Regulatory Mechanism of IncRNAs in M1/M2 Macrophages Polarization in the Diseases of Different Etiology

Ping Jiang1,2 and Xiaopeng Li3,4*

1 Guanghua Clinical Medical College, Shanghai University of Traditional Chinese Medicine, Shanghai, China, 2 Department of Rheumatology, Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China, 3 Department of Neurology, Rizhao Hospital of Traditional Chinese Medicine, Rizhao, China, 4 Integrated Traditional Chinese and Western Medicine, Shandong University of Traditional Chinese Medicine, Jinan, China

Precise expression and regulation of genes in the immune system is important for organisms to produce strong immunity towards pathogens and limit autoimmunity. In recent years, an increasing number of studies has shown that long noncoding RNAs (IncRNAs) are closely related to immune function and can participate in regulating immune responses by regulating immune cell differentiation, development, and function. As immune cells, the polarization response of macrophages (Mφs) plays an important role in immune function and inflammation. IncRNAs can regulate the phenotypic polarization of Mφs to M1 or M2 through various mechanisms; promote pro-inflammatory or anti-inflammatory effects; and participate in the pathogenesis of cancers, inflammatory diseases, infections, metabolic diseases, and autoimmune diseases. In addition, it is important to explore the regulatory mechanisms of IncRNAs on the dynamic transition between different Mφs phenotypes. Thus, the regulatory role of IncRNAs in the polarization of Mφs and their mechanism are discussed in this review.

Keywords: long noncoding RNAs, regulation, macrophages, polarization, diseases

INTRODUCTION

Macrophages (Mφs) are vital antigen-presenting cells with high heterogeneity and plasticity in the human immune system (1). Mφs can induce multiple polarization processes and exert different functions depending on the conditions (2). The local cytokine environment can lead to polarization of Mφs. Therefore, according to their expression of cell surface markers, the production of specific factors, and biological activities, Mφs are classified into the M1-like and M2-like types (3). M1 and M2 polarization is a remarkable characteristic of Mφs involved in numerous biological processes. M1 Mφs are known as classical Mφs and are activated by bacterial lipopolysaccharide or interferon (IFN)-γ. To produce and secrete higher levels of proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-12, and cyclooxygenase-2. M1 Mφs have robust antimicrobial functions and inhibit tumor growth (4). In M2 Mφs, signal
transducer and activator of transcription 6 (STAT6) is activated by IL-4 receptor α (IL-4Rα) and M2 Mφs are polarized by Th2 cytokine IL-4/IL-13. M2 Mφs have anti-inflammatory and strong phagocytic abilities to eliminate apoptotic cells and are useful for chronic infection treatment and wound healing (5). Moreover, according to the different stimuli received, M2 Mφs can be further divided into four different types: M2a, M2b, M2c, and M2d (6) (See Figure 1).

Precise regulation of Mφs polarization is a key step in controlling immune system function, clearing pathogens, and defending against external evil. The evidence accumulated in the past decade shows that LncRNAs are widely expressed and play a key role in gene regulation. LncRNAs are a potential biomarker (9) and act as crucial regulators of Mφs polarization (96). At present, TAMs are mainly divided into two subtypes (See Figure 2): M1 TAMs of classical activation pathway and M2 TAMs of alternative activation pathway. M1 TAMs have significant anti-tumor effect. In the TME, it can identify tumor cells and kill tumor cells through the corresponding signaling pathway. According to the different pathways of action, it can be divided into direct killing mechanism and antibody-dependent cytotoxicity (ADCC) mechanism (97). M2 TAMs can significantly promote tumor growth. First of all, M2 TAMs secrete cytokines such as IL-6 and CXCL-8 into the TME and directly promotes the growth of tumor cells (98). Secondly, M2 TAMs can also block the inducible nitric oxide synthase (iNOS) pathway, reduce the synthesis of NO, accelerate the production of polyamines, and then promote the proliferation of tumor cells (99). M2 TAMs also promote angiogenesis of tumor cells by secreting vascular endothelial growth factor (VEGF) and IL-17, and can release matrix metalloproteinase (MMP)-2, MMP-9 and other substances to degrade extracellular matrix, promote vascular endothelial migration and induce angiogenesis (100, 101).

Here, we review the current understanding of lncRNA functions in Mφs polarization. Using different disease models, we reviewed that different lncRNAs regulate the polarization of Mφs via different signaling pathways and act on different targets; we also explain the mechanism of these effects.

**LncRNAs Regulate Mφs Polarization in Various Cancers**

Tumor-associated macrophages (TAMs), which are specialized phagocytic cells, play an important role in the pathology and pathogenesis of cancers and are responsible for modulating the tumor microenvironment (TME) (95) (See Table 1). The microenvironment signals exposed to Mφs are the key factors that determine the phenotype of Mφs; these microenvironment signals selectively regulate their functions, including M1 and M2 polarization (96). At present, TAMs are mainly divided into two subtypes (See Figure 2): M1 TAMs of classical activation pathway and M2 TAMs of alternative activation pathway. M1 TAMs have significant anti-tumor effect. In the TME, it can identify tumor cells and kill tumor cells through the corresponding signaling pathway. According to the different pathways of action, it can be divided into direct killing mechanism and antibody-dependent cytotoxicity (ADCC) mechanism (97). M2 TAMs can significantly promote tumor growth. First of all, M2 TAMs secrete cytokines such as IL-6 and CXCL-8 into the TME and directly promotes the growth of tumor cells (98). Secondly, M2 TAMs can also block the inducible nitric oxide synthase (iNOS) pathway, reduce the synthesis of NO, accelerate the production of polyamines, and then promote the proliferation of tumor cells (99). M2 TAMs also promote angiogenesis of tumor cells by secreting vascular endothelial growth factor (VEGF) and IL-17, and can release matrix metalloproteinase (MMP)-2, MMP-9 and other substances to degrade extracellular matrix, promote vascular endothelial migration and induce angiogenesis (100, 101). M1 and M2 TAMs existed in all stages of the tumor, mainly M1 in the early stages and M2 in the late stages.
stage and M2 in the middle and late stages of the tumor. With the progression of tumor, M1 is gradually polarized to M2, and the increase number of M2 TAMs also indicates a poor prognosis. Clinical studies have confirmed that M1 TAMs polarize to M2 TAMs induced by proliferator-activated receptor (PPAR)-γ. The increase in the proportion of M2 TAMs are closely related to tumor cell proliferation and tumor tissue vascular density (MVD) (102). A new study has shown that the inhibition of nuclear factor-kappa B (NF-κB) activity and the increase of STAT3 activity in M1s represent a tumor-mediated mechanism that triggers M1/M2 deviation (103). Moreover, lncRNAs are increasingly appreciated as important regulators of gene expression (104), and multiple studies have showed (105, 106) that lncRNAs play a role and directly involved in the occurrence of cancer, apoptosis, cell migration and invasion (108, 109). As a potential biomarker for diagnosis and prediction, lncRNAs have a wide range of functions in the occurrence and development of various human diseases, especially in the occurrence and development of many cancers.

