THE ROLE OF MI (MICRO) RNAS AS BIOMARKER OF DIFFERENT HEALTH CONDITIONS

Abstract

MicroRNAs (miRNAs) are the intron transcribed small non-coding oligoribonucleotidesthat regulates the process of gene expression at both transcriptional and translational level. The regulatory role of miRNAs is associated with most of the cellular, biological and physiological processes of a cell and an organism. Any alteration in the process of regulation is reflected as altered health conditions including cancer. Intracellular, extracellular (circulating/ exosomal) miRNAs in the developed disease condition have both predictive and diagnostic value as biomarkers. Evaluation of miRNA as biomarker is helpful in assessment of clinical conditions like cancer, diabetes, viral infections, alcoholism, obesity, neuronal disorder, renal and cardiovascular disorders. Further miRNA can also serve as therapeutics in the diseased state reversing the altered clinical conditions. In this chapter association of different miRNAs as biomarker in different health conditions has been summarised and the general prospect of use of miRNAs as diagnostics and therapeutics has been discussed. Further evaluation and validation of nano based miRNA molecular or lateral flow techniques can enhance its dual role as both diagnostics and therapeutics.

Keywords: Alcoholism: Biomarker: Cancer: Dicer: Drosha:: Diagnostic: Exportin: Micro RNA: Therapeutics:

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I. INTRODUCTION

The major fraction of the RNA world consists of messenger (m), transfer (t) and ribosomal (r) RNAs are involved in coding the regular functioning of cells. The noncoding proportionate consisting of microRNAs (mi), small interfering RNAs (si) are observed to rule the RNA era for the last few decades. First miRNAdiscovered in *Caenorhabditis elegans* (Lee et al., 1993) was 22ribonucleotide long lin-*4* miRNA gene, that is partially complementary to 3' UTR of the *lin-14* mRNA. The*lin-4* miRNA binds to the UTR segment and represses *lin-14* geneexpression involved in process of larval development.Subsequently *let-7* mi RNA was discovered that represses *lin-41* gene in *C. elegans* involved inlater developmental stage transition (Reinhartet al., 2000). Gradually the miRNAs discovered were found to be 12 to 28 ribonucleotide entity involved in regulation of gene expression mechanism associated with different physiological processes in wide range of cells and tissues. The miRNAs constituting about 1%–3% of the mammalian genome (Bartel et al., 2004) were found to be associated with various vital biological processes like growth, differentiation, reproduction, lactation, pregnancy etc. Any imbalances in the genesis and regulatory mechanism usually reflects as disease condition in both humans and animals (Bartel et al., 2004; Wang and Sen, 2011). Transcribed as pre-miRNA mostly from the introns (small extent from exons) of the genes(Selbach Met al., 2008: Rodriguez A et al., 2004) with characteristic hairpin stem loop, they undergo polyadenylation followed by splicing with the help of drosha protein through microprocessor complex (Berezikov Eet al., 2007; Ali PS et al., 2012;Auyeung VCet al., 2013;Conrad T et al.,2014). The pre-miRNAs also undergo nuclear editing(Murchison EP et al., 2004; Ohman M et al., 2007;Kawahara Yet al., 2008; Winter J et al., 2009) by the enzyme ADARs (adenosine deaminases acting on RNA) and cytoplasmic editing by enzyme Dicer(Murchison EP et al., 2004; Lund Eet al., 2006). However, the functional miRNA interacts with the target mRNA through RNA-induced silencing complex (RISC) inhibiting the process of translation. So, thenon-coding micro RNAs are basically involved in gene silencing during the process of transcription and post-transcriptional gene expression regulation (Wang and Sen, 2011; Qureshi A et al., 2014;Bartel et al., 2018). This short oligoribonucleotides usually gets paired with complementary mRNA sequences either cleaving it into fragments or shortening the poly(A) tail. Thus, destabilizing the mRNA structurally and hindering the process of translation in cells (Bartel et al., 2009; Fabian et al., 2010). Apart from disruption of translation initiation miRNAs were also supposed cause hinderance in the process of histone modification and DNA methylation at the site of promoters dysregulating the process of functional gene expression (Hawkins PG et al., 2008; Tan Y et al., 2009;Bazzini AA et al., 2012; Djuranovic S et al., 2012). The dysregulated gene expression associated with various biological processes gets altered and reflected in clinical form as diseases.

II. ASSOCIATION OF mi-RNA WITH DIFFERENT HEALTH CONDITIONS

1. **miRNA as Biomarker in Cancer:** Cancer is the disease with abnormal cellular proliferation associated with dysregulated angiogenesis, adhesion, apoptosis, causing its initiation, progression and metastasis(Calin et al., 2004b). Accumulation of DNA damage caused by mutations or errors in DNA replication (Loeb and Loeb., 2000) and defects in expression of proteins or factors involved in DNA repair cause cancer. Defects in miRNAs itself or miRNAs involved in these processes (Hu and Gatti., 2011) alters the base level of gene regulation causing the abnormalities. Alterations in genes encoding

protein machineries associated with miRNA genesis and processing causes disruption in regular process of regulation of gene expression that is associated with abnormal cellular processes causing cancer. For example any alteration in synthesis, structure and regulations of genes encoding RNA polymerase II (Pol II), Poly(A)-binding protein, Ribonuclease III, Paip2b, DGCR8 , Drosha, ADARs, TARBP2, Exportin-5 (XPO5), Ran protein, AGO2, and Dicer can interrupt in formation of RISCs and miRNP complex and thus inhibiting miRNA formation (Esteller et al., 2011;Huang et al., 2014). This inhibition has been found to be associated with gene alterationsin different types of cancer. Thus, the miRNA can serve dual role as oncoactivator or oncosuppressors depending upon the activation or suppression of the genes concerned(Welch et al., 2007; Yu et al., 2010). The versatile Ras oncogene was found to be regulated by let-7 group of mi-RNAS (Esquela-Kerscher and Slack, 2006). Similarly, the expression of oncogenes PTEN and SPRY2 are also regulated by the miR-21(Meng et al., 2007; Sayed et al., 2008). Any deviation in expression and regulation of these genes was found to be associate with altered cellular processes causing cancer(Hatley et al., 2010).The miR-21 have been found to be associated with liver,lung, gastric, pancreas, colorectal, skin, thyroid, cervical and mammary gland (Volinia et al., 2006). Similarly, miR-34a, is also associated with cancer as it alters the normal process of cell cycle, development, differentiation and apoptosis targeting the molecules associated with these processes(Misso et al., 2014).Whereas miR-96 and miR-34a act as an oncosupressor down regulating the target protein associated with the process of cell invasion and migration (Yu et al., 2010) as indicated in case of glioblastoma (Liu et al., 2011; Yan et al., 2014). The miRNA that acts as oncosuppressor in one type of cancer may act as oncoactivator in cancer associated with other organs. Like miR-29a suppresses cancer in lung, liver and blood (Fabbri et al., 2007; Xiong et al., 2010; Pekarsky and Croce, 2010) but has been reported to activate colorectal and ovarian cancer (Resnick et al., 2009; Huang et al., 2010).A range of altered mi-RNA profiles has been studied and reported in cancer of blood, breasts, ovarian, prostate, pancreas and liver. (Calin et al., 2004; Iorio et al., 2005; Iorio et al., 2007; Porkka et al., 2007; Wang and Sen, 2011; Qi et al., 2013). The microRNA miR-155, that represses MLH1 expression causes colon cancer as indicated in MLH1-deficient rats.The epigenetic methylation of the MGMT gene and nonmethylation of its promoter increases microRNA miR-181d level with decreased synthesis DNA repair enzyme MGMT is associated with glioblastomas in humans (Spiegl-Kreineckeret al., 2010; Zhang et al., 2012). Expression of oncogene HMGA for HMGA1a, proteins are also regulated by miRNAs causing thyroid, prostatic, cervical, colorectal, pancreatic and ovarian cancer (Borrmann et al.,2003; Sgarra et al., 2004; Xuet al., 2004). Whereas expression of DNA repair gene of ERCC1 is inhibited by HMGA2 in case of colon cancers(Facista A, et al., 2012).

