Med Discoveries
An open access journal of science and medicine

Article Type: Review Article
Volume 2, Issue 9
Received: Aug 20, 2023
Accepted: Sep 08, 2023
Published Online: Sep 15, 2023

Disease and Circulating miRs: Updated in the Medical World

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Abstract

The abundance of circulating miRNAs-small non-coding RNAs involved in posttranscriptional regulation of gene expression- in body fluids of cancer patients holds 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. Aberrant miRNA expression is an emerging theme in 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 the serum and other body fluids, raising the possibility that circulating miRNAs could serve as useful clinical biomarkers. We reviewed the disease- and cancer-specific profiles of circulating miRNAs. We also discuss the possible functions of circulating miRNAs and their potential as non-invasive biomarkers.

Keywords: Biomarker; Circulating micro RNA; Disease; Cancer.

Introduction

The introduction of miRNAs is an emerging feature in cancer and disease research, with potential novel applications in diagnostics and therapy [1]. miRNAs are a newly discovered class of short RNAs, 18-25 nucleotides in length. Despite regulating gene expression in a post-transcriptional manner, epigenetic relationships between these gene sites and areas are clear [2,3]. miRNA expression profiles have been implicated in the control of various developmental and disease states [4,]. The last report from updating (Version 18) the miRBase database (http://mirbase.org/) reports 19,312 entries representing hairpin precursors expressing 21,643 mature miRNA products, in 168 species of which 1,612 cases have been reported for Homo sapiens. The current version of miR2 Disease, a manually created database for miRNA dysregulation in human diseases, documented 3,273 entries linking 349 human miRNAs and 163 diseases (http://www.mir2disease.org/). These biomarkers are important for identifying and representing the most important aspect of sequencing detection. miRNAs can act as regulatory agents [5]. After identifying the role of miRNAs in the development of various human cancers and diseases, cell-free miRNAs (cfmiRNAs) have been shown to be highly stable in various types of body fluids, including the blood [6]. In this Review, we provide an overview of the role of miRNA biomarkers associated with various diseases, infectious agents, and cancers as predictors of the diagnostic address in peripheral blood.

Biogenesis and origin miRNA

miRNAs are short (19-24 nucleotides in length) non-coding RNAs that regulate gene expression at the messenger RNA (mRNA) or protein levels either by promoting mRNA degradation or by attenuating protein translation. Computational predictions have estimated that more than 60% of mammalian mRNAs are targeted by at least one miRNA [7]. In addition, miRNAs were first discovered in Caenorhabditis elegans in the early 1990s [8], the role and function of these RNAs have been proven in many microorganisms [9]. The importance and relationship of cancer tissue microRNAs to patient survival has been shown in many studies; for example, in a study of 143 lung cancer samples from patients who underwent potentially curative resection, it was found that patients could be classified into two major groups according to let-7 expression; reduction of the let-

Citation: Ghazizadeh E, Nasery Z. Disease and Circulating miRs: Updated in the Medical World. Med Discoveries. 2023; 2(9): 1073.

7 expression level was associated with significantly shorter survival after resection. The expression levels of miR-15b, miR-34c, and miR-361 may predict a low risk of tumor recurrence following curative resection, with an overall accuracy of 90% in hepatocellular carcinoma [10]. In liver cancer, the loss of miR-122 expression in tumor cells segregates with specific gene expression profiles linked to cancer progression and gain of metastatic properties as tissue miRNAs [11].

