Noncoding RNA in cancer

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Abstract
Non-coding RNAs (ncRNAs) are diverse classes of RNA molecules not translated into proteins, which possess intricate regulatory and structural functions. NcRNAs belong to a family of regulatory transcripts that affect every stage of gene expression, from transcription and mRNA stability to mRNA translation. Recent evidence has uncovered critical roles for noncoding RNAs in cancer pathogenesis. For example, variation of specific microRNAs has shown to drive tumorigenesis in human cancer cells and mouse models. Long noncoding RNAs (lncRNAs) have also been related to diverse cancer phenotypes and neurological disorders. NcRNAs are deeply involved in the regulation of key genes that are associated with cancer, representing a promising area for new therapies. This review focuses on ncRNAs, their role in cancer, and the translational implications of noncoding RNA research that may contribute to the development of innovative therapeutic solutions to treat cancer, and improve patients' quality of life and survival.
Keywords: noncoding RNA (ncRNA), lncRNA, miRNA, cancer.

The noncoding genome represents around 97% of the human genome. NcRNAs can be categorized into distinct classes, based on their biogenesis, size, and biologic function. Long noncoding RNAs (16000), small noncoding RNAs (7500) and pseudogenes (15000) belong to this imense group of genes. The noncoding genome is persistently transcribed. 85% represents transcribed genome versus silent genome (15%). Long noncoding RNAs (lncRNAs) are ncRNAs bigger than 200nt, which are not translated and are seldom expressed. They also have tissue specific expression and lack of ORF and conservation.

Short regulatory ncRNAs (<200 nucleotides) include miRNAs, siRNAs, and piwi-associated RNAs (piRNAs). piRNAs are produced by a long RNA, which is a RNA polymerase II (Pol II) transcript. MicroRNAs (miRNAs) are the best characterized class of short ncRNAs (19-24 nt), which are present in animals, plants, and algae (BARTEL 2009). The first miRNA, *lin-4,* was discovered in the early 1990s. *Lin-4* and *let-7* were described as regulators of developmental timing in the nematode (LEE *et al.* 1993; WIGHTMAN *et al.* 1993 ;REINHART *et al.* 2000). miRNAs are well conserved in both plants and animals, and are thought to be a vital and evolutionarily ancient component of gene regulation (PETERSON *et al.* 2009).

Long regulatory non-coding RNA (lncRNAs) (200–100,000 nucleotides) (GUTSCHNER and DIEDERICHS 2012; PONTING *et al.* 2009) contribute to the regulation of gene expression at various levels, such as chromatin modification, transcription and post-transcriptional processing. And are functional RNA molecules involved in diverse cellular processes: epigenetic regulation (Xist, H19, Anril, Terra, ecCEBP…), proteostasis (HULC, MEG3, GAS5, PANDA, HOTAIR…), stem cell pool (AKO28326, ES1, ES2,ES3, Linc-ROR,…), cell proliferation (MALAT1, ANRIL, SRA, UCA1, HEIH…), intercellular communication (17A, Lethe, THRIL, TUC339, LNC-IL7R…), and

telomere stability (TERC, TERRA…) among others (GRAMMATIKAKIS *et al.* 2014). Human lncRNAs annotated by the GENCODE project comprise the largest public dataset containing 15,877 lncRNA genes, although it has been identified a huge number of new lncRNA genes *(IYER et al. 2015).*

Due to advances in sequencing technologies, a growing number of long noncoding RNAs (lncRNAs) have been identified, and many of them have shown to be key regulators of protein coding genes. Analyses of global transcriptome have shown that up to 70% of protein coding genes that have an antisense RNA can act as a key regulator of sense mRNA transcription (KATAYAMA *et al.* 2005). Moreover, dysregulation of lncRNAs is linked to various human diseases from neurodegeneration to cancer (WAPINSKI and CHANG 2011). A number of reports suggest that lncRNAs are critical in epigenetic regulation that can alter histone modifications in *cis* and *trans* (RINN and CHANG 2012; SABIN *et al.* 2013; JOH *et al.* 2014). A significant fraction (~20%) of lncRNAs can physically associate with the polycomb repressive complex 2 (PRC2), which suggests lncRNAs play an active role in chromatin modification and gene repression (KHALIL *et al.* 2009; GUTTMAN *et al.* 2011).

