Noncoding RNAs and human disease

Abstract:

Non-coding RNAs are functional RNAs which mainly function in regulatory processes. This review encompasses long non-coding RNAs (lncRNA), circular RNA (circRNA), small nuclear RNA (snRNA), and small nucleolar RNA (snoRNA). The focus is on latest knowledge and understanding of these RNAs as well as their significance and role in cancer, cardiovascular disease, and diabetes.

Keywords:

Noncoding RNAs, lnRNA, mitochondrial lncRNA, aging, circRNA, sponge, back-splicing, ElcircRNA, alternative splicing, miRNA, snoRNA, snRNA, snoRNA C/D box, snoRNA H/ACA box cancer, diabetes, cardiovascular disease, obesity

Introduction

Regions of the genome that did not code for proteins were assumed to be non-functional and considered of no value (1). These regions make more than 98% of the genome and contain regulatory sequences and sequences that do not code for proteins(2). This was the case until the idea that ribonucleic acids (RNAs) could have an active role in protein synthesis was proposed(3). This idea was reinforced with the discovery of an active RNA that functioned in the transferring amino acids to the messenger RNA (mRNA) –rRNA was yet to be discovered-. These RNAs were denoted as tRNA (transfer ribonucleic acid) (4). Since then the study of non-coding RNA became popular and new non-coding RNAs are frequently being discovered(2).

Of these non-coding RNAs are lncRNAs. Long non-coding RNA is one of the non-coding RNA that gained a lot of attention in the past years due to its crucial role in biological regulation(5). LncRNA is involved in many biological functions in the body depending on its location in the cell; nucleus or cytoplasm. In the nucleus, LncRNA control the recruitment of transcription factors, regulation of splicing and recruitment of chromatin modifiers. LncRNAs have different function if its located in the cytoplasm such as controlling the translation rate (6). Mitochondrial LncRNA is another type of LncRNA present in the cell where scientist believed that it regulates the expression of mitochondrial genome, but still the mechanism is not clear (7). Many clinical experiments were performed regarding the role of LncRNAs in both pathological condition such as cancer and diabetes and in physiological condition such as aging.

Another group of non-coding RNAs are small noncoding RNAs. These RNAs include snRNA, snoRNA (less than 200 nucleotide) and microRNAs (less than 70 nucleotide)(8). SnRNA and snoRNAs are both confined to the nucleus(9). SnRNA mainly assemble with proteins to make the subunits of the spliceosome(10). SnoRNAs mainly regulate the post transcriptional processing of RNAs(11).

Moreover, circular RNA (circRNA) is another non-coding RNA (nc-RNA) that has recently become a research interest in the field of untranslated RNAs (12). It was first found in RNA viruses in 1970s. However, It was thought to have formed due to splicing errors in pre-RNA due to its low count in these viruses (13). Its importance became clear with the advances in

sequencing technologies and biotechnology. Thousands of circRNA were found in different organisms including humans and their expression was found to be more than 10 times the expression of the canonical linear counterparts (14).
A unique feature in circular RNA that distinguishes it from other types of non-coding RNAs is that circular RNA forms a closed loop. This closed loop doesn't exhibit 5' – 3' polarities or have polyadenylated tails making it non-vulnerable to degradation by RNase R enzyme. Resistance to degradation by RNase R gives circular RNA longer stability inside the cells (15).

Long noncoding RNA (lncRNA)

LncRNA varies in size from 200 nucleotides to 10 kilobases depending on its location inside the cell; either in the nucleus or in the cytoplasm. LncRNA could be divided into six sections; intronic antisense, natural antisense, intergenic, bidirectional, intron-sense overlapping, and exon sense-overlapping depending on their genomic position with protein coding genes(16). **Figure will be added**. LncRNA have broad functions in the body such as regulating the basal transcriptional machinery, in gene specific transcription, chromatin modification, and in imprinting and epigenetic regulation (16).Figure (2) shows an illustration regarding function of LncRNA either in the nucleus or cytoplasm of the cell.(HOX transcript antisense RNA) HIRAIR is an experiment performed to check the mode of activation of LncRNA on adjacent cells. Up to this experiment it was believed that LncRNA could only influence adjacent cells (cis pattern). The results of this experiment showed that LncRNA plays crucial role in recruiting the chromatin modifying complexes to a specific genomic locus both in cis and trans pattern (17). It has been found that HOX transcript antisense RNA (HOTAIR) could interact with chromatin remodeling proteins such as polycomb repressive complex 2 and G9a to mediate deposition of repressive chromatin marks. lncRNAs could regulate mRNA synthesis directly at genomic loci by interacting with transcription factors or components of the basal transcriptional machinery. The cis pattern of LncRNA recruitment activities in HIRAIR experiment was as the following; in a specific genomic loci LncRNA will bind to the nearest transcription binding site which has a protein bound to it, this binding will form a hybridization between LncRNA and both binding site and transcriptional protein already attached to the binding site. As a result of the hybridization, other transcriptional proteins will bind to the binding site to start the transcriptional activity (17). Scientist were concern about the best model used to study the function and interactions of LncRNA (18). A group of scientist did a systemic experimental study on zerbafish transcriptome. The scientists were able to reconstruct 56,535 high- confidence coding and noncoding transcripts from 28,912 loci in addition to the discovery of novel transcribed regions, this suggested that zerbrafish could be used as a model to study interactions of LncRNA (18).

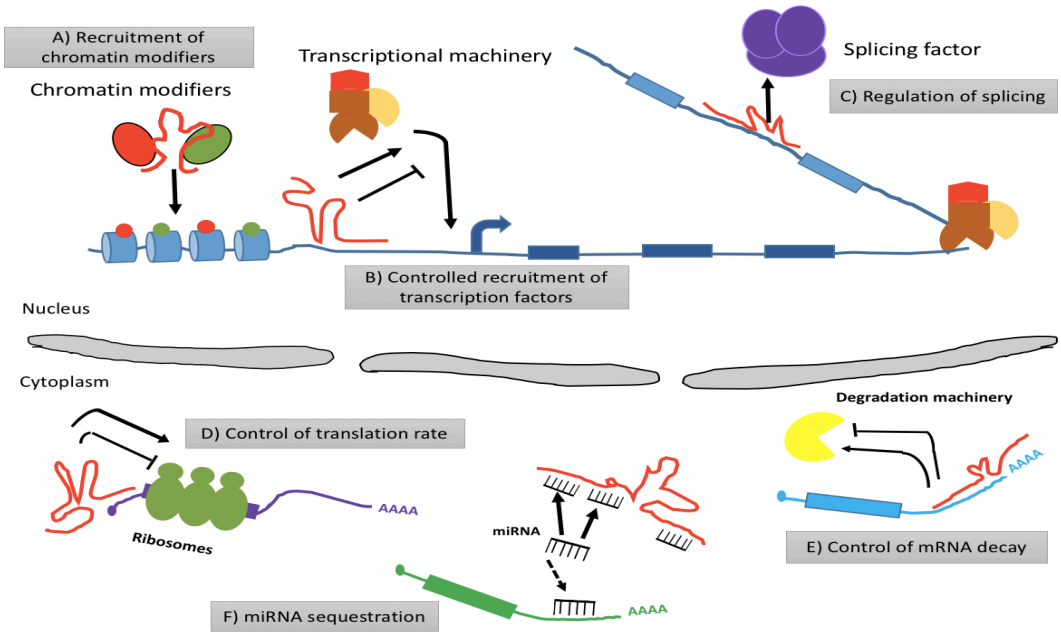

Figure (2): This figure illustrates the function of LncRNA depending on its position inside the cell either in the nucleus or cytoplasm. Inside the nucleus; (A) LncRNA(in red) has the ability to recruit chromatin modifier in order to mediate the deposition of histone marks either activatory (green dots) or inhibitory marks(red dots). (B) LncRNA control the recruitment of the transcription factors. (C) LncRNA could modulate the splicing events by directly binding to mRNA. In the cytoplasm, (D) LncRNAs control the translation rate by either enhancing or inhibiting polymerase binding to mRNAs. (E) LncRNAs could also protect mRNA from degradation by mediating the recruitment of degradation machinery. (F) LncRNAs could act as miRNA sponge which will allow the espression of mRNAs targeted by sequestered miRNA.

Circular RNA (circRNA)

Circular RNA differs from linear RNA in that its structure is formed of a covalently linked loop. That is the 5' end downstream end is covalently linked to 3' upstream end of the RNA. The mechanism in which this covalent bond occurs is known as back-splicing. (19).
There are two pathways in which circular RNA can be formed by back-splicing. The first one is lariat driven circularization. In this pathway, one or more exons are skipped during the process of splicing. This leads to the formation of a lariat that contains either one or more exons. Later, the lariat is joined by spliceosome to become an exon circle. The second pathway of biogenesis of circular RNA is termed intron-pairing driven circularization. In this case, it is the introns that covalently bind with each other forming the circular RNA. Pairing occurs due to the presence of complementary motifs in those intronic regions, and those motifs induce circularization of RNA (14). These two pathways eventually lead to the formation of three possible types of circRNA. These are: exonic circRNA, intronic circRNA, and exon-intron circRNA. Exonic circRNA only has exons, intronic circRNA only has introns, while exon-intronic circRNA has both exons and introns.

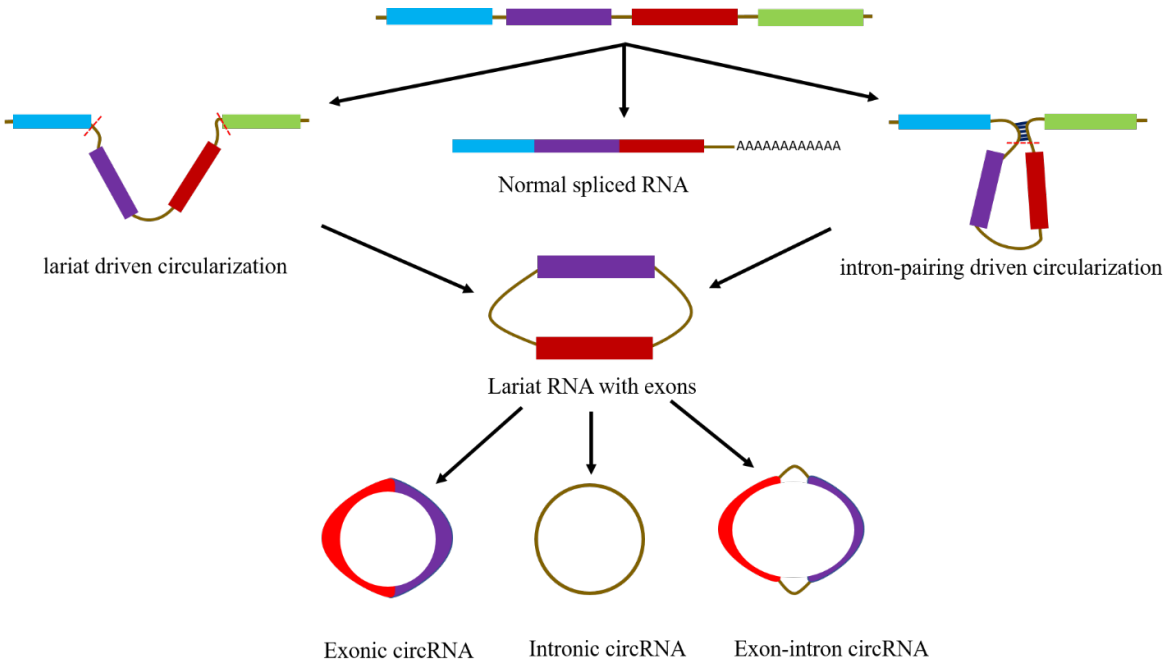

Figure 3: This diagram shows the two methods of which RNA splicing can lead to the formation of circular RNA. One is lariat driven circularization, and other is intron-pairing driven circularization. It can be seen that both of them lead to the formation of a lariat RNA which is eventually cleaved to form the final circular RNA. The final product can either be exonic circRNA, intronic circRNA, or exon-intron circRNA. The diagram also shows one way normal splicing could occur, it shows the resulting RNA with its poly-A tail that is lacking in circular RNA.

circRNA have special binding sites for microRNA (miRNA) thus, the circRNA is thought to have a role in the regulation of miRNA and its activities. When circRNA binds to miRNA it inhibits its function. This directly affects the binding of miRNA to mRNA to regulate its expression. The way circRNA binds to miRNA led to giving it the name miRNA sponge. Such activity of circRNA has been found across different types of circRNAs especially when studying disease conditions (20).

To add, it is suggested the circular RNA has a role in competing against canonical splicing. The exon that codes for the start of the main coding sequence of MuscleBlind protein (MBL) is found to be circularized. The means by which it is circularize are thought to be stemming from the exon's flanking introns. These introns have protein binding motifs which specifically bind to the MBL protein. Here, it is suggested that the MBL protein controls the circularization of its own RNA by inducing bridging between the two flanking introns. Thus, circularization will not take place if MBL protein binds to only one of the flanking introns. When the levels of MBL protein are high, more MBL protein will bind to the flanking introns on the pre-mRNA leading to increase in the production of the circular MBL which ultimately binds to the MBL protein itself (as the circular MBL protein has specific binding sites for MBL). At the same time, the MBL mRNA synthesis is reduced. It was also found that when the levels of MBL protein are decreased, the levels of circular MBL are also reduced (21). As can be seen, the competition between the formation of circular RNA and pre-mRNA splicing provides a regulatory function for these sequences and suggests a role of circular RNA in canonical splicing regulation.

