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Review Article

Relation of Circulating MicroRNAs as Biomarkers in few Diseases

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Abstract

The abundance of circulating miRNAs which are small non-coding RNAs involved in posttranscriptional regulation of gene expression in body fluids of patients with cancers, cardiovascular diseases, neurological diseases, autoimmune and infectious diseases hold great promise to identify stable and specific biomarkers, which may be useful for early diagnosis as well as to predict the clinical outcome and treatment response. Because of an aberrant miRNA expression, emerging theme for a wide variety of diseases, highlighting the fundamental role played by miRNAs in both physiological and pathological states. Recent studies have reported significant levels of miRNAs in serum and other body fluids, raising the possibility that circulating miRNAs could serve as useful clinical biomarker. We review the disease and cancer-specific profiles of circulating microRNAs. We also discuss possible functions of circulating microRNAs and their potential as non-invasive biomarkers.

Keywords: Biomarker, circulating mi RNA, cancer, cardiovascular diseases.

Introduction

Research of microRNA (miRNA) in cancer, cardiovascular and neurological diseases is an emerging field with potential novel applications in diagnostics and therapy.[1] These non-coding RNA with 18-25 nucleotides function in RNA silencing and post-transcriptional regulation of gene expression. More than 19,000 entries of miRNAs exists in the database from 168 species and 1,612 of them belongs to homo sapiens. [2]

Biogenesis and origin of miRNA

miRNA regulates gene expression by promoting mRNA degradation or by attenuating protein translation. It is estimated by computational prediction that more than 60% of mammalian mRNAs are targeted by at least one miRNA.[3] Significant number of miRNAs have been observed in extracellular fluids.[4] These secreted miRNAs are found to be stable against ribonucleases, as they may be packed in lipid vesicles or form complexes with RNA-binding proteins.[5-7] There presence in saliva, urine and plasma supports its role in signaling via the microvesicles and exosomes.[8,9] Although most miRNA sequences are found across species, some expressions are tissue specific and can be easily measured by PCR. All these characteristics makes it a good biomarker.

miRNA in cancers

miRNA is identified as an important biomarker in cancer diagnosis and treatment. [10] Many studies have strengthened the importance of miRNA as a cancer diagnostic tool. Wu and colleagues found that miR-21 and 29 were significantly upregulated in breast cancers.[11] Barroso-del and colleagues found that seven miRNAs namely miR-10b, 21, 125b, 145, 155, 191, and miR-382 had different patterns in the serum of patients with breast cancers compared to the controls. Three of these serum

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miRNAs could be valuable biomarkers as revealed by ROC curve analysis.

Even though serum miRNA-122a levels correlates as a marker for hepatocellular cancer, it is not superior to alfa-feto protein as a diagnostic tool.[12] In lung cancers including stage-I disease the plasma levels of miR-155, 197 and miR-182 severe significantly elevated compared to controls.[13] Sixty three miRNAs that were absent in the controls were found in the sera of non-small cell lung cancer patients (NSCLC).[14] Kannan and colleagues found that 380 miRNAs were dysregulated in the tissues of colorectal cancer (CRC).

The two most upregulated miRNAs 31and 135b and most downregulated miRNAs 1and 133a could identify CRC with 100% sensitivity and 80% specificity.[15] In CRC stages III and IV miR-31 was more upregulated compared to stages I and II. Whereas in the plasma group miR-21 differentiated CRC patients from controls with 90% sensitivity and specificity.[16] miR-133 and 155a have been shown to be the best combination biomarkers in identifying oral squamous cell carcinoma.[17] In gastric cancer, the serum levels of upregulated miRNAs miR-21 and 106 b are higher before surgical resection and reduces significantly after resection.[18] Serum miR-21, 146a and 148a are closely associated with gastric cancer pN stage and could be biomarker candidates to predict lymph node metastasis.[19] Plasma levels of miR-21, 210, 155 and miR-196a can differentiate pancreatic adenocarcinoma.[20]

In adult leukemia there is a decrease in miR-92a levels in the plasma. A specific profile is also observed in CLL and can help differentiate from multiple myeloma and hairy-cell leukemia. The miR marker for CLL correlates well with ZAP-70 status used as a prognostic marker and is also useful to stratify CLL.[21] miRNAs 425-5p and 93-5p are found abundantly in plasma following radiotherapy of HNSCC and may represent as novel biomarkers for therapy monitoring. Application of circulating miRNAs in cancer.