### Respiratory System Cancers
Lung cancer is the most common respiratory cancer, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of all lung cancers as the most common cancer worldwide. Increasing evidence has shown that Mφs and lncRNAs are involved in the development of inflammation and malignant transformation of tumor cells. LncRNAs are also involved in the pathogenesis of lung cancer. Li et al. (40) used lncRNA AGNAS-AS1 to explore the role of AGNAS-AS1 in the development of NSCLC. These experimental studies showed that lncRNA AGNAS-AS1 was highly expressed in M2 Mφs and NSCLC cell lines, which was significantly higher than that in M1 Mφs, and promoted the polarization of M2 Mφs and progression of NSCLC by directly inhibiting miR4319 and increasing the level of N-terminal EF-

### TABLE 1 | LncRNAs regulate polarization types of Mφs and targets in cancers.

| LncRNAs       | Polarity Types | Targets                                  | Diseases                        | References |
|---------------|----------------|------------------------------------------|---------------------------------|------------|
| LncRNA ANCR   | M1             | FOXO1                                    | Gastric cancer                  | (12)       |
| LncRNA CCAT1  | M1             | MIR-148A                                 | Colon cancer                    | (13)       |
| LncRNA GAS5   | M1             | Unknown                                  | Colorectal cancer               | (14)       |
| LncRNA LNMAT1 | M1             | COL2                                     | Bladder cancer                  | (15)       |
| LncRNA p21    | M1             | MDM2/p53/NF-κB/STAT3                    | Breast cancer                   | (16)       |
| LncRNA GNAS-AS1| M2             | MIR-433-3p                                | Breast cancer                   | (17)       |
| LncRNA BCR1   | M2             | MIR-1303/PTBP3                            | Breast cancer                   | (18)       |
| LncRNA SNHG1  | M2             | STAT6                                    | Breast cancer                   | (19)       |
| LncRNA 00337  | M2             | CD163/ARG1                               | Breast cancer                   | (20)       |
| LncRNA 00514  | M2             | Jaggedl/Notch                            | Breast cancer                   | (21)       |
| LncRNA GAS5   | M2             | PTEN                                     | Hepatocellular carcinoma        | (22)       |
| LncRNA PART1  | M2             | MIR-372-3p/TLR4                          | Hepatocellular carcinoma        | (23)       |
| LncRNA DLX6-AS1| M2            | MIR-15a-5p/CXCL17                        | Hepatocellular carcinoma        | (24)       |
| LncRNA TP73-AS1| M2            | MIR-539/MMP-8/TGF-β1                     | Hepatocellular carcinoma        | (25)       |
| LncRNA CR175E | M2             | CD163                                    | Liver cancer                    | (26)       |
| LncRNA HLA-F-AS1| M2         | MIR-375/PFN1                             | Colorectal cancer               | (27)       |
| LncRNA NBR2   | M2             | Arg-1/CD163/CD206                        | Colorectal cancer               | (28)       |
| LncRNA PTTG3P | M2             | HIF1A                                    | Colorectal cancer               | (29)       |
| LncRNA RPP1H1 | M2             | TUBB3                                    | Colorectal cancer               | (30)       |
| LncRNA MIR155H3| M2            | MIR-650/ANXA2                            | Osteosarcoma                    | (31)       |
| LncRNA RP11-361F15.2| M2 | MIR-30c-5p/CPEB4 | Osteosarcoma                  | (32)       |
| LncRNA LOC100129620| M2 | MIR-335-3p/CDK6 | Osteosarcoma                  | (33)       |
| LncRNA NEAT1  | M2             | MIR-214/B7-H3                            | Endometrial cancer              | (34, 35)   |
| LncRNA NIFK-AS1| M2            | MIR-146a                                 | Endometrial cancer              | (36)       |
| LncRNA MM2P   | M2             | STAT6                                    | Tumorigenesis                   | (37)       |
| LncRNA CAS2c  | M2             | FX                                       | Brain tumor                     | (38)       |
| LncRNA LINC01140| M2        | MIR-140-5p/FGF9                          | Bladder cancer                  | (39)       |
| LncRNA GNAS-AS1| M2            | MIR-4319/NECAB3                          | Non-small cell lung cancer      | (40)       |
| LncRNA XIST   | M2             | TCF-4                                    | Lung cancer                     | (41)       |
| LncRNA DCST1-AS1| M2        | NF-κB                                    | Oral Squamous Cell Carcinoma    | (42)       |
| LncRNA FGDS5-AS1| M2        | MIR-129-5p/BST2                          | Cervical cancer                 | (43)       |
| LncRNA C00467 | M2             | MIR-494-3p/STAT3                         | Prostate cancer                 | (44)       |
| LncRNA HOG18  | M2             | MIR-875-3p/ KLF4                          | Gastric cancer                  | (45)       |
| LncRNA TUC339 | M1/M2          | CXOR                                     | Hepatocellular carcinoma        | (46)       |
| LncRNA COX-2  | M1/M2          | IL-12/11O/iNOS/IFN-α/IFN-γ/Arg-1/Fizz-1  | Hepatocellular carcinoma        | (47)       |
| LncRNA Ma301  | M1/M2          | Caprin-1/Akt/Erk1                        | Hepatocellular carcinoma        | (48)       |
| LncRNA LNB-FA1| M1/M2          | Macrophage                               | Oral squamous cell carcinoma    | (49)       |
| LncRNA Xist   | M1/M2          | MIR-101-3p/ KLF6/CEBPγ                   | Breast cancer                   | (50)       |
| LncRNA Xist   | M1/M2          | MIR-101-3p/ KLF6/CEBPγ                   | Ovarian tumor                   | (50)       |
handcalciumbindingprotein3 (NECAB3). In addition, lncRNA GNAS-AS1 was also highly expressed in lung TAMs and clinical tumor tissues. Therefore, lncRNA GNAS-AS1 promoted the polarization of M2 Mφs and induced the progression of NSCLC through the mir-4319/NECAB3M2 axis in the tumor microenvironment, showing potential as a target for treating NSCLC. Another study on lung cancer confirmed that lncRNA XIST can also play a role by regulating Mφs. The expression of lncRNA XIST in M2 Mφs was significantly higher than that in M1 Mφs. Down-regulation of lncRNA XIST could significantly inhibit IL-4-induced M2 polarization, resulting in downregulation of M2 specific markers such as IL-10 and CD163. Due to the direct interaction between T-cell-specific transcription factor (TCF)-4 and lncRNA XIST, this inhibition was stopped by the overexpression of TCF-4. However, lncRNA XIST knockdown can restore IL-4-induced M2 polarization, further indicating the importance of TCF-4 in M2 Mφs and TAMs-induced proliferation, migration and invasion of lung cancer cells. The results showed that lncRNA XIST positively regulated the M2 polarization and interacted with TCF-4, thus regulating the development of lung cancer (41).

