



Review Article



miRNA Dysregulation of AGE/RAGE Pathway in Metabolic Syndrome: A Novel Analysis Strategy Utilizing miRNA-profiling Data

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Abstract

Metabolic syndrome (MetS) is associated with a plethora of different comorbidities. Exploring its key molecular mechanisms, such as advanced glycation end product and its receptor (AGE/RAGE) pathway, holds great potential. Numerous sources agree that targeting the AGE/RAGE pathway is a potential therapeutic strategy for MetS. However, the regulation of AGE/RAGE by microRNAs (miRNAs) in the context of MetS is still poorly understood. This review aimed to provide a systematic picture of the influence of miRNAs on AGE/RAGE in the context of MetS, with a particular focus on its ligands and receptors. This review achieves this in two ways: through an inductive “bottom-up” approach realized by a classical descriptive literature search, and through a deductive/synthetic “top-down” approach based on carefully selected miRNA profiling studies in MetS and its comorbidities. Although the initial inductive approach allowed the identification of some miRNAs of interest, almost all articles on this topic focus on the regulation of processes exclusively involved in atherogenesis. The new deductive approach has broadened the research horizon: It has enabled the discovery of new promising miRNAs and allowed for ranking different comorbid pathologies in MetS according to the degree of miRNA dysregulation of AGE/RAGE. Thus, in addition to atherosclerosis, significant miRNA dysregulation of AGE/RAGE was also described in MetS, particularly in immune cells, as well as in subcutaneous adipose tissue in obesity. This review, along with the novel approaches to systematizing the data contained therein may contribute to the understanding of MetS pathogenesis and the search for targets for the treatment of MetS.

Introduction

Metabolic syndrome (MetS) is one of the most important pathological conditions of our time. Although it is difficult to determine its exact worldwide prevalence (due to the variability of its operational definition and diagnostic criteria for different populations), the prevalence of its components is alarmingly high in many countries,¹ and MetS itself is associated with increased mortality.² According to the criteria of the American Heart Association and the National Heart, Lung, and Blood Institute (2009), MetS is diagnosed when at least three of the following criteria are present si-

multaneously: abdominal obesity (based on waist circumference), hypertension, hyperglycemia (or previously diagnosed insulin resistance (IR) or type 2 diabetes mellitus (T2DM)), elevated triglyceride levels, and decreased levels of high-density lipoprotein cholesterol (HDL-C) in the blood.¹ However, MetS is associated with many other comorbidities: non-alcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD), and especially atherosclerosis.¹ It is important also to mention less frequently discussed but equally significant diseases associated with MetS, such as polycystic ovary syndrome (PCOS) and other diabetic complications including various angiopathies, nephropathies, and even inflammatory gum disease—periodontitis—which, according to many studies, is associated with diabetes.^{3,4} For the sake of brevity, all the pathologies mentioned above (both the diagnostic criteria and the comorbid pathologies) are referred to as “MetS comorbidities” in this article.

The study of MetS is interesting not only with regard to the individual components but also from a systemic perspective—as a coherent whole—due to the comorbidity of the individual pathologies. Within this paradigm, it is of particular interest to define and

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investigate the signaling pathways that connect comorbid pathologies in MetS, like “nodes”, to form a synergistic whole. One of the promising candidates for the role of the link between MetS comorbidities is advanced glycation end products and their receptor (AGE/RAGE) signaling.

RAGEs are multiligand receptors for advanced glycation end products that are expressed on the surface of vascular and lung epithelium,^{5,6} liver,⁷ and immune cells.⁸ High RAGE expression has been found in obesity, T2DM, CVD, Alzheimer’s disease, cancer, etc.⁹ Various researchers have studied the role of the AGE/RAGE pathway in MetS and its comorbidities in depth and from different angles (e.g., relevant review articles^{10–12}) and consistently conclude that targeting the AGE/RAGE pathway is a promising strategy for the treatment of MetS comorbidities.

The targeting of different molecular mechanisms is undoubtedly an important topic at the crossroads of different biological and medical disciplines, but we should not forget that key elements in the regulation of gene activity in the human body are various epigenetic factors, in particular, microRNAs (miRNAs). Data collected over years of research point to the great importance of these small non-coding nucleic acids. The discovery of miRNA and its role in post-transcriptional gene regulation was awarded the Nobel Prize in Physiology or Medicine in 2024.

We consider the discussion of the biogenesis and functions of miRNAs irrelevant in this review, as this topic has already been described in detail in the literature—for example, in the recent ontology of 2024.¹³ Instead, we focus on the role of miRNAs in dysregulating the AGE/RAGE pathway in patients with MetS. This information can be used to develop approaches to interfere with this signaling. Although the term “miRNA regulation” is well established in the literature, we deliberately use the term “miRNA dysregulation” in our work: there are miRNAs that target genes of the AGE/RAGE pathway while they themselves are not altered in MetS and its comorbidities. The regulation performed by these miRNAs can be simultaneously significant and unchanged in MetS. We aimed to describe the part of miRNA influence on AGE/RAGE signaling that is specifically altered, i.e., dysregulated, in MetS.

miRNAs in the theranostics of MetS and its comorbidities have been extensively studied,¹⁴ but the AGE/RAGE axis, which is involved in the pathogenesis of many diseases, has been undeservedly neglected. The few reviews that exist on miRNA dysregulation of the AGE/RAGE axis focus either on one component of MetS, particularly T2DM,^{15,16} or on the best-studied RAGE receptor ligand high-mobility group protein B1 (HMGB1).¹⁷ Many studies focus only on miRNA regulation of downstream genes that act as secondary messengers in AGE/RAGE signaling — Janus kinase-signal transducer and activator of transcription (JAK/STAT), c-Jun N-terminal kinases (JNK), mitogen-activated protein kinases (MAPK), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), NADPH oxidase (NOX),¹⁶ but almost completely neglect (as we will describe below) the canonical RAGE receptor, its soluble decoy forms (endogenous soluble eRAGE and soluble sRAGE), and the other receptors that bind AGEs. In addition, the aforementioned JAK/STAT, JNK, MAPK, and NF-κB proteins are involved in a variety of signaling pathways and are not exclusively activated in the context of the AGE/RAGE axis, so it is not entirely accurate to describe their miRNA dysregulation in the context of AGE/RAGE signaling.

Therefore, this review aimed to draw a systemic picture of miRNA dysregulation of AGE/RAGE signaling in the context of MetS and its comorbidities, with particular focus on its ligands

and receptors.

This review consists of two chapters: The first (in the style of a scoping review) briefly summarizes key information on the function and involvement of the AGE/RAGE pathway in MetS and its comorbidities. The second chapter is directly dedicated to miRNA dysregulation of the AGE/RAGE pathway in the context of MetS and its comorbidities and is again divided into two parts. The first part is an inductive “bottom-up” approach implemented by a classical descriptive review: interactions between miRNAs and elements of the AGE/RAGE pathway in MetS comorbidities that have been demonstrated and published in research articles are considered—this approach allows us to get an overview of the studies performed so far. In contrast, the second deductive/synthetic “top-down” approach, which was implemented through a systematic literature search, consists of first looking for miRNAs that are differentially expressed in MetS comorbidities and then identifying among these miRNAs those that target AGE/RAGE signaling genes. This approach (which we have not found in the previous literature) allows us to significantly expand the first part and develop a more systemic view of miRNA dysregulation of the AGE/RAGE signaling pathway in the context of MetS.

AGE/RAGE signaling and its general role in the pathogenesis of MetS and its comorbidities

RAGEs are multiligand receptors for advanced glycation end products expressed in tissues with abundant vasculature, including lung, heart, nervous tissue, vascular endothelium, etc.⁹ Activation of RAGE mediates the development of a cellular response to a series of damage-associated molecular patterns (DAMPs or alarmins). Overexpression and/or hyperstimulation of RAGE has been found in patients with metabolic disorders.¹⁸ By binding to RAGE on the platelet surface, various ligands promote the activation of adhesion molecules and glycoproteins that mediate platelet aggregation and atherosclerotic plaque formation, thereby increasing the risk of microthrombosis in T2DM.¹⁹ The AGE/RAGE interaction has been found to influence changes in arterial elasticity/stiffness, reduce the bioavailability and activity of the nitric oxide molecule,²⁰ and, conversely, increase the expression of the vasoconstrictor factor endothelin-1, which contributes to the development of hypertension.²¹

The AGE/RAGE axis activates intracellular proinflammatory signaling pathways²²: NADPH oxidase–reactive oxygen species, MAP kinases: extracellular signal-regulated kinase (ERK), JNK, p38, phosphoinositide 3-kinases (PI3K) and protein kinase B alpha (AKT), and JAK–STAT. Activation of these signaling pathways stimulates the expression of NF-κB, which modulates the synthesis of proinflammatory cytokines. In addition, activation of NADPH oxidase increases both the oxidative stress of the endoplasmic reticulum and the concentration of reactive oxygen species in the mitochondria, which in turn also leads to the activation of NF-κB.

The AGE/RAGE axis thus contributes directly to the development of MetS comorbidities, which are discussed in more detail in the following sections of this chapter. [Figure 1](#) shows schematically the most important aspects of AGE/RAGE signaling and its effects on processes that are essential in the context of MetS.

