The macrophage polarization by miRNAs and its potential role in the treatment of tumor and inflammation (Review)

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Received June 24, 2023; Accepted August 18, 2023

DOI: 10.3892/or.2023.8627

Abstract. The characteristics of monocyte/macrophage lineage are diversity and plasticity, mainly manifested by M1 and M2 subtypes in the body tissues, and playing different roles in the immunity. In the polarization process of macrophages, the classic molecular mechanism is related to sequential transcription factors. Whether in tumor or inflammatory local microenvironment, the pathological factors of the local microenvironment often affect the polarization of M1 and M2 macrophages, and participate in the occurrence and development of these pathological processes. In recent years, a growing number of research results demonstrated that non-coding RNA (ncRNA) also participates in the polarization process of macrophages, in addition to traditional cytokines and transcriptional regulation signal pathway molecules. Among numerous ncRNAs, microRNAs (miRNAs) have attracted more attention from scholars both domestically and internationally, and significant progress has been made in basic and clinical research. Therefore, for improved understanding of the molecular mechanism of miRNAs in macrophage polarization and analysis of the potential value of this regulatory pathway in tumor and inflammatory intervention therapy, a comprehensive review of the progress of relevant literature research was conducted and some viewpoints and perspectives were proposed.

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Key words: microRNAs, macrophage polarization, transcription regulation, mechanism, tumor and inflammation

Contents

1. Introduction

Recent studies have clearly revealed that the monocyte/macrophage system exists in almost all tissues and organs of the organism and consists of important cell types that mediate immune response (1-3). Especially, the polarization of macrophages towards M1 or M2 type has more important pathological significance and is closely related to the occurrence and development of diseases, such as tumors or inflammation. Since abnormal polarization of macrophages has important pathological value, it is crucial to reveal the molecular mechanism of this polarization phenomenon, as it is the molecular basis for targeted intervention or reversal of abnormal polarization of macrophages to play a therapeutic role in diseases. As for the molecular mechanism of abnormal polarization of macrophages, most of previous studies have mainly focused on the research of transcriptional regulatory factors (4-6). In the recent years, with the progress of basic research on epigenetics, it has been observed that microRNAs (miRNAs or miRs) also play an

important role in macrophage polarization, especially in the local pathological processes of diseases such as tumors and inflammation. miRNA is an endogenous non-coding RNA (ncRNA), which regulates ~30 to 90% of genes in life and affects the synthesis of corresponding proteins by targeting to inhibit or promote the expression of mRNA (7). In addition to transcription factors (TFs), previous studies have shown that multiple miRNAs were also involved in regulating macrophage polarization, thereby participating in the development of inflammation and tumors (8-11). The present review focuses on the important role of macrophage polarization in tissue homeostasis and pathological regulation, as well as the latest research progress in the relationship between miRNAs and macrophage polarization towards M1 and M2, providing a theoretical basis for the treatment of inflammation and tumors.

2. Biogenesis and function of miRNA

miRNA is a class of single-strand non-coding small molecule RNA, with a length of ~18-24 nucleotides. The traditional miRNA biogenesis supports that the primary miRNA is generated by type II RNA polymerase in the nucleus, which is split by the ribonuclease Drosha/DGCR8 complex to generate precursor miRNA, and then to produce mature miRNAs after being processed by the Dicer enzyme in the cytoplasm (12). Usually, one of the main mechanisms by which miRNA acts is by targeting the 3' untranslated region of downstream genes to exert a sponge effect, which in turn inhibits the expression level of downstream target genes, regulates gene expression at the post-transcription level, and thus participates in important cellular processes (7). It is interesting that changes in the expression levels of certain important miRNAs can often be achieved through changes in the expression of target genes to regulate immune response and affect immune homeostasis. A single miRNA can target hundreds of mRNAs and affect the expression of multiple genes (13). In addition, miRNA can also be packaged with proteins or other RNAs (mRNA, circular RNA and long ncRNA) to form exosomes or microbubbles and get secreted out of cells, and subsequently taken up by receptor cells through direct membrane fusion or endocytosis, thus regulating their normal cellular activity. For example, exosome miR-223 which is derived from stem cells, can inhibit the expression of some pro-inflammatory cytokines by targeting Semaphorin 3A and STAT3 in macrophages of sepsis models (14).

It is well known that miRNA is widely present in various tissues and involved in an important role in various biological processes. In addition, numerous miRNAs, for example, miR-223 and miR-142-3p were also associated to the proliferation, differentiation and function of numerous kinds of immune cells (15). Cancer could be classified as a signaling pathway disease, which was induced by abnormal signaling pathways (16,17); however, miRNA can regulate the downstream of numerous target genes, thus affecting the status of almost all signaling pathways in cancer. On the other hand, miRNAs can also participate in the occurrence and development of certain inflammatory diseases, such as atherosclerosis (AS). For example, a recent study revealed that miR-205-5p can regulate ERBB4/AKT signaling pathway and has an inhibitory effect on the occurrence of AS (18).

It is precisely due to the widespread involvement of miRNA in diseases that it has become one of the targets for tumor treatment and inflammation control, especially in the treatment of tumors that it has demonstrated great potential. Usually, miRNAs exhibit abnormal expression or mutations in most malignant tumors and can function as oncogenes or tumor suppressor genes. Therefore, miRNA-targeted therapy has exhibited potential value for cancer treatment. At present, miRNA-mediated clinical trials have shown a favorable effect in cancer treatment. miRNAs or their analogues can be used to treat cancer by regulating and restoring the expression of cancer suppressor gene-related miRNAs, or inhibiting proto-oncogene-related miRNAs in cancer cells (19). In addition, the use of nanosomes to deliver miRNA and small molecule drugs has become increasingly widespread. For example, in the human pancreatic cancer cell line, two miR-205 mimics were used to reduce the metastasis and invasion of cancer cells (20). Therefore, a more important task is to delve into the key miRNA types which are closely related to diseases such as tumors, or upstream and downstream key genes associated with miRNAs, and screen for more significant targets or signaling pathways through *in vitro* and *in vivo* experiments. Among them, the macrophage polarization by miRNAs has also been widely concerned by scholars at home and abroad, and some important progress has been made. As for the research progress of miRNA in macrophage polarization, and as the marker for the treatment of tumors and inflammation, the present review provided a detailed introduction in the relevant paragraphs below.

3. Common diversity of macrophage polarization and functions

It has been demonstrated that macrophages not only regulate phagocytosis, exogenous antigen presentation and secretion of cytokines, but also play roles in system metabolism, hematopoiesis, angiogenesis, malignant tumors and reproduction (21). Macrophages have functional diversity and high heterogeneity. The change of the local microenvironment or under the action of different stimulators can obtain different phenotypes and then exert different functions, and this process is called polarization (Fig. 1) (22). Macrophage polarization has a significant impact on tissue repair and maintenance of tissue homeostasis, which were generally divided into two phenotypes (Fig. 1). For example, one has classically activated macrophages, namely, M1-type macrophages, which were usually induced by toll-like receptors (TLR) ligands. This subset of macrophages expresses TLR2 and TLR4, CD80, CD86, inducible nitric oxide synthase (iNOS) and major histocompatibility complex II (MHCII), and can produce a large number of cytokines to induce further polarization of macrophages in the feedback cycle, with high antigen presentation and expression of pro-inflammatory cytokines, such as IL-12, IL-23 and TNF-α, and has antitumor effects (23-25). Another alternative is to replace activated macrophages, namely M2 macrophages, which express specific antigens, such as CD206, CD163, CD209, FIZZ1 and Ym1/2. M2 macrophages can be divided into

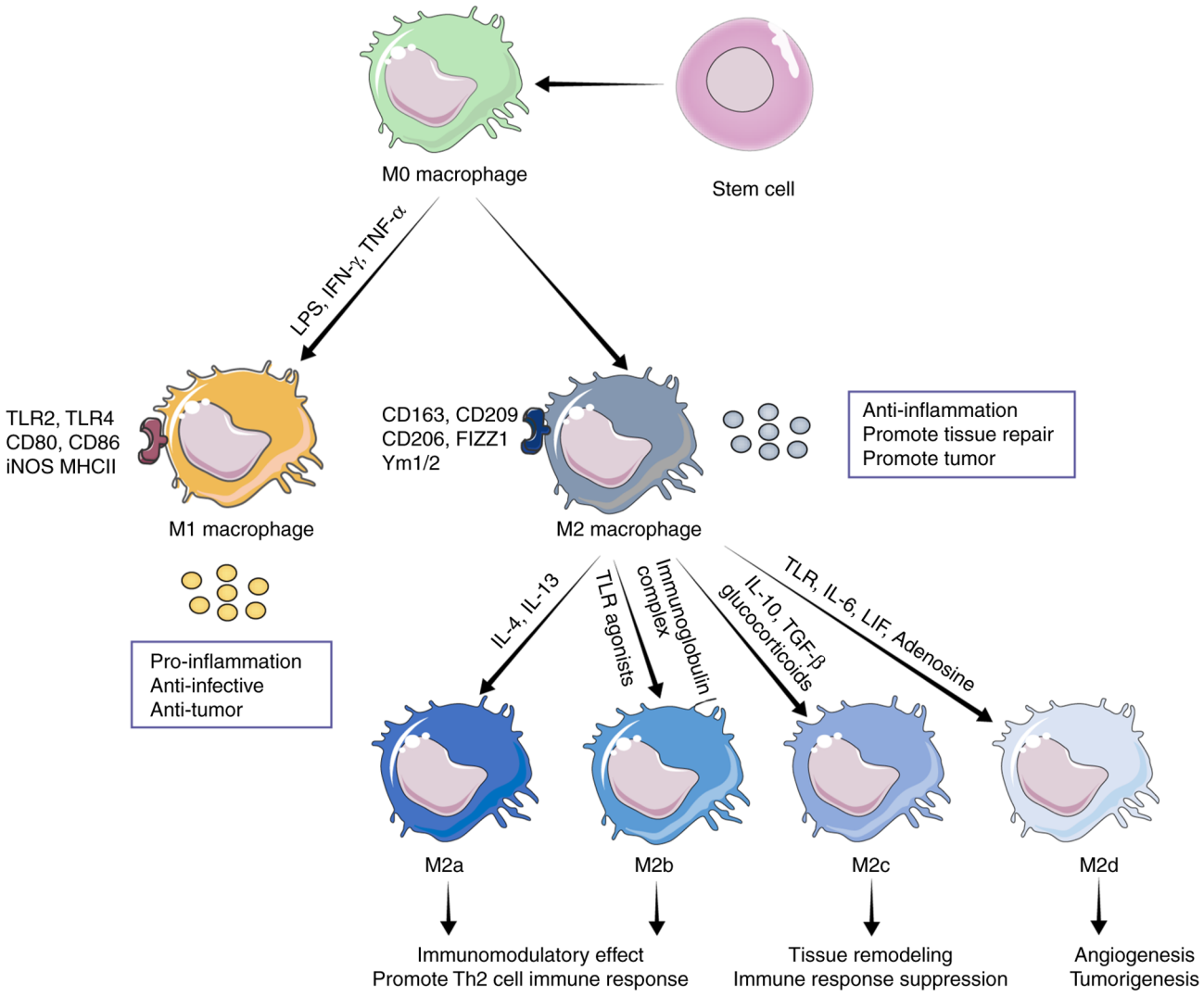

Figure 1. Macrophage phenotype and polarization. Macrophages are functionally diverse and highly heterogeneous and can differentiate into classically activated M1-type macrophages and alternatively activated M2-type macrophages under the action of different stimulating factors. Under the stimulation of LPS, IFN-γ, TNF-α, and other cytokines, M0 macrophages can polarize into M1 macrophages with pro-inflammatory, anti-infective and antitumor effects, with high expression of TLR2, TLR4, CD80, CD86, iNOS, and MHCII on the cell surface. M2 macrophages with high expression of CD206, CD163, CD209, FIZZ1 and Ym1/2, on the cell surface have anti-inflammatory, tissue repair and pro-tumor effects, and can be divided into M2a, M2b, M2c and M2d subgroups. IL-4 and IL-13 binding to receptors in Th2 cells induce the formation of M2a macrophages, and immunoglobulin complexes combined with TLR M2c macrophages are induced by IL-10, TGF-β, or glucocorticoids and are associated with immune response suppression and tissue remodeling. M2d macrophages are mainly induced by TLR and are involved in angiogenesis and tumorigenesis.

subgroups M2a, M2b, M2c and M2d. Certainly, these different subtypes of M2 cells can exert immune regulatory effects through different mechanisms of action (26-28).

Although recent research clearly indicates the types of macrophage subtypes, the polarization process of macrophages is very complex. It has been confirmed that the local microenvironment state of the tissue can affect the polarization state of macrophages, and this polarization between M1 and M2 is often reversible, and rapid type change occurs under the induction of some factors, or when responding to changes in the microenvironment (29). Thus, M1 macrophages and M2 macrophages can transform each other under different conditions. If the M2 macrophage could be induced to switch to M1 macrophage, the M1 macrophage would play an antitumor immune role to inhibit tumor growth, which indicates that the reversible way of polarization from M2 to M1 has potential therapeutic value in clinical treatment of tumors.

4. TFs and signaling pathways related to macrophage polarization

As aforementioned, the polarization of macrophages is a process of multifactorial interaction, regulated by multiple activating molecules and signaling pathways (Fig. 2). These activating molecules bind to relevant receptors on the surface of macrophages (30), activating downstream signaling pathways and further inducing phenotype-specific gene expression (31), and participating in macrophage polarization at the transcriptional level. Multiple specific signaling molecules and TFs have been demonstrated to activate macrophages, such as NF-κB, STATs, interferon regulatory factors (IRFs), CCAAT enhancer binding protein (C/EBP), peroxisome proliferator activated receptor (PPAR) and Kruppel-like factors (KLFs) (32). Among them, some are related to the M1 polarization and the others are related to M2 polarization. For example, the NF-κB

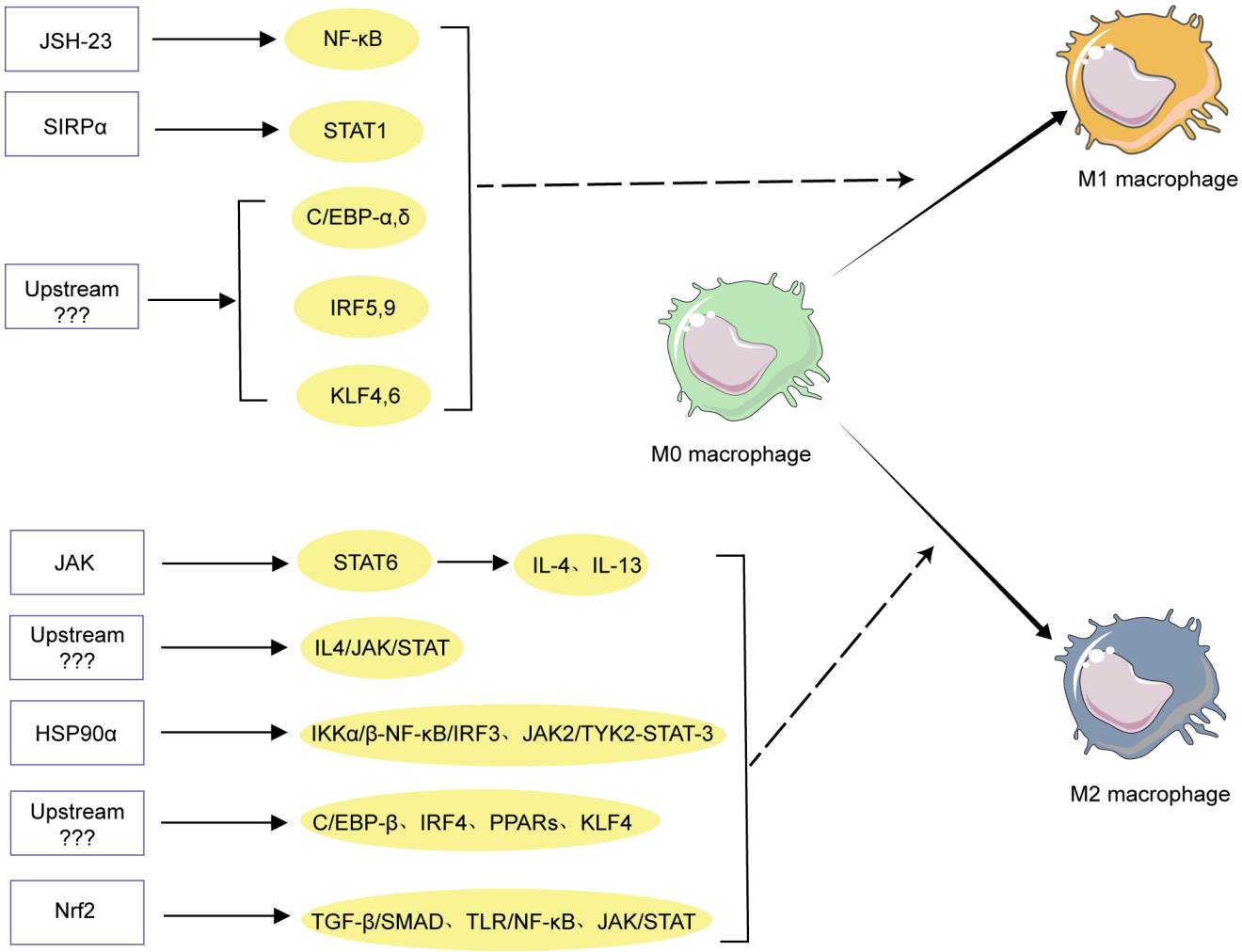

Figure 2. Polarization of macrophages is regulated by multiple activating molecules and signaling pathways. Multiple specific signaling molecules and transcription factors have been demonstrated to activate macrophages, such as NF-κB, STATs, IRF, C/EBPs, PPARs and KLFs. Among them, NF-κB, STAT1, C/EBPα, and IRF5 are related to the expression of M1 polarization-related genes, while STAT6, C/EBP-β, IRF4, PPARδ and PPARγ is involved in regulating the expression of M2 polarization related genes. PPAR, peroxisome proliferator-activated receptor; KLF, Kruppel-like factor; IRF, interferon regulatory factor; C/EBP, CCAAT enhancer binding protein.

