MicroRNA associated with dyslipidemia and coronary disease in humans

Elena Flowers¹ and Bradley E. Aouizerat¹,²

¹Department of Physiological Nursing, School of Nursing, University of California, San Francisco, California; and ²Institute for Human Genetics, University of California, San Francisco, California

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Dyslipidemia is a common risk factor for cardiovascular disease, and reductions in the levels of atherogenic lipoproteins are associated with substantially decreased risk (39). The two primary approaches to treatment for dyslipidemia are pharmacological agents and lifestyle change (39). However, even in combination these interventions are not completely effective at achieving adequate risk reduction in all individuals. One important reason that risk reduction efforts fail to achieve full success is incomplete understanding of interindividual differences in the underlying pathophysiology. While single genes and discrete environmental exposures that increase risk have been identified, for most individuals the etiology is complex (i.e., multifactorial) (10).

A recent paradigm shift in biomarker research has resulted from the development of methods to measure adaptive changes of the genome and its expression, termed epigenetics. Epigenetic events are particularly attractive for clinical research because they represent an aggregate response to many upstream events. In other words, epigenetic events are the sum of genetic risk factors and sustained environmental exposures that drive an organism toward adaptive responses to maintain homeostasis. To date, three primary epigenetic mechanisms have been identified and described in detail elsewhere: histone modification (16), DNA methylation (22), and microRNA (54).

MicroRNAs (miRs) are an epigenetic mechanism of post-transcriptional regulation of messenger RNA (mRNA), miRs function by binding to a complementary 18–24 nucleotide precursor region on mRNA known as the “seed” sequence, thereby preventing initiation of translation of mRNA to amino acids (28). miR regulation is dynamic; the function can be temporary, when the miR release the mRNA, or permanent, causing degradation of the mRNA strand (46). Currently, there are 2,042 discrete miR species identified in humans, and ~300 are detectable in blood (27). miR are the subject of numerous research studies because they currently have three potential clinical implications: 1) biomarkers of underlying disease, 2) therapeutic treatments (i.e., synthetic miRs or miR antagonists), and 3) markers for response to therapeutic interventions to prevent and treat disease. The subset of miR detectable in blood are of particular interest because their measurement is minimally invasive and blood-based diagnostic testing is common in the clinical setting. Additional studies are needed in order to determine the origins of miRs found in blood to fully understand the pathophysiological underpinnings of dyslipidemia.

Nonhuman Studies

Numerous in vitro and animal model studies have examined the regulatory role of microRNA on lipid metabolism (Table 1) (7, 8, 12, 36, 37, 42, 45). miR-122 is the most prevalent miR in animal model hepatocytes, targeting numerous genes involved in lipid metabolism in the liver (i.e., diacylglycerol O-acyltransferase 2, glycerogen synthase 1, solute carrier family 7, acetyl-coA carboxylase-α, nuclear receptor subfamily 1, group H, member 3/liver X receptor-α, fatty acid synthase,sterol regulatory element binding transcription factor-1c, cholesterol 7α-hydroxylase) and adipocytes (i.e., adenosine triphosphate binding cassette transporter-1, diacylglycerol O-acyltransferase 2) with associated changes in lipid parameters. Greater detail on the effects of miR-122 on lipid metabolism has previously been published (12). The aggregate effects of miR-122 in nonhuman studies are decreased total cholesterol and triglycerides and decreased production of the LDL receptor. Further research on miR-122 in humans is needed to determine whether this miR has the same effects as those seen in in vitro and animal model studies, as well as whether this miR might be useful as a therapeutic agent for modification of lipoprotein levels.
Recently, miR-33 has become a potential therapeutic target for dyslipidemia in animal models. In African green monkeys, inhibition of miR-33 results in decreased serum triglycerides and increased HDL (41). Additional studies in the same primate model and also in mouse models demonstrated miR-33 is located in an intron of the sterol-regulatory binding element transcription factor gene and regulates this mRNA as well as adenosine triphosphate binding cassette transporter and others (5, 12, 18, 38, 43). Although the findings from in vitro and animal model studies established the role of miR-33 in modulating biological pathways underlying dyslipidemia, the findings have limited generalizability to humans. For example, the miR-33a isoform, which is readily detectable in mice, is not expressed in humans; thus initial findings from studies of mouse models had limited implications for potential translation to clinical practice.