Origin and function of circulating miRNAs

A significant number of miRNAs have been observed outside cells, including in various body fluids [12]. Interestingly, the sustainability of these biomarkers in blood and body fluids against stabilizing factors, such as ribonucleases, is very high [10], which suggests that secreted miRNAs are likely packaged in some manner to protect them against RNase digestion. miRNAs can be shielded from degradation by packaging in lipid vesicles, complexes with RNA-binding proteins, or both [13,14]. An intriguing idea is that extracellular miRNAs are used as mediators of cell-cell communication [15,16]. In such a situation, the isolation of biomarkers from their initial position, blood, and other fluids can be a useful tool for early detection. In fact, based on factors such as biomarker stability, there are two types of cell-derived lipid vesicles: microvesicles and exosomes. Microvesicles are relatively large (~100 nm-1 μm) vesicles that are released from the cell through blebbing. On the other hand, exosomes are smaller vesicles (~30-100 nm) released when endosomal derived multivesicular bodies fuse with the plasma membrane. miRNAs have been identified in both exosomes and microvesicles derived from a variety of sources, including human and mouse mast cells [17], glioblastoma tumors, plasma, saliva, and urine [18]. These findings strongly support the important role of exosomes and microvesicles. However, more extensive research on the stability of the biomarker and the information that can be transmitted via this process is in progress. Secreted miRNAs have many desirable features as good biomarkers. Although most proteins studied as biomarkers are considered, their high cost and inefficient specificity and sensitivity are the main limitations of this study. In addition to their stability in various bodily fluids, secreted miRNAs offer several advantages. Most miRNA sequences are conserved across species; the expression of some miRNAs is specific to tissues or biological stages, and the levels of miRNAs can be easily measured by quantitative PCR, which allows for high-precision signal amplification. Another important point is to express them in some way protected, which can be of great importance in treatment interventions. Even the transportation of these biomarkers through exosomes and the immunological relationship with the drug mechanisms, gate interventional therapy has been smooth, and this approach may hasten the development of personalized medicine and therapy in the clinic. miRNA control approaches in tissues may not be appropriate for body fluids and vice versa in both normal and diseased states [19]. Despite great wonders, there are no strict standards, and we require the use of ultrasensitive methods because of the low concentration of the challenge ahead to identify them [20].

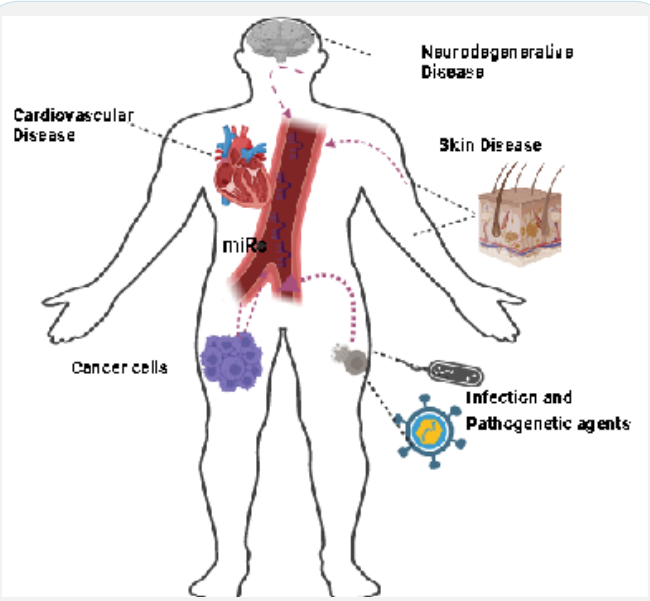

Figure 1: Schematic view of free Micro RNA in connection with certain disease in the body involved.

Application of circulating miRNAs in cancer

One of the most important studies in the field of cancer biomarkers in cancer patients is the identification of significant circulating biomarkers [21]. The first study showed that the serum level of tumor microRNA choir was correlated with improved relapse-free survival in patients with diffuse large B-cell lymphoma; high levels of miR-21 correlated with improved relapse-free survival. In an elegant experiment in a xenograft mouse prostate cancer model, the presence of circulating tumor-derived miR-629 and miR-660 was confirmed in the blood with 100% sensitivity and specificity [22]. Several independent studies have successfully demonstrated the importance of miRNAs as tools for cancer diagnosis. Wu et al. found that miR-21 and miR-29 are significantly upregulated in the serum of breast cancer patients and may be useful biomarkers for breast cancer detection [23,24]. Barroso-del et al. found that seven miRNAs (miR-10b, miR-21, miR-125b, miR-145, miR-155, miR-191, and miR-382) had different expression patterns in the serum of breast cancer patients compared to healthy controls. ROC curve analyses revealed that the three serum miRNAs could be valuable biomarkers for distinguishing breast cancer from normal controls. The microRNA-127, which exhibited reduced expression in 75% of the human cancer cells tested, was significantly increased after treatment [23,25]. Schrauder et al. performed microarray-based miRNA profiling on the whole blood of 48 early stage breast cancer patients at diagnosis, along with 57 healthy individuals as controls. This was followed by real-time semi-quantitative Polymerase Chain Reaction (RT-qPCR) validation in a separate cohort of 24 early stage breast cancer patients from a breast cancer screening unit and 24 age-matched controls using two differentially expressed miRNAs (miR-202 and miR-718) [26]. Serum miRNA-122a levels correlate with risk factors for hepatocellular carcinoma. However, the use of miRNA-122a as a diagnostic tool for hepatocellular carcinoma is not superior to the alpha-fetoprotein. Further analysis is needed to evaluate the diagnostic power of plasma miRNA-122a for hepatocellular carcinoma [27]. Other studies have provided further support for the use of circulating miRNAs as non-invasive biomarkers for a wide range of cancers, conducted extensive studies on liver cancer, and investigated the role of circulating miRNAs in early detection. Zheng and his team reported that the

