Histol Histopathol (2018) 33: 327-334

http://www.hh.um.es

Histology and Histopathology

From Cell Biology to Tissue Engineering

Review

Beyond an oncogene, Lin28 is a master regulator of cancer progression

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Summary. The RNA binding protein Lin28 is increased in most human malignancies, and elevated Lin28 is a biomarker for poor prognosis and contributes to cancer progression. Lin28 functions as a master oncogene and is involved in almost all hallmarks of cancer. In this review, we summarize the aberrant molecular expression mechanisms and pathological roles of Lin28 in cancer progression. Moreover, we elaborate on the established molecular mechanisms, from the transcriptional level to the post-transcriptional and translational levels, by which Lin28 regulates cancer progression.

Key words: Lin28, RNA binding protein, Oncogene, Cancer progression

Introduction

Two paralogues of Lin28, Lin28A and Lin28B, are conserved from *C. elegans* to humans. Lin28A was first identified in the nematode *C. elegans* (Ambros and Horvitz, 1984; Bussing et al., 2008), whereas Lin28B was first identified in human hepatocellular carcinoma (Guo et al., 2006). Lin28A and Lin28B have many similar characteristics. Structurally, both are RNA binding proteins containing a cold-shock domain (CSD) at the N-terminus and two Cys-Cys-His-Cys (CCHC)-type zinc finger domains at the C-terminus (Newman et al., 2008). Functionally, both proteins are similar in that they regulate developmental timing. They are highly expressed in embryonic stem cells (ESC) and maintain the self-renewal of stem cells. They also decrease with the initiation of differentiation and are undetectable in most mature tissues (Moss et al., 1997; Seggerson et al., 2002). Due to its role in the prevention of cellular differentiation, Lin28 has successfully been used to generate inducible pluripotent cells with other stemness factors (Yu et al., 2007). In addition to their similar structure and function, Lin28A and Lin28B also have the same subcellular distribution. Both are predominantly distributed in the cytoplasm (Wu et al., 2016), however, they can shuttle between the cytoplasm and the nucleus under certain conditions (Balzer and Moss, 2007; Piskounova et al., 2011).

Currently, both Lin28A and Lin28B are believed to act as multifunctional oncogenes to promote tumorigenesis and cancer progression. The aberrant expression of both Lin28A and Lin28B in cancer and their pathological roles in cancer progression have been extensively reviewed (Zhou et al., 2013; Jiang and Baltimore, 2016). However, the molecular mechanisms by which Lin28 promotes cancer progression are largely unexplored. Recently, numerous studies have found that Lin28 is a master oncogene that regulates cancer progression through different molecular mechanisms.

In this review, we briefly summarize the aberrant expression and the pathological roles of Lin28 in human malignant tumors, and intensively elaborate upon the established molecular mechanisms by which Lin28 regulates cancer progression.

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DOI: 10.14670/HH-11-922

The expression of Lin28 is universally increased in cancer

Elevated expression of Lin28A or Lin28B is observed in almost all malignant tumor types (Saiki et al., 2009; Helland et al., 2011; Jiang et al., 2012; Shaw et al., 2013; Wang et al., 2015; Lee and Chen, 2016). Although the expression of Lin28 is universally increased in cancer cells, the mechanisms by which the aberrant expression of Lin28 occurs have not been well addressed until now. Generally, transcriptional activation and translational enhancement are the two major mechanisms that elevate the expression of Lin28 in cancer cells.