AGEs and other RAGE ligands

AGEs are advanced glycation end products that can be either exogenous or endogenous. Their classification and chemistry can be found in detail in a very thorough review by Twarda-Clapa *et*

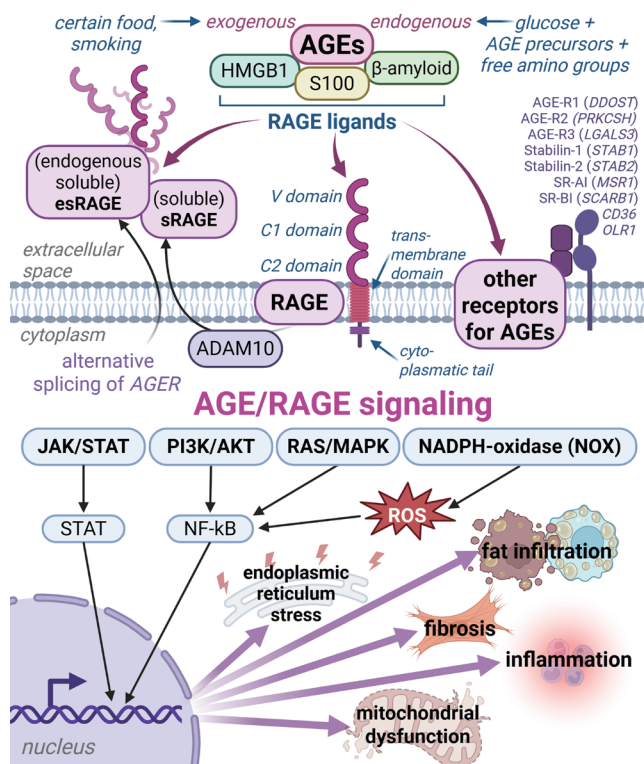


Fig. 1. Schematic representation of the AGE/RAGE axis and downstream processes relevant to MetS. ADAM10, A Disintegrin And Metalloproteinase domain 10; AGE, advanced glycation end products; esRAGE, endogenous soluble receptor for advanced glycation end products; HMGB1, high-mobility group protein B1; JAK/STAT, Janus kinase-signal transducer and activator of transcription; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K/AKT, phosphoinositide 3-kinases/protein kinase B alpha; RAGE, receptor for advanced glycation end products; RAS/MAPK, RAS proteins/mitogen-activated protein kinases; ROS, reactive oxygen species; sRAGE, soluble receptor for advanced glycation end products.

*al.*²³ AGEs are formed by a non-enzymatic condensation reaction between the carbonyl groups of reducing sugars and free amino groups of nucleic acids, proteins, or lipids.²³ Exogenous AGEs are ingested with various foods and cigarette smoke, and endogenous AGEs are formed locally as a result of hyperglycemia associated with diabetes or oxidative stress associated with adipose tissue (AT) dysfunction.^{12,22} Among the large variety of AGEs, the best known and diagnostically most significant is certainly glycated hemoglobin, which belongs to the class of glucose-derived AGEs.²³

In addition to AGEs, various proteins are ligands for RAGEs: firstly, HMGB1, also known as amorphin.⁹ HMGB1 is a nuclear non-histone protein involved in the regulation of chromatin folding, but under oxidative stress, HMGB1 becomes hyperacetylated and plays the role of a DAMP. Hyperacetylated HMGB1 acts as a ligand for the RAGE receptor and Toll-like receptor 4 on monocyte-macrophage cells,²⁴ leading to the development of an inflammatory response. It is worth noting that HMGB1 can act in an autocrine manner, i.e., it can be secreted and bound by the same cell, thus closing the AGE/RAGE axis in a vicious cycle that contributes to disease progression.²⁴ There is another large group of ligands for RAGE that are also involved in cell cycle and ion channel regulation: the calcium-binding proteins calgranulins (S100), namely S100A1, A2, A4, A5, A6, A7, A8, and A9 (the latter two

forming a dimer called calprotectin), A11, A12, A13, S100B, and S100P.²⁵ Finally, beta-amyloid peptides, which are frequently associated with the development and progression of Alzheimer's disease,²⁶ are also ligands for RAGE.⁹

RAGE and other AGE receptors

The membrane receptor RAGE (*AGER* gene) contains a signal peptide, four domains (V, C1, C2, and transmembrane domain), and a cytoplasmic tail.²⁷ In addition to the main form, RAGE has two soluble isoforms: "soluble" sRAGE and "endogenous secretory" esRAGE with an alternative amino acid sequence at the C-terminus, which are formed by proteolytic cleavage and alternative splicing, respectively.²⁷

In addition to RAGE, as shown in Figure 1, there are other forms of receptors for AGEs. First, soluble RAGE isoforms (esRAGE and sRAGE) function as extracellular decoy receptors for RAGE ligands and act as inhibitors of RAGE signaling pathways. Their synthesis has been shown to be significantly reduced in patients with metabolic disorders (obesity, T2DM).²⁸ In addition to RAGE and its soluble isoforms, there are receptors that capture AGEs – they are described in detail in the above-mentioned review.²³ Firstly, three so-called anti-RAGEs: AGE-R1 (gene *DDOST*), protein kinase C substrate AGE-R2 (gene *PRKCSH*), and galectin-3 AGE-R3 (gene *LGALS3*). There are also several scavenger receptors that bind AGEs, such as macrophage scavenger receptor 1 SR-AI (gene *MSR1*) from class A, scavenger receptor class B oxidized low-density lipoprotein (oxLDL) type I SR-BI (gene *SCARB1*), and CD36 (gene of the same name) from class B, stabilins 1 and 2 (genes *STAB1* and *STAB2*) from class H, and oxLDL receptor 1 (gene *OLR1*) from class E. There is a functional nuance – SR-A and CD36 bind AGEs as ligands, but do not promote their endocytic uptake and subsequent degradation.²⁹ In general, the diversity of receptors for AGEs is quite large, and their functional significance in the context of MetS and its comorbidities varies depending on the receptor; this topic is worth a separate discussion and will not be addressed further in this review.

AGE/RAGE and obesity

The AGE/RAGE axis plays an important role in the development of AT dysfunction,¹² by promoting AT hypertrophy, which is associated with mitophagy, impaired mitochondrial dynamics, and the development of mitochondrial dysfunction. This, in turn, leads to a decrease in the secretion of leptin and adiponectin. Disruption of the adiponectin/AMPK/M2 polarization cascade of macrophages promotes the infiltration of AT by proinflammatory M1 macrophages.³⁰ AT has the ability to accumulate AGEs, which could be related to the lower level of AGEs in the plasma of obese patients compared to healthy donors.³¹ In addition, higher expression of the *AGER* receptor in subcutaneous—but not visceral—AT might play a key role in the development of AT inflammation and IR in obese patients.³² Activation of the AGE/RAGE axis is known to suppress mitochondrial uncoupling protein 1 (UCP1) mediated thermogenesis and reduce AT browning.³³ Thus, activation of the AGE/RAGE axis contributes to the progression of obesity and its complications.

AGE/RAGE and NAFLD

The AGE/RAGE axis is involved in the development of NAFLD, one of the main components of MetS. The AGE/RAGE axis suppresses the expression of the transcription factor peroxisome proliferator-activated receptor alpha (*Ppar- α*) (and consequently suppresses the expression of the PPAR- α protein), which stimu-

lates lipolysis and subsequent beta-oxidation of fatty acids in the liver.³⁴ Suppression of PPAR- α leads to excessive accumulation of free fatty acids in the liver, resulting in steatosis. Activation of the AGE/RAGE axis may also be related to mitochondrial function—for example, suppression of mitochondrial uncoupling protein 2 (UCP2) leads to increased expression of AGE and RAGE in the liver, resulting in persistent oxidative stress, the development of inflammation, and fibrosis.³⁵

In addition to hepatocytes themselves, AGEs can also bind to liver macrophages. Thus, Kupffer cells take up AGEs, which facilitates the inflammatory response and increases the expression of NOX subunits.³⁶ There are data on the link between atherosclerosis and NAFLD via the AGE/RAGE axis: the liver, as the central metabolic organ, actively absorbs AGEs, promoting the development of chronic inflammation and the production of proinflammatory mediators, which in turn damage the vascular endothelium.³⁷ As found in a chronic intermittent hypoxia mouse model of NAFLD, the AGE/RAGE axis also stimulates the expression of the transcription factor *Nf-kB*,³⁸ which increases the expression of proinflammatory cytokines in the liver and thus stimulates the expression of *Ager* itself. This creates a vicious circle with positive feedback. It is also worth noting that C-reactive protein increases the expression of the RAGE receptor via NF- κ B p65 in human coronary artery endothelial cells.³⁹

It is important to mention a particular study by Wouters *et al.*⁴⁰ in which it was shown that knockout of the RAGE receptor in mice did not reduce the progression of steatosis due to the remaining high concentration of AGEs in the liver. The researchers suggested that to prevent the development of NAFLD, in addition to eliminating RAGE, the function of anti-RAGE receptors, whose expression is suppressed by excess AGEs, must be restored.⁴⁰

Other RAGE ligands, namely S100A11, promote the progression of hepatic steatosis by activating the AKT–mammalian target of rapamycin (mTOR) signaling pathway.⁴¹ HMGB1 can be used as a prognostic marker for NAFLD complications: elevated plasma HMGB1 levels have been shown to be associated with liver fibrosis in children with NAFLD.⁴² HMGB1 also acts as a DAMP in the context of a high-fat diet and then activates the immune response by interacting with RAGE receptors on macrophages and Kupffer cells.¹⁷ It has also been demonstrated that sRAGE and AGE levels could be used for NAFLD identification.⁴³

AGE/RAGE and T2DM

Hyperglycemia in T2DM is associated with excessive formation of AGEs in the peripheral blood. The AGE/RAGE axis has been found to stimulate the active production of mitochondrial superoxide, favoring mitochondrial dysfunction and prolonged oxidative stress.⁴⁴ Due to the development of mitochondrial dysfunction, pancreatic β -cells die, and insulin secretion therefore decreases, promoting the complications of T2DM and forming a vicious cycle.⁴⁵ Increased levels of exogenous AGEs in T2DM inhibit anti-inflammatory signaling pathways by suppressing the anti-RAGE receptor, which in turn leads to increased hyperacetylation of NF- κ B p65 and expression of the cytokine tumor necrosis factor (TNF).⁴⁶ As mentioned in the introduction, periodontitis is currently considered both one of the causes and a consequence (complication) of T2DM.⁴⁷ AGE/RAGE signaling is thought to be a link between these pathologies. It has been shown that in patients with diabetes, the AGE concentration in the blood, epithelium, and gingival vessels is higher when these diabetics suffer from periodontitis.⁴⁸ At the same time, sRAGE correlates negatively with proinflammatory cytokines. The authors therefore hypothesize

that the AGE/RAGE axis is directly related to the development of periodontitis in patients with T2DM. Last but not least, some polymorphisms in the *RAGE* receptor gene have been associated with a higher risk of developing T2DM.⁴⁹