levels of miR-155, miR-197, and miR-182 in the plasma of lung cancer patients, including stage I cancers, were significantly elevated compared to controls [28]. Moreover, 15 serum miRNAs, including miR-16, miR-92a, and miR-92b, are overexpressed in patients with prostate cancer. In a comprehensive study, miRNA expression profiles were identified in the serum of patients with lung or colorectal cancer or diabetes by extracting miRNAs from the serum. For example, 63 new miRNAs that were absent in normal controls were detected in the sera of patients with Non-Small-Cell Lung Cancer (NSCLC) [29]. All breast cancers were histologically confirmed as early stage invasive ductal carcinoma of the breast, with a tumor size ranging between 0.15 and 4.0 cm. In a study by [30] 19 of 380 miRNAs were dysregulated in CRC tissue in the tissue "training" set (P>0.05, FDR:10%). The 2 most upregulated (miR-31; miR-135b) and most downregulated (miR-1; miR-133a) miRNAs identified CRC in our "test" set with 100% sensitivity and 80% specificity [31,30]. MiR-31 was more upregulated to a greater extent in stages III and IV than in stages I and II (P<0.05). In the "plasma" group, miR-21 differentiated patients with CRC from controls with 90% specificity and sensitivity. Showed that the best combination of biomarkers, mir-133 and mir-155a, yielded a receiver operating characteristic curve value of 88%, sensitivity (91%), and specificity (71%) in distinguishing Oral Squamous Cell Carcinoma (OSCC) from healthy controls [32]. In a report on gastric cancer, serum levels of upregulated miRNAs, such as miR-21 and miR-106b, were higher in patients with gastric cancer than in controls before resection and reduced after resection [33]. In a pilot study by Shine et al., serum levels showed no differences in miRNA concentrations according to the pT stage, Lauren's classification, sex, or age. Serum levels of miR-21, miR-146a, and miR-148a are closely associated with Gastric Cancer (GC) pN stage. These serum miRNA levels could be potential biomarker candidates for predicting the presence of Lymph Node (LN) metastasis: 10 healthy donors, 16 LN-positive patients with GC, and 15 LN-negative patients with GC [34]. Then, they compared the levels of three miRNAs (miR-21, miR-146a, and miR-148a) in a total of 79 GC patients with or without LN metastasis, and the combined expression analyses of miR-21, miR-210, miR-155, and miR-196a in plasma can discriminate pancreatic adenocarcinoma patients from controls was performed in Wang J study [35]. The plasma levels of the hypoxia-related miRNA miR-210 were also altered in patients with pancreatic cancer compared to healthy controls from two independent cohorts. For instance, in a study on acute leukemia, there was a decrease in miR-92a levels in the plasma samples of all patients compared to controls. A specific profile of plasma miRNAs was also found in CLL compared to multiple myeloma, hairy-cell leukemia, and healthy control samples. The results of this study showed that circulating miRNAs were correlated with the prognosis marker ZAP-70 status and might be used to detect and stratify individuals with CLL [36]. The abundance of circulating miRNAs during radiochemotherapy reflects the therapeutic response of primary HNSCC cells to in vitro treatment. Therefore, responsive miRNAs (miR-425-5p and miR-93-5p) may represent novel biomarkers for therapy monitoring [37].