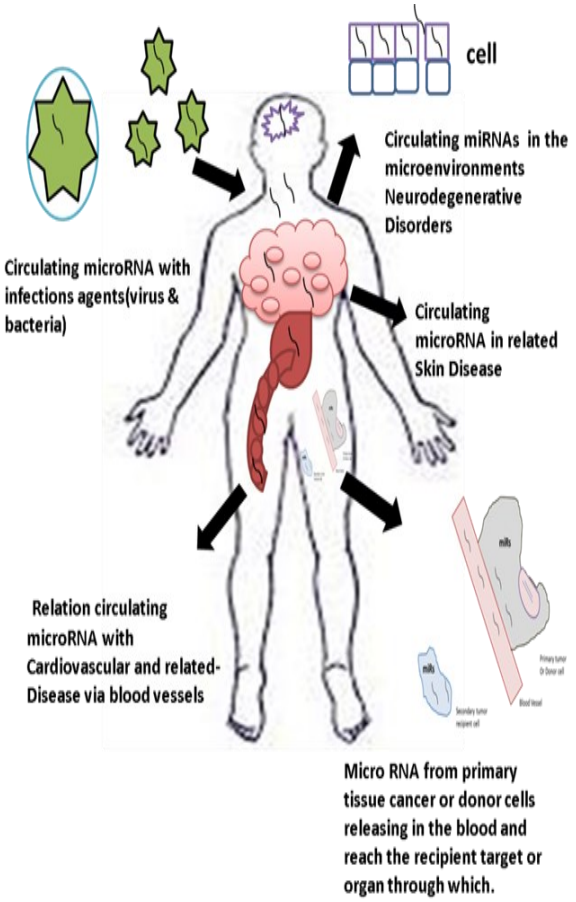

Fig 1. Schematic view of free Micro RNA in certain disease

Circulating microRNA in cardiovascular diseases

Since the discovery of circulating biomarkers, a vast literature exists on its role in relation to cardiovascular disease such as myocardial infarction, heart failure atherosclerosis and hypertension.[22] In early studies four cardiac miRNAs namely miR-208a, miR-499, miR-1, and miR-133 are found to be consistently elevated in plasma of AMI patients within hours after the onset of infarction.[23] miR-1,miR-133a, and more particularly miR-208a may even be more sensitive than the classic biomarker cTnI.[24] Reduced levels of miR-126, miR-15a, miR-29b, and miR-223 and elevated levels of miR-28-3p were reported in this study. Levels of cTN-I and NT-pro-BNP were positively correlated with miR-21 and negatively correlated with miR-126. Integrating specific pattern of miRNA levels with NT-pro-

BNP and/or cardiac troponin may improve the diagnosis of cardiovascular diseases.[25] Compared to the other microRNAs, miR-208a biomarkers can be used for early detection of AMI and MiR-1 and miR-133 may also serve to diagnose AMI.[26] miR-1 and miR-133a levels may be correlated with muscle creatine kinase levels and cTnI levels in plasma and are affected by pathology of other organs, as these miRNAs levels have also been found to increase in lung cancer and colorectal cancer. The combined assessment of the 2 myo-miRs miR-208a and miR-499 may provide an attractive signature to diagnose both acute and very recent cardiac injury miR-208, whereas miR-499 due to its role in the inflammatory process can trace myocardial injury.[27] In one of the most accepted studies, the lower levels of miR-126 were also found in atherosclerotic CAD and in patients with type 2 diabetes mellitus and may reflect the condition of vascular endothelial cells in HF patients. miR-126, miR-92a and miR-17 are determined as the most promising miRNA biomarkers in diagnosis of patients with CAD. [28]

Circulating miRNAs as biomarkers in neurodegenerative disorders

Studies show the association between circulating biomarkers packed in carriers and suspended in the fluid, and neuro degenerative diseases.[29] Study on the PBMCs identified significantly under-expressed miRNAs and showed miR-103 and miR-107 suppress Cofilin translation with the increased level of active Cofilin protein, which leads in the Cofilin rods formation.[30]

Another study using qRT-PCR, suggested that miR-1, miR-22-5p and miR-29 expression levels in total peripheral blood allow to distinguish non-treated PD from healthy subjects, and that miR-16-2-3p, miR-26a-2-3p and miR30a differentiate treated from untreated patients.[31] Among all the known miRNAs, some regulate the neuron development process, such as neurogenesis, synaptic formation, and stem cell differentiation such as miR-9, miR-124a, miR-124b, miR-135, and miR-219. Circulating miR-223 is the marker for acute ischemic stroke.[32] miR-132 and miR-212 are involved in several abnormalities like synaptic plasticity and connectivity in Schizophrenia and in neuronal cultures, the mature miR-132 stability is affected by NMDA inhibition.