The comparative level of oncoactivating and oncosupressing miRNAs in cells, tissues, serum, blood, urine and other biological fluids reflects the balance and imbalances of different cellular processes and its relation with development of cancer. Detection of normal and abnormal level of these miRNAs in the biological samples can indicate about the particular type and stage of cancer (Heneghan et al., 2010; Xing et al., 2010; Ben-Dov et al., 2014; Wang et al., 2014b; Wang et al., 2015). Further single-nucleotide polymorphisms associated with the genes and the associated miRNAs can indicate the possibility of development of cancer in the concerned group. SNPS in miR-196a2 C > T(rs11614913) and miR-499 C > T confer risks in development of

hepatocellular carcinoma and lung cancer (Chen et al., 2013; Qi et al., 2014). Thus, functional miRNA-single-nucleotide polymorphisms in miRNAs may act as biomarkers of disease risk and can predict the clinical outcome in cancer.Single Nucleotide polymorphisms (SNPs) can alter the binding of miRNAs on 3'UTRs for example the case of hsa-mir181a and hsa-mir181b on the CDON tumor suppressor gene.

2. **miRNA as Biomarker in Cardiovascular Diseases:** Development of heart and associated vascular system in human and animals is a complicated process that involves genesis, differentiation, programming and reprogramming of progenitor stem cells. The expression and repression of different genes translating into proteins and other factors involved in cardiogenesis are modulated by a group of miRNAs (Zampetaki and Mayr, 2012; Philippen et al., 2015). Alterations in the level of these miRNAs are reported to be associated with pathological conditions like heart failure, atrial fibrillation, fibrosis, hypertrophy, myocardial infarction, atherosclerosis, etc (Corsten et al., 2010; Fichtlscherer et al., 2010; da Silva and Silbiger, 2014;). Mutation and deletion of myocardial dicer gene in certain population is linked to myocardial infarction (Albinsson et al., 2010). The miRNAs are reported to be more sensitive in detection of end-stage heart failure in humans(Matkovich et al., 2009). Further profiling of miRNA has been found to be useful in differential diagnosis of heart ailments and cardiomyopathies at different stages of development(van Rooij et al., 2006b; Thum et al., 2007). The MiR-205 in humans and miRNA-712in murine has predictive value in atherosclerosis as indicated in murine experimental model. The miRNA-712 is involved in regulating expression of pro-atherogenic genes including matrix metalloproteinases (MMPs) mediating pro-inflammatory and pro-angiogenic signals. Anti-miR-712 has been found to inhibit vascular hyperpermeability, thus reducing development of atherosclerosis and immune cell mediated inflammation (Son DJ et al., 2003; Yang B et al., 2007; Basu R, et al., 2012;Keller T et al., 2017).

3. **miRNA as Biomarker in Renal Diseases:** Renal FoxD1-Dicer knockout mouse model indicates upregulatedpro-apoptoticBcl2L11 (Bim) geneand dysregulated p53 gene pathway including alteredBax, Trp53inp1, Jun, Cdkn1a, Mmp2, and Arid3a gene activity. The vast range of miRNAs like miRs□10a, 18a, 19b, 24, 30c, 92a, 106a, 130a, 152, 181a, 214, 222, 302a, 370, and 381 regulate renal Bcl2L11 (Bim) expression. Whereas, the miRs□15b, 18a, 21, 30c, 92a, 106a, 125b□5p, 145, 214, 222, 296□5p and 302a regulate p53-effector gene expression. The alteration in transcription of these genes was found to be associated with defective renal functioning due to lower number of renin cells, smoothening of arterioles, mesangial loss and glomerular aneurysms (Phua YL, etal., 2015).

4. **miRNA as Biomarker in Neural Diseases:** The miRNAs- 132 / 134/ 124 are reported to be involved in the process of dendritogenesis whereas miR-134 and 138 are associated with synapse maturation. Abnormal functioning of these miRNAs along with silencing of dicer causes neurodegenerationas reflected in alzheimer,schizophrenia and anxiety disorders (Maes OC et al., 2009; Hébert SSet al., 2010; Hommers LGet al., 2015: Hosseinian S etal., 2020). Further loss of motoneuron-specific microRNA-218 causes systemic neuromuscular failure (Amin ND et al.,2015).

5. **miRNA as Biomarker in Stroke:** Ischemic strokes is a pathophysiological condition resulted from decreased blood supply to brain due to arterial blockage depriving the brain getting essential nutrients, glucose, oxygen etc. Different miRNAS are found to be actively involved posttranslational gene silencing in the process of inflammation, angiogenesis, and apoptosis resulting in cerebral ischemia (Rinkand Khanna S, 2011; Ouyang et al.,2013)

6. **miRNA as Biomarker in Alcoholism:** Around 35 miRNAS are discovered to be involved in the process of addiction associated alterations in downstream gene expression related to functioning of brain, synaptic transmission and neural adaptations. The medial prefrontal cortex miRNAs dysregulate translation of the genes associated with cell cycle, apoptosis, cell adhesion, neuronal development, synaptic transmission and cell signaling (Lewohl JM et al., 2011; Tapocik JD et al., 2013; Gorini G et al., 2013).In mice, it has been observed that chronic alcoholism induces upregulation of the microRNA-155 that causes TLR4 mediated neuroinflammation (Lippai et al., 2013) responsible for abnormal behaviour. Similarly, the overexpression of miRNA-206 and down expression miRNA-382 in rat medial prefrontal cortex was reported to downregulate BDNF and DRD1expression causing synaptic plasticity (Li J et al., 2013; Tapocik JD et al., 2014).