Circulating microRNA in cardiovascular and related-disease

Since the discovery of circulating biomarkers, a vast body of literature on their role in cardiovascular disease and related illnesses such as myocardial infarction, HF, atherosclerosis, hypertension, and DM has been conducted [38,39]. In early studies, four cardiac miRNAs (miR-208a, miR-499, miR-1, and miR-133) were consistently elevated in the plasma of AMI patients within hours after the onset of infarction deficiency at this early stage [40]. However, D'Alessandra et al. were unable to detect elevated levels of circulating miR-208a in all AMI patients. Collection of samples and low concentration of the miR-208a biomarker in the early stages can be justified by the fact that all samples must be collected on average 9 h after the onset of AMI symptoms, which is well after miRNA levels have peaked in the blood stream [41]. Because these biomarkers are useful for early assessment, the low levels of miR-208 in the blood compared with other muscle-enriched miRNAs in the early phase after AMI (3 h), miR-1, miR-133a, and, more particularly, miR-208a, may be more sensitive than the classic biomarker cTnI [42]. Reduced levels of miR-126, miR-15a, miR- 29b, and miR-223 and elevated levels of miR-28-3p reported in this study. The levels of cTN-I and NT-pro-BNP were positively correlated with miR-21 and negatively correlated with miR-126. Integrating specific patterns of miRNA levels with NT-pro-BNP and/or cardiac troponin levels may improve the diagnosis of cardiovascular diseases [43]. Compared to other microRNAs, miR-208a biomarkers can be used for the early detection of AMI, and MiR-1 and miR-133 may also serve to diagnose AMI [44]. miR-1 and miR-133a levels may be correlated with muscle creatine kinase levels and cTnI levels in plasma and affected by the pathological characteristics of other organs, as these miRNA levels have also been found to increase in the bloodstream of patients with lung cancer and colorectal cancer. Therefore, the experimental results of evaluating circulating miRNAs as biomarkers for early diagnosis make research in this area a priority. In another study [45] the combined assessment of the two 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, owing to its role in the inflammatory process, can trace recently occurring signs of myocardial injury. The rationale for this relationship can be found in a variety of cardiovascular diseases and diabetes [46]. In one of the most accepted studies, lower levels of miR-126 were also found in atherosclerotic CAD and in patients with type 2 DM and may reflect the condition of vascular endothelial cells in patients with HF. miR-126, miR-92a, and miR-17 are the most promising miRNA biomarkers for the diagnosis of CAD [47]. In addition, vascular smooth muscle cell-enriched miR-145 is an inflammatory miRNA introduced in the Fukushima study [44]. Microarray analysis of miRNA expression in whole blood samples of the CAD cohort in the Fichtlscherer study revealed two miRNAs, miR-140 and miR-182, which differed between CAD and control subjects [48]. Interestingly, the expression of miR-92 increased after cardiac rehabilitation, which is in line with the study by [48], in which miR-92 was reduced in the plasma of CAD patients. Extensive network analysis revealed a unique plasma miRNA signature for DM, including Type II diabetes. The first population-based prospective study have recently performed on circulating miRNAs (n =822) showed that miR-126 was among the miRNAs most consistently associated with type II diabetes, but [49]. Identified miR-31 as a promising biomarker for diabetic microvascular complications; a reduction in the levels of some of these miRNAs (miR-126, miR-15a, and miR-223) was already detectable years before the manifestation of diabetes [49]. Interestingly, the first study to show a panel of serum miRNAs for obesity and compare them with miRNAs identified in serum for diabetes and obesity with diabetes [50], in this study, similar levels of 13 miRNAs in plasma (miR-15a, miR-20b, miR-21, miR-24, miR-126, miR-191, miR-197, miR-223, miR-28-3p, miR-150, miR-29b, miR-320, and miR-486) in diabetic patients with or without drug treatment. In conclusion, this study supports the use of miR-15b, miR-138,

