TINCR: An IncRNA with dual functions in the carcinogenesis process

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\textbf{ABSTRACT}

Long non-coding RNAs (lncRNAs) have prominent roles in the pathogenesis of human cancers. Several studies have shown oncogenic or tumor suppressor roles of lncRNAs in different human tissues. Thus, these transcripts have been regarded as putative targets in treatment of cancer. The IncRNA terminal differentiation-induced non-coding RNA (TINCR) has an especial position in this regard, as it exerts different opposite roles in the pathogenesis of different human cancers. While it is up-regulated in gastric, esophageal, bladder and breast cancer; it is down-regulated in glioma, retinoblastoma and prostate cancer. Notably, data regarding expression profile of this lncRNA in a number of human cancers such as colon cancer, squamous cell carcinoma, non-small cell lung cancer (NSCLC) and hepatocellular carcinoma (HCC) are controversial. Expression level of this lncRNA has been associated with clinical outcome in patients with gastric cancer, colorectal cancer, NSCLC and head and neck squamous cell carcinoma. Moreover, Kaplan-Meier analyses have shown correlation between expression levels of TINCR and patients survival in patients with lung cancer and HCC. A number of cellular pathways such as Wnt/\beta-catenin, ERK1/2-SKP3 and MAPK signaling pathways have been identified as targets of this IncRNA in different cancers. Moreover, the rs8113645, rs2288947 and rs8105637 within this lncRNA have been associated with risk of gastric and colorectal cancer. In conclusion, although the role of TINCR in the carcinogenesis is essential, based on the conflicting data regarding the direction of effect of this IncRNA, therapeutic targeting of this lncRNA is a complicated issue which should be considered in a tissue-specific or even individualized manner.

1. Introduction

Long non-coding RNAs (lncRNAs) as a group of transcripts with sizes more than 200 nt are considered as important regulators of genes expression and carcinogenesis process. These transcripts participate in multiple cellular processes such as epigenetic regulation of gene expression, modulation of expression at transcriptional and post-transcriptional levels, thus influencing cell proliferation, apoptosis, migration and stability of the genome [1]. Several lncRNAs have been demonstrated to affect the carcinogenesis process [2]. Notably, they usually exert either oncogenic roles or tumor suppressor role in human cancers [3]. Yet, a number of lncRNAs have recently identified that their role in the carcinogenesis process depends on the tissue where they are expressed. Among these IncRNAs is the terminal differentiation-induced non-coding RNA (TINCR) [4–7]. This IncRNA has a 3733 nt length and its expression has been recognized at a late phase of human epidermal differentiation [8]. It regulates expression of several important differentiation genes such as FLG, LOR, ALOXE3, ALOX12B, ABCA12, CASP14 and ELOVL3 at post transcriptional level. Notably mutations in a number of these genes have been associated with skin diseases [8]. Functional studies have revealed the presence of a TINCR-25-nucleotide ‘TINCR box’ motif in target mRNAs that mediates interaction between these mRNAs and TINCR [8]. Additional in silico analyses predicted the role of TINCR in esophageal development as well [9]. Based on the data provided by Human Protein Atlas RNA-seq dataset, TINCR has been shown to have specific expression in skin, placenta and esophagus [9]. Subsequent studies reported its aberrant expression in a wide array of human malignancies. The most important note about this lncRNA is its different roles in the pathogenesis of different cancers. In this review, we summarize the available data regarding the role of this lncRNAs in human cancers.