AGE/RAGE and CVD

In addition to the listed MetS comorbidities, the AGE/RAGE pathway actively influences the progression of CVD. The involvement of this axis in the pathogenesis of various CVDs has been discussed in detail in a recent review.⁵⁰ We would like to highlight and add the most important molecular patterns influenced by the AGE/RAGE axis in this context. For example, excessive addition of AGEs to primary human aortic epithelial cells disrupts mitochondrial dynamics by acting on the mitochondrial regulatory genes *DRP1*, *MFN1*, *MFN2*, and *OPA1*.⁵¹ The AGE/RAGE axis also suppresses the expression of *SIRT1*,⁴⁶ the master regulator of mitochondrial biogenesis,⁵² and decreases the expression of the antioxidant *SOD2*, which favors myocardial dysfunction.⁵³ The AGE/RAGE axis promotes the development of persistent oxidative stress, in part through activation of NOX.⁵⁴ In addition, the AGE/RAGE axis increases the permeability of endothelial cells and facilitates the uptake of excess LDL by vascular smooth muscle cells.⁵⁵ AGE binding to RAGE activates multiple signaling pathways that promote atherogenesis, including increased expression of macrophage inflammatory factor-1 (MIP-1), interleukin 1 (IL-1) and TNF, which mediate leukocyte adhesion and vascular inflammatory responses, leading to mitochondrial dysfunction and endothelial cell death.⁵⁶

AGE/RAGE and PCOS

Last but not least, we turn to the effects of AGE/RAGE signaling on the development of PCOS. The etiology of PCOS still does not seem to be fully understood, but AGE/RAGE signaling appears to be a promising target in the development of this comorbid pathology of MetS. According to the results of a recent meta-analysis by Bahreiny *et al.*,⁵⁷ there is a clear link between AGE levels in serum and the development of PCOS. In addition, AGEs accumulate in granulosa cells and disrupt hormonal balance by decreasing ERK1/2 activation through effects on luteinizing and follicle-stimulating hormones,^{58,59} which may lead to the progression of both PCOS and the development of other MetS comorbidities, i.e., IR.³ For example, serum HMGB1 levels have been found to be associated with IR in PCOS patients.⁶⁰

The dynamics of the concentration of protective sRAGE in the follicular fluid of PCOS patients are contradictory. One study showed that the sRAGE concentration in the follicular fluid of PCOS patients was significantly reduced compared to non-PCOS patients,⁶¹ while another study with a similar cohort found no significant differences in follicular fluid sRAGE concentration.⁶²

AGEs promote the main component of PCOS pathogenesis—chronic inflammation—by activating the AGE/RAGE/NF- κ B cascade.⁶³ In addition, activation of NF- κ B (and also NADPH oxidase) leads to the development of oxidative stress. This process plays an essential role in any nosology of MetS and is also crucial in the pathogenesis of PCOS.⁶⁴ Finally, endoplasmic reticulum stress, which is also associated with the accumulation of AGEs in granulosa cells, might lead to PCOS progression.⁶⁵

miRNA dysregulation of AGE/RAGE signaling in MetS and its comorbidities

Since miRNAs can regulate the expression of multiple target

genes, miRNA molecules and their target genes are linked in an intricate network of signaling pathways. Some miRNAs are tissue-specific, while others can be packaged into vesicles and move through the body in the peripheral blood in freely circulating form (aggregated with Argonaute proteins) or as part of exosomal vesicles.⁶⁶ Thus, pathologically altered tissue can use miRNA to influence other tissues. Numerous studies on pathologies associated with MetS suggest that miRNA is a suitable and fairly accurate diagnostic and prognostic biomarker,¹⁶ making the search for specific miRNAs associated with disease development relevant today.

Although the role of AGEs and their receptors in the context of MetS is quite well defined, as described above, their epigenetic miRNA dysregulation in MetS, which may be important for both therapy and diagnostics of this syndrome and its comorbidities, has not yet been described in detail. Therefore, we were confronted with the task of systematizing the disparate data on miRNA-messenger RNA (mRNA) interactions available in the world literature and databases and compiling them in the most informative way possible. We opted for two approaches: inductive “bottom-up” (AGE/RAGE axis genes – miRNAs targeting them in the context of MetS comorbidities) and deductive “top-down” (miRNAs significantly differentially expressed in MetS comorbidities – their (experimentally proven) target genes – AGE/RAGE axis genes among the target genes and the degree of miRNA influence on them).

Inductive “bottom-up” approach: Key genes of the AGE/RAGE axis and the miRNAs targeting them in the context of MetS comorbidities

In this section, we focus on what we believe to be the most important target genes of the AGE/RAGE axis, whose functions and roles in MetS have already been mentioned: RAGE ligands (*HMGB1*, various *S100s*), the RAGE receptor, and other receptors for AGEs (*DDOST*, *PRKCSH*, *LGALS3*, *STAB1*, *STAB2*, *SR-AI*, *SR-BI*, *CD36*, *OLRI*). This section is a classic descriptive review, so the criteria for article selection were relatively soft:

1. The search for articles on the topic was performed using the following queries (variable-specific queries are in *italics*): “(*gene of interest*) and (miRNA) and (*MetS comorbidity*)” in the PubMed database.
2. Original research articles were selected in which the data were obtained from human biomaterials or human cell models.
3. All retracted articles were excluded.
4. The year of publication was not taken into account.

The description of the studies presented below is also supplemented by Table 1, in which the studies are described in a concise and model-oriented form.^{67–85}

AGEs

Both exogenous and endogenous AGEs undoubtedly play an important role in AGE/RAGE signaling; however, it is not possible to consider their miRNA dysregulation because neither the AGEs themselves (there are no specific genes and therefore no mRNA transcripts for them), nor the transcripts of the genes of the enzymes that form them (since, as mentioned above, the reactions of AGE formation do not require enzymes), can be the subject of direct miRNA regulation. Note that in this regard, it would be more accurate to use the term “ligand/RAGE signaling” in our review, but the term “AGE/RAGE signaling” is generally accepted and implies, among other things, the involvement of non-glycated ligands, so we have chosen not to replace it.

HMGB1 (gene *HMGB1*)

When vascular endothelial cells were treated with excess glucose, administration of an hsa-miR-126 mimetic significantly reduced inflammation and oxidative stress. It has been shown that the protective effect of hsa-miR-126 is precisely due to the suppression of *HMGB1* (a proven direct target of miR-126) and NOX (as a consequence of *HMGB1* suppression).⁶⁷ Hsa-miR-126 has been proposed as a marker for the prediction of prediabetes and T2DM: a significant decrease of this miRNA was found in the blood of patients with T2DM.⁸⁶ In a cell experiment with primary human endothelial progenitor cells, the expression of hsa-miR-126 decreased significantly when AGEs were added.⁸⁷ Thus, hsa-miR-126 not only interferes with the genes of the AGE/RAGE axis but is also influenced by AGEs themselves. This leads to the hypothesis that a decreased *HMGB1* level can be observed in diabetes due to increased AGEs.

In the livers of patients with hepatocellular carcinoma (which can develop as a result of NAFLD), miR-320a-3p was significantly reduced. Researchers found that hsa-miR-320a suppressed *HMGB1* in the liver, preventing it from functioning as a DAMP. On the contrary, suppression of hsa-miR-320a-3p promoted the activation of the AGE/RAGE axis through increased expression of *HMGB1*. In addition, a negative correlation between hsa-miR-320a-3p and *HMGB1* was found in liver tissue from hepatocellular carcinoma patients.⁶⁸ It is known that the plasma level of hsa-miR-320a was reduced in women with MetS compared to non-MetS women with a normal body mass index and showed a significant negative correlation with body mass index, waist circumference, triglyceride level, glucose level, and the homeostasis model assessment of insulin resistance index.⁶⁹ Another miRNA, hsa-miR-328-3p, significantly reduced *HMGB1* expression, homeostasis model assessment of insulin resistance levels, and ox-LDL-induced inflammation in a cell-based model of endothelial dysfunction in atherosclerosis.⁷⁰

S100 (various genes listed in section 1.1)

No studies were found on the relationship between miRNA and S100 in the context of MetS and its comorbidities.

Beta-amyloid (gene *APP*)

The authors have chosen not to include this gene in this review for the following reasons:

1. Beta-amyloid as a RAGE ligand is not the *APP* gene product itself, but peptides (beta-amyloid fibrils) formed by proteolytic cleavage of the *APP* product; therefore, miRNA regulation of beta-amyloid cannot be directly considered⁸⁸;
2. Beta-amyloid fibrils are primarily associated with neurodegenerative diseases, and their role in MetS is secondary.