Although there is growing evidence to support miR regulation of lipoprotein metabolism, the translational implications of studies from in vitro and animal model studies are limited. Currently published reviews in this area have not concentrated on findings from studies in humans with more imminent translational potential (i.e., miRs as surrogate biomarkers for underlying pathophysiology). The primary focus of this review is the synthesis of findings from studies of miR regulation of lipid metabolism in humans.

**HUMAN STUDIES**

**Cardiovascular Risk Factors**

There is a small but growing body of literature about miR expression and dyslipidemia in humans, and particularly blood-based expression of miR associated with underlying pathologies.

## Table 1. Nonhuman studies reporting microRNA expression associated with dyslipidemia

<table>
<thead>
<tr>
<th>MicroRNA</th>
<th>Cell/Tissue Source</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-33a/b</td>
<td>human (hsa) cell lines, mouse (mmu) models, primate (sae) models</td>
<td>Fernandez-Hernando et al. (7)</td>
</tr>
<tr>
<td>miR-27, miR-33a/b, miR-3a, miR-103/107, miR-122, miR-124, miR-143, miR-148, miR-182, miR-370, miR-378/378*</td>
<td>human (hsa) cell lines</td>
<td>Fernandez-Hernando et al. (8)</td>
</tr>
<tr>
<td>miR-let7, miR-9, miR-24, miR-26, miR-29, miR-33a/b, miR-3a, miR-103/107, miR-122, miR-208, miR-375</td>
<td>mouse (mmu) models</td>
<td></td>
</tr>
<tr>
<td>miR-9, miR-96</td>
<td>rat (rno) cell lines</td>
<td></td>
</tr>
<tr>
<td>miR-122</td>
<td>human (hsa) cell lines, mouse (mmu) models</td>
<td>Flowers et al. (12)</td>
</tr>
<tr>
<td>miR-370</td>
<td>human (hsa) cell lines</td>
<td>Najafi-Shoushtari et al. (37)</td>
</tr>
<tr>
<td>miR-106b</td>
<td>human (hsa) cell lines, mouse (mmu) models</td>
<td></td>
</tr>
<tr>
<td>miR-122</td>
<td>human (hsa) cell lines, mouse (mmu) models</td>
<td></td>
</tr>
<tr>
<td>miR-370</td>
<td>human (hsa) cell lines</td>
<td></td>
</tr>
<tr>
<td>miR-33</td>
<td>human (hsa) cell lines, mouse (mmu) models</td>
<td>Rayner et al. (41)</td>
</tr>
<tr>
<td>miR-33a/b</td>
<td>human (hsa) cell lines, mouse (mmu) models, primate (sae) models</td>
<td>Rottiers et al. (45)</td>
</tr>
<tr>
<td>miR-17, miR-197, miR-509-5p, miR-92a, miR-320a</td>
<td>blood plasma Chinese coronary artery disease</td>
<td>Moore et al. (36)</td>
</tr>
<tr>
<td>miR-370</td>
<td>human (hsa) cell lines</td>
<td></td>
</tr>
<tr>
<td>miR-122</td>
<td>human (hsa) cell lines</td>
<td></td>
</tr>
<tr>
<td>miR-370</td>
<td>human (hsa) cell lines</td>
<td></td>
</tr>
<tr>
<td>miR-378/378*</td>
<td>human (hsa) cell lines</td>
<td></td>
</tr>
<tr>
<td>miR-33</td>
<td>human (hsa) cell lines</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Human studies reporting microRNA expression associated with dyslipidemia**