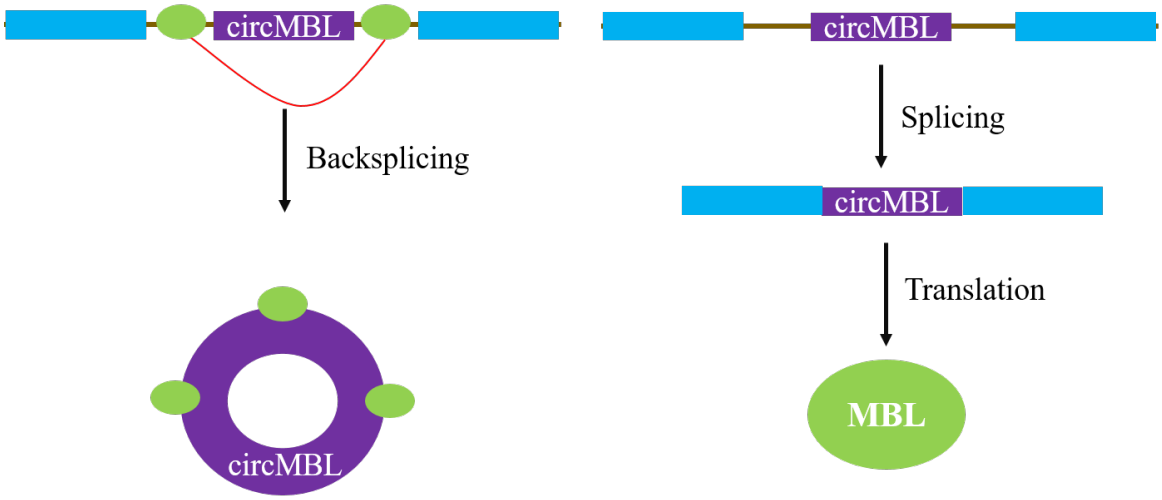

Figure 4: Illustrates how MBL proteins interacts with its own RNA to regulate its expression by binding to the coding exon to form circMBL. However, when the levels of MBL protein are low, circRNA will not be formed, and the mRNA will form proceeded by its translation to form MBL protein.

Another function of circRNAs is its regulation of parental gene expression. It is believed that certain circRNAs function to regulate parental genes by interacting with small nuclear ribonucleoproteins (snRNPs) and DNA polymerase II directly in order to enhance gene expression. Exon-intron circular RNA (EIciRNA) which can be seen in Diagram 1 is mainly located inside the nucleus and found interacting with U1 snRNPs to enhance the expression of its gene by interacting with DNA polymerase II transcription complex. It is also noted that the parental regulatory function of ElciRNA is mediated by U1 snRNPs (22).
It was recently found that circRNA can be translated to proteins. The first observation of a circular RNA that can be translated is the one of hepatitis δ virus circular RNA which was translated to a single stranded 122 amino acids protein when the virus was encapsulated (23). To add, it was found that circMbl isoform detected in fly head extracts can be translated to proteins. The same study found that some circRNAs use the starting codon of their host mRNA and are translated by membrane bound ribosomes which are bound to them (24). Another study found using artificial circRNA with an internal ribosome entry site (IRES) sequence can be translated into a functional green fluorescent protein in vitro (25). Lastly, translation of circRNA in human cells was found to be initiated by increasing levels of N^6-methyladenosine. It was also found that the levels of N^6- methyladenosine increases in the case of heat shock. This finding predicts that proteins derived from circular RNA can have a role in cells response to external stress (26).
Circular RNA has shown to have three functions in gene regulation in which it acts as a MiRNA sponges, modulators of alternative splicing, as well as regulators of parental genes. Recently, new field of research has emerged due to the discovery of translation potential of circRNA which indicates a potential role of circRNA proteins. Due to the early age of circular RNA research, many aspects of its functionality are still unknown and yet to be discovered.

Small noncoding RNAs: microRNA (miRNA), small nuclear RNA (snRNA) and small nucleolar RNA

MicroRNA

MicroRNAs (miRNAs) are small, RNA molecules encoded in the genomes of plants and animals. These highly conserved, ~21-mer RNAs regulate the expression of genes by binding to the 3'-untranslated regions (3'-UTR) of specific mRNAs. Although the first published description of an miRNA appeared ten years ago (27), only in the last two to three years has the breadth and diversity of this class of small, regulatory RNAs been appreciated. A great deal of effort has gone into understanding how, when, and where miRNAs are produced and function in cells, tissues, and organisms. Each miRNA is thought to regulate multiple genes, and since hundreds of miRNA genes are predicted to be present in higher eukaryotes (28), the potential regulatory circuitry afforded by miRNA is enormous. Several research groups have provided evidence that miRNAs may act as key regulators of processes as diverse as early development(29), cell proliferation and cell death (30), apoptosis and fat metabolism (31), and cell differentiation(32). Recent studies of miRNA expression implicate miRNAs in brain development(33), chronic lymphocytic leukemia (34), colonic adenocarcinoma, Burkitt's Lymphoma (34), and viral infection (35) suggesting possible links between miRNAs and viral disease, neurodevelopment, and cancer. There is speculation that in higher eukaryotes, the role of miRNAs in regulating gene expression could be as important as that of transcription factors.

SnRNA

Small nuclear RNA (snRNA) are stretches of non-protein-coding RNA. snRNAs were first documented as low molecular weight RNA fractions in a study aimed to analyze the different fractions of RNA using agarose-gel electrophoresis. These low molecular-weight RNA molecules were recovered after repeating the experiment multiple times, indicating that they were not degradation products of higher molecular weight RNAs(36). These small RNA molecules were analyzed and found to be methylated and are localized to the nucleus of the cells(37). Moreover, further analysis of these molecules revealed their high uridine content (hence, the letter U was used to denote the different classes of these RNA molecules) (38). The next discovery that greatly affected the way scientists thought about small nuclear RNAs was the discovery of DNA. A couple of years after DNA was discovered, scientists discovered the presence of long RNA molecules (known as pre-mRNA today) within the nucleus. However, when compared to cytoplasmic mRNA, the pre-mRNA was much longer(39). Sequences of mRNA and their corresponding DNA templates were analyzed in1977 and it was found that some sequences, known as introns, in the cytoplasmic mRNA were missing, or spliced out(40). The question that arose next was how are introns spliced out? The answer to this question was found in snRNAs' contribution to the formation of spliceosomes. Beside their function in splicing, more recent studies have shown a regulatory role of snRNAs in gene expression.

snRNAs are divided into two classes based on common characteristics between members of each class. The first class is the Sm class, which comprise snRNAs U1, U2, U4, U5, U7, U11, U12, and U4atac. These snRNAs are synthesized by RNA polymerase II. Whereas U6 and U6atac belong to the class Lsm and are synthesized by RNA polymerase III (41, 42). Sm class RNAs are transcribed in the nucleus, exported to the cytoplasm where they are modified and returned to the nucleus where they assemble with proteins to form small nuclear ribonucleicproteins (snRNP). On the other hand, Lsm class RNAs are modified within the nucleus and do not require to be transported outside the nucleus.(42). Moreover, two types of spliceosomes exist, major (contributing greater percentage of RNA splicing) and minor spliceosomes (contributing to a small percentage of RNA splicing The major spliceosome consists of U1, U2, U4, U5, and U6, whereas the minor spliceosome consists of U5, U11, U12, U4atac, and U6atac(10).

The main function of snRNAs is to form the spliceosome, a ribonucleoprotein (made of protein subunits and RNA molecules), which is the maestro of RNA splicing. The premature RNA has conserved intron sequences at the 5'(AG/GU) and 3' end known as consensus sequences. These sequences are recognized by the the snRNA component of the spliceosome. Once they have been recognized, a double transesterification at both ends occurs resulting in the release of the intron as a lariat(43). The U1 first recognizes the 5' split site on the premature mRNA and initiate the assembly of the spliceosome(44). The U2 then recognizes the branch site (45). U4, U5 and U6 assemble together and from a tri-snRNA which assembles with the U1 and the U2 forming the complete spliceosome structure(43). The spliceosome then catalyzes the double transesterification reaction, where the 2'OH on the branch site attacks the 5' splicing site and forming a lariat. The free 5'OH of the exon then attacks the 3' split sites, leading to the ligation of two exons together(43).

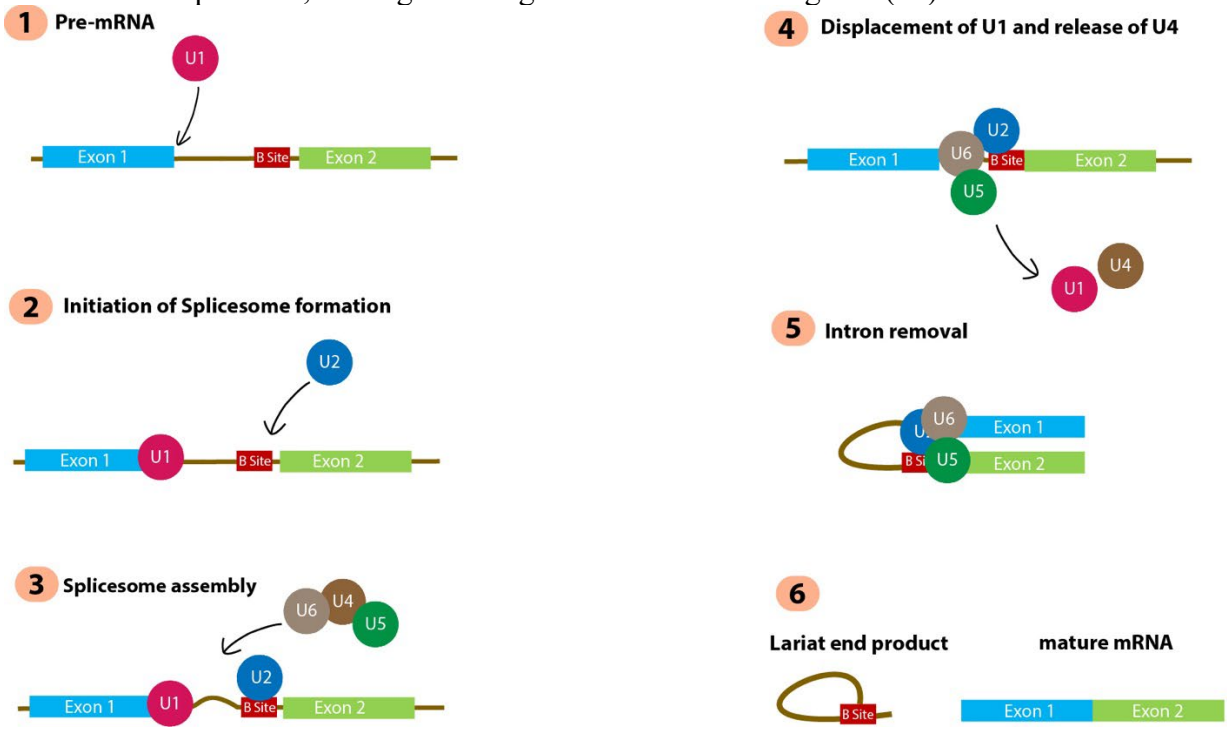

Figure 3: The process of splicing a pre-mature mRNA containing exons and introns into a mature mRNA containing only exons. **1)** U1 snRNP recognized and attaches to the 5' splice site of exon 1 through complementary base pairing. **2)** U2 snRNP recognizes and attaches to the branch site (B site) through complementary base pairing. **3)** U4, U5, and U6 tri-snRNP complex assembles and binds to the pre-mature mRNA creating the splicesome. **4)** U6 displaces U1 and U4 is released. **5)** The premature mRNA bends to bring the 5' splice close to the branch site. The spliceosome catalyzes the breakage of the 5' split site and the ligation of this site to the branch site. **6)** The splicing process is completed and the end products released are a lariat structure and a mature mRNA.

SnoRNA

Similar to snRNA are small nucleolar RNAs (snoRNA), which are short strands of single stranded RNA (ssRNA) that are confined to the nucleus and range in size from about 70 to 150 nucleotides(9). In contrast to snRNA which play a role in cellular splicing and regulation of transcription, snoRNAs play major role in RNA modification. SnoRNAs are classified into two families based on structural similarities. Both families are involved in post transcriptional

modifications of rRNAs, and to a lesser extent tRNA and snRNA(9, 11). The first family is designated C/D box, because it has two conserved regions the C (UGAUGA) region and the D (CUGA) region. Members of this family are mainly involved in the methylation of rRNA. Methylation is achieved by the addition of a methyl group to nucleotide within the premature RNA(46). The second family is the H/ACA box, which also have two conserved sequences, the H (ANANNA) region and the ACA (ACA) region. This family of snoRNA is involved in pseudouridylation. Pseudouridylation is the process in which the nucleotide uridine is converted to an isomer known as pseudouridine. In a pseudouridine molecules, the uracil is attached to the ribose through a carbon-carbon bond rather than the original nitrogen-carbon bond found in the uridine molecule(47). Both families of snoRNAs carry their function by recognizing sequences that are near the nucleotide that is to be modified. The catalysis of actual modification is carried by the proteins attached to the snoRNAs(48). Similar to snRNAs, each family of snoRNA has a specific set of four proteins attached to it. Proteins that attach to the C/D box include fibrillarin, Snu13p, Nop56p, Nop58p. The proteins associated with H/ACA box include Cbf5p, Nhp2p Nop10p, and Gar1p (49). These proteins assemble with the snoRNA to form the complex responsible for executing the fine post-transcriptional nucleotide modification. This complex is known as small nucleolar ribonucleoprotein (snoRNP) –not to be confused with snRNP which is the functional unit of a spliceosome- (9). SnoRNAs seem to be involved in alternative splicing(50). Snord115 has been shown to play a role in the inclusion of an exon known as Vb into the serotonin receptor. Deletion of snord115 was associated with also Prader-Wili Syndrome (50, 51). In addition, snoRNA seems to play a role in oncogenesis(52-54) and the cell's susceptibility to stress(55).

