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Noncoding RNAs and cancer

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Abstract: New and diverse groups of noncoding RNAs are beginning to be discovered. These noncoding RNAs are grouped based on their sizes, genomic positions, or distinctive functions ranging from the regulation of chromatin structure and gene expression to genome stability maintenance. Among noncoding RNAs, microRNAs are the best studied and understood small RNAs with direct and indirect roles in normal and in cancer cells. Given the high rate of transcription from noncoding parts of the genome, other noncoding elements are also of great interest. It is also of interest to understand that there may be interesting cases of crosstalk and/or coregulation between the noncoding and the coding portion of the genome. Therefore, deregulated expression of noncoding RNAs can be considered to cause significant alterations in cancer cells. The complexities of the genome and transcriptome still remain mesmerizing. As we better understand these complexities, we will be able to improve our understanding of human conditions and will hopefully develop tools to improve the ways in which we deal with diseases, particularly cancer. Here, based on recent findings, we provide a descriptive profile of noncoding RNA classes, their roles, and their potential contributions to the complex events of tumorigenesis.

Key words: Noncoding RNAs, cancer, long noncoding RNAs, small noncoding RNAs, microRNAs

1. Introduction

Following the completion of the human genome a decade ago, we came across a surprisingly low number of protein-coding genes in the human genome compared to the initial predictions. The low number of protein-coding genes, corresponding to only 2% of the human genome, was surprising, because it meant that we were undervaluing the potential roles of alternative promoter usage, alternative splicing, alternative polyadenylation, and so on to explain the vast diversity of proteins in cells. It was also a realization that the rest of the genome must also have some role, either structural or functional. Indeed, over the years, studies have documented widespread transcription across 70%–90% of the genome with approximately 9000 small RNAs, 1100 microRNAs (miRNAs; http://microRNA.org), 32,000 long noncoding RNAs (lncRNAs), and 11,000 expressed pseudogenes (Bernstein et al., 2012; Volders et al., 2013). Based on increasing evidence, it has become clear that this nonprotein-coding portion of the genome is critical in managing the greater complexity of higher eukaryotes during development and in different physiological and/or disease states, especially cancer. While most of the focus is on miRNAs as small noncoding RNAs, other long or small noncoding RNAs are attracting attention in normal and in cancer cells. Here we provide an overview of currently known noncoding RNA elements (Figure 1), their functions, and their connections with disease states, especially cancer (Table). In the first part, lncRNAs and their subclasses will be discussed. The second part focuses on small noncoding RNAs.

2. Long noncoding RNA classes

lncRNAs are transcripts of longer than ~200 nucleotides with little or no protein-coding capacity (it is possible that some lncRNAs encode small peptides). In humans, with exceptions, lncRNAs are generally polyadenylated and are spliced to generate a small number of exonic regions (Derrien et al., 2012). On the other hand, evidence suggests some lncRNAs to be processed and stabilized by other mechanisms such as RNase P cleavage to generate a mature 3' end, capping by snoRNP complexes at both ends, or formation of circular structures (Zhang et al., 2013a).

The lncRNA genes are positioned throughout various chromosomal regions of the genome. Therefore, the accepted classification of lncRNAs is generally based on their locations, whether they are intergenic, intronic, or found in the antisense strand [also known as natural antisense transcripts (NATs)] or upstream to annotated protein-coding genes. With the advancements of sequencing methods, along with other noncoding RNAs,

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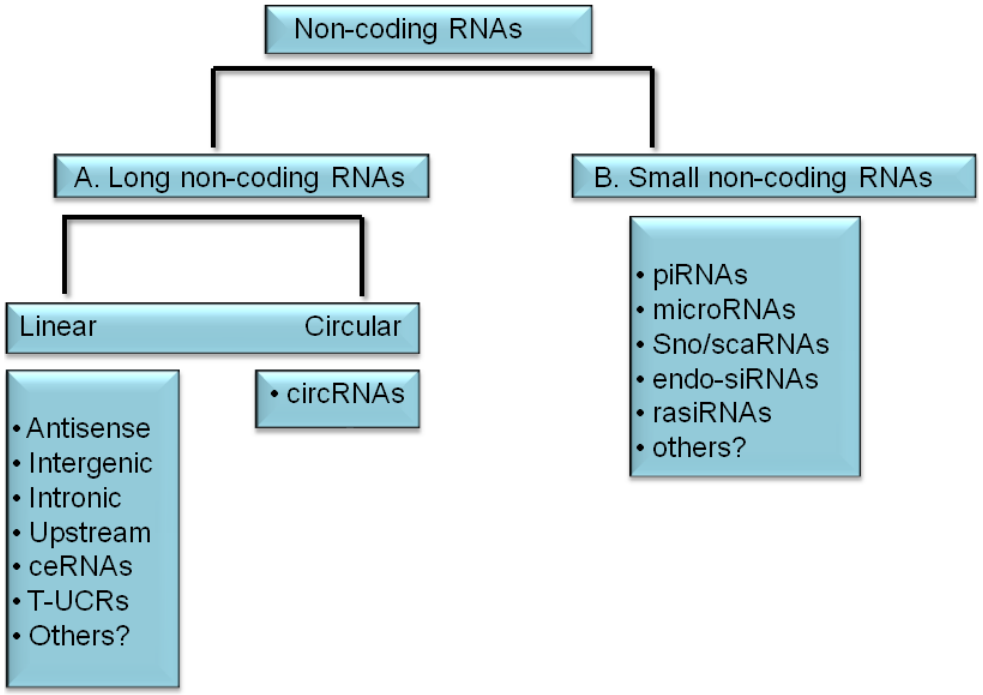

Figure 1. Noncoding RNA classes. Based on size, noncoding RNAs can be divided into long or small noncoding RNAs. Further subgroups are based on genomic positions, structures, or functions.

