

## Review Article

# Noncoding RNAs and Macrophage Differentiation in Metabolic Diseases, Atherosclerosis, and Cancer

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## Keywords

• Metabolic; Obesity; Type 2 diabetes; Non-alcoholic fatty liver disease; Atherosclerosis; Cancer; Noncoding RNA; Regulation

## Abstract

Increased infiltration of monocytes in white adipose tissue, pancreas, liver, and arteries is the initial step in the pathogenesis of metabolic diseases, obesity, type 2 diabetes, non-alcoholic fatty liver diseases, and atherosclerosis. They tend to differentiate into M1 macrophages, associated with mitochondrial and endoplasmic reticulum oxidative stress, insulin resistance, and inflammation. Furthermore, many studies link metabolic diseases to an increased risk of several cancer types. However, tumor-associated macrophages are predominantly M2. Of interest, a cluster consisting of miR-17, miR-27a, miR-29a, miR-34a, miR-125b, miR-130b, miR-140, miR-155, and miR-222 tend to be overexpressed in cardiometabolic tissues, inducing M1 macrophage polarization and immune-mediated cell death. In contrast, they tend to be suppressed in tumors associated with M2 macrophage polarization and immunosuppression. Often LPS, inflammatory cytokines, leukotrienes, C-reactive protein, glucose, and oxidized LDL tend to upregulate these noncoding RNAs in metabolic and vascular tissues, while hypoxia, MYC, IFN- $\gamma$ , TGF- $\beta$ , and lactate tend to downregulate them in tumors. However, a consistent study of the regulation of the proposed cluster related to stages in disease development is lacking.

## INTRODUCTION

Metabolic diseases, obesity, type 2 diabetes, and non-alcoholic fatty liver diseases (NAFLD) are associated with increased infiltration in white adipose tissue, pancreas, or liver of monocytes which differentiate into macrophages. The balance between pro- and anti-inflammatory regulators of macrophages resulting in M2 to M1 polarization depends on oxidative stress, insulin resistance, and inflammation depend on the balance between pro- and anti-inflammatory regulators of macrophages resulting in M2 to M1 polarization [1-3]. M1 macrophages, induced by interferon (IFN)- $\gamma$ , tumor necrosis factor (TNF)- $\alpha$ , and toll-like receptor (TLR) ligands, produce proinflammatory cytokines like interleukin (IL)-1 $\beta$ , IL-6, and IL-12, and TNF- $\alpha$ , and high levels of reactive oxygen species (ROS) and nitrogen species [4]. On the other hand, IL-4, IL-10, IL-13, and immune complexes activate M2 macrophages, which secrete anti-inflammatory cytokines like IL-10, C-C motif chemokine ligand (CCL)-18, and CCL22 [5]. In addition, they express the mannose receptor CD206 (or MRC1), the scavenging receptor CD163, and dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) [6]. Generally, nuclear factor kappa B (NF- $\kappa$ B), interferon regulatory factor (IRF), and signal transducer and activator of transcription (STAT)-1 activate M1 macrophages. In contrast, STAT3 and STAT6 activate M2 macrophages. However, NF- $\kappa$ B induces p62, limiting the NOD-like receptor family pyrin domain

containing 3 (NLRP3)-inflammasome activation [7]. Herein, STAT6 coordinates with peroxisome proliferator-activated receptor (PPAR)- $\gamma$  and PPAR- $\delta$ , Krüppel-like factor 4 (KLF4), KLF2, and MYC to induce M2 genes and inhibit NF- $\kappa$ B/ hypoxia-inducible factor 1, alpha (HIF-1 $\alpha$ ) signaling and expression of M1 genes. Although TLR induction leads to NF- $\kappa$ B activation and the production of inflammatory molecules by M1 macrophages, NF- $\kappa$ B activation also activates a genetic program essential for resolving inflammation. Moreover, the induction of p50 NF- $\kappa$ B homodimers is essential for M2 polarization [5]. However, one must be aware that these two macrophage phenotypes are extremes of a continuum of functional states [8,9].

In addition, M2 cells depend on oxidative phosphorylation (OXPHOS) for their energy production [10]. On the contrary, HIF-1 $\alpha$ , AMP-activated protein kinase (AMPK), and NF- $\kappa$ B favor glycolysis and inhibit oxidative phosphorylation (OXPHOS) in M1 macrophages, associated with increased production of reactive oxygen species (ROS).

In addition, the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/ AKT serine/threonine kinase (AKT) pathway is a bridge between metabolic control, insulin signaling, and inflammation. Indeed, PI3K/AKT is critical in restricting proinflammatory and promoting anti-inflammatory responses in macrophages by negatively regulating TLR and NF- $\kappa$ B signaling.

The transforming growth factor (TGF)- $\beta$  and IL-10 promote M2 polarization via PI3K/Akt signaling. Furthermore, a crosstalk between the STAT6 and PI3K activation is required for IL-4-induced M2 macrophage activation [11]. Nevertheless, several AKT isoforms have different effects on macrophage polarization, with AKT1 ablation giving rise to an M1 and AKT2 ablation resulting in an M2 phenotype [12].

Many studies link metabolic diseases with the risk of atherosclerosis. Overall, diseased vascular cells are also characterized by oxidative stress, inflammation, insulin resistance, and a shift from M2 to M1 macrophages [13].

In addition, many studies also link metabolic diseases to an increased risk of developing several cancer types [14]. Above, we discussed how inflammatory cytokines contribute to developing low-grade systemic inflammation and aberrant NLRP3 activation, driving chronic inflammatory state and eventually leading to cell death. However, while inflammatory cytokines and NLRP3 inflammation are detrimental to the pathogenesis of metabolic diseases, they may play a beneficial role in some cancers [15]. As in metabolic tissues, tumor-associated macrophages (TAMs) derive from circulating monocytes recruited by chemokines (CCL-2, CCL-3, CCL-4, CCL-5, CCL-7, CCL-8, CXCL-12) and cytokines (VEGF, platelet-derived growth factor, colony-stimulating factor 1, and IL-10) [16]. However, hypoxia polarizes macrophages toward an M2 phenotype through TGF- $\beta$  [17]. In addition, IL-4, IL-6, IL-8, IL-10, IL-11, IL-17, IL-18, IL-33, NF- $\kappa$ B, GM-CSF, and TNF- $\alpha$  induce M2 TAM polarization [18]. M2-type TAMs promote and support the occurrence and development of tumors, while M1-type TAMs inhibit tumor growth. In addition, NF- $\kappa$ B activation is crucial in activating tumor-associated macrophages (TAMs). They first exist as undifferentiated macrophages M0, which can again be polarized into M1 macrophages by bacterial components, IFN- $\gamma$ , LPS, TLR, or M2a macrophages by IL-4 and IL-13, M2b macrophages by TLR, M2c macrophages by glucocorticoid, and M2d macrophages by IL-6. M1 macrophages are anti-oncogenic, releasing proinflammatory cytokines IL-1 $\beta$  and IL-12 and cytotoxic ROS and TNF[19]. In contrast, M2 TAMs secrete IL-6 and chemokine (C-X-C motif) ligand (CXCL)-8 with an immunosuppressive action.

Our goal was to perform an unbiased literature search of noncoding RNAs controlling the polarization of macrophages. More specifically, we searched noncoding RNAs inducing similar effects in metabolic tissues and vascular tissues while searching noncoding RNAs showing contrasting up- or downregulation in metabolic tissues such as adipose tissues, pancreas, and liver, compared to tumors, thus favoring M1 macrophages in cardiometabolic tissues and M2 macrophages in tumors. We have chosen noncoding RNAs because they can respond to stress conditions rapidly, and a change in their expression is reversible in contrast to inherited genome mutations [20,21].

### Macrophages in Inflammation, Oxidative Stress and Insulin Resistance in Obese White Adipose Tissue

Adipocytes in obese white adipose tissue secrete

proinflammatory proteins such as leptin, resistin, TNF- $\alpha$ , and IL-6. In contrast, anti-inflammatory adiponectin levels are low [22]. This adipokine imbalance contributes to the proinflammatory state characteristic of obesity and obesity-related complications [23] (Figure 1).

While leptin increases in obesity, the expression of leptin receptors (LepRs) decreases, leading to leptin resistance. In addition, leptin activates the Janus kinase (JAK)-2- STAT3 pathway [24]. STAT3 activates SOCS3, which inhibits leptin-induced signals [25]. In addition, SOCS3 binds to insulin receptor substrates (IRS)-1 and IRS-2, leading to their ubiquitination, degradation, and insulin resistance [26]. Leptin also increases local expression of TNF- $\alpha$ , further impairing insulin sensitivity by downregulating the tyrosine kinase activity of insulin receptors (IRs) and decreasing the expression of glucose transporter (GLUT)-4[27,28]. Furthermore, reduced insulin signaling impairs the PI3K/AKT/ mechanistic target of the rapamycin kinase (mTOR) pathway, hampering M2 macrophage differentiation [29].