Several transcription factors, including c-myc, NF-κB, STAT3, β-catenin and SOX2, have been reported to promote the transcription of Lin28A or Lin28B in different cancer types (Chang et al., 2009; Iliopoulos et al., 2009; Cimadamore et al., 2013; Guo et al., 2013). In addition, there are several post-transcriptional regulatory mechanisms that contribute to the up-regulation of Lin28. First, the decreased expression of miRNAs targeting Lin28, such as let-7 and miR-181, is one of the mechanisms underlying the up-regulation of Lin28 in cancer cells (Li et al., 2012b; Wu et al., 2016). Second, the aberrant expression of RNA binding proteins may be involved in the over-expression of Lin28 in some cancer types. For example, tristetraprolin (TTP) binds to the AU rich element within the 3'UTR of Lin28 mRNA and causes the degradation of Lin28 mRNA (Kim et al., 2012). However, TTP is usually decreased in cancer (Fallahi et al., 2014). Insulin-like growth factor 2 mRNA-binding protein 3 (IMP3), an RNA binding protein that regulates RNA stability and translation, has been reported to bind and stabilize Lin28B mRNA in cancer (Jonson et al., 2014). The ribonuclease DIS3 has been found to bind and degrade Lin28B mRNA and thus decrease Lin28B levels. However, DIS3 is one of the most frequently mutated genes in cancer, including multiple myeloma (Segalla et al., 2015). Third, RNA editing may also influence the production of Lin28. It has been found that mRNAs containing inverted Alu repeats in their 3'UTR are inefficiently exported to the cytoplasm due to nuclear retention mediated by RNA editing (Kim et al., 2004). Lin28 mRNA contains inverted repeat *Alu* elements in its 3'UTR which contribute to its recognition by adenosine deaminases acting on RNA (ADARs). ADARs can edit Lin28 mRNA by catalyzing the hydrolytic deamination of adenosines (A) to inosines (I); the edited Lin28 RNA is retained in the paraspeckle (Bass, 2002; Chen and Carmichael, 2009). Although it is unclear how cancer cells overcome the nuclear retention of Lin28 mRNA caused by RNA editing, there must be some mechanisms in cancer cells that bypass or attenuate this restriction. Finally, it has been reported that the aberrant regulation of post-translational modifications on the Lin28 protein could increase its stability. For example, in pluripotent stem cells, upon the activation of MAPK/ERK, the stabilization of Lin28 is significantly enhanced due to direct phosphorylation by ERK (Tsanov et al., 2017), whereas in neurons, upon stimulation with growth factors, the HIV TAR-RNA-binding protein (TRBP) accumulates due to MAPK-dependent phosphorylation allowing the phosphorylated TRBP to bind Lin28 and enhance its stability (Amen et al., 2017). These results suggest that MAPK signaling promotes the stability of Lin28. The ubiquitin ligase TRIM71 (the human TRIM-NHL domain-containing protein) has been reported to induce the degradation of the Lin28B protein via the ubiquitin-mediated proteosomal degradation mechanism (Lee et al., 2014). However, further experiments are needed to determine whether the MAPK signaling pathway also enhances the stability of the Lin28 protein, or if TRIM71 is aberrantly regulated in cancer cells.

Lin28 promotes cancer progression

It has been widely reported that Lin28 proteins are frequently up-regulated in various malignancies. High levels of the Lin28 protein are associated with cell transformation and tumorigenesis. In addition, Lin28 plays an important role in cancer progression and is a marker for poor prognosis.

In 2009, Viswanathan et al. was the first to provide evidence that Lin28 promotes cellular transformation (Viswanathan et al., 2009). They over-expressed LIN28 in NIH/3T3 cells and found that these cells can form colonies in soft agar and promote tumor development in nude mice by repressing let-7 family miRNAs and de-repressing let-7 targets (Viswanathan et al., 2009). King et al. found that Lin28B can transform immortalized colonic epithelial cells resulting in the formation of colonies in soft agar and improved metastatic ability (King et al., 2011). Some studies have indicated that Lin28 might be the key epigenetic switch linking inflammation to cell transformation. Iliopoulos et al. reported that a positive inflammatory feedback loop between NF-κB, Lin28, Let-7 and IL6 forms an epigenetic switch that permits cell transformation (Iliopoulos et al., 2009). Madison et al. observed that enhanced expression of Lin28B promoted the transformation of crypts to form intestinal polyps and adenocarcinoma *in vivo* (Madison et al., 2013). Thus, Lin28 is associated with cell transformation and plays an important role during the occurrence of cancer.

The role of Lin28 in cancer proliferation has been well documented (Wang et al., 2015; Wang et al., 2016a). Lin28 can promote cell proliferation through different means, such as activating proliferation-associated transcription factors (Chen et al., 2014), upregulating the expression of cell cycle-related factors (Li et al., 2012a), stimulating cellular proliferation signaling pathways (Feng et al., 2012), facilitating ribosomal protein synthesis (Peng et al., 2011) and enhancing glucose metabolism (Song et al., 2015). Most

studies have confirmed the stimulatory effect of Lin28 on cell proliferation, however, Song et al proposed that Lin28 can inhibit proliferation, disrupt cell cycle progression and induce apoptosis in gastric cancer cells (Song et al., 2015). Thus, it is conceivable that Lin28 can inhibit cancer cell proliferation under certain conditions.