Implications of ncRNAs in cancer

Cancer is characterized by uncontrollable cell growth resulting from a complex multistep accumulation of sequential genetic alterations. Previously, it has been shown the role of RNA-protein interactions in the regulation of oncogenic and tumor suppressive genes. However, the precise functions of many individual ncRNAs are still an enigma (POLISENO *et al.* 2010; KALYANA-SUNDARAM *et al.* 2012). Although there is cumulative evidence that ncRNAs are essential for cell proliferation and survival under physiologic conditions, and their deregulation is linked to oncogenesis (see table 1 and 2) (KEUN *et al.* 2009; CALIN *et al.* 2007; SPIZZO *et al.* 2012; LI *et al.* 2013).

To date, the role of **miRNA** in cancer has been far better characterized than lncRNAs, and their expression profiles can be used in the classification of human cancers (LU *et al.* 2005). miRNAs can act as tumor suppressors and oncogenes which are down- and up-regulated in cancer, respectively. One of the first oncogenic miRNA described was *miR17-92* (see table 1) which has pleiotropic functions in the cell. miR17-92 is overexpressed in lung and colon cancer, lymphoma, multiple myeloma and medulloblastoma (MENDELL 2008), and its absence induces an increase of the proapoptotic protein Bim and inhibits the pro-B to pre-B cell development (HE *et al.* 2005).

In contrast, *miR15* and *miR-16* are tumor-suppressive miRNAs by the induction of apoptosis of transformed cells and cell cycle regulation. Some studies demonstrated the relation of *miR15* and *miR16* to chronic lymphocytic leukemias (CALIN *et al.* 2002), epithelial malignancies and ovarian cancer (BHATTACHARYA *et al.* 2009).

Table 1. Cancer-related miRNAs

NAME	CANCER TYPE	FUNCTION
miR 17-92	lung and colon, lymphoma, multiple myeloma and medulloblastoma	oncogenic
miR-21	breast, lung, pancreatic and prostate,	oncogenic
miR-10b	breast and lung	oncogenic
miR-22	gastric	oncogenic
	hepatocellular, lung, colorectal, ovarian and breast	tumor supressive
miR-373	breast	oncogenic
miR 15-16	CLL (chronic lymphocytic leukaemia)	tumor supressive
Let-7 family	pancreatic	oncogenic
	breast, lung, hepatocellular, prostate,ovarian and neuroblastoma	tumor supressive
miR-31	breast	tumor supressive
miR-335	breast	tumor supressive
miR-34	breast, gastric and renal cell carcinoma	oncogenic
	lung, pancreatic, colon and prostate	tumor supressive
miR-26a	glioma	oncogenic
miR-29 family	lung, breast, CLL	tumor supressive
miR-101	prostate and bladder	tumor supressive
miR-124a family	breast, colorectal, ling, leukemia and lymphoma	tumor supressive
miR-127	bladder	tumor supressive
miR-143 and 145	breast and colon	tumor supressive
miR-148a	breast, colorectal, melanoma and lung	tumor supressive
miR-155	breast and lung cancer. B-cell lymphomas	oncogenic
miR-200 family	breast and gastric	tumor supressive
miR-221 and 222	hepatocellular and thyroides	oncogenic

Table 1 also shows other miRNAs with oncogenic and tumor suppressive functions. In addition to cancer-associated miRNAs, Qiao and colleagues described the first evidence of the role of piRNAs in cancer (QIAO *et al.* 2002). Hiwi, Piwi family member, is overexpressed in seminomas but not in nonseminomas or in somatic tumors of the adult testis (QIAO *et al.* 2002). SnoRNAs are also involved in the beginning of the Prader-Willy syndrome (PWS), and are induced by the genetic loss of the 15q11–q13 locus (normally active only on the paternal allele). This site is characterized by several copies of the HBII-85 snoRNA, whose loss seems to be correlated with the PWS phenotype, both in human and in mice (MOURTADA-MAARABOUNI *et al.* 2009).

Many **lncRNAs** were first characterized by their repressive functions, including ANRIL, HOTAIR, H19, KCNQ1OT1, and (RINN *et al.* 2007; YAP *et al.* 2010; GIBB *et al.* 2011) (see table 2). These lncRNAs exert their repressive function by connection with histone-modifying or chromatin-remodeling protein complexes (PRENSNER and CHINNAIYAN 2011a). In addition, they can regulate the expression of some genes related with tumorigenesis (LUO *et al.* 2001; LUJAMBIO and ESTELLER 2009; MAES *et al.* 2010). For example, satellite repeats in heterochromatin are normally repressed and are highly expressed in multiple cancers (TING *et al.* 2011). Another lncRNA, *HULC*, has been shown to be overexpressed in hepatocellular carcinoma, in which may act as miRNA sponge, and in colorectal cancer. *HULC* is implicated in liver metastasis (MATOUK *et al.* 2007). These examples illustrate the possibility of the role of ncRNAs as biomarkers or therapeutic targets to cancer.