Table. Noncoding RNAs associated with diseases.

Name	Class	Disease	Function	Reference
PCA3	lincRNA	Prostate cancer	Overexpressed/biomarker potential	Sartori and Chan, 2014
CDKN2B-AS1	antisense ncRNA-cis	Susceptibility for cardiovascular diseases, cancer, Alzheimer disease	Epigenetic silencing of INK4 locus	Yu et al., 2008; Yap et al., 2010
BACE1-AS	antisense ncRNA-cis	Alzheimer disease	Increased stability of BACE1 mRNA and protein	Faghihi et al., 2008
MALAT1	intergenic lncRNA	Nonsmall cell lung cancer	Alternative splicing and epigenetic regulation	Ji et al., 2003; Tripathi et al., 2010; Yang et al., 2011b
HOTAIR	antisense intergenic RNA-trans	Various cancers	Bridging chromatin with chromatin-modifying proteins, especially with the polycomb repressive complexes	Nahkuri and Paro, 2012
XIST	lncRNA	Various, myelodysplastic syndrome	Nuclear compartmentalization and propagation of H3K27 methylation, X inactivation	Yildirim et al., 2013
15q11–q13 snoRNAs	snoRNA	Prader–Willi syndrome	Associate strongly with Fox family splicing regulators and alter patterns of splicing	Yin et al., 2012
PRNCR1 and *PCGEM1*	lncRNAs	Prostate cancer	Enhancer-derived, leads to activation of androgen receptor	Yang et al., 2013
PTENP1	lncRNA	Various cancers	Pseudogene of PTEN, microRNA sponge	Poliseno et al., 2010
HULC	lncRNA	Hepatocellular carcinoma	microRNA sponge to downregulate miRNA-372	Panzitt et al., 2007; Wang et al., 2010
Lethe	lncRNA	Inflammatory signaling	Pseudogene transcribed by NF-kB	Rapicavoli et al., 2013

lncRNA discovery has immensely accelerated. It turns out that lncRNA expression is tightly controlled in a spatial, temporal, cell-type specific manner suggesting functional relevance.

Given the vast number of lncRNAs in the genome, delineating the function of lncRNAs is a topic of great interest. Among various examples of lncRNA functions (splicing, translation, etc.), it seems that lncRNAs exert their main functions by providing a kind of guidance mechanism for directing epigenetic changes to the chromatin structure (Figure 2). lncRNAs can modulate chromatin architecture by binding to complementary sequences of partially single-stranded chromosomal DNA or nascent transcripts. Upon this interaction, chromatin-modifying proteins such as trithorax or polycomb groups of proteins can be recruited to the site where epigenetic alterations such as DNA methylation, nucleosome position changes, and histone modifications will take place (Nahkuri and Paro, 2012). This way, lncRNAs can function as adaptors that aid in linking specific chromatin loci with chromatin-remodeling complexes as well as transcription factors. In addition, they can bind to transcription factors as decoys (Rapicavoli et al., 2013) to regulate their interactions with DNA or to miRNAs and act as sponges so that a specific pool of miRNAs fail to bind to the target mRNAs, etc.

lncRNAs are also emerging as important regulators of immune cell differentiation and activation in innate and adaptive immunity pathways (Fitzgerald and Caffrey, 2014). As we improve our understanding of how lncRNAs function, it seems there will be exciting developments in the field of cancer diagnosis and therapeutics. A promising example is the overexpressed prostate cancer gene 3 (PCA3) lncRNA that may prove to be better than existing biomarkers for prostate cancer (Sartori and Chan, 2014).

Significant effort has been focused on new discovery of lncRNAs and their expression profiles. Studies so far also provided functional evidence on the mechanism of lncRNA actions. Several lncRNAs whose functions are validated experimentally can be listed as *XIST* (X inactive-specific transcript), *HOTAIR* (HOX transcript antisense), and *HULC* (highly upregulated in cancer) (Volders et al., 2013). Here we will try to summarize recent literature on exemplary lncRNAs based on a classification of their genomic positions.

