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Review Article

The role of long non-coding RNAs in human carcinoma

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ABSTRACT

Long non-coding RNAs (LncRNAs) are usually longer than 200 nucleotides in length, which have 4 functions including signal, decoy, guide and scaffold in cells. Many studies have shown that the expression of LncRNAs is differentially between normal tissues and cancers, including hepatocellular carcinoma (HCC), bladder cancer, epithelial ovarian cancer, gastric cancer and other cancers, which suggests that alterations in the expression of LncRNAs could promote or inhibit tumor growth. However, the exact mechanisms by which LncRNAs play their roles in the normal and tumor cells remain unclear. This article reviews the role of LncRNAs in some common human carcinomas especially in HCC.

Keywords: Long non-coding RNAs, Human carcinoma, HCC, Gene regulation

INTRODUCTION

Tumor burden is a serious problem to many countries and people. There are many studies that focused on the mechanisms and therapeutic methods of human carcinoma. However, the genetic mechanisms behind human carcinoma are largely unknown, still need to be further explored for finding out new management of human carcinoma and improving the effect of therapy.

Non-coding RNAs, such as small inference RNAs (siRNAs), micro RNAs (miRNAs), PIWI-interacting RNAs (piRNAs) and long non-coding RNAs (LncRNAs), which account 90% of human RNAs, are the RNAs that do not encode proteins. But they have been found to play key roles in multiple cellular processes, such as immune response, cell proliferation and migration, angiogenesis and apoptosis.[1] The early articles showed that LncRNAs were initially deemed to be the products of a 'noisy' and unimportant transcription which were derived from RNA polymerase distortion.[2] LncRNAs are usually longer than 200 nucleotides in length, which were characterized by complicated molecular structures and obscure molecular functions.[3] Recent studies suggest that we can use computational transcriptome prediction to identify LncRNAs.[4]

Studies have demonstrated that the most important functions of LncRNAs were signal, decoy, guide and scaffold.[5,6] LncRNAs regulate gene expression at epigenetic, transcriptional and post-transcriptional levels, which are involved in many biologic functions, including genomic imprinting, chromosome dosage-compensation, X-chromosome silencing, chromosome modification, intranuclear transport, transcriptional activation, and interference.[7] With multiple biologic functions, more and more studies demonstrate LncRNAs play important roles in human carcinomas.[8,9] In recent years, LncRNAs are being regard as ether cancer promotors or tumor suppressors, they can't be treated as useless transcriptional 'noise' anymore.[10] Lots of studies found that LncRNAs might interact with DNA, RNA or protein and modulate the expression of genes which result in human carcinoma, and the levels of LncRNAs could recognize as potential biomarkers, which can contribute to the diagnoses and therapies of human carcinoma.[11-13]

Here, review current findings of LncRNAs in human carcinoma.

LNCRNAS IN HUMAN CARCINOMAS

The dysregulation of LncRNAs is linked to many human diseases and tumors. LncRNA LINC01093 is downregulated in CCl4-induced mice liver fibrosis tissues and promoted hepatocyte apoptosis, which can be abolished by the over expressed LINC01093.[14] LncRNAs HOTTIP (HOXA transcript at the distal tip), which can regulate miR-455-3p via competing endogenous RNA (ceRNA), play pivotal roles in osteoarthritis (OA) by negatively regulated miR-455-3p and increased the chemokine CCL3 levels in human primary chondrocyte.[15,16] Some LncRNAs are the potential regulators of proliferative retinopathy, and some LncRNAs may be involved in modulating host immune response to TB infection.[17,18] Furthermore, more and more studies have demonstrated that LncRNAs are aberrantly expressed in human carcinomas.

Urologic cancers

Recent studies have shown that LncRNAs could be used as biomarkers in prostate, kidney and bladder cancer and be recognized as new therapeutic targets.[19] Zhang et al found that LncRAN might play an important role in the pathogenesis of human bladder cancer.[20] They measured the expression of 11 candidate LncRNAs in exosome, and found that the high LncRNA UBC1 expression was linked to lower recurrence-free survival.[21] Through other studies about LncRNAs in renal cell carcinoma, Song et al suggested that RCCRT1, one kind of LncRNA, was upregulated in the renal cell carcinoma compared with adjacent tissues and promoted migration and invasion of renal cell carcinoma.[22] In prostate cancer, LncRNA ARLNC1, regulated by androgen receptor (AR), is strongly associated with AR signaling in prostate cancer progression. ARLNC1 could be induced by AR and further stabilized the AR transcript via RNA-RNA interaction, which was very important in prostate cancer growth.[23] Ren et al found that LncRNA MALAT-1 might be needed to maintain prostate tumorigenicity, indicating that it was involved in prostate cancer progression, and was a new potential therapeutic target for castration resistant prostate cancer.[24]