In addition, the sustained exposure to leptin and activation of the JAK-STAT1 pathway inhibits the expression of PPAR- $\gamma$ , which is required for adipogenesis and preventing M1 macrophage differentiation [30,31]. STAT1 activation, reinforced by IFN- $\gamma$ , promotes M1-like macrophages. The shift of M2 to M1 macrophages decreases IL-4 and IL-13, inactivating the JAK-STAT6 pathway and IL-10, thereby inactivating JAK-STAT3, preventing M2 macrophage polarization [32]. Furthermore, the decrease of IL-4 and IL-13 impairs PPAR- $\gamma$ . In addition, IL-1 $\beta$ -induced IL-20 stimulates the differentiation of monocytes into M1 macrophages, upregulating netrin one, leptin, and monocyte chemoattractant protein 1 (MCP-1) in adipocytes, and TNF- $\alpha$ , MCP-1, and netrin one and its receptor in macrophages [33]. M1 macrophages, also induced by IFN- $\gamma$ , produce proinflammatory cytokines like IL-1 $\beta$ , IL-6 and IL-12, and TNF- $\alpha$ .

In addition, HIF-1 $\alpha$ , AMPK, and NF- $\kappa$ B favor glycolysis and inhibit OXPHOS in M1 macrophages, producing high levels of ROS [4]. Furthermore, the elevated adipose tissue mass in obesity liberates large amounts of free fatty acids (FFAs) into the bloodstream, contributing to insulin resistance by reducing insulin signaling, shifting mitochondrial oxidation from glucose to FFAs, and diminishing the insulin secretory response to glucose of islet  $\beta$  cells [34]. Although one usually only considers M1 and M2 macrophages, multiple macrophage populations appear in adipose tissue along the M2 to M1 continuum. In addition, they appear to utilize both glycolysis and OXPHOS in obesity [35]. In addition, the transfer of mitochondria from adipocytes to macrophages results in higher mitochondrial mass, lower mitochondrial membrane potential, and elevated mitochondrial ROS [36].

Finally, the increased infiltration of monocytes in white adipose tissue may add to obesity. Indeed, increased CCL2 (or monocyte chemoattractant protein-1, MCP-1) in obese mice was associated with increased adipose tissue mass [37]. In contrast, exosomes from adipose-derived stem cells could polarize

macrophages to an anti-inflammatory phenotype via upregulating the expression of NF-E2-like basic leucine zipper transcriptional activator (NRF2). In addition, NRF2 restores the antioxidant activity of superoxide dismutase (SOD) and catalase (CAT), upregulating heme oxygenase (HO)-1 and NAD(P)H quinone dehydrogenase 1 (NQO1), thereby alleviating LPS-induced accumulation of ROS, and inhibiting nuclear translocation of NF- $\kappa$ B p65 and inflammation [38].

In contrast to leptin, adiponectin secretion and circulating adiponectin levels are inversely proportional to body fat content. Advanced glycation end products (AGEs) and TNF- $\alpha$  in obesity impair sirtuin (SIRT)-1, forkhead box O1 (FOXO1), and PPAR coactivator 1 $\alpha$  (PGC-1 $\alpha$ ) and, in turn, suppress adiponectin production and downregulate the adiponectin receptor (ADIPOR1/R2) [39]. In addition, low adiponectin hampers VEGF-A expression through adiponectin receptors, PI3K/AKT/mTOR and HIF-1 $\alpha$  signaling cascades [40]. Low adiponectin may also lead to mitochondrial dysfunction associated with decreased mitochondrial antioxidant enzyme cytochrome oxidase 1 (MTCOI or COX1) and of PGC-1 $\alpha$  and OXPHOS impairing fatty acid oxidation and inducing ROS generation and inflammation even when insulin sensitivity is retained [41] (Figure 1).

### Role of Noncoding RNA in Macrophage Polarization, Inflammation, and Insulin Resistance in Obese White Adipose Tissue

MiR-141-3p improves AKT phosphorylation and enhances insulin signal transduction [42]. Let-7 represses the CREB-regulated transcription coactivator (mTORC1), causing insulin resistance with increased NLRP3 inflammasome activation [43]. In addition, increased expression of miR-17 [44], miR-103 [45], miR-143-145 cluster, miR-155 [46], miR-221-222 [47], and miR-377 [48], are associated with obesity-associated insulin resistance and inflammation. However, the ADP-ribosylation factor 3 circular RNA (circARF3) acts as an endogenous miR-103 sponge, restraining the NF- $\kappa$ B-signalling pathway and suppressing NLRP3 inflammasome activation [45]. In addition, microRNA-181b improves insulin sensitivity by improving endothelial cell function in white adipose tissue [49]. However, microRNA-181b is low in obese adipose tissue (Figure 1).

Several miRs are associated with M1 macrophage polarization and adipose tissue inflammation: adipocyte exosomal miR-34a by repressing KLF4 and by regulating CXCL10 and CXCL11, activating JAK-STAT signaling; miR-27a and miR-130b by repressing PPAR- $\gamma$  and activating NF- $\kappa$ B; miR-125b-5p by activating NF- $\kappa$ B; and miR-155 by targeting arginase-2 which in mitochondria is crucial for OXPHOS and IL-10-mediated downregulation of inflammatory succinate, HIF-1 $\alpha$ , and IL-1 $\beta$  [50]. However, the X inactive specific transcript (XIST) may sponge miR-125b [51]. In addition, the myocardial infarction-associated transcript (MIAT or GOMAFU) reduced M2 polarization in macrophages and induce endoplasmic reticulum (ER) stress and inflammation in mice [52]. In contrast, miR-181b represses vascular cell adhesion molecule (VCAM-1), inhibiting STAT1 and Pleckstrin homology domain

leucine-rich repeat protein phosphatase, dephosphorylating AKT, and reducing TNF- $\alpha$  levels, while miR-146a decreased IL-1 $\beta$  levels [53]. However, as miR-181b, miR-146a is decreased in obese adipose tissue.

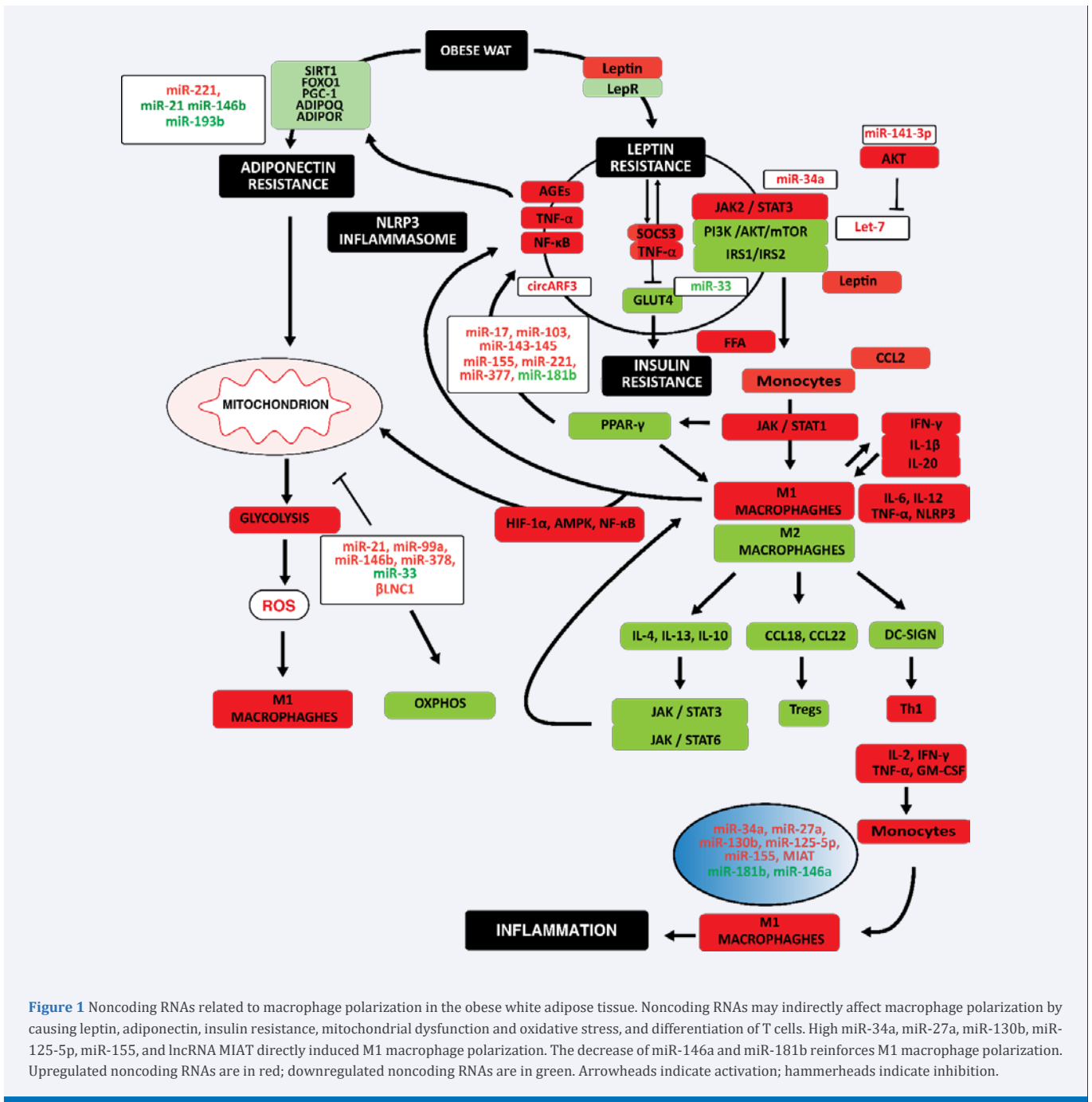
Leptin-induced miR-221 downregulates the adiponectin receptor one and impairs adiponectin action [54]. Low miR-21 decreases adiponectin mRNA and protein expression [55], while low miR-193b is associated with decreased adiponectin and regulators [56]. A decrease of miR-146b-5p in monocytes reduces adiponectin's anti-inflammatory but not insulin-signaling action, increasing mitochondrial ROS [41].