Metastasis is one of the hallmarks of cancer progression. Substantial evidence has revealed that Lin28 accelerates metastasis in various cancer types (Zhou et al., 2013; Balzeau et al., 2017). Lin28B was found to be overexpressed in colon cancer, and a high level of Lin28B can result in extensive cancer cell metastasis in mice (Hamano et al., 2012). Lin28 can promote the invasiveness of esophageal cancer cells and is associated with tumor aggressiveness (Hamano et al., 2012). The involvement of Lin28 in the regulation of cancer cell invasion and metastasis is associated with the epithelial-to-mesenchymal transition (EMT) (Liang et al., 2016; Sato et al., 2017). Mechanistically, by suppressing the biogenesis of let-7 family miRNAs (discussed later), Lin28 indirectly enhances the expression of some oncogenes that facilitate EMT; on the other hand, Lin28 directly binds and alters the expression of certain metastasis associated genes. For example, Lin28A inhibits the translation of E-cadherin while promoting the expression of HMGA1, which facilitates EMT by inducing the expression of Slug and Snail (Wang et al., 2015).

The molecular mechanisms of Lin28 mediated regulation of cancer progression

Multiple studies have confirmed that Lin28 regulates miRNAs or mRNA molecules by directly binding special motifs on the target RNAs. The structural basis for the RNA-binding specificity of Lin28 has been partly revealed in the past few years. Human Lin28 has two binding RNA domains (RBDs): a cold-shock domain (CSD) at the N-terminus and a Zn-knuckle domain (ZKD) composed of two Cys-Cys-His-Cys (CCHC)-type zinc finger domains at the C-terminus (Moss et al., 1997) which mediate the combination of Lin28 with its target RNAs. Currently, several models have been proposed to explore the interaction between Lin28 and its target RNAs. Based on the interaction between Lin28 and pre-let-7, the CSD of Lin28 was proposed to insert into the loop at one end of the central stem-loop structure while the two CCHC-type zinc fingers recognize the G-rich element (GGAG, GAAG or AGGG motif) at the other end of RNAs (Loughlin et al., 2011; Nam et al., 2011). Alternatively, Lin28 binding sites may contain two GGAG motifs within a region that can be folded to form a weak hairpin structure (Stefani et al., 2015). Recently, a novel model of the secondary structure of RNAs has been proposed in which Lin28 recognizes the stable planar structures of 4 guanines termed a G-quartets (G4s) in its target RNAs (O'Day et al., 2015).

Lin28 regulates the biogenesis of microRNAs

Until now, the let-7 family has been the best studied family of miRNAs regulated by Lin28. The blocking of let-7 is regarded as one of the most important mechanisms for Lin28 function across multiple biological processes. Lin28 can recognize and bind GGAG motifs within the loop structure of pri-let-7 and pre-let-7 via CSD and CCHC zinc fingers, which blocks let-7 precursor processing by Drosha and Dicer (Piskounova et al., 2008). Then, Lin28 recruits TUT4/TUT7to induce oligo-uridylation at the 3'terminus of pre-let-7 (Heo et al., 2008, 2009; Hagan et al., 2009), whereas oligo-uridylated pre-let-7 not only resists Dicer cleavage, but is also more susceptible to the 3'-5' exonuclease Dis312 (Mullen and Marzluff, 2008; Chang et al., 2013). In addition, methylation of Lin28a by SET7/9 leads to greater stability and translocation to the nucleus, resulting in the sequestration of pri-let-7 in the nucleus and the inhibition of mature let-7 biogenesis (Kim et al., 2014). Although most studies demonstrated that Lin28 repressed the maturation of let-7, it has been noted that not all members of the let-7 family can be regulated by Lin28. Of the twelve let-7 isoforms, human let-7a-3 escapes Lin28-mediated suppression. The murine orthologous let-7c-2 also displayed lower affinity for Lin28 binding (Triboulet et al., 2015). The mechanism for this process involves a five-nucleotide long sequence forming the short apical stem-loop in the let-7c-2 preE bulge, which compromises the interaction between the CSD of Lin28 and pre-let-7c-2loop (Triboulet et al., 2015)

In addition to the let-7 family, Lin28 can also regulate other miRNAs. It was reported that Lin28B combines with miR-17~92 and miR-363 through GGAG motifs to positively regulate the biogenesis of these miRNAs (Peters et al., 2016; Warrander et al., 2016). Lin28 also interacted with pre-miR-302d through its CSD and then decreased the level of miR-302d (Balzer et al., 2010). Lin28B maintains the stem cell properties of hepatoblasts by suppressing the maturation of both let-7b and miR-125a/b (Takashima et al., 2016). Additionally, Lin28 can inhibit the expression of miR-107 in gastric cancer cells (Teng et al., 2015). Thus, Lin28 is a potent post-transcriptional regulator for miRNAs by either promoting or inhibiting their maturation.

