Circulating MicroRNA Synergistic Orchestrators of Drug Response in Metabolic Syndrome

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***Abstract*—Metabolic syndrome (MetS) is a cluster of cardiometabolic risk factors — central obesity, hypertension, dyslipidemia and insulin resistance — that together raise risk of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). MicroRNAs (miRNAs) are non-coding RNAs that regulate gene expression post-transcriptionally and circulate in biofluids in stable forms (exosomes, microvesicles, or protein-bound). This review examines circulating miRNA (c-miRNA) signatures in the pathogenesis of MetS and in the modulation of drug response through direct regulation of drug-metabolizing enzymes (DMEs), drug transporters, and drug targets. Definitions and mechanisms are described, c-miRNA signatures associated with MetS components are presented, mechanistic links between c-miRNAs and pharmacokinetics/pharmacodynamics (PK/PD) are examined, and synergistic interactions between c-miRNAs and commonly used therapeutics in MetS (statins, antihypertensives, antidiabetics, and anti-obesity drugs) are explored.**

***Index Terms*—Metabolic Syndrome, MicroRNAs, Synergism, Statins, Antihypertensives, Antidiabetics, Circulating miRNA, Drug Response**

I. INTRODUCTION AND SCOPE

Metabolic syndrome (MetS) is affecting an increasing fraction of the global population and represents a major public health challenge due to its association with T2DM and CVD. Individual variation in drug response for MetS components—lipid-lowering agents, antihypertensives, glucose-lowering therapies, and anti-obesity medications — limits clinical outcomes. Circulating microRNAs (c-miRNAs) are attractive molecular mediators and biomarkers because they reflect tissue state, can modulate gene networks, and influence expression of enzymes and transporters involved in drug handling. This review synthesizes current knowledge on c-miRNA signatures in MetS and explores how they may act synergistically with drugs to alter therapeutic efficacy and toxicity.

II. DEFINITIONS AND KEY CONCEPTS

2.1. Metabolic Syndrome

Metabolic syndrome is a cluster of interrelated disorders that increase the risk of atherosclerotic cardiovascular diseases, including myocardial infarction (MI), cerebrovascular accidents (CVA), and peripheral vascular diseases (PVD), as we l as abdominal obesity, insulin resistance, and type II diabetes mellitus.

2.2. MicroRNA

MicroRNA (miRNA), originally discovered in Caenorhabditis elegans, is found in most eukaryotic organisms, including humans. miRNAs are single-stranded, non-coding RNA molecules that regulate mRNA to prevent protein production by two distinct mechanisms. Mature miRNAs are synthesised through a two-step cleavage process of primary miRNA (pri-miRNA), fo lowed by assimilation into the effector complex RNA-induced silencing complex (RISC). The miRNA functions as a guide by base-pairing with target mRNA to negatively regulate its expression.

2.3. Concept of Synergism in Pharmacology

Synergism occurs when the combined effect of two agents (e.g., a miRNA perturbation and a drug) is greater than the sum of their separate effects. In the context of c-miRNAs and drugs, synergy can be pharmacokinetic (miRNAs altering drug metabolism or transport, thereby increasing drug exposure) or pharmacodynamic (miRNAs and drugs acting on the same pathway or compensatory pathways to produce amplified effects). Recognizing such synergies is important for understanding variability in drug response and for designing combination therapies.

Types of synergism include:

Additive Synergism: The combined effect equals the sum of individual effects — for example, if Drug A lowers blood pressure by 10 mmHg and Drug B by 5 mmHg, together they lower it by 15 mmHg.

Potentiative Synergism: One drug enhances the effect of another. Drug A may have minimal effect alone, but when combined with Drug B, significantly boosts the overa l outcome.

III. MICRORNA: MECHANISMS AND SOURCES

3.1. miRNA-Mediated Gene Regulation

miRNAs bind to specific sequences at the 3′ UTR of target mRNAs to induce translational repression and mRNA deadenylation and decapping. Binding sites have also been detected in 5′ UTR and coding regions. Binding to 5′ UTR and coding regions produces gene silencing effects, while miRNA interaction with promoter regions has been reported to induce transcription.

3.2. MicroRNA-Mediated Gene Silencing via miRISC

The minimal miRNA-induced silencing complex (miRISC) consists of the guide strand and AGO. The target specificity of miRISC is due to its interaction with complementary sequences on target mRNA, called miRNA response elements (MREs). The degree of MRE complementarity determines whether there is AGO2-dependent slicing of target mRNA or miRISC-mediated translational inhibition and target mRNA decay.