IL-4 induced miR-21, miR-99a, miR-146b, and miR-378 in exosomes while reducing miR-33, improving mitochondrial function and OXPHOS, enhancing insulin-dependent glucose uptake through PPAR- $\gamma$ -driven expression of GLUT4 [57]. In addition, the lncRNA BLNC1 is crucial for retaining mitochondrial function by stimulating the transcription of PGC-1 $\beta$  [58] (Figure 1).

### Macrophages in Inflammation, Oxidative Stress, and Insulin Resistance in Type 2 Diabetes

Insulin binding to IRs in cell membranes leads to the phosphorylation and activation of several IRS proteins. Phosphorylated IRS proteins interact with PI3K, leading to its activation and transfer to the plasma membrane. Especially the phosphatase and tensin homolog (PTEN) and SOCS family regulate PI3K [59,60]. PI3K is essential in GLUT4 translocation and glucose uptake [61,62]. However, excess nutrients such as amino acids and glucose overstimulate mTORC1, downregulating insulin signalling [63,64]. Additionally, decreasing the mTORC2 complex impairs the phosphorylation of AKT and translocation of GLUT4 to the plasma membrane, decreasing glucose transport [65]. The increase of mTORC1 over mTORC2 in type 2 diabetes compromises cellular defense systems such as SIRT1 and NQO1 [66]. In addition, the decrease in SIRT1 impairs glucose-stimulated insulin secretion (GSIS) in pancreatic  $\beta$  cells [67]. Furthermore, impaired AKT phosphorylation and decreased SIRT1 impair FOXOs induction of antioxidant proteins: Mn-SOD (SOD-2), Cu, Zn-SOD (SOD-1), peroxiredoxin-3, PRX3, and PRX5, glutathione peroxidase-1 (GPX-1), and mitochondrial thioredoxin (TRX2) and mitochondrial thioredoxin reductase (TRXR2) [68]. This decrease in antioxidant proteins increases ROS and decreases protection by autophagy (Figure 2).

Increased ROS inhibits the IRS/PI3K/AKT/mTOR pathway. It impairs PPAR- $\gamma$  signaling pathways and its anti-inflammatory effect by inhibiting the glucose-induced activation of p38, NF- $\kappa$ B, and STAT1, resulting in reduced expression of PPAR- $\gamma$  target genes, CD36, and ATP binding cassette subfamily G member 1 (ABCG1), in M2 macrophages. In addition, impaired IRS2-mediated PI3K activity in macrophages induces resistance to IL-4 in association with overexpression of SOCS3 [69]. SOCS3 increases toll-like receptor (TLR4)-mediated M1 macrophage polarization and  $\beta$  cell apoptosis [70]. In addition, TLR-2 and TLR-7/9 activate M1 macrophages and inflammation with



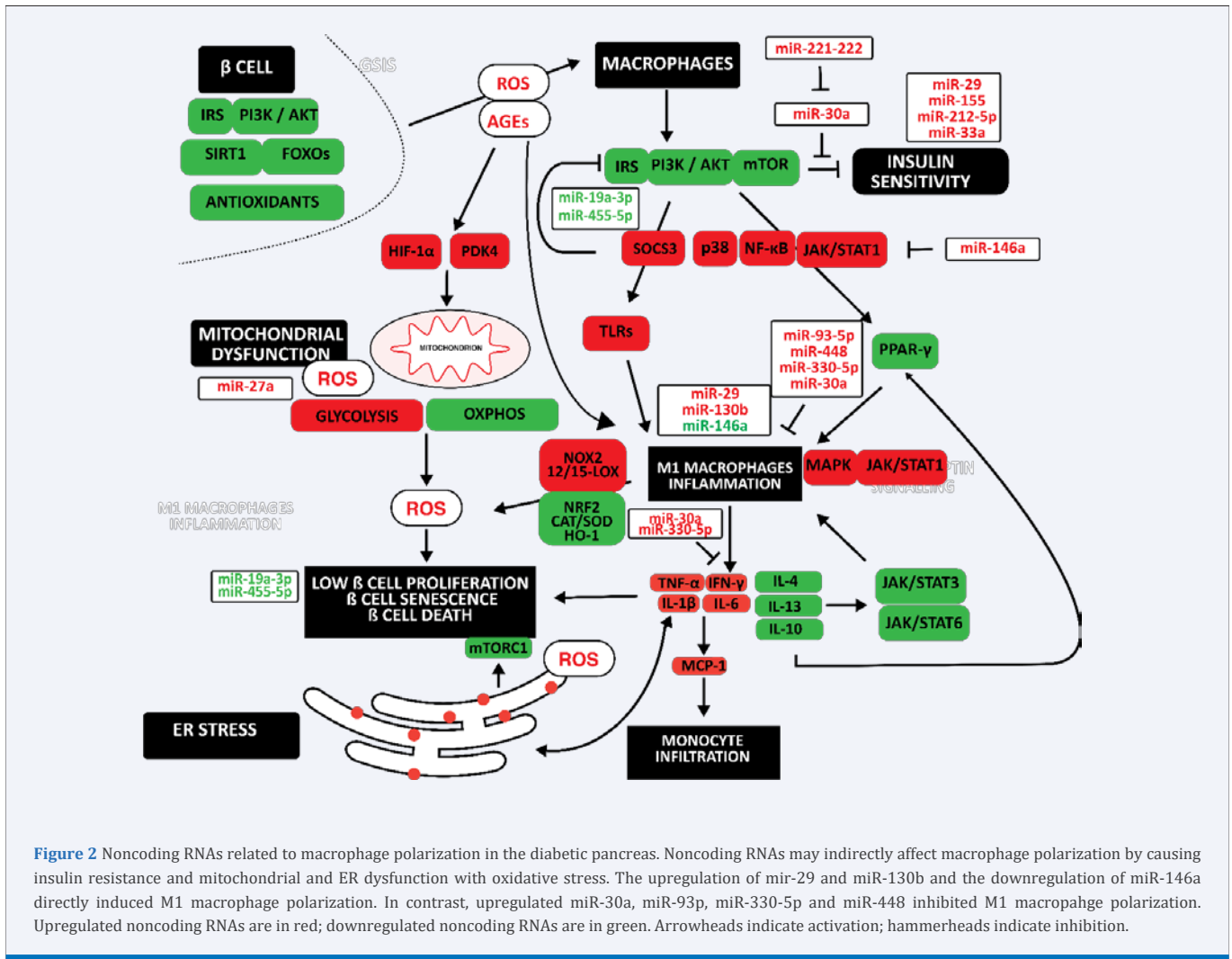
**Figure 1** Noncoding RNAs related to macrophage polarization in the obese white adipose tissue. Noncoding RNAs may indirectly affect macrophage polarization by causing leptin, adiponectin, insulin resistance, mitochondrial dysfunction and oxidative stress, and differentiation of T cells. High miR-34a, miR-27a, miR-130b, miR-125-5p, miR-155, and lncRNA MIAT directly induced M1 macrophage polarization. The decrease of miR-146a and miR-181b reinforces M1 macrophage polarization. Upregulated noncoding RNAs are in red; downregulated noncoding RNAs are in green. Arrowheads indicate activation; hammerheads indicate inhibition.

increased TNF-α, IL-1β, IL-6, IFN-γ, and ROS, favoring M1 macrophage differentiation [71]. In addition, low IL-13 anti-inflammatory function in type 2 diabetes increases monocyte- and macrophage-derived inflammatory cytokines causing β cell death [72]. Furthermore, advanced glycation end products (AGEs) induced M1 polarization through the HIF-1α/ pyruvate dehydrogenase kinase 4 (PDK4) axis, indicating a shift to anaerobic glycolysis [73]. Increased oxidative stress is also due to decreased NRF2 and increased NOX2 expression, resulting in low levels of the antioxidants SOD and CAT in M1 macrophages and loss of protection against inflammation in a diabetic background [74]. The decrease in NRF2 may be due to increased arachidonate

15-lipoxygenase (15-LOX) and 12-LOX, increasing ROS, the proportion of anti-inflammatory macrophages, and loss of β cell mass in a diabetic mouse model [75]. Furthermore, a decrease in the antioxidant HO-1, inhibiting KLF4, CD163, and CD206, promotes M1 macrophage differentiation [76].