Non-coding RNAs in selected diseases

Cancer

LncRNA

As mentioned earlier LncRNAs have different roles in gene specific transcription, chromatin modification, and in imprinting and epigenetic regulation (16). These functions showed the importance of LncRNA in the body, and their absence in the cell will result in several diseases and abnormalities especially in conditions related to cancer and genomic imprinting. Recent studies showed that LncRNA has been seen in correlation with malignancy in breast and prostate cancer, where in breast cancer lncRNA BCAR4 enhanced cell migration and metastasis, while in prostate cancer overexpression of lncRNA SChLAP1 could lead to increase the metastatic progression up to 2.45 fold higher (56). Mutation in the germline could affect and alter the function of LncRNA which lead to the development of many diseases. Further explaining about the correlation between cancer and malignancy with long non-coding RNA will be discussed further in more details throughout the article. Experimental studies showed the interaction between LncRNA and cancer in terms of initiation and progression of various cancers. Lung cancer is one of the cancers where scientists studied this correlation. In one of the studies, the regulation of LncRNA was identified by establishing an experiment to check the SMAD3 affect on LncRNAs in Epithelial-Mesenchymal-Transition (EMT) process. This process simply is performed by the polarization of epithelial cells to be transformed into fibroblast such as mesenchymal cells. The cell markers of the epithelial cell changed as cell transformation was successfully achieved. The protein function and expression of transformed cells changed and showed

more motile and invasive form (57). Three human cell lines A549, H1299 which are lung cancer epithelial cell lines and 293T were used in the previous experimental, total RNA was extracted and then quantitative polymerase chain reaction were performed. A microarray data collection regarding the expression of 291 LncRNA were examined in both cancerous and adjacent normal lung cells. A close attention was given to the role of LINC01186 in the lung cancer. The results showed that LINC01186 plays a significant role in down regulating the TGF-β1 treated cells (TGF-β1 function to promote cancer metastasis) (57). The practical studies showed that LINC01186 was significantly downregulated in TGF-β1 treated cells, where the presence of LINC01186 inside the cancerous lung cell will inhibit migration, invasion and colony formation to the adjacent healthy cells (57). Comparing the results of this experiment with others it seems that LINC01186 been expressed in several cancers, which suggests that LINC01186 could be used as a molecular marker in many tumors types.

Taurine up-regulated gene 1(TUG1) is another LncRNA that has an effect on several type of cancers especially esophageal squamous cell carcinoma where experiments showed that this LncRNA enhances the cell proliferation and migration of this type of cancer (58). From 96 patient's human OSCC tissues and matched adjacent normal tissues were taken to perform the experiment. The apoptotic rate of the damaged cells was examined using flow cytometry. The results showed that TUG1 was up-regulated in both OSCC tissues and cell lines. This means that knocking down TUG1 from the cell will lead to the inhibition of the proliferation and growth of the cells, and it will lead to induces apoptosis in OSCC cell lines. These two hypothesis were proven by two experiments using CCK-8 assay and flow cytometry respectively. Overexpression of TUG1 was correlated strongly with TNM stage, tumor grade, and lymph node metastasis. Other LncRNA such as UCA1 showed similar effect of that in TUG1 in oral squamous cell carcinoma. Long non-coding RNA (TUG1) showed also some effect on cervical cancer in addition to OSCC. Similar methods were used such as PCR, western blot and flow cytometry to check for cell ability to go apoptosis and to check the activity of LncRNA in cervical cancer. Westron blot simply was performed by extracting the protein from the cells using radioimmunoprecipitation assay buffer(RIPA). The protein is the separated using SDS PAGE electrophoresis. The separated protein is then being transferred to polyvinylidene difluoride membrane. Blocking of the reaction was performed using milk. Primary antibodies such as rabbit polyclonal anti-β-caten- in antibody and rabbit polyclonal anti-cyclin D1was used. After an overnight incubation at 4°C the primary antibody was detected using chemiluminescent kit (58). Cervical cancer cells showed significant expression of LncRNA TUG1. The results also suggested that the level of expression increases as the size of malignant cell increases. Invasion and migration of the cervical cancer in addition to cell proliferation and cell apoptosis could be decreases when TUG1 is knocked down (58). Chronic myeloid leukemia (CML) is one of the diseases where experimental studies also showed the effect of lncRNA-BGL3 on regulation of the disorder. Microarray of cDNAs encoding lncRNAs was obtained to test for the different expression of LncRNA in CML. The result of the experiment performed showed that BGL3 was upregulated by altering Bcr-Abl kinetic activity in leukemic cells. The overexpression of BGL3 helped the leukemic cells to undergo apoptosis therefore inhibit Bcr-Abl-induced tumorigenesis in vivo. All these data supported the concept where lncRNA- BGL3 also act as tumor suppressor during the Bcr-Abl-induced leukemogenesis. The impact of LncRNA on malignant cell is obtained either by inhibiting the proliferation and growth of the cell or induce malignant cell apoptosis. Based on literature reading it seems that LncRNA has an evenly distributed relationship between all the type of cancer.

CircRNA

CircRNA_100290 is a circRNA that is upregulated in oral squamous cell carcinoma (OSCC) and it's expression is linked to the expression of CDK6. In vivo and in vitro knockdown of this circRNA resulted in decrease CDK6 and decrease proliferation of cancerous cells. It was found that it binds directly to miR-29 family, thus regulating the levels of CDK6 which is the direct target of the miR-29 family. CDK6 is a type of cyclin-dependent kinase and it plays a role in cellular progression from G1 phase. Thus, CDK6 has a tumor inducing function and its downregulation by CircRNA_100290 suppresses tumor development (59). Another circRNA that plays role in cancer is Hsa_circ_0004277 which is found to be down regulated in patients with acute myeloid leukemia (AML). Moreover, treating patients with chemotherapy led to restoring the normal levels of this circRNA, as well as increase in WDR37 . The change in Hsa_circ_0004277 levels during chemotherapy provides a possibility for it to be used as a diagnostic biomarker that indicates successful recovery as well as it can be used as target for therapy (60). To add, translocations in PML/RARa which is a very common translocation in acute promeolytic leukemia (APL) patients can lead to the formation of fusion-circular RNAs. That is the circular RNA is made of part of one chromosome and another part from another chromosome. Circular RNAs generating from this translocation are termed f-circPR. F-circPR were found to contribute to the cellular changes found in APL as well as giving cells resistance to chemotherapy (61)

The expression of circRNA_100876 in non-small lung cancer tissues in comparison to their adjacent normal tissues showed that the levels of circRNA_100876 was elevated in cancerous tissues in comparison to normal controls. Also, the elevated levels of this circular RNA were found to be linked to lower survival rate in patients with non-small lung cancer (62).
Gliomas are cancers with highest mortality rate. Two circRNAs were found to be related to glioma. One is circTTBK2 which is upregulated in glioma tissues. Increased expression of this circular RNA led to the increase of proliferation, invasion, and migration of cancerous cells, and it also inhibited apoptosis. It was found that circTTBK2 acts as a sponge for MiR-217 (which is usually reduced in glioma cells). The combination of overexpression of MiR-217 and knockdown of circ-TTBK2 resulted in regression in tumor size of glioma in vivo (63). The other circRNA that can be used as a marker for glioma is cZNF292. Silencing of cZNF292 in glioma cell lines U251 and U87MG resulted in suppression of cellular proliferation and tube formation which indicates a role of this circular RNA in the development of glioma (64).
Hsa_circ_0067934 is a circRNA that is found to be linked to esophageal squamous cell carcinoma. A knockdown of hsa_circ_0067934 using SiRNA resulted in the inhibition of proliferation and migration of esophageal squamous cell carcinoma cells and blocked the cell cycle indicating the role of this circRNA in the progression of the disease as it is found to be overexpressed in these patients (65).
To add, the miRNA ZKSCAN1 and its circular RNA circZKSCAN1 are decreased in patients with hepatocellular carcinoma. When both miRNA and CircRNA we silenced, led increase of cellular proliferation and invasion took place. However, when this circRNA was upregulated in cancer cells as well as in mice, it led to the repression of the cancer. This indicates a possible therapeutic role of circZKSCAN1 in treating patients with hepatocellular carcinoma (66). Another circRNA related to hepatocellular carcinoma is hsa_circ_0004018. Its levels were found to correlate with different markers of hepatocellular carcinoma as it decreases in hepatocellular carcinoma tissue (67).
On the other hand, circPVT1 is found to be upregulated in gastric cancer patients. Silencing CircPVT1 leads to the inhibition of proliferation of gastric cancer cells. This circRNA could bind to miR-125 and inhibit its activity (68). Although circPVT1 is upregulated in gastric cancer patients, Hsa_circ_0000096 is usually downregulated in those patients. A knockdown

of Hsa_circ_0000096 results in inhibition of cell migration and proliferation in vitro and in vivo. It is found to affect cancer cells growth by regulating cyclin D1, CDK6, MMP-2 and MMP-9 (69). Similar to this circRNA is hsa_circ_0001895 which was also found to be decreased in gastric cancer cell lines as well as in tissue specimens from diseased patients in comparison to its levels in the tissue of non-cancerous tissue (healthy control). Interestingly, hsa_circ_0001895 was found to be decreased in pre-cancerous tissue as well. The decrease of this circRNA in precancerous tissue indicate that it can be used as a helpful marker to identify pre-cancerous tissue (70). Another circRNA with relevance to gastric cancer is hsa_circ_0000190. A study suggests that hsa_circ_0000190 can be used as a biomarker to diagnose gastric cancer. This is because which it is found to be downregulated in gastric cancer and its levels to be associated with the diameter of the tumor, lymphatic and distal metastasis, as well as TNM stage and levels of CA19-9. Thus, this circular RNA can be used as a biomarkers as it has better sensitivity and specificity than the currently used markers for diagnosis of gastric cancer which are CA19-9 and CEA (71).
The expression of circCCDC66 is found to be upregulated in histological sections of cancer tissue and polyps. When circCCDC66 is knocked down, the humors growth is inhibited as well as cancer invasion. Moreover, gain of function/loss of function studies on this circRNA revealed It has a role in the pathogenesis in colorectal cancer and it works by controlling oncogenes (72). Another circRNA playing role in colorectal cancer is circBANP. It is normally overexpressed in colorectal cancer tissues and a knockdown of it results in a significant decrease in the proliferation of cancerous cells (73). To add, hsa_circ_001988 is also linked to colorectal cancer and its levels are down regulated in cancerous tissue in comparison to its levels in non-cancerous tissue taken from the same person (74). The upregulation of circ_001569 in colorectal cancer leads to the increase in the amounts of miR-145 targets E2F, BAG4, and FMNL2 which leads to increase in cellular proliferation and invasion. This occurs due to its actions as a sponge for miR-145. The authors overexpressed and silenced circ_001569 to study its effect on colorectal cancer cells. They found that the cells in which this circular RNA was overexpressed showed increase in proliferation and migration while cells who had it silenced experienced decreased proliferation and invasion (75). Zhang et al. found two circular RNAs that can be used as diagnostic markers for colorectal cancer. These two are hsa_circRNA_103809 and hsa_circRNA_104700. They are both downregulated in colorectal cancer tissue in comparison to normal tissues. Moreover, the levels of hsa_circRNA_103809 was associated with metastasis to lymph nodes, and hsa_circRNA_104700 showed a significant association as well with distal metastasis (76). Lastly, hsa_circ_0000069 was found to be significantly upregulated in tissue samples from patients with colorectal cancer. Functional studies using a knockdown revealed its ability to inhibit the growth of cancerous tissue in vitro. However, more studies need to be done to study its effect in vivo (77).

MicroRNA

B-cell chronic lymphocytic leukemia showed the first indication that presented alterations in the expression level of miRNAs on tumor cells (27). Subsequently, different types of cancer produced a massive amount of data by expression profiles of miRNAs in tumor tissues and derived cell lines, that has been detected in. The significant work of Lu and colleagues in 2005 exhibited that miRNA tumor profiles are informative, reflecting the developmental lineage and differentiation state of the tumor. Furthermore, they could effectively categorize each tumor type through miRNA profiling, while messenger profiles were not proficient to do it (27).