**Urinary System Cancers**

Prostate cancer (PC) is one of the most common tumors in the urinary system, and methods for its diagnosis and treatment have rapidly progressed in recent years; however, therapeutic
effects remain unsatisfactory (110). Recently, the therapeutic value of lncRNAs in regulating Mφs in the TME has been widely explored, and a Chinese research team has found (44) that lncRNA LINC00467 may be beneficial for treating PC. Additionally, the lncRNA LINC00467 mainly exists in the cytoplasm, and its expression is upregulated in PC tissues and cells to enhance polarization of the M2 phenotype via the miR-494-3p/STAT3 axis. While M2 polarization can activate the STAT3 pathway, enhance the tumor enhancement of M2, and consequently promote the growth and migration of PC cells (44).

Compared with PC, bladder cancer is among the most serious malignant tumors worldwide. Although the incidence of muscle-invasive bladder cancer (MIBC) is low, the overall mortality rate is high. Chen et al. (15) found that a new lncRNA named LNMAT1 through sequencing of five MIBC organizations. Its expression in MIBC tissues was significantly upregulated and positively correlated with the intensity of M2 infiltration around the tumors. Further experiments showed that overexpression of LNMAT1 in vivo activated M2 polarization by mediating heterogeneous nuclear Ribonucleoprotein L (hnRNPL) to promote the transcription of its target gene, CCL2. Furthermore, this lncRNA can induce the expression of CCL2 in bladder cancer cells, upregulate CCL2 to stimulate TAMs to secrete VEGF-C, participate in lymphogenesis, promote lymphatic metastasis and lymphangiogenesis, and accelerate the invasiveness of bladder cancer cells. These findings elaborate that LNMAT1 regulates the polarization of TAMs and mediates lymphatic metastasis, revealing a carcinogenic role for LNMAT1 in bladder cancer progression. Differential genes of lncRNA LINC01140 and fibroblast growth factor 9 (FGF9) were found in another study of an online microarray expression profile (GSE77952) of MIBC (39). By the analysis of polymerase chain reaction (PCR) and enzyme linked immunosorbent assay (ELISA), revealed a positive correlation between the expression of LINC01140 and FGF9. FGF9 and LINC01140 were highly expressed in M2 Mφs; after knocking down FGF9 and LINC01140, the viability and invasive ability of MIBC cells were significantly inhibited, leading to a decrease in the M2 markers IL-10 and Arg1 and weakened M2 polarization.

In addition, by using the competing endogenous RNA mechanism, it was found that inhibition of miR-140-5p significantly reversed the expression and effects of LINC01140 and FGF9, thus affecting M2 polarization. Finally, LINC01140, miR-140-5p and FGF9 form a lncRNA-miRNA-mRNA mechanism axis, which influences M2 polarization by regulating the TME, thereby affecting the progression of MIBC.

**Digestive System Cancers**

Oral squamous cell carcinoma (OSCC) is a digestive system cancer that is also a common type of head and neck cancer. The occurrence and progress of OSCC are closely related to Mφs. M2 Mφs accelerate the progression of OSCC through a complex cross-talk mechanism and are regulated by lncRNAs. The NF-κB signaling plays an important role in tumor development. Ai et al. (42) found that deletion of lncRNA DCST1AS1 hindered the progression of OSCC by inhibiting the NF-κB signaling pathway. Its overexpression can cause M2 polarization to promote the growth and differentiation of OSCC cells and accelerate the development of cancer by regulating the tumor immune environment. Another lncRNA, LBXI-AS1, is secreted by RBPJ-overexpression (RBPJ-OE) Mφs and belongs to the exocrine RNA. Its mechanism is mediated via the miR-182-5p/FOXO3 pathway. As a competing endogenous RNA, LBXI-AS1 stimulates Mφs by acting on miR-182-5p and fork head box protein O3 (FOXP3), causing Mφs polarization and activating Mφs to regulate the development of tumor cells (49).

Gastric cancer (GC) is a common disease affecting the digestive system. In recent years, research on GC has mainly focused on the molecular mechanism and attempts to identify new therapeutic targets. LncRNAs and Mφs polarization were shown to be closely related to the development of GC. M1 polarization can kill tumor...
cells and inhibit tumor lymphangiogenesis and angiogenesis (111). Overexpression of lncRNA ANCR in Mφs significantly reduced the expression of the M1 polarization marker IL-1β and IL-6, thus inhibiting M1 polarization. Co-culture of Mφs with GC cells showing high expression of lncRNA ANCR resulted in significantly enhanced invasiveness and migration of GC cells. FOXO1 is the target gene of the lncRNA ANCR. On one hand, FOXO1 can promote Mφs to produce inflammatory factors and induce M1 polarization. In contrast, lncRNA ANCR accelerates the ubiquitination of FOXO1 and inhibits its expression. After downregulation of FOXO1, M1 polarization was also inhibited. Based on these results, overexpression of lncRNA ANCR can downregulate FOXO1, thus inhibiting M1 polarization and promoting the development of GC cells (12). Other lncRNA can affect GC progression by influencing M2 polarization. M2 Mφs can induce GC cells growth, and lncRNA HCG18 can positively regulate M2 polarization. Specifically, lncRNA HCG18 can bind to miR-875-3p and target krüppel-like factor4 (KLF4) regulation, as well as upregulate KLF4 by reducing the expression of miR-875-3p in Mφs, thereby promoting M2 polarization. M2 Mφs have anti-inflammatory effects, secrete inflammatory cytokines to kill tumor cells, slow GC development, and play a role in immune surveillance (45).