The sarcoendoplasmic reticulum Ca(2+) ATPase 2b (SERCA2b) pump maintains a steep Ca(2+) concentration gradient between the cytosol and ER lumen in the pancreatic β cell, required for maintaining insulin production and secretion, maintenance of ER function and β cell survival. However, IL-1β activates AMPK and induces inducible nitric oxide synthase





(iNOS), increasing NO, and decreasing SERCA2b mRNA and protein expression, leading to ER stress and  $\beta$  cell death [77]. In addition, ER stress inhibits mTORC1, impairing  $\beta$  cell expansion [78] (Figure 2)

### Role of Noncoding RNA in Macrophage Polarization, Inflammation, and Insulin Resistance in Type 2 Diabetes

MiR-30a blocks inflammatory IL-1 $\beta$  in immune cells, islet cells, and IFN- $\gamma$  in inflammatory cells, thereby retaining insulin sensitivity [79]. However, miR-29 and miR-221 are associated with insulin resistance and inflammation, the latter by counteracting the action of miR-30a, increasing M1 macrophage polarization, inflammation, and insulin resistance [80,81]. MiR-155 enriched in exosomes released by obese adipocytes block PPAR $\gamma$  and insulin sensitivity [82]. M1-polarised macrophages secrete exosomes enriched in miR-212-5p, impairing insulin secretion and sensitivity by targeting the SIRT2 gene and regulating the Akt/GSK-3 $\beta$ / $\beta$ -catenin pathway [83]. MiR-33a impairs ABCA1 expression in pancreatic islets, thereby increasing lipid deposition and insulin resistance [84]. Reducing

miR-19a-3p and miR-455 in type 2 diabetes increases SOCS3 expression [85,86]. miR-27a increases mitochondrial ROS by reducing levels of NRF2, and GPX1 [87].

MiR-29 recruits monocytes and activates them to macrophages [81]. MiR-130b promoted M1 macrophage polarization by targeting PPAR- $\gamma$  [88]. MiR-146a-5p inhibited tumor necrosis factor receptor-associated factor-6 (TRAF6)/ STAT1 signaling pathway, promoting M2 macrophage polarization [89]. However, high glucose-induced lncRNA HLA complex group 18 (HCG18) targeted miR-146a, increasing TNF receptor-associated factor 6 (TRAF6) expression and inflammatory TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 levels [90]. In contrast, exosomal miR-93-5p and miR-448 inhibited TLR4 expression [91,92]. TLR2/6- and TLR4-activated macrophages reduced insulin secretion partly via reducing INS1, INS2, and PDX [93]. MiR-330-5p directly upregulated the inhibitory receptor T cell immunoglobulin and mucin domain-containing-3 (TIM3), inhibiting IFN- $\gamma$  expression, inducing M2 macrophage polarization, and improving insulin sensitivity [94] (Figure 2).

### Macrophages in Inflammation, Oxidative Stress,

## and Insulin Resistance in Non-Alcoholic Fatty Liver Disease with Obesity and Type 2 Diabetes

Nutrient excess and low physical activity are also associated with increased lipid uptake, lipogenesis, and decreased fatty acid oxidation, resulting in increased intrahepatic triglyceride levels, hepatic steatosis, and NAFLD. Increased gluconeogenesis is associated with increased intrahepatic glucose and insulin resistance. Among many proposed treatments, weight loss reduces NAFLD [95] (Figure 3).

Increased liver glucose and lipid levels are associated with mitochondrial dysfunction and mitochondrial ROS, which promote inflammation, insulin resistance, and cell death, aggravating the development of NAFLD [96,97]. Hepatocellular injury attracts inflammatory cells, mainly monocytes, which differentiate into macrophages surrounding ballooned hepatocytes as crown-like structures [98]. However, the Kupffer cell is the most highly represented macrophage type [99]. The number of M1-polarized macrophages, possibly induced by IRF5, increases at the early stages of liver disease and promotes or exacerbates fibrosis, cirrhosis, and eventual liver failure [100,101]. In addition, the oxidative stress-related 12-LOX catalyzes the conversion of membrane polyunsaturated fatty acids to oxidized proinflammatory lipid intermediates, linking inflammation to insulin resistance [102].

Lipotoxicity is also associated with releasing danger-associated molecular patterns (DAMPs), which stimulate innate immunity through TLR4 and induce NLRP3 inflammation leading to cell death [103]. In addition, abnormal lipid accumulation often coincides with ER stress in hepatocytes, leading to an adaptive unfolded protein response, causing inflammation and cell death [104]. Significantly, the p53 ortholog p63 and JAK link ER stress to inflammation through NF- $\kappa$ B [105]. BCL2 family members, BAK and BAX, promote apoptosis in response to ER stress [106] (Figure 3).

## Role of Noncoding RNA in Macrophage Polarization, Inflammation, and Insulin Resistance in Non-Alcoholic Fatty Liver Disease

Elevated miR-17 in type 2 diabetes with NAFLD increases free fatty acids-induced hepatocyte steatosis and decreases insulin sensitivity [107]. MiR-17 also contributes to steatosis by decreasing the expression of cytochrome P450 family seven subfamilies A member 1, an ER membrane protein that catalyzes the conversion of cholesterol to bile acids [108]. Increased miR-21 and decreased PPAR- $\alpha$  increase fatty acid uptake, de novo lipogenesis, gluconeogenesis, and glucose output, ultimately leading to insulin resistance [109,110]. MiR-29 increases lipogenesis and circulating triglyceride levels in a SIRT1-dependent manner [111]. MiR-34a, induced by inflammatory resistin, is associated with increased triglyceride content, decreased mitochondrial content, and impaired mitochondrial function, for example, by targeting SIRT1 [112]. IL-6 and TNF- $\alpha$  induce miR-101, repressing ABCA1 and increasing lipid deposition [113]. High hepatic miR-141 and miR-200c levels are associated with high triglyceride levels associated with

decreased microsomal triglyceride transfer protein and PPAR- $\alpha$  and increased sterol regulatory element binding transcription factor 1 and Fas cell surface death receptor, inflammation, and macrophage activation [114]. MiR-150 overexpression was associated with hepatic steatosis and insulin resistance in NAFLD mice by regulating the expression of genes related to gluconeogenesis, fatty acid uptake, and  $\beta$ -oxidation [115]. MiR-217 [116], decreased the expression of PPAR- $\alpha$  and SIRT1, thereby increasing lipid accumulation in hepatocytes. MiR-190b increases triglyceride and total cholesterol levels and induces glucose intolerance and insulin resistance by repressing IRS2/AKT signaling [117]. MiR-199a-5p aggravated liver lipid accumulation in mouse hepatocytes, accompanied by down-regulation of hepatic macrophage stimulating one and modulation of hepatic lipogenesis and lipolysis, including sterol regulatory element binding protein (SREBP-1c) and AMPK signaling cascade [118]. MiR-873-5p induced lipid accumulation, inflammation, and fibrosis by inhibiting fatty acid  $\beta$ -oxidation in the mitochondria [119]. Elevated expression of the lncRNA regulator of AKT signaling associated with HCC and RCC (lncRNA ARSR) is associated with enhanced hepatic lipogenesis via upregulating SREBP-1c [120]. High hepatocellular carcinoma-upregulated lncRNA (HULC) levels are associated with liver lipid deposition, hepatic fibrosis, and apoptosis [121]. Furthermore, low levels of miR-30c-5p increase lipid accumulation [122]. Low levels of lncRNA suppressor of hepatic gluconeogenesis and lipogenesis (lncSHGL in mice or B4GALT1-AS1 in humans) in fatty livers of obese diabetic mice were associated with elevated gluconeogenic and lipogenic gene expression [123]. In contrast, the circRNA low-density lipoprotein receptor (circLDLR) increases SIRT1 by targeting miR-667-5p, inhibiting the triglyceride and cholesterol content in hepatocytes and promoting autophagy [124].

Furthermore, cholesterol-induced miR-192-5p inhibited the protein expression of mTOR, further inhibiting the phosphorylation levels of AKT and activating FOXO1, subsequently inducing an inflammatory response [125]. Downregulation of miR-122-5p in Kupffer cells activated glycolysis, induced inflammation and fibrosis, and impaired insulin signaling [126]. In contrast, mesenchymal cell-derived exosomal miR-24-3p restrained ROS generation and inflammation by inhibiting Keap-1, potentiating NRF2 and antioxidant capacity [127] (Figure 3).