7. **miRNA as Biomarker in Obesity:** The miR-155, miR-221, and miR-222 (Romao JM et al., 2011are reported to be negatively expressed during the process of adipogenesis in both immortalized and primary hMSCs causing repression of PPARγ and CCAAT/enhancer-binding protein alpha (CEBPA) associated with differentiation (Zuo Y et al., 2006).The overexpression of let-7 classes of miRNAs (Frost RJ,andOlson EN, 2011; Zhu H et al., 2011; Jun-Hao ETet al., 2016)in course of aging is found to be the reason for development of insulin resistance, obesity and diabetes. Let-7 accumulates in human tissues during the course of aging causing dysregulation of gene expression associated with obesity and associated risks.

8. **miRNA as Biomarker in Hemostasis:** miRNAs also play crucial roles in the regulation of complex enzymatic cascades including the hemostatic blood coagulation system (Teruel-Montoya R et al., 2015). Large scale studies of functional miRNA targeting have recently uncovered rationale therapeutic targets in the hemostatic system (Nourse Jet al., 2018; Nourse J and Danckwardt S. 2021) They have been directly linked to Calcium homeostasis in the endoplasmic reticulum, which is critical in cell differentiation in early

9. **miRNA as Biomarker in Pregnancy and Associated Conditions:** miRNAs are also reported control the important physiological processes like pregnancy and associated reproduction disorders. miRNAs play vital role in different stages of pregnacy like fertilization, endometrial receptivity, vasculature development, uterine immunomodulation, immunosuppression, implantation, labor and also in conditions like abortions and foetal loss. The uteral hormones most likely estrogen and progesterone regulates the action of miRNAs in the process of transcription, processing, RNA editing, function and intracellular localization etc. Estrogen upregulates the expression of miR-451/429/99b/155 and 7a while downregulates miR-24 and -181b expression in the endometrium during pregnancy (Qian K et al., 2009: Nothnick WB et al, 2010; Xia HF et al., 2010a,b: Zhu XM et al., 2010: Williams KC et al., 2012; Liu Fet al, 2012; Morandi F and Pistoia V. 2013). Further miR-152/ 148a has been reported to be associated with

maternal recognition of foetus. The role of miR-451 and miR-210 in immunomodulation of uterine microenvironment has also specific role in maternal recognition and implantation of foetus.

The miRNA clusters C19MC including miR517a-3P, miR519a-3P, miR-520c-3P,miR-371-3 (Bortolin-Cavaille et al., 2009: Luo L et al., 2012; Donker RB et al., 2012;Kurashina R et al., 2014) expressed in trophoblast and placenta-derived stromal cells have been evaluated as a biomarkerfor pregnancy disorders like pre-term laborand pre-eclampsia.

III. PREDICTION AND DETECTION OF miRNAS

Several online software's (MicroTar, miTarget, mirror, PicTar, Rna 22 etc) are available to detect miRNA, its interaction with target RNAs, its predictive performance etc. Further, miRNAs are reported in intracellularly and extracellularly also. Extracellular miRNA in serum, blood,urine sweat, lymph and other biological fluids can be detected by PCR and the expression status can be studied by RT-PCR. Circulating miRNAs have already been assessed as biomarkers for prediction and confirmation of myocardial infarction and cardiovascular diseases (Ai et al., 2010; Wang et al., 2010).Exosomal miRNAs has also beenfunctionally evaluated as biomarker for assessment of disease conditions. Techniques like microarray, northern blot analysis, real-time PCR, in situ hybridization, NGS etc have been employed for detection, estimation and analysis of miRNAs associated with a particular clinical condition (Sempere et al., 2004; Thomson et al., 2004; Valoczi et al., 2004; Chen et al., 2005; Kloosterman et al., 2006; Wang et al., 2009; Wang et al., 2014a; Wang et al., 2015). Accurately determination of expression level of miRNAs in a specific cell, tissue, organ, body fluids associated with specific clinical condition is the prerequisite for assessment of miRNA as diagnostics.

RFERENCE

[1] Lee RC, Feinbaum RL, Ambros V. 1993. The C-Elegans Heterochronic Gene Lin-4 Encodes Small Rnas with Antisense Complementarity to Lin-14. Cell. 75 (5) 843–854.
[2] Reinhart BJ, Slack FJ, Basson M, Pasquinelli AE, Bettinger JC, Rougvie AE, Horvitz HR, Ruvkun G. 2000. "The 21-nucleotide let-7 RNA regulates developmental timing in Caenorhabditis elegans". Nature. 403 (6772): 901–6. Bibcode:2000 Nature 403. 901R.
[3] Bartel DP. 2004. MicroRNAs: Genomics, biogenesis, mechanism, and function. Cell. 116 (2) 281–297.
[4] Wang J, Sen S. 2011. MicroRNA functional network in pancreatic cancer: From biology to biomarkers of disease. J Biosciences. 36 (3) 481–491.
[5] Selbach M, Schwanhäusser B, Thierfelder N, Fang Z, Khanin R, Rajewsky N. 2008. Widespread changes in protein synthesis induced by microRNAs". Nature. 455 (7209): 58–63. Bibcode: 2008 Natur. 455...58S.
[6] Rodriguez A, Griffiths-Jones S, Ashurst JL, Bradley A. 2004. Identification of mammalian microRNA host genes and transcription units. Genome Research. 14 (10A): 1902–10.
[7] Conrad T, Marsico A, Gehre M, Orom UA. 2014. Microprocessor activity controls differential miRNA biogenesis in Vivo. Cell Reports. 9 (2): 542–54.
[8] Auyeung VC, Ulitsky I, McGeary SE, Bartel DP. 2013. Beyond secondary structure: primary-sequence determinants license pri-miRNA hairpins for processing. Cell. 152 (4): 844–58.
[9] Ali PS, Ghoshdastider U, Hoffmann J, Brutschy B, Filipek S. 2012. Recognition of the let-7g miRNA precursor by human Lin28B. FEBS Letters. 586 (22): 3986–90.
[10] Berezikov E, Chung WJ, Willis J, Cuppen E, Lai EC. 2007. Mammalian mirtron genes. Molecular Cell. 28 (2): 328–36.