2.1. Linear lncRNAs

2.1.1. Antisense lncRNAs (also known as natural antisense transcripts)

LncRNAs that reside on opposite strands of protein-coding genes are called NATs and named after the protein-coding gene with an "-AS" suffix according to the HUGO Gene

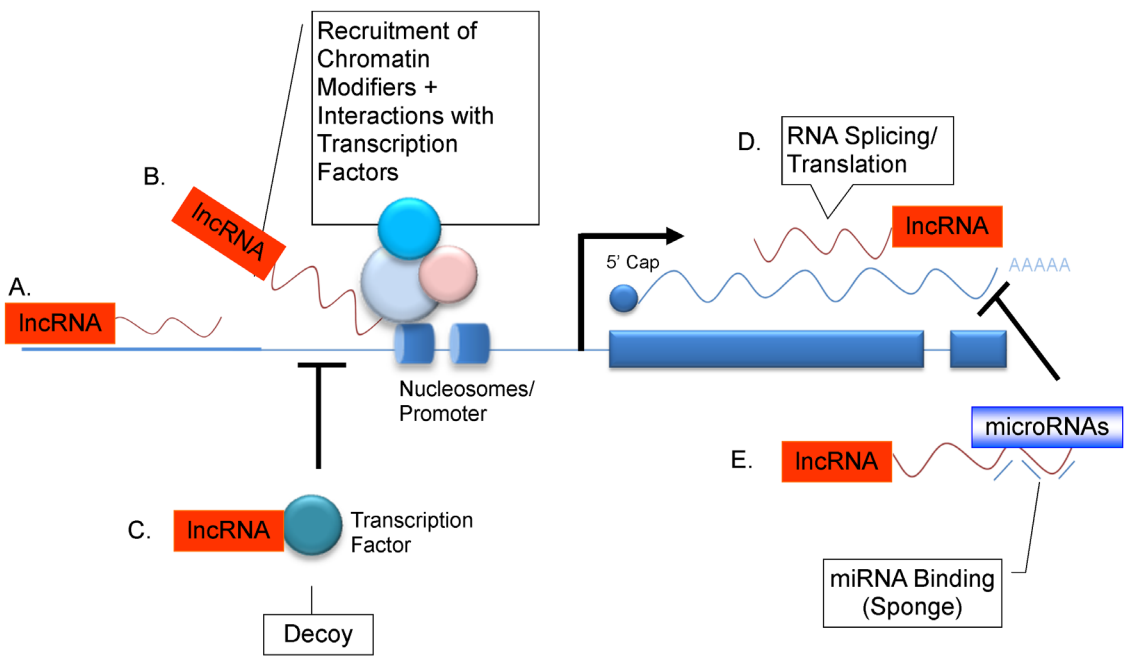

Figure 2. **A**- LncRNAs can bind to regions of ssDNA to form a DNA-RNA heteroduplexes, or to dsDNA to form triplexes (DNA-DNA-RNA). **B**- lncRNAs can be tethered to a chromatin through association with chromatin-modifying proteins and/or transcription factors. **C**- lncRNAs can act as RNA decoys (e.g., Lethe). **D**- lncRNAs can take roles in RNA splicing/translation (e.g., sno-lncRNAs). **E**- lncRNAs in the form of endogenous competitors can bind to microRNAs and alter their mRNA target interactions.

Nomenclature Committee. NATs can act in cis or in trans. A cis-NAT overlaps with its complementary gene, whereas a trans-NAT does not overlap with its complementary gene. *CDKN2B-AS1* (also known as ANRIL, antisense ncRNA in the INK4 locus) is an example of a cis-acting lncRNA. Mouse and human fibroblast studies showed combined binding of polycomb proteins and ANRIL to lead to epigenetic silencing of the INK4 locus (Yu et al., 2008; Yap et al., 2010). *BACE1-AS* is another cis-acting lncRNA that is antisense to the *BACE1* gene that codes the β-secretase-1 enzyme. The *BACE1-AS* increase in Alzheimer disease may contribute to the increased stability of BACE1 mRNA and protein, which is a crucial enzyme in Alzheimer disease pathophysiology (Faghihi et al., 2008).

Trans-acting NATs (i.e. complementary to a nonoverlapping region in the genome) exist as well. Examples of trans-acting NAT will be discussed below.

2.1.2. Intergenic lncRNAs

A well-studied example of an intergenic lncRNA (lincRNA) is *MALAT1* (metastasis-associated lung carcinoma transcript 1), which is ubiquitously expressed and localized to the nucleus in normal tissues, and it sequence is strongly conserved from zebrafish to humans. *MALAT1* has been linked to alternative splicing and epigenetic regulation (Tripathi et al., 2010; Yang et al., 2011b). *MALAT1* was initially identified in nonsmall cell lung cancers as a prognostic marker of survival (Ji et al., 2003). However, loss of *MALAT1* did not affect alternative splicing or cell cycle progression, (Gutschner et al., 2013); instead, *MALAT1*-deficient cells were impaired in cell migration and defective in forming metastatic tumor nodules. Surprisingly, loss of function mouse models did not generate a significant phenotype (Zhang et al., 2013a).