MiR-155 is associated with decreased binding of PPAR response element and PPAR- $\alpha$  and increased MCP1 production. Kupffer cells isolated from miR-155 deficient mice exhibited an M2 phenotype predominantly when exposed to M1 polarized signals [128]. In addition, lipotoxic hepatocytes released miR-192-5p-enriched exosomes, which induced M1 macrophage activation and increased iNOS, IL-6, and TNF- $\alpha$  expression. In contrast, miR-144 targeted TLR2, reducing TLR2, TNF- $\alpha$ , and IFN- $\gamma$  expression, preventing activation of NF- $\kappa$ B and inhibiting the progression of NASH in rats [129]. Finally, miR-146b inhibited inflammation and steatosis by targeting TRAF6 and IRAK1 [130]. IL-6 secreted by myeloid cells induced macrophages to release miR-223-enriched exosomes. MiR-223 3p reduced the infiltration of monocytes, neutrophils, and early activated macrophages and downregulated the transcriptional expression of the proinflammatory cytokines

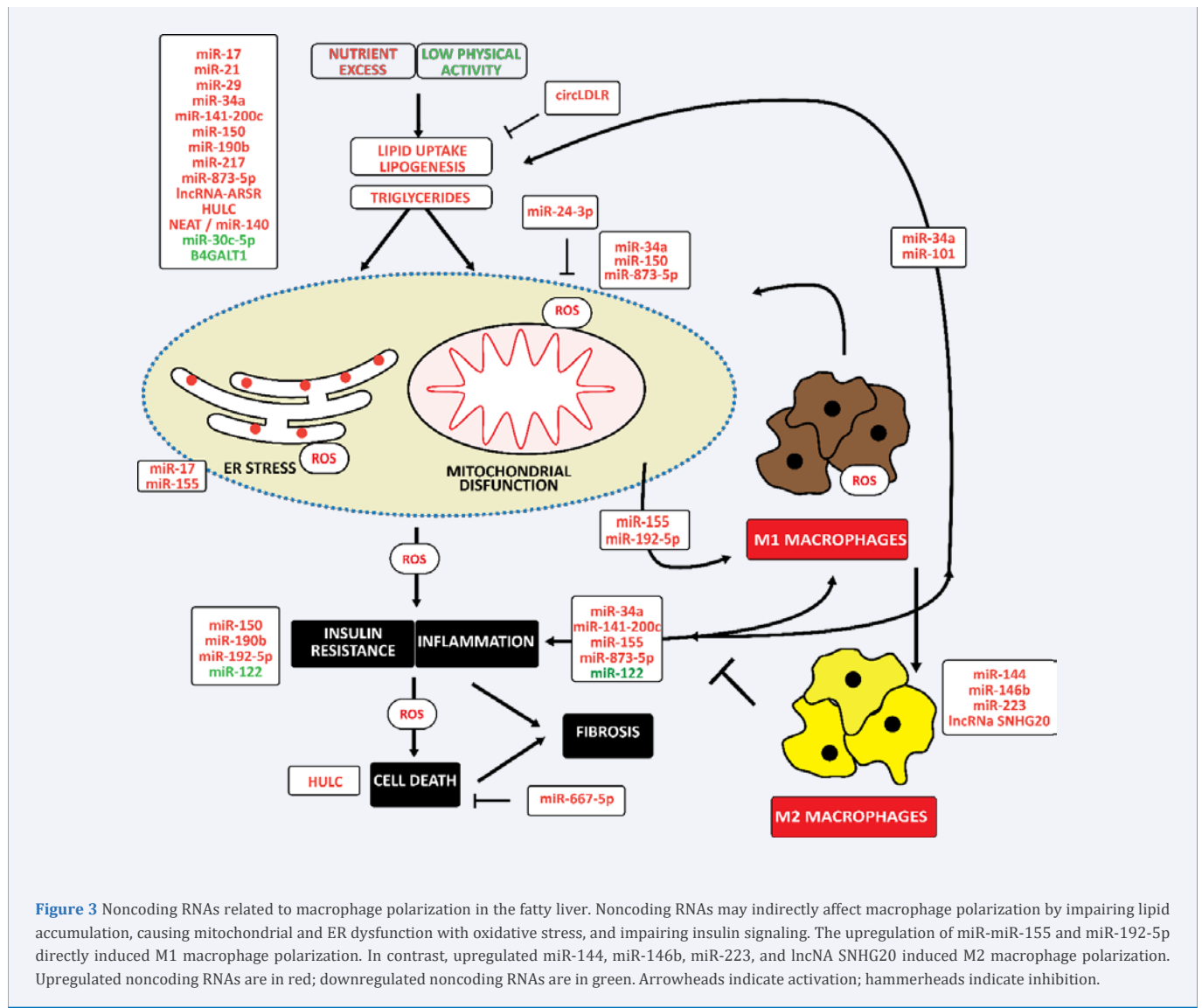
IL-6 and IL-12, and the chemokines CCL2, CCL3, CXCL1, and CXCL2, mitigating fibrosis [131]. LncRNA small nucleolar RNA host gene 20 (SNHG20) overexpression induced M2 polarization through activating STAT6 [132] (Figure 3).

### Macrophages in Inflammation, Oxidative Stress, and Insulin Resistance in Atherosclerosis

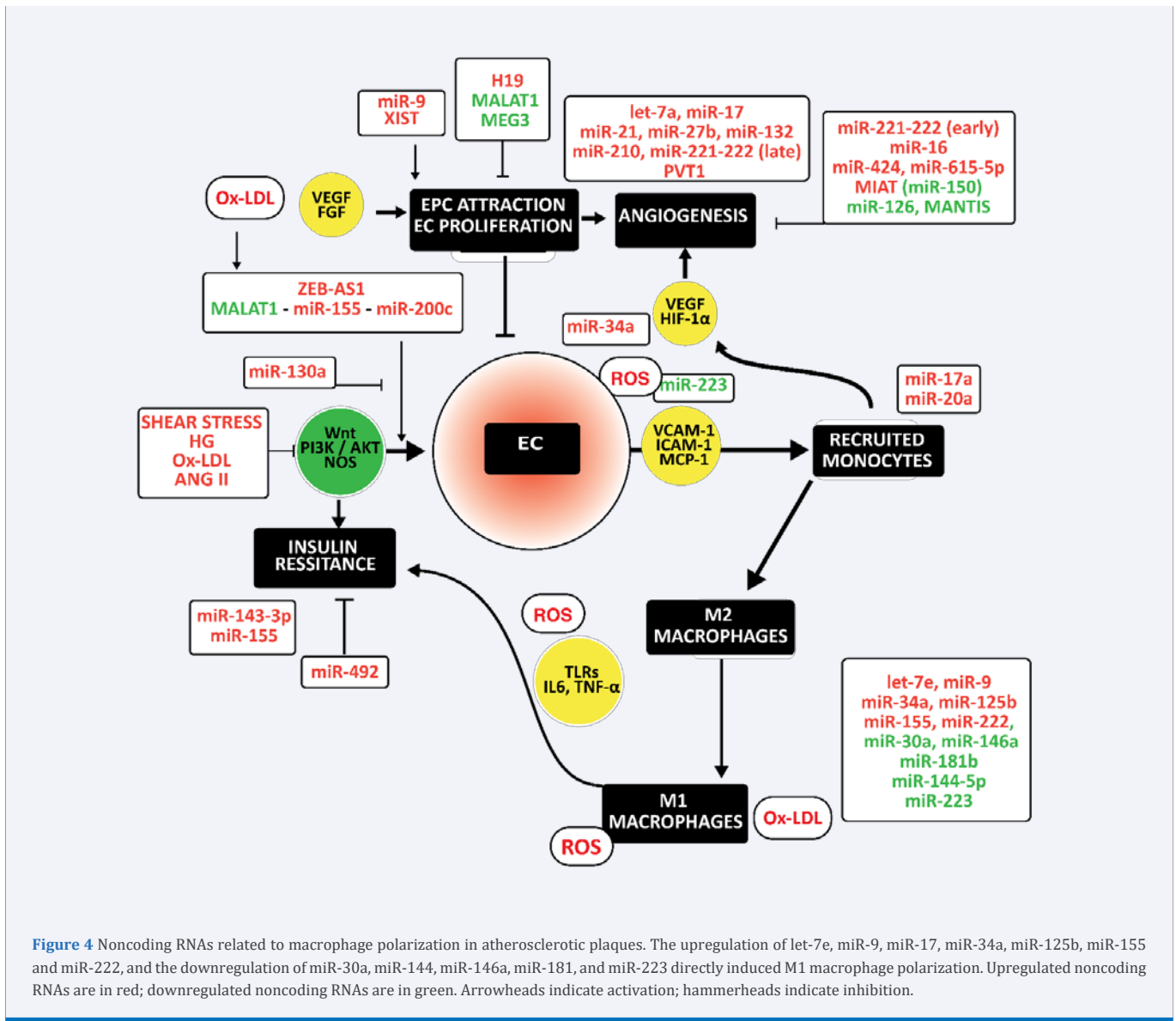
Atherosclerosis develops in medium and large arteries at sites of high shear stress. Shear stress, high glucose, angiotensinogen (ANG II), and ox-LDL impair non-canonical Wnt and PI3K/AKT/NOS signaling, causing endothelium dysfunction [133,134]. Endothelial dysfunction is associated with the secretion of adhesion molecules and the C-C motif chemokine receptor 2 (CCR2; or MCP-1 receptor). They facilitate the adhesion and infiltration of monocytes, which differentiate into macrophages [135]. ANG II causes endothelial injury and induces the migration of inflammatory cells, oxidative stress, angiogenesis, and vascular smooth muscle cell (VSMC) proliferation and differentiation by regulating the expression of integrins [136] (Figure 4).