Digestive system carcinomas

Studies showed that LncRNAs may play an important role in digestive system carcinomas. Some of these LncRNAs might function as both diagnostic markers and the treatment targets of digestive system carcinomas.[25] Zhang et al found that LncRNA HOXC-AS3 which was significantly increased in gastric cancer tissues and promoted proliferation and migration was correlated with clinical outcomes of gastric cancer.[26] And some other documents demonstrated that MALAT1 acting as a promotor of gastric cancer cell proliferation by regulating splicing factor2/alternative splicing factor (SF2/ASF), and the pathway H19/miR-675/RUNX1 modulating gastric cancer progression might serve as new targets for gastric cancer therapy.[27,28] As for metastasis of gastric cancer, Wang et al indicated that synuclein-gamma (SNCG), a metastasis-associated gene in gastric cancer, up-regulated by LncRNA AK058003 through DNA demethylation mediated hypoxia-induced gastric cancer cell metastasis and invasion, suggesting that AK058003 may be a new biomarker of gastric cancer.[29] LncRNA PVT1, the first LncRNA found in human cancers, was over expressed in Barrett's esophagus and esophageal adenocarcinoma and the positive feedback was discovered between PVT1 and yes-associated protein (YAP), which could both be inhibit by the antisense oligonucleotide (ASO) of PVT1.[30]

Gynecological cancers

For the past few years, LncRNAs are emerging as either oncogenes or tumor suppressor factors and play a potential role in female reproductive system carcinomas. Qiu et al demonstrated that estrogen (E2) regulated LncRNAs TC0101441 expression in estrogen receptor α (ERα) positive epithelial ovarian cancer cells and that this regulation was ERα-dependent. TC0101441 was involved in E2-induced epithelial ovarian cancer cell metastasis.[31] Moreover, multiple of LncRNAs participated as ceRNA in mesenchymal ovarian cancer, and LncRNA PTAF was one of them, which induced elevated snail homolog 2 (SNAI2) expression by acting as ceRNA and competitively binding to miR-25, which in turn promoted ovarian cancer cell epithelial mesenchymal transformation (EMT) and invasion.[32] Wang and his colleagues suggested that LncRNA PVT1, activated by c-Myc, played an important role in cervical cancer cell progression, which sponged miR-486-3p and released its repression of extracellular matrix protein 1 (ECM1), indicating that PVT1 was thought to the potential target in cervical cancer therapy.[33]

Lung adenocarcinoma and breast cancer

Pan et al suggested that people with lung adenocarcinoma who had high levels of LncRNA ZXF1 expression had a relatively poor prognosis. And they also found that suppression of LncRNA ZXF1 by siRNA reduced the metastasis of tumor cells in vitro.[34] Other documents showed that LncRNA HOTAIR (HOX transcript antisense intergenic RNA) was important for cell growth and viability. HOTAIR was activated by JMJD6, a bifunctional lysyl hydroxylase and arginine demethylase. Knockdown of HOTAIR caused apoptosis in breast cancer cells.[35] The up-regulation of HOTAIR in triple-negative breast cancer was associated with lymph nodes metastasis and poor prognosis.[36]

Pituitary tumor and glioma

Studies showed that LncRNA MEG3 was a tumor

suppressor in the pituitary and its inactivation contributes to non-functioning adenomas (NFA) progression. MEG3 and miR-376B-3P were decreased in patients with clinical nonfunctioning pituitary adenomas (CNFPA), and their transcriptional levels were highly associated with invasive CNFPAs. Moreover, excessive expression of MEG3 and miR-376B-3P inhibited tumorigenesis and promoted apoptosis in PDFS cells.[37] Zhang and colleagues indicated that the significant roles of LncRNAs in the biogenesis, proliferation and differentiation of gliomas, and provided a critical platform for future studies.[38] Through acting as oncogenes or tumor suppressors, LncRNAs might contribute to glioma initiation, progression and metastasis.[39]

Melanoma and squamous cell carcinomas

The expression of LncRNA Llme23 is only detected in human melanoma cell lines. Knocking down Llme23 apparently reduced the malignant property of YUSAC cells, one kind of human melanoma cell lines, accompanied by the repressed expression of proto-oncogene Rab23.[40] Steroid receptor RNA activator (SRA), a LncRNA, participated in the proliferation, migration, and invasion of human melanoma cell lines, including B16 cells and A375 cells. Inhibition of SRA could significantly reduce melanoma development, which was mediated by p38 activation.[41] The therapy of melanoma is still pool, these studies provided new ways to improve the prognosis of melanoma.