3.3. MicroRNA-Mediated Translational Activation

Although most studies focus on how miRNAs inhibit gene expression, some have reported upregulation of gene expression by miRNAs. In serum-starved cells, AGO2 and Fragile-x-mental retardation related protein 1 (FXR1) were associated with AU-rich elements (AREs) at 3′ UTR to activate translation. Several miRNAs, including let-7, were found to activate translation during cell cycle arrest but inhibit translation in proliferating cells.

3.4. Post-Transcriptional Gene Regulation by miRNA

miRNA matching with 3′ UTR of the mRNA is required for functional inhibition of target genes. Research has expanded to recognition sites in coding regions or 5′ UTR. For instance, miR-24 can inhibit Jab1 translation by directly binding to both 3′ UTR and 5′ UTR. miR-122 can bind to the 5′ UTR of the positive-strand of HCV RNA genome to slow down decay of the viral genome. miR-10a interacts with the 5′ UTR of mRNAs encoding ribosomal proteins to enhance their translation.

3.5 Sources of Circulating miRNAs

microRNAs are considered a new class of biomarkers due to their stability and presence in almost all body fluids including saliva, serum, plasma, and milk. miRNA release occurs through: (1) passive leakage from cells suffering injury, chronic inflammation, or apoptosis; (2) active secretion by cell-derived membrane vesicles such as microparticles (MPs), exosomes, shedding vesicles, and apoptotic bodies; and (3) active secretion by a protein-miRNA complex, whereby miRNAs associate with lipoproteins (e.g., HDL) and Argonaute protein (e.g., Ago2). RNA binding protein (RBP) plays an irreplaceable role in the selective secretion of miRNA into extracellular exosomes or microvesicles.

IV. METABOLIC SYNDROME

4.1. Definition

MetS is an interconnected physiological, biochemical, clinical, and metabolic condition that directly increases the risk of atherosclerotic cardiovascular disease (ASCVD) and T2DM. It encompasses unhealthy body measurements and abnormal laboratory test results including dyslipidemia, hypertension, glucose intolerance, pro-inflammatory state, and a pro-thrombotic state.

4.2 Diabesity

Diabesity involves genetic and environmental factors. Severe obesity is a major risk factor for T2DM. Approximately 60 – 90% of a l patients with T2DM are estimated to be obese (BMI ≥ 30 kg/m²) or overweight (BMI ≥ 25 kg/m²). For every kilogram gain in body weight, the risk of diabetes increases by approximately 9%. Visceral obesity being more metabolica ly and lipolytica ly active releases more free fatty acids (FFAs) into the bloodstream, increasing cellular uptake and subsequent mitochondrial β-oxidation, which inhibits glucose metabolism through substrate competition.

4.3 Diabetes Mellitus

Diabetes is a complex syndrome characterized by hyperglycaemia induced by altered insulin secretion or poor insulin action. Type 1 diabetes (T1D) accounts for approximately 5% of all cases and is associated with autoimmunity against pancreatic beta cells. Type 2 diabetes (T2D) accounts for 90 – 95% of diabetic individuals worldwide. Gestational diabetes affects 3 – 9% of pregnant women. Hyperglycaemia contributes to oxidative stress through glucose auto-oxidation, formation of advanced glycated products (AGEs), and increased oxidation of arachidonic acid.

4.4 Dyslipidemia

Dyslipidemia is characterized by high plasma concentration of triglycerides (TG), reduced HDL, and increased LDL and apolipoprotein levels. The increased flow of FFAs into the bloodstream stimulates the synthesis of triglycerides and the production of apolipoproteins B100 and VLDL. Small, dense LDL particles are associated with increased cardiovascular risk and can more quickly cross the arterial wall and bind more easily to proteoglycans. Circulating LDL oxidized through interaction with free radicals becomes ox-LDL, which triggers atherosclerotic plaque development.

4.5 Para-Inflammation

The inflammatory state accompanying metabolic syndrome is not accompanied by infection or signs of autoimmunity, nor by massive tissue injury. This condition is often called 'low-grade' chronic inflammation or 'meta-inflammation' (metabolically triggered inflammation). This intermediate state between basal and inflammatory states plays an important pathophysiological role in MetS progression.