Hepatocellular carcinoma (HCC) is a common tumor of the digestive system with a high incidence in Asia. M2 Mφs can promote tumor angiogenesis and induce cancer cell metastasis, but the mechanism of Mφs polarization is unclear. Four studies have explained the role of this mechanism in HCC development through the regulation of different lncRNAs on M2 polarization. It has been found (26) that M2 Mφs can promote human umbilical vein endothelial cell angiogenesis when M2-THP-1 cells are co-cultured with these cells. In mouse model of H22 tumor cells, lncRNA CENDE downregulated the expression of CD163, STAT-6, and VEGF by promoting M2 polarization, thus indirectly regulating tumor angiogenesis. In a study of SMCC-7721 cells, the supernatant of TAMs significantly promoted cell invasiveness. The expression of lncRNA GAS5 is downregulated in M2 Mφs and TAMs, which has been shown to be related to Mφs polarization in the progression of HCC. This lncRNA plays a regulatory role by regulating the expression of the target protein phosphatase and tensin homolog (PTEN) to inhibit M2 polarization of TAMs in SMCC-7721 cells (22). M2 polarization can also interact with the miR-372-3p/TLR4 axis, thus affecting the delivery of lncRNA PART1 into liver cancer tissues and cells via tumor-derived extracellular vesicles, inducing the upregulation of PART1 and Toll-like receptor 4 (TLR4) and downregulation of miR-372-3p, and promoting the proliferation and invasion of liver cancer cells. Additionally, miR-372-3p can bind to PART1 and negatively regulate TLR4, act on extracellular vesicles, and induce M2 polarization in HCC tissues, thus promoting the occurrence of HCC (23). The microRNA-15a-5p/CXCL17 axis is another regulatory pathway of M2 polarization in HCC. A previous study showed (24) that lncRNA DLX6-AS1, miR-15a-5p, and CXCL17 were highly expressed in HCC cells, and exosomes were isolated from HCC cells and co-cultured with M2 Mφs. The results showed that extracellular ubiquitin induced and intracellular HCC-exosomes transported DLX6-AS1 to Mφs, targeted binding to miR-15a-5p, and regulated CXCL17 expression to stimulate M2 polarization. In addition, Wnt ligands in tumor cells can stimulate M2 polarization, which can jointly accelerate the development and metastasis of HCC cells in vivo and in vitro. Furthermore, numerous studies have shown that different lncRNAs (lncRNA COX-2, lncRNA TUC339, and lncRNA Ma301) induce M1 and M2 polarization in the tumor microenvironment through different action targets (E-cadherin, caprin-1) and pathways (Akt/Erk1/2 pathway), decrease the levels of iNOS and TNF-α in M1 Mφs, and increase the levels of Arg-1 and Fizz-1 in M2 Mφs. LncRNAs also promote the production of various inflammatory factors, chemokines and eoxin, thus acting on the immune response of tumors and inhibiting pathological processes such as immune escape and invasion of HCC. These studies provide a new theoretical basis for treating HCC (46–48).

With the aging of the population and poor lifestyle, the global morbidity and mortality of colorectal cancer (CRC) are increasing each year. In epigenetic studies, lncRNAs were confirmed to be closely related to the pathogenesis of CRC. For example, lncRNA RPP4 functions in CRC by binding to miR7-5p (112). Previous studies also showed that Mφs are involved in the pathogenesis of numerous cancers. Is there a regulatory relationship between lncRNAs and Mφs that interfere with the progression of CRC? Related studies found that lncRNAs HLA-F-AS1, NBR2, PTTG3P, and RPPH1 induce the polarization response of tumor-associated Mφs by acting on the corresponding targets or pathways, thus participating in the pathological development of CRC. Mechanistically, lncRNA MIR155HG (31) and lncRNA HLA-F-AS1 (27) can competitively bind with miR-650 and miR-375, reverse-regulate the expression of miR-650 and miR-375, and indirectly target annexin A2 (ANXA2) and profolin 1 (PFN1). Inhibiting of miR-650 and miR-375 promoted the expression of ANXA2 and PFN1 in CRC-derived extracellular vesicles. This mechanism further stimulated increased M2 Mφs marker expression, induced M2 Mφs phenotypic polarization, and accelerated CRC cells invasion. In contrast, lncRNA NBR2 can activate M1 polarization, inhibit M2 polarization, and regulate the polarization of TAMs to promote the release of inflammatory factors such as TNF-α, IL1-β, and IL-10, thus acting on the TME. However, after knockout of the lncRNA NBR2 gene, these effects were reversed (28). A similar process occurs with lncRNA PTTG3P (29). Under the action of hypoxia-inducible factor-1-α (HIF-1α), the hypoxia environment induces the overexpression of PTTG3P to promotes M2 polarization and stimulates tumor development. In addition, exosomes can mediate Mφs polarization. Liang et al. (30) found that the expression of lncRNA RPPH1 is upregulated in CRC, which is related to poor prognosis. In terms of the mechanism, RPPH1 binds to β-III tubulin and prevents its ubiquitination, which induces the transformation of epithelial-mesenchymal transition and accelerates the metastasis of cancer cells. Further studies showed that RPPH1 is closely related to exosomes, which can transfer into Mφs by exosomes to mediate M2 polarization and promote tumor growth and migration.
Reproductive System Cancers
Breast cancer occurs following uncontrolled proliferation of breast epithelial cells via the action of various carcinogenic factors and is considered as an important role in cancer progression. The IncRNA BCRT1/miR-1303/PTBP3 and IncRNA Xist/miR-101-3p/KLF6/C/EBPα can regulate the progression of breast cancer. In the IncRNA BCRT1/miR-1303/PTBP3 axis (18), polypyrimidine tract binding protein 3 (PTBP3) promotes breast cancer, and the expression of IncRNA BCRT1 in breast cancer tissues is significantly increased, which is related to the poor prognosis of patients. In the mechanism of action, IncRNA BCRT1 can bind to miR-1303 and act on PTBP3 to inhibit its expression. After overexpression, IncRNA BCRT1 significantly promotes M2 polarization mediated by exosomes. After M2 polarization, inflammatory factors such as TNF-α and IL-6 are produced, which promote cancer in tumor microenvironment; this effect is more obvious in hypoxic environments. Phenotypic transformation of TAMs mediates tumor immune escape. Zhao et al. (50) found that the expression of IncRNA Xist and C/EBPα was upregulated in M1 Mφs, whereas the expression of miR-101-3p was downregulated. IncRNA Xist knockout inhibited the expression of C/EBPα and KLF6 and induced the transformation from M1 to M2, thus promoting the proliferation and migration of breast cancer cells. Therefore, IncRNA Xist competes with miR-101-3p to regulate the expression of C/EBPα and KLF6 to mediate Mφ polarization, promote the expression of IncRNA Xist in M1 Mφs and inhibit the expression of miR-101-3p in M2 Mφs, thus inhibiting the progression of breast cancer. TAMs reprogram their specific functional phenotype in the tumor environment to promote cancer progression and metastasis. Zhou et al. (16) showed that IncRNA p21 was significantly upregulated in Mφs. Knockout of P21 led to mouse double minute 2 (MDM2)-induced proteasome-dependent degradation of p53 and activated the NF-κB/STAT3 pathway, which promoted Mφs polarization to pro-inflammatory M1 and accelerated the progression of breast cancer. These results show that IncRNA p21 plays a key role in regulating the function of TAMs and can be a new therapeutic target for breast cancer.