[11] Kawahara Y, Megraw M, Kreider E, Iizasa H, Valente L, Hatzigeorgiou AG, Nishikura K 2008. Frequency and fate of microRNA editing in human brain". Nucleic Acids Research. 36 (16): 5270–80.
[12] Winter J, Jung S, Keller S, Gregory RI, Diederichs S. 2009. Many roads to maturity: microRNA biogenesis pathways and their regulation. Nature Cell Biology. 11 (3): 228–34.
[13] Ohman M. 2007. A-to-I editing challenger or ally to the microRNA process. Biochimie. 89 (10): 1171–6.
[14] Murchison EP, Hannon GJ. 2004. miRNAs on the move: miRNA biogenesis and the RNAi machinery. Current Opinion in Cell Biology. 16 (3): 223–9
[15] Lund E, Dahlberg JE. 2006. Substrate selectivity of exportin 5 and Dicer in the biogenesis of microRNAs. Cold Spring Harbor Symposia on Quantitative Biology. 71: 59–66.
[16] Bartel DP. 2018. Metazoan MicroRNAs. Cell. 173 (1): 20–51.
[17] Qureshi A, Thakur N, Monga I, Thakur A, Kumar M. 2014. VIRmiRNA: a comprehensive resource for experimentally validated viral miRNAs and their targets. Database. 2014: bau103.
[18] Bartel DP. 2009. MicroRNAs: target recognition and regulatory functions. Cell. 136 (2): 215–33.
[19] Fabian MR, Sonenberg N, Filipowicz W 2010. Regulation of mRNA translation and stability by microRNAs. Annual Review of Biochemistry. 79: 351–79.
[20] Bazzini AA, Lee MT, Giraldez AJ April 2012. Ribosome profiling shows that miR-430 reduces translation before causing mRNA decay in zebrafish. Science. 336 (6078): 233–7.
[21] Djuranovic S, Nahvi A, Green R April 2012. miRNA-mediated gene silencing by translational repression followed by mRNA deadenylation and decay. Science. 336 (6078): 237–40.
[22] Tan Y, Zhang B, Wu T, Skogerbø G, Zhu X, Guo X, He S, Chen R February 2009. Transcriptional inhibiton of Hoxd4 expression by miRNA-10a in human breast cancer cells. BMC Molecular Biology. 10 (1): 12.
[23] Hawkins PG, Morris KV March 2008. RNA and transcriptional modulation of gene expression. Cell Cycle. 7 (5): 602–7.
[24] Calin GA, Liu CG, Sevignani C, Ferracin M, Felli N, Dumitru CD, Shimizu M, Cimmino A, Zupo S, Dono M, Dell'Aquila ML, Alder H, Rassenti L, Kipps TJ, Bullrich F, Negrini M, Croce CM. 2004a. MicroRNA profiling reveals distinct signatures in B cell chronic lymphocytic leukemias. Proceedings of the National Academy of Sciences of the United States of America. 101 (32) 11755–11760.
[25] Calin GA, Sevignani C, Dan Dumitru C, Hyslop T, Noch E, Yendamuri S, Shimizu M, Rattan S, Bullrich F, Negrini M, Croce CM. 2004b. 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. 101 (9) 2999–3004.
[26] Loeb KR, Loeb LA 2000. Significance of multiple mutations in cancer. Carcinogenesis. 21 (3): 379–385. d
[27] Hu H, Gatti RA June 2011. MicroRNAs: new players in the DNA damage response. Journal of Molecular Cell Biology. 3 (3): 151–158.
[28] Esteller M. 2011. Non-coding RNAs in human disease. Nature reviews Genetics. 12 (12) 861–874.
[29] Huang JT, Wang J, Srivastava V, Sen S, Liu SM. 2014. MicroRNA Machinery Genes as Novel Biomarkers for Cancer. Frontiers in oncology. 4: 113.
[30] Huang ZH, Huang D, Ni SJA, Peng ZL, Sheng WQ, Du X. 2010. Plasma microRNAs are promising novel biomarkers for early detection of colorectal cancer. Int J Cancer. 127 (1) 118–126.
[31] Esquela-Kerscher A, Slack FJ. 2006. Oncomirs - microRNAs with a role in cancer. Nature reviews Cancer. 6 (4) 259–269.
[32] Welch C, Chen Y, Stallings RL. 2007. MicroRNA-34a functions as a potential tumor suppressor by inducing apoptosis in neuroblastoma cells. Oncogene. 26 (34) 5017–5022.
[33] Yu SN, Lu ZH, Liu CZ, Meng YX, Ma YH, Zhao WG, Liu JP, Yu J, Chen J. 2010. miRNA-96 Suppresses KRAS and Functions as a Tumor Suppressor Gene in Pancreatic Cancer. Cancer Res. 70 (14) 6015–6025.
[34] Meng F, Wehlbe-Janek H, Henson R, Ghoshal K, Jacob ST, Patel T. 2007. Microrna-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular carcinoma. Gastroenterology. 132 (4) A730–A730.
[35] Sayed D, Rane S, Lypowy J, He MZ, Chen IY, Vashistha H, Yan L, Malhotra A, Vatner D, Abdellatif M. 2008. MicroRNA-21 targets Sprouty2 and promotes cellular outgrowths. Mol Biol Cell. 19 (8) 3272–3282.
[36] Hatley ME, Patrick DM, Garcia MR, Richardson JA, Bassel-Duby R, van Rooij E, Olson EN. 2010. Modulation of K-Ras-Dependent Lung Tumorigenesis by MicroRNA-21. Cancer cell. 18 (3) 282–293.
[37] Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, Visone R, Iorio M, Roldo C, Ferracin M, Prueitt RL, Yanaihara N, Lanza G, Scarpa A, Vecchione A, Negrini M, Harris CC, Croce CM. 2006. A

microRNA expression signature of human solid tumors defines cancer gene targets.Proceedings of the National Academy of Sciences of the United States of America. 103 (7) 2257–2261.

[38] Misso G, Di Martino MT, De Rosa G, Farooqi AA, Lombardi A, Campani V, Zarone MR, Gulla A, Tagliaferri P, Tassone P, Caraglia M. 2014. Mir-34: A New Weapon Against Cancer? Mol Ther-Nucl Acids. 3

[39] Yu SN, Lu ZH, Liu CZ, Meng YX, Ma YH, Zhao WG, Liu JP, Yu J, Chen J. 2010. miRNA-96 Suppresses KRAS and Functions as a Tumor Suppressor Gene in Pancreatic Cancer. Cancer Res. 70 (14) 6015–6025.

[40] Liu Y, Gao G, Yang C, Zhou K, Shen B, Liang H, Jiang X. 2014. The role of circulating microRNA-126 (miR-126): a novel biomarker for screening prediabetes and newly diagnosed type 2 diabetes mellitus. International journal of molecular sciences. 15 (6) 10567–10577.