TABLE 1 Key Drugs Used in MetS Components

Sr.	Disease	Drug Name	Class
1	Diabesity	Semaglutide	GLP-1 RA
2	Diabesity	Tirzepatide	GLP-1/GIP dual agonist
3	Diabetes Mellitus	Metformin	Biguanide
4	Diabetes Mellitus	Empagliflozin	SGLT2 Inhibitor
5	Dyslipidemia	Atorvastatin	Statin
6	Dyslipidemia	Fenofibrate	Fibrate
7	Para-inflammation	Celecoxib	COX-2 Inhibitor
8	Para-inflammation	Prednisone	Corticosteroid

V. SYNERGISTIC EFFECTS OF CIRCULATING MIRNA AND DRUGS IN METABOLIC SYNDROME

5.1 Definition of Synergism

The term synergy comes from the Greek word 'synergos', meaning 'working together'. Synergy is broadly defined as the interaction or cooperation of two or more substances to produce a combined effect greater than the sum of their separate parts. In pharmacology, synergism is used in the treatment of multidrug-resistant bacterial infections, cancerous, and multifactorial diseases where pharmacological and therapeutic agents affect several pathways simultaneously, making treatment more effective.

5.2 miRNA Regulation of Drug Metabolism

5.2.1 GLP-1 Receptor Agonists for Obesity

GLP-1 receptor agonists (RAs) have become central in managing obesity and type 2 diabetes, primarily through appetite suppression and metabolic regulation. Through central pathways, GLP-1 RAs modulate brain regions controlling appetite. Through peripheral pathways, they improve glycaemic control by enhancing insulin secretion, reducing glucagon release, delaying gastric emptying, and regulating gut hormones. They also reduce triglycerides and LDL cholesterol, mitigate adipose tissue inflammation, and

minimize ectopic fat deposition.

5.2.2Mechanisms of Antihypertensive Drugs

Thiazide diuretics (hydrochlorothiazide) and thiazide-like agents (chlorthalidone, indapamide) inhibit the Na/Cl pump in the distal convoluted tube, increasing sodium excretion and potassium loss. ACE inhibitors prevent conversion of angiotensin I to angiotensin I, a potent vasoconstrictor, reducing blood pressure by dilating vessels and decreasing aldosterone secretion. Beta-blockers inhibit catecholamines from binding to beta receptors, producing a negative inotropic effect that reduces heart rate and oxygen consumption. Alpha-blockers act as antagonists of α-adrenergic receptors, inhibiting sympathetic nervous system activation.

5.2.3Mechanisms of Lipid-Lowering Drugs

Statins competitively inhibit HMG-CoA reductase, the rate-limiting step of cholesterol synthesis, primarily targeting hepatocytes. By inhibiting this enzyme, statins reduce de novo cholesterol synthesis, activate the SREBP-2 pathway, and increase the level of the LDL receptor, resulting in higher hepatic uptake of apoB-containing lipoproteins. Ezetimibe inhibits Niemann – Pick C1-Like 1 (NPC1L1) and thus intestinal cholesterol absorption; 10 mg of ezetimibe reduces fractional cholesterol absorption rates by 54%.

5.2.4Antidiabetic Drug Mechanisms

Metformin activates adenosine monophosphate-activated protein kinase (AMPK) in the liver, inhibiting gluconeogenesis and reducing hepatic glucose synthesis. It also improves insulin sensitivity by activating insulin receptor expression and enhancing tyrosine kinase activity. SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) inhibit SGLT2 in the proximal convoluted tubule, preventing glucose reabsorption and enhancing urinary glucose excretion. Alpha-glucosidase inhibitors (acarbose, voglibose, miglitol) delay carbohydrate absorption in the gastrointestinal tract by competitive inhibition of intestinal enzymes.

VI. CIRCULATING MIRNA SIGNATURES IN METABOLIC SYNDROME

6.1 C-miRNA Associated with Central Obesity

Circulating miRNAs originate from cells or tissues and are released into the circulation packaged in extrace lular vesicles (EVs) or bound to lipoproteins or Argonaute-2 (AGO2). Via the circulation, they can reach and affect the metabolism of distant organs and contribute to pathogenesis, development, and progression of obesity. Select circulating miRNAs appear to be associated with obesity (e.g., miR-140, -142, -125, and -423) or with obesity-related metabolic disturbances (e.g., miR-122 and -34 with NAFLD and insulin resistance, and miR-103 and -107 with T2D and insulin resistance in children and adults).

6.2 C-miRNA Associated with Hypertension

The molecular mechanisms by which miRNAs regulate hypertension are complex and multifaceted. miRNAs target the 3′ UTR of mRNA molecules, regulating synthesis of specific proteins involved in cardiovascular function including blood vessel tone, cardiac function, and inflammation. Research has highlighted miRNA-based therapies as capable of modulating expression of key genes involved in hypertension, leading to improvements in blood pressure and cardiovascular function.