Squamous cell carcinomas (SCCs) are aggressive malignancies. Expression of LncRNA CCAT1 was increased in SCCs and might play an important role in migration and invasion.[42] Li and colleagues reported that HOTAIR was up-regulated in the tissues of laryngeal SCC tissues and contributed to progression of laryngeal SCC.[43] Moreover, LncRNA LINC01503 was expressed at significantly higher levels in esophageal and head and neck SCCs than in non-tumor tissues, which was negative with shorter survival times of patients and maybe selected as a biomarker of aggressive SCCs in patients.[44]

LNCRNAS IN HCC

Recently, multiple of studies have indicated that altered patterns of LncRNAs in HCC despite the precise mechanism of their action is still largely unclear.[45] These mRNA-like transcripts have been involved in the development of HCC with the functions of transcriptional, post-transcriptional and epigenetic mechanisms.[46]

LncRNAs in the development of HCC

Wang et al revealed that the LncRNA lncTCF7 was over expressed in liver cancer tissues and cancer stem cells, which could accelerate liver cancer stem cells self-renewal and tumor migration via activation of Wnt signaling and recruiting the SWI/SNF complex to the TCF7 promoter.[47] And another LncRNA UFC1, which is a target of microRNA34a, inhibits apoptosis in HCC cells and accelerate growth of xenograft tumors in mice. It interacts with the mRNA stabilizing protein HuR to modulate levels of β-catenin in hepatocellular carcinoma cells.[48] Using XAV-939, a β-catenin inhibitor significantly reduced cell invasion and migration caused by LncRNA UFC1 overexpression.[49] HOTAIR played an important role in hepatocarcinogenesis via promoting the release of exosomes by inducing multivesicular bodies (MVB) transport to the plasma membrane.[50] In addition, HOTAIR was found to be a decoy of miR-130a-3p which regulated hypoxia-inducible factor 1α (HIF1-α) and the procession of glycolysis which was a character of tumor metabolism, knockdown of HOTAIR suppressed glycolysis in HCC cells treated by hypoxia.[51]

Recently, Wu et al found the LncRNA MER52A, which was specific expressed in HCC cells, was significantly up-regulated in HCC and could accelerate tumor growth in vitro and in vivo. The effect of this LncRNA depended on stabilizing p120-catenin and then triggered the activation of Rho GTPase, which at last promoted invasion and metastasis of HCC cells.[52] And Xu et al concluded that the overexpression of LncRNA URHC could accelerate cell proliferation and suppress apoptosis by reducing zipper containing kinase (ZAK) expression and down regulating the ERK/MAPK pathway.[53] Some other studies have found that LncRNA MALAT1 was over expressed in HCC cells. MALAT1 would link the inflammatory response to the progress of HCC by recruiting brahma-related gene 1 (BRG1), a catalytic subunit of chromatin remodeling complex switching/sucrose non-fermentable (SWI/SNF), to the promoter region of oncogene, and simultaneously activating the NF-κB pathway to release inflammatory factors. Knockdown MALAT1 reduced both the inflammation and the proliferation of HCC cells and promote its apoptosis.[54]

Cui et al indicated that LncRNA HULC was responsible for the perturbations in circadian rhythm by up-regulating circadian oscillator CLOCK in hepatoma cells, which promoting hepatocarcinogenesis. Apparently, they found that the high expression of HULC resulted in disordering the expression pattern and prolonging the periodic expression of CLOCK in hepatoma cells. Moreover, some evidences demonstrated that CLOCK was involved in the HULC-enhanced proliferation of hepatoma cell in vitro and in vivo.[55] What's more, HULC also play a key role in liver cirrhosis by modulating oxidative stress.[56] HULC also participated in the progress of HBV which was one of the key factors for HCC.[57] Furthermore, Xie et al have found that HULC was differentially expressed in the tissues and plasma of the HCC patients compared with those of healthy controls, suggesting that the expression of HULC in plasma can be used as a new diagnostic and/or prognostic biomarker for HCC.[58]

LncRNAs as HCC suppressors

The p53-stabilizing and activating RNA (PSTAR), a LncRNA, play an important role in p53-mediated cell cycle arrest and apoptosis of HCC cells, which reduced cell proliferation and inhibited tumorigenicity. PSTAR may act as a novel therapeutic target in the treatment of HCC. The down regulation of PSTAR was associated with poor prognosis of HCC patients.[59] And Mo et al found that FAM99B, a liver specific LncRNA, was down regulated in HCC tissues compared with adjacent normal tissues by using bioinformatic analysis. The low level FAM99B was linked to poor survival in HCC patients. The overexpression of FAM99B significantly inhibited cell proliferation, migration, and invasion in vitro. Therefore, lncRAN FAM99B would be an HCC suppressor.[60] Phosphatase and tensin homolog (PTEN) is a tumor suppressor by regulating tumor metabolism and growth.[61] The LncRNA TCL6 can promote the expression of PTEN by targeting miR-106a-5p, which suggested that TCL6 as a tumor-suppressive via directly binding to miR-106a-5p in HCC.[12] Another LncRNA F11-AS1 also be looked as a tumor suppressor by mediating the expression of PTEN via binding with and negatively regulating miR-3146.[62]