In addition, after Zong (19) successfully induced M2 polarization by IL-4/IL-13 experimentally, the RNA level of IncRNA SNHG1 determined using qRT-PCR was increased, indicating that this IncRNA is involved in M2 polarization. Further experiments showed that IncRNA SNHG1 knockout inhibited phosphorylation of STAT6 and indirectly weakened M2 polarization. Subsequent transplantation of Mφs mixed with other cells accelerated the growth of breast cancer cells. The IncRNA SNHG1 regulates M2 polarization to affects cell growth and invasion. IncRNA 00337 (20) and IncRNA 00514 (21) have similar mechanisms and can both affect the development of breast cancer by regulating M2 TAMs polarization.

Other Systemic Cancers
In addition to the above common cancers, Mφs polarization is involved in the pathological mechanisms of osteosarcoma and brain tumors. Osteosarcoma is common in children and adolescents. The IncRNA LOC100129620 can promote the proliferation and migration of osteosarcoma cells in vivo (33) by binding to miR-335-3p and regulating cyclin-dependent kinases 6 (CDK6), thus promoting angiogenesis and Mφs polarization. In contrast, LOC100129620 gene knockout decreased the infiltration and M2 TAMs polarization, and inhibited the development of osteosarcoma. In glioblastoma multiforme, Zhang found (38) that coagulation factor X (FX) was highly expressed and positively correlated with the concentration of TAMs. FX is secreted in the tumor microenvironment, has a strong chemotactic effect on Mφs, promotes the phosphorylation and activation of ERK1/2 and AKT in Mφs, and stimulates Mφs to M2 polarization. In addition, FX was identified as the target gene of miR-338-3p. The IncRNA CASC2c interacts with miR-338-3p and binds with FX to jointly inhibit the expression of FX and finally inhibit M2 polarization.

In summary, IncRNAs and Mφs play important role in multi-system cancers such as the respiratory, digestive, and reproductive systems. Through the analysis of the results of the above studies, it can be found that the mechanism of IncRNAs regulating Mφs polarization is mainly through the IncRNA-miRNA-mRNA axis. A large number of animal experiments and clinical trials have confirmed that M2 TAMs play an important role in tumor growth, invasion and metastasis, while M1 TAMs can inhibit tumor formation. It is also found that M2 polarization occurs more frequently and the mechanism of action is more complex than that of M1 in the occurrence and development of cancers. The presence of a large number of M2 Mφs in tumor tissue indicates a poor prognosis, which has a positive reference value for the clinical treatment of M2 Mφs. In the TME, TAMs produce a polarization response, secrete inflammatory factors and chemokines, regulate immune responses, and participate in the occurrence and development of cancers, which is important in cancer pathogenesis. Therefore, blocking Mφs from reaching tumor tissue, clearing Mφs and inhibiting the activation or repolarization of TAMs in TME has become a hot issue in the field of tumor immune research. Based on the understanding of the function of TAMs and the relationship between M1 and M2 Mφs, reversing the polarization of M1 to M2 Mφs is likely to be a key target for future tumor therapy. However, tumor treatment is a systematic project, and the effect of any single treatment is very limited. Regulating Mφs polarization through IncRNAs acting on different targets and pathways can provide new hope for the treatment of many types of cancers. Through the study of these IncRNAs in vivo and in vitro, TAMs can be polarized into pro-inflammatory or anti-inflammatory state, so as to develop new strategies to change the phenotype of Mφs. These cell therapies can be further combined with currently available chemotherapy and radiotherapy options to improve therapeutic effectiveness (113).

LncRNAs Regulate Mφs Polarization in Inflammatory Diseases
In addition to resisting pathogens, Mφs play a key role in eliminating inflammation and repairing damaged tissues. The polarization response of Mφs is essential for immunity and dynamic balance. In the early stage of tissue injury, Mφs are activated to produce a pro-inflammatory effect, thereby
removing cell fragments and pathogens (114). During this phase of transformation, MΦs change their phenotype and play a key role in inflammation regression and tissue repair (115).

Osteoarthritis (OA) is a joint degenerative disease that often occurs in the elderly, and affects joint activity and function. Currently, there is no efficient and standardized treatment. A large number of studies has shown that many inflammatory cells and inflammatory factors, such as IL-6, IL10, TNF-α, are involved in the pathogenesis of OA (116). For example, M1 MΦs secrete pro-inflammatory cytokines. Under the influence of the inflammatory microenvironment, M1 MΦs are activated and secrete high levels of inflammatory mediators, infiltrating synovial tissues and chondrocytes, leading to apoptosis and accelerating the development of OA, which is considered as a key factors regulating the pathogenesis of OA (117). The results of a previous study suggested (58) that osteopontin (OPN) affect M1 polarization. Overexpression of OPN can promote M1 MΦs polarization, produce pro-inflammatory cytokines and degrading enzymes, and act on chondrocytes to exert a cytotoxic effect. Further experiments showed that lncRNA XIST acts on OPN indirectly. It binds to miR-376c-5p competitively through the competing endogenous RNA mechanism, thus weakening the inhibition of miR-376c-5p on OPN, and then affects M1 polarization. In addition, Xist gene knockout affects M1 MΦs and chondrocyte apoptosis. The effect of the lncRNA XIST/miR-376c-5p/OPN axis on M1 MΦs and the inflammatory microenvironment may be a new mechanism of apoptosis in OA chondrocytes. A similar mechanism was found in the lncRNA IGHCyl (90). This lncRNA is mainly located in the cytoplasm of MΦs and competitively binds to miR-6891-3p via the NF-κB signaling pathway, and regulates TLR4 to inhibit MΦs proliferation and inflammation, ultimately affecting OA development.

M1 and M2 polarization play important roles in lung inflammation and injury (118). Targeting MΦs polarization and affecting the inflammatory microenvironment may be useful for treating pneumonia. LncRNA GAS5 plays a key role in cell proliferation, invasion, apoptosis, and MΦs polarization (119). In a study of childhood pneumonia, Chi et al. (53), showed that overexpression of lncRNA GAS5 inhibits JAK2/STAT3 signal transduction, which promotes M1 polarization. The specific mechanism involves the miRNA-mRNA action axis: GAS5 combined with miR-455-5p can promote the expression of SOCS3, and then inhibit the JAK2/STAT3 pathway, thus promoting phenotypic polarization of MΦs from M2 to M1. These findings have potential for the development of therapeutic strategies against pneumonia. The mechanisms by which lncRNAs regulate M1 or M2 polarization in the pneumonia microenvironment are similar; for example, lncRNA p21 and lncRNA NKILA promote M2 polarization through NF-κB signaling pathway (54, 64). Moreover, through the PI3K/AKT pathway, lncRNA Gmi16410 reduces the expression of TNF-α in MΦs, inhibits inflammation, and stimulates polarization of MΦs induced by PM2.5, which participates in the activation of MΦs and process of inflammation (78). In addition, these effects have been described in numerous studies.