<table>
<thead>
<tr>
<th>MicroRNA Identified</th>
<th>Tissue Source</th>
<th>Racial Characteristics</th>
<th>Phenotype</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia: miR-103, miR-17, miR-183, miR-197, miR-23a, miR-509-5p, miR-584, miR-652</td>
<td>whole blood</td>
<td>Singaporean</td>
<td>metabolic syndrome components</td>
<td>Karolina et al. (26)</td>
</tr>
<tr>
<td>BMI: miR-197, miR-23a, miR-509-5p</td>
<td>whole blood</td>
<td>Singaporean</td>
<td>metabolic syndrome components</td>
<td>Karolina et al. (26)</td>
</tr>
<tr>
<td>miR-17, miR-197, miR-509-5p, miR-92a, miR-320a</td>
<td>exosomes</td>
<td>Singaporean</td>
<td>metabolic syndrome components</td>
<td>Flowers et al. (12a)</td>
</tr>
<tr>
<td>miR-100, miR-106b, miR-125b, miR-143, miR-148a, miR-17/17*, miR-18a, miR-20a, miR-21, miR-221, miR-374a, miR-7, miR-93, miR-96</td>
<td>whole blood</td>
<td>South Asian</td>
<td>high triglycerides/low HDL</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia: miR-103, miR-17, miR-183, miR-197, miR-23a, miR-509-5p, miR-584, miR-652</td>
<td>exosomes</td>
<td>Singaporean</td>
<td>metabolic syndrome components</td>
<td></td>
</tr>
<tr>
<td>BMI: miR-197, miR-23a, miR-509-5p</td>
<td>whole blood</td>
<td>Singaporean</td>
<td>metabolic syndrome components</td>
<td></td>
</tr>
<tr>
<td>miR-17, miR-197, miR-509-5p, miR-92a, miR-320a</td>
<td>blood plasma</td>
<td>Chinese</td>
<td>coronary artery disease</td>
<td>Gao et al. (15)</td>
</tr>
<tr>
<td>miR-34</td>
<td>peripheral blood mononuclear cells</td>
<td>Japanese</td>
<td>coronary artery disease</td>
<td>Tabuchi et al. (49)</td>
</tr>
</tbody>
</table>

* qPCR, quantitative polymerase chain reaction; BMI, body mass index; HDL, high-density lipoprotein cholesterol.
perturbations in lipid metabolism and/or sequelae [e.g., coronary artery disease (CAD)] (Table 2). Karolina et al. (26) characterized miRs in whole blood and exosomes in 265 Singaporean patients with and without the metabolic syndrome and its component risk factors (i.e., dyslipidemia, hypertension, and Type 2 diabetes). Using microarray-based screening of known human miRs followed by validation of a subset of targets by quantitative polymerase chain reaction (qPCR), they identified unique miR profiles characterizing three risk factor profiles associated with metabolic syndrome (26). Eight miR species (miR-103, miR-17, miR-183, miR-197, miR-23a, miR-509-5p, miR-584, miR-652) were unique to the metabolic syndrome and dyslipidemia cluster \( (n = 41) \) compared with the controls \( (n = 17) \) by microarray (26). Three of these (miR-197, miR-23a, miR-509-5p) were also significantly correlated with body mass index. \( (26) \). Only a subset (miR-17, miR-197, miR-509-5p) were detectable by qPCR in exosomes. \( (26) \). Flowers et al. \( (12a) \) similarly used microarray methods to screen for the presence of 85 known miR species in South Asian men with \( (n = 22) \) and without \( (n = 22) \) atherogenic dyslipidemia. Fifteen miRs \( (\text{miR-100, miR-106b, miR-125b, miR-143, miR-148a, miR-17, miR-17*, miR-18a, miR-20a, miR-21, miR-221, miR-374a, miR-7, miR-93, miR-96}) \) were found to be differentially expressed at a magnitude of at least twofold. Of note, miR-17 was observed to be differentially expressed by microarray-based measurement in both studies and has previously been observed to target and suppress angiogenic pathways in in vitro studies \( (6, 24) \). Karolina et al. \( (26) \) observed increased expression in dyslipidemic individuals compared with healthy controls (fold change 2.77), whereas Flowers et al. \( (12a) \) observed decreased expression (fold change -2.27). One possible explanation for these apparently discrepant findings is the specific dyslipidemic phenotype selected for case status was primarily focused on hypercholesterolemia [i.e., LDL \( > 3.4 \) mmol/l or total cholesterol \( > 5.0 \) mmol/l \( (26) \) compared with hypertriglyceridemia, i.e., HDL \( < 1.03 \) mmol/l and triglycerides \( > 1.7 \) mmol/l \( (12a) \)] and the differing racial background of each sample.