RAGE (gene *AGER*)

Surprisingly, only one paper was found on miRNA dysregulation of the major receptor of the AGE/RAGE axis: hsa-miR-5591-5p directly targeted the 3'-UTR of *AGER* and repressed its expression. *In vitro*, hsa-miR-5591-5p was shown to promote AT stem cell survival and enhance the ability to repair diabetic wounds via the AGE/AGER axis.⁷¹ It is worth noting that the journal editors left a note on 01/20/2022 that the study is under investigation, but as of 11/22/2024, the article has not yet been retracted.

sRAGE

Researchers found that hsa-miR-21-3p was significantly in-

Table 1. miRNA regulation of ligands and receptors in the AGE/RAGE signaling pathway

microRNA-No	Target	Experimental model of MetS comorbidities	Changes in the level of miRNA expression in the experiment	References
hsa-miR-126-3p and mmu-miR-126-3p	HMGB1	Endothelial dysfunction in atherosclerosis: <i>in vitro</i> HUVECs treated with high-glucose medium; <i>in vivo</i> high-fat diet fed diabetic ApoE ^{-/-} mice with induced pancreatic injury	Downregulated in HUVECs upon high-glucose treatment; reduced levels in aortic tissues of diabetic ApoE ^{-/-} mice	67
hsa-miR-320a-3p	HMGB1	Hepatocellular carcinoma: hepatic tissue from hepatocellular carcinoma patients; <i>in vitro</i> HepG2 and SK-hep-1 hepatocytes	Aberrant (mostly reduced) levels in tumoral tissues from hepatocellular carcinoma patients; reduced levels in the plasma of MetS patients	68,69
hsa-miR-328-3p	HMGB1	Endothelial dysfunction in atherosclerosis: HUVECs treated with oxLDL	Downregulated in HUVECs upon oxLDL treatment	70
hsa-miR-5591-5p and mmu-miR-5591-5p	AGER	Diabetic wound as a T2DM complication: <i>in vitro</i> primary human ADSCs treated by AGEs; <i>in vivo</i> diabetic mice wound model	Downregulated in ADSCs upon AGEs treatment	71
hsa-miR-21-3p	ADAM10	Endothelial dysfunction in atherosclerosis: human aortic VSMCs and human VECs treated by high-glucose medium	Upregulated in VECs (but not in VSMCs) upon high-glucose treatment	72
hsa-miR-128-3p	LGALS3	T2DM patients with or without MCI: PBMCs	Reduced levels in PBMCs of T2DM patients with MCI	73
hsa-miR-204-5p	MSRI	Foam cells in atherosclerosis: BMDMs, HMDMs, TEPMs and Raw 264.7 macrophages treated with oxLDL	Downregulated in HMDMs upon oxLDL treatment	74
hsa-miR-24-3p	SCARB1	Models of cells involved in cholesterol homeostasis: HepG2 hepatocytes and PMA-induced THP-1 macrophages incubated with differently labeled HDL	NI	75
hsa- and, respectively mmu-miR-185-5p/miR-96-5p/miR-223-3p	SCARB1	Models of cells, involved in cholesterol homeostasis: <i>in vitro</i> HepG2, Bel-7402 and HL-7702 hepatocytes treated with Dil-HDL and PMA-induced THP-1 macrophages; <i>in vivo</i> high-fat diet fed ApoE ^{-/-} mice	Livers of the high-fat diet fed ApoE ^{-/-} mice: miR-185-5p and miR-96-5p levels reduced. THP-1 upon PMA stimulation: miR-185-5p, miR-96-5p and miR-223-3p levels increased	76
hsa-miR-223-3p and mmu-miR-223-3p	SCARB1	Models of cells, involved in cholesterol homeostasis: <i>in vitro</i> J774 macrophages and Huh7 hepatocytes treated with LPDS, HCAECs treated with HDL-C; <i>in vivo</i> cocoa butter diet fed ApoE ^{-/-} mice	Downregulated in J774 and Huh7 upon LPDS treatment and upregulated upon LDL-C treatment, elevated levels in cocoa butter diet fed ApoE ^{-/-} mice	77
hsa-miR-758-5p	CD36	Foam cells in atherosclerosis: THP-1 macrophages, treated with fluorescently labeled Dil-oxLDL	NI	78
hsa-miR-26a-5p	CD36	NAFLD (steatohepatitis): HepG2 hepatocytes treated with PM _{2.5} liposoluble extracts	Downregulated upon PM _{2.5} liposoluble extracts treatment	79
hsa-miR-204-3p	CD36	Foam cells in atherosclerosis: BMDMs, HMDMs, TEPMs and Raw 264.7 macrophages treated with oxLDL	hsa-miR-204-3p is localized in the nuclei of BMDMs, HMDMs and TEPMs. The levels in the cytoplasmic fractions remained unchanged upon oxLDL treatment	74
hsa-let-7g-5p and mmu-let-7g-5p	OLR1	Proliferation and migration of vascular smooth muscle cells (neointimal hyperplasia) in atherosclerosis: <i>in vitro</i> HASMCs treated with oxLDL; <i>in vivo</i> high-fat diet fed C57BL/6J mice	Downregulated upon oxLDL treatment. Was also on a high-fat diet fed mice as well in serum of hypercholesterolemic human subjects compared with healthy controls	80

Table 1. (continued)

microRNA-No	Target	Experimental model of MetS comorbidities	Changes in the level of miRNA expression in the experiment	References
hsa-let-7g-5p and mmu-let-7g-5p	OLR1	Neointimal hyperplasia in atherosclerosis: <i>in vitro</i> HASMCs treated with oxLDL; <i>in vivo</i> high-fat diet fed ApoE ^{-/-} mice	NI	81
hsa-miR-590-5p and mmu-let-7g-5p	OLR1	Angiogenesis in atherosclerosis: <i>in vitro</i> HUVECs treated with oxLDL; <i>in vivo</i> Marigel plugs inserted in the mice subcutaneous space	Downregulated upon oxLDL treatment	82
hsa-miR-320a-3p	OLR1	Endothelial dysfunction in atherosclerosis: HUVECs treated with oxLDL	Downregulated upon oxLDL treatment	83
hsa-miR-98	OLR1	Endothelial dysfunction in atherosclerosis: <i>in vitro</i> hypoxic injured HUVECs; plasma from patients with single-vessel, double-vessel, and multi-vessel coronary artery disease / healthy controls	Downregulated upon hypoxic injury in HUVECs and reduced in patients with occluded coronary artery disease	84
hsa-miR-24-3p	OLR1	No particular pathology: two human hepatic cell lines with different genotypes for rs1050286 (HeLa A/G versus HepG2 A/A)	NI	85

ADSCs, adipose-derived stem cells; AGE, advanced glycation end products; BMMDs, bone marrow-derived macrophages; Dil, 1,1'-dioctadecyl-3,3',3''-tetramethylindocarbocyanine perchlorate; HASMCs, human aortic smooth muscle cells; HCAECs, human coronary artery endothelial cells; HDL-C, high-density lipoprotein cholesterol; HMDMs, human monocyte-derived macrophages; HUVECs, human umbilical vein endothelial cells; LDL-C, low-density lipoprotein cholesterol; LPDS, lipoprotein-depleted serum; MCI, mild cognitive impairment; MetS, metabolic syndrome; miRNA, microRNA; NAFLD, non-alcoholic fatty liver disease; NI, not indicated; oxLDL, oxidized low-density lipoprotein; PBMCs, human peripheral blood mononuclear cells; PM2.5, particulate matter with an aerodynamic diameter less than 2.5 µm; PMA, phorbol-12-myristate-13-acetate; RAGE, receptor of advanced glycation end products; T2DM, type 2 diabetes mellitus; TEPMs, thioglycollate-elicited peritoneal macrophages; THP-1, a human monocytic cell line derived from an acute monocytic leukemia patient; VECs, human vascular endothelial cells; VSMC, vascular smooth muscle cells.

creased in vascular epithelial cells at high glucose concentrations in the culture medium. It was established that hsa-miR-21-3p targets *ADAM10*, an enzyme that stimulates the formation of sRAGE. When the expression of hsa-miR-21-3p increased, *ADAM10* was degraded to a greater extent, leading to a decrease in sRAGE levels and progression of atherosclerosis.⁷²

AGE-R1 (gene *DDOST*) and AGE-R2 (gene *PRKCSH*)

No studies were found on the relationship between miRNA and these genes in the context of MetS and its comorbidities.

AGE-R3 (galectin-3, gene *LGALS3*)

In a study of mild cognitive impairment (MCI) in T2DM, the plasma levels of galectin-3 were found to be significantly elevated in the group of patients with MCI. On this basis, the authors suggested using galectin-3 as a prognostic marker for MCI in T2DM. In the same study, hsa-miR-128-3p was found to be significantly reduced in the peripheral blood mononuclear cells (PBMCs) of T2DM patients and negatively correlated with the expression level of *LGALS3* in PBMCs. Hsa-miR-128-3p directly targets the 3'-UTR of *LGALS3*.⁷³

Stabilins 1 and 2 (genes *STAB1* and *STAB2*)

No studies were found on the relationship between miRNA and stabilins in the context of MetS and its comorbidities.

SR-AI (gene *MSR1*)

Hsa-miR-204-5p suppressed *MSR1* by directly targeting its 3'-UTR. The expression level of hsa-miR-204-5p was significantly reduced in the foam cell model of atherosclerosis.⁷⁴

SR-BI (gene *SCARB1*)

It was shown that hsa-miR-24-3p significantly reduced the uptake of HDL-C in HepG2 and THP1 cell cultures. The authors of the study demonstrated that this effect was achieved by inhibiting the *SCARB1* receptor (proven to be a direct target of hsa-miR-24-3p) in hepatocytes and macrophages, which is responsible for selective HDL-C uptake. Thus, the hsa-miR-24-3p antagonist could play a protective role in atherosclerosis.⁷⁵ Hsa-miR-185-5p, hsa-miR-96-5p, and hsa-miR-223-3p also led to a similar phenomenon: the addition of their mimetics to HepG2 cells resulted in significantly reduced uptake of labeled HDL-C. All three miRNAs were shown to directly target *SCARB1* and, as in the study described above, contributed to the development of atherosclerosis by interfering with this gene (as they impeded cholesterol metabolism in hepatocytes). It is noteworthy that the authors of the study did not address the other side of the issue—namely, the effects of oxLDL uptake on the liver itself and the possible development of NAFLD.⁷⁶ A similar study showed that hsa-miR-223-3p in Huh7 cells also regulated HDL-C uptake by suppressing *SCARB1*.⁷⁷ *SCARB1* is highly expressed not only in the liver but also in endothelial cells: it was also shown that inhibition of hsa-miR-223-3p led to increased *SCARB1* levels and HDL-C uptake in human coronary artery endothelial cells.