Cervical cancer

MiRNA's profiling in cervical tissue has many challenges associated with it, one of which that Pereira *et al*. have presented in 2010, which has highlighted the importance of considering the variable factors that may influence miRNA expression profiles between patients when analyzing miRNA profiling outcomes in cervical tissue. For instance, natural genetic variation, age, viral infections, and non-neoplastic diseases (78). Another study in 2015 by How *et al*. presented other Sources of variation of expression in cervical tissues. For example, intratumor heterogeneity, specimen preservation differences, and profiling platform differences (79).
Regardless of the challenges with miRNA profiling, many studies have shown positive results of expression in MiRNAs involved in the development and progression of cervical cancer. Lee and co-workers used TaqMan real-time quantitative PCR array to analyze the differential expression of 157 human mature miRNAs. The study included ten normal tissues and ten primary invasive squamous cell carcinomas (ISCC) tumor biopsies. The results showed that 68 miRNAs up-regulated and two were down-regulated,10 miRNAs with fold changes of more than 100 were over-expressed. Namely, miR-199-s, miR-9, miR199a*, miR-199a, miR-199b, miR-145, miR-133a, miR-133b, miR-214 and miR-127. On the other hand, the only two under expressed miRNAs were miR-149 and miR-203 (80). In a study with 102 cervical cancer tumor biopsies, quantitative RT-PCR was used to examine the expression profile of 96 miRNAs that are cancer-related. 10 miRNAs have been selected to predict the all in all survival in the patient group using a backing vector machine mathematic algorithm. Significantly, miR-200a was related to overall survival. Gene set enrichment and gene ontology based analyses, showed that miR-200a could control cancer phenotype by regulating metastasis processes (81). Furthermore, a study that showed the expression of miR-100 in 125 cervical tissues. MiR-100 showed reduced tendency in low-grade CIN, high-grade CIN to cervical cancer tissues, and a significant decrease in HPV positive cervical cancer cell lines. In addition, miR-100 expression through PLK1 (Polo-like kinase1) negatively influenced cell cycle, apoptosis, and cell proliferation. Moreover, PLK1 and miR-100 expression was negatively associated in CIN3 and cervical cancer tissues. Hence, the researchers have identified miR-100 a role "at least partly" in the development of cervical cancer by the means of loss of inhibition to target gene PLK1 (82). Table (1) summarize the miRNAs involved in the progress of cervical cancer.

Breast cancer
Breast carcinoma, is one of the most prevalent cancer in women. Breast tumors are categorized into four classes (luminal A, luminal B, HER2 over expressing, and basal) according to their difference in phenotypes, susceptibility to specific treatments, gene expression, and prognosis (83).

It has been shown that multiple miRNAs are associated with a given cancer signature. In breast cancer, up-regulation of miR-21 has been reported across tumor specimens whereas other miRNAs (miR-141, miR-200b, miR- 200c, miR-214, miR-221, and miR-222) exhibited irregular pattern of expression (84). In two of the four ER^-, PR^-, $HER2^-$ tumor specimens, miR-205 was highly expressed, which may be indicative of an association between miR-205 expression with this aggressive tumor subtype (84). The specificity of miRNA expression at different stages of the breast tumor is such that the level of miRNA expressions can be used to distinguish breast cell lines according to their malignancy status. For example, the expressions of several miRNAs have been observed to be elevated in tumorigenic cell lines compared with nontumorigenic cell lines (85). In the same study, it was shown that in the breast tumor tissue, miR-21 was frequently having higher levels in carcinoma cells than in matching normal tissue.

In another study [16] whose results were confirmed by microarray and Northern blot analyses, the differentially expressed miRNAs, miR-10b, miR-125b, miR145, miR-21, and miR-155 were demonstrated to be among the most consistently deregulated in breast cancer. The miR-10b, miR-125b, and miR-145 were down-regulated and miRNA-21 and miR-155 were up-regulated. The miRNA genes have been reported to be frequently deleted in human cancer and interestingly, miR-125b which is down regulated in breast cancer is located at chromosome 11q23-24, one of the most frequently deleted regions in breast cancer (86).

The results of these studies indicate that the differential expressions of miRNAs and their correlation with specific breast cancer bio-pathological features such as tumor stage, vascular invasion, estrogen and progesterone receptor expressions may in the future be used in the clinic as biomarkers to specific stages of breast cancer.

Colorectal cancer

Experimental data performed on colorectal cancer and CRC cell lines have demonstrated several miRNAs to function as Oncomirs (refers to tumor suppressor and oncogenic effects of mirRNAs). Several miRNAs (miR-17-92, miR-21, miR-135) are identified as oncogenic miRs and others (miR-34, miR-126, miR-143) are identified as tumor suppressor miRs because they are involved in myc, PTEN, PDCD4, APC pathways and p53, CDK, p85β, KRAS pathways, respectively (87).

The Wnt/β-catenin pathway plays a central role in early colorectal tumor development. More than 60% of all colorectal adenomas and carcinomas have mutation in the APC gene, leading to stimulation of the Wnt pathway via free β-catenin (88). Recently, miR-135 family has been shown to regulate the adenomatous polyposis coli gene in colorectal cancer. The miR-135a and miR-135-b target the 3′-untranslated region and decrease the translation of the APC transcript in vitro. Interestingly, up-regulation of miR- 135 was also found *in vivo* in colorectal adenomas and carcinomas and correlated with low APC levels (89). These results suggest that the miR-135 family is deregulated in neo-plastic colorectal tissues.

The down-regulation of Ecadherin and the successive loss of cell-cell adhesion are described by EMT, thus leading to a mesen-chymal phenotype which contributes to the invasiveness and dissemination of epithelial tumor cells in several carcinomas including colorectal cancer (90). The members of miR-200 family (miR-200a, miR-200b, miR-200c, miR-141 and miR-429) that are suppressed by TGF-β-signaling have been shown to have functional link to EMT (91). Thus, the miR-200 family members might act as important regulators of epithelial phenotype in colorectal cancer.

Reduced levels of miR-143 and miR-145 in colonic adenomas and carcinomas are demonstrated by investigations on paired colorectal neoplasias and normal mucosal samples (92). The reduction of these two miRNAs in CRC and additional two miRNAs (miR-126 and miR-133b) has been confirmed by others (93, 94). Although many studies have shown increased or reduced levels of miRNAs in colon adenocarcinomas, however, very few studies have evaluated the association between mirRNA expression patterns and colon cancer prognosis or therapeutic outcome.

In a recent report, this question was addressed by a study involving microRNA microarray expression profiling of tumors and paired nontumor tissues on a cohort of 84 patients with incident colon adeno-carcinoma (95). In this study, thirty-seven mirRNAs were reported to be differentially expressed in tumors from the test cohort. Expression patterns of mirRNAs were shown to be systematically altered in colon adeno-carcinomas and a high miR-21

expression was demonstrated to be associated with poor survival and poor therapeutic outcome. In another study, forty-eight clinical colorectal samples (24 samples with 24 paired normal samples) were evaluated for the presence of miRNAs and their significance as markers for disease prognosis (96). Among the ten miRNAs, miR-15b, miR-181b, miR-191, and miR-200c were highly expressed and miR-200c was significantly associated with patient survival.

Table (1): Non-coding RNAs and their associations with different types of cancer.

Disease	Name of RNA	Regulation in Disease	Target gene	Reference
Acute Myeloid Leukemia	hsa_circ_0004277	Downregulated	Not identified	(60)
Breast cancer	miR-9, miR10b, miR-21, miR-27a, miR-29a, miR-96, miR-146a, miR-155, miR-181, miR-191, miR-196a, miR-221/222, miR-373, miR-375, miR-520c, and miR589	Upregulated	Not identified	(97-99)
Breast cancer	miR-30a, miR-31, miR-34a, miR-125, miR-126, miR-146a, miR-146b, miR-195, miR-200, miR-205, miR-206, miR-221, and let-7	Down regulated	Not identified	(97, 99-103)
Breast Cancer	LncRNA BCAR4	Upregulated	GLI2	(104)
Breast cancer	U3, U8	Downregulated	Unknown, RNA28S (respectively)	(105)
Cervical cancer	miR-99a, miR-203, miR-513, miR-29a	Downregulated	IGF-1, BCL2L2, VEGFA and CDK6	(78)
Cervical cancer	miR-203	Upregulated	p63-family	(82)
Cervical cancer	miR-372	Downregulated	CDK2, Cyclin A1	(106)
Cervical cancer	miR-200a, miR-205	Basal expression	ZEB1, ZEB2 and SIP1	(107)
Cervical cancer	miR-148a	Upregulated	PTEN, P53INP1 and TP53INP2	(78)
Cervical cancer	miR-34a	Downregulated	p18Ink4c, CDK4, CDK6, Cyclin E2, E2F1, E2F3, E2F5, BCL2,	(108, 109)

			BIRC3, and DcR3	
Cervical cancer	miR-218	Downregulated	LAMB3	(110)
Cervical cancer	miR-145	Downregulated	IGF-1	(78)
Cervical cancer	miR-148a	Upregulated	PTEN, P53INP1 and TP53INP2	(78)
Cervical cancer	miR-10a, miR-196a, miR-132	Upregulated	(HOX) genes	(78)
Cervical cancer	miR-886-5p	Upregulated	BAX	(110)
Cervical cancer	miR-100	Downregulated	PLK1	(82)
Cervical cancer	LncRNA TUG1	Upregulated		(111)
Cervical cancer	LncRNA BGL3	Downregulated	Bcr-Abl	(112)
Colorectal cancer	miR- 135 family	Down regulated	Not identified	(89)
Colorectal cancer	miR-200a, miR-200b, miR-200c, miR-141 and miR-429	Down regulated	Not identified	(90)
Colorectal cancer	miR-143, miR-145, miR-126 and miR-133b	Down regulated	Not identified	(94, 113)
Colorectal Cancer	circCCDC66	Upregulated	Not identified	(72)
Colorectal Cancer	circBANP	Upregulated	Not identified	(73)
Colorectal Cancer	hsa_circ_0000069	Upregulated	Not identified	(77)
Colorectal Cancer	hsa_circRNA_103809	Downregulated	Not identified	(76)
Colorectal Cancer	hsa_circRNA_104700	Downregulated	Not identified	(76)
Colorectal cancer	hsa_circ_001988	Downregulated	Not identified	(74)
Colorectal cancer	circ_001569	Upregulated	miR-145/ E2F5, BAG4, FMNL2	(75)
Colorectal cancer (CRC)	SNORD126	Downregulated	Unknown	(52)
Embryonic Kidney Cancer	7SK	Upregulated	P-TEFb	(114)
Esophageal squamous cell carcinoma	hsa_circ_0067934	Upregulated	miR-145	(65)
Food intake	SNORD116	Downregulated	Unknown	(115)
Gallbladder cancer	SNORA74B	Downregulated	RNA28S	(115)
Gastric Cancer	circPVT1	Upregulated	miR-125	(68)
Gastric Cancer	hsa_circ_0000096	Downregulated	cyclin D1, CDK6, MMP-2 and MMP-9.	(69)
Gastric Cancer	hsa_circ_0001895	Downregulated	Not identified	(70)

Gastric cancer	hsa_circ_0000190	Downregulated	Not identified	(71)
Glioma	circTTBK2	Upregulated	miR-217	(63)
Glioma	cZNF292	not mentioned	PRR11, Cyclin A, p-CDK2, VEGFR-1/2, p-VEGFR-1/2, EGFR	(64)
Hepatocellular Carcinoma	circZKSCAN1	Downregulated	Not identified	(66)
Hepatocellular carcinoma	hsa_circ_0004018	Downregulated	miR-129-5p	(67)
Hepatocellular carcinoma (HCC)	SNORD126	Downregulated	Unknown	(52)
Hyperphagia, obesity and hypogonadism	SNORD116	Downregulated	Unknown	(116)
Leukemia	f-circPR	Newly Formed due to translocation	Not identified	(61)
Lipotoxicity in Diabetes	U32a	Downregulated	RNA18S	(55)
Lipotoxicity in Diabetes	U33	Downregulated	RNA18S, RNA28S	(55)
Lipotoxicity in Diabetes	U35a	Downregulated	RNA28S	(55)
Lung cancer	lncRNA LINC01186	Downregulated	SMAD3	(117)
Lung cancer	U3, U8	Downregulated	Unknown, RNA28S (respectively)	(105)
Non small cell lung cancer	circRNA_100876	Upregulated	MiR-136/ MMP13	(62)
Oral squamous cell carcinoma	LncRNA TUG1	Upregulated	Wnt/β	(118)
Oral Squamous Cell Carcinoma	circRNA_100290	Upregulated	miR-29/ CACNA1C	(59)
Pancreatic ductal adenocarcinoma	SNORA23	Downregulated	RNA28S	(54)
Prostate cancer	LncRNA SChLAP1	Upregulated	SWI/SNF complex and SNF5	(119)
Prostate cancer	LncRNA UCA1	Upregulated	ATF2	(120)
Prostate Cancer	SNORA55	Downregulated	RNA18S	(121)

SnRNA & snoRNA

The mention of snRNAs and their relation to cancer has been minimal in the literature. However, family 7SK has been described as potential therapeutic agents against cancer. Overexpression of 7SK induced cellular apoptosis in different cancerous cell lines by inhibiting the activity of positive elongation factor b (P-TEFb). Another interesting observation is that stem cells had higher concertation of 7SK than differentiated cells(114, 122). These finding demonstrates the regulatory that 7SK in cellular proliferation.