[41] Yan Z, Wang J, Wang C, Jiao Y, Qi W, Che S. 2014. miR-96/HBP1/Wnt/beta-catenin regulatory circuitry promotes glioma growth. FEBS letters. 588 (17) 3038–3046.

[42] Fabbri M, Garzon R, Cimmino A, Liu Z, Zanesi N, Callegari E, Liu S, Alder H, Costinean S, Fernandez-Cymering C, Volinia S, Guler G, Morrison CD, Chan KK, Marcucci G, Calin GA, Huebner K, Croce CM. 2007. MicroRNA-29 family reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B. Proceedings of the National Academy of Sciences of the United States of America. 104 (40) 15805–15810.

[43] Xiong YJ, Fang JH, Yun JP, Yang J, Zhang Y, Jia WH, Zhuang SM. 2010. Effects of MicroRNA-29 on Apoptosis, Tumorigenicity, and Prognosis of Hepatocellular Carcinoma. Hepatology. 51 (3) 836–845.

[44] Pekarsky Y, Croce CM. 2010. Is miR-29 an Oncogene or Tumor Suppressor in CLL? Oncotarget. 1 (3) 224–227.

[45] Resnick KE, Alder H, Hagan JP, Richardson DL, Croce CM, Cohn DE. 2009.The detection of differentially expressed microRNAs from the serum of ovarian cancer patients using a novel real-time PCR platform. Gynecol Oncol. 112 (1) 55–59.

[46] Huang ZH, Huang D, Ni SJA, Peng ZL, Sheng WQ, Du X. 2010. Plasma microRNAs are promising novel biomarkers for early detection of colorectal cancer. Int J Cancer. 127 (1) 118–126.

[47] Calin GA, Liu CG, Sevignani C, Ferracin M, Felli N, Dumitru CD, Shimizu M, Cimmino A, Zupo S, Dono M, Dell'Aquila ML, Alder H, Rassenti L, Kipps TJ, Bullrich F, Negrini M, Croce CM. 2004a. MicroRNA profiling reveals distinct signatures in B cell chronic lymphocytic leukemias. Proceedings of the National Academy of Sciences of the United States of America. 101 (32) 11755–11760.

[48] Iorio MV, Ferracin M, Liu CG, Veronese A, Spizzo R, Sabbioni S, Magri E, Pedriali M, Fabbri M, Campiglio M, Menard S, Palazzo JP, Rosenberg A, Musiani P, Volinia S, Nenci I, Calin GA, Querzoli P, Negrini M, Croce CM. 2005. MicroRNA gene expression deregulation in human breast cancer. Cancer Res. 65 (16) 7065–7070.

[49] Iorio MV, Visone R, Di Leva G, Donati V, Petrocca F, Casalini P, Taccioli C, Volinia S, Liu CG, Alder H, Calin GA, Menard S, Croce CM. 2007; MicroRNA

[50] Porkka KP, Pfeiffer MJ, Waltering KK, Vessella RL, Tammela TLJ, Visakorpi T. 2007 MicroRNA expression profiling in prostate cancer. Cancer Res. 67 (13) 6130–6135.

[51] Wang J, Sen S. 2011. MicroRNA functional network in pancreatic cancer: From biology to biomarkers of disease. J Biosciences. 36 (3) 481–491.

[52] Qi J, Wang J, Katayama H, Sen S, Liu SM. 2013. Circulating microRNAs (cmiRNAs) as novel potential biomarkers for hepatocellular carcinoma. Neoplasma. 60 (2) 135–142.

[53] Valeri N, Gasparini P, Fabbri M, Braconi C, Veronese A, Lovat F, Adair B, Vannini I, Fanini F, Bottoni A, Costinean S, Sandhu SK, Nuovo GJ, Alder H, Gafa R, Calore F, Ferracin M, Lanza G, Volinia S, Negrini M, McIlhatton MA, Amadori D, Fishel R, Croce CM. 2010. "Modulation of mismatch repair and genomic stability by miR-155". Proceedings of the National Academy of Sciences of the United States of America. 107 (15): 6982–7.

[54] Zhang W, Zhang J, Hoadley K, Kushwaha D, Ramakrishnan V, Li S, Kang C, You Y, Jiang C, Song SW, Jiang T, Chen CC. 2012. miR-181d: a predictive glioblastoma biomarker that downregulates MGMT expression. Neuro-Oncology. 14 (6): 712–9.

[55] Spiegl-KreineckerS, Pirker C, Filipits M, Lötsch D, Buchroithner J, Pichler J, Silye R, Weis S, Micksche M, Fischer J, Berger W. 2010. O6-Methylguanine DNA methyltransferase protein expression in tumor cells predicts outcome of temozolomide therapy in glioblastoma patients. Neuro-Oncology. 12 (1): 28–36.

[56] Sgarra R, Rustighi A, Tessari MA, Di Bernardo J, Altamura S, Fusco A, Manfioletti G, Giancotti V. 2004. Nuclear phosphoproteins HMGA and their relationship with chromatin structure and cancer". FEBS Letters. 574 (1–3): 1–8.

[57] Xu Y, Sumter TF, Bhattacharya R, Tesfaye A, Fuchs EJ, Wood LJ, Huso DL, Resar LM. 2004. The HMG-I oncogene causes highly penetrant, aggressive lymphoid malignancy in transgenic mice and is overexpressed in human leukemia". Cancer Research. 64 (10): 3371–5.

[58] Borrmann L, Schwanbeck R, Heyduk T, Seebeck B, Rogalla P, Bullerdiek J, Wisniewski JR. 2003. High mobility group A2 protein and its derivatives bind a specific region of the promoter of DNA repair gene ERCC1 and modulate its activity. Nucleic Acids Research. 31 (23): 6841–51.

[59] Facista A, Nguyen H, Lewis C, Prasad AR, Ramsey L, Zaitlin B, Nfonsam V, Krouse RS, Bernstein H, Payne CM, Stern S, Oatman N, Banerjee B, Bernstein C. 2012. Deficient expression of DNA repair enzymes in early progression to sporadic colon cancer. Genome Integrity. 3 (1): 3. doi:10.1186/2041-9414-3-3. PMC 3351028. PMID 22494821.

[60] Chen X, Ba Y, Ma LJ, Cai X, Yin Y, Wang KH, Guo JG, Zhang YJ, Chen JN, Guo X, Li QB, Li XY, Wang WJ, Zhang Y, Wang J, Jiang XY, Xiang Y, Xu C, Zheng PP, Zhang JB, Li RQ, Zhang HJ, Shang XB, Gong T, Ning G, Wang J, Zen K, Zhang JF, Zhang CY. 2008b Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. Cell Res. 18 (10) 997–1006.