HOTAIR (HOX antisense intergenic RNA) itself is derived from mammalian the *HOXC* homeotic cluster and can regulate *HOXD* (on a different chromosome) expression. *HOTAIR* also operates in trans as part of a structural scaffold by bridging chromatin with chromatin-modifying proteins, especially with the polycomb repressive complexes (Nahkuri and Paro, 2012). Owing to this function, *HOTAIR* overexpression in cancer leads to genome-wide changes in the chromatin-modifying complex binding sites. Interestingly, *HOTAIR* expression was recently reported to be inversely correlated with miR-141 expression in renal carcinoma cells (Chiyomaru et al., 2014). In essence, *HOTAIR* promotes malignancy, including proliferation and invasion, whereas miR-141 functions as a tumor suppressor. This inverse correlation is due to direct binding of miR-141 to *HOTAIR* in a sequence specific manner, supressing *HOTAIR* expression and functions including proliferation and invasion. Moreover, *HOTAIR* is overexpressed in breast, colorectal, hepatocellular, gastrointestinal, and pancreatic carcinomas (Beckedorff et al., 2013a). These findings are also important to question the interactions of noncoding RNAs and microRNAs, further complicating our current understanding of microRNAs and their targets.

XIST is another lncRNA that contributes to nuclear compartmentalization and propagation of H3K27 methylation on the inactivated X chromosome (Xi), from which Xist is transcribed to equalize gene expression between the sexes. H3K27 methylation is a common histone modification directing silencing. Interestingly, Xist-deficient mouse hematopoietic stem cells show aberrant maturation and age-dependent loss, leading to highly aggressive myeloproliferative neoplasm and myelodysplastic syndrome (Yildirim et al., 2013). *TSIX* is another lncRNA that is transcribed from the opposite strand of Xist to repress Xist, leading to DNA methylation of the Xist promoter (Ohhata et al., 2011).

2.1.3. Intronic lncRNAs

lncRNAs that reside in introns of protein-coding genes are called intronic lncRNAs. Sequences encoded within introns appear to host an unexplored reservoir of novel, functional RNAs known as sno-lncRNAs and antisense intronic lncRNAs (St Laurent et al., 2012). While the majority of lncRNAs are found within intergenic regions, these intronic lncRNAs [no 5′ cap and no 3′ poly(A) tail] originate from excised introns. Although it is generally accepted that most of the excised introns or intron fragments are degraded after splicing, this observation may not hold true for some that are longer than 200 nucleotides and that could accumulate to high levels in cells (Yang et al., 2011a). It appears that these spliced intronic sequences that reside in the nucleus have important roles as they harbor functional noncoding regions. We already know that a large number of snoRNAs are encoded within such intronic regions (Filipowicz and Pogacic, 2002). Recently it became clear that some intronic regions harboring 2 snoRNAs are processed from their ends by the snoRNP machinery after splicing, but the internal intronic sequences between snoRNAs are not removed, leading to the accumulation of lncRNAs with snoRNA ends (sno-lncRNAs). Such RNAs appear to be widely expressed in cells. An abundant class of sno-lncRNAs (15q11–q13) is found to be deleted in Prader–Willi syndrome, and these sno-lncRNAs are associated strongly with Fox family splicing regulators and alter patterns of splicing (Yin et al., 2012). Given these roles, deregulated expression of host genes and therefore of spliced intronic regions that harbor snoRNAs may have consequential effects on gene regulation in many aspects in cancer cells.

sno-independent cases of antisense intronic lncRNAs exist as well. *RASSF1A* (Ras association domain family 1 isoform A) is a tumor-suppressor gene shown to control cell proliferation in several tumors. *ANRASSF1*

is an antisense intronic lncRNA that is transcribed from the opposite strand of the *RASSF1* gene. Expression of *RASSF1A* and *ANRASSF1* follows an opposite pattern in cancer cells. *ANRASSF1* forms an RNA/DNA hybrid and recruits chromatin-modifying enzymes to the *RASSF1A* promoter, reducing the expression of *RASSF1A* and increasing cell proliferation (Beckedorff et al., 2013b).

2.2. Upstream/enhancer RNAs

The discovery that enhancer regions upstream of coding genes are transcriptionally active themselves was an astonishing finding in terms of understanding genomic complexity. Moreover, transcription from enhancer regions seems to be evolutionarily conserved, suggesting vital roles. Convincing evidence for the function of enhancer region transcripts comes from knockdown of specific lncRNAs (Orom et al., 2010). When specific lncRNAs are depleted, neighboring genes' expressions were also downregulated. Such effects of lncRNAs can also be classified as a positive cis action where lncRNA-mediated enhancer–promoter looping occurs. Interesting studies revealed that genome-wide upregulation of estrogen induced lncRNAs positioned at enhancer sites/estrogen receptor binding sites of estrogen-responsive genes (Hah et al., 2013; Li et al., 2013). Similarly, *PRNCR1* and *PCGEM1* are 2 lncRNAs that are required for the activation of androgen receptor in prostate cancer cells. These lncRNAs are overexpressed in many aggressive prostate cancers, aiding androgen-dependent cell proliferation (Yang et al., 2013). Such enhancer-derived noncoding RNAs seem to enhance transcriptional potential of genes by creating a permissive chromatin structure and/or physically interacting with activator proteins. These findings provide insight into how enhancer sites may have an influence on the promoter and eventually on gene expression. Therefore, not surprisingly, deregulated expression of such RNAs may have significant consequences on gene expression patterns.