signaling pathway was involved in host immune responses as a pro-inflammatory signaling pathway (33), which is involved in the regulation of macrophage polarization (34). Wu *et al* (35) observed that macrophages in patients with Behcet's disease (BD), expressed higher CD86 antigen, higher serum IL-12, TNF-α and lower CD163 antigen, which could enhance cell phagocytic ability and promote differentiation of Th1 cells, while the application of NF-κB inhibitors could weaken the M1 like phenotype stimulated by BD serum, indicating NF-κB has a regulatory effect on M1 polarization stimulated by BD serum. A recent study also reported that NF-κB phosphorylation participates in M1 polarization of macrophages in foreign body reaction (FBR). In the lipopolysaccharides (LPS)-induced inflammatory microenvironment *in vitro*, JSH-23, an inhibitor of NF-κB, could precisely inhibit PLA induced NF-κB phosphorylation and M1 macrophage polarization, which results in the inhibition of FBR through their anti-inflammatory and anti-adhesion effects (36). These all indicated that NF-κB was involved in macrophage polarization.

Janus family of kinases (JAKs) are composed of four members, such as JAK1, JAK2, JAK3 and Tyk2 (37). The JAK kinase family can phosphorylate STATs, called the JAK-STAT signaling pathway, to regulate its downstream genes. In the STAT family, STAT1 and STAT3 are two important family types, but they sometimes exhibit different functional characteristics. For example, in the presence of IFN-γ, STAT1 is an important mediator that activates the polarization of pro-inflammatory macrophages, while STAT3 can activate the polarization of anti-inflammatory macrophages (38). A recent related study have demonstrated that by disrupting the synthesis of hyaluronic acid in glioblastoma or blocking its binding to the receptor CD44 on macrophages, signal-regulatory protein alpha (SIRPα), can be induced to increase or enhance the phosphorylation of STAT1 in macrophages and inhibits STAT3 phosphorylation, which can induce M1 type macrophage generation and inhibit the growth of glioblastoma (39). In addition, the TF KLF4 in rheumatoid arthritis can promote M1 polarization by regulating STAT1 (40). The JAK-STAT6 pathway is related to the M2 polarization, which is mainly due to the modulation of IL-4 and IL-13, thereby activating PPARγ. On the other hand, the expression of key nuclear TFs such as KLF4 can induce the specific markers of

M2 macrophage (41). Fan *et al* (42) demonstrated that extracellular heat shock protein 90α (HSP90α) can induce activation of JAK2/TYK2/STAT3 signaling pathways to promote M2 polarization (42). Liu *et al* (43) indicated that activating the IL4/JAK/STAT signaling pathway through mechanical stimulation can also regulate macrophage polarization towards the M2 subtype, thereby promoting tendon-bone healing in mouse rotator cuff repair. A different study also pointed out that activating nuclear factor erythroid 2-related factor 2 (Nrf2) can inhibit M1 polarization and promote M2 polarization through three signaling pathways, such as JAK/STAT, TGFβ/SMAD and TLR/NF-κB and potential signal transduction pathways, as well as signaling pathways, such as NLRP3, Notch, PI3K/Akt and MAPK (44). In addition, the SENP1-Sirt3 signaling pathway can promote M2 macrophage polarization by reducing glutamate dehydrogenase1 (GLUD1) acetylation and promoting GLUD1-mediated aKG production (45). The aforementioned studies indicated that M1 or M2 polarization is regulated by specific signaling molecules and TFs. In summary, based on the aforementioned literature analysis and the results of literature analysis not specifically presented, it is preliminarily indicated that TF C/EBPα, C/EBPδ, STAT1, IRF9, NF-κB or KLF6 were usually involved in M1 macrophage polarization, while STAT3, STAT6, C/EBPβ, PPARs, c-myc, KLF4, IRF4 and GATA3 are associated with M2 macrophage polarization (Fig. 2). As for the specific roles of these listed transcription regulatory factors, although most literature results have reached consistent conclusions, their functional characteristics under different environmental conditions still need further exploration.

To further demonstrate the complexity of the role of transcriptional regulatory proteins, or their role in macrophage polarization, only some illustrative examples were provided. For example, it is interesting that even different members of the same transcriptional regulatory proteins play different roles in the polarization process of macrophages, for instance, in the IRF family, IRF4 promotes M2 polarization by upregulating expression of IL-10 in colon mucosal cancer (46). However, IRF5 plays a pro-inflammatory role by activating Akt2 to participate in M1 macrophage polarization (47). As for lipoxin A4 (LXA4), not only does it participate in the M1 polarization process in LPS-induced M1 macrophage polarization, but it is also related to the M2 polarization process in IL-4-induced M2 macrophage polarization, through the FPR2/IRF5 signaling pathway and FPR2/IRF4 signaling pathway respectively (48). C/EBPα of the C/EBP family can promote M1-type macrophage polarization, while C/EBPβ promotes M2 polarization (49). Akt1 inhibits the sensitivity of macrophages to inflammatory stimuli and promotes M2 macrophage polarization while Akt2 can promote M1 macrophage polarization, and knocking down Akt2 can enhance the expression of C/EBPβ and promotes polarization of M2 macrophages (50). Therefore, macrophage polarization is considered an important regulator of homeostasis and pathology in the organism's tissues, and a key determinant of disease occurrence, development and regression. Macrophages involve multiple TFs and signaling pathways in maintaining M1/M2 phenotype balance. Therefore, understanding the signaling pathway mechanisms that regulate macrophage polarization is an extremely important step in the treatment of diseases.

5. The role of miRNAs in macrophage polarization

The reason why the transcriptional regulatory factors related to macrophage polarization were first introduced or their related signaling pathways were summarized, is because miRNA often interacts with these important transcriptional regulatory proteins, thereby exerting the polarization regulation process of macrophages (51-53). Macrophage polarization, as a key regulator of environmental homeostasis in the human organism, relies on the expression of key TFs, whose expression is modulated by miRNA (54-56). Recently, with the gradual discovery of some miRNAs that regulate macrophage polarization, significant progress has been made in the study of the role of miRNA in macrophage polarization (7,8,57), and some research results have achieved positive consensus and demonstrated favorable application potential (58,59). Therefore, next, the progress of miRNAs in macrophage polarization and the impact of miRNA on the treatment of tumor and non-tumor diseases were mainly summarized.

miRNAs are involved in M1 macrophage polarization. Among them, the miRNAs in macrophage polarization, have received widespread attention from domestic and foreign scholars, and some important progress has been made. First, as a star miRNA, miRNA-155 has been widely studied for its role in macrophage polarization, and many studies so far revealed that miRNA-155 was involved in promoting M1 polarization (60-65), for example, the expression of miRNA-155 was significantly upregulated when macrophages polarized to the M1 phenotype, however, its expression was obviously downregulated when macrophages polarized to M2 phenotype. In addition, silencing miR-155 significantly promoted the polarization of M2 macrophages, and overexpression of miRNA-155 could induce a switch from M2 to M1 phenotype (60). It has been reported that miR-155 participates in inflammation and tumors by regulating multiple signaling molecules, which can modulate macrophage polarization in the immune microenvironment, and affect the host's anti-infection or tumor ability. However, the potential mechanisms of macrophage polarization during inflammation and tumor development remain unclear and complicated. In some cases, there may even be different mechanisms and outcomes. For example, one study investigated the mechanism by which miR-155 affects tumor-associated macrophage (TAM) polarization at a molecular level in hepatocellular carcinoma (HCC) initiated by hepatitis B virus infection. As compared with HBV^- HCC tissues, miR-155 was significantly highly expressed in HBV^+ HCC tissues. In addition, miR-155 overexpression significantly promoted M2-type macrophage polarization by the miR-155/SHIP1 axis, which accelerated HCC cell invasion, proliferation and migration. This finding provides new insights into the development of novel therapeutic strategies for combatting HBV^+ HCC and a new reference for exploring antitumor immunotherapy (61). Recently, it has been reported that miR-155-5p can regulate M1-type macrophage polarization by targeting downstream SOCS1/JAK1/STAT1 axis and participate in liver fibrosis and hepatic lymphangiogenesis in cirrhosis (62). Besides, miR-155-5p can regulate M1 polarization by other pathways, such as SOCS1/NF-κB pathway (63), and let-7a-5p can also target suppressor of cytokine signaling

1 (SOCS1) to modulate NF-κB, and activate M1 macrophages (64). Shenlian extract was demonstrated to inhibit the M1 polarization by inhibiting miR-155, upregulating SOCS3 and blocking the JAK2/STAT3 signaling pathway, thereby reducing tissue damage and cell apoptosis (65). Another literature study on the role of miRNA-155 in macrophage polarization suggested that miR-155 could induce M1 polarization by way of directly targeting the IL13Rα1 (IL-13 receptor α 1, IL13Rα1), which interferes with the activation of STAT6 and indirectly regulates the expression of other M2 related genes (66).

In addition to miRNA-155 playing a role in macrophage polarization, other miRNAs have also been reported to play a role in macrophage polarization. Histone demethylase jumonji domain containing 1C (JMJD1C) targets methyltransferase like 3 (METTL3) by upregulating miR-302a, inhibits SOCS2 expression through m6A modification, and promotes M1 polarization to prevent the occurrence of glioma (67). Overexpression of miR-130b-3p in LPS-treated mice inhibited M1 polarization in lung and peritoneal macrophages by inhibiting the expression of IRF1, thereby reducing inflammation in mouse lung tissue (68). It was revealed that the concentration of M2-related miRNAs, such as miR-146a and miR-223 in the serum of patients with sepsis was significantly reduced, and overexpression of miR-146a could inhibit expressions of TLR4-NF-κB pathway protein interleukin 1 receptor associated kinase 1 (IRAK1) and TNF receptor associated factor 6 (TRAF6), thereby inducing inhibition of M1 macrophage polarization, and reducing inflammation caused by sepsis (69). On the contrary, miR-495 can promote the M1 polarization and inflammatory cytokines by inhibiting the expression of the obesity-related gene FTO alpha-ketoglutarate dependent dioxygenase (FTO), which leads to the exacerbation of inflammatory response in adipose tissue (57). Furthermore, the PI3K/AKT signaling pathway activated by miR-21 can cause M1-type polarization of macrophages and lead to fibrosis in pig liver tissue (70), the activation of PPARδ regulated by miR-9 in monocytes may play an important role in human M1 pro-inflammatory cells, while it does not play a role in M2 anti-inflammatory macrophages (71), and a recent study demonstrated that miR-9 enriched in HPV^+ head and neck squamous cell carcinoma extracellular vesicles (EVs) can be transported to macrophages and result in arrest in M1 phenotype by downregulation of the expression of PPARδ (72). Another study revealed that efficient gene transfer complex RM125b carrying miR-125b can promote the polarization of M1 type macrophages. At the same time, it was also observed that RM125b can significantly inhibit the growth of tumor through TAM M1 polarization and reduce the proliferation of tumor cells (73). In addition, miR-125b-5p can promote M1 polarization after mycobacterium tuberculosis infection, which is related to A20/NF-κB-axis (74). In summary, some miRNAs have been confirmed to be closely polarized with M1, and the target and function of their action have been preliminarily determined (Table I).

miRNAs are involved in M2 macrophage polarization. In addition to playing an important role in M1 polarization, some miRNAs also play important roles in M2 polarization. Among the M2 polarization related miRNAs, one representative miRNA with consistent research results is miRNA-21, which has attracted the attention of numerous scholars. Some scholars indicated that expression of miR-21 was significantly increased in patients with non-small cell lung cancer (NSCLC) and radiation-induced lung injury (RILI). The protective effects of miR-21-overexpressing bone marrow mesenchymal stem cells (BMSCs) against RILI was also assessed in rat models. Animal-based experiments demonstrated that treatment with BMSCs had a remarkable effect on alleviating RILI of rats, and cell-based experiments demonstrated that BMSCs notably inhibited M1 polarization with a miR-21 dependent manner. These results indicated that BMSCs with miR-21 overexpression could be a potential therapeutic strategy for RILI (75). Furthermore, Xue *et al* (76) revealed that in the livers of mice exposed to arsenite, there were elevated levels of miRNA-21 and more extensive liver fibrosis. Arsenite induces the M2 polarization of macrophages via miR-21 regulation of PTEN, which is involved in the activation of hepatic stellate cells and hepatic fibrosis, which establish a previously unknown mechanism for arsenicosis-induced fibrosis. To identify the molecular mechanism by which miR-21 regulates macrophage polarization in sepsis-induced intestinal injury, Li *et al* (77) used a bioinformatics approach to predict the putative binding site between miR-21 and STAT1, and their targeting relationship was demonstrated by a luciferase reporter assay. The results indicated that miR-21 overexpression significantly inhibited the total and phosphorylated levels of STAT1, the miR-21 targeted STAT1 signaling and overexpression of miR-21 significantly promoted M2 polarization, thereby alleviating intestinal injury caused by sepsis. miR-21 in EVs can promote macrophage polarization towards the M2-type by targeting programmed cell death protein 4 PDCD4, reducing sepsis (78). A different study has confirmed that cigarette smoke extract can induce the M2 polarization by modulating the expression of miR-21, and the downregulation of miR-21 could inhibit M2 polarization in chronic obstructive pulmonary disease (79). However, a number of previous studies have reported opposite results to the aforementioned results, as miRNA-21appeared to play a role in promoting M1 polarization and inhibiting M2 polarization under certain conditions. For instance, Wang *et al* (80) identified that prostaglandin E2 (PGE2) induced M2 polarization was contributed to the inhibition of miR-21 expression by activation of its direct target STAT3, and silencing the STAT3 gene could abolish this PGE2-mediated expression of M2 genes in miR-21 deficient macrophages. These data suggested that the M1 polarization will be induced if miR-21 was upregulated. In a different study which investigated the relationship between miRNA-21 regulation of macrophage polarization and disease occurrence and development, most results indicated that miRNA-21 not only plays an important role in balancing inflammatory states, but also participates in the process of tumor occurrence and development (81). According to another study, miR-21 can promote chemotherapy resistance in ovarian cancer by regulating M2 polarization (82). In hypoxic environments, high levels of miR-21 expression can promote M2 polarization and induce the progression of lung cancer by targeting IRF1 (83). In addition, miR-21 in the exocrine body of bladder cancer cells can regulate PI3K/AKT signalling by inhibiting PTEN activation of macrophages and enhancing STAT3 expression, promoting