CD36 (gene *CD36*)

The miRNA mimetic hsa-miR-758-5p interfered with *CD36* in a foam cell model of atherosclerosis: hsa-miR-758-5p negatively regulated macrophage binding of oxLDL and reduced cholesterol accumulation in macrophages, which is suggested by the researchers as a promising strategy for the treatment of atherosclerosis.⁷⁸ In human monocyte-derived macrophages, hsa-miR-204-3p sup-

pressed the expression of *CD36*, but according to the results of the luciferase reporter assay, there is no direct canonical interaction between hsa-miR-204-3p and *CD36*. The researchers demonstrated an alternative pathway: hsa-miR-204-3p was found to be translocated to the nucleus where, together with the Argonaute-2 protein, it did not repress translation as canonically assumed, but rather affected the nuclear transcription of the *CD36* gene.⁷⁴ Another miRNA, hsa-miR-26a, interfered with *CD36* (its proven direct target) in a cellular model of steatosis and steatohepatitis, thereby suppressing the processes of cellular lipogenesis.⁷⁹

OxLDL receptor 1 (gene *OLR1*)

The receptor for oxLDL (the protein is often referred to as lectin like oxidized low density lipoprotein receptor 1 (LOX-1) in studies) is associated with the development of atherosclerosis. When oxLDL was added to the primary cell culture of human aortic smooth muscle cells, the expression of *OLR1* increased significantly in response to an increase in the concentration of its major ligand. At the same time, the addition of oxLDL suppressed the expression of hsa-let-7g, which directly targets *OLR1*. This negative relationship between oxLDL level and hsa-let-7g expression could explain the fact that oxLDL causes an increase in *OLR1* expression in a cellular model of atherosclerosis.⁸⁰ This was later also demonstrated in hyperlipidemic mice (ApoE^{-/-}): intravenous administration of hsa-let-7g mimetics attenuated atherosclerotic lesion formation, which was accompanied by a significant reduction in Lox-1 production. Taken together, these studies suggest that hsa-let-7g has a protective and anti-atherosclerotic effect by suppressing *OLR1*.⁸¹

The hsa-miR-590-5p mimetic significantly reduced levels of *OLR1* (its proven direct target) in a model of endothelial dysfunction in atherosclerosis, thereby preventing oxLDL-mediated angiogenesis.⁸² In a similar cell model of atherosclerosis, hsa-miR-320a-3p was also shown to interfere with *OLR1* (its proven direct target), leading to increased cell viability.⁸³ Decreased expression of hsa-miR-98 was detected in the human umbilical vein endothelial cell line (when cultured under hypoxic conditions), and the level of hsa-miR-98 was also decreased in the plasma of patients with single-, double-, and multivessel coronary artery disease. The hsa-miR-98 mimetic decreased *OLR1* levels and thereby significantly increased the viability of endothelial cells in culture.⁸⁴ No luciferase reporter was used in this study, so a direct link between hsa-miR-98 and *OLR1* could not be established.

In addition, the strength of miRNA-mRNA interaction may depend on the presence of some polymorphisms. For example, hsa-miR-24-3p (*OLR1* is a proven direct target) interfered differently with *OLR1* in HeLa and HepG2 cell cultures, depending on the presence of the rs1050286 polymorphism: thus, *OLR1* was significantly more strongly suppressed in the HeLa cell line (the hsa-miR-24-3p site in the *OLR1* gene is heterozygous) than in the HepG2 cell culture (the binding site in the *OLR1* gene is homozygous for the polymorphism).⁸⁵

Thus, the influence of miRNAs on AGE receptors and their ligands in the context of MetS and its comorbidities seems to be poorly studied: There are virtually no data on miRNA regulation of the major AGE receptors, and data on scavenger receptors focus on the uptake of different cholesterol fractions and not on AGEs.

Deductive “top-down” approach: Differentially expressed miRNAs in MetS comorbidities and their involvement in dysregulation of the AGE/RAGE axis

The inductive “bottom-up” approach presented in the previous

section has proven to be rather insufficiently systemic: It remains unclear to what extent comorbid pathologies in MetS differ in how miRNAs modulate AGE/RAGE signaling. Finally, the literature search conducted revealed a lack of data on miRNA dysregulation of central genes of the AGE/RAGE axis, namely the ligands S100s and various receptors for AGEs.

For all these reasons, we decided to complement our review with a reverse deductive (or synthetic-systematic) “top-down” approach. Briefly, this approach can be described as follows: We collected human miRNA profiling data related to MetS comorbidities and derived differentially expressed miRNAs (DEMs) from these studies. We then performed an automated search for target genes of the collected DEMs in the miRTarBase database for experimentally proven miRNA-target interactions (MTIs) and compared the target genes of these DEMs with genes of the AGE/RAGE pathway (extended WikiPathways WP2324 pathway) to analyze the degree of miRNA dysregulation of this pathway in the context of MetS. In implementing this approach, we faced a number of important dilemmas that required compromises in either the scope of our analysis or its accuracy.

A search for human miRNA profiling studies was performed in PubMed and Gene Expression Omnibus. We selected studies based on the following parameters/aspects:

1. Pathology. MetS itself and the following comorbidities were considered: obesity, IR, atherosclerosis, NAFLD, periodontitis, and PCOS.
2. Localization of the tissue sample. Preference was given to tissues “corresponding” to the pathology: e.g., liver in NAFLD, subcutaneous white adipose tissue (sWAT) in obesity, etc. Two exceptions were made that are worth explaining in more detail: Obesity was also considered in visceral AT exosomes in addition to sWAT, as visceral AT is an active metabolic organ and can contribute significantly to systemic miRNA dysregulation via exosomes.⁸⁹ MetS was considered both in plasma (which contains circulating miRNAs, and can therefore be considered a systemic reflection of miRNA dysregulation) and in PBMCs, as meta-inflammation is one of the key aspects of MetS.⁹⁰ In the context of the above, we use the term “pathology-localization” in this review for the sake of clarity. This means that the effects of miRNA dysregulation in pathology are considered in a specific organ/tissue and not in pathology in general.
3. Method to study miRNA expression. We limited ourselves to data obtained exclusively with microarrays: This method has acceptable parameters for both accuracy and performance and, moreover, is commonly used in miRNA profiling practice.⁹¹
4. All retracted articles were excluded.
5. The year of publication was not taken into account.

As the analysis of the original articles has shown, even within the same method, there is no agreement on how to define “differential expression” (i.e., DEMs). Therefore, we included in our deductive analysis those miRNAs that were defined as DEMs by the authors themselves according to their own criteria. It is important to emphasize that the miRNAs considered in this section are not equivalent in their potential contribution to dysregulation of the AGE/RAGE pathway, as the strength of the interaction is influenced by the level of miRNA expression (and by other factors that we have not considered in this approach, such as the strength of miRNA binding to its target, steric accessibility of the landing site, etc.).

Studies describing the tissue type, patient sample, and number of miRNAs analyzed, as well as the number of DEMs identified by the authors, are listed in Table 2.^{89,90,92-106}

Table 2. miRNA profiling studies included in the top-down approach

Disease	Biological sample	Case group and control group	Micro array size	Number of DEMs	References
Metabolic syndrome	PBMCs isolated immediately after blood collection	Subjects undergoing venipuncture: 20 MetS and 10 healthy control subjects	1146 human miRNAs (detected 688)	52 up- and 29 downregulated	90,92
Metabolic syndrome	Blood plasma	Women undergoing venipuncture under 8–12 h fasting conditions: 10 MetS, 8 healthy non-obese	1773 human miRNAs (detected NI)	8 up- and 13 downregulated	93,94
Obesity	Adipocyte-exosomes from visceral AT (greater omentum)	Adolescent women undergoing bariatric surgery or unrelated abdominal procedures: 7 obese and 5 lean	1773 human miRNAs (detected NI)	16 up- and 28 downregulated	89,95
Obesity	Abdominal subcutaneous white AT	Women undergoing: 1: elective surgical procedures: 6 non-obese and 13 obese without T2DM; 2: fat biopsy by needle aspiration: 26 non-obese and 30 obese	1: 723 human miRNAs (detected NI); 2: 678 human miRNAs (detected NI)	1: 5 up- and 4 downregulated; 2: 2 up- and 18 downregulated, 1 miRNA is common (hsa-miR-139-5p downregulated)	1: 96,97 ; 2: 98,99
Insulin resistance	Abdominal subcutaneous white AT	Women undergoing fat biopsy by needle aspiration: 8 obese insulin-resistant and 21 obese insulin-sensitive	847 human miRNAs (detected 205)	4 up- and 10 downregulated	100,101
NAFLD	Liver tissue	Subjects undergoing a laparoscopic gastric bypass or sleeve gastrectomy: 15 NAFLD and 15 non-NAFLD (histology proven)	1438 human miRNAs (detected between 299 and 389)	39 up- and 1 downregulated	102
Atherosclerosis	Vascular samples (plaques)	Subjects undergoing endarterectomy, or an abdominal aortic bypass, or coronary artery bypass: 12 atherosclerotic plaques from peripheral arteries and 6 non-atherosclerotic left internal thoracic arteries (each biospecimen from different subject)	866 human miRNAs (detected NI)	42 up- and 33 downregulated	103
PCOS	Ovarian theca interna tissue	Women undergoing laparoscopy and/or ovarian wedge resection: 10 PCOS and 8 non-PCOS with normal insulin sensitivity	1700 miRNAs annotated in miRBase 16.0 (detected NI)	7 up- and 3 downregulated (targeting insulin action related and androgen producing related genes)	104
Periodontitis	Gingival tissue	Subjects with severe periodontitis: 10 normal-weight and 10 obese (without T2DM)	1773 human miRNAs (detected NI)	13 up- and 22 downregulated	105,106

AT, adipose tissue; MetS, metabolic syndrome; miRNA, microRNA; NAFLD, non-alcoholic fatty liver disease; NI, not indicated by the authors; PBMC, peripheral blood mononuclear cells; PCOS, polycystic ovary syndrome; T2DM, type 2 diabetes mellitus.

There are two main approaches to determine the MTI: bioinformatic prediction and experimental confirmation. Bioinformatic methods are based on nucleotide sequence and/or machine learning; experimental methods are based on next-generation sequencing, microarrays, polymerase chain reaction, western blot, luciferase reporter, and other methods.¹⁰⁷ Confirmed miRNA–target interactions are collected in specialized databases (miRTarBase, DIANA–TarBase, and miRecords). The authors acknowledge and draw the reader’s attention to the fact that experimental methods of MTI verification are inevitably subject to the so-called streetlight effect (or drunkard’s search), i.e., they limit the list of MTIs to those that, for one reason or another, have previously been of interest to researchers (appeared on a microarray or were selected for polymerase chain reaction/blot/luciferase reporters, etc.). Despite

this bias, experimental methods were favored in this review as they better and more accurately reflect the current state of knowledge. MTIs were searched in miRTarBase v. 9.0 (this database is not only large, but the data in it are also regularly revised).¹⁰⁷ miRTarBase v. 9.0 contains both low-throughput (more accurate) and high-throughput (less accurate) experimental methods for MTI detection, which the reader should consider when evaluating the results presented.

