it was reported as a highly expressed transcript of pluripotency and embryonic stem cells, and subsequent reports confirmed that Linc-ROR regulate the self-renew of human embryonic stem cell by targeting microRNA and upregulating the expression of core transcription factors(Sox2, Oct-4 and Nanog) [14].Moreover, Linc-ROR plays a critical role in maintaining iPSCs and embryonic stem cells (ESCs) by preventing the activation of cellular stress pathways, including the p53 response.Subsequently, further studies found that Linc-ROR inhibited p53 translation by interacting with heterogeneous nuclear ribonucleoprotein I (hnRNP I) of DNA damage [49], and clarified a link between Linc-ROR and oncogenes c-Myc in cancer progression [50].In addition, it has been reported that Linc-ROR is involved in the regulation of Wnt/β-catenin, Hippo/YAP, MAPK/ERK, EMT and hypoxia signaling pathways.In short, increasing evidence suggests Linc-ROR represents a potent tumor promoter that plays an important role in the malignant development of tumors. In pancreatic cancer, Linc-ROR induces ZEB1 expression to promote EMT, enhance the invasion and metastasis ability of cancer cells, and promote the occurrence of pancreatic cancer. This paper also proposed that Linc-ROR/ZEB1 /EMT may be the regulatory axis of pancreatic cancer stem cells, as ZEB1 can regulate CSCs [51]. Most notably, Linc-ROR has been found to be aberrantly expressed not only in different cancers, but also highly expressed in CSCs and is able to interact with miRNAs and maintain stem cell pluripotency [52].Recognizing the fact that inhibition of Linc-ROR may reduce the chance of CSCs becoming the origin of cancer and can facilitate related research and cell therapy, we therefore explore the possible function of Linc-ROR in CSCs.

Firstly, Linc-ROR is a positive regulator of CSCs. As a reprogramming regulator, Linc-ROR was validated to be elevated in human induced pluripotent stem cells(iPSC) and able to modulate iPS-mediated reprogramming, possibly by interacting with chromatin modification complexes to contribute to regulating different epigenetic structures in pluripotent cells [53].The core transcription factors (TFs), such as Sox2, Oct-4 and Nanog, are expressed in various tumors and are associated with undifferentiated phenotypes, underscoring that iPSCs are functionally and phenotypically similar to ESC, and pluripotency is induced by reprogramming these cells into iPSCs by exogenously introducing these TFs into mouse or human adult cells [54].However, the influence of Linc-ROR may be consumed when there are plentiful microRNAs, and Linc-ROR prevents microRNA mediated repression of TFs (Sox2, Oct-4 and Nanog) in self-renewing human embryonic stem cells (ESCs).For example, Linc-ROR has previously been shown to act as a molecular "sponge" and competitively regulate Sox2 expression with miR-145, thereby achieving pluripotency maintenance in human amniotic epithelial cells (HuAEC), regulating their efficiency of directed β-islet--like cell differentiation, and helping to restore islet function [55].Linc-ROR also acts as a microRNA sponge to regulate the expression of the core transcription factors Oct4, Sox2, and Nanog during self-renewal in human embryonic stem cells.Overall, this role in regulating core transcription factors by acting as microRNA "sponges" is visible in a variety of cancers.For example, miR-145 is a relatively commonly induced microRNA of Linc-ROR promoting CSC properties.The expression of Sox2, Oct-4 and Nanog is induced by negative regulation of miR-145 in endometrial cancer thereby differentiation of cancer stem cells [56].In OA, chondrogenic differentiation and chondrogenesis of BMSCs (MSCs) are promoted by acting as competitive endogenous RNAs for miR-138 and miR-145 and activating Sox9 [57].What's more, Linc-ROR can also mediate the acquisition of CSC properties by other microRNAs, including let-7 miRNA family, as well as miR-93–5p, miR-320a, miR-320b,miR-15b, miR-33a, miR-129, miR-206 and so on [58,59]. Indeed, Linc-ROR acts as a sponge for microRNAs that target major CSCs-associated core transcription factors (e.g., Sox2, Oct4, and Nanog) and exhibits positive effects on the self-renewal of CSCs and

maintenance, which are required for pluripotent stem cell phenotypes and their proliferation [60].