Table I. miRNAs involved in macrophage polarization and possible functions.

miRNAs	Phenotype promoted	Target genes or pathways	Function	(Refs.)
miR-155	M2	SHIP1; SOCS3/ JAK2/STAT3	Accelerate the proliferation, migration and invasion of hepatocellular carcinoma cells	(61,65)
miR-155-5p	M1	SOCS1/JAK1/ STAT1 or SOCS1/ NF-κb	Promote liver fibrosis; attenuate Cx43 protein degradation after MI	(62,63)
Csi-let-7a-5p	M1	SOCS1/NF-κb	Injury to the biliary tract	(64)
miR-302a	M1	METTL3/m6A/ SOCS2	Prevent the occurrence of glioma	(67)
miR-130b-3p	M2	IRF1	Reduce the inflammation of lung tissue in mice	(68)
miR-495	M1	FTO	Aggravate insulin resistance and adipose tissue inflammation	(57)
miR-21	M1	PI3K/AKT	Promote liver fibrosis in pigs	(70)
miR-21	M2	PTEN/STAT3/ PI3K/AKT or STAT1or PDCD4 or IRF1	Promote liver fibrosis, lung cancer, ovarian cancer, bladder cancer; Protect the intestinal injury caused by sepsis; Reduce sepsis	(76-78,82-84)
miR-9	M1	PPARδ	Increase the radiosensitivity of HPV+HNSCC	(72)
miR-125b-5p	M1	A20/NF-κB	Alleviate chronic MTB infection in mice	(74)
miR-182	M2	TLR4/NF-κB	Alleviate inflammation in myocardial infarction	(85,86)
miR-146a	M2	TLR4/NF-κB	Reduce sepsis-induced cardiac dysfunction, inflammatory cell infiltration and inflammatory cytokine production; Promote healing of diabetic ulcers	(87,88)
miR-21a-5p	M2	KLF6 ERK1/2	Reduce atherosclerosis	(90)
miR-19b-3p	M2	PTPRD/STAT3	Aggravated adenocarcinoma of the lung	(91)
miR-27a-3p	M2	EZH1/KDM3A/ CTGF	Promote the development of glioma	(92)
miR-34a	M1	KIF4	Promote obesity-induced fat inflammation	(93)

miRNAs, microRNAs.

M2 polarization and leading to an increase of migration and invasion of cancer cells (84). Ma *et al* (85) observed that miR-182 expression in macrophages could directly inhibit the expression of TLR4, leading to the inactivation of NF-κB to induce M2 polarization of TAMs. In addition, the therapeutic delivery of miR-182 antagonist with EVs can lead to inhibition of miR-182, which resulted in tumor suppression in various models of breast cancer (BC). This is consistent with a previous study which demonstrated that miR-182 can alleviate inflammation in myocardial infarction by regulating TLR4 in macrophages (86). Through literature review, it was observed that another miRNA type related to M2 macrophage polarization is miRNA-146a. For instance, miR-146a overexpression can lead to an increase in M2 phenotype markers. On the contrary, knocking down miR-146a promotes M1 polarization and reduces M2 polarization (87). In terms of its molecular mechanism of action, a previous study revealed that miR-146a, at least partially, targets Notch1, PPARγ and inhibin beta A subunit (INHBA) to regulate macrophage polarization. miR-146a can induce M2 polarization by inhibiting TLR4/NF-κB axis, thus promoting the healing of diabetes ulcers (88). In addition, miR-125a-5p is a regulatory factor for the immune regulation of M2b macrophages (89). However, the secretion of miR-21a-5p from mesenchymal stem cells (MSCs) could induce M2 polarization and alleviate AS by targeting KLF6 and ERK1/2 pathways (90). Chen *et al* (91) demonstrated that lung adenocarcinoma (LUAD) cells can induce M2 polarization of TAMs *in vivo*, and the M2 polarization can promote the invasion, migration and tumor metastasis of LUAD cells. miR-19b-3p derived from exosomes of LUAD cells also inhibited STAT3 dephosphorylation by targeting protein tyrosine phosphatase receptor type D (PTPRD) in TAMs, leading to activation of STAT3 and polarization of M2 macrophages, thus positive feedback aggravates the development of cancer. The small miR-27a-3p released from EVs of glioblastoma can induce macrophage polarization towards the

M2 type through the EZH1/KDM3A/CTGF axis, promoting the occurrence of glioblastoma (92). The EV miR-34a, secreted by adipocytes, could inhibit M2 polarization by downregulating KLF4 expression, promoting obesity-induced adipose inflammation (93). After reviewing the aforementioned articles, it was observed that some miRNAs have been confirmed to be closely related to the polarization of M2 macrophages and have clear targets and characteristics of function (Table I).

Numerous other miRNAs involved in macrophage polarization need to be further clarified. The results reported in the aforementioned studies indicated that certain types of miRNAs may play an important role in the polarization, function and regulation of macrophage polarization. The main molecular mechanism by which these miRNAs manipulate the macrophage polarization process is often through the regulation of downstream key target genes or signaling pathways, thereby affecting the balance of pro-inflammatory and anti-inflammatory responses, or playing an important role in the occurrence and development of tumors. Therefore, in addition to understanding the positive miRNAs associated with macrophage polarization as aforementioned, it is necessary to further detect other new miRNAs and analyze whether they make sense in clinical validation. In a recent study, Zhang *et al* (94) investigated the differential expression of 109 miRNAs during the polarization of M1 and M2 macrophages in humans and mice. The results showed that in LPS and IFN-γ stimulated mouse bone marrow-derived macrophages (BMDM), the expression of miR-127-3p, miR-155-5p, miR-181a, miR-204-5p and miR-451 were significantly upregulated, while the expression of miR-125-5p, miR-143-3p, miR-145-5p and miR-146a-3p were significantly increased in IL-4-induced mouse BMDM cells. In a different study, whether in polarized BMDM cells or PMA-induced THP-1 cells, after exposure to IFN-γ/LPS treatment, miR-27a, miR-29b, miR-125a, miR-146a and miR-155 were significantly upregulated. However, after IL-4 co-treatment, the expression of miR-26a and miR-193b was significantly increased (95). Curtale *et al* (96) confirmed that miR-155 is highly expressed in M1 polarized macrophages, while miR-146a, miR-125b and miR-127 are highly expressed under M2 polarized conditions. Furthermore, the important role of miR-15 in macrophage polarization and inflammation was elucidated (60,97,98). In addition, previous studies demonstrated that miR-127 and miR-125b induce M1 polarization by targeting the expression levels of Bcl-6 and IRF4 genes, respectively, thereby increasing the expression and release of pro-inflammatory cytokines (99,100). It should be particularly emphasized at this point that the inhibitory effect of miR-127 on Bcl-6 will lead to a decrease in the expression of dual specificity phosphatase 1 (Dusp1) and an increase in the phosphorylation level of JNK. Knocking down its expression leads to a decrease in the expression of M1 characteristic genes and promotes the transcription level of M2-related genes (99). There are also results confirming that overexpression of miR-720 can reduce the expression level of GATA3, ultimately leading to inhibition of the M2 polarization level (101). Other miRNAs that are highly expressed in M2 macrophages include miR-511-3p, miR-223 and let-7c (96,102), which have been revealed to significantly promote M2 polarization. Some slightly reported miRNA types are involved in the polarization process of macrophages to varying degrees. For example, miR-511-3p is also highly expressed in TAMs (103) and promotes the expression level of M2-related genes. miR-223 can limit the polarization and pro-inflammatory activity of M1 macrophages by targeting the TF Pknox1 (104,105). Similarly, Zhang *et al* (106) demonstrated that there was a loss of let-7c and elevated expression of p21-activated kinase 1 (PAK1) in human and murine macrophages induced by inflammatory stimuli, and the let-7c dependent upregulation of PAK1 by upstream EZH2 could promote macrophage M1 polarization. Usually, the expression of let-7c is higher in M2 macrophage than that in M1 macrophage, the overexpression of let-7c reduces the expression of M1-related genes and increases the M2 markers, and the opposite result will occur when knocking down let-7c (107). These results preliminarily indicated that macrophage polarization is also related to miR-23a, miR-27a and miR-24-2, their expression is downregulated in M1 polarization and upregulated in M2 polarization. More interestingly, overexpression of miR-23a or miR-27a can promote the expression of pro-inflammatory cytokines by acting on different signaling pathways, while inhibiting the expression level of M2-type cytokines. For example, miR-23a reduces M2 cytokine production by targeting TNF inducible protein 3 (TNFAIP3), then JAK1 and STAT6, while miR-27a can target interferon regulatory factor 4 (IRF4) and peroxisome proliferators γ (PPAR γ) to regulate the express of ion-inflammatory factors and activate their receptors (108).

In summary, in this section, a preliminary summary and analysis of some miRNAs that have been less reported have been conducted. However, the molecular mechanism of miRNA in macrophage polarization is relatively complex, involving the interaction between its upstream regulatory factors and downstream target genes. In terms of the types of miRNAs polarized by macrophages M1 and M2, both directions of polarization have relatively specific associations with miRNA types and have different effects on inhibiting or promoting macrophage polarization (Fig. 3). As for their exact role and molecular pathways in driving macrophage polarization, further validation and clarification are needed. Therefore, in addition to the confirmed miRNAs related to M1 or M2 polarization aforementioned, other related miRNAs have recently been discovered and are being further confirmed (Table II).

6. Therapeutic role of macrophage polarization induced by miRNA for tumors and inflammation

Although it has been confirmed that numerous miRNAs can regulate different macrophage functions, it is known that only a few miRNAs are closely related to the polarization of macrophages. Increasing evidence suggests that miRNAs in different tissues and cell types have their specificity, and numerous studies have detected miRNA patterns in various macrophage types and their potential roles in macrophage polarization (109). So far, it has been observed that specific miRNA mimics or anti-inflammatory drugs can control immune and inflammatory responses, and it has been preliminarily confirmed that the use or intervention of these miRNAs can play a role in treating inflammatory diseases (110-112).

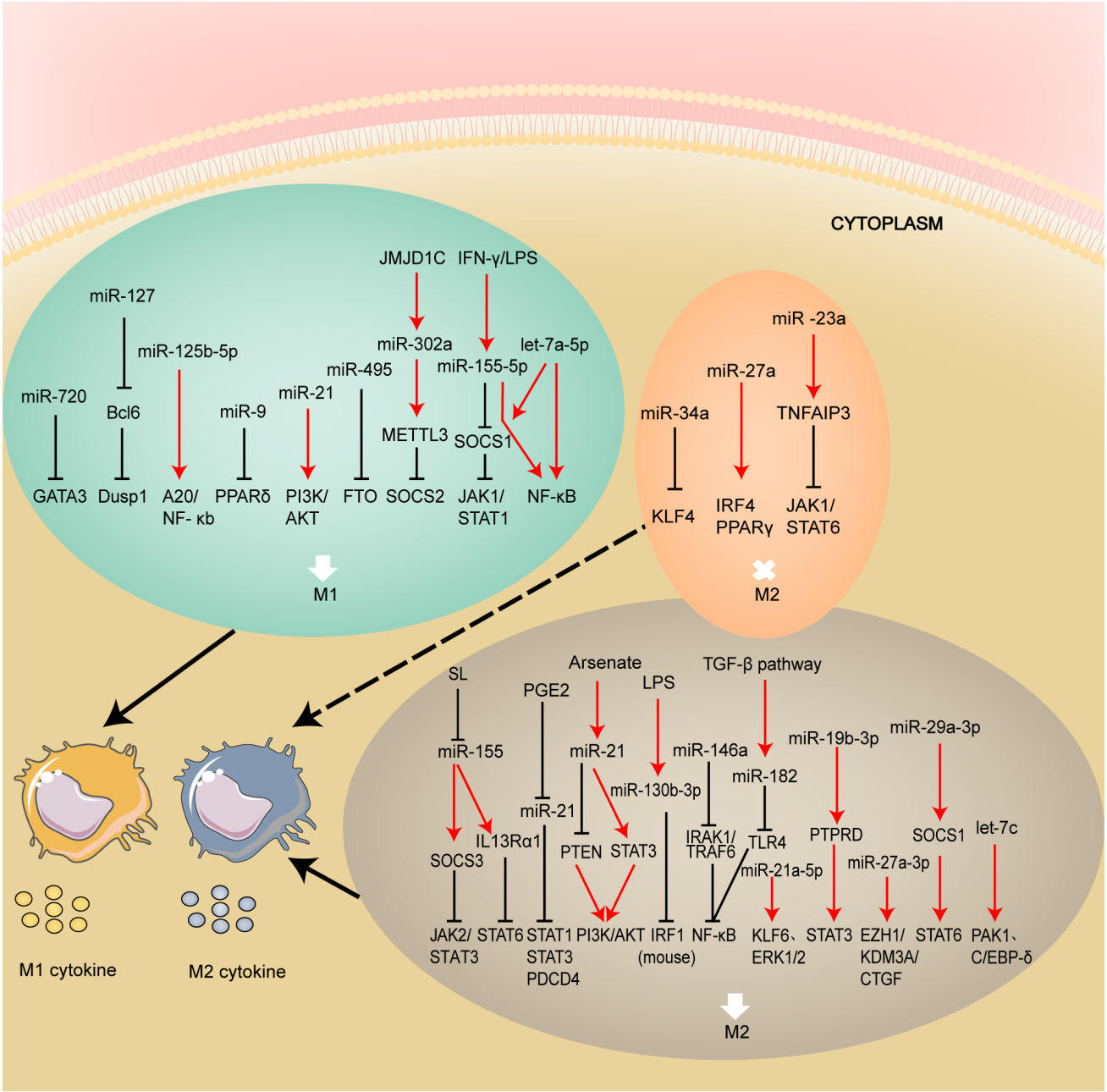

Figure 3. Schematic of miRNAs involved in macrophage polarization. The role of miRNAs in macrophage polarization is relatively complex, involving the interaction between its upstream regulatory factors and downstream target genes. In terms of types of miRNAs involved in polarization of macrophages, some important miRNAs have been demonstrated to promote polarization of M1 and M2 macrophages, whereas a number of other miRNAs could inhibit polarization of both of them. These polarization related miRNAs and their signaling pathways will be potential target for treatment. miRNAs, microRNAs.

However, in addition to the potential role of miRNA in acute and chronic inflammation, it is necessary to conduct more research on miRNA expression in diseases, such as inflammation and tumors (113). Identifying specific targets for any single miRNA remains a major challenge, and some advanced technologies are continuously determining the target of miRNA action (114). Therefore, further studies are needed to determine the precise function and effects of miRNAs, especially their regulatory effects on macrophage polarization before being used as targets for therapies.