2.3. Noncoding competing endogenous RNAs

Noncoding competing endogenous RNAs (ceRNAs) are hypothesized to act as microRNA sponges (Salmena et al., 2011). It is indeed plausible to assume coding and noncoding RNA targets to crosstalk through their ability to compete for miRNA binding sites. Experimental evidence comes from *PTEN* and its pseudogene, *PTENP1*. Several binding sites for miRNAs that target *PTEN* are also found in the 3'-UTR of *PTENP1* mRNA. It turns out that the pseudogene *PTENP1* can regulate *PTEN* and exert a growth-suppressive role by acting as a miRNA binding decoy (Poliseno et al., 2010). Further examples support these findings. LncRNA *HULC* is one of the upregulated genes in hepatocellular carcinoma (Panzitt et al., 2007). CREB (cAMP response element binding protein) is involved in the upregulation of *HULC* (Wang et al., 2010). *HULC* may act as an endogenous 'sponge', which downregulates miRNA-372. This, in turn, leads to increased levels of its target gene, which can then induce the phosphorylation and activation of CREB as part of an autoregulatory loop.

Another example is *Lethe*, a pseudogene lncRNA. *Lethe* is transcribed by NF-kB, a transcription factor important in inflammation. In turn, *Lethe* binds directly to NF-kB and inhibits NF-kB DNA binding activity. These findings suggest that *Lethe* functions as a decoy, possibly to control the strength of the inflammatory response by directly interacting with the transcription factor (Rapicavoli et al., 2013). Another class of lncRNAs, circular RNAs (circRNAs, discussed below), can also be considered as ceRNAs as they also harbor miRNA binding sites.

2.4. Transcribed ultraconserved regions

Transcribed ultraconserved region (T-UCR) transcripts are a novel class of lncRNAs that are transcribed from regions of the genome that can be considered as ultraconserved regions (UCRs). These regions were discovered upon the completion of genome sequencing of different species. It turns out, interestingly, that approximately 500 regions, UCRs, were found to be conserved (100% identity with no insertions or deletions) between the orthologous regions of the human, rat, and mouse genomes. These regions are considered as mutational cold spots. Furthermore, significant underrepresentation of single-nucleotide polymorphisms (SNPs) within UCRs also confirms their evolutional and functional importance (Katzman et al., 2007; Yang et al., 2008). These genomic elements are longer than 200 bp (range: 200–779 bp), generally map to fragile sites, and can be intergenic, intronic, exonic, partly exonic, and exon-containing. Given their enrichment in cancer-associated genomic instability sites, genome-wide profiling revealed that T-UCRs have distinct expression signatures in different cancers with prognostic correlation (Calin et al., 2007; Scaruffi, 2011). Hypermethylation of T-UCR CpG islands has also been reported in colon cancer, breast cancer, lung cancer, melanomas, leukemias, and lymphomas (Lujambio et al., 2010). While the high homology implies a conserved function, we are far from understanding the functions of T-UCRs. Based on current findings, there are certain functions attributed to T-UCRS, such as long-range enhancer activity, transcriptional regulation, splicing, and epigenetic regulation (Scaruffi, 2011). Understanding the roles of T-UCRs within these and potentially other contexts could pave the way for a better understanding of normal and cancer-related regulatory mechanisms.

2.5. Circular RNAs

circRNAs can form naturally occurring circular structures that attract much attention because of their ability to bind and sequester miRNAs to abolish the repression of target mRNAs. circRNAs form by head-to-tail circularization of

exons with covalently joined ends (Memczak et al., 2013) or from lariat introns (Zhang et al., 2013b). Recent studies have suggested interesting roles of these circRNAs in gene expression. One example is exonic *CDR1as* (antisense to cerebellar degeneration-related protein 1), also known as *CIRS7*. *CDR1as* is predominantly expressed in the brain and has more than 70 miRNA binding sites; thus, *CDR1as* was categorized as a miRNA sponge (Hansen et al., 2013). *CDR1as* strongly suppresses miR-7 activity, resulting in increased levels of miR-7 targets. Testis-specific circRNA, sex-determining region Y (Sry), also serves as a miR-138 sponge, suggesting that the miRNA sponge effects achieved by circRNA formation may be a widely utilized system in cells (Hansen et al., 2013). However, intron-derived circRNAs are interestingly less likely to harbor miRNA binding sites; they accumulate in the nucleus and interact with RNA polymerase II (Zhang et al., 2013b). Therefore, they may have transcriptional roles other than recruitment of miRNAs.

3. Small noncoding RNAs

3.1. piwiRNAs (piRNAs)

piRNAs are small RNAs of 24–32 nucleotides long that are Dicer-independent and generally bind to PIWI proteins (a subfamily of argonaute proteins). piRNAs and PIWI proteins are known for their protective role in genome stability maintenance in germ lines (Brennecke et al., 2007). piRNAs are transcribed from regions that harbor expressed transposable elements. piRNAs and PIWI form complexes to recognize these transcripts and direct their cleavage. For a long time, piRNAs were considered to be germline-specific defense elements for transposable elements, especially when PIWI depletion led to increased transposable element activity (Siomi et al., 2011). Surprisingly, PIWI is also expressed in somatic cells while nongermline-specific piRNAs have been described in genome rearrangement and epigenetic programming, with biological roles in stem-cell function, whole-body regeneration, memory, and possibly cancer (Ross et al., 2014). Interestingly, PIWI proteins have been implicated in DNA methylation as well, pointing to a role in epigenetic regulation (Esteller, 2011). In support of this, a piRNA was implicated in DNA methylation of an imprinted mouse locus (Watanabe et al., 2011).