MΦs have also been widely reported to be involved in the pathogenesis of cardiovascular inflammatory diseases. Viral myocarditis is a type of heart inflammatory disease caused by viruses, that can lead to heart failure in severe cases. There is increasing evidence that MΦs polarization plays an important role in coxsackievirus B3-induced viral myocarditis. Zhang et al. (67) found that lncRNA AK085865 can increase the susceptibility to viral myocarditis by regulating the MΦs polarization. It specifically binds to interleukin enhancer-binding factor (ILF2) and promotes M2 MΦs polarization by negatively regulating the ILF2-ILF3 complex-mediated miRNA-192 pathway. Overexpression of miRNA-192 can also effectively stimulate the transformation of myocardial infiltrating MΦs to the M2 phenotype. This reveals the key mechanism by which lncRNA AK085865 regulates MΦs polarization and act on myocarditis. LncRNA MEG3 participates in the regulation of M1/M2 MΦs via another pathway (68); it regulates tumor necrosis factor receptor-associated factor 6 (TRAF6) expression by binding to miR-233. Inhibitory MEG3 can downregulate the NF-κB pathway; inhibited the expression of iNOS, TNF-α, and CD86; reduced the expression of M1 MΦs; promoted the expression of Arg-1 and Fizz-1; increased the M2 polarization, and finally reduced cardiomyocyte injury.

In traumatic diseases, lncRNA GBP9 regulates MΦs polarization and reduces the inflammatory response after spinal cord injury through corresponding pathways. Studies have shown that after spinal cord injury, MΦs first differentiate into M1 MΦs under the stimulation of lipopolysaccharide and TNF-α, and TLRs on the cell surface are activated, which induces the recruitment of downstream protein myeloid differentiation factor 88, activates NF-κB, JAK-STAT, and other pathways; and promotes M1 to release TNF-α, CCL8, and other molecules (57, 120).

Moreover, M2 MΦs surface receptors that bind to IL-4 and IL-13 can promote the phosphorylation of STAT6 and stimulate M2 MΦs. M2 MΦs can highly express IL-10, transforming growth factor (TGF)-β and neurotrophic factors, which can inhibit the nerve cell apoptosis and pro-inflammatory effects of M1, as well as promote nerve tissue repair (121). Zhou et al. found (57) that lncRNA GBP9 competitively binds to miR-34a to eliminate the inhibition of suppressor of cytokine signaling-3 (SOCS3), thus regulating STAT1/STAT6 signaling and MΦs polarization. After M1 polarization, M1 showed stronger phagocytosis and antigen presentation ability. In M1 MΦs, lncRNA GBP9 overexpression significantly decreased the expression of p-STAT1, SOCS3, IL-6, and IL-12, whereas in M2 MΦs, the same overexpression increased the concentration of SOCS3 and decreased the production of p-STAT6, IL-10, and TGF-β1, indicating that lncRNA GBP9 overexpression promoted M1 polarization. In contrast, after silencing lncRNA GBP9, the M2 polarization response was enhanced, nerve repair factor was secreted, and spinal cord injury was improved.

**LncRNAs Regulate MΦs Polarization in Infections**

M1 MΦs have a strong cytotoxic effect on infected cells and are resistant to infection. Human immunodeficiency virus (HIV) infection poses a challenge to human health. Studies have shown
that $M\Phi$s polarization is associated with HIV infection and that these cells are immune to virus-induced cell death. $M\Phi$s play an important role in early antiviral immune responses and late restorative responses in the process of HIV infection (122). These $M\Phi$s show good prospects for treating HIV infection by blocking the aggregation of $M\Phi$s at the inflammatory site or changing the $M\Phi$s polarization. Boliar et al.’s data (92) showed that the expression of IncRNA SAF was significantly upregulated in HIV-1-infected $M\Phi$s. Downregulation of SAF can increase the activity of caspase-3/7 in virus-infected $M\Phi$s. This caspase-induced apoptosis occurs only in HIV-1-infected $M\Phi$s, but not in other cells, resulting in a significant reduction of HIV-1 virus in $M\Phi$s. Therefore, targeting of IncRNA SAF is a potential method for inducing the death of $M\Phi$s infected by HIV-1.

**LncRNAs Regulate $M\Phi$s Polarization in Metabolic Diseases**

Recent studies revealed that the mechanism by which lncRNAs regulate $M\Phi$s are important in the development of metabolic diseases, such as diabetes. Diabetes mellitus is related to insulin resistance. It can promote inflammatory responses and induce neurovascular complications through the proliferation, polarization, and dysfunction of $M\Phi$s (123). Das et al. (86) studied the role of IncRNA Dnm3os in diabetes. The results showed that in $M\Phi$s, a decrease in nucleolin and overexpression of $Dnm3os$ changed the modification of intracellular histone, enhanced the promoter H3K9ac, recruited histone acetyltransferase, and targeted upregulated the genes related to inflammation and immune response such as NKx3-2, AP1, STAT, and IRF1, which promoted phagocytosis, whereas knockout of $Dnm3os$ weakened these responses. In addition, nucleolin gene knockout increased the expression of pro-inflammatory factor IL-6 in $M\Phi$s, which is further enhanced by IncRNA $Dnm3os$-regulated $M\Phi$s. Diabetic peripheral neuropathy (DPN) is the main complication of type 2 diabetes mellitus. It has been reported that the expression of $M\Phi$s in patients with DPN is significantly increased and mediates the secretion of inflammatory factors such as IL-1 and IL-6, which promotes the occurrence and development of DPN (4). Further studies (52) showed that in DPN, IncRNA $HCG18$ competitively binds to miR-146a and regulates TNF receptor associated factor 6 (TRAF6) to promote $M\Phi$s polarization and inflammatory factor secretion. MiR-146a can negatively regulate the expression of TRAF6, whereas inhibition of TRAF6 can reverse the promoting effect of $HCG18$ on $M\Phi$s. $HCG18$ stimulates $M\Phi$s activation via the TRAF6/NF-κB pathway. Therefore, IncRNA $HCG18$ can promote the proliferation of $M\Phi$s in DPN and accelerate the development of disease by regulating the miR-146a/TRAF6 axis.