2. Cell line studies

Several studies have assessed expression profile of this IncRNA in various cancer cell lines. These studies have also assessed he effects of...
| Cancer type                  | Targets/Regulators and Signaling                                                                 | Assessed cell lines                                                                 | Function                                                                                      | Reference |
|-----------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-----------|
| Gastric cancer              | STAU1, KLF2, CDKN2B/P15 and MGC803, BGC823, MKN45 and the normal gastric epithelial cell line GES-1, and the normal human breast epithelial cell line (MCF-10A), Normal human prostate epithelial cell lines (RWPE-1 and P69), SV-40-immortalized human prostatic epithelial cell line (THLE-2). | HGC27, AGS, MGC803, BGC823, MKN45, AGS, SK-1, SNU-1, and the normal gastric epithelial cell line GES-1 | An approximately two-fold upregulated expression could be observed in GC cell lines.        | [6]       |
| Colorectal cancer           | miR-375-5p/DKK1 and miR-125b signaling pathway                                                                                                     | HCT116, HCT8, HT29, SW620, and SW480                                                  | miR-375-5p/PI3K/Akt/mTOR signaling pathway                                                                 | [12]      |
| Esophageal squamous cell carcinoma (ESCC) | miR-137/miR-133a signaling pathway                                                                                                                  | SNU-182 and SNU-398                                                                     | miR-137/miR-133a role in cell cycle progression, invasion, and metastasis.                  | [29]      |
| Non-small cell lung cancer (NSCLC) | miR-20a, miR-125b, and miR-154 signaling pathway                                                                                                    | LNCaP, PC3, H1299, H522, H1650, and H460                                                  | miR-20a, miR-125b, and miR-154 role in cell cycle progression, invasion, and metastasis. | [20]      |
| Hepatocellular carcinoma (HCC) | miR-137/miR-133a signaling pathway                                                                                                                  | Huh7                                                                                   | miR-137/miR-133a role in cell cycle progression, invasion, and metastasis.                  | [30]      |
| Breast cancer               | miR-214-5p/ROCK1 signaling pathway                                                                                                                  | H1581 and SNU-475                                                                      | miR-214-5p/ROCK1 role in cell cycle progression, invasion, and metastasis.                 | [14]      |
| Bladder cancer              | miR-21 signaling pathway                                                                                                                              | H650 and H1581                                                                         | miR-21 role in cell cycle progression, invasion, and metastasis.                           | [18]      |
| Retinoblastoma              | PTEN signaling pathway                                                                                                                               | Y79 and WERI-Rb-1                                                                       | PTEN role in cell cycle progression, invasion, and metastasis.                             | [26]      |
silencing of or forced over-expression of this lncRNA in cell proliferation, apoptosis of invasive properties of these cells. TINCR silencing in human gastric cancer cell lines has decreased cell proliferation and colony formation [6]. In the following sections, we describe the role of this lncRNA in different cancer cell lines.

2.1. Gastric cancer

Expression of TINCR has been significantly higher in gastric cancer cell line compared with a human gastric epithelial cell line [10]. Notably, in gastric cancer cell lines, the nuclear transcription factor SP1 has a prominent role in induction of expression of this lncRNA. The oncogenic role of TINCR in gastric cancer cells is mediated through its interaction with STA1U protein. This interaction can modulate stability and expression of KLF2 and subsequently regulate expression of cyclin-dependent kinase genes [6]. Moreover, E2F1 enhances expression of TINCR in gastric cancer cells. Forced over-expression of E2F1 enhances gastric cancer cells proliferation, while its silencing reduces cell proliferation through hindering cell cycle progression in these cells. This transcription factor enhances growth of gastric cancer cells via induction of TINCR expression. TINCR interacts with STA1U protein to affect stability and expression of the CDKN2B transcript, thus enhancing the proliferation of these cells [11].

2.2. Colorectal cancer

In colorectal cancer cells, mechanistic studies revealed conflicting results. Small interfering RNA (siRNA)-mediated silencing of TINCR in HCT116 and HT28 cells suppressed cell proliferation, inhibited colony forming capacity and decreased cells migration and invasion [12]. On the other hand, another study in SW620 and HTC116 cells demonstrated the role of this lncRNA in suppression of proliferation and migration. Yet, a radioresistant colorectal cancer cell line (SW620R) showed over-expression of TINCR. Notably, TINCR silencing decreased radioresistance of these cells [13].

2.3. Non-small cell lung cancer (NSCLC)

NSCLC is another cancer type in which mechanistic studies of TINCR showed conflicting results. This lncRNA has been shown to interact with BRAF to enhance its kinase activity, therefore resulting in activation of MAPK pathway [14]. On the other hand, other have shown that this lncRNA decreases expression of miR-21 in NSCLC and suppresses cancer cell migration and invasion [15].

2.4. Hepatocellular carcinoma (HCC)

In HCC, two distinct studies showed association between over-expression of this lncRNA and induction of apoptosis via regulation of P53 and enhancement of cell proliferation via modulation of the miR-214-5p/ROCK1 axis, respectively [16,17]. Consistent with the latter study, depletion of this lncRNA in other HCC cell lines decreased oncogenic behavior through modulation of miR-218-5p/DDX5/akt signaling [18].