**Coronary Artery Disease**

Two studies have reported blood-based differential expression of miRs in individuals with and without CAD, with associated alterations in lipoprotein profiles. Gao et al. \( (15) \) studied 355 Chinese patients who underwent coronary angiography, 255 of whom had dyslipidemia (total cholesterol \( \geq 5.72 \) mmol/l and/or triglycerides \( \geq 1.7 \) mmol/l). qPCR was used to measure blood plasma expression of miR-122, miR-370, miR-33a, and miR-33b, miRs frequently examined in in vitro and animal model studies of lipid metabolism \( (15) \). Hyperlipidemic patients displayed statistically significantly greater expression of both miR-122 and miR-370, and this effect was attenuated in those treated with statins \( (15) \). Both miRs were positively associated with total cholesterol, triglycerides, and LDL cholesterol, but no relationship was observed for HDL cholesterol \( (15) \). Patients with CAD also displayed greater expression of both miRs, and this relationship remained significant after adjusting for covariates, including lipoprotein levels \( (15) \). Of note, the two miR-33 isoforms were undetectable in plasma \( (15) \). In a similar study, Tabuchi et al. \( (49) \) studied miR-34 in 70 Japanese patients undergoing coronary angiography and 48 controls with no symptoms of CAD. The patients with CAD were randomized to receive one of two statins following angiography \( (49) \). This study also used qPCR but quantified miR expression from peripheral blood mononuclear cells, which are a subset of the cell types found in whole blood \( (49) \). MiR-34 was chosen based on prior data from in vitro studies indicating that this miR regulates silent information regulator 1 (SIRT1), which has antiatherosclerotic effects by influencing vascular endothelial cell homeostasis and is a proposed therapeutic target of statins. miR-34 showed statistically significantly greater expression in patients with CAD compared with the controls and an inverse association with SIRT1 protein levels \( (49) \). Posttreatment, no differences between the two statin groups for miR-34 or SIRT1 levels were observed \( (49) \). Comparisons of pre- and poststatin treatment were not reported, thus no determination of the effects of statins on miR-34 or SIRT1 levels can be made. Both of these studies provide evidence that individual circulating miRs are associated with underlying pathophysiology (i.e., dyslipidemia and CAD). Although the samples, covariates (i.e., statin therapy), and miR measurement methods were similar between these two studies, there was no overlap in the miR targets tested. Furthermore, the studies evaluated different tissue sources (i.e., plasma vs. peripheral blood mononuclear cells) and used different reference genes to calculate normalized miR expression. Although comparison of the miR results is not possible, this aggregate set of miR species with a plausible role in lipid metabolism warrant further investigation.

**METHODOLOGICAL CONSIDERATIONS**

There are several important methodological considerations for interpretation of studies of miR expression associated with dyslipidemia in humans \( (11) \). The first is the tissue source used for detection of miRs. Similar to mRNA, miR expression varies among tissues. In most cases, peripheral blood is the most readily accessible tissue source in routine clinical care, which is a fundamental driver of widespread interest in circulating miRs as a biomarker(s) for underlying disease processes and risk. miRs are readily detectable in the circulation and are differentially expressed in numerous disease states and/or pathophysiological processes compared with healthy controls \( (3, 35) \). miRs are detectable in several blood compartments: plasma, serum, exosomes, microparticles, platelets, erythrocytes, and leukocytes \( (14, 19, 51, 56) \). Prior studies of miR and lipid metabolism examined several discrete blood compartments \( (Fig. 1) \). Comparison of blood-based expression of miRs must consider the specific source from which miR were isolated. For example, in the studies of miR expression and CAD, Gao et al. \( (15) \) quantified miRs in blood plasma, whereas Tabuchi et al. \( (49) \) studied peripheral blood mononuclear cells. Even plasma and serum show some differences in the specific species and quantity of miRs detectable \( (56) \). To date, it is unclear whether detection of blood-based miRs detects causal pathways to disease or whether miRs originate from apoptotic cells in ischemic or damaged solid organs that are sloughed into the circulation. Depending on the origin of the miRs and underlying pathophysiology (i.e., blood-based vs. solid organ-based), some miRs may need compartment-specific measures and others will not. There are examples of both types of biomarkers in routine clinical use at present. Cardiac troponins,
which are released into the circulation by ischemic cardiomyocytes, reflect a causal relationship and are widely used in clinical care to diagnose myocardial infarction. By contrast, elevated LDL cholesterol is used to identify individuals who are at high risk for atherosclerosis, but the biomarker itself is not diagnostic for CAD. Additional studies are needed to determine the origins of circulating miR to understand the primary physiology. Regardless of the underlying causal relationship, blood-based miR expression has the potential to be a useful marker for disease.