In summary, LncRNAs are implicated in multiple functions during cancer, such as

development (RAO *et al.* 2017), sustainment of proliferative signaling (MEG3, SRA…), evasion of growth suppressors (ANRIL, GAS5…), induction of angiogenesis (MVIH, aHIF…), activation of invasion and metastasis (HULS, MALAT1…), resistance to cell death (bcl2/IgH AS…) and enabling of replicative immortality (TERC, TERRA…) (RAO *et al.* 2017).

Over the last several years, approaches to demonstrate the important role of ncRNAs have been published. Similar observations have been also made using murine models. Some examples are described above:

(1) The Metastasis-Associated-in-Lung Adenocarcinoma -Transcript-1 (MALAT-1) is an ncRNA that is highly expressed in several tumor types. The overexpression and RNA interference (RNAi) approaches were used for the analysis of the biological functions of MALAT-1 RNA. In non-small cell lung cancer (NSCLC), MALAT-1 displays the strongest association with genes involved in cancer like cellular growth, movement, proliferation, signaling, and immune regulation (SCHMIDT *et al.* 2011).

(2) The overexpression of AK081227 mediated by the Mecp2 loss is associated with the downregulation of its host coding protein gene, the gamma-aminobutyric acid receptor subunit Rho 2 (Gabrr2). The transcriptional dysregulation of lncRNA upon Mecp2 loss contributes to the neurological phenotype of Rett syndrome and highlights the complex interaction between ncRNAs and coding-RNAs (PETAZZI *et al.* 2013).

(3) The knockdown of the antisense noncoding mitochondrial RNAs (ASncmtRNAs) generates a new murine noncoding mitochondrial RNAs (ncmtRNAs) model, which could be potent targets for melanoma therapy. This has been the first potential non-nuclear target for melanoma therapy (LOBOS-GONZALEZ *et al.* 2016).

Table 2. Cancer-related lncRNAs

NAME	CANCER	FUNCTION
HOTAIR	breast , colorectal and hepatocellular	oncogenic
MALAT1	breast, prostate, colon, liver and uterus	oncogenic
HULC	hepatocellular	oncogenic
ANRIL	breast, prostate and leukaemia	oncogenic
	coronary artery disease (CAD) and periodontitis (PD)	tumor supressive
H19	bladder, lung, liver, breast, esophagus, colorectal and pancreatic	oncogenic
PCA3	prostate	oncogenic
PCAT-1	prostate	oncogenic
uc.73a	leukemia	oncogenic
PCGEM1	prostate	oncogenic
TUC338	hepatocellular	oncogenic
UCA1/CUDR	bladder, colon, cervix, lung, thyroid, liver, breast, esophagus, stomach	oncogenic
Spry4-it1	melanoma	oncogenic
BC200	breats, cervix, esophagus, lung, ovary, parotid, tongue	oncogenic
MEG3	brain	tumor supressive
SRA	breast, uterus, ovary	tumor supressive
GAS5	breast and renal cell carcinoma	tumor supressive
PTENP1	prostate, colon	tumor supressive
Linc-p21	lung (mouse models)	tumor supressive

1.- ncRNAs-diagnostic tools

Biomarkers are biological indicators of disease states used to classify cancer types or subtypes (HUI *et al.* 2011). Novel cancer diagnostics, prognostics and anti-cancer approaches based upon ncRNA biology are quickly developing during the last years (CALIN and CROCE 2006; SPIZZO *et al.* 2012). Focusing on latest reports, miRNA expression has been used to distinguish between acute lymphoblastic leukemia and acute myeloid leukemia (AML) (MI *et al.* 2007). Moreover, several groups predicted the outcome in solid tumors using miRNA expression such as colon adenocarcinomas (SCHETTER *et al.* 2008), squamous cell lung cancer (RAPONI *et al.* 2009) and hematological malignancies including AML (MARCUCCI *et al.* 2008). In addition, it has been described the correlation between circulating miRNA levels and the response to a given anticancer agent (HUI *et al.* 2009). The best example is *miR-21*, which is up-regulated in human cancers and the levels of circulating *miR-21* were higher in patients with hormone-refractory prostate cancer, whose disease was resistant to docetaxel-based chemotherapy, in comparison with patients who had chemo sensitive disease (ZHANG *et al.* 2011).