Lin28 regulates the stability and translation of mRNAs

In 2007, investigators found that Lin28 can bind IGF-2 mRNA and increase its translation efficiency by driving the IGF-2 mRNA into polysomes in differentiating muscle cells (Polesskaya et al., 2007). This study provided the initial evidence that Lin28 can directly bind and regulate mRNAs. Soon after, a series of cell cycle regulators (including Oct4, cyclin A/D and CDK6) and H2A mRNAs were found to be the targets of Lin28 in ES cells, and it was also shown that Lin28 can

enhance the translation of these mRNAs (Xu and Huang, 2009; Xu et al., 2009; Dai et al., 2012). In 2011, some growth and survival associated mRNAs were identified as the targets of Lin28 by genome-wide studies in ES cells (Peng et al., 2011). Further studies indicated that Lin28 enhances the translation of those genes by recruiting RNA helicase A (RHA) to polysomes (Jin et al., 2011; Peng et al., 2011). In addition to the effect on translation, Lin28 might influence the stability of specific mRNAs during differentiation (Balzer and Moss, 2007). Lin28 binding to target mRNAs compensates for the Drosha-dependent mRNA destabilization because the LREs in the target mRNA participates in Drosha-dependent regulation (Qiao et al., 2012). In malignancy, Lin28 can also directly bind to oncogene mRNAs and increase their translation, such as HER2 and BMP4, subsequently inducing cell proliferation (Feng et al., 2012; Ma et al., 2013; Wang et al., 2014). However, Lin28 also inhibits the translation of its target mRNAs. For example, Lin28 downregulates the translation of Hmga2 by binding a highly conserved element in the 3'UTR of Hmga2 during ESC differentiation (Parisi et al., 2017). Consistently, Lin28A has been demonstrated to act as a suppressor that inhibits ER-associated translation in ES cells (Cho et al., 2012).

With an increase in the number of identified Lin28 target mRNAs, numerous studies have explored the motifs within mRNAs recognized by Lin28. It was shown that a GGAGA sequence enriched in the loop structures of mRNAs is the Lin28-binding site, which is found in a quarter of human transcripts (Wilbert et al., 2012). In a few genome-wide studies, several potential Lin28 binding sites in the targets mRNA, including GGAGA, AYYHY (Y=U,C and H=A,C,U) and AAGNNG, have been revealed (Cho et al., 2012; Wilbert et al., 2012; Hafner et al., 2013). There is no doubt that an increasing number of mRNA targets of Lin28 will be found following the identification of the Lin28 binding site. The currently known target mRNAs regulated by Lin28 are summarized in Table 1.

Lin28 modulates RNA Splicing

Lin28 preferentially binds to the transcripts encoding splicing factors, such as hnRNP F, TIA-1, FUS/TLS and TDP-43, and enhances their translation, subsequently resulting in widespread splicing changes in breast cancer cells (Wilbert et al., 2012). In prostate cancer, Lin28 was found to induce the generation of AR splice variants by upregulating splicing factors such as hnRNP A1/2R, and

Table 1. The known mRNAs regulated by Lin28 and their functions.

Genes	Functions	References
cyclins	Regulation of cell cycle	Xu et al., 2009
CDK1/2/4	Regulation of cell cycle	Xu et al., 2009
CDC2/20	Regulation of cell cycle	Xu et al., 2009
IGF1R	Regulation of cell proliferation	Brunetti et al., 2001
Igf2bp1	Regulation of cell proliferation	Yang et al., 2015b
HK1	Potentiation cellular metabolism	Peng et al., 2011
PDHA1	Potentiation cellular metabolism	Peng et al., 2011
PDHB	Potentiation cellular metabolism	Peng et al., 2011
HER2	Increase cellular proliferation	Feng et al., 2012
RPS13	Increase cellular proliferation	Peng et al., 2011
EEF1G	Increase cellular proliferation	Peng et al., 2011
EIF4A	Increase cellular proliferation	Peng et al., 2011
HMGA2	Promotes EMT	Dangi-Garimella et al., 2009; Parisi et al., 2017
GSK3B	Regulation of cell proliferation	Yao et al., 2016
BMP4	Regulation of cell proliferation	Ma et al., 2013
PFKP	Regulation of cell proliferation	Xiong et al., 2017
IDH3B	Regulation of cell proliferation	Xiong et al., 2017
NDUFB3/8/10	Regulation of cell proliferation	Xiong et al., 2017
E-cadherin	Promotes metastasis	Xiong et al., 2017
CTNNB1	Promotes metastasis	Yao et al., 2016
ZEB-1/-2	Promotes metastasis	Papathomas et al., 2016
MMP2	Promotes metastasis	Papathomas et al., 2016
SF1	Promotes metastasis	Papathomas et al., 2016
HMGA1	Activation of insulin signaling	Papathomas et al., 2016
IGF2	Activation of insulin signaling	Brunetti et al., 2001
VEGF	Angiogenesis	Wu et al., 2013
gamma-H2AX	Potentiation genome instability	Dickey et al., 2009
TP53	Potentiation genome instability	Poon et al., 2016
PSEN1	Form of familial Alzheimer's disease	Poon et al., 2016
PRAME	Regulation of pluripotency and suppressing somatic/germ cell differentiation	Nettersheim et al., 2016
RPL23	Apoptosis resistance	Tsanov et al., 2017
SUMO1	Increase cellular proliferation	Sahin et al., 2014