The second consideration is how miRs are measured. Until recently, the gold standard for measurement was qPCR, and for practical reasons (i.e., cost, access to resources, data analysis), it remains the primary method reported in the literature. Whole transcriptome sequencing is the next generation of measurement for RNA, including miR, improving measurement of miR considerably through more accurate quantitation of the miR species and number. Another option, microarray, uses hybridization to detect the type and number of miRs present and offers higher throughput and greater sensitivity and specificity compared with qPCR (11). There are several commercially available platforms for both microarray and qPCR-based quantitation of miRs. Comparison studies show a high level of variability in the discrete miR species detected and correlation in the magnitude of expression between commercial miR measurement products (2, 56), suggesting that some caution should be taken in comparing results of studies using differing measurement platforms and commercial products.

Commonly, studies of gene expression report normalized expression, in which expression of each individual sample is standardized to the expression of a reference gene or combination of genes that is ubiquitously expressed at constant levels in most tissue types across individuals (1, 50, 52). Such normalization controls for variation in the starting quantity of biological material that could otherwise skew comparisons of relative expression between groups (i.e., diseased vs. nondiseased). However, for miR, a universally accepted normalizer control has not been identified. A commonly used normalizer is the small nuclear RNU6b. However, recent studies have reported considerable variation of expression of this RNA (40, 57). Normalization to the average expression of all measured miRs in all samples in a single experiment, normalization to the least variable miR in each experiment, and alternative approaches have been proposed (4, 33, 34, 58). To date, there is no universally accepted method for normalization of expression, and different strategies used between studies are an important consideration for interpreting conclusions.

GENE-ENVIRONMENT INTERACTIONS

A potential implication of miR activity is modulation of the effects of environmental exposures. Gene-environment interactions are widely known to effect risk factors for cardiovascular disease, including dyslipidemia (10). MiRs may be the structural cause of gene-environment interactions, as is the case when a DNA polymorphism lies in the miR coding site or...
within the seed sequence in the promoter region of the mRNA target and secondary exposure to an environmental insult triggers deleterious consequences. For example, a single nucleotide polymorphism in the lipoprotein lipase (LPL) gene (rs13702) appears to lie within the miR-410 seed sequence. (44). This polymorphism is also linked to a gene-environment interaction, as the rare C allele is associated with an additive inverse relationship between polyunsaturated fat intake and triglycerides (44). Genome-wide association data indicate that the rare C allele is associated with lower triglycerides and higher HDL, and in vitro transfection of the genomic region containing the rare C allele along with a miR-410 mimic results in gain of function of LPL compared with transfection with the common T allele (44). Furthermore, there is a dose-dependent response for the miR-410 mimic in the major allele transfected cells (44).

Alternatively, miR may be a mechanism for gene-environment interactions through its inherent regulatory function on gene expression, resulting in increased or decreased expression of an mRNA target as an adaptive response to environmental exposure. For example, workers exposed to perfluoralkyl chemicals (PFCs) in their workplace show an inverse correlation between blood levels of PFCs and HDL, and array-based differential expression of nine miRs (miR-127, miR-601, miR-106b, miR-24, miR-199a-3p, miR-92a, miR-26b, miR-30c, miR-30b) compared with nearby residents of the same community who were not exposed to PFCs (55). These differences were validated by qPCR for miR-26b and miR-199a-3p, and a linear association was seen between fold-change miR expression and blood levels of PFCs (55). Another example of how miR may function to allow an organism to adapt to environmental changes is through diet-induced miR activity. We were unable to find any published studies describing the effect of dietary factors on miR activity and dyslipidemia performed in humans, but several in vitro and animal model studies of other conditions indicate that this relationship is plausible (23, 25, 29, 31, 47, 48, 53, 60). Increasing interest in the implications of miRs in the area of gene-environment interactions is evidenced by the recent creation of the miREnvironment Database, which cross-references miR species with environmental risk factors and phenotypes (59).