**LncRNAs Regulate $M\Phi$s Polarization in Autoimmune Diseases**

Rheumatoid arthritis (RA) is a common autoimmune disease with a complex pathogenesis, and its incidence is increasing. In RA, TNF-α produced by $M\Phi$s can trigger synovial cells to produce cytokines, leading to the development of arthritis. Infiltrating $M\Phi$s in the joint synovium plays an important role in the pathogenesis of RA, and the degree of infiltration is related to the activity of the disease and degree of joint erosion (124). A study showed (61) that silencing of IncRNA $H19$ altered the expression of lipopolysaccharide in $M\Phi$s from patients with RA, induced $M\Phi$s polarization, and reduced the expression of factors such as IL-6 and CXCL10. However, overexpression of $H19$ showed the opposite effects by promoting $M\Phi$s polarization and aggravating arthritis in mice. In practice, IncRNA $H19$ is highly expressed in patients with RA. Increased expression of KDM6A, promotes $M\Phi$s polarization and aggravates arthritis. Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) characterized by extensive inflammation, demyelination and axonal loss (125, 126). Lesions often occur in the brain and spinal cord. Due to unknown etiology and complex pathophysiological mechanisms, the etiology and pathogenesis of MS have not been fully elucidated (127, 128). Microglia can be divided into M1 and M2 functional subtypes; they play a central role in inflammatory process and neuronal destruction in MS (129). It has been found that M2 polarized microglia can promote neuronal survival, neure growth and oligodendrocyte progenitor cell (OPC) differentiation (130, 131). In epigenetics, IncRNA Gas5 is an epigenetic regulator of microglial polarization. It is highly expressed in microglia of patients with MS and can inhibit M2 polarization of microglia. The specific mechanism is that Gas5 suppresses the transcription of TRF4, a key factor regulating M2 polarization, through recruiting the polycomb repressive complex 2 (PRC2), thus inhibiting M2 polarization. Therefore, this study suggests that IncRNA Gas5 may be a promising target for the treatment of MS (76).

**Conclusion**

$M\Phi$s constantly convert between two extreme polarization states, M1 and M2. $M\Phi$s are involved in the pathogenesis and progression of many diseases. Identifying the key regulators of $M\Phi$s polarization is important for developing treatments for diseases. An increasing number of IncRNAs has been identified in the process of $M\Phi$s polarization. There is a close relationship between IncRNAs and $M\Phi$s, which play an important regulatory role in $M\Phi$s. Their multifunctional capabilities and heterogeneous working mechanisms make them potential targets for treating diseases. In conclusion, IncRNAs exhibit tremendous effects on $M\Phi$s differentiation and polarization. The interaction between IncRNAs and $M\Phi$s is involved in the development of multiple systemic diseases and provides useful targets for the interference of macrophage involved disorders.

However, compared with the study of small molecule RNA, IncRNAs are still in the initial stage, and their function and regulation mechanism still need to be further clarified. In order to fully realize the therapeutic value of IncRNAs and the development of corresponding therapeutic drugs, there are still some difficulties to be overcome. First of all, we need to improve the method of transporting IncRNAs to specific areas. Because of
the long length of IncRNA, it is difficult to deliver full-length IncRNAs, so we need an accurate and efficient means of transport to ensure the stability of IncRNAs. Secondly, we need to establish a complete, detailed and specific IncRNAs database to record the specific regulatory cell types and target genes of each IncRNA. Finally, we need to solve the difficulty of finding homologous IncRNA. Especially in animal experiments, due to the epigenetic differences between animals and humans, the human IncRNAs may not exist in animals. This requires techniques such as gene knockout to build animal models, which makes the experiment more difficult. In recent years, with the deepening of research, the experimental techniques related to IncRNAs have been continuously developed, an increasing number of IncRNAs have been found, and play an important role in the occurrence and development of various diseases, and can be used as genes related to diagnosis and treatment. In particular, there is an increasing number of studies on IncRNAs regulating M2 polarization and participating in the development of various diseases, which provides a new research content for future research. On the basis of fully understanding the mechanism of action, appropriate genetic engineering drugs are developed to achieve the purpose of prevention, diagnosis and treatment.

**AUTHOR CONTRIBUTIONS**

PJ wrote the manuscript. XL conceived the study. All authors have reviewed and approved the final version of the manuscript.

**ACKNOWLEDGMENTS**

We would like to thank Editage (www.editage.cn) for English language editing.