Infiltrated monocytes differentiate into anti-inflammatory M2 macrophages. They secrete TGF-β and IL-10, which counteract vascular inflammation and immune cell activation. However, TGF-β also induces fibrosis in combination with IL-17 produced by inflammatory Th17 cells [137]. In addition, endothelial injury and subsequent adhesion of inflammatory cells result in ROS release, which polarizes M2 towards pro-inflammatory M1 macrophages [138]. This activation involves increased expression of TLRs and downstream NF-κB, which elicit the release of pro-inflammatory cytokines, such as IL-6 and TNF-α [139]. The interleukin-1 receptor-associated kinase-3 (IRAK3 or IRAK-M) inhibits macrophage activation and inflammatory cytokine secretion primarily by blocking TLR signaling [140]. IRAK3 negatively regulates signaling by preventing the dissociation of IRAK1 and IRAK4 from MyD88 and forming IRAK-TNF receptor-associated factor-6 (TRAF6) complexes [141]. Low IRAK3 is associated with high superoxide dismutase (SOD)-2, a mitochondrial oxidative stress marker [140].

Activated macrophages secrete myeloperoxidase (MPO)



**Figure 3** Noncoding RNAs related to macrophage polarization in the fatty liver. Noncoding RNAs may indirectly affect macrophage polarization by impairing lipid accumulation, causing mitochondrial and ER dysfunction with oxidative stress, and impairing insulin signaling. The upregulation of miR-miR-155 and miR-192-5p directly induced M1 macrophage polarization. In contrast, upregulated miR-144, miR-146b, miR-223, and lncNA SNHG20 induced M2 macrophage polarization. Upregulated noncoding RNAs are in red; downregulated noncoding RNAs are in green. Arrowheads indicate activation; hammerheads indicate inhibition.



**Figure 4** Noncoding RNAs related to macrophage polarization in atherosclerotic plaques. The upregulation of let-7e, miR-9, miR-17, miR-34a, miR-125b, miR-155 and miR-222, and the downregulation of miR-30a, miR-144, miR-146a, miR-181, and miR-223 directly induced M1 macrophage polarization. Upregulated noncoding RNAs are in red; downregulated noncoding RNAs are in green. Arrowheads indicate activation; hammerheads indicate inhibition.

and NADPH oxidase (NOX), oxidizing LDL. Ox-LDL damages the endothelium, closing a vicious circle [142]. Macrophages express scavenger receptors [143, 144]. Uptake of ox-LDL via these scavenger receptors is not harmful if levels of ATP-binding cassette transporters are adequate. Then macrophages transfer the surplus of cholesterol to HDL, facilitating further transport from the arterial wall to the liver, ultimately leading to bile release. If not, excess lipid accumulation leads to foam cell formation, ultimately leading to cell bursts, exposing extracellular debris that causes microthrombi, exacerbating inflammatory cells' infiltration. Scavenger receptors are, however, not only present at the surface of macrophages but also on the surface of endothelial cells (ECs). For example, the scavenger receptor SR-ECI cooperates with TLRs to trigger inflammatory innate immune responses [145](Figure 4).

**Role of Noncoding RNA in Macrophage Polarization, Inflammation, and Insulin Resistance in**

**Atherosclerosis**

MiR-155-5p and miR-143-3p may cause insulin resistance in atherosclerotic vessels by targeting AKR and insulin growth factor receptor, respectively [146]. In contrast, miR-492 improved blocked insulin resistance induced by p-STAT3, SOCS, and P-selectin in ECs [147].

Zinc finger E-box-binding homeobox two antisense RNA 1 (ZEB1-AS1) mediates ox-LDL-induced EC injury. Ox-LDL sequesters p53 from binding to the ZEB-AS1 promoter, thereby up-regulating ZEB-AS1 [148]. The metastasis-associated lung adenocarcinoma transcript one lncRNA (MALAT1) is lower in human plaques than in normal arteries and lower in symptomatic than asymptomatic plaques. Low MALAT1 is associated with endothelial dysfunction and loss of protection against ox-LDL-induced cytokine release and apoptosis via upregulation of miR-155, increased by hypertension and inflammation [149].



Also, the decrease of MALAT1 and the up-regulation of miR-200c-3p is associated with oxygen-glucose deprivation [150]. In contrast, miR-130a activates the PI3K/AKT/eNOS pathway, thereby retaining EC viability and NO release while it decreases inflammatory cytokine levels and cell apoptosis [151] (Figure 4).

The repair of endothelium requires the attraction of endothelial progenitor cells (EPCs) and EC proliferation. MiR-9 promotes migration and invasion of EPCs by attenuating TRPM7 expression by activating the PI3K/AKT autophagy pathway [152]. X inactive specific transcript (XIST) stimulates hypoxia-induced angiogenesis [153]. In contrast, the H19 imprinted maternally expressed transcript lncRNA (H19) decreases EC proliferation and increases apoptosis by up-regulating mitogen-activated protein kinase and NF- $\kappa$ B [154,155]. Ablation of MALAT1 and maternally expressed three lncRNA (MEG3), particularly in type 2 diabetes, is associated with reduced EC proliferation and migration and increased inflammation [156,157].

Several miRs correlate positively with angiogenesis. Let-7a is high in patients with hypertension, atherosclerosis, cardiac hypertrophy, and fibrosis [158]; miR-21 is upregulated by ANG II [159]; and miR-27b by shear stress [160]. MiR-132 is high in patients with heart failure [161], and miR-210 in patients with aortic stenosis [162]. Two members of the miR-17-92 cluster have opposite effects on angiogenesis. MiR-17 potentiates angiogenesis by facilitating the expression of HIF-1 $\alpha$  and VEGF, which regulate each other. However, miR-92 blocks angiogenesis by silencing the integrin subunit alpha5 [163]. Increased miR-221/222 in initial atherosclerotic plaques inhibits angiogenesis [164]. However, in advanced plaques, chronic inflammation down-regulates miR-221/222 in ECs and decreases the growth arrest-specific homeobox by decreased repression of ZEB2, resulting in increased angiogenesis [165]. PVT1 oncogene (PVT1) binds and degrades miR-26b and promotes angiogenesis [166].

Functionally, miR-16 and miR-424 inhibit angiogenesis via blocking VEGF [167-170]. Increased miR-615-5p in response to vascular tissue injury inhibits VEGF/AKT/eNOS signaling [171]. Myocardial infarction-associated transcript (MIAT) in diabetes impairs angiogenesis by silencing miR-150, generating a negative feedback loop with VEGF [172,173]. The decrease of miR-126 and MANTIS inhibits angiogenic sprouting and alignment of ECs in response to shear stress and inflammation [174,175] (Figure 4).

Endothelial injury is associated with increased infiltration of monocytes, which differentiate into macrophages. MiR-17a and miR-20a induce hypoxia-induced infiltration of monocytes and activation of macrophages [176-178]. Ox-LDL significantly up-regulates let-7e in ECs, promoting NF- $\kappa$ B activation and translocation to the nucleus by inhibiting its target gene I $\kappa$ B $\beta$  and subsequently increasing inflammation and the expression of adhesion molecules. In addition, miR-34a silences p53-small interfering RNA that attenuates high-glucose-induced endothelial inflammation and oxidative stress by repressing sirtuin (SIRT)-1 [179].

MiR-9 enhances M1 macrophage polarization by inhibiting

PPAR- $\delta$  [180]. Palmitate, ox-LDL, TNF- $\alpha$ , or IL-6 significantly induced miR-34a, inducing M1 macrophage polarization and inhibiting *ABCA1* and *ABCG1* expressions [181]. MiR-125b, upregulated in association with CAD, downregulates scavenger receptor class B member 1 in both human and mouse macrophages and VSMCs, thereby impairing macrophage cholesterol efflux [182]. MiR-155 promoted the ox-LDL-induced ERK1/2 phosphorylation and NLRP3 inflammasome activation in apoE KO mice [183]. Ox-LDL induces toll-like receptor adaptor molecule one that up-regulates miR-155 in macrophages, associated with activation of the ERK1/2 and SOCS1/STAT3/NF- $\kappa$ B signaling and elevation of IL6 and TNF- $\alpha$  levels [184]. Exosomes derived from M1 macrophages aggravated neointimal hyperplasia by delivering miR-222 into VSMCs [185].