Macrophage polarization induced by miRNA for treatment of tumors. With the continuous deepening of research on the mechanism of action and biological functions of miRNAs, it has been identified that certain important miRNAs have certain physiological and pathological effects. Therefore, some scholars have gradually transitioned from basic research to applied research and have achieved favorable therapeutic effects in disease experiments and clinical treatments. Especially prominent is the research on the treatment of inflammatory diseases and tumors with miRNAs. One of the therapeutic effects is based on the role of miRNA in macrophage polarization. Because whether it is an inflammatory disease or a malignant tumor, it is to some extent related to the polarization of macrophages. Thus, whether miRNA is a new tool for human cancer treatment has attracted the attention of

Table II. A number of different miRNAs involved in macrophage polarization.

miRNAs	Phenotype promoted	Target genes or pathways	Function	(Refs.)
miR-181a, miR-204-5p, miR-451, miR-29b, miR-125a	M1	Unidentified	Upregulated in M1 polarized macrophages	(94,95)
miR-146a	M1	Unidentified	Upregulated in M1 polarized macrophages	(95)
miR-143-3p, miR-145-5p, miR-26a, miR-193b	M2	Unidentified	Upregulated in M2 polarized macrophages	(94,95)
miR-127	M1	Bcl6	Increase expression of proinflammatory cytokines	(99)
miR-125b	M1	IRF4	Increase expression of proinflammatory cytokines	(100)
miR-511-3p	M2	IRF1	High expressed in tumor-associated macrophages, supporting the expression of M2-related genes	(103)
miR-223	M2	Pknox1	Promote the anti-inflammatory response and inhibits the pro-inflammatory activity of M1 macrophages	(104,105)
let-7c	M2	PAK1, C/EBP-δ	Decrease expression of M1-related genes (i.e., iNOs and IL-12) and increase M2 markers	(106)
miR-23a	M2	TNFAIP3, JAK1/STAT6	Promote the expression of proinflammatory cytokines and reduce production of M2-type cytokines	(108)
miR-27a	M1	IRF4, PPAR γ	Promote the expression of proinflammatory cytokines and reduce production of M2-type cytokines	(108)

miRNAs, microRNAs.

numerous scholars. For instance, in the research of tumors, miRNAs are mainly divided into two categories based on their different effects on tumor cells, such as promoting tumors and inhibiting tumors. However, it is worth noting that certain miRNAs occasionally have a dual effect of promoting or inhibiting tumors under different environmental conditions. In conclusion, macrophages are important immune cells in the tumor microenvironment (TME), and miRNAs can regulate the proliferation, metastasis and therapeutic response of tumor cells mainly by influencing the polarization of macrophages, which has been observed in various cancers. Naturally, miRNAs associated with macrophages are a feasible new treatment method for tumor immunotherapy. Therefore, after determining the exact role of a certain miRNA, its targeted therapeutic effect in treatment should be evaluated and a series of necessary clinical studies should be conducted. With the deepening understanding of immunotherapy, the current anticancer treatment research is increasingly focused on the direction of the TME. It is known that miRNAs play a crucial role in regulating genetic information and expression and mediate interactions between tumor cells and numerous components in TME. Macrophages are abundant in TME, and their different polarization directions can promote or inhibit tumor growth and progression by regulating biological behaviors such as macrophage recruitment, infiltration and polarization. In a review article describing the relationship between macrophage activation and miRNA, Zhou *et al* (115) focused on the progress and prospects of targeted therapy based on miRNA, novel clinical biomarkers and drug delivery systems. Through analysis of research studies, it was observed that crosstalk between tumor-related macrophages and miRNAs plays a key role in the TME. It was also pointed out that miRNA-based therapies can be designed in two different directions. One is to reduce the level of carcinogenic miRNAs or increase the content of tumor suppressive miRNAs (116). In terms of the relationship between cancer miRNAs, tumor suppressor miRNAs and macrophage polarization aforementioned, various miRNAs play different roles in the M2 polarization of cancer TAM. Among them, miRNAs that promote M2 polarization or inhibit M1 polarization are referred to as 'oncogenes', mainly including miR-19a-3p, miR-21, miR-29a-3p, miR-145, miR-195-5p, miR-224, miR-301a-3p, miR-1246 and miR-let-7 that promote M2 polarization. Correspondingly, another type of miRNAs that promotes M1 polarization or inhibits M2 polarization is called a 'tumor inhibitor', such as miR-142-3p and miR-155 that promote M1 polarization. The other two types of ncRNAs are designated as 'juggle tumor inhibitors' or 'juggle oncogenes'. Juggle tumor inhibitors refer to ncRNAs that promote M1 polarization, and these Juggle oncogenes inhibit M1 polarization. Multiple tumor suppressor miRNAs include miR-16, miR-34a and miR-142-3p, while the main oncogene miRNAs include miR-503, among others. Therefore, further research on the role of miRNAs in cancer macrophage polarization may lead to more precise screening of macrophage polarization modulators for different cancer treatment methods (117). It has

been proved so far that miRNA plays a significant role in the diagnosis and treatment of clinical diseases, the first batch of human miRNA therapy drugs have entered the first phase of clinical trials, and recently entered the second phase of clinical trials for advanced tumors. As proof, the miR-155 oligomeric inhibitor Cobomarsen is used for the treatment of T-cell leukemia/lymphoma. In addition, the miR-16 analog TargomiR can be used for the treatment of mesothelioma (118). ncRNA, as a regulatory factor for macrophage polarization, can also mediate immune responses to various cancers by reprogramming TME, thereby regulating immune responses (119). MiRNA mimics and antagonists that can reprogram TME are currently being tested in human clinical trials and may become a new promising treatment strategy (120). In particular, miR-138 mimics can specifically target and bind to PDL-1 and CTLA-4 mRNA, mimic the effects of anti-PD-1 and anti-CTLA-4 antibodies, and inhibit their expression (121). Li *et al* (122) observed that miR-498 may inhibit esophageal cancer by inhibiting macrophage autophagy and M2-like polarization through MDM2/ATF3. There are also a number of studies indicating that miRNA-related therapies have improved efficacy and safety than small interfering RNA (siRNA)-based therapies (123). In subsequent studies on miRNA therapy, it was revealed that injecting miRNA-based drugs into tumors can improve their specificity and efficacy while reducing side effects. For example, injecting cationic liposomes/pVAXmiR-143 complex into tumors can inhibit subcutaneous tumor growth *in vivo* (124). Intra-tumoral injection of miR-19a-3p can downregulate the expression of fos-related antigen-1 (Fra-1) and effectively reduce the invasive ability of BC (125). The administration of miR-142-3p microbubbles derived from TAM can significantly inhibit tumor growth in tumor-bearing mice, indicating the potential anticancer value of miRNA administration in TME (126). In addition, due to the ability of miRNAs to interact with specific target genes, they have a significant role in regulating gene expression, and interference in their related signaling pathways will also be a targeted intervention pathway for tumor treatment. In TME, tumors and mesenchymal cells can cross-communicate through various factors. One of the strategies for the immune escape of tumor cells is to release miRNA, which regulates the polarization and activity of circulating or local monocytes/macrophages to perform tumor-promoting effects. On the other hand, miRNAs derived from macrophages can also exert antitumor functions. In a previous comprehensive article, the author provided a detailed summary and analysis of the latest developments in miRNA-mediated crosstalk between tumor cells and macrophages and their uptake patterns in TME (127). However, there is relatively little systematic research on the function and mechanism of miRNA in tumor tissue TAMs. Li *et al* (128) demonstrated that miR-146a promotes the expression of a number of M2 macrophage phenotype molecules and confirmed that overexpression of miR-222 inhibits TAM chemotaxis by targeting C-X-C motif chemokine ligand 12 (CXCL12) and inhibiting C-X-C motif chemokine receptor 4 (CXCR4), thereby inhibiting tumor cell proliferation and tumor growth. The main reason is that miRNA affects the growth of breast tumors by promoting M2-type polarization or regulating the recruitment of TAMs. These results suggested that endogenous miRNAs may play an important role in controlling the polarization and function of TAMs in BC. Pirlog *et al* (129) analyzed the role of miRNAs in TME macrophage polarization and the role of this macrophage polarization in NSCLC regions. The results confirmed that the normal recovery of macrophage polarization in TME can produce significant antitumor effects. A different study also revealed that miR-16 can produce significant antitumor activity by promoting the polarization of M1-like macrophages (130). In terms of research on miR-19a-3p, it has been detected that it is involved in the induction of the polarization of M2-like macrophages and is involved in the progression and invasion of breast tumors (110), or in the promotion of the occurrence of colitis-related colorectal cancer (CRC). However, so far, the mechanism by which miR-19a-3p induces M2-like macrophages has not been elucidated (131).

In addition, a number of studies have also demonstrated that other miRNAs involved in M2 macrophage polarization play a role in promoting tumor occurrence and development. For instance, overexpression of miR-19a-1p induces the progression and metastasis of BC (125), tumor-derived exosomes miR-21 cause polarization of M2 macrophages, promoting the growth of head and neck tumors (132), and miR29a-3p promotes polarization of M2 macrophages by activating SOCS1/STAT6 signals, leading to invasion of oral squamous cell carcinoma and tumor cell proliferation (133). On the contrary, significant progress has been made regarding the role of M1 polarization in tumors. For instance, Zhang *et al* (134) comprehensively summarized the role of miRNA-34 in tumors and concluded that miRNA-34 exhibits dysregulation in various human cancers. miR-34a can inhibit M2 polarization and drive M1 polarization. Currently, its main functional localization is tumor-suppressive miRNAs. With the development of phase I clinical trials of miR-34a mimetic MRX34, the importance of miR-34 has become increasingly recognized and plays a crucial role in inhibiting tumor progression. In addition, it has potential value as a candidate therapeutic drug for miRNAs (135,136). A different study also showed that the expression of miR-34a in triple-negative BC mediated M1 polarization while antagonizing miR-34a could promote M2 polarization. However, there have been opposing studies regarding miR-34a stimulation of invasion and metastasis in CRC (135). miR-142-3p is a tumor inhibitor that promotes the polarization of macrophage M1 phenotype and has been revealed to inhibit the growth of glioma. It has favorable therapeutic potential in anti-glioma therapy (136). miR-145 was revealed to be a communication tool between TAM and cancer cells, leading to the tumor-promoting effect induced by TME. The main reason is that it has inhibitory effects on M1 and promotes polarization of M2-like macrophages, indicating that its siRNA has favorable therapeutic prospects for tumors (137). As previously described, miR-155 is one of the most widely studied miRNAs in different cancers and is involved in driving M1 polarization in macrophages and its mimetics are candidate drugs for treating various tumors (60,138). Furthermore, a number of miRNAs involved in potential tumor treatment have attracted the attention of scholars. For example, it was revealed that miRNA-224 is involved in inhibiting the progression of prostate cancer (PC) by downregulating TRIB1 to induce the transformation of M2 macrophages into M1 cells (139).

miR-301a-3p promotes the metastatic phenotype of human pancreatic carcinoma cell line PANC-1 cells by inducing M2 macrophages to differentiate from stromal macrophages. In addition, knocking out miR-301a-3p significantly weakens the polarization of macrophages towards the M2 type, thereby reducing the invasion, migration and metastasis ability of PANC cells *in vivo* and *in vitro* (140). miR-503 plays a crucial role in promoting brain metastasis by inducing M1 to M2 macrophage polarization in BC patients (141). miR-1246, as an EV derived from hypoxic glioma cells, is assigned to induce M2-like macrophage polarization (142), while in ovarian cancer, miR-1245 also enhances chemotherapy resistance through M2-like cell polarization (143). miRNA let-7b plays an important role in regulating macrophage polarization, thereby enhancing the presence of TAM in PC. When treated with let-7b inhibitors, it leads to reduced migration and angiogenesis of PC cells (144). According to previous studies, let-7c also has a role in regulating inflammation and related cytokines through macrophages in the occurrence and development of lung cancer (145). Additionally, it has been reported that the lin-28B-let-7-HMGA2 axis is involved in the induction of BC through M1 macrophage activation (146), and miR-let-7a has also been exhibited to participate in M2 macrophage polarization (147). Although it is not yet clear how miRNA-let-7b regulates macrophage phenotype and function, results have confirmed that TAM treated with let-7b inhibitors reduces angiogenesis and migration in PC (144). However, further research is needed to verify the role of miRNA in tumor therapy by regulating macrophage polarization.

The role of macrophage polarization is induced by exosomal miRNAs in treatment of tumors. An increasing number of results demonstrated that cells in some microenvironments can regulate the process of macrophage polarization in the form of an exocrine body or microbubble. For example, in the study of the lung metastasis model of breast adenocarcinoma mice, Xun *et al* (148) preliminarily confirmed that miR-138-5p was transferred from BC cells to tumor-related macrophages through exosomes, and the polarization of M2 macrophages was achieved by reducing the expression of lysine demethylase 6B (KDM6B). Therefore, interfering with this exosome-derived miR-138-5p may become a potential target for cancer treatment. Xu *et al* (149) preliminarily demonstrated that miR-3184-3p is enriched in cerebrospinal fluid EVs of glioma patients, and promotes tumor progression by directly promoting glioma cell proliferation and promoting M2-like macrophage polarization. The results indicate that interfering with the exosomes miR-3184 may be a possible pathway for future glioma treatment (149). Ma *et al* (85) used cationic mannan-modified EVs to effectively target macrophages in the breast tumor mouse model experiment, thereby inhibiting M2 cell polarization by inhibiting the expression of miR-182 and achieving the goal of treating cancer. Macrophages are abundant in TME and their M2 dominant polarization is conducive to the malignant proliferation of tumors. Various forms of miRNAs, including exo-miRNAs, can dually induce/inhibit macrophage polarization and regulate tumor progression and treatment response by influencing various molecular pathways (150). In the gastric cancer liver metastasis (GC-LM) model, it was revealed that the expression level of miR-519a-3p in serum EVs of patients with GC-LM was significantly higher than that of patients without LM. This exo-miR-519a-3p mainly activates the MAPK/ERK pathway by targeting DUSP2, leading to M2-like polarization in macrophages. M2 like polarized macrophages can accelerate the development of GC-LM. The results indicated that exo-miR-519a-3p plays a crucial role in mediating the interaction between primary GC cells and hepatic macrophages, and is a potential therapeutic target for GC-LM (151). Ma *et al* (152) investigated whether exosomes derived from NSCLC affect TAMs and whether TAMs provide feedback regulation on the progression of NSCLC. The results demonstrated that miR-181b was upregulated in EVs derived from NSCLC patient serum and NSCLC cells. This EV derived from NSCLC cells can enhance the polarization of macrophage M2 by regulating the miR-181b/JAK2/STAT3 axis. The silencing of miR-181b in NSCLC cells and the use of JAK2 inhibitors in macrophages blocked this effect. Therefore, the involvement of extracellular miR-181b in crosstalk between NSCLC cells and TAMs is also a potential therapeutic target for NSCLC (152). Although some studies have confirmed that macrophage-derived exosomes (MDE) are involved in tumor progression, their role in glioma is not fully understood. In an experiment on the activation of macrophage, it was observed that the circRNA BTG (circBTG2) in macrophage exosomes is upregulated, which contributed to inhibiting tumor progression through circBTG2/miR-25-3p/PTEN pathway, indicating that miRNA-25 and circBTG2 can be considered as diagnostic biomarkers and potential targets for the treatment of glioma (153). Chuang *et al* (154) confirmed that the exosomes transfected with miR-155 and miR-125b could reverse M2 phenotype polarization induced by pancreatic cancer and promote M2-like cells to transform into M1 macrophages. Similarly, macrophages in glioblastoma TME secrete EVs containing miR-21, and their levels are related to the M2 polarization state. Reducing the secretion of miR-21 EVs by macrophages can reduce the polarization state of M2 and achieve the goal of inhibiting tumor growth. In addition, whether it is miR-195-5p (155), miR-130a (156), or miR-31-3p (157,158), they are all related to the polarization of macrophages and may also mediate the interaction between tumor cells and macrophages. Interfering with exosomes containing these miRNAs has the potential for targeted treatment of tumors. Binenbaum *et al* (159) observed that MDE significantly reduced the sensitivity of pancreatic ductal adenocarcinoma (PDAC) cells to gemcitabine *in vitro* and *in vivo*. This effect is mediated by the transfer of miR-365 in MDE. MiR-365 weakens the effect of gemcitabine by upregulating the adenosine triphosphate pool and inducing cytidine deaminase in cancer cells. In mice carrying PDAC, miR-365 translocation in TAM was found to induce gemcitabine resistance. The use of MDE as antagomir carriers can improve the efficacy of chemotherapy in cancer and uncover new treatment options for combating malignant tumors (159). The research results of Moradi-Chaleshtori *et al* (160) indicated that exosomes can effectively deliver miR-130 to macrophages, leading to upregulation of M1-specific markers and cytokines, as well as downregulation of M2-specific markers and cytokines. The use of miRNA-containing EVs to reverse M2 macrophages to the M1 phenotype may be one of the therapeutic strategies for combating cancer invasion and metastasis. Chen *et al* (161)

focused on the regulatory effects of miRNA on macrophage differentiation, functional polarization and cell crosstalk, and detected that crosstalk between tumor cells and macrophages is crucial for the formation and progression of TME, miRNA can act as different forms of communication mediators, such as microbubbles or EVs. Papillary thyroid cancer (PTC) is an endocrine malignancy, and the role and molecular mechanism of miR-655-3p in PTC are currently unclear. A study conducted by Qiao *et al* (162) revealed that overexpression of miR-655-3p with mimics significantly reduced tumor cell viability, chemotaxis and invasiveness. Exosomes miR-655-3p inhibits growth, invasion, and macrophage M2 polarization in papillary thyroid carcinoma by targeting CXCR4. The results indicated that the regulation of exosomes miR-655-3p/CXCR4 may be a potential therapeutic strategy for PTC (162). Some scholars have also conducted corresponding research on the relationship between extracellular miRNAs and drug resistance. Previous studies have shown that cancer-associated fibroblasts (CAFs) regulate gemcitabine resistance by transferring exosomes miRNA-106b to cancer cells. Recently, it has been proven that TAM can promote resistance to gemcitabine. However, the role of CAF in regulating cancer TAM function remains unclear. Zhao *et al* (163) extracted primary CAFs from tumor tissue of PC patients and obtained CAFs-derived exosomes (CAFs-Exo). The results showed that conditional mediators derived from CAFs have a higher potential to promote M2 polarization in macrophages. Furthermore, it was revealed that miRNA-320a can transfer from CAFs to macrophages through EVs, thereby promoting M2 polarization. Pretreatment of CAFs with miRNA-320a inhibitors reduced the expression of miRNA-320a in CAFs-Exo and resulted in reduced polarization of M2 macrophages. Therefore, targeted intervention of this pathway may be an effective way to combat PC (163). Some scholars have observed that in addition to the prevention and treatment of EV delivery, miRNA can also mediate the transmission of miRNA between cells through EVs. Loading of miR-124 into 293T-derived EVs formed miR-124-EVs. The results revealed that miR-124-EVs had an effective antitumor effect in both glioblastoma cells and microglia cells. The main mechanism of its effect is that EV-mediated miR-124 delivery can inhibit the growth of human glioblastoma cells and inhibit the polarization of M2 microglia. These findings provide substantial evidence for the development of potential therapeutic strategies using miRNA-loaded EVs (164).