SnoRNAs have been linked to the proliferative ability of cancerous cells in different types of cancers and to the metastatic ability of these cancerous cells. A class of snoRNA known as snora23 increased significantly in metastatic tumor cell lines, and the knock down of genes responsible for its synthesis reduced cellular proliferation and metastasis(54). SnoRNA55 snoRNA was also shown to induce growth and metastasis in prostate cancer patients(121). Moreover, classes of snoRNA such as U3 and U8 were shown to interfere with the function of p53 gene in metastatic cells, and their absence lead to normal cellular apoptosis, indicating their oncogenic effect(105). In addition, snora74B also increases in patients with gallbladder cancer, and its silencing in vitro resulted promoted normal cellular apoptosis(53). It is clear that snRNA can be used in therapy, whereas snoRNAs play an important role in the progression of cancer, and hence their control may present therapeutic benefits in cancer treatment.

Diabetes

LncRNA

Mitochondrial genome is different from the nuclear in which the mitochondrial genome is compact, circular, double stranded DNA which only encode 13 proteins, and two rRNAs and 22 tRNAs which are required for 13 proteins translation. Excluding rRNAs and tRNAs Noncoding RNAs make up 15% of the human mitochondrial transcriptome (123). Deep sequencing was used in one of the articles to detect RNAs generated from the non-coding region in the mitochondria (123). Three abundant mitochondrial LncRNAs (ND5, ND6, and Cytb) showed that their expression is being regulated by nuclear-encoded mitochondrial processing proteins, which suggest that mitochondrial lncRNAs may influence the regulation of mitochondria gene expression (123). Diabetes is a disorder that showed the impact of mitochondrial LncRNA expression on different diabetes related diseases. Mitochondrial Long noncoding RNA ASncmtRNA-2 showed an upregulated expression level in Diabetic nephropathy (DN) (124). Mouse model was used to test for this experiment. The results of RNA isolation and PCR showed that ASncmtRNA-2 was upregulated in mice with DN. These results proved that ASncmtRNA-2 increased as the DN cell developed. Measurement of intracellular reactive oxygen species (ROS) was performed since ROS induces the oxidative damage to both intra and extracellular compartment of the kidney (124). The result of the experiment indicated that inhibition of ROS by L-NAME could reduce the upregulation of ASncmtRNA-2.

Researches showed that mitochondrial LncRNA helps in the regulation of ROS production. An example of these mitochondrial LncRNA which regulate the production of ROS is ASncmtRNA-2. A hypothesis was introduced regarding the topic to see which factor contribute and impact the other. The hypothesis suggested that ASncmtRNA-2 could function as a substrate which will stimulate the formation of ROS (124). Overexpression of

ASncmtRNA-2 in ND diseases means that the amount of the substrate (ASncmtRNA-2) will increase and as a result the production of ROS will be high. A study has shown that the levels of hsa_circ_0054633 increase respectively between normal individuals, pre-diabetics, and patients with type two diabetes mellitus. However, this study was focused only on studying Chinese population, so these results may differ in other populations (124).

CircRNA

A study have shown that the levels of hsa_circ_0054633 increase respectively between normal individuals, pre-diabetics, and patients with type two diabetes mellitus. However, this study was focused only on studying Chinese population, so these results may differ in other populations (125). In addition to hsa_circ_0054633, Overexpression of Cdr1as in islet cells results in increasing the insulin content and secretion by the islet cells (126).

MicroRNA

A prospective population-based cohort including 80 patients with type two diabetes mellitus (T2DM) and 80 ages- and sex-matched controls showed that, in patients with diabetes, miR-28-3p was overexpressed, and 12 other microRNAs were underexpressed (127). Decreased circulating miR-126 was a significant predictor of DM. miR-15a, miR-29b, miR-126, and miR-223 were decreased in the subjects with DM (127). In pancreatic β-cell, islets, enriched miR-375 was increased in subjects with T2DM and modulated β-cell function through several physiological mechanisms. miR-375 inhibits insulin secretion and transcription, maintains β-cell mass, proliferation, and regeneration, and promotes embryonic pancreas development (128). Besides, it was found that microRNAs control the insulin signal transduction pathways in target tissues. Insulin resistance refers to the failure of target tissues, including the liver, skeletal muscle, and adipose tissues, to respond adequately to circulating insulin. Clinical studies have reported underexpressed miR-133 and overexpressed miR-503 in skeletal muscle, while increased miR-181a and decreased miR-17-5p, miR-132, and miR-134 have been observed in the omentum (129, 130). In addition, miR-147 and miR-197 were increased in subcutaneous fat tissue while miR-27a, miR-30e, miR-155, miR-210, and miR-140 were decreased (127). As the above findings suggest, microRNAs aid in the prognosis of diabetes and could be pharmacological targets in diabetes.

SnRNA & snoRNA

Although no direct relation has been established between snRNA nor snoRNA and diabetes, oxidative stress was linked to a some classed of snoRNAs. Oxidative stress is induced in diabetic patients and it is one of the main contributors to diabetic consequences such as nephropathy and retinopathy(131). Hence, we a link between diabetes and snoRNAs can be established. U33a, U33, and U35a have been linked to lipotoxicity in diabetes. These snoRNAs made the cells susceptible to apoptosis as a result of lipotoxicity and oxidative stress. Down regulation of U32a U33 and U55a lead the cells to become capable of withstanding lipotoxic stress and undergo normal life cycle and apoptosis(55).

Cardiovascular Disease

CircRNA

Heart hypertrophy and failure was affected by the circRNA HRCR. It was found to act as miR-223 sponge as it inhibits its function and lead to increase in ARC expression. Normally, HRCR is bound to miR-223 in vivo. Decreased ARC expression is found in patients with heart failure (132). CircRNA_000203 was found to be overexpressed in diabetic mouse

myocardium and in mouse Ang-II induced cardiac fibroblasts. The overexpression of circRNA_000203 is found to act as a sponge for miR-26b-5p. Inhibiting miR-26b-5p leads to increasing the expression of certain fibrosis related genes (133). Overexpression of Cdr1as increases the size of cardiac infarction in mice. While, the miR-7a overexpression leads to reversing these effects (134).

SnRNA & snoRNA

Similar to diabetes, neither snRNAs or snoRNAs were directly associated with cardiovascular diseases, however, the small of snRNAs as therapeutic agents to treat hypertrophic myocardiopathy was described in mice studies. U7 snRNA inserted into a vector can be used to transport antisense oligonucleotides (AON) to cardiac cells to promote exon skipping and correct this genetic disorder(135).

Obesity and Nutritional deficiency

MicroRNA

Obesity is an energy-rich condition associated with overnutrition, which impairs systemic metabolic homeostasis and elicits stress (136). Adipose tissue is an important contributor to the pathophysiology of obesity, and there are two types of adipose tissue that exist in mammals: white adipose tissue (WAT) and brown adipose tissue (BAT) (137). Most of the body's adipose tissue is composed of WAT that serves as a source of free fatty acids, which are used as an energy substrate through oxidative phosphorylation of adenosine triphosphate (ATP) (138). White adipose tissue can be found in various anatomical sites. WAT main regions are: intraabdominal around the omentum, intestines and peri-renal areas, and subcutaneous in the buttocks, thighs and abdomen. Furthermore, WAT can also be found in muscle, epicardial, visceral, perivascular and kidney (139). WAT functions in the regulation of the metabolism through adipocyte differentiation, energy homeostasis, and insulin sensitivity (140).

Various studies have used the microarray assay and the candidate gene approach to show the expression profiles of microRNAs in white adipose tissue of obese and normal males and females, but the exact number of miRNAs that are differentially expressed in obese human WAT remains to be established nevertheless the numbers are likely to be very small. Till now, studies have shown the upregulation of approximately 10 miRNAs (Table 1) and the down regulation of approximately 30 miRNAs (Table 2) that have been described in this tissue type. Although the functional roles of these miRNAs in the development of obesity are not yet known, the actions of several of these transcripts in human fat cells have, partially, been characterized.

Table (2): Up regulated microRNA's in white adipose tissue of obese humans:

Method	MicroRNA	Tissue / cell	Function	Reference
Microarray analysis	miR-519d	Subcutaneous WAT	Unknown	Martinelli et al. (2010) (141).
Microarray analysis	miR-99a, miR-199a-5p, miR-125b, miR-221 and miR-1229	Subcutaneous WAT	Unknown	Ortega et al. (2010) (142).

Candidate gene approach	miR-146b	Subcutaneous and visceral WAT	Unknown	Chen et al. (2014) (143).
Microarray analysis	miR-21	Subcutaneous WAT	Unknown	Keller et al. (2011) (144).
Microarray analysis	miR-222 and miR-342-3p	Subcutaneous WAT	Unknown	Arner et al. (2012) (145).
Microarray analysis	miR-221	Subcutaneous WAT	Unknown	Meerson et al. (2013) (146).

Table (3): Down regulated microRNA's in white adipose tissue of obese humans

Method	MicroRNA	Tissue / cell	Function	Reference
Microarray analysis	miR-150 and miR-659	Subcutaneous WAT	Unknown	Martinelli et al. (2010) (141).
Microarray analysis	miR-130b, miR-139-5p, miR-185 and miR-484	Subcutaneous WAT	Unknown	Ortega et al. (2010) (142).
Candidate gene approach		Subcutaneous and visceral WAT	Unknown	Chen et al. (2014) (143).
Microarray analysis	miR-143	Subcutaneous WAT	Unknown	Keller et al. (2011) (144).
Microarray analysis	let-7a, let-7d, let-7i, miR-16, miR-26a, miR-30c, miR-92a, miR-126, miR-139-5p, miR-143, miR-145, miR-151-5p, miR-193a-5p, miR-193b, miR-197, miR-484-5p, miR-378 and miR-652	Subcutaneous WAT	let-7d, miR-26a, miR-30c, miR-145, miR-193 and miR-652 regulate lipolysis [12] Some of these miRNAs regulate production of CCL2[10] and TNF [12] miR-143, miR-145 and miR-378 influence adipocyte differentiation [13,14,15,16].	Arner et al. (2012) (145).
Microarray analysis	miR-193a-3p and miR-193b-5p	Subcutaneous WAT	Unknown	Meerson et al. (2013) (146).
Microarray analysis	miR-17-5 p and miR-132	Visceral WAT	miR-132 regulates the immune system	Heneghan et al. (2011) (147).

Microarray analysis	miR-141 and miR-520 m	Visceral WAT	miR-144 and miR-520e might regulate glucose metabolism	Capobianco et al. (2012) (148).
Candidate gene approach	miR-221	Visceral WAT	Unknown	Chou et al. (2013) (149)
Candidate gene approach	miR-125a	Subcuatneous and visceral and WAT	Unknown	Diawara et al. (2014) (150)
Candidate gene approach	miR-200a and miR-200b	Visceral WAT	Unknown	Oger et al. (2014) (151)

SnRNA & snoRNA

There was no direct link between snRNAs or snoRNA and obesity or nutritional deficiencies. However, studies have shown that snord116, a class of snoRNAs, plays a role in the hyperphagia seen in those suffering from Prader Wili Syndrome (PWS). Loss of snord116 gene cluster was observed in a PWS patient and the associated hyperphagia and hypogonadism were imputed to the function of snord116 in the hypothalamus (116). Moreover, animal models have shown that the loss of the snord116 gene increased food intake in mice, however it did not induce obesity in mice. This discrepancy between humans and mice suffering from the same deletion can be attributed to differences in mice and human metabolism(115).

Noncoding RNAs in health and disease

LncRNA and aging

As the human being become older the cells and organs show a reduction in their functional ability, and in some cases, it could lead to complete loss of function, disease and later to death. Scientist tried to understand the mechanism of aging in order to try to either slow it down or stop it. Phenotypic changes regarding aging is driven from the genetic expression inside the cell.

LncRNAs that modulate telomere length is one of the aspect discussed regarding LncRNA and aging. Telomeres is considered as a repetitive nucleotide sequences at each end of a chromosome which play a role in protecting the end of the chromosome (152). During DNA replication, the telomerase reverse transcriptase (TERT) bind to the telomerase and extend the length of telomerase as a protection process. The length of the telomerase in regulated by both Telomerase ribonucleoprotein complex that contain two proteins TERT and the lncRNA *TERC* (telomerase RNA component), and by telomeric repeat containing RNA lncRNA *TERR* (152). LncRNA TERC has an important role in maintaining telomere length which could prevent againg and premature senescence. An experiment on TERC deficient mice showed short telomeres, chromosomal instability which lead to premature aging (153). LncRNA TERC acts synergically with LncRNA TERRA. As the TERC maintains the length of telomerase, polymerase II transcribe LncRNA TERRA which will prevent telomerase elongation (152). Either over or under expression of LncRNA TERRA could lead to premature senescence and aging. A mutation in the gene DNA methyltransferase 3B (*DNMT3B*) could lead to hypomethylation of telomeric region which elevate the level of TERRA that affect the telomerase elongation (152). **Figure will be added.**

LncRNA and its association with epigenetic alterations is another aspect discussed in aging

and senescence. During aging the DNA methylation declines is some genes while in other genes such as tumor suppressor gene DNA methylation increases during aging (152). *Xist* is one of the LncRNAs that is responsible for imprinting and silencing of the X chromosome. In senescent cells the levels of *Xist* decline (154). *pRNA* is another LncRNA which regulate the transcription of ribosomal RNA as it interacts with DNA the target site of the transcription factor TTF1(153). Increase the methylation rate of rDNA was observed Werner syndrome fibroblasts. Heterochromatin formation is a distinctive feature of senescence and aging. The loss of heterochromatin activity with aging is believed to affect many cellular processes associated with aging. Heterochromatin maintenance and formation is directly related to chromosomal stability (153).