6.3. C-miRNA Associated with Dyslipidemia and Hepatic Lipid Metabolism miRNAs are involved in multiple processes of hypercholesterolemia, including lipid synthesis (miR-122), fatty acid biosynthesis (miR-33), and lipoprotein formation and secretion (miR-27a). miRNAs are also involved in HDL metabolism from synthesis to clearance. Therapies based on miR-34 and miR-122 are already in phase 2 clinical trial development, indicating that miRNAs as therapeutic agents for hyperlipidemia are becoming a clinical reality.

6.4. C-miRNA Associated with Pro-Inflammation

Inflammation is primarily regulated by miRNAs through their altered expression in immune cells. The biogenesis of miRNAs is often regulated at different stages during the inflammatory response. miRNAs regulate different stages of inflammation — initiation, expansion, and resolution — through positive and negative feedback mechanisms. In positive feedback, the cascade restricts pathogen invasion and promotes tissue repair. In negative feedback (activated during severe inflammation), tissue homeostasis is maintained.

Table 2 Key miRNA-Drug Synergistic Interactions in MetS

Sr.	Disease/Domain	miRNA	Drug	Interaction
1	Dyslipidemia/NAFLD	miR-122	Statins	Synergistic lipid lowering
2	Cholesterol/HDL regulation	miR-33a/b	Statins	ABCA1-mediated cholesterol efflux
3	Insulin sensitivity/Endothelial	miR-126	Pioglitazone	PI3K/AKT/mTOR activation
4	Inflammation/Insulin resistance	miR-146a, miR-155	Metformin	NF-κB pathway modulation

VII. TREATMENT OF METABOLIC SYNDROME

7.1 Lifestyle Modifications

All components of metabolic syndrome are linked with lifestyle; a healthy lifestyle is an effective way of treating risk factors and preventing associated cardiovascular complications. The primary goal is to create a balance between calorie requirement and intake. Recommended modifications include physical activity, a healthy diet, avoiding tobacco use, good sleep hygiene, and decreased alcohol consumption. Contemporary guidelines recommend a 7 – 10% reduction in baseline body weight over 12 months. The American Heart Association recommends 150 minutes of moderate-intensity or 70 minutes of high-intensity physical activity weekly. A diet rich in vegetables, fruits, legumes, whole grains, nuts, and fish is recommended to reduce cardiovascular disease risk.

7.2. Pharmacological Management

Pharmacologic options are considered after ensuring implementation of a healthy lifestyle. Drug therapy is commonly recommended for dyslipidemia, hypertension, and insulin resistance or diabetes me litus. The drugs recommended for treating insulin resistance include metformin, DPP-4 inhibitors, GLP-1 agonists, and pioglitazone. Patients with metabolic syndrome typica ly require multiple medications and must be monitored closely for treatment compliance.

7.3Combination Antihypertensive Therapy

When monotherapy fails, combination therapy should be considered. Combining two antihypertensive medications reduces blood pressure approximately five times more than doubling the dose of one drug. ARB-diuretic or ACE inhibitor-CCB combinations are superior to beta-blocker-diuretic combinations. When the combination of two medications does not achieve the treatment goal, a third agent (usually from thiazide-like diuretics, CCB, ACE inhibitors, or ARBs) should be added.

7.4 Surgical Management

Patients with severe obesity may benefit from bariatric surgery, considered the most influential single therapy for metabolic syndrome. Common procedures include laparoscopic adjustable gastric banding, laparoscopic Roux-en-Y gastric bypass, and laparoscopic sleeve gastrectomy. Bariatric surgery is recommended for patients with BMI $\geq$ 40 kg/m² or BMI $\geq$ 35 kg/m² with comorbidities. Long-term follow-up is essential to avoid surgical, nutritional, and psychiatric complications.

VIII. CONCLUSION

Circulating microRNAs are mechanistically and clinically relevant in metabolic syndrome. They serve both as biomarkers reflecting pathophysiology and as modulators of drug response through effects on drug-metabolizing enzymes (DMEs), transporters, and signalling networks. Key miRNAs such as miR-122, miR-33a/b, miR-126, miR-146a, and miR-155 have demonstrated synergistic interactions with statins, antidiabetics, and anti-inflammatory drugs used in MetS management. Future research priorities include standardizing c-miRNA measurement, validating reproducible multi-miRNA signatures across cohorts, integrating miRNA profiling with pharmacogenomics for precision prescribing, and advancing miRNA-based therapeutics through robust safety testing.

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