[61] Heneghan HM, Miller N, Kelly R, Newell J, Kerin MJ. 2010; Systemic miRNA-195 Differentiates Breast Cancer from Other Malignancies and Is a Potential Biomarker for Detecting Noninvasive and Early Stage Disease. Oncologist. 15 (7) 673–682. [PubMed: 20576643]

[62] Xing LX, Todd NW, Yu L, Fang HB, Jiang F. 2010; Early detection of squamous cell lung cancer in sputum by a panel of microRNA markers. Modern Pathol. 23 (8) 1157–1164.

[63] Ben-Dov IZ, Tan YC, Morozov P, Wilson PD, Rennert H, Blumenfeld JD, Tuschl T. 2014; Urine MicroRNA as Potential Biomarkers of Autosomal Dominant Polycystic Kidney Disease Progression: Description of miRNA Profiles at Baseline. PloS one. 9 (1)

[64] Wang J, Zhang KY, Liu SM, Sen S. 2014b; Tumor-Associated Circulating MicroRNAs as Biomarkers of Cancer. Molecules. 19 (2) 1912–1938. [PubMed: 24518808]

[65] Wang WX, Rajeev BW, Stromberg AJ, Ren N, Tang GL, Huang QW, Rigoutsos I, Nelson PT. 2008; The expression of microRNA miR-107 decreases early in Alzheimer's disease and may accelerate disease progression through regulation of beta-site amyloid precursor protein-cleaving enzyme 1. J Neurosci. 28 (5) 1213–1223. [PubMed: 18234899]

[66] Qiu L, Zhang W, Tan EK, Zeng L. 2014; Deciphering the function and regulation of microRNAs in Alzheimer's disease and Parkinson's disease. ACS chemical neuroscience. 5 (10) 884–894. [PubMed: 25210999]

[67] Chen Z, Xu L, Ye X, Shen S, Li Z, Niu X, Lu S. 2013; Polymorphisms of microRNA sequences or binding sites and lung cancer: a meta-analysis and systematic review. PloS one. 8 (4) e61008. [PubMed: 23613771]

[68] Philippen LE, Dirkx E, da Costa-Martins PA, De Windt LJ. 2015. Non-coding RNA in control of gene regulatory programs in cardiac development and disease. Journal of molecular and cellular cardiology.

[69] Zampetaki A, Mayr M. 2012; MicroRNAs in vascular and metabolic disease. Circulation research. 110 (3) 508–522.

[70] Corsten MF, Dennert R, Jochems S, Kuznetsova T, Devaux Y, Hofstra L, Wagner DR, Staessen JA, Heymans S, Schroen B. 2010. Circulating MicroRNA-208b and MicroRNA-499 Reflect Myocardial Damage in Cardiovascular Disease. Circ-Cardiovasc Gene. 3 (6) 499–506.

[71] Fichtlscherer S, De Rosa S, Fox H, Schwietz T, Fischer A, Liebetrau C, Weber M, Hamm CW, Roxe T, Muller-Ardogan M, Bonauer A, Zeiher AM, Dimmeler S. 2010. Circulating MicroRNAs in Patients With Coronary Artery Disease. Circulation research. 107 (5) 677–U257.

[72] da Silva AMG, Silbiger VN. 2014. miRNAs as biomarkers of atrial fibrillation. Biomarkers. 19 (8) 631–636.

[73] Albinsson S, Suarez Y, Skoura A, Offermanns S, Miano JM, Sessa WC. 2010; MicroRNAs are necessary for vascular smooth muscle growth, differentiation, and function. Arteriosclerosis, thrombosis, and vascular biology. 30 (6) 1118–1126.

[74] Matkovich SJ, Van Booven DJ, Youker KA, Torre-Amione G, Diwan A, Eschenbacher WH, Dorn LE, Watson MA, Margulies KB, Dorn GW. 2009. Reciprocal Regulation of Myocardial microRNAs and Messenger RNA in Human Cardiomyopathy and Reversal of the microRNA Signature by Biomechanical Support. Circulation. 119 (9) 1263–U1277.

[75] van Rooij E, Sutherland LB, Liu N, Williams AH, McAnally J, Gerard RD, Richardson JA, Olson EN. 2006b. A signature pattern of stress-responsive microRNAs that can evoke cardiac hypertrophy and heart

failure. Proceedings of the National Academy of Sciences of the United States of America. 103 (48) 18255–18260.

[76] Thum. 2007. MicroRNAs in the human heart: A clue to fetal gene reprogramming in heart failure. 116: 258. 2007; Circulation. 116 (6) E135–E135.

[77] Son DJ, Kumar S, Takabe W, Kim CW, Ni CW, Alberts-Grill N, Jang IH, Kim S, Kim W, Won Kang S, Baker AH, Woong Seo J, Ferrara KW, Jo H (2013). The atypical mechanosensitive microRNA-712 derived from pre-ribosomal RNA induces endothelial inflammation and atherosclerosis. Nature Communications. 4: 3000.

[78] Keller T, Boeckel JN, Groß S, Klotsche J, Palapies L, Leistner D, et al. 2017. Improved risk stratification in prevention by use of a panel of selected circulating microRNAs. Scientific Reports. 7 (1): 4511.

[79] Yang B, Lin H, Xiao J, Lu Y, Luo X, Li B, Zhang Y, Xu C, Bai Y, Wang H, Chen G, Wang Z. 2007. The muscle-specific microRNA miR-1 regulates cardiac arrhythmogenic potential by targeting GJA1 and KCNJ2. Nature Medicine. 13 (4): 486–91.

[80] Basu R, Fan D, Kandalam V, Lee J, Das SK, Wang X, Baldwin TA, Oudit GY, Kassiri Z. 2012. Loss of Timp3 gene leads to abdominal aortic aneurysm formation in response to angiotensin II. The Journal of Biological Chemistry. 287 (53): 44083–96.

[81] Phua YL, Chu JY, Marrone AK, Bodnar AJ, Sims-Lucas S, Ho J. 2015. Renal stromal miRNAs are required for normal nephrogenesis and glomerular mesangial survival. Physiological Reports. 3 (10): e12537.

[82] Maes OC, Chertkow HM, Wang E, Schipper HM. May 2009. MicroRNA: Implications for Alzheimer Disease and other Human CNS Disorders. Current Genomics. 10 (3): 154–68.

[83] Cuellar TL, Davis TH, Nelson PT, Loeb GB, Harfe BD, Ullian E, McManus MT. 2008. Dicer loss in striatal neurons produces behavioral and neuroanatomical phenotypes in the absence of neurodegeneration. Proceedings of the National Academy of Sciences. 105 (14): 5614–19.

[84] Hébert SS, Papadopoulou AS, Smith P, Galas M, Planel E, Silahtaroglu AN, Sergeant N, Buée L, De Strooper B 2010. Genetic ablation of Dicer in adult forebrain neurons results in abnormal tau hyperphosphorylation and neurodegeneration. Human Molecular Genetics. 19 (20): 3959–69.