MiR-30a-5p reduced atherosclerotic lesions in apoE KO mice, reduced levels of pro-inflammatory cytokines, increased levels of anti-inflammatory cytokines, and decreased the ratio of M1/M2 macrophages [186]. However, LPS and ox-LDL reduce the expression of miR-30a-5p. ApoE increased the expression of miR-146a, inhibiting macrophage proinflammatory responses and atherosclerosis in the settings of hyperlipidemia in mice [187]. However, lncRNA H19 inhibits miR-146a in mouse aorta with lipid-loaded macrophages and atherosclerosis [188]. Furthermore, hypermethylation at the promoter of miR-181b, observed in blood monocytes of CAD patients, directly decreases miR-181b activity, increasing M1 macrophage polarization and inhibiting M2 macrophage polarization, accelerating atherosclerosis [189]. MiR-144-5p is downregulated in abdominal aortic aneurysms. MiR-144 suppressed ox-LDL-induced upregulation of M1 macrophage markers, including IL-1 $\beta$ , TNF $\alpha$ , prostaglandin-endoperoxide synthase 2, and nitric oxide synthase 2, in macrophages in abdominal aortic aneurysm, probably by targeting TLR2 [190]. MiR-223 may block the activation of the NLRP3 inflammasome and M1 macrophage polarization [191], but its level is reduced in diseased hearts [192] (Figure 4).

### Noncoding RNAs Related to Macrophage Differentiation in Cardiometabolic Diseases, Which are also to Cancer

Above, we found that high levels of miR-9, miR-17, miR-27a, miR-29, miR-34a, miR-125b-5p, miR-130b, miR-140, miR-155, miR-192-5p, and miR-222, and low levels of miR-30a, miR-144, miR-146a/b, miR-181b and miR-223 are associated with M1 macrophage polarization. Therefore, we reviewed changes in their expression related to cancer. Figure 5 illustrates the similarities and differences between cardiometabolic tissues and tumors.

MiR-9, enriched in exosomes from head and neck squamous cell carcinoma cells, was transported into macrophages, inducing M1 macrophage polarization via downregulation of PPAR- $\delta$  [193]. Exosomal hsa\_circ\_0017252 secreted by gastric cancer cells attenuated cancer progression by suppressing macrophage M2-like polarization by targeting miR-17 [194]. MiR-27a suppressed

the JAK1/STAT-6 pathway and reduced the production of M2-type cytokines by targeting IRF4 and PPAR- $\gamma$  [195]. However, the miR-23a/27a/24-2 cluster was low in TAMs of breast cancer patients, and macrophages overexpressing the miR-23a/27a/24-2 cluster inhibited tumor growth. EZH2-induced reduction of miR-29 decreased M1 macrophage-associated TNF- $\alpha$ , NOS2, and IL-6 [196]. TAMs secrete TGF- $\beta$ 1, promoting the proliferation and invasion of cancer cells by downregulating miR-34a [197]. M2-targeted HA-PEI/PEG nanoparticles with miR-125b-5p induced M1 TAMs in pancreatic tissues derived from pancreatic adenocarcinoma [198]. However, miR-125b-5p is often downregulated in breast cancer cells [199]. Hsa-let-7c-5p, hsa-miR-130b-3p, and hsa-miR-142-3p correlated with activated dendritic cells, naïve CD4 T cells, and M1 macrophages in melanoma, but often they are downregulated [200]. M2 macrophages or TAMs exposed to miR-130-enriched exosomes differentiated to M1, evidenced by the expression of IRF5, MCP1, CD80, and the secretion of IL-1 $\beta$  and TNF- $\alpha$  [201,202]. MiR-140 targeted the lncRNA LINC01140-CM, and silencing of this lncRNA significantly decreased the protein levels of the M2 marker CD206 while increasing the M1 marker CD16 in macrophages. Moreover, M2 markers IL-10 and Arg1 were low, while M1 markers iNOS and TNF- $\alpha$  were increased [203]. However, miR-140 is often decreased in tumors [204]. In addition, miR-155 reprograms TAMs to proinflammatory M1 macrophages [205]. However, MIR155HG is expressed higher in M2 macrophages and lower in M1 and sponges miR-155 [206]. Furthermore, ROS downregulated miR-155-5p expression in exosomes from tumor cells, which were taken up by macrophages, modulating their phenotype and the tumor microenvironment and favoring tumor growth [207]. The decrease of miR-222 in TAMs promoted tumor growth [208].

MiR-30a retained M2 TAM-induced EMT [209]. However, miR-30a is often downregulated, as in ovarian cancer [210]. The downregulation of miR-144 in hepatocellular carcinoma was associated with decreased M1 macrophage polarization and antitumor activity [211]. NIFK antisense RNA 1 suppressed miR-146a and M2-like polarization of macrophages [212]. Low miR-181b is associated with increased monocyte infiltration [213]. The transfer of miR-181b from cancer cells to macrophages favored M2 macrophage polarization [214].

Finally, hypoxic epithelial ovarian cancer secreted exosomes enriched in miR-223, triggering the recruitment of macrophages recruitment and their differentiation into M2 TAMs [215] (Figure 5).

## DISCUSSION

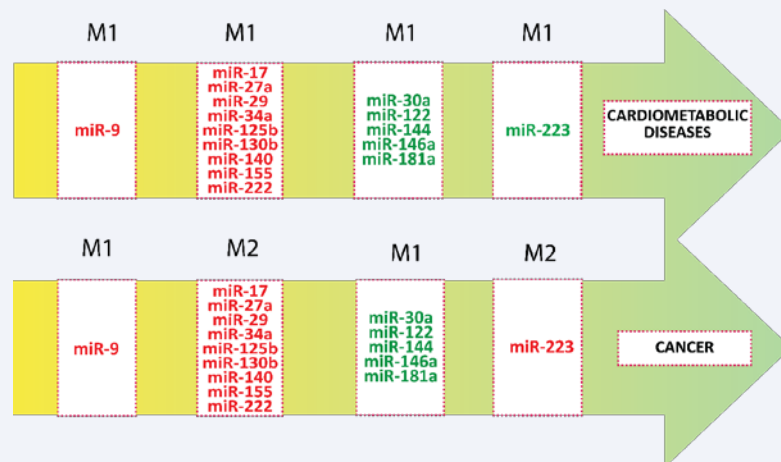
Our literature search revealed that miR-9, miR-17, miR-27a, miR-29, miR-30a, miR-34a, miR-122, miR-125b, miR-130b, miR-140, miR-144, miR-146a, miR-155, miR-181b, miR-222, and miR-223 are related to macrophage polarization in association with metabolic diseases, atherosclerosis, and cancer. Of interest, miR-9 induces M1 polarization in cardiometabolic tissues and tumors. Then the group consisting of miR-17, miR-27a, miR-29a,

miR-34a, miR-125b, miR-130b, miR-140, miR-155, and miR-222 tend to be overexpressed in cardiometabolic tissues, inducing M1 macrophage polarization and immune-mediated cell death. In contrast, they tend to be suppressed in tumors associated with M2 macrophage polarization and immunosuppression. Furthermore, the group of miR-30a, miR-122, miR-144, miR-146a/b, and miR-181b tend to be downregulated in cardiometabolic tissues and tumors, associated with M1 macrophage polarization and immune-mediated cell death in cardiometabolic tissues and tumors. Finally, the downregulation of miR-223 in cardiometabolic tissues is associated with M1 macrophage polarization, where its upregulation in tumors induces M2 TAMs.

Clinically, miR-9 was increased in patients with chronic heart failure, experiencing the primary endpoint of cardiac death, heart transplantation, or mechanical circulatory support implantation [216]. The increase of the miR-17-92 family in patients with cardiovascular diseases was associated with lipid metabolism [217]. A rise of miR-27a, miR-29a, and miR-34a predicted the development of cardiovascular diseases, particularly in T2DM patients [218]. MiR-125b is associated with vascular calcification [219]. Increased hsa-miR-130a-3p and hsa-miR-140-5p and decreased hsa-miR-144-5p were associated with atrial fibrillation [220]. In addition, miR-140-5p was upregulated in the acute stage following cerebral ischemia [221]. Gensini score in coronary heart disease patients correlated with miR-155 [222]. MiR-222-3p predicted poor prognosis in patients with carotid atherosclerosis [223], and atrial fibrillation in patients with degenerative valvular heart disease [224].

Triiodothyronine (T3) rescued post-ischemic mitochondrial activity and cell viability by restoring miR-30a expression and downregulating p53. The concomitant decrease in p53 protein content reduces Bax expression and limits mitochondrial membrane depolarization resulting in preserved mitochondrial function and decreased apoptosis and necrosis [225]. MiR-122 was significantly upregulated three months post-bariatric surgery in sera of patients with improved endothelial function [226]. However, increased miR-122 and miR-370 were associated with CAD presence, even after adjustment for other cardiovascular risk factors [227]. MiR-146a correlated inversely with TNF- $\alpha$  levels in patients with stable CAD, irrespective of other metabolic or inflammatory markers, and with the severity of coronary artery disease [228]. In patients with type 2 diabetes, plasma miR-181b negatively correlated with the procoagulant state (TF protein, TF activity, D-dimer levels) and markers of vascular inflammation [229]. In addition, hsa-mir-181 correlated with a functional cardiac benefit from bypass surgery [230]. Lack of miR-223 induction leads to severe coronary pathology characterized by VSMC dedifferentiation and medial damage in patients with Kawasaki disease [231].