Therapeutic potential of miRNA-induced macrophage polarization in inflammation-related disease. It has been proven that the polarization state of macrophages under different pathological conditions can promote or alleviate various inflammations (158,165-167). Therefore, miRNAs that regulate macrophage polarization can also regulate inflammatory responses or become targets for the treatment of inflammatory diseases such as sepsis, obesity, cancer and multiple sclerosis. Among them, sepsis is a severe inflammatory response syndrome and the main cause of death in hospital intensive care units (168-171). The pathophysiology of sepsis is very complex, often involving simultaneous activation of pro-inflammatory and anti-inflammatory responses (172). Given the complex balance between pro-inflammatory and anti-inflammatory responses, the role of macrophage polarization in sepsis remains unclear to this day. However, the study of miRNAs involved in macrophage polarization will help reveal the pathogenesis of sepsis (173-179). Numerous research results have preliminarily confirmed that miRNAs that inhibit M1 polarization or activate M2 polarization may have favorable therapeutic potential in sepsis. For example, previous studies have exhibited that serum concentrations of M2 phenotype-related miRNAs, such as miR-146a and miR-223, in patients with sepsis are significantly reduced (180). Among them, overexpression of miR-146a can inhibit expression of TLR4-NF-κB pathway proteins, and block sepsis-induced inflammatory cell infiltration (69). Wang *et al* (180) observed the role of circulating miR-223 in sepsis and observed an association between a decrease in miR-223 levels and an increase in sepsis severity. However, a recent study by Benz *et al* revealed that serum miR-223 levels cannot predict the prognosis or survival rate of sepsis in critically ill patients (181). The conflicting results between these two studies can be partially explained by differences in experimental procedures. The aforementioned research results appear to confirm that miR-146a and miR-223, as macrophage polarization modulators, appear to be related to clinical outcomes in patients with sepsis. However, despite extensive research on the changes in miRNA expression in sepsis, the exact role of miRNA-induced macrophage polarization in sepsis remains unclear and further exploration is needed (173). There are also other studies on the role of miRNA-induced macrophage polarization in other inflammatory-related diseases. For example, polarized macrophages are involved in different disease processes such as obesity (182-187), cancer (158,165-167), and multiple sclerosis (188,189). Regulating macrophage activation or replacing activated miRNAs in these disease states may have therapeutic effects. Overall, overexpression of miRNAs such as M2-related miR-223 (15,105) and inhibition of miRNAs such as M1-related miR-33 and miR-155 are beneficial for the control of inflammation (190,191). Similarly, the increased expression of pro-inflammatory miR-155 (188) and the downregulation of anti-inflammatory miR-124 (189) is associated with the deterioration of multiple sclerosis, and the intervention of these two miRNAs is also a possible target for inflammation control. In addition, the increased expression levels of miR-19a-3p (125), miR-16 (130), miR-155 (60,192), and miR-511-3p (103) all promote the activation of TAMs to varying degrees, affecting local inflammation of the tumor. By contrast, as aforementioned, MSC-derived EVs contain miR-21a-5p, which activates macrophage polarization and reduces macrophage infiltration by targeting the KLF6 and ERK1/2 signaling pathways, thereby slowing down the development of AS (90). The disruption of miRNA-33-mediated aerobic glycolysis and mitochondrial oxidative phosphorylation balance is also related to the M2 polarization level of macrophages and is mainly due to the targeted regulation of miR-33 on AMP-activated protein kinase (AMPK). The antagonism of miR-33 can reduce plaque inflammation and play a protective role in AS (193). According to previous studies, miR-101 plays a crucial role in macrophage polarization and innate immune response. Overexpression of miR-101 in macrophages increases M1-related cytokine expression levels (194). Gao *et al* (195) demonstrated that the miR-101/MKP-1/

mitogen-activated protein kinase pathway plays a potential anti-inflammatory target. Liu *et al* (196) revealed that macrophages treated with TLR2, TLR3, or TLR4 ligands showed a decrease in the expression level of miR-147 while silencing miR-147 increased the expression level of inflammatory cytokines. In addition, miR-203 has been demonstrated to play a negative role in regulating the immune response to LPS, subsequently reducing inflammatory mediators such as TNF-α and IL-6 expression (197). Xie *et al* have confirmed that overexpression of miR-27a in MDM can increase the level of pro-inflammatory cytokines while knocking down miR-27a can reduce the expression of these cytokines. miR-27a mainly prevents excessive inflammatory response driven by TLR2/4 in macrophages by reducing the secretion of IL-10 (198). Therefore, the aforementioned literature research results clearly indicated that in addition to the antitumor effect of miRNA by regulating M1 and M2 polarization, an increasing number of research results indicated that this regulatory mode also plays an important role in inflammation prevention and control. For instance, M1 and M2 phenotypes play a unique role in the progression of inflammatory-related diseases such as sepsis, obesity, cancer and multiple sclerosis. Therefore, miRNA regulation of macrophage polarization also demonstrates the potential for targeted therapy in the treatment of inflammatory-related diseases (9). Lv *et al* (199) investigated the role of extracellular miRNAs derived from tubular epithelial cells (TECs) in the development of renal tubulointerstitial inflammation. Research has revealed that extracellular miR-19b-3p mediates communication between damaged TECs and macrophages, leading to M1 macrophage activation. The EV/miR-19b-3p/SOCS1 axis plays a crucial pathological role in renal tubulointerstitial inflammation and is a new therapeutic target for renal diseases (199). Macrophage polarization is also involved in the development and progression of asthma. Some miRNAs can participate in the development of asthma by inducing M1/M2 polarization. Therefore, targeting miRNAs to regulate macrophage polarization may have therapeutic potential in allergic asthma and other allergic diseases (58). The results of the study conducted by Arora *et al* (200) suggested that miRNAs and other TFs can induce changes in the macrophage phenotype. Understanding the mechanism of macrophage polarization and its phenotype regulation will help design new inflammatory treatment strategies (200). Qiu *et al* (201) reviewed and analyzed the key role of epigenetic modifications in the regulation of macrophage polarization. They support that miRNA epigenetically-mediated macrophage polarization may be a potential target for the treatment of ischemic stroke and may provide a promising treatment strategy for neuronal damage after cerebral ischemia (201). Recent studies have also shown that EVs derived from mesenchymal stromal cells (MSCs) play an important role in macrophage immune regulation after myocardial ischemia/reperfusion (I/R) and in heart injury repair. MSC-derived exosome (MSC-Exo) alters the polarization state of macrophages by shuttle miR-182, thereby alleviating myocardial I/R injury in mice. It was also hypothesized that MSC-Exo can serve as a potential therapeutic tool for myocardial I/R injury (86). Dang and Leelahavanichkul explored the polarization phenomenon of miRNA-induced anti-inflammatory macrophages based on the close relationship between inflammatory macrophages and sepsis. The research results revealed that overexpression of miR-223 and miR-146a in RAW264.7 plays an inducing role in M2 macrophage polarization. Further research confirmed that the anti-inflammatory state induced by miR-223 is not only related to HIF-1 α. The downregulation of the interfering glycolytic pathway is related and can prevent LPS-induced polarization of M1 macrophages. In the LPS model, pretreatment with miR-223 overexpressed macrophages and IL-4 reduced the severity of sepsis. Therefore, the concept of inducing anti-inflammatory macrophages through cell energy destruction for the treatment of sepsis was proposed (202). Neuroinflammation is the main cause of secondary neuronal damage, but the immune mechanism of brain cell damage in neonatal hypoxic-ischemic encephalopathy remains unclear. A previous study demonstrated that miR-210 is a new regulator of microglia activation in neonatal hypoxic-ischemic brain injury, and also a potential therapeutic target for neonatal hypoxic-ischemic brain injury (203). Macrophages also play a crucial role in the pathogenesis of AS, but their molecular mechanism remains unclear. For example, Xu *et al* (204) observed that miR-34a plays a central role in the regulation of macrophage cholesterol outflow, inflammation and AS, which indicates that miR-34a is a promising target for the treatment of heart metabolic diseases. There is increasing research on the role of MSCs and MSC-Exos in alleviating myocardial I/R injury. Gao *et al* (205) attempted to find an ideal microRNA candidate and determine whether it could replicate the cardioprotective effects of MSCs and MSC-Exos. The results indicated that miR-125a-5b is enriched in MSC-Exos, and its modified oligonucleotide miR-125a-5p atomic can increase the polarization of M2 macrophages, promote angiogenesis and help improve myocardial cell apoptosis and inflammation, thereby achieving effective therapeutic goals (205). The aforementioned studies indicated that miRNAs play crucial regulatory role in macrophage polarization, inflammation and tumor development. Given that the balance between M1/M2 macrophages plays an important role in the occurrence and development of numerous diseases, and miRNA can regulate the balance between M1/M2 cells in various ways, identifying miRNAs related to the dynamic changes in macrophage polarization and understanding their role in regulating this process is of great significance for exploring the molecular basis of disease progression and developing new miRNA-targeted therapy strategies.

7. Conclusions

In conclusion, it is known that macrophage polarization plays an important role in numerous physiological and pathological conditions, such as infection, inflammation, immunity, regeneration and tumors. In the past few years, significant progress has been made in regulating TFs of macrophage polarization, as well as epigenetic modification mechanisms including miRNA. It has been revealed that miRNAs can play inflammatory and immune regulatory roles by participating in the polarization process of macrophages. However, the molecular mechanism of miRNA in macrophage polarization is relatively complex, involving the interaction between its upstream regulatory factors and downstream target genes.

The current research focus remains on how miRNA regulates the polarization process of macrophages by regulating downstream target genes or signal axes. In terms of the types of miRNAs polarized by macrophages M1 and M2, both directions of polarization have relatively specific associations with miRNA types and have different effects on inhibiting or promoting macrophage polarization. The specific regulatory effect of the same miRNA is related to the specific pathological microenvironment and induction drugs. Some miRNAs even exhibit opposite reported results of inhibiting or promoting macrophage polarization. It is precisely due to the important role of miRNA in regulating macrophage polarization that it plays an important role in inflammation, immune response and tumor growth. At present, there are numerous studies on the regulation of macrophage polarization by miRNAs involved in inflammation and tumor occurrence and development, and some important miRNA types have been preliminarily confirmed. At the same time, *in vitro* and *in vivo* experiments have confirmed that these miRNA mimics or inhibitors play an important role in inflammation control and tumor treatment. miRNA is expected to become a target for treating diseases related to inflammation or tumors. Although both basic research and early clinical findings indicated significant potential for drug development based on miRNA expression interference, there have been no studies of phase III clinical studies to date. Therefore, in-depth exploration of miRNA on macrophage polarization will help to improve understanding of the biological functions of macrophages, and further provide a more effective theoretical basis and treatment strategies for treating diseases centered on macrophage polarization.

Acknowledgements

Not applicable.

Funding

The present study was supported by the 'Twelfth Five-Year' National Science and Technology Support Program (grant no. 2013BAI07B02), the Natural Science Foundation of China (grant no. 81573467), the Natural Science Foundation of Shandong (grant nos. ZR2020QH160 and ZR2021MH080), The Foundation for Jinan's Clinical Science and Technology Innovation (grant no. 202134001) and the Cultivation Fund of the first affiliated hospital of Shandong First Medical University (Shandong Qianfoshan Hospital; grant no. QIPY2020NSFC0819).

Availability of data and materials

Not applicable.

Authors' contributions

QL and GSJ conceived and designed the article. CZW, XDW and DFZ surveyed the literature and wrote the manuscript. XLS, YHW and JW surveyed the literature and provided suggestions. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Haniffa M, Bigley V and Collin M: Human mononuclear phagocyte system reunited. Semin Cell Dev Biol 41: 59-69, 2015.
2. Santoni G, Morelli MB, Amantini C, Santoni M, Nabissi M, Marinelli O and Santoni A: 'Immuno-Transient Receptor Potential Ion Channels': The role in monocyte- and macrophage-mediated inflammatory responses. Front Immunol 9: 1273, 2018.
3. Kawakami A, Iwamoto N and Fujio K: Editorial: The role of monocytes/macrophages in autoimmunity and autoinflammation. Front Immunol 13: 1093430, 2022.
4. Zhou D, Huang C, Lin Z, Zhan S, Kong L, Fang C and Li J: Macrophage polarization and function with emphasis on the evolving roles of coordinated regulation of cellular signaling pathways. Cell Signal 26: 192-197, 2014.
5. Juhas U, Ryba-Stanislawowska M, Szargiej P and Mysliwska J: Different pathways of macrophage activation and polarization. Postepy Hig Med Dosw (Online) 69: 496-502, 2015.
6. Lawrence T and Natoli G: Transcriptional regulation of macrophage polarization: Enabling diversity with identity. Nat Rev Immunol 11: 750-761, 2011.
7. Li H, Jiang T, Li MQ, Zheng XL and Zhao GJ: Transcriptional regulation of macrophages polarization by MicroRNAs. Front Immunol 9: 1175, 2018.
8. Kishore A and Petrek M: Roles of macrophage polarization and macrophage-derived miRNAs in pulmonary fibrosis. Front Immunol 12: 678457, 2021.
9. Essandoh K, Li Y, Huo J and Fan GC: MiRNA-mediated macrophage polarization and its potential role in the regulation of inflammatory response. Shock 46: 122-131, 2016.
10. Shapouri-Moghaddam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili SA, Mardani F, Seifi B, Mohammadi A, Afshari JT and Sahebkar A: Macrophage plasticity, polarization, and function in health and disease. J Cell Physiol 233: 6425-6440, 2018.
11. Mohapatra S, Pioppini C, Ozpolat B and Calin GA: Non-coding RNAs regulation of macrophage polarization in cancer. Mol Cancer 20: 24, 2021.
12. Okada C, Yamashita E, Lee SJ, Shibata S, Katahira J, Nakagawa A, Yoneda Y and Tsukihara T: A high-resolution structure of the pre-microRNA nuclear export machinery. Science 326: 1275-1279, 2009.
13. Lu TX and Rothenberg ME: MicroRNA. J Allergy Clin Immunol 141: 1202-1207, 2018.
14. Wang X, Gu H, Qin D, Yang L, Huang W, Essandoh K, Wang Y, Caldwell CC, Peng T, Zingarelli B, *et al*: Exosomal miR-223 contributes to mesenchymal stem Cell-elicited cardioprotection in polymicrobial sepsis. Sci Rep 5: 13721, 2015.
15. Ying W, Tseng A, Chang RC, Morin A, Brehm T, Triff K, Nair V, Zhuang G, Song H, Kanameni S, *et al*: MicroRNA-223 is a crucial mediator of PPARγ-regulated alternative macrophage activation. J Clin Invest 125: 4149-4159, 2015.
16. Derynck R, Turley SJ and Akhurst RJ: TGFβ biology in cancer progression and immunotherapy. Nat Rev Clin Oncol 18: 9-34, 2021.
17. Majumder S, Crabtree JS, Golde TE, Minter LM, Osborne BA and Miele L: Targeting Notch in oncology: The path forward. Nat Rev Drug Discov 20: 125-144, 2021.
18. Huang P, Zhang Y, Wang F, Qin M and Ren L: MiRNA-205-5p regulates the ERBB4/AKT signaling pathway to inhibit the proliferation and migration of HAVSMCs induced by ox-LDL. Pathol Res Pract 233: 153858, 2022.