[85] Hommers LG,Domschke K, Deckert J. 2015). Heterogeneity and individuality: microRNAs in mental disorders. Journal of Neural Transmission. 122 (1): 79–97.

[86] Hosseinian S,Arefian A, Rakhsh-Khorshid H. 2020. A meta-analysis of gene expression data highlights synaptic dysfunction in the hippocampus of brains with Alzheimer's disease. Scientific Reports. 10 (1): 8384.

[87] Amin ND, Bai G, Klug JR, Bonanomi D, Pankratz MT, Gifford WD, Hinckley CA, Sternfeld MJ, Driscoll SP, Dominguez B, Lee KF, Jin X, Pfaff SL. 2015. Loss of motoneuron-specific microRNA-218 causes systemic neuromuscular failure. Science. 350 (6267): 1525–9.

[88] "Stroke Facts | cdc.gov". www.cdc.gov. 15 March 2019. Retrieved 5 December 2019.

[89] Rink C, Khanna S 2011. MicroRNA in ischemic stroke etiology and pathology. Physiological Genomics. 43 (10): 521–528.

[90] Ouyang YB, Stary CM, Yang GY, Giffard R. 2013. microRNAs: innovative targets for cerebral ischemia and stroke. Current Drug Targets. 14 (1): 90–101.

[91] Lewohl JM, Nunez YO, Dodd PR, Tiwari GR, Harris RA, Mayfield RD. 2011. Up-regulation of microRNAs in brain of human alcoholics. Alcoholism: Clinical and Experimental Research. 35 (11): 1928–37.

[92] Tapocik JD, Solomon M, Flanigan M, Meinhardt M, Barbier E, Schank JR, Schwandt M, Sommer WH, Heilig M. 2013. Coordinated dysregulation of mRNAs and microRNAs in the rat medial prefrontal cortex following a history of alcohol dependence. The Pharmacogenomics Journal. 13 (3): 286–96.

[93] Gorini G, Nunez YO, Mayfield RD. 2013. Integration of miRNA and protein profiling reveals coordinated neuroadaptations in the alcohol-dependent mouse brain. PLOS ONE. 8 (12): e82565. Bibcode:2013PLoSO...882565G.

[94] Lippai D, Bala S, Csak T, Kurt-Jones EA, Szabo G. 2013. Chronic alcohol-induced microRNA-155 contributes to neuroinflammation in a TLR4-dependent manner in mice. PLOS ONE. 8 (8): e70945.

[95] Li J, Li J, Liu X, Qin S, Guan Y, Liu Y, Cheng Y, Chen X, Li W, Wang S, Xiong M, Kuzhikandathil EV, Ye JH, Zhang C 2013. MicroRNA expression profile and functional analysis reveal that miR-382 is a critical novel gene of alcohol addiction. EMBO Molecular Medicine. 5 (9): 1402–14.

[96] Tapocik JD, Barbier E, Flanigan M, Solomon M, Pincus A, Pilling A, Sun H, Schank JR, King C, Heilig M. March 2014. microRNA-206 in rat medial prefrontal cortex regulates BDNF expression and alcohol drinking. The Journal of Neuroscience. 34 (13): 4581–8.

[97] Romao JM, Jin W, Dodson MV, Hausman GJ, Moore SS, Guan LL. 2011. MicroRNA regulation in mammalian adipogenesis. Experimental Biology and Medicine. 236 (9): 997–1004.
[98] Skårn M, Namløs HM, Noordhuis P, Wang MY, Meza-Zepeda LA, Myklebost O (April 2012). "Adipocyte differentiation of human bone marrow-derived stromal cells is modulated by microRNA-155, microRNA-221, and microRNA-222". Stem Cells and Development. 21 (6): 873–83. doi:10.1089/scd.2010.0503. hdl:10852/40423. PMID 21756067.
[99] Zuo Y, Qiang L, Farmer SR March 2006. Activation of CCAAT/enhancer-binding protein (C/EBP) alpha expression by C/EBP beta during adipogenesis requires a peroxisome proliferator-activated receptor-gamma-associated repression of HDAC1 at the C/ebp alpha gene promoter". The Journal of Biological Chemistry. 281 (12): 7960–7.
[100] Frost RJ, Olson EN 2011. Control of glucose homeostasis and insulin sensitivity by the Let-7 family of microRNAs. Proceedings of the National Academy of Sciences of the United States of America. 108 (52): 21075–80. Bibcode:2011PNAS.10821075F.
[101] Zhu H, Shyh-Chang N, Segrè AV, Shinoda G, Shah SP, Einhorn WS, Takeuchi A, Engreitz JM, Hagan JP, Kharas MG, Urbach A, Thornton JE, Triboulet R, Gregory RI, Altshuler D, Daley GQ. 2011. The Lin28/let-7 axis regulates glucose metabolism. Cell. 147 (1): 81–94.
[102] Jun-Hao ET, Gupta RR, Shyh-Chang N. 2016. Lin28 and let-7 in the Metabolic Physiology of Aging. Trends in Endocrinology and Metabolism. 27 (3): 132–141.
[103] Teruel-Montoya R, Rosendaal FR, Martínez C. 2015. MicroRNAs in hemostasis. Journal of Thrombosis and Haemostasis. 13 (2): 170–181.
[104] Nourse J, Braun J, Lackner K, Hüttelmaier S, Danckwardt S. 2018. Large-scale identification of functional microRNA targeting reveals cooperative regulation of the hemostatic system. Journal of Thrombosis and Haemostasis. 16 (11): 2233–2245.
[105] Nourse J, Danckwardt S. 2021. A novel rationale for targeting FXI: Insights from the hemostatic microRNA targetome for emerging anticoagulant strategies. Pharmacology & Therapeutics. 218: 107676.
[106] Qian K, Hu L, Chen H, Li H, Liu N, Li Y, et al. 2009. Hsa-miR-222 is involved in differentiation of endometrial stromal cells in vitro. Endocrinology. 150:4734–4743.
[107] Nothnick WB, Healy C, Hong X. 2010. Steroidal regulation of uterine miRNAs is associated with modulation of the miRNA biogenesis components Exportin-5 and Dicer1. Endocrine. 37:265–273.
[108] Xia HF, Jin XH, Song PP, Cui Y, Liu CM, Ma X. 2010. Temporal and spatial regulation of miR-320 in the uterus during embryo implantation in the rat. Int J Mol Sci. 11:719–730.
[109] Xia HF, Jin XH, Song PP, Cui Y, Liu CM, Ma X. 2010. Temporal and spatial regulation of let-7a in the uterus during embryo implantation in the rat. J Reprod Dev. 56:73–78.
[110] Zhu XM, Han T, Wang XH, Li YH, Yang HG, Luo YN, et al. 2010. Overexpression of miR-152 leads to reduced expression of human leukocyte antigen-G and increased natural killer cell mediated cytolysis in JEG-3 cells. Am J Obstet Gynecol. 202:592. e1–592.e7.
[111] Williams KC, Renthal NE, Gerard RD, Mendelson CR. 2012. The microRNA (miR)-199a/214 cluster mediates opposing effects of progesterone and estrogen on uterine contractility during pregnancy and labor. Mol Endocrinol. 26:1857–1867.
[112] Liu F, Lou YL, Wu J, Ruan QF, Xie A, Guo F, et al. 2012. Upregulation of microRNA-210 regulates renal angiogenesis mediated by activation of VEGF signaling pathway under ischemia/perfusion injury in vivo and in vitro. Kidney Blood Press Res. 35:182–191.
[113] Morandi F, Pistoia V. 2013. Soluble HLA-G modulates miRNA-210 and miRNA-451 expression in activated CD4+ T lymphocytes. Int Immunol.25:279–285.
[114] Bortolin-Cavaille ML, Dance M, Weber M, Cavaille J. 2009. C19MC microRNAs are processed from introns of large Pol-II, non-protein-coding transcripts. Nucleic Acids Res. 37:3464–3473
[115] Luo L, Ye G, Nadeem L, Fu G, Yang BB, Honarparvar E, et al. 2012. MicroRNA-378a-5p promotes trophoblast cell survival, migration and invasion by targeting Nodal. J Cell Sci. 125:3124–3132.
[116] Donker RB, Mouillet JF, Chu T, Hubel CA, Stolz DB, Morelli AE, et al. 2012. The expression profile of C19MC microRNAs in primary human trophoblast cells and exosomes. Mol Hum Reprod. 18:417–424.
[117] Kurashina R, Kikuchi K, Iwaki J, Yoshitake H, Takeshita T, Takizawa T. 2014. Placenta-specific miRNA (miR-512-3p) targets PPP3R1 encoding the calcineurin B regulatory subunit in BeWo cells. J ObstetGynaecol Res. 40:650–660.
[118] Qureshi A, Thakur N, Monga I, Thakur A, Kumar M (1 January 2014). "VIRmiRNA: a comprehensive resource for experimentally validated viral miRNAs and their targets". Database. 2014: bau103. doi:10.1093/database/bau103. PMC 4224276. PMID 25380780.
[119] Kumar M. "VIRmiRNA". Resource for experimental viral miRNA and their targets. Bioinformatics center, CSIR-IMTECH.