2.5. Breast cancer

SP1 has a similar role in induction of TINCR expression in breast cancer cell lines. Up-regulation of this lncRNA in these cells enhanced cell proliferation, anchorage-independent growth and inhibited cell apoptosis in these cells. Notably, TINCR exerts its oncogenic role through competing with miR-7 and modulating KLF4 expression [19]. Another study in breast cancer demonstrated the role of TINCR in stimulation of tumorogenesis through modulating expression of miR-125b and its target gene ERBB2. Through this molecular axis, TINCR inhibits apoptosis in breast cancer cells [20]. Finally, TINCR has been shown to be over-expressed in trastuzumab-resistant breast cancer cells compared with sensitive cells. Its silencing has changed the trastuzumab resistance phenotype and reversed the attained epithelial-mesenchymal transition (EMT) in these cells. Its interaction with miR-125b has been shown to release HER-2 and prompt trastuzumab resistance. The CREB-binding protein-mediated H3K27 acetylation at the promoter region of TINCR has been suggested as the underlying mechanism for over-expression of TINCR in breast cancer [21].

2.6. Other cancers

In esophageal squamous cell carcinoma cells (SCC), siRNA-mediated silencing of TINCR repressed cell proliferation, migration and invasion. Moreover, this approach led to induction of apoptosis and inhibition of cell cycle progression [22]. A single study in oral SCC verified the results of this study [23]. However, another study in diverse types of SCC originated from cervix, head and neck and lung implied a tumor suppressor role for this lncRNA as TINCR silencing by siRNA enhanced cell growth and migration of these cells [24].

Other studies in glioma [25], prostate cancer [5] and retinoblastoma [26] indicated a tumor suppressor role for TINCR. Table 1 summarizes the results of cell line studies that assessed expression and function of TINCR in various malignancies.

3. In vivo studies

A number of studies have investigated the effects of TINCR silencing or over-expression in xenograft animal models. In gastric cancer, the results of in vivo studies were consistent with the proposed oncogenic role of TINCR from cell line studies since two independent studies showed decreased tumor growth following TINCR knock-down in xenograft animal models [4,6]. In colorectal cancer, two in vivo studies revealed inconsistent results. Zhang et al. have compared the tumor growth in BALB/c mice after subcutaneous injection of HCT116-shTINCR or HCT116-NC. Notably, they reported larger sizes and more rapid growth of tumors in sh-TINCR group. Furthermore, these tumors had higher Ki-67 proliferation index, higher rate of metastatic foci in the lung and the liver compared with the control group. Thus, they suggested that TINCR silencing intensely stimulates tumor growth and metastasis [7]. On the other hand, Yu et al. have shown that stable knockdown of TINCR in HCT116 cells inhibits cancer cells growth and metastasis in BALB/c nude mice [12]. Two independent in vivo studies in breast cancer reached the similar results confirming the oncogenic role of TINCR in this kind of cancer [19,21]. Notably, the latter also verified the effects of this lncRNA in induction of Trastuzumab resistance [21]. Besides, TINCR knock-down has suppressed growth of NSCLC in xenograft model through modulating expression of miR-29b [28]. However, experiments in a mouse xenograft model which was established through subcutaneous injection of glioma cells have shown lower growth rate and tumor weight in TINCR overexpressing cells. Furthermore, protein levels of Ki-67 and RPL36 were lower in TINCR-overexpressing tumors. Thus, TINCR has been shown to suppress glioma growth in vivo [25]. Table 2 shows summary of studies which assessed function of TINCR in animal models.

4. Human studies

Several studies have compared expression of TINCR between human tumor samples and non-cancerous samples from the same tissues. A number of studies have reported up-regulation of this lncRNA in gastric, esophageal, bladder and breast cancer tissues compared with the corresponding non-cancerous tissues [4,6,28,31]. However, other studies have demonstrated down-regulated TINCR in glioma, retinoblastoma and prostate cancer [5,25,26]. Notably, data regarding expression profile of this lncRNA in a number of human cancers such as colon cancer, squamous cell carcinoma, non-small cell lung cancer and HCC
are controversial [7,12,14,16,22,23,30]. Expression level of this lncRNA has been associated with clinical outcome in patients with gastric cancer [6], colorectal cancer [12], head and neck SCC [24], non-small cell lung cancer [14] and some other cancers. Notably, Kaplan-Meier analyses have shown correlation between expression levels of this lncRNA and patients survival in both directions. This issue has been reported in patients with lung cancer [14,15] and HCC [18,30]. Table 3 summarizes the results of studies which reported aberrant expression of TINCR in clinical samples.

Based on the importance of lncRNAs in differentiating the disease status in clinical samples, a number of studies have assessed the diagnostic power of TINCR in different cancer types. This approach has been performed on both tissue samples and plasma samples. Based on the measured area under curve (AUC) values in receiver operating characteristic (ROC) curves, the best diagnostic power has been reported in colorectal cancer where plasma levels of this lncRNA could differentiate patients from healthy controls with 92% accuracy [12]. Moreover, expression levels of this lncRNA could discriminate oral SCC tissues from adjacent non-cancerous tissues with diagnostic power of 87% [23]. Table 4 summarizes the results of studies which assessed diagnostic power of this lncRNA in clinical samples.