Stem cells are defined as the progenitor cells for the proliferation of specific cells and tissues which perform specific functions in the body. With aging the regenerative ability of the stem cells declines, it also responds to some alternation such as DNA damage and cell cycle inhibition which promote aging. Pluripotency in the human body is strictly regulated by some transcriptional factors such as Oct4, Sox2 and Nanog along with several other coregulators(152). The presence of some LncRNAs in the body could regulate some stem cell transcription factors which will help in the regulation of LncRNAs expression. LncRNA *AK028326* is regulated by transcription factor Oct4, while *AK141205* is repressed by Nanog. Any mutation or knockdown of these two LncRNAs could lead to transcriptional factors alteration which affect pluripotency and gene expression in the cell (155). In a study performed the result showed that the expression of 28 LncRNAs in Induced pluripotent stem cells iPSCs was higher than in Embryonic stem cells(ESCs), which suggest their importance role in iPSCs. LncRNA *linc- RoR* is one of the these LncRNAs that regulate human ESCs reprogramming. Overexpression of this LncRNA will cause programing initiation which support the hypothesis that *linc- RoR* could act as miRNA sponge to regulate the transcription factors such as Oct4, Nanog, and Sox2 in hESCs (156). *linc- RoR* could lower the levels of cell cycle regulator and tumor suppressor p53 by the interaction with p-*hnRNP I* which is needed for p53 mRNA translation (152). All these finding support that *linc- RoR* is consider an important stem cell regulator of cell growth and survival which controls cellular senescence.

circRNA and cellular growth

CircHIPK3 is found to function in cellular proliferation and growth. That is this circRNA which is derived from exon 2 in the HIPK3 gene, so it was named circHIPK3. The study characterized this type of circRNA and silenced it to find that it inhibited the growth of cells. It has been shown to bind to miR-124 and inhibits its activity (125). Moreover, in normal cells, circ-Foxo3 is found to be upregulated. The down-regulation of this circular RNA is found to have an association with the development of cancer. CDK2 is a marker that is associated with the transition of the cell cycle from G1 to S phase. P21 is a known CDK inhibitor along with P27. This study showed that circ-Foxo3 interacts with CDK2 and P21 forming a complex that inhibits the progression of the cell cycle (157).

SnRNA in health and disease

Small nuclear RNAs are involved in post transcriptional processing of the pre-mRNA in healthy individuals. However, the relation of snRNAs to disease have not been widely studied. SnRNPs and their associated proteins (LSm proteins) are the main structures studied, and research have been focused on the proteins moiety of snRNP rather than RNA moiety(158). This can be attributed to the fact that snRNAs are known to function in site recognition rather than in the catalytic activity on the spliceosome during splicing. On the

other hand, many species of snoRNA have been associated to disease and they have been studied in greater depth and associations of many snoRNAs and disease have established. Example of snoRNA species associated with disease include snora23 (in cancer), U33 (in lipotoxicity), snord116 (in hyperphagia). This section discusses the several types of small noncoding RNAs and their relation to disease. It is worth to mention that snRNA plays a role in diseases related to exon skipping and viral infections. Utilizing U1 snRNA gene may provide a safe therapeutic possibility to patients suffering from splicing diseases such as hemophilia, cystic fibrosis and spinal muscular atrophy with mutated 5' exonic splice sites mutations. Mutating the 5' prime end of U1 snRNA would improve the splicing site recognition by the U1 snRNP within the spliceosome (159). It has also been shown that inserting a functional beta-globin gene to a U7 snRNA gene through a vector to beta-thalassemia HeLa cells has significantly increased the production of normal beta-globin, providing an easier therapeutic method than gene replacement (160). Intriguingly, snRNA induction has been associated with viral infections, and controlling the levels of snRNA in host cells provides means to tackle these infections (161).

References

1. Ohno S, editor So much" junk" DNA in our genome. Brookhaven symposia in biology; 1972.
2. Alexander RP, Fang G, Rozowsky J, Snyder M, Gerstein MB. Annotating non-coding regions of the genome. Nat Rev Genet. 2010;11(8):559-71.
3. Crick FH, editor On protein synthesis. Symp Soc Exp Biol; 1958.
4. Holley RW, Apgar J, Everett GA, Madison JT, Marquisee M, Merrill SH, et al. Structure of a ribonucleic acid. Science. 1965;147(3664):1462-5.
5. Kung JT, Colognori D, Lee JT. Long noncoding RNAs: past, present, and future. Genetics. 2013;193(3):651-69.
6. Wang KC, Chang HY. Molecular mechanisms of long noncoding RNAs. Mol Cell. 2011;43(6):904-14.
7. Rackham O, Shearwood AM, Mercer TR, Davies SM, Mattick JS, Filipovska A. Long noncoding RNAs are generated from the mitochondrial genome and regulated by nuclear-encoded proteins. RNA. 2011;17(12):2085-93.
8. Eddy SR. Non-coding RNA genes and the modern RNA world. Nat Rev Genet. 2001;2(12):919-29.
9. Makarova JA, Ivanova SM, Tonevitsky AG, Grigoriev AI. New functions of small nucleolar RNAs. Biochemistry (Mosc). 2013;78(6):638-50.
10. Hall SL, Padgett RA. Conserved sequences in a class of rare eukaryotic nuclear introns with non-consensus splice sites. J Mol Biol. 1994;239(3):357-65.
11. Carmen L, Michela B, Rosaria V, Gabriella M. Existence of snoRNA, microRNA, piRNA characteristics in a novel non-coding RNA: x-ncRNA and its biological implication in Homo sapiens. Journal of Bioinformatics and Sequence Analysis. 2009;1(2):031-40.
12. Qu S, Yang X, Li X, Wang J, Gao Y, Shang R, et al. Circular RNA: A new star of noncoding RNAs. Cancer Lett. 2015;365(2):141-8.
13. Sanger HL, Klotz G, Riesner D, Gross HJ, Kleinschmidt AK. Viroids are single-stranded covalently closed circular RNA molecules existing as highly base-paired rod-like structures. Proceedings of the National Academy of Sciences of the United States of America. 1976;73(11):3852-6.
14. Jeck WR, Sorrentino JA, Wang K, Slevin MK, Burd CE, Liu J, et al. Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA. 2013;19(2):141-57.
15. Suzuki H, Tsukahara T. A view of pre-mRNA splicing from RNase R resistant RNAs. Int J Mol Sci. 2014;15(6):9331-42.
16. Chen S, Dong C, Qian X, Huang S, Feng Y, Ye X, et al. Microarray analysis of long noncoding RNA expression patterns in diabetic nephropathy. Journal of diabetes and its complications. 2017;31(3):569-76.
17. Yang L, Froberg JE, Lee JT. Long noncoding RNAs: fresh perspectives into the RNA world. Trends in biochemical sciences. 2014;39(1):35-43.
18. Pauli A, Valen E, Lin MF, Garber M, Vastenhouw NL, Levin JZ, et al. Systematic identification of long noncoding RNAs expressed during zebrafish embryogenesis. Genome research. 2012;22(3):577-91.
19. Wang PL, Bao Y, Yee MC, Barrett SP, Hogan GJ, Olsen MN, et al. Circular RNA is expressed across the eukaryotic tree of life. PLoS One. 2014;9(6):e90859.
20. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, et al. Natural RNA circles function as efficient microRNA sponges. Nature. 2013;495(7441):384-8.

21. Ashwal-Fluss R, Meyer M, Pamudurti Nagarjuna R, Ivanov A, Bartok O, Hanan M, et al. circRNA Biogenesis Competes with Pre-mRNA Splicing. Molecular Cell.56(1):55-66.
22. Li Z, Huang C, Bao C, Chen L, Lin M, Wang X, et al. Exon-intron circular RNAs regulate transcription in the nucleus. Nat Struct Mol Biol. 2015;22(3):256-64.
23. Kos A, Dijkema R, Arnberg AC, van der Meide PH, Schellekens H. The hepatitis delta (delta) virus possesses a circular RNA. Nature. 1986;323(6088):558-60.
24. Pamudurti NR, Bartok O, Jens M, Ashwal-Fluss R, Stottmeister C, Ruhe L, et al. Translation of CircRNAs. Mol Cell. 2017;66(1):9-21 e7.
25. Wang Y, Wang Z. Efficient backsplicing produces translatable circular mRNAs. RNA. 2015;21(2):172-9.
26. Yang Y, Fan X, Mao M, Song X, Wu P, Zhang Y, et al. Extensive translation of circular RNAs driven by N6-methyladenosine. Cell Res. 2017;27(5):626-41.
27. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, et al. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proceedings of the National Academy of Sciences of the United States of America. 2004;101(9):2999-3004.
28. Griffiths-Jones S, Grocock RJ, van Dongen S, Bateman A, Enright AJ. miRBase: microRNA sequences, targets and gene nomenclature. Nucleic Acids Research. 2006;34(suppl_1):D140-D4.
29. Griffiths-Jones S. The microRNA Registry. Nucleic Acids Research. 2004;32(suppl_1):D109-D11.
30. Grimson A, Farh KK-H, Johnston WK, Garrett-Engele P, Lim LP, Bartel DP. MicroRNA Targeting Specificity in Mammals: Determinants beyond Seed Pairing. Molecular Cell. 2007;27(1):91-105.
31. Hutvágner G, Zamore PD. A microRNA in a Multiple-Turnover RNAi Enzyme Complex. Science. 2002;297(5589):2056-60.
32. Kozomara A, Griffiths-Jones S. miRBase: integrating microRNA annotation and deep-sequencing data. Nucleic Acids Research. 2011;39(suppl_1):D152-D7.
33. Lee Y, Kim M, Han J, Yeom KH, Lee S, Baek SH, et al. MicroRNA genes are transcribed by RNA polymerase II. The EMBO Journal. 2004;23(20):4051-60.
34. Lewis BP, Shih Ih, Jones-Rhoades MW, Bartel DP, Burge CB. Prediction of Mammalian MicroRNA Targets. Cell.115(7):787-98.
35. Lund E, Güttinger S, Calado A, Dahlberg JE, Kutay U. Nuclear Export of MicroRNA Precursors. Science. 2004;303(5654):95-8.
36. Tsanev R. Direct spectrophotometric analysis of ribonucleic acid fractionation by agar-gel electrophoresis. Biochim Biophys Acta. 1965;103(3):374-82.
37. Weinberg RA, Penman S. Small molecular weight monodisperse nuclear RNA. J Mol Biol. 1968;38(3):289-304.
38. Hodnett JL, Busch H. Isolation and characterization of uridylic acid-rich 7 S ribonucleic acid of rat liver nuclei. J Biol Chem. 1968;243(24):6334-42.
39. Sharp PA. The discovery of split genes and RNA splicing. Trends Biochem Sci. 2005;30(6):279-81.
40. Berget SM, Moore C, Sharp PA. Spliced segments at the 5' terminus of adenovirus 2 late mRNA. Proc Natl Acad Sci U S A. 1977;74(8):3171-5.
41. Reddy R, Henning D, Das G, Harless M, Wright D. The capped U6 small nuclear RNA is transcribed by RNA polymerase III. J Biol Chem. 1987;262(1):75-81.