In addition to normal physiological roles, cancer-related findings are also intriguing. For example, somatic LINE1 element-induced insertional mutagenesis has been described in various epithelial cancers (Lee et al., 2012). Such insertions tend to occur in commonly mutated cancer genes that may serve for tumorigenesis-related events in transformed cells. Accordingly, PIWI increases in these situations may have a suppressive and protective role. Indeed, PIWI expression has been studied in various somatic cancers and was proposed as a potential biomarker. In other cases, PIWI overexpression (PIWIL2) leads to antiapoptotic signaling and cell proliferation (Esteller, 2011). It is clear that further research is needed to delineate the PIWI expression deregulation in cancers and whether it has any causative or protective roles. PIWI proteins have also been implicated in stem-cell renewal mechanisms (Ross et al., 2014).

Recently, mature piRNAs and PIWI proteins were detected in cancer cell mitochondria (Kwon et al., 2014). Further experiments are going to be exciting for investigation of the role of the piRNA-PIWI pathway in mitochondria in connection with cancer and possibly altered metabolic pathways and/or oxidative stress conditions.

3.2. microRNAs

miRNAs are small noncoding RNAs of 19–25 nucleotides long that inhibit the translation and/or stability of mRNAs by binding to 3'-UTRs. Based on the explosive number of studies in the literature, we know that miRNAs are involved in various different processes including cell-cycle regulation, differentiation, inflammation, apoptosis, and migration, mainly by controlling gene expression. Regulatory roles of miRNAs have been shown in almost all signaling pathways; consequently, dysregulation of miRNAs has been implicated in the development of human diseases including cancer.

miRNA genes are distributed throughout the genome, either between protein-coding genes (intergenic) or in their introns (intragenic). Almost all of the miRNA genes are transcribed by RNA polymerase II (Pol II) (Lee et al., 2004), possessing a 5' cap and a 3' poly(A) tail (Cai et al., 2004). Still, a small group of Alu repeat-associated miRNAs have been shown to be transcribed by RNA polymerase III (Pol III) (Borchert et al., 2006).

miRNA biogenesis is a multistep enzymatic process that starts in the nucleus and ends in the cytoplasm. First, Pol II transcribes the miRNA gene into pri-miRNA (primary miRNA). These are transcripts of several kilobases long, which are characterized by stem-loop structures harboring the mature miRNA. In the nucleus, pri-miRNAs are cotranscriptionally recognized by the Microprocessor complex (Gregory et al., 2004; Han et al., 2004). The main components of the Microprocessor complex, the Drosha/DGCR8 heterodimer crops the pri-miRNAs into pre-miRNAs (precursor miRNAs), which are long hairpin structures of 60–100 nucleotides (Han et al., 2004). DGCR8 is an RNA binding protein that is responsible for pri-miRNA hairpin recognition, while Drosha is an RNase III enzyme cropping the pri-miRNA. Next, Exportin-5 and its partner Ran-GTP recognize pre-miRNAs from their ~2 nt 3' overhangs and transport them to the cytoplasm (Yi et al., 2003). In the cytoplasm, another

RNase III, Dicer, recognizes pre-miRNAs and cleaves them into ~22 nt long miRNA/miRNA* duplexes (Hutvagner et al., 2001; Lee et al., 2003). When miRNA duplexes interact with argonaute (Ago) proteins, the RNA-induced silencing complex (RISC) is formed. RISC usually binds to the 3'-UTR of target mRNAs by recognizing specific sequences called "seed sequences" with partial complementarity. RISC binding to the 3'-UTR causes either cleavage or translational repression of the mRNAs. In addition to canonical miRNA 3'-UTR targeting, some discrepancies have been reported, such as miRNAs binding to 5'-UTR of the mRNA to increase target gene translation (Orom et al., 2008).

3.2.1. miRNAs and cancer

miRNAs have been implicated in cancer development and progression since their discovery. Currently, it is well known that miRNAs can be upregulated or downregulated in numerous cancers (Erson and Petty, 2008; Selcuklu et al., 2009). When miRNAs are downregulating tumor suppressor genes, they function as oncogenes/oncomiRs. On the other hand, they are called tumor-suppressor miRNAs when they are targeting oncogenes. Important regulatory roles of miRNAs have been implicated to affect all 6 hallmark capabilities of cancer (Hanahan and Weinberg, 2011) including sustaining proliferative signaling, evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis, and resisting cell death. However, miRNAs are also implicated in 2 emerging hallmarks: deregulating cellular energetics and avoiding immune destruction.