19. Zhu S, Cheng X, Wang R, Tan Y, Ge M, Li D, Xu Q, Sun Y, Zhao C, Chen S and Liu H: Restoration of microRNA function impairs MYC-dependent maintenance of MLL leukemia. Leukemia 34: 2484-2488, 2020.
20. Mittal A, Chitkara D, Behrman SW and Mahato RI: Efficacy of gemcitabine conjugated and miRNA-205 complexed micelles for treatment of advanced pancreatic cancer. Biomaterials 35: 7077-7087, 2014.
21. Wculek SK, Dunphy G, Heras-Murillo I, Mastrangelo A and Sancho D: Metabolism of tissue macrophages in homeostasis and pathology. Cell Mol Immunol 19: 384-408, 2022.
22. Sica A and Mantovani A: Macrophage plasticity and polarization: In vivo veritas. J Clin Invest 122: 787-795, 2012.
23. Wang N, Liang H and Zen K: Molecular mechanisms that influence the macrophage m1-m2 polarization balance. Front Immunol 5: 614, 2014.
24. Liu YC, Zou XB, Chai YF and Yao YM: Macrophage polarization in inflammatory diseases. Int J Biol Sci 10: 520-529, 2014.
25. Martinez FO and Gordon S: The M1 and M2 paradigm of macrophage activation: Time for reassessment. F1000Prime Rep 6: 13, 2014.
26. Hao NB, Lu MH, Fan YH, Cao YL, Zhang ZR and Yang SM: Macrophages in tumor microenvironments and the progression of tumors. Clin Dev Immunol 2012: 948098, 2012.
27. Mosser DM and Edwards JP: Exploring the full spectrum of macrophage activation. Nat Rev Immunol 8: 958-969, 2008.
28. Liao X, Sharma N, Kapadia F, Zhou G, Lu Y, Hong H, Paruchuri K, Mahabeleshwar GH, Dalmas E, Venteclef N, *et al*: Krüppel-like factor 4 regulates macrophage polarization. J Clin Invest 121: 2736-2749, 2011.
29. Locati M, Mantovani A and Sica A: Macrophage activation and polarization as an adaptive component of innate immunity. Adv Immunol 120: 163-184, 2013.
30. Zhou L, Cao X, Fang J, Li Y and Fan M: Macrophages polarization is mediated by the combination of PRR ligands and distinct inflammatory cytokines. Int J Clin Exp Pathol 8: 10964-10974,
31. El KK and Stenmark KR: Contribution of metabolic reprogramming to macrophage plasticity and function. Semin Immunol 27: 267-275, 2015.
32. Schultze JL, Schmieder A and Goerdt S: Macrophage activation in human diseases. Semin Immunol 27: 249-256, 2015.
33. Alharbi KS, Fuloria NK, Fuloria S, Rahman SB, Al-Malki WH, Javed Shaikh MA, Thangavelu L, Singh SK, Rama Raju Allam VS, Jha NK, *et al*: Nuclear factor-kappa B and its role in inflammatory lung disease. Chem Biol Interact 345: 109568, 2021.
34. Ning H, Chen H, Deng J, Xiao C, Xu M, Shan L, Yang C and Zhang Z: Exosomes secreted by FNDC5-BMMSCs protect myocardial infarction by anti-inflammation and macrophage polarization via NF-κB signaling pathway and Nrf2/HO-1 axis. Stem Cell Res Ther 12: 519, 2021.
35. Wu X, Wang Z, Shi J, Yu X, Li C, Liu J, Zhang F, Chen H and Zheng W: Macrophage polarization toward M1 phenotype through NF-κB signaling in patients with Behçet's disease. Arthritis Res Ther 24: 249, 2022.
36. Wang S, Lu M, Wang W, Yu S, Yu R, Cai C, Li Y, Shi Z, Zou J, He M, *et al*: Macrophage polarization modulated by NF-κB in polylactide membranes-treated peritendinous adhesion. Small 18: e2104112, 2022.
37. Xu P, Shen P, Yu B, Xu X, Ge R, Cheng X, Chen Q, Bian J, Li Z and Wang J: Janus kinases JAKs): The efficient therapeutic targets for autoimmune diseases and myeloproliferative disorders. Eur J Med Chem 192: 112155, 2020.
38. Liang Y, Yang N, Pan G, Jin B, Wang S and Ji W: Elevated IL-33 promotes expression of MMP2 and MMP9 via activating STAT3 in alveolar macrophages during LPS-induced acute lung injury. Cell Mol Biol Lett 23: 52, 2018.
39. Yan T, Wang K, Li J, Hu H, Yang H, Cai M, Liu R, Li H, Wang N, Shi Y, *et al*: Suppression of the hyaluronic acid pathway induces M1 macrophages polarization via STAT1 in glioblastoma. Cell Death Discov 8: 193, 2022.
40. Ye Q, Luo F and Yan T: Transcription factor KLF4 regulated STAT1 to promote M1 polarization of macrophages in rheumatoid arthritis. Aging (Albany NY) 14: 5669-5680, 2022.
41. Rinnenthal JL, Goebel HH, Preusse C, Lebenheim L, Schumann M, Moos V, Schneider T, Heppner FL and Stenzel W: Inflammatory myopathy with abundant macrophages (IMAM): The immunology revisited. Neuromuscul Disord 24: 151-155, 2014.
42. Fan C, Chen C, Chen L, Chua KV, Hung H, Hsu JT and Huang TS: Extracellular HSP90α Induces MyD88-IRAK Complex-associated IKKα/β-NF-κB/IRF3 and JAK2/TYK2-STAT-3 signaling in macrophages for tumor-promoting M2-polarization. Cells 11: 229, 2022.
43. Liu Y, Wang L, Li S, Zhang T, Chen C, Hu J, Sun D and Lu H: Mechanical stimulation improves rotator cuff tendon-bone healing via activating IL-4/JAK/STAT signaling pathway mediated macrophage M2 polarization. J Orthop Translat 37: 78-88, 2022.
44. Wang L and He C: Nrf2-mediated anti-inflammatory polarization of macrophages as therapeutic targets for osteoarthritis. Front Immunol 13: 967193, 2022.
45. Zhou W, Hu G, He J, Wang T, Zuo Y, Cao Y, Zheng Q, Tu J, Ma J, Cai R, *et al*: SENP1-Sirt3 signaling promotes α-ketoglutarate production during M2 macrophage polarization. Cell Rep 39: 110660, 2022.
46. Hu L, Li S, Li H, Lai B and Wen H: Interferon regulatory factor 4 (IRF4) promotes lipopolysaccharide-induced colonic mucosal epithelial cell proliferation by regulating macrophage polarization. Eur Surg Res 63: 257-268, 2022.
47. Hedl M, Yan J and Abraham C: IRF5 and IRF5 Disease-risk variants increase glycolysis and human m1 macrophage polarization by regulating proximal signaling and akt2 activation. Cell Rep 16: 2442-2455, 2016.
48. Yuan J, Lin F, Chen L, Chen W, Pan X, Bai Y, Cai Y and Lu H: Lipoxin A4 regulates M1/M2 macrophage polarization via FPR2–IRF pathway. Inflammopharmacology 30: 487-498, 2022.
49. Yuan Q, Zhao B, Cao YH, Yan JC, Sun LJ, Liu X, Xu Y, Wang XY and Wang B: BCR-associated Protein 31 regulates macrophages polarization and wound healing function via early growth response 2/C/EBPβ and IL-4Rα/C/EBPβ pathways. J Immunol 209: 1059-1070, 2022.
50. Arranz A, Doxaki C, Vergadi E, Martinez De La Torre Y, Vaporidi K, Lagoudaki ED, Ieronymaki E, Androulidaki A, Venihaki M, Margioris AN, *et al*: Akt1 and Akt2 protein kinases differentially contribute to macrophage polarization. Proc Natl Acad Sci USA 109: 9517-9522, 2012.
51. Vaghf A, Khansarinejad B, Ghaznavi-Rad E and Mondanizadeh M: The role of microRNAs in diseases and related signaling pathways. Mol Biol Rep 49: 6789-6801, 2022.
52. Panni S, Lovering RC, Porras P and Orchard S: Non-coding RNA regulatory networks. Biochim Biophys Acta Gene Regul Mech 1863: 194417, 2020.
53. Liu ZP, Wu C, Miao H and Wu H: RegNetwork: An integrated database of transcriptional and post-transcriptional regulatory networks in human and mouse. Database (Oxford) 2015: bav095, 2015.
54. Gov E and Arga KY: Interactive cooperation and hierarchical operation of microRNA and transcription factor crosstalk in human transcriptional regulatory network. Iet Syst Biol 10: 219-228, 2016.
55. Bartel DP: MicroRNAs: Target recognition and regulatory functions. Cell 136: 215-233, 2009.
56. Saliminejad K, Khorram KH, Soleymani FS and Ghaffari SH: An overview of microRNAs: Biology, functions, therapeutics, and analysis methods. J Cell Physiol 234: 5451-5465, 2019.
57. Ghafouri-Fard S, Abak A, Tavakkoli AS, Shoorei H, Taheri M and Samadian M: The impact of non-coding RNAs on macrophage polarization. Biomed Pharmacother 142: 112112, 2021.
58. Saradna A, Do DC, Kumar S, Fu QL and Gao P: Macrophage polarization and allergic asthma. Transl Res 191: 1-14, 2018.
59. Viktoriia K, Polina V, Andrey E, Timur F and Gennady S: Biochemical and molecular inducers and modulators of M2 macrophage polarization in clinical perspective. Int Immunopharmacol 122: 110583, 2023.
60. Cai X, Yin Y, Li N, Zhu D, Zhang J, Zhang CY and Zen K: Re-polarization of tumor-associated macrophages to pro-inflammatory M1 macrophages by microRNA-155. J Mol Cell Biol 4: 341-343, 2012.
61. Fei Y, Wang Z, Huang M, Wu X, Hu F, Zhu J, Yu Y, Shen H, Wu Y, Xie G and Zhou Z: MiR-155 regulates M2 polarization of hepatitis B virus-infected tumor-associated macrophages which in turn regulates malignant progression of hepatocellular carcinoma. J Viral Hepat 30: 417-426, 2023.
62. Bi J, Liu J, Chen X, Shi N, Wu H, Tang H and Mao J: MiR-155-5p-SOCS1/JAK1/STAT1 participates in hepatic lymphangiogenesis in liver fibrosis and cirrhosis by regulating M1 macrophage polarization. Hum Exp Toxicol 42: 9603271221141695, 2023.