TINCR has a number of single nucleotide polymorphisms (SNPs) which might affect expression or function of this lncRNA. Based on the importance of this lncRNA in human malignancies, these SNPs are expected to modify the risk of cancer. Ma et al. have assessed association between four tag SNPs (rs8113645, rs2288947, rs8105637, rs12610531) across the entire TINCR locus and risk of gastric cancer in a Chinese population [32]. Notably, they reported associations between rs8113645 and rs2288947 variant alleles and decreased risks of gastric cancer in the assessed population. Genotypes having A allele of rs8113645 and G allele of rs2288947 reduced risk of this cancer. Particularly, the observed associations were more prominent in younger persons, males, nonsmokers, and persons from rural areas. The functional role of the rs8113645 has been verified through the observed lower tissue expression of TINCR in GA + AA genotype carriers [32]. In another study, Zheng et al. assessed association between three tag SNPs (rs2288947, rs8105637 and rs12610531) and colorectal cancer in a Chinese population. They reported associations between rs2288947 and rs8105637 SNPs and risk of this cancer in their cohort of patients. Notably, the mentioned SNPs were cancer metastasis to lymph nodes as well [33]. Table 5 summarizes the results of studies which assessed association between TINCR SNPs and risk of cancer.

5. Conclusions

Several lncRNAs have been reported to affect carcinogenesis process [3]. Among the newly assessed lncRNAs in this regard is the TINCR. TINCR is an lncRNA whose function in human malignancies is tissue-specific. This means that TINCR exert oncogenic effects in some human tissues and tumor suppressive effects in others. This observation can be explained by a tissue-specific influence of this lncRNA on distinct signaling pathways and molecular targets which are prominent in each tissue. However, a more complicated issue has been raised when assessing function of this lncRNAs in some tissues such as colon, lung and hepatic tissues in which different studies revealed controversial results regarding the role of this lncRNA. In cancer cell lines, this observation might be explained by the diversity of cancer cell lines, passage number and other culture conditions. Yet, when this issue is assessed in clinical samples, it best reflects the heterogeneity of cancerous cells and their behavior and necessitates a personalized approach for treatment of cancer patients. Perhaps, the presence of other genetic or environmental factors is important in determination of the role of this lncRNA.

TINCR has a sponging effect on a number of miRNAs. For instance, in gastric tissues, it exerts a competing endogenous RNA (ceRNA) role to modulate PDK1 expression by sponging miR-375 [4]. In colorectal and hepatic tissues, TINCR has been shown to exert its effect in some human settings, more strict criteria should be applied for selection of patients. TINCR in the carcinogenesis. Meanwhile, different roles of this lncRNA in diverse tissues further support the critical role of tissue context or tumor microenvironment in this process. Thus, a holistic point of view which is brought by a system biology method is required for understanding the complex interaction network that determines or modifies the role of TINCR in each tissue or context.

Declaration of competing interest

The authors declare they have no conflict of interest.