Nextly, as is well known, many signaling pathways are significantly associated with the development of tumors.Therefore, we summarize some of the Linc-ROR regulatory signaling pathways related to tumor development, and explore how these signaling pathways contribute to tumor development in cancer stem cells. Notably, the Wnt/β-catenin signaling pathway, also called canonical Wnt signaling pathway, is a conserved signaling axis that controls a large number of biological processes during animal development and life cycle, including various physiological processes involved in proliferation, differentiation, apoptosis, migration, invasion, and tissue homeostasis.For example, Linc-ROR can promote migration of ovarian cancer cells by activating the Wnt/β-catenin protein signaling pathway, which leads to activation of EMT signaling [61].Of course, Wnt/β-catenin signaling is also associated with regulating pluripotency, self-renewal and differentiation ability of stem cells. However, the relationship between Linc-ROR and Wnt/β-catenin signaling remains unknown and is needed to be further studied in cancer stem cells. Linc-ROR can also cause the activation of the Hippo/YAP pathway and promote proliferation, migration, and invasion of pancreatic cancer cells [62].The Hippo/YAP pathway, an evolutionarily conserved regulator of tissue growth and cell fate, is a potential pathway capable of regulating tissue homeostasis, organ size, and stem cells and is considered important for human cancer [63,64].It has been shown that YAP1 inhibitor CA3 can inhibit the growth of CSCs in radiation-resistant EAC cells with high YAP1 expression and reduce the number of these cells in Esophageal Adenocarcinoma [65].The MAPK/ERK signaling pathway plays a fundamental role in controlling key cellular processes including cell survival and proliferation, and improper regulation of this pathway leads to abnormal cell behavior promoting carcinogenesis, which includes increased cell growth and proliferation, dedifferentiation, and survival [66].Furthermore, as we know, the MAPK/ERK signaling pathway is negatively regulated by mitogen-activated protein kinase phosphatases, in which the protein kinase phosphatase DUSP7 can participate in ERK dephosphorylation [67].Interestingly, knockdown of Linc-ROR increased DUSP7 protein stability, leading to inhibition of ERK phosphorylation, and re-overexpression of Linc-ROR restored all of these phenotypes, suggesting that Linc-ROR promotes estrogen-dependent growth and activation of the MAPK/ERK pathway in breast cancer cells by regulating the ERK-specific phosphatase DUSP7 [68].Wnt/β-catenin, Hippo/YAP, MAPK/ERK rank-linked signaling pathways are very likely to be abnormally activated or regulated to some extent under the pressure of cumulative mutations or loss of regulation, resulting in changes in stem cell characteristics present in CSC, enhanced self-renewal ability, and enhanced malignant proliferation ability.Linc-ROR acts as a trigger molecule for these signaling pathways, and we speculate that it is also able to regulate these signaling pathways in various cancer stem cells through various downstream target genes.

In addition, Linc-ROR, as a non-coding RNA, has unlimited exploration possibilities in mediating the role of information exchange between cells and thus promoting tumor development. Extracellular vesicles (EVs; including exosomes and microvesicles) can transport proteins, lipids, microRNAs, mRNAs, DNA, and more recently LncRNAs from one cell to another. Recently, exosomes have become increasingly popular, and in the microenvironment, they become important mediators of information exchange between tumor cells and stromal cells, delivering and exchanging their abundant components, including LncRNA [69]. In pancreatic cancer, exosome Linc-ROR can mediate crosstalk between cancer cells and adipocytes via the HIF1α/ZEB1 axis and promote pancreatic cancer tumor growth [70]. Similarly, exosomes from CSC clones can be isolated, purified, and quantified in thyroid cancer stem-like cells, and CSC exosomes can induce EMT and increase the invasive potential of normal thyroid cells through metastasis and Linc-ROR expression, and targeting this mechanism can provide effective therapeutic strategies for the treatment of invasive thyroid cancer [71]. Transfer of ncRNAs (e.g., miRNAs or LncRNAs) via EVs may represent a novel mechanism for cell-to-cell communication that promotes tumor growth and metastasis. Presently, because Linc-ROR from cancer stem cells and exosomes is poorly understood, perhaps in-depth studies can make a significant contribution to drug therapy in the clinic.

Potential clinical applications of Linc-ROR in human cancer

Cancer develops very rapidly. It's difficult to make a rapid diagnosis for cancer patients early, and in particular specific biomarkers are also lacking in current medical conditions. For that, it is essential to identify and monitor specific cancer biomarkers for cancer-related molecular differences that are suitable for early diagnosis. These biomakers will help to develop optimal treatment options and gain valuable treatment time for cancer patients. There is an abundance of evidence to support the fact that long non-coding RNAs (LncRNAs) can influence cancer development and progression through diversified signaling pathways. Due to the abnormal expression and specificity in tumors, LncRNAs have the potential to become cancer biomarkers. However, the number and types of LncRNAs are too large, resulting in the incomplete determination of many molecular functions of LncRNAs, which is difficult to accurately predict tumor progression.Tables 1 and 2