RACIAL ANCESTRY AND miR EXPRESSION

Although the currently published studies reporting miR expression associated with dyslipidemia do not lend themselves to direct comparison because of differences in study design, sample, and methods, we can anticipate that future studies will incorporate comprehensive screening of miR targets detectable in blood in samples with well-characterized phenotypes, creating the possibility of direct comparison. The trajectory of miR-based research, although relatively new, closely follows the arc of both genetic (i.e., DNA polymorphisms) and gene-expression (i.e., mRNA) studies. Particularly in genetic studies, there exists variability among studies in the observed associations between gene polymorphisms and risk phenotypes (21). This is particularly true for multifactorial phenotypes like dyslipidemia (17) and CAD (30). Proposed alternative explanations for discrepant findings in genetic studies include unknown and unmeasured gene-gene and gene-environment interactions (10, 30). Differences in the underlying prevalence of gene polymorphisms among racial groups may add another layer of complexity to the aforementioned interactions (13, 32). While the myriad gene-gene and gene-environment interactions for dyslipidemia have yet to be fully characterized, methods to quantify population substructure (i.e., racial ancestry), have been developed, namely measurement of ancestry informative markers (AIMs) that distinguish five racial groups on the basis of genotype prevalence (20). To date, no studies investigating the corollary for miRs have been reported. We posit that differential expression of miRs might be influenced in part by differences in underlying genetic makeup between ancestry groups. For example, four of the studies on miRs and lipid metabolism cited above had samples of Asian ancestry (i.e., Singaporean, South Asian, Chinese, Japanese), racial groups that, although categorized as Asian, may not share equal genetic commonalities. Thus, confounding may occur in studies of miRs in humans when genetic background is not properly accounted for in data analyses. Further investigation of possible miR AIMs will bring to light the prospect of controlling for differences in ancestry that may be confounding observed associations or lack of associations between miR expression and disease states.

CONCLUSION

Dyslipidemia is a complex, multifactorial risk factor for cardiovascular disease that arises in the setting of both genetic and environmental exposures. miRs are an epigenetic mechanism of regulation of gene expression that facilitate dynamic adaptation of organisms to their environment. As such, miRs are an appealing possible biomarker with two important implications: 1) earlier detection of impending cardiovascular risk than is currently available through routine screening of lipid protein levels, and 2) elucidation of the underlying genetic mechanisms at play in a given individual. As blood is readily accessible in clinical care, there is particular interest in detection of both causal and noncausal blood-based miR expression associated with underlying pathophysiology. In addition to the biomarker implications, the possibility exists that miRs may be a therapeutic agent, through either administration of synthetic miR or miR antagonists. To date, a number of in vitro and animal model studies describing miR regulation of lipoprotein metabolism have been published, but less is known about these mechanisms in humans, with virtually no data to describe the molecular functions of miR in humans. The few human studies consistently show differential expression of miRs in blood compartments of individuals with dyslipidemia and/or CAD. Methodological differences in the design of these studies (i.e., miR tissue source, specific miR targets evaluated, measurement method) limit the possibility for making meaningful conclusions about which miR are of potential clinical relevance for detection and treatment of dyslipidemia as well as comparison of results between studies. Additional possible methodological and study design issues relevant to studies of miRs and dyslipidemia include gene-environment interactions and racial ancestry. Further work is needed to evaluate the full cadre of blood-based miRs associated with dyslipidemia in humans and to delve into possible racial differences in the prevalence and variability of individual miR species and the presence of gene-environment interactions exerting pressure on miR regulation of gene expression.
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AUTHOR CONTRIBUTIONS
Author contributions: E.F. conception and design of research; E.F. analyzed data; E.F. interpreted results of experiments; E.F. prepared figures; E.F. drafted manuscript; E.F. and B.E.A. edited and revised manuscript; E.F. and B.E.A. approved final version of manuscript.

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