Circulating microRNA in skin and autoimmune disease

As the diseases affecting the skin and immune system are closely related the circulating biomarkers are found to work well in their diagnosis and prognosis.[33] Serum miR-21 levels were significantly up-regulated, correlating with serum IgG levels in dermatomyositis. Serum levels of miR-223 and miR-7 were down-regulated , while serum miR-142-3p and miR-92 was not changed in dermatomyositis patients.[34] Psoriatic patients have positive association with cardiovascular diseases, so that the expression of cell-free circulating microRNA-33 and microRNA-126 in plasma from psoriatic patients and the relationship with clinical parameters have been identified. Similarly, Pivarcsi and colleagues recently reported up - or downregulation of miR-128a, let-7d, miR-142-3p and miR-181a in sera from psoriasis patients compared with normal subjects.[35]

In another study Serum miR-150 levels were found to be decreased in Systemic Sclerosis (SSc) patients.[36] Patients with lower serum miR-150 levels had more severe clinical manifestations. Patients with lower serum miR-196a levels had a significantly higher ratio of diffuse cutaneous scleroderma (dSSc) limited cutaneous sclerodermal lesion, a higher modified Rodnan total skin thickness score, and a higher prevalence of pitting scars than those with higher miR-196a levels.[37] Patients with SSc showed miR-142-3p levels which were significantly higher than those in patients with systemic lupus erythematosus, dermatomyositis and scleroderma.[38] Serum level of miR-142-3p correlated with the severity of SSc fibrosis and may be useful diagnostic markers for the presence of SSc and differentiation of SSc from scleroderma spectrum disorder.[39, 40]

Table 1. Circulating micro-RNA association with clusters of diseases

Disease	miRNA type
Cardiovascular disease	
Acute myocardial infarction	miR-1, miR-208b, miR-499, miR-30a, miR-126, miR-195
Coronary arterial disease	miR-17/92cluster, miR-155, miR-145, miR-135a, miR-145
Type II diabetes	miR-9, miR-29a, miR-30d, miR34a, miR-124a, miR146a, and miR-375
Neurodegenerative disorders	
Parkinson's disease	miR-1, miR-22-5p, miR-16-2-3p, miR-26a-2-3p and miR30a, miR-10b, miR-21, miR-125b, miR-141, miR-200a, miR-200b, and miR-200c
Alzheimer's disease	as miR-9, miR-124a, miR-124b, miR-135, and miR-219 miR -223
Huntington's disease	hsa-let-7f, miR-126, -1259, -142-3p, -15b, -186, -519e and -768-5p
Stroke	hsa-let-7e, miR-1184, -1246, -1261, -1275, -1285, -1290, -181a, -25*, -513a-5p, -550, -602, -665, -891a, -933, -939
Skin and autoimmune-disease	
Psoriasis	miR-223 , miR-7
Systemic Sclerosis	miR-128a, let-7d, miR-142-3p , miR-181a, miR-142-3p
SSE	miR-16, miR-223, miR-451, miR-21

Table 2. Circulating micro-RNA association with clusters of infectious diseases

Virusal and bacterial infections	miRNA type
Esptein Barr virus	miR-BART17-5p, miR-122,
Chronic hepatitis C	miR-34a, miR-16 and miR-21, miR-146a, miR-125b
Tuberculosis	hsa-miR-378, hsa-miR-483-5p, hsa-miR-22, hsa-miR-29c, hsa-miR-101 and hsa-miR-320b
Bacille Calmette Guérin	mmu-miR-31, mmu-miR-150, and mmu-miR-146a, miR-155 and miR-155

Circulating microRNA and viral and bacterial infections

Viral and bacterial infections have been associated with cf-microRNA and there is significant development of many biomarkers for their early detection. Presence of circulating miR-BART17-5p and EBV DNA in a larger series of nasopharyngeal carcinoma (NPC) plasma samples have been shown.[41,42] Serum miR-122 may serve as a surrogate of hepatic miR-122, and a higher pretreatment serum miR-122 level can help predict virologic responses to pegylated IFN plus ribavirin therapy. Serum levels of miR-34a and miR-122 may represent novel, noninvasive biomarkers of diagnosis and histological disease severity in patients with chronic hepatitis C infection (CHC).[43] Serum levels of miR-122 were elevated in cHCV patients and correlated with increased ALT and AST levels and serum miR-155 levels. [44] Three microRNAs with higher expression in active tuberculosis patients have been positively evaluated for use as a biomarker namely miR-155, in stimulated PBMCs.[45] and miR-29a in pooled serum.[46] (Table 2). In addition to expression analysis, microRNA single nucleotide polymorphism (SNP) analysis has revealed a correlation between SNPs in miR-146a (rs2910164) and miR-499 (rs3746444) and increased pulmonary tuberculosis susceptibility in certain populations.