and miR-376a extracted from serum samples as potential predictive tools for obesity and type 2 diabetes. Sebastiani and colleagues analyzed the expression of 384 microRNAs in serum pools from three groups of T2D patients: 12 T2D patients without any chronic complications, 12 T2D patients with macrovascular complications, and 12 with microvascular complications; 223 miRNAs were expressed in T2D, 224 in T2D patients with microvascular complications, and 221 in T2D patients with microvascular complications [51]. Research studies have shown that miR-31 is a promising biomarker for diabetic microvascular complications, but further prospective studies in the clinical setting are required to establish the reality until serum circulating levels of this microRNA [52,46,53]. In conclusion, miR-133 and miR-1 are reported to be expressed specifically in cardiac and skeletal muscles. The miR-133 family comprises three members: miR-133a-1 (expressed in cardiac and skeletal muscles), miR-133a-2 (expressed in cardiac and skeletal muscles), and miR-133b (expressed specifically in cardiac muscles) [54,49,55] (Table 1). Tissue-specific miRNAs in circulation have been explored as potential circulating biomarkers for specific organs, for example, skeletal muscle-specific miR-1, -499, -133, and -206 in the plasma of patients with Chronic Obstructive Pulmonary Disease (COPD) patients [56] and cardiac specific miR-133a, -208a, and -499 in Myocardial Infarction [57].

Circulating miRNAs as biomarkers for neurodegenerative disorders

Numerous studies have been conducted on the association between circulating biomarkers packed in carriers suspended in fluid and degenerative diseases of the nervous system [58,59]. For example, a study on PBMCs obtained from 19 patients and 13 controls identified 18 significantly under-expressed miRNAs, and showed that miR-103 and miR-107 suppressed cofilin translation with an increased level of active cofilin protein, which leads to the formation of cofilin rods formation [60]. Another study, using qRT-PCR, suggested that miR-1, miR-22-5p, and miR-29 expression levels in total peripheral blood allow the distinction of non-treated PD from healthy subjects, and that miR-16-2-3p, miR-26a-2-3p, and miR30a differentiate between treated and untreated patients [61,62]. The use of CSF levels of seven miRNAs, miR-10b, miR-21, miR-125b, miR-141, miR-200a, miR-200b, and miR-200c, allowed the authors to achieve high accuracy in separation between all classes of samples. Geekiyanage and colleagues compared the concentrations of five miRNAs, namely miR-137, miR-181c, miR-9, miR-29a, and miR-29b, in the serum of patients with Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) with serum levels of age-matched controls [63]. Gaughwin described the search for a plasma miRNA that could be used for early diagnosis of Huntington's Disease (HD). The authors showed that one of these miRNAs, miR-34b, was significantly elevated in plasma from carriers of mutant Huntingtin (mHTT) prior to symptom onset. A high level of expression is valuable because this marker has not been considered a specific marker of the brain [64]. Among all the known miRNAs, some regulate neuronal development processes, 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 a marker of acute ischemic stroke occurrence, subtypes, and infarct volume [65]. miR-132 and miR-212 are involved in several abnormalities, such as synaptic plasticity and connectivity in schizophrenia, and in neuronal cultures, the stability of mature miR-132 is affected by NMDA inhibition. Several other miRNAs, such as miR-21, miR-29a, and miR-132, have been identified as p53 regulated and also they gets regulated after seizure formation. miR-34a can help cure epilepsy, as it can only be controlled by medication. previously shown to be regulated in the brain and blood after brain injury are likely accounted for by changes in miRNA expression [66]. Therefore, the possible use of blood miRNAs as biomarkers for brain injury that selected blood miRNAs may correlate with miRNA changes in the brain and that many of the miRNAs (e.g., miR-298, miR-155, and miR-362-3p) were upregulated or down regulated by more than two-fold in both the brain and blood after several different injuries. Results from study of the expression panel of circulatory microRNA-145 in healthy control subjects (N = 14) and ischemic stroke patients (N = 32) showed that Circulatory microRNA-145 expression is significantly higher in ischemic stroke patients than in control subjects [62]. This result demonstrates that hemostatic mechanisms are affected by ischemic stroke. We conclude that circulating microRNA-145 is a potential biomarker for ischemic stroke. Eight miRNAs (hsa-let-7f, miR-126, -1259, -142-3p, -15b, -186, -519e, and -768-5p) were poorly expressed across the three stroke subtypes (LA, large artery stroke; SA, small artery stroke; CEmb, cardioembolic stroke) [67]. Similarly, among the 138 highly expressed miRNAs, 17 miRNAs (hsa-let-7e, miR-1184, -1246, -1261, -1275, -1285, -1290, -181a, -25*, -513a-5p, -550, -602, -665, -891a, -933, -939 and -923) were identified as highly expressed in all subtypes of stroke [68,61]. The observed increase in brain-specific miR-124 levels further demonstrates the utility of miRNAs as accessible biomarkers for monitoring tissue injury originating from a specific organ. A subset of 30 miRNAs was selectively upregulated in both male and female ICH patients with intracerebral hemorrhage. at first based on their tissue expression patterns determined by q-PCR analysis, muscle-enriched miRNAs (miR-1, miR-133a, and miR-499) and cardiac-specific miR-208a were selected as candidates for this study [69] (Table 1). Using miRNA microarray and real-time PCR analyses, miR-1, miR-133a, and miR-499 were found to be present in very low abundance, and miR-208a was absent in the plasma of healthy people [70]. In another study, blood miR-210 was found to be a novel sensitive biomarker for the clinical diagnosis and prognosis of acute cerebral ischemia [66].