Zhao, Tianhe et al.,pointed out that Linc-ROR expression was significantly higher in breast cancer tissues and plasma, and the expression level was closely related to lymph node metastasis in plasma, but the expression level of Linc-ROR in postoperative plasma was lower than that before surgery, which indicated that Linc-ROR may be a prognostic marker for breast cancer in clinical practice [72]. Interestingly, this author also found that Linc-ROR had higher sensitivity and specificity than traditional markers CEA and CA153 in the same breast cancer patient by ROC curve comparison. This gives us a hint that Linc-ROR combined with traditional biomarkers may yield better diagnostic capabilities.Besides,in NSCLC patients, there are some clinical parameters that are positively correlated with high Linc-ROR expression levels, such as advanced TNM stage and distant metastasis.In addition, patients with higher Linc-ROR expression had markedly shorter 5-year overall survival (OS) and disease-free survival (DFS) [73]. Similarly, in gastric cancer patients, Linc-ROR was highly expressed in gastric cancer tumor tissues compared with paired normal tissues and was closely associated with poor prognosis, indicating that it's possible for Linc-ROR to become a potential predictive biomarker in gastric cancer [74].Recent studies have found that the overall distribution of rs6420545 and rs4801078 genotypes of Linc-ROR has a close relationship with advanced tumor grade and lymph node metastasis, respectively, and Linc-ROR gene variants may make a great contribution in metastasis and progression mainly occurred in advanced events of OSCC tumorigenesis, and these variants can be used for precise therapeutic management of this cancer, especially in prognosis [75].

The above findings suggest that Linc-ROR may serve as a suitable marker for the diagnosis of multiple cancers. But there is still much room to explore the specific molecular mechanisms by which Linc-ROR plays a pivotal part in various cancers. Linc-ROR therefore requires further exploration and validation in this field, especially in clinical applications.

Table 1
This table summarizes the above several transcription factors in the mentioned tumors.

Cancer type	Key transcription factors	Reference
colorectal cancer(CRC)	Sox2,Oct-4,Nanog	[16]
breast cancer	Oct-4	[18]
hepatoma	Oct-4	[19]
osteosarcoma	Sox2	[25]
pancreatic cancer	Sox2,Nanog	[26]
lung cancer	Oct-4,Nanog,Sox-2	[30]

Table 2
The role of Linc-ROR in various cancer types.

LncRNA	Cancer type	Mechanism	Function	Reference
Linc-ROR	breast cancer	hnRNP I - p53 axis	response to DNA damage	[49]
		DUSP7-MAPK/ERK signaling	promote estrogen-dependent growth	[68]
	colorectal cancer	interact with hnRNP I and AUF1, upregulate c-Myc	promote proliferation and tumor growth,as a potential marker of CSCs	[50]
		upregulate ZEB1 and activated EMT	promote proliferation and metastasis, as a potential marker of CSCs	[51]
	pancreatic cancer	sponge let-7 miRNA family, as well as miR-93–5p, miR-320a, miR-320b	promote proliferation, invasiveness and stem cell properties	[58]
		HIF1α-ZEB1 axis, EMT	maintain the growth and metastasis of PC cells	[70]
	endometrial cancer	negatively regulate miR-145, upregulate Oct4, Sox2 and Nanog	regulate stemness, enhance the differentiation and self-renewal of CSCs	[56]
	sophageal squamous cell carcinoma	sponge miR-15b, miR-33a, miR-129, miR-206,	regulate stemness and maintain the growth of CSCs	[59]
	ovarian cancer	activate Wnt/β-catenin and EMT signaling	promote metastasis and as a potential marker of CSCs	[61]
	thyroid cancer	transported by exosomes and activate EMT signaling	promote metastasis and proliferation of CSCs	[71]

Conclusion

The development in cancer is a complex process of multiple regulatory mechanisms, in which cancer cells are able to switch between stemness and non-stemness states and actively respond to the stimuli from genetic or epigenetic changes, various different factors of the microenvironment, and activation of cellular developmental programs. These alterations can endow cancer stem cells with self-renewal and proliferation ability, express key molecules that maintain stem cell properties, enhance their migration ability, increase drug resistance as well as high tumorigenic ability, which leads to poor prognosis of cancer. Linc-ROR has been widely acknowledged as a transcript highly expressed in pluripotency and embryonic stem cells, and was able to lead to the higher expression of the core transcription factors (e.g., Oct4, Sox2, and Nanog). It was shown that Linc-ROR could be a critical factor in regulating cancer stem cell properties in further studies. So we believe that Linc-ROR could become an interesting potential therapeutic target for cancer stem cells. However, many articles have investigated the mechanism of Linc-ROR in tumor cells or CSCs at present, but no specific literature has been found to verify the function of Linc-ROR in non-malignant cells. The fact shows that there is still a lot of room to study the role of Linc-ROR.A deeper understanding of the mechanisms of stem cell regulation at the biological and clinical levels may be expected to bright the development of new treatments..

Conflict of interest

The authors declare no conflicts of interest.

Declaration of interests

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.

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