The study of lncRNAs is a fast growing field of research. *HOTAIR* can be a potential biomarker for the existence of lymph node metastasis in hepatocellular carcinoma (HCC) (GENG *et al.* 2011). *HULC* (PANZITT *et al.* 2007) or other lncRNA, *MALAT1* (LAI *et al.* 2012) can be used as a prognostic markers. One of the lncRNAs utilized in a clinical test is *PCA3* (prostate cancer associated), which can be detected in urine samples obtained after a prostatic massage (MARKS *et al.* 2007). The detection of both miRNAs and lncRNAs in body fluids, such as blood or urine, and its use as non-invasive cancer biomarkers is an active area of research due to their high stability and resistance to storage and handling (TINZL *et al.* 2004; MITCHELL *et al.* 2008).

2.- ncRNAs in cancer therapy

As many miRNA and lncRNA are deregulated in cancer, many researchers now focus on their role as therapeutic targets (AL OLABY and AZZAZY 2011). miRNA therapy is being used to down-regulate or block the function of oncogenic miRNAs or up-regulate their tumor-suppressive function. There are several approaches to control oncogenic miRNA expression: by introducing mRNAs targeting specific miRNAs or by using antisense single-stranded oligonucleotides complementary to miRNA, which acts as miRNA sponges and miRNA antagonists, respectively (MERIKALLIO *et al.* 2011; DIALLO *et al.* 2011); BRODERICK *et al.* 2011). Alternatively, new techniques to re-express miRNAs with tumor suppressor roles are constantly emerging, as the administration of synthetic miRNA becomes a common therapy (TRANG *et al.* 2010). It has also been reported the successful systemic delivery of miRNAs as anti-cancer approaches in preclinical models using liposomes viral vectors (KOTA *et al.* 2009; RAI *et al.* 2011) and nanoparticles (SU *et al.* 2011). A better understanding of the molecular mechanisms of lncRNAs in cancer might lead to development of more effective cancer therapies in the near future. Recently, it has been published the role of 7SL ncRNA in the treatment of cancers. This function could be related with tumor suppressor p53, which suggest that targeting 7SL may be effective in the treatment of cancers with reduced p53 levels (ABDELMOHSEN *et al.* 2014). A more recent report demonstrated the link between miR-155 and SMARCA4 expression levels in theprognosis of patients with lung tumors. This seems to be be due to oncogenic properties of miR-155 in lung

cancer by its role inhibiting *SMARCA4 (COIRA et al. 2015).*

NcRNAs can also be related to **chemo resistance** by damaging the response through cell cycle arrest, enhanced DNA damage repair and inhibition of apoptosis (LIPOVICH *et al.* 2010; GOLDMAN 2003; HARRIES 2012). Several lncRNAs in cancer can up-regulate drug resistance gene (*CUDR*) and antagonize the apoptotic effect of cisplatin in bladder cancer cells (D'ADDA DI FAGAGNA 2008). Moreover, the growth arrest-specific 5 lncRNA *Gas5,* which contributes to glucocorticoid resistance, is associated with therapeutic resistance (YANG *et al.* 2012) (KINO *et al.* 2010). *PANDA is* increased in a subset of breast cancer cells that contributes to anthracycline resistance, a crucial component of breast cancer chemotherapy (SOTILLO and THOMAS-TIKHONENKO 2011). They are also many p53-regulated lncRNAs, which are induced in response to DNA damage and promote chemo resistance (AMIT and HOCHBERG 2010). *HULC lncRNA* may also act as an endogenous sponge to reduce miRNA levels and inhibit their functional activity (PANZITT *et al.* 2007). This functional and structural innovation of lncRNAs offers potential as anticancer therapeutics that can prevent the emergence of drug resistance commonly seen with current agents (MALEK *et al.* 2014).

Conclusions

Highly relevant functions of ncRNAs have been recently demonstrated. Based on recent discoveries in genome editing in simple organisms, similar technologies might soon become available to the study of mammalian systems (HOCKEMEYER *et al.* 2011); (WANG *et al.* 2013); (JINEK *et al.* 2012). A key area of research would be 1) to link lncRNA–miRNA interactions and human diseases, and 2) to functionally characterize other lncRNAs (e.g., very long lncRNAs, pseudo genes, antisense RNAs) and other small RNAs (e.g., piRNAs, siRNAs, snoRNAs). A stronger collaboration between molecular biologists, bioinformaticians and systems biologists will help identifying the critical nodes in these complex systems and their implications in cancer. This synergic work may help providing novel potential drug candidates that can be translated into the clinic.

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