42. Matera AG, Terns RM, Terns MP. Non-coding RNAs: lessons from the small nuclear and small nucleolar RNAs. Nat Rev Mol Cell Biol. 2007;8(3):209-20.
43. Will CL, Luhrmann R. Spliceosome structure and function. Cold Spring Harb Perspect Biol. 2011;3(7).
44. Moore MJ, Query CC, Sharp PA. Splicing of precursors to mRNAs by the spliceosome. COLD SPRING HARBOR MONOGRAPH SERIES. 1993;24:303-.
45. Shao W, Kim HS, Cao Y, Xu YZ, Query CC. A U1-U2 snRNP interaction network during intron definition. Mol Cell Biol. 2012;32(2):470-8.
46. Tollervey D, Kiss T. Function and synthesis of small nucleolar RNAs. Curr Opin Cell Biol. 1997;9(3):337-42.
47. Peculis B. RNA processing: pocket guides to ribosomal RNA. Curr Biol. 1997;7(8):R480-2.
48. Balakin AG, Smith L, Fournier MJ. The RNA world of the nucleolus: two major families of small RNAs defined by different box elements with related functions. Cell. 1996;86(5):823-34.
49. Ellis JC, Brown DD, Brown JW. The small nucleolar ribonucleoprotein (snoRNP) database. RNA. 2010;16(4):664-6.
50. Kishore S, Stamm S. The snoRNA HBII-52 regulates alternative splicing of the serotonin receptor 2C. Science. 2006;311(5758):230-2.
51. Kishore S, Khanna A, Zhang Z, Hui J, Balwierz PJ, Stefan M, et al. The snoRNA MBII-52 (SNORD 115) is processed into smaller RNAs and regulates alternative splicing. Hum Mol Genet. 2010;19(7):1153-64.
52. Fang X, Yang D, Luo H, Wu S, Dong W, Xiao J, et al. SNORD126 promotes HCC and CRC cell growth by activating the PI3K-AKT pathway through FGFR2. J Mol Cell Biol. 2016.
53. Qin Y, Meng L, Fu Y, Quan Z, Ma M, Weng M, et al. SNORA74B gene silencing inhibits gallbladder cancer cells by inducing PHLPP and suppressing Akt/mTOR signaling. Oncotarget. 2017;8(12):19980-96.
54. Cui L, Nakano K, Obchoei S, Setoguchi K, Matsumoto M, Yamamoto T, et al. Small Nucleolar Noncoding RNA SNORA23, Upregulated in Human Pancreatic Ductal Adenocarcinoma, Regulates Expression of SYNE2 to Promote Growth and Metastasis of Xenograft Tumors in Mice. Gastroenterology. 2017.
55. Michel CI, Holley CL, Scruggs BS, Sidhu R, Brookheart RT, Listenberger LL, et al. Small nucleolar RNAs U32a, U33, and U35a are critical mediators of metabolic stress. Cell Metab. 2011;14(1):33-44.
56. Schmitt AM, Chang HY. Long noncoding RNAs in cancer pathways. Cancer Cell. 2016;29(4):452-63.
57. Hao Y, Yang X, Zhang D, Luo J, Chen R. Long noncoding RNA LINC01186, regulated by TGF-β/SMAD3, inhibits migration and invasion through Epithelial-Mesenchymal-Transition in lung cancer. Gene. 2017;608:1-12.
58. Liang S, Zhang S, Wang P, Yang C, Shang C, Yang J, et al. LncRNA, TUG1 regulates the oral squamous cell carcinoma progression possibly via interacting with Wnt/β-catenin signaling. Gene. 2017;608:49-57.
59. Chen L, Zhang S, Wu J, Cui J, Zhong L, Zeng L, et al. circRNA_100290 plays a role in oral cancer by functioning as a sponge of the miR-29 family. Oncogene. 2017.
60. Li W, Zhong C, Jiao J, Li P, Cui B, Ji C, et al. Characterization of hsa_circ_0004277 as a New Biomarker for Acute Myeloid Leukemia via Circular RNA Profile and Bioinformatics Analysis. Int J Mol Sci. 2017;18(3).

61. Guarnerio J, Bezzi M, Jeong JC, Paffenholz SV, Berry K, Naldini MM, et al. Oncogenic Role of Fusion-circRNAs Derived from Cancer-Associated Chromosomal Translocations. Cell. 2016;165(2):289-302.
62. Yao JT, Zhao SH, Liu QP, Lv MQ, Zhou DX, Liao ZJ, et al. Over-expression of CircRNA_100876 in non-small cell lung cancer and its prognostic value. Pathol Res Pract. 2017.
63. Zheng J, Liu X, Xue Y, Gong W, Ma J, Xi Z, et al. TTBK2 circular RNA promotes glioma malignancy by regulating miR-217/HNF1beta/Derlin-1 pathway. J Hematol Oncol. 2017;10(1):52.
64. Yang P, Qiu Z, Jiang Y, Dong L, Yang W, Gu C, et al. Silencing of cZNF292 circular RNA suppresses human glioma tube formation via the Wnt/beta-catenin signaling pathway. Oncotarget. 2016;7(39):63449-55.
65. Xia W, Qiu M, Chen R, Wang S, Leng X, Wang J, et al. Circular RNA has_circ_0067934 is upregulated in esophageal squamous cell carcinoma and promoted proliferation. Sci Rep. 2016;6:35576.
66. Yao Z, Luo J, Hu K, Lin J, Huang H, Wang Q, et al. ZKSCAN1 gene and its related circular RNA (circZKSCAN1) both inhibit hepatocellular carcinoma cell growth, migration, and invasion but through different signaling pathways. Mol Oncol. 2017;11(4):422-37.
67. Fu L, Yao T, Chen Q, Mo X, Hu Y, Guo J. Screening differential circular RNA expression profiles reveals hsa_circ_0004018 is associated with hepatocellular carcinoma. Oncotarget. 2017.
68. Chen J, Li Y, Zheng Q, Bao C, He J, Chen B, et al. Circular RNA profile identifies circPVT1 as a proliferative factor and prognostic marker in gastric cancer. Cancer Lett. 2017;388:208-19.
69. Li P, Chen H, Chen S, Mo X, Li T, Xiao B, et al. Circular RNA 0000096 affects cell growth and migration in gastric cancer. Br J Cancer. 2017;116(5):626-33.
70. Shao Y, Chen L, Lu R, Zhang X, Xiao B, Ye G, et al. Decreased expression of hsa_circ_0001895 in human gastric cancer and its clinical significances. Tumour Biol. 2017;39(4):1010428317699125.
71. Chen S, Li T, Zhao Q, Xiao B, Guo J. Using circular RNA hsa_circ_0000190 as a new biomarker in the diagnosis of gastric cancer. Clin Chim Acta. 2017;466:167-71.
72. Hsiao KY, Lin YC, Gupta SK, Chang N, Yen L, Sun HS, et al. Non-coding effects of circular RNA CCDC66 promote colon cancer growth and metastasis. Cancer Res. 2017.
73. Zhu M, Xu Y, Chen Y, Yan F. Circular BANP, an upregulated circular RNA that modulates cell proliferation in colorectal cancer. Biomed Pharmacother. 2017;88:138-44.
74. Wang X, Zhang Y, Huang L, Zhang J, Pan F, Li B, et al. Decreased expression of hsa_circ_001988 in colorectal cancer and its clinical significances. Int J Clin Exp Pathol. 2015;8(12):16020-5.
75. Xie H, Ren X, Xin S, Lan X, Lu G, Lin Y, et al. Emerging roles of circRNA_001569 targeting miR-145 in the proliferation and invasion of colorectal cancer. Oncotarget. 2016;7(18):26680-91.
76. Zhang P, Zuo Z, Shang W, Wu A, Bi R, Wu J, et al. Identification of differentially expressed circular RNAs in human colorectal cancer. Tumour Biol. 2017;39(3):1010428317694546.
77. Guo JN, Li J, Zhu CL, Feng WT, Shao JX, Wan L, et al. Comprehensive profile of differentially expressed circular RNAs reveals that hsa_circ_0000069 is upregulated and

promotes cell proliferation, migration, and invasion in colorectal cancer. Onco Targets Ther. 2016;9:7451-8.
78. Pereira PM, Marques JP, Soares AR, Carreto L, Santos MA. MicroRNA expression variability in human cervical tissues. PLoS One. 2010;5(7):e11780.
79. How C, Pintilie M, Bruce JP, Hui AB, Clarke BA, Wong P, et al. Developing a prognostic micro-RNA signature for human cervical carcinoma. PLoS One. 2015;10(4):e0123946.
80. Lee JW, Choi CH, Choi JJ, Park YA, Kim SJ, Hwang SY, et al. Altered MicroRNA expression in cervical carcinomas. Clinical cancer research : an official journal of the American Association for Cancer Research. 2008;14(9):2535-42.
81. Hu X, Schwarz JK, Lewis JS, Jr., Huettner PC, Rader JS, Deasy JO, et al. A microRNA expression signature for cervical cancer prognosis. Cancer Res. 2010;70(4):1441-8.
82. Li BH, Zhou JS, Ye F, Cheng XD, Zhou CY, Lu WG, et al. Reduced miR-100 expression in cervical cancer and precursors and its carcinogenic effect through targeting PLK1 protein. European journal of cancer (Oxford, England : 1990). 2011;47(14):2166-74.
83. Sorlie T. Molecular portraits of breast cancer: tumour subtypes as distinct disease entities. European journal of cancer (Oxford, England : 1990). 2004;40(18):2667-75.
84. Sempere LF, Christensen M, Silahtaroglu A, Bak M, Heath CV, Schwartz G, et al. Altered MicroRNA expression confined to specific epithelial cell subpopulations in breast cancer. Cancer Res. 2007;67(24):11612-20.
85. Iorio MV, Ferracin M, Liu CG, Veronese A, Spizzo R, Sabbioni S, et al. MicroRNA gene expression deregulation in human breast cancer. Cancer Res. 2005;65(16):7065-70.
86. Negrini M, Rasio D, Hampton GM, Sabbioni S, Rattan S, Carter SL, et al. Definition and refinement of chromosome 11 regions of loss of heterozygosity in breast cancer: identification of a new region at 11q23.3. Cancer Res. 1995;55(14):3003-7.
87. Hermeking H. p53 enters the microRNA world. Cancer Cell. 2007;12(5):414-8.
88. Powell SM, Zilz N, Beazer-Barclay Y, Bryan TM, Hamilton SR, Thibodeau SN, et al. APC mutations occur early during colorectal tumorigenesis. Nature. 1992;359(6392):235-7.
89. Nagel R, le Sage C, Diosdado B, van der Waal M, Oude Vrielink JA, Bolijn A, et al. Regulation of the adenomatous polyposis coli gene by the miR-135 family in colorectal cancer. Cancer Res. 2008;68(14):5795-802.
90. Spaderna S, Schmalhofer O, Hlubek F, Berx G, Eger A, Merkel S, et al. A transient, EMT-linked loss of basement membranes indicates metastasis and poor survival in colorectal cancer. Gastroenterology. 2006;131(3):830-40.
91. Burk U, Schubert J, Wellner U, Schmalhofer O, Vincan E, Spaderna S, et al. A reciprocal repression between ZEB1 and members of the miR-200 family promotes EMT and invasion in cancer cells. EMBO reports. 2008;9(6):582-9.
92. Michael MZ, SM OC, van Holst Pellekaan NG, Young GP, James RJ. Reduced accumulation of specific microRNAs in colorectal neoplasia. Molecular cancer research : MCR. 2003;1(12):882-91.
93. Bandres E, Cubedo E, Agirre X, Malumbres R, Zarate R, Ramirez N, et al. Identification by Real-time PCR of 13 mature microRNAs differentially expressed in colorectal cancer and non-tumoral tissues. Molecular cancer. 2006;5:29.
94. Guo C, Sah JF, Beard L, Willson JK, Markowitz SD, Guda K. The noncoding RNA, miR-126, suppresses the growth of neoplastic cells by targeting phosphatidylinositol 3-kinase signaling and is frequently lost in colon cancers. Genes, chromosomes & cancer. 2008;47(11):939-46.

95. Schetter AJ, Leung SY, Sohn JJ, Zanetti KA, Bowman ED, Yanaihara N, et al. MicroRNA expression profiles associated with prognosis and therapeutic outcome in colon adenocarcinoma. Jama. 2008;299(4):425-36.
96. Xi Y, Formentini A, Chien M, Weir DB, Russo JJ, Ju J, et al. Prognostic Values of microRNAs in Colorectal Cancer. Biomarker insights. 2006;2:113-21.
97. Hui AB, Shi W, Boutros PC, Miller N, Pintilie M, Fyles T, et al. Robust global micro-RNA profiling with formalin-fixed paraffin-embedded breast cancer tissues. Laboratory investigation. 2009;89(5):597-606.
98. Piva R, Spandidos DA, Gambari R. From microRNA functions to microRNA therapeutics: Novel targets and novel drugs in breast cancer research and treatment (Review). International journal of oncology. 2013;43(4):985-94.
99. Christodoulatos GS, Dalamaga M. Micro-RNAs as clinical biomarkers and therapeutic targets in breast cancer: Quo vadis. World J Clin Oncol. 2014;5(2):71-81.
100. Kim S-J, Shin J-Y, Lee K-D, Bae Y-K, Sung KW, Nam SJ, et al. MicroRNA let-7a suppresses breast cancer cell migration and invasion through downregulation of CC chemokine receptor type 7. Breast Cancer Research. 2012;14(1):R14.
101. Jang K, Ahn H, Sim J, Han H, Abdul R, Paik SS, et al. Loss of microRNA-200a expression correlates with tumor progression in breast cancer. Translational Research. 2014;163(3):242-51.
102. Zhao F-l, Dou Y-c, Wang X-f, Han D-c, Lv Z-g, Ge S-l, et al. Serum microRNA-195 is down-regulated in breast cancer: a potential marker for the diagnosis of breast cancer. Molecular biology reports. 2014;41(9):5913-22.
103. Hu J, Xu J, Wu Y, Chen Q, Zheng W, Lu X, et al. Identification of microRNA-93 as a functional dysregulated miRNA in triple-negative breast cancer. Tumor Biology. 2015;36(1):251-8.
104. Xing Z, Park PK, Lin C, Yang L. LncRNA BCAR4 wires up signaling transduction in breast cancer. RNA Biol. 2015;12(7):681-9.
105. Langhendries JL, Nicolas E, Doumont G, Goldman S, Lafontaine DL. The human box C/D snoRNAs U3 and U8 are required for pre-rRNA processing and tumorigenesis. Oncotarget. 2016;7(37):59519-34.
106. Melar-New M, Laimins LA. Human papillomaviruses modulate expression of microRNA 203 upon epithelial differentiation to control levels of p63 proteins. Journal of virology. 2010;84(10):5212-21.
107. Tian R-Q, Wang X-H, Hou L-J, Jia W-H, Yang Q, Li Y-X, et al. MicroRNA-372 is down-regulated and targets cyclin-dependent kinase 2 (CDK2) and cyclin A1 in human cervical cancer, which may contribute to tumorigenesis. Journal of Biological Chemistry. 2011;286(29):25556-63.
108. Wang X, Meyers C, Guo M, Zheng ZM. Upregulation of p18Ink4c expression by oncogenic HPV E6 via p53-miR-34a pathway. International journal of cancer. 2011;129(6):1362-72.
109. Martinez I, Gardiner A, Board K, Monzon F, Edwards R, Khan S. Human papillomavirus type 16 reduces the expression of microRNA-218 in cervical carcinoma cells. Oncogene. 2008;27(18):2575-82.
110. Li J-H, Xiao X, Zhang Y-N, Wang Y-M, Feng L-M, Wu Y-M, et al. MicroRNA miR-886-5p inhibits apoptosis by down-regulating Bax expression in human cervical carcinoma cells. Gynecologic oncology. 2011;120(1):145-51.