Originally, the same list of genes considered in the previous section (ligands and receptors only) was intended for this section. However, these genes have a relatively low number of experimentally proven MTIs, which limits the applicability of such an approach for them (as you can see in Supplementary Table 1 on the “Limited Analysis” list). In this context, it was decided to

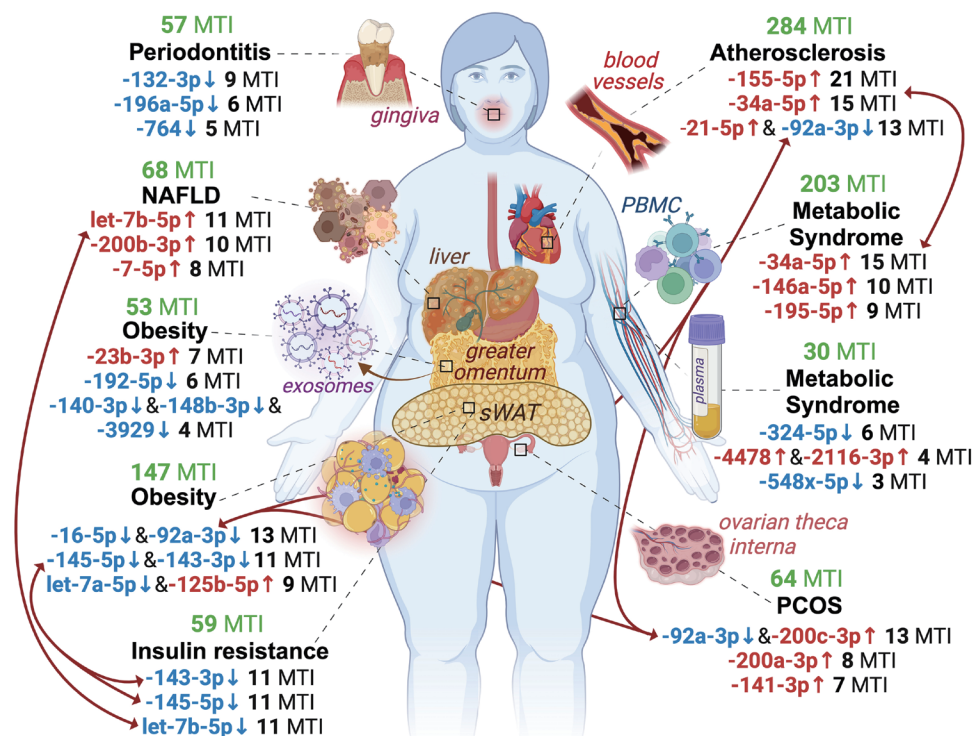


Fig. 2. miRNA dysregulation of AGE/RAGE signaling by differentially expressed miRNAs (DEMs) in pathology-localizations. For each pathology-localization, the total number of miRNA-target interactions (MTIs) with AGE/RAGE signaling genes and the top miRNAs (by number of MTIs) are shown. The color of the miRNA and the direction of the arrow indicate whether the miRNA is upregulated (red, up) or downregulated (blue, down) in this pathology-localization. Common miRNAs are connected by arrows. AGE, advanced glycation end products; miRNA, microRNA; NAFLD, non-alcoholic fatty liver disease; OTI, ovarian theca interna; PBMC, peripheral blood mononuclear cells; PCOS, polycystic ovary syndrome; RAGE, receptor of advanced glycation end products; sWAT, subcutaneous white adipose tissue.

extend the list of signaling genes to all genes of the AGE/RAGE pathway. Genes involved in AGE/RAGE signaling were exported from WP2324 (<https://www.wikipathways.org/pathways/WP2324.html>) and supplemented with the following genes: *CD36*, *PRKCSH*, *STAB1*, *STAB2*, *OLRL1*, and *SCARB1* (other receptors for AGEs,²³ *HMGB1*, *S100A1*, *S100A4*, *S100A6*, *S100A7*, *S100A8*, *S100A9*, *S100A11*, *S100A12*, *S100A13*, *S100A14*, *S100B*, *S100P* (ligands for the RAGE receptor),^{25,108} *ADAM10* (metalloprotease that determines the formation of sRAGE¹⁰⁹), *SOD2* (superoxide dismutase, fulfills similar functions as *SOD1*, which is already listed in WP2324¹¹⁰), *NOX1*, *CYBB*, *NOX3*, *NOX4*, *NOX5* (in WP2324 signaling they are listed under the general name “NOX” but are not listed as specific genes themselves; evidence for their common involvement can be found at the link¹¹¹).

miRNA dysregulation of the common AGE/RAGE axis: Comparison of different pathology-localizations in MetS comorbidities

Using the described approach, 304 unique DEMs were collected, of which 41 DEMs were found in more than one pathology-localization. Of these recurrent DEMs, 25 showed similar dynamics of expression changes in all pathology-localizations (increased or decreased everywhere), while the remaining 16 showed inconsistent (opposite) dynamics. The following observation was also very interesting: When comparing the lists of DEMs, it was found that the localization shaped the similarity of the altered miRNA profile much more than the pathology itself. Thus, obesity was considered in two localizations: in exosomes derived from visceral AT (44

DEMs) and in sWAT (combined) (28 DEMs),^{89,96,98} a comparison of these lists did not reveal a single common miRNA. However, the miRNA profile in sWAT was considered in another study, but then in IR,¹⁰⁰ and comparison of the profiles in obesity (28 DEMs) and IR (14 DEMs) revealed five common DEMs with complete concordance of expression dynamics (in both pathologies hsa-miR-143-3p, hsa-miR-145-5p, hsa-miR-26a-5p, hsa-miR-378a-3p, and hsa-miR-652-3p were downregulated in sWAT).

AGE/RAGE signaling was found to be significantly dysregulated by DEMs in each MetS comorbidity, as shown in Figure 2, which shows how many MTIs were found in each of the pathologies, as well as the three most “significant” (with the largest number of MTIs with AGE/RAGE signaling genes) miRNAs. The greatest dysregulation was observed in atherosclerosis in plaque samples (64 of 75 DEMs targeted AGE/RAGE pathway genes with 284 experimentally proven MTIs), MetS in PBMCs (64 of 81 DEMs with 203 MTIs), and obesity in sWAT (27 of 28 DEMs with 147 MTIs). The results obtained are somewhat consistent with the findings of the above “bottom-up” approach (see Table 1), as a significant part of the information on miRNA dysregulation of AGE/RAGE genes that we found in research articles was specifically described in the context of atherosclerosis.

The full results of the analysis (all DEMs in the pathology-localizations retrieved from the studies and all their MTIs with AGE/RAGE signaling genes) are listed in Supplementary Table 1. Supplementary Table 1 comprises six sheets (all contents are listed on their corresponding sheet “Description”), it is not necessary for the understanding of this article: all important results of the analysis

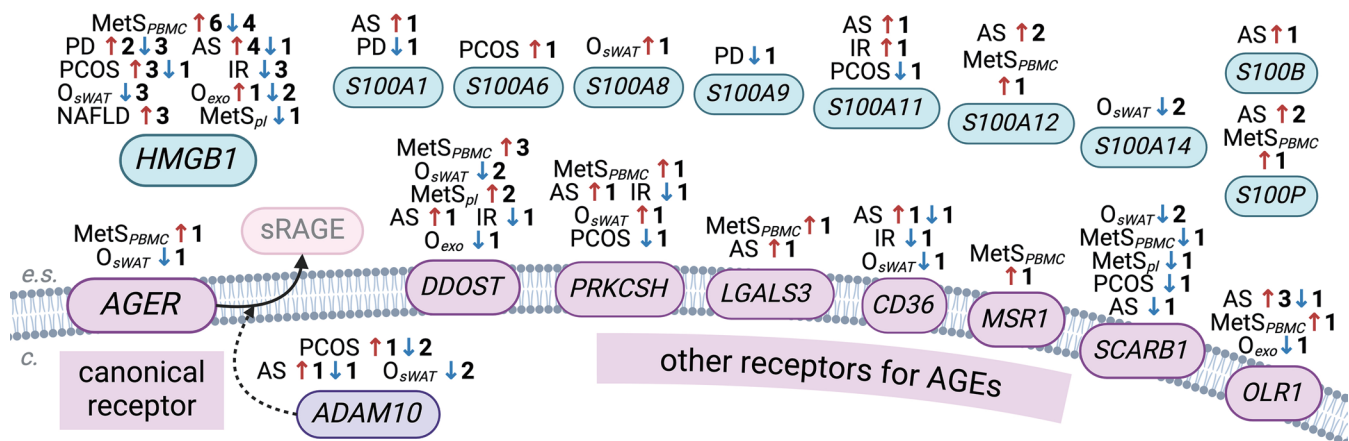


Fig. 3. miRNA dysregulation of AGE/RAGE genes with differentially expressed miRNAs (DEMs) in pathology-localizations: focus on genes of interest (ligands and receptors). The pathology-localizations and their DEMs targeting a specific gene are listed above the genes. Next to it is a number with an arrow (up or down): the number represents the total number of miRNA–target interactions (MTIs) between elevated DEMs (red arrow pointing up) and decreased DEMs (blue arrow pointing down) and that particular gene. AGE, advanced glycation end products; AS, atherosclerosis; c., cytoplasm; e.s., extracellular space; IR, insulin resistance; MetS_{PBMC}, metabolic syndrome in peripheral blood mononuclear cells; MetS_{pl}, metabolic syndrome in plasma; miRNA, microRNA; NAFLD, non-alcoholic fatty liver disease; O_{exo}, obesity in adipocyte-exosomes; O_{sWAT}, obesity in subcutaneous white adipose tissue; PCOS, polycystic ovary syndrome; PD, periodontitis; RAGE, receptor of advanced glycation end products.

are presented graphically and in tables in the article itself. The supplementary table is added merely for the transparency of the publication and may be useful for those readers who wish to reproduce a similar method or check the validity of the conclusions drawn in this article.