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| Cancer type                  | Numbers of clinical samples (tissues, serum, etc.) | Expression (Tumor vs. Normal) | Kaplan-Meier analysis | Univariate cox regression | Multivariate cox regression | Reference |
|-----------------------------|----------------------------------------------------|-----------------------------|-----------------------|---------------------------|-----------------------------|-----------|
| Gastric cancer (GC)         | 80 primary GC tissue samples and paired adjacent non-tumor tissue samples | Up                           | High expression of TINCR predicted poor OS ($p < 0.001$) | TINCR expression was a significant prognostic indicator of DFS in patients with GC | TINCR was an independent poor prognostic indicator for DFS and OS in GC | [6]       |
| Colorectal cancer           | 80 pairs of CRC tissues and adjacent non-tumor tissues, 80 CRC plasma and 80 normal control | Up                           | High expression of TINCR was a significant prognostic indicator of DFS in patients with CRC | TINCR expression was an independent predictor of poor OS | TINCR was an independent poor prognostic indicator for DFS and OS in CRC | [4]       |
| Squamous cell carcinoma (SCC) | 56 primary SCC tissue samples and paired adjacent non-tumor tissues, 56 SCC plasma and 56 normal control | Up                           | High expression of TINCR was a significant prognostic indicator of DFS in patients with SCC | TINCR expression was an independent predictor of poor OS | TINCR was an independent poor prognostic indicator for DFS and OS in SCC | [22]      |
| Head and neck squamous cell carcinoma (HNSCC) | Plasma samples from 162 patients with GC, 110 healthy controls, 28 patients with precancerous lesions and 21 normal controls | Up                           | High expression of TINCR was a significant prognostic indicator of DFS in patients with HNSCC | TINCR expression was an independent predictor of poor OS | TINCR was an independent poor prognostic indicator for DFS and OS in HNSCC | [12]      |
| Oral squamous cell carcinoma (OSCC) | 48 pairs of primary OSCC tissues and adjacent normal tissues | Up                           | High expression of TINCR was a significant prognostic indicator of DFS in patients with OSCC | TINCR expression was an independent predictor of poor OS | TINCR was an independent poor prognostic indicator for DFS and OS in OSCC | [25]      |
| Lung cancer                 | 45 cases of lung cancer tumor tissues and adjacent normal tissues | Down                         | Low levels of TINCR were significantly correlated with poor outcome of patients with lung cancer | TINCR was an independent poor prognostic indicator for DFS and OS in lung cancer | TINCR was an independent poor prognostic indicator for DFS and OS in lung cancer | [26]      |
| Non-small cell lung cancer  | 44 NSCLC tissue samples and normal adjacent tissue controls, 26 patients with preoncotic lesions and 21 normal controls | Up                           | High expression of TINCR was a significant prognostic indicator of DFS in patients with NSCLC | TINCR expression was an independent predictor of poor OS | TINCR was an independent poor prognostic indicator for DFS and OS in NSCLC | [14]      |
| Hepatocellular carcinoma (HCC) | 248 pairs of HCC tissues and normal adjacent tissues | Up                           | High expression of TINCR was a significant prognostic indicator of DFS in patients with HCC | TINCR expression was an independent poor prognostic indicator for DFS and OS in HCC | TINCR was an independent poor prognostic indicator for DFS and OS in HCC | [18]      |
| Bladder cancer (BCa)        | 49 paired BCa tissues and corresponding noncancerous tissues | Up                           | High expression of TINCR was a significant prognostic indicator of DFS in patients with BCa | TINCR expression was an independent predictor of poor OS | TINCR was an independent poor prognostic indicator for DFS and OS in BCa | [31]      |
**Table 4**

Diagnostic value of TINCR in cancers.

| Cancer Type                  | Numbers of clinical samples | Distinguish between                                      | Area Under Curve | Sensitivity | Specificity | Reference |
|------------------------------|-----------------------------|----------------------------------------------------------|------------------|-------------|-------------|-----------|
| Gastric cancer (GC)          | 80 GC tissue samples and paired adjacent non-tumor tissue samples | GC tissue vs paired adjacent non-tumor tissue            | 0.701            | 0.65        | 0.71        | [6]       |
|                              | 30 patients and 30 controls | Plasma TINCR levels from patients with GC vs. healthy controls. | 0.70             | 0.73        | 0.63        | [10]      |
| Colorectal cancer            | 80 patients with CRC and 80 healthy controls | Plasma TINCR levels from patients with CRC vs. healthy controls. | 0.922            | 97.5        | 80.0        | [12]      |
| Oral squamous cell carcinoma (OSCC) | 48 paired OSCC and adjacent non-tumor tissues | OSCC tissue vs paired adjacent non-tumor tissue | 0.871            | 75.0        | 85.4%       | [23]      |

**Table 5**

TINCR polymorphisms and their association with cancer risk.

| Cancer type                  | Cases/Control | SNP ID       | OR (95%CI) | p-value | Description                                                                 | Reference |
|------------------------------|---------------|--------------|------------|---------|------------------------------------------------------------------------------|-----------|
| Gastric cancer               | 602/602       | rs8113645    | 0.70 (0.55–0.89) | 0.003   | GA and AA genotypes were significantly associated with decreased GC risk. GA + AA genotype carriers had lower TINCR mRNA expression levels compared with common genotype in both normal and GC tissues. | [32]      |
| Colorectal cancer            | 1400/1400 (Stage I: 600, Stage II: 800) | rs2288947    | 0.83 (0.70–0.99) | 0.037   | The G allele was associated with 23% decreased risk of colorectal cancer. AG and GG genotypes were significantly associated with decreased GC risk. | [33]      |
|                              |               | rs8105637    | 0.77 (0.67–0.88) | 1.2 × 10⁻⁴| The A allele was associated with 22% increased risk of colorectal cancer. |           |
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