LncRNA promote HCC metastasis

Metastasis is the main cause of cancer-related death, and some studies found several LncRNA contributed to the metastasis of HCC. Ma et al identified LncRNA MITA1 which was regulated by AMPK pathway and DNA methylation and was upregulated in HCC patients, promoted early migration and invasion of HCC cells by promotes epithelial-mesenchymal transformation (EMT), an early and central step of metastasis[63]. Yuan et al reported that LncRNA ATB, activated by TGF-β, accelerated HCC cell metastasis by binding the miR-200 family, up-regulating zinc finger ebox binding homeobox1 (ZEB1) and ZEB2, and then inducing epithelial mesenchymal transformation (EMT). On the other hand, LncRNA-ATB promoted hepatocellular carcinoma cells colonization at the site of metastasis by binding IL-11 mRNA, elevating IL-11 mRNA stability, resulting in autocrine of IL-11, and then activating STAT3 signaling.[64] Some other LncRNA also play an important role in tumor metastasis. LncRNA SNHG8 acted as a sponge of miR-149 and counteracted the tumor suppressive effects of mi R-149 in HCC cells, which resulted HCC tumorigenesis and metastasis.[65] Some LncRNA's was found to inhibit the metastasis of HCC. LncRNA miR503HG, the host gene of miR503, is decreased in HCC and significantly associated with the time of HCC recurrence, which was an independent risk factor for recurrence and survival. miR503HG could promote the heterogeneous nuclear ribonucleoprotein A2/B1 (HNRNPA2/B1) degradation and suppressed the NF-κB signaling pathway in HCC cells.[66] LncRNA MIR31HG also can suppressed the metastasis by decreased the expression of oncogenic miR-575, and enhanced the expression of suppression of tumorigenicity 7 like (ST7L).[67] Therefore, the role of LncRNA in the metastasis of HCC is very complicated because of the quantity of LncRNA and their functions are diverse. More works are need to clarify their exact roles.

LncRNAs as prognostic factors of HCC

There are many factors that should be taken into consideration when predicting the outcomes and prognosis of hepatocellular carcinoma, such as the tumor size, number, the age of patients, tumor stage, hemoglobin levels, hepatic function.[68] Need some more accurate biomarkers for precise medication. LncRNA RGMB-AS1, an independent favorable prognostic factor for hepatocellular carcinoma patients, associated with clinical stage, tumor size and metastasis. The overexpression of RGMB-AS1 expression suppressed hepatocellular carcinoma cells proliferation, migration and invasion, and promoted cells apoptosis.[69] Li et al suggested that LncRNA SNHG and LncRNA UCA1 in tissue or serum of HCC patients may serve as prognostic biomarkers for HCC prognosis, as patients with higher expression of pooled SNHG/UCA1 had significant poor survival.[70] Chen et al indicated that LncRNA NKILA was down-regulated in HCC and deceased NKILA had a close relationship to large tumor size. Low NKILA in HCC patients showed poor prognosis and lower 5-year overall survival rates, which could be selected as an effective prognostic biomarker.[71] What's more, LncRNA GAS5-AS1 may be another biomarker of diagnosis and prognosis for HCC patients. This LncRNA in the plasma samples of HCC patients was lower than health people, and patients with lower GAS5-AS1 expression had a relatively poor prognosis.[72] Even though, lots of LncRNAs are significantly associated with the prognosis of HCC patients, the application of these LncRNAs need more observations and studies.

CONCLUSION

LncRNAs could regulate gene expression via epigenetic, transcriptional and post-transcriptional manner, and were involved in other biologic process, including genomic imprinting, chromosome dosage-compensation, X-chromosome silencing, chromosome modification, intranuclear transport, transcriptional activation, and interference. Recently, LncRNAs are seemed as an important factor that control the development of human carcinoma, expanding our horizon on the novel biomarkers and new therapeutic targets. However, the LncRNAs field is still in its infancy, both challenges and hopes arise from the studies of LncRNAs. With complicated molecular structure, LncRNAs interact with DNA, RNA and protein, modulating a lot of genes expression. And the annotation of LncRNAs remains challenging and incomplete, and our ability to predict the structure and function of LncRNAs remains limited. LncRNAs likely play potential roles in progression of HCC and other human carcinoma through diverse

mechanisms, which need further study. A crucial question between LncRNAs and HCC is how LncRNAs interact with glucolipid metabolism, hormones and micro-environmental variation to control the progression and function of HCC. Finally, more efforts are needed to explore the potential role of LncRNAs in progression of human carcinoma. In general, further studies on the detailed mechanism of LncRNAs in progression of human carcinoma, including HCC would eventually create a new avenue of cancer management.

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