63. Yang HT, Li LL, Li SN, Wu JT, Chen K, Song WF, Zhang GB, Ma JF, Fu HX, Cao S, *et al*: MicroRNA-155 inhibition attenuates myocardial infarction-induced connexin 43 degradation in cardiomyocytes by reducing pro-inflammatory macrophage activation. Cardiovasc Diagn Ther 12: 325-339, 2022.
64. Yan C, Zhou Q, Wu J, Xu N, Du Y, Li J, Liu JX, Koda S, Zhang BB, Yu Q, *et al*: Csi-let-7a-5p delivered by extracellular vesicles from a liver fluke activates M1-like macrophages and exacerbates biliary injuries. Proc Natl Acad Sci USA 118: e2102206118, 2021.
65. Song M, Cui X, Zhang J, Li Y, Li J, Zang Y, Li Q, Yang Q, Chen Y, Cai W, *et al*: Shenlian extract attenuates myocardial ischaemia-reperfusion injury via inhibiting M1 macrophage polarization by silencing miR-155. Pharm Biol 60: 2011-2024, 2022.
66. Gwiggner M, Martinez-Nunez RT, Whiteoak SR, Bondanese VP, Claridge A, Collins JE, Cummings JRF and Sanchez-Elsner T: MicroRNA-31 and MicroRNA-155 are overexpressed in ulcerative colitis and regulate IL-13 signaling by targeting interleukin 13 receptor α-1. Genes (Basel) 9: 85, 2018.
67. Zhong C, Tao B, Yang F, Xia K, Yang X, Chen L, Peng T, Xia X, Li X and Peng L: Histone demethylase JMJD1C promotes the polarization of M1 macrophages to prevent glioma by upregulating miR-302a. Clin Transl Med 11: e424, 2021.
68. Guo Q, Zhu X, Wei R, Zhao L, Zhang Z, Yin X, Zhang Y, Chu C, Wang B and Li X: miR-130b-3p regulates M1 macrophage polarization via targeting IRF1. J Cell Physiol 236: 2008-2022, 2021.
69. Gao M, Wang X, Zhang X, Ha T, Ma H, Liu L, Kalbfleisch JH, Gao X, Kao RL, Williams DL and Li C: Attenuation of cardiac dysfunction in polymicrobial sepsis by MicroRNA-146a is mediated via targeting of IRAK1 and TRAF6 expression. J Immunol 195: 672-682, 2015.
70. Cui W, Zhou S, Wang Y, Shi X and Liu H: Cadmium exposure activates the PI3K/AKT signaling pathway through miRNA-21, induces an increase in M1 polarization of macrophages, and leads to fibrosis of pig liver tissue. Ecotoxicol Environ Saf 228: 113015, 2021.
71. Thulin P, Wei T, Werngren O, Cheung L, Fisher RM, Grandér D, Corcoran M and Ehrenborg E: MicroRNA-9 regulates the expression of peroxisome proliferator-activated receptor delta in human monocytes during the inflammatory response. Int J Mol Med 31: 1003-1010, 2013.
72. Tong F, Mao X, Zhang S, Xie H, Yan B, Wang B, Sun J and Wei L: HPV + HNSCC-derived exosomal miR-9 induces macrophage M1 polarization and increases tumor radiosensitivity. Cancer Lett 478: 34-44, 2020.
73. Hu A, Chen X, Bi Q, Xiang Y, Jin R, Ai H and Nie Y: A parallel and cascade control system: Magnetofection of miR-125b for synergistic tumor-association macrophage polarization regulation and tumor cell suppression in breast cancer treatment. Nanoscale 12: 22615-22627, 2020.
74. Luo XB, Li LT, Xi JC, Liu HT, Liu Z, Yu L and Tang PF: Negative pressure promotes macrophage M1 polarization after Mycobacterium tuberculosis infection via the lncRNA XIST/microRNA-125b-5p/A20/NF-κB axis. Ann N Y Acad Sci 1514: 116-131, 2022.
75. Bao P, Zhao W, Mou M and Liu X: MicroRNA-21 mediates bone marrow mesenchymal stem cells protection of radiation-induced lung injury during the acute phase by regulating polarization of alveolar macrophages. Transl Cancer Res 9: 231-239, 2020.
76. Xue J, Xiao T, Wei S, Sun J, Zou Z, Shi M, Sun Q, Dai X, Wu L, Li J, *et al*: miR-21-regulated M2 polarization of macrophage is involved in arsenicosis-induced hepatic fibrosis through the activation of hepatic stellate cells. J Cell Physiol 236: 6025-6041, 2021.
77. Li Z, Yang B, Gao M, Xiao X, Zhao S and Liu Z: Naringin improves sepsis-induced intestinal injury by modulating macrophage polarization via PPARγ/miR-21 axis. Mol Ther Nucleic Acids 25: 502-514, 2021.
78. Yao M, Cui B, Zhang W, Ma W, Zhao G and Xing L: Exosomal miR-21 secreted by IL-1beta-primed-mesenchymal stem cells induces macrophage M2 polarization and ameliorates sepsis. Life Sci 264: 118658, 2021.
79. Lu J, Xie L and Sun S: The inhibitor miR-21 regulates macrophage polarization in an experimental model of chronic obstructive pulmonary disease. Tob Induc Dis 19: 1-10, 2021.
80. Wang Z, Brandt S, Medeiros A, Wang S, Wu H, Dent A and Serezani CH: MicroRNA 21 is a homeostatic regulator of macrophage polarization and prevents prostaglandin E2-mediated M2 generation. PLoS One 10: e115855, 2015.
81. Sheedy FJ: Turning 21: Induction of miR-21 as a key switch in the inflammatory response. Front Immunol 6: 19, 2015.
82. An Y and Yang Q: MiR-21 modulates the polarization of macrophages and increases the effects of M2 macrophages on promoting the chemoresistance of ovarian cancer. Life Sci 242: 117162, 2020.
83. Jin J and Yu G: Hypoxic lung cancer cell-derived exosomal miR-21 mediates macrophage M2 polarization and promotes cancer cell proliferation through targeting IRF1. World J Surg Oncol 20: 241, 2022.
84. Lin F, Yin HB, Li XY, Zhu GM, He WY and Gou X: Bladder cancer cell-secreted exosomal miR-21 activates the PI3K/AKT pathway in macrophages to promote cancer progression. Int J Oncol 56: 151-164, 2020.
85. Ma C, He D, Tian P, Wang Y, He Y, Wu Q, Jia Z, Zhang X, Zhang P, Ying H, *et al*: miR-182 targeting reprograms tumor-associated macrophages and limits breast cancer progression. Proc Natl Acad Sci USa 119: e2114006119, 2022.
86. Zhao J, Li X, Hu J, Chen F, Qiao S, Sun X, Gao L, Xie J and Xu B: Mesenchymal stromal cell-derived exosomes attenuate myocardial ischaemia-reperfusion injury through miR-182-regulated macrophage polarization. Cardiovasc Res 115: 1205-1216, 2019.
87. Huang C, Liu XJ, QunZhou, Xie J, Ma TT, Meng XM and Li J: MiR-146a modulates macrophage polarization by inhibiting Notch1 pathway in RAW264.7 macrophages. Int Immunopharmacol 32: 46-54, 2016.
88. Peng X, He F, Mao Y, Lin Y, Fang J, Chen Y, Sun Z, Zhuo Y and Jiang J: miR-146a promotes M2 macrophage polarization and accelerates diabetic wound healing by inhibiting the TLR4/NF-κB axis. J Mol Endocrinol 69: 315-327, 2022.
89. Schulert GS, Fall N, Harley JB, Shen N, Lovell DJ, Thornton S and Grom AA: Monocyte MicroRNA expression in active systemic juvenile idiopathic arthritis implicates MicroRNA-125a-5p in polarized monocyte phenotypes. Arthritis Rheumatol 68: 2300-2313, 2016.
90. Ma J, Chen L, Zhu X, Li Q, Hu L and Li H: Mesenchymal stem cell-derived exosomal miR-21a-5p promotes M2 macrophage polarization and reduces macrophage infiltration to attenuate atherosclerosis. Acta Biochim Biophys Sin (Shanghai) 53: 1227-1236, 2021.
91. Chen J, Zhang K, Zhi Y, Wu Y, Chen B, Bai J and Wang X: Tumor-derived exosomal miR-19b-3p facilitates M2 macrophage polarization and exosomal LINC00273 secretion to promote lung adenocarcinoma metastasis via Hippo pathway. Clin Transl Med 11: e478, 2021.
92. Zhao G, Yu H, Ding L, Wang W, Wang H, Hu Y, Qin L, Deng G, Xie B, Li G and Qi L: microRNA-27a-3p delivered by extracellular vesicles from glioblastoma cells induces M2 macrophage polarization via the EZH1/KDM3A/CTGF axis. Cell Death Discov 8: 260, 2022.
93. Pan Y, Hui X, Hoo R, Ye D, Chan C, Feng T, Wang Y, Lam KSL and Xu A: Adipocyte-secreted exosomal microRNA-34a inhibits M2 macrophage polarization to promote obesity-induced adipose inflammation. J Clin Invest 129: 834-849, 2019.
94. Zhang Y, Zhang M, Zhong M, Suo Q and Lv K: Expression profiles of miRNAs in polarized macrophages. Int J Mol Med 31: 797-802, 2013.
95. Graff JW, Dickson AM, Clay G, McCaffrey AP and Wilson ME: Identifying functional microRNAs in macrophages with polarized phenotypes. J Biol Chem 287: 21816-21825, 2012.
96. Curtale G, Rubino M and Locati M: MicroRNAs as molecular switches in macrophage activation. Front Immunol 10: 799, 2019.
97. Martinez-Nunez RT, Louafi F and Sanchez-Elsner T: The interleukin 13 (IL-13) pathway in human macrophages is modulated by microRNA-155 via direct targeting of interleukin 13 receptor alpha1 (IL13Ralpha1). J Biol Chem 286: 1786-1794, 2011.
98. Zhang Y, Zhang M, Li X, Tang Z, Wang X, Zhong M, Suo Q, Zhang Y and Lv K: Silencing MicroRNA-155 attenuates cardiac injury and dysfunction in viral myocarditis via promotion of M2 phenotype polarization of macrophages. Sci Rep 6: 22613, 2016.
99. Ying H, Kang Y, Zhang H, Zhao D, Xia J, Lu Z, Wang H, Xu F and Shi L: MiR-127 modulates macrophage polarization and promotes lung inflammation and injury by activating the JNK pathway. J Immunol 194: 1239-1251, 2015.
100. Chaudhuri AA, So AY, Sinha N, Gibson WS, Taganov KD, O'Connell RM and Baltimore D: MicroRNA-125b potentiates macrophage activation. J Immunol 187: 5062-5068, 2011.
101. Zhong Y and Yi C: MicroRNA-720 suppresses M2 macrophage polarization by targeting GATA3. Biosci Rep 36: e00363, 2016.

102. Cobos JV, Bradley EJ, Willemsen AM, van Kampen AH, Baas F and Kootstra NA: Next-generation sequencing of microRNAs uncovers expression signatures in polarized macrophages. Physiol Genomics 46: 91-103, 2014.
103. Squadrito ML, Pucci F, Magri L, Moi D, Gilfillan GD, Ranghetti A, Casazza A, Mazzone M, Lyle R, Naldini L and De Palma M: miR-511-3p modulates genetic programs of tumor-associated macrophages. Cell Rep 1: 141-154, 2012.
104. Liu Y, Chen Q, Song Y, Lai L, Wang J, Yu H, Cao X and Wang Q: MicroRNA-98 negatively regulates IL-10 production and endotoxin tolerance in macrophages after LPS stimulation. Febs Lett 585: 1963-1968, 2011.
105. Zhuang G, Meng C, Guo X, Cheruku PS, Shi L, Xu H, Li H, Wang G, Evans AR, Safe S, *et al*: A novel regulator of macrophage activation: miR-223 in obesity-associated adipose tissue inflammation. Circulation 125: 2892-2903, 2012.
106. Zhang W, Liu H, Liu W, Liu Y and Xu J: Polycomb-mediated loss of microRNA let-7c determines inflammatory macrophage polarization via PAK1-dependent NF-kappaB pathway. Cell Death Differ 22: 287-297, 2015.
107. Banerjee S, Xie N, Cui H, Tan Z, Yang S, Icyuz M, Abraham E and Liu G: MicroRNA let-7c regulates macrophage polarization. J Immunol 190: 6542-6549, 2013.
108. Ma S, Liu M, Xu Z, Li Y, Guo H, Ge Y, Liu Y, Zheng D and Shi J: A double feedback loop mediated by microRNA-23a/27a/24-2 regulates M1 versus M2 macrophage polarization and thus regulates cancer progression. Oncotarget 7: 13502-13519, 2016.
109. Wu XQ, Dai Y, Yang Y, Huang C, Meng XM, Wu BM and Li J: Emerging role of microRNAs in regulating macrophage activation and polarization in immune response and inflammation. Immunology 148: 237-248, 2016.
110. Alam MM and O'Neill LA: MicroRNAs and the resolution phase of inflammation in macrophages. Eur J Immunol 41: 2482-2485, 2011.
111. Liu G and Abraham E: MicroRNAs in immune response and macrophage polarization. Arterioscler Thromb Vasc Biol 33: 170-177, 2013.
112. Bi Y, Liu G and Yang R: MicroRNAs: Novel regulators during the immune response. J Cell Physiol 218: 467-472, 2009.
113. Wu XQ, Huang C, Liu XH and Li J: MicroRNA let-7a: A novel therapeutic candidate in prostate cancer. Asian J Androl 16: 327-328, 2014.
114. Thomas M, Lieberman J and Lal A: Desperately seeking microRNA targets. Nat Struct Mol Biol 17: 1169-1174, 2010.
115. Zhou X, Chen B, Zhang Z, Huang Y, Li J, Wei Q, Cao D and Ai J: Crosstalk between Tumor-associated macrophages and MicroRNAs: A key role in tumor microenvironment. Int J Mol Sci 23: 13258, 2022.
116. Rupaimoole R and Slack FJ: MicroRNA therapeutics: Towards a new era for the management of cancer and other diseases. Nat Rev Drug Discov 16: 203-222, 2017.
117. Zhang C, Han X, Yang L, Fu J, Sun C, Huang S, Xiao W, Gao Y, Liang Q, Wang X, *et al*: Circular RNA circPPM1F modulates M1 macrophage activation and pancreatic islet inflammation in type 1 diabetes mellitus. Theranostics 10: 10908-10924, 2020.
118. van Zandwijk N, Pavlakis N, Kao SC, Linton A, Boyer MJ, Clarke S, Huynh Y, Chrzanowska A, Fulham MJ, Bailey DL, *et al*: Safety and activity of microRNA-loaded minicells in patients with recurrent malignant pleural mesothelioma: A first-in-man, phase 1, open-label, dose-escalation study. Lancet Oncol 18: 1386-1396, 2017.
119. Cortez MA, Anfossi S, Ramapriyan R, Menon H, Atalar SC, Aliru M, Welsh J and Calin GA: Role of miRNAs in immune responses and immunotherapy in cancer. Genes Chromosomes Cancer 58: 244-253, 2019.
120. Shah MY, Ferrajoli A, Sood AK, Lopez-Berestein G and Calin GA: microRNA therapeutics in cancer-an emerging concept. EBioMedicine 12: 34-42, 2016.
121. Smolle MA, Calin HN, Pichler M and Calin GA: Noncoding RNAs and immune checkpoints-clinical implications as cancer therapeutics. FEBS J 284: 1952-1966, 2017.
122. Li D, Yan M, Sun F, Song J, Hu X, Yu S, Tang L and Deng S: miR-498 inhibits autophagy and M2-like polarization of tumor-associated macrophages in esophageal cancer via MDM2/ATF3. Epigenomics 13: 1013-1030, 2021.
123. Garofalo M and Croce CM: MicroRNAs as therapeutic targets in chemoresistance. Drug Resist Updat 16: 47-59, 2013.
124. Jiang Q, Yuan Y, Gong Y, Luo X, Su X, Hu X and Zhu W: Therapeutic delivery of microRNA-143 by cationic lipoplexes for non-small cell lung cancer treatment in vivo. J Cancer Res Clin Oncol 145: 2951-2967, 2019.
125. Yang J, Zhang Z, Chen C, Liu Y, Si Q, Chuang TH, Li N, Gomez-Cabrero A, Reisfeld RA, Xiang R and Luo Y: MicroRNA-19a-3p inhibits breast cancer progression and metastasis by inducing macrophage polarization through downregulated expression of Fra-1 proto-oncogene. Oncogene 33: 3014-3023, 2014.
126. Zhang J, Shan WF, Jin TT, Wu GQ, Xiong XX, Jin HY and Zhu SM: Propofol exerts anti-hepatocellular carcinoma by microvesicle-mediated transfer of miR-142-3p from macrophage to cancer cells. J Transl Med 12: 279, 2014.
127. Syed SN, Frank AC, Raue R and Brune B: MicroRNA-A tumor trojan horse for tumor-associated macrophages. Cells 8: 1482, 2019.
128. Li Y, Zhao L, Shi B, Ma S, Xu Z, Ge Y, Liu Y, Zheng D and Shi J: Functions of miR-146a and miR-222 in Tumor-associated macrophages in breast cancer. Sci Rep 5: 18648, 2015.
129. Pirlog R, Cismaru A, Nutu A and Berindan-Neagoe I: Field Cancerization in NSCLC: A new perspective on MicroRNAs in macrophage polarization. Int J Mol Sci 22: 746, 2021.
130. Jang JY, Lee JK, Jeon YK and Kim CW: Exosome derived from epigallocatechin gallate treated breast cancer cells suppresses tumor growth by inhibiting tumor-associated macrophage infiltration and M2 polarization. BMC Cancer 13: 421, 2013.
131. Wang T, Xu X, Xu Q, Ren J, Shen S, Fan C and Hou Y: miR-19a promotes colitis-associated colorectal cancer by regulating tumor necrosis factor alpha-induced protein 3-NF-κB feedback loops. Oncogene 36: 3240-3251, 2017.
132. Hsieh CH, Tai SK and Yang MH: Snail-overexpressing cancer cells promote M2-like polarization of tumor-associated macrophages by delivering MiR-21-abundant Exosomes. Neoplasia 20: 775-788, 2018.
133. Cai J, Qiao B, Gao N, Lin N and He W: Oral squamous cell carcinoma-derived exosomes promote M2 subtype macrophage polarization mediated by exosome-enclosed miR-29a-3p. Am J Physiol Cell Physiol 316: C731-C740, 2019.
134. Zhang L, Liao Y and Tang L: MicroRNA-34 family: A potential tumor suppressor and therapeutic candidate in cancer. J Exp Clin Cancer Res 38: 53, 2019.
135. Rokavec M, Oner MG, Li H, Jackstadt R, Jiang L, Lodygin D, Kaller M, Horst D, Ziegler PK, Schwitalla S, *et al*: IL-6R/STAT3/miR-34a feedback loop promotes EMT-mediated colorectal cancer invasion and metastasis. J Clin Invest 124: 1853-1867, 2014.
136. Xu S, Wei J, Wang F, Kong LY, Ling XY, Nduom E, Gabrusiewicz K, Doucette T, Yang Y, Yaghi NK, *et al*: Effect of miR-142-3p on the M2 macrophage and therapeutic efficacy against murine glioblastoma. J Natl Cancer Inst 106: dju162, 2014.
137. Shinohara H, Kuranaga Y, Kumazaki M, Sugito N, Yoshikawa Y, Takai T, Taniguchi K, Ito Y and Akao Y: Regulated polarization of tumor-associated macrophages by miR-145 via colorectal cancer-derived extracellular vesicles. J Immunol 199: 1505-1515, 2017.
138. Sethupathy P, Borel C, Gagnebin M, Grant GR, Deutsch S, Elton TS, Hatzigeorgiou AG and Antonarakis SE: Human microRNA-155 on chromosome 21 differentially interacts with its polymorphic target in the AGTR1 3'untranslated region: A mechanism for functional single-nucleotide polymorphisms related to phenotypes. Am J Hum Genet 81: 405-413, 2007.
139. Lin ZY, Huang YQ, Zhang YQ, Han ZD, He HC, Ling XH, Fu X, Dai QS, Cai C, Chen JH, *et al*: MicroRNA-224 inhibits progression of human prostate cancer by downregulating TRIB1. Int J Cancer 135: 541-550, 2014.
140. Wang X, Luo G, Zhang K, Cao J, Huang C, Jiang T, Liu B, Su L and Qiu Z: Hypoxic Tumor-derived exosomal miR-301a mediates M2 macrophage polarization via PTEN/PI3Kγ to promote pancreatic cancer metastasis. Cancer Res 78: 4586-4598, 2018.
141. Xing F, Liu Y, Wu SY, Wu K, Sharma S, Mo YY, Feng J, Sanders S, Jin G, Singh R, *et al*: Loss of XIST in breast cancer activates MSN-c-Met and reprograms microglia via exosomal miRNA to promote brain metastasis. Cancer Res 78: 4316-4330, 2018.
142. Qian M, Wang S, Guo X, Wang J, Zhang Z, Qiu W, Gao X, Chen Z, Xu J, Zhao R, *et al*: Hypoxic glioma-derived exosomes deliver microRNA-1246 to induce M2 macrophage polarization by targeting TERF2IP via the STAT3 and NF-κB pathways. Oncogene 39: 428-442, 2020.
143. Kanlikilicer P, Bayraktar R, Denizli M, Rashed MH, Ivan C, Aslan B, Mitra R, Karagoz K, Bayraktar E, Zhang X, *et al*: Exosomal miRNA confers chemo resistance via targeting Cav1/p-gp/M2-type macrophage axis in ovarian cancer. EBioMedicine 38: 100-112, 2018.