then promoting the resistance of cancer cells to targeted therapeutics (Tummala et al., 2016). Recently, Yang et al also found that the splicing factor hnRNP A1 was associated with Lin28 by MS analysis. However, RIP-Seq data indicated that Lin28 was not enriched at the hnRNP A1 locus. This study suggests that Lin28 can modulate the splicing process in breast cancer cells independent of hnRNP A1 (Yang et al., 2015a). Thus, Lin28 can alter the RNA splicing process in cancer cells by affecting the translation of splicing factors.

Lin28 regulates gene transcription

As an increasing number of studies have focused on the RNA targets directly regulated by the RNA binding protein Lin28 at the post-transcriptional or translational levels, some have suggested that Lin28 may regulate gene expression at the transcriptional level. Hudson et al. previously demonstrated that the CSD structure in some protein molecules can bind single-stranded DNA (Hudson and Ortlund, 2014). Additionally, some other RNA binding proteins, such as the splicing regulator SRSF2, have been revealed to function as transcription factors (Mo et al., 2013). These findings raise the possibility that Lin28 may also exhibit DNA binding activity. As expected, Zeng et al. defined a DNA binding characteristic of Lin28A, providing novel evidence that Lin28A directly regulates transcription. Further, they found that Lin28A recognizes DNA consensus sequences within active transcriptional bubbles and recruits Tet1 to co-regulate gene transcription by modulating the cytosine modification status (Zeng et al., 2016).

Conclusions and perspectives

In summary, the RNA binding protein Lin28 is universally increased in human malignancies, and high levels of Lin28 are poor prognosis markers and contribute to the progression of a variety of cancer types. Mechanistically, Lin28 not only regulates the biogenesis of miRNAs, either by inhibiting or promoting their maturation and then indirectly regulating gene expression, but also directly regulates the transcription, splicing, stability and translation of mRNAs. As an oncogene, Lin28 has been demonstrated to promote cellular proliferation, angiogenesis, metastasis, cell death resistance, metabolism reprogramming, tumor-associated inflammation, genome instability, and immune surveillance escape by cancer cells (Wang et al., 2015). As an RNA binding protein, in addition to miRNAs, Lin28 may bind to and regulate the stability of other types of non-coding RNAs, such as lncRNAs and pseudogene transcripts, and then indirectly regulate the expression of protein-coding genes via a competing endogenous RNA (ceRNA) mechanism. However, no related results have been reported, but it would be an interesting research direction in this field. Additionally, our recent research implied that the functions of Lin28 mRNA and protein in colorectal cancer may not by consistent (Wang et al., 2016b). Considering that the mRNA molecules of both Lin28A and Lin28B contain a long 3'-UTR, which is five-times longer than the coding region, the mRNAs of Lin28 may have some novel but protein-coding independent functions. However, this hypothesis must be validated by further experiments. Established studies suggest that Lin28 is a master regulator of cancer progression and would be a valuable target for future cancer therapy.

Acknowledgements: This work was supported by the National Natural Science Foundation of China (Grant No. 81302061 to Tianzhen Wang, Grant No. 81401961 and 81641101 to Xiaobo Li, Grant No. 81400443 to Xin Wang), the Postdoctoral Scientific Research Development Fund of Heilongjiang Province (Grant No. LBH-Q14104 to Xiaobo Li and Grant No. LBH-Q15082 to Tianzhen Wang), the Heilongjiang Postdoctoral Fund (grant No. LBH-Z16118 to Di Wu), the Natural Science Foundation of Heilongjiang Province (Grant No. H2016006 to Xiaobo Li), the Heilongjiang Provincial Health Bureau (Grant No. 2014-411 to Yinji Jin) and the Wu-Lian-De Youth Science Foundation of Harbin Medical University (Grant No.WLD-QN1411 to Xiaobo Li).

Conflict of Interest: The authors declare that they have no conflicts of interest with the content of this article.

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Accepted July 26, 2017