Circulating microRNA in skin and autoimmuno-disease

Since diseases affecting the skin and immune system are closely related, circulating biomarkers work well in diagnosis and prognosis, and serum levels of miRNAs have also been determined in dermatomyositis patients [71]. Serum miR-21 levels were significantly upregulated, correlating with the serum IgG levels. Serum levels of miR-223 and miR-7 were downregulated, whereas serum levels of miR-142-3p and miR-92 were not changed in dermatomyositis patients [72]. Some circulating miRNAs have been identified to be involved in the posttranscriptional regulation of lipid metabolism genes (microRNA-33) [73] and in the regulation of vascular development and angiogenesis (microRNA-126) [74]. In contrast, psoriatic patients have a positive association with cardiovascular diseases; therefore, the expression of cell-free circulating microRNA-33 and microRNA-126 in plasma from psoriatic patients and their relationship with clinical parameters have been identified. Similarly, Pivarcsi and colleagues recently reported the upregulation or downregulation of miR-128a, let-7d, miR-142-3p, and miR-181a in sera from psoriasis patients compared to normal subjects [75]. In another study [76], serum miR-150 levels were decreased in patients with Systemic Sclerosis (SSc); therefore, patients with SSc 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), a higher modified Rodnan total skin thickness score, and a higher prevalence of pitting scars than those with higher miR-196a levels [77]. In Sing et al. found that the serum levels of miR-92a were significantly higher in patients with SSc than in normal subjects, and higher levels of miR-92a in patients leading to telangiectasia at a lower frequency than those with normal levels [78]. Another study showed that miR-142-3p levels were significantly higher in patients with SSc than in those with systemic lupus erythematosus, dermatomyositis, scleroderma [79], Scleroderma Spectrum Disorder (SSD), and healthy control subjects. Serum levels of miR-142-3p correlate 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 [80-84]. Serum miR-146a levels were inversely correlated with Systemic Lupus Erythematosus (SLE) disease activity and the degree of proteinuria, whereas serum miR-146a and miR-155 levels were positively correlated with glomerular filtration rate in Wang and colleagues [85]. Several other miRNAs (miR-16, miR-223, miR-451, and miR-21) were upregulated in patients with SLE and rheumatoid arthritis (Table 1). In Osteoarthritis, let-7e was a negative predictor for total joint arthroplasty, with an adjusted HR of 0.75 (95% CI 0.58 to 0.96; p=0.021) when normalised to U6, and 0.76 (95% CI 0.6 to 0.97; p=0.026) after normalisation to the Ct average. miRNA-454 was inversely correlated with severe knee or hip osteoarthritis with an adjusted HR of 0.77 (95% CI 0.61 to 0.97; p=0.028) when normalised to U6 [86].