144. Wang Z, Xu L, Hu Y, Huang Y, Zhang Y, Zheng X, Wang S, Wang Y, Yu Y, Zhang M, *et al*: miRNA let-7b modulates macrophage polarization and enhances tumor-associated macrophages to promote angiogenesis and mobility in prostate cancer. Sci Rep 6: 25602, 2016.
145. Shin JI and Brusselle GG: Mechanistic links between COPD and lung cancer: A role of microRNA let-7? Nat Rev Cancer 14: 70, 2014.
146. Guo L, Cheng X, Chen H, Chen C, Xie S, Zhao M, Liu D, Deng Q, Liu Y, Wang X, *et al*: Induction of breast cancer stem cells by M1 macrophages through Lin-28B-let-7-HMGA2 axis. Cancer Lett 452: 213-225, 2019.
147. Jerome T, Laurie P, Louis B and Pierre C: Enjoy the silence: The story of let-7 MicroRNA and cancer. Curr Genomics 8: 229-233, 2007.
148. Xun J, Du L, Gao R, Shen L, Wang D, Kang L, Chen C, Zhang Z, Zhang Y, Yue S, *et al*: Cancer-derived exosomal miR-138-5p modulates polarization of tumor-associated macrophages through inhibition of KDM6B. Theranostics 11: 6847-6859, 2021.
149. Xu H, Li M, Pan Z, Zhang Z, Gao Z, Zhao R, Li B, Qi Y, Qiu W, Guo Q, *et al*: miR-3184-3p enriched in cerebrospinal fluid exosomes contributes to progression of glioma and promotes M2-like macrophage polarization. Cancer Sci 113: 2668-2680, 2022.
150. Entezari M, Sadrkhanloo M, Rashidi M, Asnaf SE, Taheriazam A, Hashemi M, Ashrafizadeh M, Zarrabi A, Rabiee N, Hushmandi K, *et al*: Non-coding RNAs and macrophage interaction in tumor progression. Crit Rev Oncol Hematol 173: 103680, 2022.
151. Qiu S, Xie L, Lu C, Gu C, Xia Y, Lv J, Xuan Z, Fang L, Yang J, Zhang L, *et al*: Gastric cancer-derived exosomal miR-519a-3p promotes liver metastasis by inducing intrahepatic M2-like macrophage-mediated angiogenesis. J Exp Clin Cancer Res 41: 296, 2022.
152. Ma J, Chen S, Liu Y, Han H, Gong M and Song Y: The role of exosomal miR-181b in the crosstalk between NSCLC cells and tumor-associated macrophages. Genes Genomics 44: 1243-1258, 2022.
153. Shi L, Cao Y, Yuan W, Guo J and Sun G: Exosomal circRNA BTG2 derived from RBP-J overexpressed-macrophages inhibits glioma progression via miR-25-3p/PTEN. Cell Death Dis 13: 506, 2022.
154. Chuang HY, Su YK, Liu HW, Chen CH, Chiu SC, Cho DY, Lin SZ, Chen YS and Lin CM: Preclinical evidence of STAT3 inhibitor pacritinib overcoming temozolomide resistance via downregulating miR-21-enriched exosomes from M2 Glioblastoma-associated macrophages. J Clin Med 8: 959, 2019.
155. Wang T, Ren Y, Liu R, Ma J, Shi Y, Zhang L and Bu R: miR-195-5p suppresses the proliferation, migration, and invasion of oral squamous cell carcinoma by targeting TRIM14. Biomed Res Int 2017: 7378148, 2017.
156. Pakravan G, Foroughmand AM, Peymani M, Ghaedi K, Hashemi MS, Hajjari M and Nasr-Esfahani MH: Downregulation of miR-130a, antagonized doxorubicin-induced cardiotoxicity via increasing the PPARγ expression in mESCs-derived cardiac cells. Cell Death Dis 9: 758, 2018.
157. Anandappa G, Lampis A, Cunningham D, Khan KH, Kouvelakis K, Vlachogiannis G, Hedayat S, Tunariu N, Rao S, Watkins D, *et al*: miR-31-3p expression and benefit from Anti-EGFR inhibitors in metastatic colorectal cancer patients enrolled in the prospective phase II PROSPECT-C trial. Clin Cancer Res 25: 3830-3838, 2019.
158. Sokilde R, Persson H, Ehinger A, Pirona AC, Ferno M, Hegardt C, Larsson C, Loman N, Malmberg M, Rydén L, *et al*: Refinement of breast cancer molecular classification by miRNA expression profiles. BMC Genomics 20: 503, 2019.
159. Binenbaum Y, Fridman E, Yaari Z, Milman N, Schroeder A, Ben David G, Shlomi T and Gil Z: Transfer of miRNA in Macrophage-derived exosomes induces drug resistance in pancreatic adenocarcinoma. Cancer Res 78: 5287-5299, 2018.
160. Moradi-Chaleshtori M, Shojaei S, Mohammadi-Yeganeh S and Hashemi SM: Transfer of miRNA in tumor-derived exosomes suppresses breast tumor cell invasion and migration by inducing M1 polarization in macrophages. Life Sci 282: 119800, 2021.
161. Chen C, Liu JM and Luo YP: MicroRNAs in tumor immunity: Functional regulation in tumor-associated macrophages. J Zhejiang Univ Sci B 21: 12-28, 2020.
162. Qiao L, Dong C, Jia W and Ma B: Exosomal miR-655-3p inhibits growth, and invasion and macrophage M2 polarization through targeting CXCR4 in papillary thyroid carcinoma. Acta Biochim Pol 69: 773-779, 2022.
163. Zhao M, Zhuang A and Fang Y: Cancer-associated fibroblast-derived exosomal miRNA-320a promotes macrophage M2 polarization in vitro by regulating PTEN/PI3Kγ signaling in pancreatic cancer. J Oncol 2022: 9514697, 2022.
164. Hong S, You JY, Paek K, Park J, Kang SJ, Han EH, Choi N, Chung S, Rhee WJ and Kim JA: Inhibition of tumor progression and M2 microglial polarization by extracellular vesicle-mediated microRNA-124 in a 3D microfluidic glioblastoma microenvironment. Theranostics 11: 9687-9704, 2021.
165. Labonte AC, Tosello-Trampont AC and Hahn YS: The role of macrophage polarization in infectious and inflammatory diseases. Mol Cells 37: 275-285, 2014.
166. Bashir S, Sharma Y, Elahi A and Khan F: Macrophage polarization: The link between inflammation and related diseases. Inflamm Res 65: 1-11, 2016.
167. Biswas SK, Chittezhath M, Shalova IN and Lim JY: Macrophage polarization and plasticity in health and disease. Immunol Res 53: 11-24, 2012.
168. Hawiger J, Veach RA and Zienkiewicz J: New paradigms in sepsis: From prevention to protection of failing microcirculation. J Thromb Haemost 13: 1743-1756, 2015.
169. Mayr FB, Yende S and Angus DC: Epidemiology of severe sepsis. Virulence 5: 4-11, 2014.
170. Martin GS: Sepsis, severe sepsis and septic shock: Changes in incidence, pathogens and outcomes. Expert Rev Anti Infect Ther 10: 701-706, 2012.
171. Melamed A and Sorvillo FJ: The burden of sepsis-associated mortality in the United States from 1999 to 2005: An analysis of multiple-cause-of-death data. Crit Care 13: R28, 2009.
172. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, Moldawer LL and Moore FA: Persistent inflammation and immunosuppression: A common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg 72: 1491-1501, 2012.
173. Essandoh K and Fan GC: Role of extracellular and intracellular microRNAs in sepsis. Biochim Biophys Acta 1842: 2155-2162, 2014.
174. Tsujimoto H, Ono S, Efron PA, Scumpia PO, Moldawer LL and Mochizuki H: Role of Toll-like receptors in the development of sepsis. Shock 29: 315-321, 2008.
175. Cristofaro P and Opal SM: The Toll-like receptors and their role in septic shock. Expert Opin Ther Targets 7: 603-612, 2003.
176. Savva A and Roger T: Targeting Toll-like receptors: Promising therapeutic strategies for the management of sepsis-associated pathology and infectious diseases. Front Immunol 4: 387, 2013.
177. Weighardt H and Holzmann B: Role of Toll-like receptor responses for sepsis pathogenesis. Immunobiology 212: 715-722, 2007.
178. Foley NM, Wang J, Redmond HP and Wang JH: Current knowledge and future directions of TLR and NOD signaling in sepsis. Mil Med Res 2: 1, 2015.
179. Salomao R, Martins PS, Brunialti MK, Fernandes ML, Martos LS, Mendes ME, Gomes NE and Rigato O: TLR signaling pathway in patients with sepsis. Shock 30 (Suppl 1): S73-S77, 2008.
180. Wang JF, Yu ML, Yu G, Bian JJ, Deng XM, Wan XJ and Zhu KM: Serum miR-146a and miR-223 as potential new biomarkers for sepsis. Biochem Biophys Res Commun 394: 184-188, 2010.
181. Fabian B, Sanchari R, Christian T, Christoph R and Tom L: Circulating MicroRNAs as Biomarkers for Sepsis. Int J Mol Sci 17: 78, 2016.
182. Arner P and Kulyte A: MicroRNA regulatory networks in human adipose tissue and obesity. Nat Rev Endocrinol 11: 276-288, 2015.
183. Monteiro R and Azevedo I: Chronic inflammation in obesity and the metabolic syndrome. Mediators Inflamm 2010: 289645, 2010.
184. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA and Chen H: Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 112: 1821-1830, 2003.
185. Gregor MF and Hotamisligil GS: Inflammatory mechanisms in obesity. Annu Rev Immunol 29: 415-445, 2011.
186. Nishimura S, Manabe I and Nagai R: Adipose tissue inflammation in obesity and metabolic syndrome. Discov Med 8: 55-60, 2009.
187. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, Capeau J and Feve B: Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw 17: 4-12, 2006.
188. Moore CS, Rao VT, Durafourt BA, Bedell BJ, Ludwin SK, Bar-Or A and Antel JP: miR-155 as a multiple sclerosis-relevant regulator of myeloid cell polarization. Ann Neurol 74: 709-720, 2013.

189. Ponomarev ED, Veremeyko T, Barteneva N, Krichevsky AM and Weiner HL: MicroRNA-124 promotes microglia quiescence and suppresses EAE by deactivating macrophages via the C/EBP-alpha-PU.1 pathway. Nat Med 17: 64-70, 2011.
190. Karunakaran D, Richards L, Geoffrion M, Barrette D, Gotfrit RJ, Harper ME and Rayner KJ: Therapeutic inhibition of miR-33 promotes fatty acid oxidation but does not ameliorate metabolic dysfunction in diet-induced obesity. Arterioscler Thromb Vasc Biol 35: 2536-2543, 2015.
191. Yang Y, Yang L, Liang X and Zhu G: MicroRNA-155 promotes atherosclerosis inflammation via targeting SOCS1. Cell Physiol Biochem 36: 1371-1381, 2015.
192. Yu F, Jia X, Du F, Wang J, Wang Y, Ai W and Fan D: miR-155-deficient bone marrow promotes tumor metastasis. Mol Cancer Res 11: 923-936, 2013.
193. Ouimet M, Ediriweera HN, Gundra UM, Sheedy FJ, Ramkhelawon B, Hutchison SB, Rinehold K, van Solingen C, Fullerton MD, Cecchini K, *et al*: MicroRNA-33-dependent regulation of macrophage metabolism directs immune cell polarization in atherosclerosis. J Clin Invest 125: 4334-4348, 2015.
194. Zhu QY, Liu Q, Chen JX, Lan K and Ge BX: MicroRNA-101 targets MAPK phosphatase-1 to regulate the activation of MAPKs in macrophages. J Immunol 185: 7435-7442, 2010.
195. Gao Y, Liu F, Fang L, Cai R, Zong C and Qi Y: Genkwanin inhibits proinflammatory mediators mainly through the regulation of miR-101/MKP-1/MAPK pathway in LPS-activated macrophages. PLoS One 9: e96741, 2014.
196. Liu G, Friggeri A, Yang Y, Park YJ, Tsuruta Y and Abraham E: miR-147, a microRNA that is induced upon Toll-like receptor stimulation, regulates murine macrophage inflammatory responses. Proc Natl Acad Sci USA 106: 15819-15824, 2009.
197. Wei J, Huang X, Zhang Z, Jia W, Zhao Z, Zhang Y, Liu X and Xu G: MyD88 as a target of microRNA-203 in regulation of lipopolysaccharide or Bacille Calmette-Guerin induced inflammatory response of macrophage RAW264.7 cells. Mol Immunol 55: 303-309, 2013.
198. Xie N, Cui H, Banerjee S, Tan Z, Salomao R, Fu M, Abraham E, Thannickal VJ and Liu G: miR-27a regulates inflammatory response of macrophages by targeting IL-10. J Immunol 193: 327-334, 2014.
199. Lv LL, Feng Y, Wu M, Wang B, Li ZL, Zhong X, Wu WJ, Chen J, Ni HF, Tang TT, *et al*: Exosomal miRNA-19b-3p of tubular epithelial cells promotes M1 macrophage activation in kidney injury. Cell Death Differ 27: 210-226, 2020.
200. Arora S, Dev K, Agarwal B, Das P and Syed MA: Macrophages: Their role, activation and polarization in pulmonary diseases. Immunobiology 223: 383-396, 2018.
201. Qiu M, Xu E and Zhan L: Epigenetic regulations of Microglia/macrophage polarization in ischemic stroke. Front Mol Neurosci 14: 697416, 2021.
202. Dang CP and Leelahavanichkul A: Over-expression of miR-223 induces M2 macrophage through glycolysis alteration and attenuates LPS-induced sepsis mouse model, the cell-based therapy in sepsis. PLoS One 15: e236038, 2020.
203. Li B, Dasgupta C, Huang L, Meng X and Zhang L: MiRNA-210 induces microglial activation and regulates microglia-mediated neuroinflammation in neonatal hypoxic-ischemic encephalopathy. Cell Mol Immunol 17: 976-991, 2020.
204. Xu Y, Xu Y, Zhu Y, Sun H, Juguilon C, Li F, Fan D, Yin L and Zhang Y: Macrophage miR-34a is a key regulator of cholesterol efflux and atherosclerosis. Mol Ther 28: 202-216, 2020.
205. Gao L, Qiu F, Cao H, Li H, Dai G, Ma T, Gong Y, Luo W, Zhu D, Qiu Z, *et al*: Therapeutic delivery of microRNA-125a-5p oligonucleotides improves recovery from myocardial ischemia/reperfusion injury in mice and swine. Theranostics 13: 685-703, 2023.