[120] Tuddenham L, Jung JS, Chane-Woon-Ming B, Dölken L, Pfeffer S (February 2012). "Small RNA deep sequencing identifies microRNAs and other small noncoding RNAs from human herpesvirus 6B". Journal of Virology. 86 (3): 1638–49. doi:10.1128/JVI.05911-11. PMC 3264354. PMID 22114334.

[121] Zheng H, Fu R, Wang JT, Liu Q, Chen H, Jiang SW (April 2013). "Advances in the techniques for the prediction of microRNA targets". International Journal of Molecular Sciences. 14 (4): 8179–87. doi:10.3390/ijms14048179. PMC 3645737. PMID 23591837.

[122] Agarwal V, Bell GW, Nam JW, Bartel DP (August 2015). "Predicting effective microRNA target sites in mammalian mRNAs". eLife. 4: e05005. doi:10.7554/eLife.05005. PMC 4532895. PMID 26267216.

[123] Ai J, Zhang R, Li Y, Pu JL, Lu YJ, Jiao JD, Li K, Yu B, Li ZQ, Wang RR, Wang LH, Li Q, Wang N, Shan HL, Li ZY, Yang BF. 2010. Circulating microRNA-1 as a potential novel biomarker for acutemyocardial infarction. BiochemBioph Res Co. 391 (1) 73–77.

[124] Wang GK, Zhu JQ, Zhang JT, Li Q, Li Y, He J, Qin YW, Jing Q. 2010. Circulating microRNA: a novel potential biomarker for early diagnosis of acute myocardial infarction in humans. Eur Heart J. 31(6) 659–666.

[125] Sempere LF, Freemantle S, Pitha-Rowe I, Moss E, Dmitrovsky E, Ambros V. 2004. Expression profiling of mammalian microRNAs uncovers a subset of brain-expressed microRNAs with possible roles in murine and human neuronal differentiation. Genome biology. 5 (3)

[126] Thomson JM, Parker J, Perou CM, Hammond SM. 2004. A custom microarray platform for analysis of microRNA gene expression. Nat Methods. 1 (1) 47–53.

[127] Valoczi A, Hornyik C, Varga N, Burgyan J, Kauppinen S, Havelda Z. 2004. Sensitive and specific detection of microRNAs by northern blot analysis using LNA-modified oligonucleotide probes. Nucleic Acids Res. 32 (22)

[128] Chen CF, Ridzon DA, Broomer AJ, Zhou ZH, Lee DH, Nguyen JT, Barbisin M, Xu NL, Mahuvakar VR, Andersen MR, Lao KQ, Livak KJ, Guegler KJ. 2005. Real-time quantification of microRNAsby stem-loop RT-PCR. Nucleic Acids Res. 33 (20).

[129] Corsten MF, Dennert R, Jochems S, Kuznetsova T, Devaux Y, Hofstra L, Wagner DR, Staessen JA, Heymans S, Schroen B. 2010. Circulating MicroRNA-208b and MicroRNA-499 ReflectMyocardial Damage in Cardiovascular Disease. Circ-Cardiovasc Gene. 3 (6) 499–506.

[130] Kloosterman WP, Wienholds E, de Bruijn E, Kauppinen S, Plasterk RHA. 2006. In situ detection of miRNAs in animal embryos using LNA-modified oligonucteotide probes. Nat Methods. 3 (1) 27–29.

[131] Wang J, Chen JY, Chang P, LeBlanc A, Li DH, Abbruzzesse JL, Frazier ML, Killary AM, Sen S. 2009. MicroRNAs in Plasma of Pancreatic Ductal Adenocarcinoma Patients as Novel Blood-Based Biomarkers of Disease. Cancer Prev Res. 2 (9) 807–813.

[132] Wang J, Paris PL, Chen JY, Ngo V, Yao H, Frazier ML, Killary AM, Liu CG, Liang H, MathyC, Bondada S, Kirkwood K, Sen S. 2015; Next generation sequencing of pancreatic cyst fluid microRNAs from low grade-benign and high grade-invasive lesions. Cancer Lett. 356 (2) 404–409.