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

Cardiovascular and Related-Disease	Type	Source
AMI	miR-1, miR-208b, miR-499, miR-30a, miR-126, miR-195	Plasma
CAD	miR-17/92cluster miR-155 miR-145, miR-135a, miR-145	Serum, plasma
Type II diabetes	miR-9, miR-29a, miR-30d, miR34a, miR-124a, miR146a, and miR-375	Serum, plasma
Neurodegenerative Disorders		
PD	miR-1, miR-22-5p, miR-16-2-3p, miR-26a-2-3p and miR30a	Serum, plasma
AD	miR-10b, miR-21, miR-125b, miR-141, miR-200a, miR-200b, and miR-200c	Serum, plasma
HD	as miR-9, miR-124a, miR-124b, miR-135, and miR-219 miR-223	Serum, plasma
Stroke	hsa-let-7f, miR-126, -1259, -142-3p, -15b, -186, -519e and -768-5p hsa-let-7e, miR-1184, -1246, -1261, -1275, -1285, -1290, -181a, -25*, -513a-5p, -550, -602, -665, -891a, -933, -939	Serum, plasma
Skin and Autoimmuno-Disease		
Psoriatic	miR-223, miR-7	Serum
SSC	miR-128a, let-7d, miR-142-3p , miR-181a, miR-142-3p	Serum
SSE	miR-16, miR-223, miR-451, miR-21	Serum, plasma

HF: Heart Failure; AM: Acute Myocardial Infarction; CAD: Coronary Artery Disease; PBMC: Peripheral Blood Mononuclear Cell; AP: Angina Eoris; PD: Parkinson's Disease ; AD: Alzheimer's Disease; HD: Huntington's Disease.

Circulating microRNA and virusal and bacterial infections

Circulating viral and bacterial infections associated with cf-microRNA are important for the development of many of these biomarkers and for early detection. The presence of circulating miR-BART17-5p (one of the miR-BARTs hereafter referred to as miR-BART17) and EBV DNA in a larger series of Nasopharyngeal Carcinoma (NPC) plasma samples is shown [87,88]. The second aim was to determine whether circulating miR-BART17 was carried by plasma exosomes. miR-BART17 was significantly more abundant in plasma samples from patients with NPC than in non-NPC samples from EBV-infected donors. Above a threshold of 506 copies/mL, the detection of miR-BART17 was highly specific for NPC patients (ROC curve analysis: AUC=0.87, true positive rate=0.77, false positive rate=0.10). In this relatively small series, the concentration of plasma miR-BART17 and the plasma EBV DNA load were not correlated. When plasma samples were fractionated, miR-BART17 was co-purified with a protein-rich fraction, but not with exosomes [88]. In another study, the circulating levels of miRNAs in stage assessment in patients with Chronic Hepatitis C infection (CHC) or Non-Alcoholic Fatty Liver Disease (NAFLD) showed that miR-122, miR-34a, miR-16, and miR-21 are commonly deregulated in liver fibrosis and hepatocellular carcinoma. In both CHC and NAFLD patient groups, serum levels of miR-122 and miR-34a were correlated with liver enzyme levels, fibrosis stage, and inflammation activity [89]. In Hung Su et al. study, determinated miR-122 levels also correlated with serum lipids in NAFLD patients. The validation cohort confirmed a significantly greater pretreatment serum miR-122 level in patients with SVR than in those with NR (P=0.025) [90]. 62 CHC patients, 29 patients with CHC and HCC, and 19 healthy controls were prospectively enrolled, and the data showed that the serum miR-21 level is a marker for necroinflammatory activity but does not differ between patients with HCV and HCV-induced HCC [91]. In conclusion, serum miR-122 may serve as a surrogate for 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 CHC or NAFLD [92]. In another study [93] also detected increased serum miR-155 levels in patients with HCV compared with controls. Another study showed that serum miR-125b and miR-146a levels were also increased in HCV patients [94]. Serum levels of miR-122 were elevated in cHCV patients and correlated with increased