Sustaining proliferative signaling and evading growth suppressors are 2 fundamental hallmarks of tumorigenesis. In normal cells, homeostasis is preserved by controlling both mitogenic growth signals and antiproliferative signals. When miRNA profiles are altered in cancer cells, cell cycle regulators that are targeted by those miRNAs are also deregulated. For instance, the let-7 family of miRNAs has been shown to inhibit the RAS oncogene (Johnson et al., 2005). Loss of let-7 expression has been linked to increased expression of RAS and progression of acute myeloid leukemia (Garzon et al., 2008) and lymphocytic leukemia (Marton et al., 2008). Evasion of apoptosis is another hallmark of cancer. MiRNAs are able to repress or induce apoptosis by targeting proapoptotic or antiapoptotic genes, respectively. MiR-21 is an oncomiR that is overexpressed in almost all human cancers (Kumarswamy et al., 2011; Li et al., 2012) . MiR-21 targets apoptotic genes such as *PTEN* (Meng et al., 2007), and *PDCD4* (Asangani et al., 2008), thus preventing programmed cell death, apoptosis.

Besides interfering with apoptosis, cancer cells avoid senescence and acquire a limitless replicative potential either by homologous recombination events at telomeres (Bailey et al., 2004) or by abnormal telomerase enzyme activation (Davison, 2007). The role of miRNAs in this scenario was revealed after expression levels of miR-138 were associated with telomerase deregulation (Mitomo et al., 2008). According to this study, miR-138 inhibits the human telomerase reverse transcriptase (hTERT) gene, and thus loss of miR-138 leads to increased hTERT in thyroid carcinomas. Another aspect of cancer cells is that they are capable of producing high amounts of proangiogenic factors to stimulate new blood vessel formation. A number of miRNAs such as miR-126, miR-378, and miR-296 have been named angioMiRs as a result of their contribution to angiogenesis (Wang and Olson, 2009). Vascular endothelial growth factor (VEGF) levels, which are high in most tumors, are controlled at multiple levels. In zebrafish, miR-126 was found to repress negative regulators of the VEGF pathway, hence regulating angiogenesis and vascular integrity (Fish et al., 2008).

Tumor invasion and metastasis is the leading cause of morbidity and mortality in human cancers. A series of complicated events including cellular detachment, microenvironmental motility, and spread to distant organs is orchestrated by various proteins (Chambers et al., 2002). Involvement of miRNAs has been shown in various studies showing miRNA's effects on invasion and metastasis events (Baranwal and Alahari, 2010). For instance, overexpression of miR-10b has been shown in metastatic breast cancer cases (Ma et al., 2007). In this case, increased expression of miR-10b suppresses HOXD10 (homeobox D10) levels, which leads to increased RHOC (Ras homolog gene family, member C) levels, hence enhancing cells invasive and metastatic abilities.

Hallmarks of cancer have been evolving as the accumulating scientific data indicates the importance of cellular processes in cancer such as cellular energetics and avoidance of immune destruction. As with the previous 6 hallmarks, these newly emerging ones are also complicated with miRNA regulations. Evasion of immune surveillance by numerous strategies has been shown to be an ability of cancer (Curtale and Citarella, 2013). For example, miR-155 has been shown to an important regulator of immune system function (Rodriguez et al., 2007). MiR-155 regulates cytokines, chemokines, and transcription factors, which are necessary for normal immune function (Rodriguez et al., 2007). miRNA regulation during immune responses in cancer is also of great interest (Pedersen and David, 2008). For instance B7-H3, a surface immune-modulatory protein, inhibits natural killer cells and T cells. In normal tissues, expression of miR-29 decreases B7-H3 protein levels (Xu et al., 2009). However, miR-29 is downregulated in solid tumors such as sarcomas and neuroblastomas, such that B7-H3 protein levels are increased. The correlation between low miR-29 levels and B7-H3 expression has implications in immune system evasion of solid tumors.

Finally, cancer cell metabolism has gained attention with another cancer hallmark in recent years. As the existence of a metabolic switch in cancer cells is known, involvement of microRNAs has also been investigated. For example, miR-378 has been implicated in a metabolic shift in breast cancer cells by inhibiting expression of ERRγ (estrogen-related receptor γ) and GABPA (GA-binding protein α), thus causing reduction in TCA cycle gene expression and oxygen consumption leading to cellular proliferation (Eichner et al., 2010).

As exemplified in all hallmarks of cancer, regulatory roles of miRNAs in cancer development and progression are substantial. Therefore, therapeutics strategies regarding inhibition or mimicking miRNAs are being investigated for treatment of human diseases including cancer (Ling et al., 2013; Nana-Sinkam and Croce, 2013). The first cancer-targeted miRNA drug, MRX34, is a liposome based miR-34 mimic that entered phase I clinical trials for hepatocellular carcinoma treatment (Bader, 2012; Bouchie, 2013). Mir-34 has been shown to be a tumor-suppressor miRNA as it regulates multiple oncogenes such as BCL2, cyclin D1, and MYC, which are involved in the regulation of the cell cycle, proliferation, antiapoptosis, metastasis, and chemoresistance (Bader, 2012). Mir-34 is downregulated in hepatocellular carcinomas; hopefully this replacement strategy will display potential therapeutic applications for miRNAs.