Interesting data were also obtained from the DEMs themselves, for example: hsa-miR-34a-5p, which has 15 known MTIs involving 15 AGE/RAGE axis genes (*AKT1*, *CASP3*, *CASP8*, *CASP9*, *CYBB*, *CYCS*, *HMGB1*, *MAP2K1*, *MAPK3*, *MMP2*, *MMP7*, *NFKB1*, *S100P*, *SRC*, and *STAT1*), was elevated in PBMCs in MetS as well as in atherosclerotic plaques. It is well known that monocyte-macrophage cells transform into foamy macrophages in the presence of excess lipids and make an undeniable contribution to atherogenesis.¹¹² Indeed, hsa-miR-34a-5p has already been shown to promote atherosclerosis development,¹¹³ but its effects in the context of the AGE/RAGE axis have not yet been considered.

As mentioned above, expression of hsa-miR-145-5p and hsa-miR-143-3p was significantly reduced in sWAT in both obesity and IR – both miRNAs have 11 MTIs with a total of 19 AGE/RAGE axis genes (genes common to both miRNAs are in bold): *AKT1*, *CD36*, *EGFR*, *HIF1A*, *HRAS*, *IRS1*, *MAPK1*, *MMP13*, *MMP14*, *MMP2*, *MMP9*, *ROCK1*, *SMAD2*, *SMAD3*, *SPI*, *STAT1*, *STAT3*, *STAT5A*, and *TIRAP*, suggesting an important role of AGE/RAGE signaling in the development of these pathologies.

A striking finding was that hsa-miR-92a-3p (13 MTIs with the genes *ADAM10*, *DIAPH1*, *EZR*, *HIF1A*, *HMGB1*, *MAPK8*, *MAPK9*, *NFKB1*, *PRKCA*, *SCARB1*, *SPI*, *STAT3*, and *TIRAP*) was simultaneously reduced in obesity (sWAT), atherosclerosis, and PCOS. The development of PCOS is associated with obesity and the progression of CVD, including atherosclerosis: Women with PCOS have higher intima-media thickness (one of the diagnostic criteria for atherosclerosis) compared to the control group.¹¹⁴ Thus, reduced hsa-miR-92a-3p expression could represent a link between the development of atherosclerosis in obesity and PCOS.

However, some significant DEMs related to dysregulation of the AGE/RAGE axis showed contradictory expression dynamics in different pathology-localizations. For example, let-7b-5p, which has 11 MTIs with 11 AGE/RAGE axis genes (*DIAPH1*,

HIF1A, *HMGB1*, *HRAS*, *MAPK1*, *MSN*, *NFKB1A*, *SOD2*, *SPI*, *STAT1*, and *STAT5A*), was elevated in the liver in NAFLD but decreased in sWAT in IR. Glucose intolerance is recognized as an important factor in the pathogenesis of NAFLD,¹¹⁵ so the presence of common DEMs between these pathologies was expected (however, there was only one such DEM – the let-7b-5p mentioned above). Nonetheless, the different directions of the changes in their expression leave many questions unanswered: it is not clear what consequences this has both in the broadest sense and in the context of AGE/RAGE signaling.

miRNA dysregulation of AGE/RAGE pathway receptors and their ligands in pathology-localizations with MetS comorbidities

As written above, there is particularly little information in the literature on miRNA dysregulation of genes of greatest interest for this topic: AGE/RAGE ligands and receptors. Therefore, we further focused on the interpretation of the data obtained specifically for these genes. The results of the analysis are shown graphically in Figure 3. Accordingly, the *HMGB1* ligand and the *DDOST* receptor were the most miRNA-dysregulated genes in MetS comorbidities.

For other ligands (except *HMGB1* and *OLR1*) and receptors of the AGE/RAGE axis, the data were rather sparse. We would like to emphasize again that the picture shown does not reflect the actual extent of miRNA dysregulation, but the part studied so far, as the genes of interest have a different number of known experimentally proven MTIs. This is reflected in Table 3,¹⁰⁷ which clearly shows that many AGE/RAGE axis genes have very few experimentally confirmed MTIs, namely *S100A1*, *A4*, *A6*, *A7*, *A8*, *A9*, *A12*, *A14*, *S100B*, *S100P*, as well as *AGER* itself, and the anti-receptors *PRKCSH*, *LGALS3*, and the scavenger receptor *MSR1* have fewer than 10 entries in miRTarBase v. 9.0. And there are no entries at all for the genes *S100A13*, *STAB1*, and *STAB2*. Based on this information, it was possible to calculate the “fraction of miRNA dysregulation” for the genes of interest in the MetS comorbidities. Thus, for the ligands *S100A6*, *S100A12*, *S100A14*, *S100P*, *AGER* itself, and for *PRKCSH*, of all known MTIs, ≥50% were associated with MetS,

Table 3. Fraction of miRNA-dysregulated major genes of the AGE/RAGE axis in MetS comorbidities (The number of experimentally proven MTIs was calculated from the miRTarBase v. 9.0 database¹⁰⁷)

Gene	All miRTarBase v. 9.0 entries (MTIs)	Entries for DEMs in MetS comorbidities (MTIs)	Fraction of MTIs for MetS comorbidities in all miRTarBase v. 9.0 MTIs
<i>HMGB1</i>	179	30	17%
<i>S100A1</i>	4	1	25%
<i>S100A4</i>	1	0	0%
<i>S100A6</i>	1	1	100%
<i>S100A7</i>	1	0	0%
<i>S100A8</i>	3	1	33%
<i>S100A9</i>	7	1	14%
<i>S100A11</i>	24	3	13%
<i>S100A12</i>	2	2	100%
<i>S100A13</i>	ND	ND	ND
<i>S100A14</i>	2	2	100%
<i>S100B</i>	3	1	33%
<i>S100P</i>	4	2	50%
<i>AGER</i>	3	2	67%
<i>ADAM10</i>	15	5	33%
<i>DDOST</i>	16	7	44%
<i>PRKCSH</i>	6	3	50%
<i>LGALS3</i>	3	1	33%
<i>CD36</i>	21	2	10%
<i>STAB1</i>	ND	ND	ND
<i>STAB2</i>	ND	ND	ND
<i>MSR1</i>	7	1	14%
<i>SCARB1</i>	14	3	21%
<i>OLR1</i>	81	6	7%

AGE, advanced glycation end products; DEMs, differentially expressed miRNAs; MetS, metabolic syndrome; miRNA, microRNA; MTIs, miRNA–target interactions; ND, no data; RAGE, receptor of advanced glycation end products.

confirming the importance of their miRNA dysregulation in the context of this syndrome.

Finally, it remained to compare the results of the bottom–up and top–down approaches and to find out whether there were common miRNAs between them. It turned out that a significant proportion matched: of the 17 miRNAs for which studies were found in the first approach (see Table 1), eight were also found in the alternative second approach.

hsa-miR-126-3p – was downregulated in the cell model of atherosclerosis and suppressed *HMGB1*⁶⁷; was downregulated in PBMCs in MetS and sWAT in obesity; has MTIs with *AKT1*, *IRS1*, *MMP7*, *NFKB1A*, and *ROCK1*.

hsa-miR-328-3p – was downregulated in the cellular model of atherosclerosis and suppressed *HMGB1*⁷⁰; was upregulated in PBMCs in MetS; has MTIs with *EZR*, *HMGB1*, and *DIAPH1*.

hsa-miR-21-3p – was upregulated in a cellular model of atherosclerosis and suppressed *ADAM10*⁷²; was upregulated in plaques in atherosclerosis; has MTIs with *CYCS*, *CDC42*, *STAT3*, *RHOA*, *EGFR*, and *CASP8*.

hsa-miR-758-5p – suppressed *CD36* in a cell model of foamy

macrophages in atherosclerosis⁷⁸; was downregulated in visceral AT exosomes in obesity; has no MTIs with AGE/RAGE signaling genes.

hsa-miR-26a-5p – was downregulated in a cell model of NAFLD and suppressed *CD36*⁷⁹; was downregulated in sWAT in obesity and in IR; has MTIs with *NOS2* and *PRKCD*.

hsa-miR-128-3p – suppressed *LGALS3*; was downregulated in PBMCs in diabetics with MCI⁷³; was upregulated in plaques in atherosclerosis and in PBMCs in MetS; has MTIs with *EGFR*, *CASP3*, *MAP2K1*, *MAPK14*, *SP1*, *SMAD2*, *LGALS3*, and *IRS1*.

hsa-miR-185-5p – suppressed *SCARB1* in cellular models of cholesterol uptake in atherosclerosis; was downregulated in the liver of diabetic mice fed a high-fat diet⁷⁶; was downregulated in sWAT in obesity; has MTIs with *AKT1*, *CDC42*, *DIAPH1*, *RHOA*, *SCARB1*, and *SOD2*.

let-7g-5p – suppressed *OLR1* in cell models of neointimal hyperplasia in atherosclerosis,^{80,81} was downregulated in this model⁸⁰; was upregulated in ovarian theca tissue in PCOS; has MTIs with *CASP3*, *HMGB1*, *SMAD2*, and *SOD2*.

The data obtained allow us to consider these miRNAs as prom-

ising for closer applied studies, as their role as DEMs in MetS comorbidities has been demonstrated, as well as the fact that these miRNAs directly target key genes in AGE/RAGE signaling.