111. Hu Y, Sun X, Mao C, Guo G, Ye S, Xu J, et al. Upregulation of long noncoding RNA TUG1 promotes cervical cancer cell proliferation and migration. Cancer Med. 2017;6(2):471-82.
112. Guo G, Kang Q, Zhu X, Chen Q, Wang X, Chen Y, et al. A long noncoding RNA critically regulates Bcr-Abl-mediated cellular transformation by acting as a competitive endogenous RNA. Oncogene. 2015;34(14):1768-79.
113. Bandrés E, Cubedo E, Agirre X, Malumbres R, Zarate R, Ramirez N, et al. Identification by Real-time PCR of 13 mature microRNAs differentially expressed in colorectal cancer and non-tumoral tissues. Molecular cancer. 2006;5(1):29.
114. Keramati F, Seyedjafari E, Fallah P, Soleimani M, Ghanbarian H. 7SK small nuclear RNA inhibits cancer cell proliferation through apoptosis induction. Tumour Biol. 2015;36(4):2809-14.
115. Qi Y, Purtell L, Fu M, Lee NJ, Aepler J, Zhang L, et al. Snord116 is critical in the regulation of food intake and body weight. Sci Rep. 2016;6:18614.
116. de Smith AJ, Purmann C, Walters RG, Ellis RJ, Holder SE, Van Haelst MM, et al. A deletion of the HBII-85 class of small nucleolar RNAs (snoRNAs) is associated with hyperphagia, obesity and hypogonadism. Hum Mol Genet. 2009;18(17):3257-65.
117. Hao Y, Yang X, Zhang D, Luo J, Chen R. Long noncoding RNA LINC01186, regulated by TGF-beta/SMAD3, inhibits migration and invasion through Epithelial-Mesenchymal-Transition in lung cancer. Gene. 2017;608:1-12.
118. Liang S, Zhang S, Wang P, Yang C, Shang C, Yang J, et al. LncRNA, TUG1 regulates the oral squamous cell carcinoma progression possibly via interacting with Wnt/beta-catenin signaling. Gene. 2017;608:49-57.
119. Malik B, Feng FY. Long noncoding RNAs in prostate cancer: overview and clinical implications. Asian J Androl. 2016;18(4):568-74.
120. Zhang S, Dong X, Ji T, Chen G, Shan L. Long non-coding RNA UCA1 promotes cell progression by acting as a competing endogenous RNA of ATF2 in prostate cancer. Am J Transl Res. 2017;9(2):366-75.
121. Crea F, Quagliata L, Michael A, Liu HH, Frumento P, Azad AA, et al. Integrated analysis of the prostate cancer small-nucleolar transcriptome reveals SNORA55 as a driver of prostate cancer progression. Mol Oncol. 2016;10(5):693-703.
122. Abasi M, Bazi Z, Mohammadi-Yeganeh S, Soleimani M, Haghpanah V, Zargami N, et al. 7SK small nuclear RNA transcription level down-regulates in human tumors and stem cells. Med Oncol. 2016;33(11):128.
123. Rackham O, Shearwood A-MJ, Mercer TR, Davies SM, Mattick JS, Filipovska A. Long noncoding RNAs are generated from the mitochondrial genome and regulated by nuclear-encoded proteins. RNA. 2011;17(12):2085-93.
124. Gao Y, Chen ZY, Wang Y, Liu Y, Ma JX, Li YK. Long non-coding RNA ASncmtRNA-2 is upregulated in diabetic kidneys and high glucose-treated mesangial cells. Experimental and Therapeutic Medicine. 2017;13(2):581-7.
125. Zhao Z, Li X, Jian D, Hao P, Rao L, Li M. Hsa_circ_0054633 in peripheral blood can be used as a diagnostic biomarker of pre-diabetes and type 2 diabetes mellitus. Acta Diabetol. 2017;54(3):237-45.
126. Xu H, Guo S, Li W, Yu P. The circular RNA Cdr1as, via miR-7 and its targets, regulates insulin transcription and secretion in islet cells. Sci Rep. 2015;5:12453.

127. Zampetaki A, Kiechl S, Drozdov I, Willeit P, Mayr U, Prokopi M, et al. Plasma microRNA profiling reveals loss of endothelial miR-126 and other microRNAs in type 2 diabetes. Circulation research. 2010;107(6):810-7.
128. Mao Y, Mohan R, Zhang S, Tang X. MicroRNAs as pharmacological targets in diabetes. Pharmacological research. 2013;75:37-47.
129. Gallagher IJ, Scheele C, Keller P, Nielsen AR, Remenyi J, Fischer CP, et al. Integration of microRNA changes in vivo identifies novel molecular features of muscle insulin resistance in type 2 diabetes. Genome medicine. 2010;2(2):9.
130. Kloting N, Berthold S, Kovacs P, Schon MR, Fasshauer M, Ruschke K, et al. MicroRNA expression in human omental and subcutaneous adipose tissue. PLoS One. 2009;4(3):e4699.
131. Tangvarasittichai S. Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus. World J Diabetes. 2015;6(3):456-80.
132. Wang K, Long B, Liu F, Wang JX, Liu CY, Zhao B, et al. A circular RNA protects the heart from pathological hypertrophy and heart failure by targeting miR-223. Eur Heart J. 2016;37(33):2602-11.
133. Tang CM, Zhang M, Huang L, Hu ZQ, Zhu JN, Xiao Z, et al. CircRNA_000203 enhances the expression of fibrosis-associated genes by derepressing targets of miR-26b-5p, Col1a2 and CTGF, in cardiac fibroblasts. Sci Rep. 2017;7:40342.
134. Geng HH, Li R, Su YM, Xiao J, Pan M, Cai XX, et al. The Circular RNA Cdr1as Promotes Myocardial Infarction by Mediating the Regulation of miR-7a on Its Target Genes Expression. PLoS One. 2016;11(3):e0151753.
135. Gedicke-Hornung C, Behrens-Gawlik V, Reischmann S, Geertz B, Stimpel D, Weinberger F, et al. Rescue of cardiomyopathy through U7snRNA-mediated exon skipping in Mybpc3-targeted knock-in mice. EMBO Mol Med. 2013;5(7):1128-45.
136. Haslam D, James W. Obesity lJ J. Lancet. 2005;366(9492):1.
137. Wozniak SE, Gee LL, Wachtel MS, Frezza EE. Adipose tissue: the new endocrine organ? A review article. Digestive diseases and sciences. 2009;54(9):1847-56.
138. Gesta S, Tseng Y-H, Kahn CR. Developmental origin of fat: tracking obesity to its source. Cell. 2007;131(2):242-56.
139. Balistreri CR, Caruso C, Candore G. The role of adipose tissue and adipokines in obesity-related inflammatory diseases. Mediators of inflammation. 2010;2010.
140. Arner E, Arner P. Health and obesity: not just skin deep. Science. 2013;342(6158):558-9.
141. Martinelli R, Nardelli C, Pilone V, Buonomo T, Liguori R, Castanò I, et al. miR-519d overexpression is associated with human obesity. Obesity. 2010;18(11):2170-6.
142. Ortega FJ, Moreno-Navarrete JM, Pardo G, Sabater M, Hummel M, Ferrer A, et al. MiRNA expression profile of human subcutaneous adipose and during adipocyte differentiation. PloS one. 2010;5(2):e9022.
143. Chen L, Dai Y-M, Ji C-B, Yang L, Shi C-M, Xu G-F, et al. MiR-146b is a regulator of human visceral preadipocyte proliferation and differentiation and its expression is altered in human obesity. Molecular and cellular endocrinology. 2014;393(1):65-74.
144. Keller P, Gburcik V, Petrovic N, Gallagher IJ, Nedergaard J, Cannon B, et al. Gene-chip studies of adipogenesis-regulated microRNAs in mouse primary adipocytes and human obesity. BMC endocrine disorders. 2011;11(1):7.
145. Arner E, Mejhert N, Kulyté A, Balwierz PJ, Pachkov M, Cormont M, et al. Adipose tissue microRNAs as regulators of CCL2 production in human obesity. Diabetes. 2012;61(8):1986-93.

146. Meerson A, Traurig M, Ossowski V, Fleming J, Mullins M, Baier L. Human adipose microRNA-221 is upregulated in obesity and affects fat metabolism downstream of leptin and TNF-α. Diabetologia. 2013;56(9):1971-9.
147. Heneghan H, Miller N, McAnena O, O'Brien T, Kerin M. Differential miRNA expression in omental adipose tissue and in the circulation of obese patients identifies novel metabolic biomarkers. The Journal of Clinical Endocrinology & Metabolism. 2011;96(5):E846-E50.
148. Capobianco V, Nardelli C, Ferrigno M, Iaffaldano L, Pilone V, Forestieri P, et al. miRNA and protein expression profiles of visceral adipose tissue reveal miR-141/YWHAG and miR-520e/RAB11A as two potential miRNA/protein target pairs associated with severe obesity. Journal of proteome research. 2012;11(6):3358-69.
149. Chou W-W, Wang Y-T, Liao Y-C, Chuang S-C, Wang S-N, Juo S-H. Decreased microRNA-221 is associated with high levels of TNF-α in human adipose tissue-derived mesenchymal stem cells from obese woman. Cellular Physiology and Biochemistry. 2013;32(1):127-37.
150. Diawara MR, Hue C, Wilder SP, Venteclef N, Aron-Wisnewsky J, Scott J, et al. Adaptive expression of microRNA-125a in adipose tissue in response to obesity in mice and men. PloS one. 2014;9(3):e91375.
151. Oger F, Gheeraert C, Mogilenko D, Benomar Y, Molendi-Coste O, Bouchaert E, et al. Cell-specific dysregulation of microRNA expression in obese white adipose tissue. The Journal of Clinical Endocrinology & Metabolism. 2014;99(8):2821-33.
152. Grammatikakis I, Panda AC, Abdelmohsen K, Gorospe M. Long noncoding RNAs (lncRNAs) and the molecular hallmarks of aging. Aging (Albany NY). 2014;6(12):992.
153. Azzalin CM, Reichenbach P, Khoriauli L, Giulotto E, Lingner J. Telomeric repeat–containing RNA and RNA surveillance factors at mammalian chromosome ends. Science. 2007;318(5851):798-801.
154. Sado T, Brockdorff N. Advances in understanding chromosome silencing by the long non-coding RNA Xist. Philosophical Transactions of the Royal Society B: Biological Sciences. 2013;368(1609):20110325.
155. Mohamed JS, Gaughwin PM, Lim B, Robson P, Lipovich L. Conserved long noncoding RNAs transcriptionally regulated by Oct4 and Nanog modulate pluripotency in mouse embryonic stem cells. Rna. 2010;16(2):324-37.
156. Loewer S, Cabili MN, Guttman M, Loh Y-H, Thomas K, Park IH, et al. Large intergenic non-coding RNA-RoR modulates reprogramming of human induced pluripotent stem cells. Nature genetics. 2010;42(12):1113-7.
157. Du WW, Yang W, Liu E, Yang Z, Dhaliwal P, Yang BB. Foxo3 circular RNA retards cell cycle progression via forming ternary complexes with p21 and CDK2. Nucleic Acids Res. 2016;44(6):2846-58.
158. Cooper TA, Wan L, Dreyfuss G. RNA and disease. Cell. 2009;136(4):777-93.
159. Fernandez Alanis E, Pinotti M, Dal Mas A, Balestra D, Cavallari N, Rogalska ME, et al. An exon-specific U1 small nuclear RNA (snRNA) strategy to correct splicing defects. Hum Mol Genet. 2012;21(11):2389-98.
160. Gorman L, Suter D, Emerick V, Schumperli D, Kole R. Stable alteration of pre-mRNA splicing patterns by modified U7 small nuclear RNAs. Proc Natl Acad Sci U S A. 1998;95(9):4929-34.
161. Meseda CA, Srinivasan K, Wise J, Catalano J, Yamada KM, Dhawan S. Non-coding RNAs and heme oxygenase-1 in vaccinia virus infection. Biochem Biophys Res Commun. 2014;454(1):84-8.