Conclusion

Extensive research on miRNA biomarkers in exosomes are providing potential information on diagnosis, management and prognosis of diseases. Many challenges exists in studying miRNAs and more sensitive methods to detect them are being developed.

References

1. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004.116; 2: 281-97.
2. Available at http:// www.mir2disease.org
3. Berezikov E, Cuppen E. Approaches to microRNA discovery. Nature genetics 2006. 38: S2-S7.
4. Chim SS, Shing TK. Detection and characterization of placental microRNAs in maternal plasma. Clinical chemistry 2008. 5; 43: 482-90.
5. Friedman RC, Farh KKH. Most mammalian mRNAs are conserved targets of microRNAs. Genome research 2009; 19: 92-105.
6. Mitchell PS, Parkin RK. Circulating microRNAs as stable blood-based markers for cancer detection. Proceedings of the National Academy of Sciences 2008; 105 (30): 10513-518.
7. Turchinovich AL. Weiz. Characterization of extracellular circulating microRNA. Nucleic acids research: gkr 2011; 254.
8. Turchinovich A, Weiz L. Extracellular miRNAs: the mystery of their origin and function. Trends in biochemical sciences 2011; 37(11): 460-65.
9. Song My, Pan Kf. Identification of serum microRNAs as novel non-invasive biomarkers for early detection of gastric cancer. PLoS One 2012; (7)3: e33608.
10. Calin GA, Croce CM. MicroRNA signatures in human cancers. Nature Reviews Cancer 2006; 6(11): 857-66.
11. Wu J, Lu C. Analysis of microRNA expression profiling identifies miR-155 and miR-155* as potential diagnostic markers for active tuberculosis: a preliminary study. Human immunology 2012;73(1): 31-37.
12. Luo J, Chen M. Circulating microRNA-122a as a diagnostic marker for hepatocellular carcinoma. OncoTargets and therapy 2013. 6: 577.
13. Zheng D, Haddadin S. Plasma microRNAs as novel biomarkers for early detection of lung cancer. International journal of clinical and experimental pathology 2011; 4(6): 575.
14. Chen X, Ba Y. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. Cell research 2008; 18(10): 997-1006.

15. Kanaan Z, Rai SN. Plasma miR-21: a potential diagnostic marker of colorectal cancer. Annals of surgery 2012; 256(3): 544-51.

16. Rabinowits G, Gerçel-Taylor C. Exosomal microRNA: a diagnostic marker for lung cancer. Clinical lung cancer 2009;10(1): 42 -46.

17. Shiiba M, Uzawa K. MicroRNAs in head and neck squamous cell carcinoma (HNSCC) and oral squamous cell carcinoma OSCC. Cancers 2010; 2(2): 653-69.

18. Rotkrua P, Shimada S. Circulating microRNAs as biomarkers for early detection of diffuse-type gastric cancer using a mouse model. British journal of cancer 2013. 108; 4: 932-40.

19. Kim SY, Jeon TY. Validation of circulating miRNA biomarkers for predicting lymph node metastasis in gastric cancer. The Journal of Molecular Diagnostics2013; 15(5): 661-69.

20. Wang J, Chen J. MicroRNAs in plasma of pancreatic ductal adenocarcinoma patients as novel blood-based biomarkers of disease. Cancer prevention research 2009; 2 (9): 807-13.

21. Tanaka M, Oikawa K, et al. 2009. Down-regulation of miR-92 in human plasma is a novel marker for acute leukemia patients. PloS one 4; 5: e5532.

22. Januzzi JL, van R. Kimmenade. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients. European heart journal 2006. 27; 3: 330-37.

23. Dickinson BA, Semus HM. Plasma microRNAs serve as biomarkers of therapeutic efficacy and disease progression in hypertension-induced heart failure. European journal of heart failure 2013; 15(6): 650-59.