Taken together, additional research on novel miRNAs and their targets will enhance our knowledge of the roles of these regulators and hopefully these findings will speed the development of diagnostic and therapeutic applications for cancer. It is also worth noting that mRNAs can evade miRNA binding by alternative polyadenylation at 3'-UTRs (Sandberg et al., 2008; Akman and Erson-Bensan, 2014). There is increasing evidence that some oncogenes may switch to shorter 3'-UTRs to avoid microRNA regulation in cancer cells (Mayr and Bartel, 2009; Akman et al., 2012).

3.3. snoRNAs/scaRNAs

Small nucleolar RNAs (snoRNAs) and small Cajal body-specific RNAs (scaRNAs) are noncoding RNAs involved in the maturation of other RNA molecules. Small nucleolar RNAs (snoRNAs) are a class of small RNA molecules (60–300 bp) that are components of small nucleolar ribonucleoproteins (snoRNPs) to modify rRNA precursors during their maturation for ribosome assembly. These posttranscriptional modifications are either 2′-O-methylation by the C/D box snoRNAs or pseudouridylation by the H/ACA box snoRNAs in the nucleolus where ribosomes are formed. Several hundred snoRNAs have been mapped to intronic regions where they are processed by exonucleolytic trimming (Zhang et al., 2013b).

It is clear that cells must coordinate ribosomal biogenesis with other cellular processes including cell proliferation. Not surprisingly, hyperactive ribosomal biogenesis has been implicated as a feature of cancer cells (Ruggero and Pandolfi, 2003). Initial studies also suggested a potentially direct link between snoRNAs and cancer. For example, h5sn2, a H/ACA box snoRNA, was found to be significantly downregulated in human meningiomas compared with normal brain tissues (Chang et al., 2002). Later, several studies addressed the significance of genomic instability regions that harbor snoRNA genes in various cancer types (Mannoor et al., 2012). Furthermore, deregulated expression of snoRNAs along with small nucleolar ribonucleoprotein, fibrillarin, in murine and human breast cancer appears to be critical for tumorigenicity both in vitro and in vivo (Su et al., 2014).

On the other hand, scaRNAs can modify snRNAs that mediate mRNA splicing. Deregulated expression of both snoRNAs and scaRNAs has been documented in various cancer types (Ronchetti et al., 2013; Lawrie et al., 2014). Altered sno/scaRNAs expression and its consequences in terms of disease pathology are of future interest.

3.4. Endogenous small interfering RNAs (endo-siRNAs)

Initially, nematodes and *Drosophila* were demonstrated to have a well-defined endo-siRNA pathway. Deep-sequencing small RNA analysis helped the discovery of mammalian/human endo-siRNAs that are ssRNAs of 20 nucleotides long that originate from endogenous dsRNAs such as antisense transcripts (cis- or trans-NATs), transposable elements, and hairpin RNA transcripts to repress either transposable elements or endogenous mRNAs (Okamura et al., 2008; Okamura and Lai, 2008).

Interestingly, a subset of differentially expressed endo-siRNAs that directly regulate LINE-1 expression is depleted in human breast cancer cells compared to normal breast cells. These endo-siRNAs seem to regulate endogenous LINE-1 expression through increased DNA methylation of the LINE-1 5'-UTR promoter (Chen et al., 2012). Global mechanisms to regulate production of such endo-siRNAs and consequences of deregulated production of endo-siRNAs remain to be investigated in cancer cells.

3.5. rasiRNAs (repeat-associated small interfering RNAs)

rasiRNAs have been identified in plants, fission yeast, *Drosophila*, and zebrafish. In mammals, rasiRNAs have not been specifically described. Hence a link between cancer and rasiRNAs has not been established yet. RasiRNAs are thought to have roles in gene silencing of repetitive sequence elements and transposable elements. RasiRNAs are most abundant in testes and early embryos, where regulation of transposon activity is critical and chromatin modeling occurs (Aravin et al., 2003).

4. Conclusion

With the advancements of sequencing and high throughput analyses, we now better appreciate the significance of the noncoding part of our genome. The long undervalued noncoding transcripts are indeed quite abundant in cells performing various functions. Not only these functions but also how they interact with other noncoding RNAs, coding RNAs, and DNA is interesting to observe. These intertwined relationships will definitely provide a better understanding of the complexities of our cells. A better perspective on these normal events will then help us improve our knowledge on disease states, mainly cancer, where genomic instability and deregulated expression of genes is common. Hence, noncoding RNAs carry the potential for diagnostic and/or therapy strategies once their gene structures, expression profiles, and specific functions are better delineated. miRNAs are already considered as valuable biomarkers in certain tissue types/cancer types given their specific expression profiles in normal and cancer cells. Based on current evidence, at least some noncoding RNAs appear to have significant functions during gene expression, development, and differentiation. Consequently, their deregulation is highly associated with disease states. For example, there are clinical trials pursuing the use of noncoding RNAs in determining the predisposition to specific cancers. For the future, noncoding RNAs will not only be considered as biomarkers but also as targets for therapy. Such therapy approaches may utilize RNAi, aptamers, ribozymes, and small molecule drugs to target deregulated noncoding RNAs. It appears these and other novel approaches will be of great interest not only for cancer but other diseases such as cardiovascular and neurological diseases. Hopefully a comprehensive understanding of the genome and transcriptome will be the key to advances in such applications.

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