ALT, AST, and serum miR-155 levels [95]. Chronic liver inflammation can lead to progressive liver damage. Because the serum miR-21 level is a marker for necroinflammatory activity, microRNAs (miRNAs) regulate inflammation (miR-155, -146a and-125b) as well as hepatocyte function (miR-122) [96,97]. panel data of six serum miRNAs (hsa-miR-378, hsa-miR-483-5p, hsa-miR-22, hsa-miR-29c, hsa-miR-101, and hsa-miR-320b) showed significant differences among pulmonary TB patients, healthy controls (P,0.001) and differential diagnosis groups (including patients with pneumonia, lung cancer, and chronic obstructive pulmonary disease) (P,0.05) [98]. In a pilot study by Roderburg et al., a panel of miR-29a, miR-197-3p, miR-505-3p, miR-652, miR-20a, miR-21, miR-34a, miR-122, miR-133a, miR-223, miR-571, let7, and others were deregulated in the serum compared to healthy controls, several of which were also correlated with the degree of liver fibrosis. The results of this study showed that elevated miR-122 serum levels correlated with hepatic cell death and necroinflammatory activity in patients with HCV infection, but not with fibrosis stage or liver function. Finally, the results of these alterations in serum levels of specific circulating miRNAs might allow a differential diagnosis between the different etiologies of chronic liver disease [97].

Logistic regression analysis of a combination of six serum miRNAs revealed that the sensitivity and specificity of TB diagnosis were 95.0% and 91.8%, respectively [98]. The miRNA-gene regulatory networks revealed that several miRNAs may regulate target genes involved in immune pathways and participate in the pathogenesis of pulmonary TB.M. bovis BCG infection in mice resulted in enhanced expression of mmu-miR-31, mmu-miR-150, and mmu-miR-146a. In contrast, the human homolog of the same miRNAs is significantly lower in the Peripheral Blood Mononuclear Cells (PBMCs) of patients with tuberculosis than in healthy controls [99], suggesting a role for these miRNAs in the control of chronic inflammation. By targeting the TLR signaling cascade, miR-31, miR-150, and mir-146a [100,99] may dampen uncontrolled inflammation that leads to tissue damage, a major cause of pulmonary morbidity and mortality in tuberculosis [101]. Three miRNAs with higher expression in active tuberculosis patients than in healthy controls have been positively evaluated for use as biomarkers: miR-155 and miR-155 in stimulated PBMCs [102] and miR-29a in pooled serum [98] (Table 2). In addition to expression analysis, microRNA Single Nucleotide Polymorphism (SNP) analysis revealed a correlation between SNPs in miR-146a (rs2910164) and miR-499 (rs3746444), and increased pulmonary tuberculosis susceptibility in certain populations.

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

Virtual and Bacterial infections	Type	Source
EBV-infection	miR-BART17-5p, miR-122,	Plasma
CHC	miR-34a, miR-16 and miR-21, miR-146a, miR-125b	Plasma, serum
TB	hsa-miR-378, hsa-miR-483-5p, hsa-miR-22, hsa-miR-29c, hsa-miR-101 and hsa-miR-320b	Serum
BCG infection	mmu-miR-31, mmu-miR-150, and mmu-miR-146a, : miR-155 and miR-155	Plasma, serum plasma

CHC: Chronic Hepatitis C; BCG: Bacille Calmette-Guérin; TB: Tuberculosis.

Conclusion

Most biomarker enduring work can be found in exosomes, and represents a potentially informative biomarker. In recent years, genetic advertising biomarkers have clarified the importance of their role in cancer and many other diseases of the blood and fluids. The presence of cell-free methylated-DNA and miRNAs in blood has opened up new perspectives in the development of cancer biomarkers for early cancer detection in a non-invasive manner. These results suggest that not all miRNAs in the circulation are influenced by aging, but only some miRNAs may be selectively changed by aging [103]. In addition to stunning advances, sensitive methods for their detection are growing. They are a valuable presence in the room, and a large sensitivity to treatment with early detection has come into development. In summary, circulating miRNAs may be promising biomarkers for the early detection of cancer or for predicting clinical outcomes. In the future, the need to use sensitive and fast methods to identify expression profiles to identify new biomarkers, along with sensitive and accurate methods for identifying true and real biomarkers, as well as the validation of promising candidates in large prospective studies. In the not too distant future, by taking all necessary standards, identifying circulating biomarkers in the early detection of many infectious diseases, genetic, degenerative immune therapies for which there hardly could be a revolution bring. Nevertheless, the promise of using miRNAs as readily detectable and measurable components of the blood remains great and has the potential to aid in the diagnosis and treatment of cancer and other disorders.

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