24. Cheng Y, Tan N. A translational study of circulating cell-free microRNA-1 in acute myocardial infarction. Clinical Science 2010; 119: 87-95.

25. Jiang Y, Wang Hy, et al.2014. Peripheral blood miRNAs as a biomarker for chronic cardiovascular diseases. Scientific reports 4.

26. Fukushima Y, Nakanishi M. Assessment of plasma miRNAs in congestive heart failure. Circulation Journal 2011; 75(2): 336-40.

27. Adachi T, Nakanishi M. Plasma microRNA 499 as a biomarker of acute myocardial infarction. Clinical chemistry 2010; 56(7): 1183-185.

28. Bonora E, Kiechl S. Population-based incidence rates and risk factors for type 2 diabetes in White individuals The Bruneck Study. Diabetes 2004; 53(7): 1782-789.

29. Teplyuk NM, Mollenhauer B. MicroRNAs in cerebrospinal fluid identify glioblastoma and metastatic brain cancers and reflect disease activity. Neuro-oncology: nos 2012. 074.

30. Mok SS, Losic D. The β-amyloid peptide of Alzheimer's disease decreases adhesion of vascular smooth muscle cells to the basement membrane. Journal of neurochemistry 2006; 96(1): 53-64.

31. Liu DZ, Tian Y. Brain and blood microRNA expression profiling of ischemic stroke, intracerebral hemorrhage, and kainate seizures. Journal of Cerebral Blood Flow & Metabolism 2010; 3(1): 92-101.

32. Hu S, Huang M. MicroRNA-210 as a novel therapy for treatment of ischemic heart disease. Circulation 2010; 122(11) suppl 1: S124-S131.

33. Oshikawa, Y., M. Jinnin. Decreased miR-7 expression in the skin and sera of patients with dermatomyositis. Acta dermato-venereologica 2013; 93(3): 273-76.

34. Ahmed FE, Jeffries CD. Diagnostic microRNA markers for screening sporadic human colon cancer and active ulcerative colitis in stool and tissue. Cancer Genomics -Proteomics 2009; 6(5): 281-95.

35. Pivarcsi A, Meisgen F. Changes in the level of serum microRNAs in patients with psoriasis after antitumour necrosis factor-α

therapy. British Journal of Dermatology 2013; 169(3): 563-70.

36. Takemoto R, Jinnin M. Hair miR-29a levels are decreased in patients with scleroderma. Experimental dermatology 2013; 22 (12): 832-33.

37. Zhao X, Tang Y. MicroRNA-125a contributes to elevated inflammatory chemokine RANTES levels via targeting KLF13 in systemic lupus erythematosus. Arthritis & Rheumatism 2010; 62(11): 3425-435.

38. Menéndez P, Villarejo P. Serum microRNA-21 usefulness in inflammatory pathology of the colon. Revista de Gastroenterología de México 2013; 78(02): 70-74.

39. Fields PE, Kim ST. Cutting edge: changes in histone acetylation at the IL-4 and IFN-γ loci accompany Th1/Th2 differentiation. The Journal of Immunology 2002; 169(2): 647-50.

40. Hughes T, Webb R. DNA methylome in human CD4+ T cells identifies transcriptionally repressive and non-repressive methylation peaks. Genes and immunity 2010; 11(7): 554-60.

41. Gourzones C, Gelin A. Extra-cellular release and blood diffusion of BART viral microRNAs produced by EBV-infected nasopharyngeal carcinoma cells. Virol J 2010; 7 271: 1-12.

42. Gourzones C, Ferrand FR. Consistent high concentration of the viral microRNA BART17 in plasma samples from nasopharyngeal carcinoma patients-evidence of non-exosomal transport. Virol J 2013; 10 (1): 119.

43. Bihrer V, Friedrich-Rust M. Serum miR-122 as a biomarker of necroinflammation in patients with chronic hepatitis C virus infection. The American journal of gastroenterology 2011; 106(9): 1663-669.

44. Xu G, Zhang Z. microR-142-3p downregulates IRAK-1 in response to Mycobacterium bovis BCG infection in macrophages. Tuberculosis 2013; 93(6): 606-11.

45. Wu J, Lu C. Analysis of microRNA expression profiling identifies miR-155 and miR-155* as potential diagnostic markers for active tuberculosis: a preliminary study. Human immunology 2012; 73(1): 31-37.

46. Zhang X, Guo J, 13. Screening and identification of six serum microRNAs as novel potential combination biomarkers for pulmonary tuberculosis diagnosis.