The limitations and further perspectives of the deductive “top-down” approach

In this review, we analyzed studies related to miRNA dysregulation of the major genes involved in the AGE/RAGE axis in MetS comorbidities. First, we performed a classic descriptive review of the relevant research studies. As this section was based on individual publications and conducted “bottom-up”—from the AGE/RAGE axis genes of interest to the miRNAs targeting them in models of MetS comorbidities—we labeled this approach “inductive”. The main conclusion that can be drawn from the inductive approach is that the information available in the literature on miRNA dysregulation of the AGE/RAGE axis is very limited. First, most information is devoted to the *HMGB1* ligand and selected scavenger receptors (namely *OLR1* and *SCARB1*), whereas miRNA dysregulation of *AGER* (including its soluble isoforms), other receptors for AGEs, and all *S100* calgranulins remains virtually unexplored. Second, most studies were performed in atherosclerosis models (14 of the 19 articles), which inevitably gives a biased picture in the context of the whole MetS. Third, the studies focus primarily on miRNA regulation of cholesterol uptake processes (as a significant proportion of AGE receptors primarily take up various lipoproteins) rather than on AGEs themselves. Theoretically, the data obtained can be extrapolated to AGE signaling, but this has yet to be confirmed in practice.

Thus, the inductive approach proved to be insufficiently systemic and did not allow us to draw a holistic picture of miRNA dysregulation of the AGE/RAGE axis in MetS. This prompted us to test an alternative approach—“top-down”, i.e., in the opposite direction: from miRNAs significant for MetS comorbidities to genes of interest. This approach has been termed “deductive” or, alternatively, “synthetic” in the context of this work, as we merged data from different MetS comorbidities into a single system. The deductive approach has given us promising insights, but it is necessary to point out the hardly avoidable shortcomings of the deductive synthetic approach. The results we have obtained have a number of limitations:

1. The parameters used to determine the “DEM” in miRNA profiling studies vary, and therefore, the possible effects of these regulatory interactions differ as well.
2. The initial amount of miRNA contained in the microarray (i.e., the pool from which the DEM could be determined) varies between studies, which might affect the occurrence of false negatives in subsequent analysis.
3. The degree of acquired knowledge about the respective miRNA—and accordingly the number of its known MTI entries in databases—varies, which may, in turn, influence the occurrence of false negatives.
4. The inductive approach presents much less data, but their quality is higher, as almost all articles include the luciferase reporter method (the gold standard for determining the MTI), while the databases (such as miRTarBase) also include “less strongly evidenced” MTIs (e.g., proven by next-generation sequencing).

However, despite the limitations, the synthetic approach seems promising as it allows disparate data to be summarized in a formalized representation that is more accessible for analysis and understanding. We believe that the innovative synthetic approach we propose is the major advantage of our article. It is universal, as it can be applied to other signaling or molecular mechanisms in

all pathologies or conditions (in which miRNA profiling has been performed). In the future, the approach can be improved by adding a layer of meta-analysis of data from different miRNA profiling studies (with standardization of “DEM” criteria between different studies) and/or introducing bioinformatic predictions instead of accessing databases of experimentally proven MTIs. The latter will significantly broaden the scope of the analysis and include miRNAs that have not been studied so far.

The main findings of the review and clinical implications

The inductive approach identified two notable miRNAs targeting two different AGE/RAGE axis genes: hsa-miR-320a-3p (targets *HMGB1* and *OLR1*) and hsa-miR-24-3p (*SCARB1* and *OLR1*). Both miRNAs have a significant impact on processes associated with the development of atherosclerosis: endothelial dysfunction due to hyperlipidemia (hsa-miR-320a-3p) and cholesterol biogenesis in macrophages and hepatocytes (hsa-miR-24-3p). The deductive approach has allowed us to rank the comorbid pathologies according to the degree of miRNA dysregulation of AGE/RAGE signaling: the highest number of MTIs with AGE/RAGE axis genes was found for atherosclerosis in plaque biopsies, MetS in PBMC, and obesity in sWAT. Furthermore, it was possible to add to the information on miRNA dysregulation of *DDOST*, *PRKCSH*, and various *S100* genes. Moreover, the deductive approach uncovered miRNAs associated with different pathologies, such as hsa-miR-92a-3p, which is dysregulated in three pathology-localizations (PCOS in ovarian theca, atherosclerosis in plaques, and obesity in sWAT). The investigation of such miRNAs could be promising with regard to their integrative function between different MetS comorbidities.

In comparison to similar reviews by colleagues Piperi *et al.*¹⁶ and Shrivastav *et al.*,¹⁵ we did not consider the issue of miRNA downregulation of AGE/RAGE signaling exclusively in T2DM and its complications, but attempted to provide a holistic picture in MetS. At the same time, we only used results obtained on human biomaterial and cell lines in our work to avoid unjustified extrapolation from animal models to human molecular physiology. In addition, we tried to pay attention to the least-studied targets—the receptors for AGEs and other ligands of AGE/RAGE signaling—and not only to the RAGE receptor and downstream genes, as has been done by colleagues. This approach allowed us to obtain a more detailed picture of miRNA dysregulation of the AGE/RAGE signaling pathway in MetS and even to discover “common” miRNAs between the pathologies (the aforementioned hsa-miR-92a-3p, as well as hsa-miR-34a-5p, hsa-miR-145-5p, hsa-miR-143-3p, and hsa-let-7b-5p), which hypothetically have high therapeutic potential.

The treatment of MetS and its main component, obesity, is one of the most important challenges of modern healthcare, as the prevalence of this disease is steadily increasing worldwide and has already reached the status of an international epidemic: over 13% of the world’s population already suffers from this disease.^{116,117} Once a person has been diagnosed with obesity, the first step is to try to change the patient’s lifestyle.¹¹⁷ One of the promising areas here appears to be the Internet of Things—it seems that the use of personalized and accessible monitoring can motivate patients and increase their adherence to intervention strategies, even in children and adolescents with obesity.¹¹⁸ However, as the summary of randomized controlled trials of lifestyle modification for weight loss shows, this approach has a relatively small effect, and many patients require more radical steps. Although bariatric (metabolic)

surgery remains the most effective and long-term treatment option,¹¹⁷ it seems very important to bring more benign and technologically advanced treatments into widespread use. In terms of drug therapy, the range of pharmacotherapeutic agents available for the treatment of obesity is very large, with new drugs being developed every year. Without wishing to diminish the merits of this approach in any way, it must be emphasized that the development of gene therapy strategies to influence MetS has been and continues to be very promising, as an alternative or adjunct to conventional drugs.

Targeting the promising miRNAs identified in our analysis has been shown to affect key metabolic and pro-inflammatory signaling pathways. For example, overexpression of mmu-miR-145 (via a lentiviral vector) in db/db mouse models suppressed macrophage infiltration into the liver, reduced body weight, and optimized glucose metabolism, and also significantly reduced the size of atherosclerotic plaques in the aorta of Apoe^{-/-} mice.¹¹⁹ Inhibition of mmu-miR-143-3p (by intravenous administration of antagomirs) protected against insulin resistance in mouse models of MetS.¹²⁰ A meta-analysis of seven animal studies showed that mmu-miR-34a antagonists improved the lipid profile of the liver by lowering cholesterol, triglyceride, aspartate aminotransferase, and alanine aminotransferase levels, demonstrating high therapeutic potential in NAFLD.¹²¹ As for hsa-miR-92a-3p, which according to our analysis showed potential in three pathologies, there is indeed evidence that it is a promising therapeutic target: For example, simultaneous inhibition (by intravenous retro-orbital injection) of mmu-miR-92a-3p and mmu-miR-489-3p significantly reduced the area of atherosclerotic lesions in the aorta of Apoe^{-/-} mice.¹²² Transfection of hsa-miRNA-92a-3p mimic into hTERT-immortalized human aortic endothelial cells resulted in reduced basal as well as NADPH-stimulated superoxide generation in a cellular model; furthermore, high concentrations of hsa-miR-92a-3p in epicardial adipose tissue were associated with a lower risk of cardiovascular events in patients.¹²³ A PCOS cell model transfected with the hsa-miR-92a-3p mimetic showed a significant decrease in the expression of *CYP17A1*, *CYP11A1*, and *DENND1A* genes (genes of the steroidogenic pathway that produces androgens), which represents a promising therapeutic approach for PCOS characterized by hyperandrogenism.¹²⁴

Thus, the promising miRNAs identified by our proposed analytical strategy certainly have therapeutic potential, which is confirmed by third-party studies. However, there are no studies directly linking the therapeutic effect of these miRNAs to AGE/RAGE signaling—this currently appears to be a major gap that needs to be addressed. In addition, we reiterate that unexpectedly few studies were found addressing miRNA targeting of non-canonical receptors for AGEs and other gene-encoded ligands for RAGE. And since these receptors and ligands are produced by a variety of cells and tissues, it is very important to pay more attention to them in further studies—only then will we be able to gain a more holistic understanding of the role of this signaling in MetS.

For the reasons mentioned in section 2.2.3, the classic literature review (inductive approach) proved to be insufficiently systematic and failed to draw a holistic picture of miRNA dysregulation of the AGE/RAGE axis in MetS. This prompted us to test an alternative approach: from miRNAs significant for MetS comorbidities to genes of interest. This approach has been termed “deductive” or, as another option, “synthetic” in the context of this work, as we merged data from studies addressing the different MetS comorbidities into a single system. The deductive approach has allowed us to rank the comorbid pathologies according to the degree

of miRNA dysregulation of AGE/RAGE signaling. Based on the information from the literature, this article is the first to propose such a strategy.

Conclusions

Our review confirms the original idea in several respects: miRNA dysregulation of AGE/RAGE signaling in the context of MetS and its comorbidities seems significant but insufficiently studied. Even with a deductive approach, one cannot help but notice that there are few data on the influence of miRNAs on important receptor genes for AGEs, especially on “non-canonical” ones, such as anti-RAGEs and scavenger receptors that capture AGEs, and also on their gene-encoded ligands, such as S100 proteins and HMGB1. The review therefore comprehensively highlights the gaps in this area of knowledge and can serve as a guide for future research.

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Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Conceptualization (MB, SV, ML, MV, NT), data curation (MB, SV, ML), formal analysis (MB, SV, ML, MV, NT), funding acquisition (LL), investigation (MB, SV, ML, MV, NT), methodology (MB, ML, NT, LL), project administration (MV, LL), resources (LL), software (NT), supervision (MV, LL), validation (LL), visualization (MB, SV), writing - original draft (MB, SV, ML), and writing - review & editing (MV, NT, LL). All authors have approved the final version and publication of the manuscript.

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