Furthermore, it is essential to gain insight into differences in regulating this first group of miRs in cardiometabolic tissues compared to tumors. For example, hypoxia and HIF-1 $\alpha$  [232,233], and high glucose up-regulate miR-17 in cardiometabolic tissues [234]. IL-6 increases miR-17, but IFN- $\gamma$  suppresses miR-17 in



**Figure 5** Comparison of expression of noncoding RNAs related to macrophage polarization in metabolic tissues and tumors. Upregulation of miR-9 and downregulation of miR-30a, miR122, miR144, miR-146a, and miR-181 are associated with M1 macrophage polarization in cardiometabolic tissues and tumors. Differences in expression of miR-17, miR-27a, miR-29, miR-34a, miR-125b, miR130b, miR-140, miR-155, and miR-222 may explain M1 macrophage polarization in cardiometabolic tissues compare to M2 macrophage polarization in tumors. Upregulated noncoding RNAs are in red; downregulated noncoding RNAs are in green.

tumors, thereby reverting anti-inflammatory and anti-oxidative action in breast tumors [235-237]. MiR-27a levels increased with levels of hs-C-reactive protein and oxidized LDL, and the expression level of miR-27a was inversely related to ABCA1 and ABCG1 [238]. However, hypoxia promotes lung cancer cell proliferation, migration, invasion, and EMT by inhibiting the miR-27a expression [239]. Furthermore, MYC first upregulates miR-27a, but its promoter gets methylated early in prostate carcinogenesis, concomitantly with the loss of MYC regulatory activity. Along with prostate cancer progression, the miR-27a-5p promoter becomes hypomethylated, allowing MYC to resume its regulatory activity. However, the altered cellular context averts miR-27a-5p from accomplishing its tumor-suppressive function [240]. In addition, hypoxia-reoxygenation and inflammatory IL-1 $\beta$  and IL-18 MCL1 induced miR-29, while the anti-apoptotic apoptosis regulator, BCL2 family member (MCL1), repressed miR-29 [241]. In contrast, high MYC in tumors represses miR-29 through a co-repressor complex with EZH2 that also represses miR-26a and miR-146a [242-246]. Finally, SMAD3 mediates the downregulation of miR-29 by TGF- $\beta$ 1 in tumors [247]. IL-6 or TNF- $\alpha$ -activated p65 could bind to the miR-34a promoter and enhance its activity, increasing its transcription. NF- $\kappa$ B induces miR-34a with FN- $\gamma$  and ROS, downregulating SIRT1 [248,249]. Consequently, the inhibition of SIRT1 stimulates NF- $\kappa$ B-induced inflammation. In contrast, hypoxia down-regulates miR-34a, thereby promoting EMT by targeting the NOTCH signaling axis [250]. Furthermore, MYC inhibits miR-34a expression directly or by inducing lncRNA-SNHG7, which silences miR-34a [251,252]. Finally, TGF- $\beta$  secreted by tumor-associated macrophages promotes proliferation and invasion of colorectal cancer via the silencing of miR-34a, thereby upregulating VEGF [197]. Glucose upregulates miR-125b-5p, mediating some of the deleterious effects of hyperglycemia in  $\beta$  cells [253]. In addition, CRP, TNF- $\alpha$ , IL-6, IL-17, and IL-23 were positively related to miR-125b [211].

Significantly IL-6/STAT3 signaling induced miR-125 [254]. In contrast, AKT1 and AKT3 activation in drug-resistant colon cancer cells downregulated miR-125b-5p, leading to GLUT5 expression [255]. In addition, ROS inhibit miR-125b expression by increasing its promoter methylation [256]. Furthermore, MYC downregulates the miR-100/let-7a-2/miR-125b-1 cluster [257]. Increased levels of miR-130, miR-140-5p, miR-142-3p, miR-143, and miR-222, and decreased concentrations of miR-15a, miR-146a, miR-423-5p, and miR-520c-3p are strongly linked to measures of BMI, waist circumference, leptin, insulin, HOMA-IR, TG, and HDL-cholesterol [258]. TGF- $\beta$ 1 decreased the expression of miR-130b in colorectal cancer cells [259]. In addition, IGF-1 was inversely related to miR-130b, miR-9-5p, miR-9-3p, and miR-181d [260]. IL-1 $\beta$  induces miR-140-3p [261], and TGF- $\beta$ /SMAD3 inhibits the expression of miR-140 [262]. Furthermore, the oncogenic flap endonuclease 1 targeted miR-140-5p, downregulated in hepatocellular carcinoma, allowing TGF- $\beta$ 1-induced EMT [263]. MiR-155-5p and its host gene MIR155HG are enhanced by antigen receptor stimulation of B- and T-cells or by TLR agonist stimulation of macrophages and dendritic cells [264]. Moreover, LPS induces miR-155, exerting a regulatory effect on NLRP3 inflammasome activation in ox-LDL-induced macrophages [183,265]. However, ROS in tumors inhibited the expression of miR-155, thereby inhibiting macrophage infiltration and activation of cytotoxic CD8<sup>+</sup> T cells [207]. The lactic acid in tumors with elevated IL33 and mast cell infiltration also suppresses miR-155-5p in a HIF-1 $\alpha$ -dependent manner [266]. Prolonged exposure to LPS and TNF- $\alpha$  upregulated the expression of miR-222 [267,268]. In addition, the high-mobility group box one protein, a late inflammatory cytokine that signals danger to the immune system through the receptor for AGEs and TLRs, induces the expression of miR-222 in cancer cells [269]. In contrast, IFNs inhibit the expression of miR-222 and miR-27a [265]. In addition, the snail family transcriptional repressor two



induced EMT by inhibiting E-cadherin expression by repressing miR-222 [270].

Next is the group of downregulated miRs in cardiometabolic and tumor tissues. MiR-30a and miR-26a levels inversely correlate to IL1- $\beta$  [271]. TGF- $\beta$ -induced lincRNA-p21 promotes liver inflammation and fibrosis by inhibiting miR-30a [272]. In addition, hypoxia downregulates miR-30a [273]. MiR-122 expression is regulated by liver-enriched transcription factors such as hepatocyte nuclear factor (HNF)1 $\alpha$ , HNF3 $\beta$ , HNF4 $\alpha$ , HNF6, and CCAAT/enhancer-binding protein (C/EBP) $\alpha$ . A positive feedback loop exists between C/EBP $\alpha$  and miR-122 and between HNF6 and miR-122, whereas a negative feedback loop exists between MYC and miR-122 in hepatocellular carcinoma cells [274]. Furthermore, hypoxia reduces miR-122-5p in hepatocellular cancer cells [275]. TNF $\alpha$  and ceramide reduced miR-144/451[276].

Leukotriene B4, an inflammation mediator derived from arachidonic acid by 5-lipoxygenase and 5-lipoxygenase-activating protein, activates macrophages by inducing miR-155, miR-146b, and miR-125b [277,278]. In addition, IL-6 correlated positively with miR-146a/b in breast cancer tissues. However, overexpression of oncogenic RAS, MYC, NF- $\kappa$ B, JUN, TRAF6, and IRAK4 was inversely related to miR-146 [279]. Ox-LDL induces MIAT that silences miR-181b [280], and increases TUG1 [281]. TGF- $\beta$ 1 significantly upregulated the expression of miR-181a-5p, miR-181b-5p, and miR-181d-5p in renal cancer cells [282]. In addition, GM-CSF and IL-6-activated STAT3 and CEBP $\beta$  synergistically induced the expression of miR-21a, miR-21b, and miR-181b [283]. In contrast, hypoxia reduced miR-181b levels [284].

In conclusion, our literature search revealed noncoding RNAs which regulate macrophage differentiation in cardiometabolic tissues and tumors. Especially the inverse regulation of miR-17, miR-27a, miR-29a, miR-34a, miR-125b, miR-130b, miR-140, miR-155, and miR-222 in cardiometabolic tissues compared to tumors may explain the predominant M1 polarization of macrophages in cardiometabolic tissues compared to the M2 macrophage polarization in tumors. However, M1 and M2 phenotypes are extremes of a continuum of functional states. Although insight into the molecular targets regulated by these miRs is rising, essential information about their regulation is largely lacking. Moreover, information from studies focusing on only one or a few of these miRs led to this theoretical model, but cluster analysis is yet to be performed. In addition, insight into the stage-dependent changes in miR cluster expression is missing. Therefore, further research on the kinetics of changes in expression related to the metabolic reprogramming of macrophages is warranted.

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