**REFERENCES**

1. Dong R, Zhang B, Tan B, Lin N. Long non-coding RNAs as the Regulators and Targets of Macrophage M2 Polarization. Life Sci (2021) 266:118895. doi: 10.1016/j.lfs.2021.118895
2. Funes SC, Rios M, Escobar-Vera J, Kalergis AM. Implications of Macrophage Polarization in Autoimmunity. *Immunology* (2018) 154:186–95. doi: 10.1111/imm.12910
3. Murray PJ. Macrophage Polarization. *Annu Rev Physiol* (2017) 79:541–66. doi: 10.1146/annurev-physiol-022516-034339
4. Sharpour-Moghadam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili S-A, Mardani F, et al. Macrophage Plasticity, Polarization, and Function in Health and Disease. *J Cell Physiol* (2018) 233:45–42. doi: 10.1002/jcp.26249
5. Atri C, Guerfali F, Laouini D. Role of Human Macrophage Polarization in Inflammation During Infectious Diseases. *Int J Mol Sci* (2019) 18:1801. doi: 10.3390/ijms19061801
6. Chinetti-Gbaguidi G, Colin S, Staels B. Macrophage Subsets in Atherosclerosis. *Nat Rev Cardiol* (2015) 12:10–7. doi: 10.1038/nrcardio.2014.173
7. Chen L-L. Linking Long Noncoding RNA Localization and Function. *Trends Biochem Sci* (2016) 41:761–72. doi: 10.1016/j.tibs.2016.07.003
8. Statello L, Guo C-J, Chen L-L, Huarte M. Gene Regulation by Long Non-coding RNAs and its Biological Functions. *Nat Rev Mol Cell Biol* (2021) 22:96–118. doi: 10.1038/s41580-020-00315-9
9. Zhou X, Xie D, Huang J, Lu A, Wang R, Jin Y, et al. Therapeutic Effects of (5R)-5-Hydroxytriptolide on Fibroblast-Like Synoviocytes in Rheumatoid Arthritis via IncRNA WAKMAR2/miR-4478/E2F1/p53 Axis. *Front Immunol* (2021) 12:605166. doi: 10.3389/fimmu.2021.605166
10. Sica A, Mantovani A. Macrophage Plasticity and Polarization: In Vivo Veritas. *J Clin Invest* (2012) 122:87–95. doi: 10.1172/JCI59643
11. Mohapatra S, Pappini C, Oporlat B, Calin GA. Non-Coding RNAs Regulation of Macrophage Polarization in Cancer. *Mol Cancer* (2021) 20:24. doi: 10.1186/s12934-021-01313-x
12. Xie C, Guo Y, Lou S. LncRNA ANCR Promotes Invasion and Migration of Gastric Cancer by Regulating FoxO1 Expression to Inhibit Macrophage M1 Polarization. *Dig Dis Sci* (2020) 65:2863–72. doi: 10.1007/s10620-019-01609-1
13. Liu J, Ding D, Jiang Z, Du T, Liu J, Kong Z. Long non-coding RNA CCAT1/miR-148a/PcK5 Prevents Cell Migration of Prostate Cancer by Altering Macrophage Polarization. *Prostate* (2019) 79:105–12. doi: 10.1002/pros.23716
14. Ahmad I, Valverde A, Naqvi RA, Naqvi AR. Long Non-Coding RNAs RN7SK and GAS5 Regulate Macrophage Polarization and Innate Immune Responses. *Front Immunol* (2020) 11:40981. doi: 10.3389/fimmu.2020.604981
15. Chen C, He W, Huang J, Wang B, Li H, Cai Q, et al. LNMAT1 Promotes Lympathic Metastasis of Bladder Cancer via CCL2 Dependent Macrophage Recruitment. *Nat Commun* (2019) 9:3826. doi: 10.1038/s41467-018-01652-x
16. Zhou L, Tian Y, Guo F, Yu B, Li J, Xu H, et al. LncRNA-P21 Knockdown Reverses Tumor-Associated Macrophages Function by Promoting MD2 to Antagonize* P53* Activation and Alleviate Breast Cancer Development. *Cancer Immunol Immunother* (2020) 69:835–46. doi: 10.1007/s00262-020-02511-0
17. Liu S-Q, Zhou Z-Y, Dong X, Guo L, Zhang K-J. LncRNA GNAT1-AS1 Facilitates ER+ Breast Cancer Cells Progression by Promoting M2 Macrophage Polarization via Regulating miR-433-3p/GATA3 Axis. *BioSci Rep* (2020) 40:BSR20200626. doi: 10.1042/BSR20200626
18. Liang Y, Song X, Li Y, Chen B, Zhao W, Wang L, et al. LncRNA BCRT1 Promotes Breast Cancer Progression by Targeting miR-1303/PTBP1 Axis. *Mol Cancer* (2020) 19:85. doi: 10.1186/s12943-020-01206-5
19. Zong S, Dai W, Guo X, Wang K. LncRNA-SNHG1 Promotes Macrophage M2-Like Polarization and Contributes to Breast Cancer Growth and Metastasis. *Aging* (2021) 13:23169–81. doi: 10.18632/aging.203609
20. Xing Z, Zhang M, Liu J, Liu G, Feng K, Wang X. LINCO0037 Induces Tumor Development and Chemoresistance to Paclitaxel of Breast Cancer by Recruiting M2 Tumor-Associated Macrophages. *Mol Immunol* (2021) 138:1–9. doi: 10.1016/j.molimm.2021.07.009
21. Tao S, Chen Q, Lin C, Dong H. Linc00514 Promotes Breast Cancer Metastasis and M2 Polarization of Tumor-Associated Macrophages via Jagged1-Mediated Notch Signaling Pathway. *J Exp Clin Cancer Res* (2020) 39:191. doi: 10.1186/s13046-020-01676-x
22. Wang X, Li F, Zhao W, Gao Z, Shen B, Xu H, et al. Long Non-coding RNA GAS5 Overexpression Inhibits M2-Like Polarization of Tumour-Associated Macrophages in SMCC-7721 Cells by Promoting PTEN Expression. *Int J Exp Pathol* (2020) 101:215–22. doi: 10.1111/iep.12374
23. Zhou J, Che J, Xu L, Yang W, Zhou W, Zhou C. Tumor-Derived Extracellular Vesicles Containing Long Noncoding RNA PART1 Exert Oncogenic Effect in Hepatocellular Carcinoma by Polarizing Macrophages Into M2. *Dig Liver Dis* (2021) S1590-8658(21)00374-1. doi: 10.1016/j.dld.2021.07.005
24. Wang L, Lin J, Ma X, Xu D, Shi C, Wang W, et al. Exosomal DLX6-AS1 From Hepatocellular Carcinoma Cells Induces M2 Macrophage Polarization to Promote Migration and Invasion in Hepatocellular Carcinoma through microRNA-15a-5p/CXCL17 Axis. *J Exp Clin Cancer Res* (2021) 40:177. doi: 10.1186/s13046-021-01973-z
25. Chen J, Huang Z-B, Liao C-J, Hu X-W, Li S-L, Qi M, et al. LncRNA TP73-AS1/miR-539/MMP-8 Axis Modulates M2 Macrophage Polarization in Hepatocellular Carcinoma via TGF-B1 Signaling. *Cell Signal* (2020) 75:109738. doi: 10.1016/j.cellsig.2020.109738
61. Zuo X, Zhu Y, Ding C, Zhang W, Guan H, Li C, et al. LncRNA H19 Regulates Macrophage Polarization and Promotes Freund's Complete Adjuvant-Induced Arthritis by Upregulating KDM6A. *Int Immunopharmacol* (2021) 93:107402. doi: 10.1016/j.intimp.2021.107402

62. Luo Y-Y, Yang Z-Q, Lin X-F, Zhao F-L, Tu H-T, Wang L-I, et al. Knockdown of IncRNA PVT1 Attenuated Macrophage M1 Polarization and Relieved Septis Induced Myocardial Injury via miR-29a/HMGBl Axis. *Cytokine* (2021) 143:155509. doi: 10.1016/j.cyt.2021.155509

63. Han X, Huang S, Xue P, Fu J, Liu L, Zhang C, et al. LncRNA PTTPRE-AS1 Modulates Macrophage Activation and Infectious Diseases by Epigenetic Promotion of PTTPRE. *Sci Adv* (2019) 5eaax9230. doi: 10.1126/sciadv.aaa9230

64. Li Q, Lu L, Li X, Lu S. Long non-coding RNA NKL1 Alleviates Airway Inflammation in Asthmatic Mice by Promoting M2 Macrophage Polarization and Inhibiting the NF-kb Pathway. *Biochem Biophys Res Commun* (2021) 571:46–52. doi: 10.1016/j.bbrc.2021.07.023

65. Xia I, Wang X, Liu L, Fu J, Xiao W, Liang Q, et al. Lnc-BAZZ2B Promotes M2 Macrophage Activation and Inflammation in Children With Asthma Through Stabilizing BAZZ2B pre-mRNA. *J Allergy Clin Immunol* (2014) 124:911–922.e9. doi: 10.1016/j.jaci.2014.06.034

66. Pei W, Zhang Y, Li X, Luo M, Chen T, Zhang M, et al. LncRNA AK085865 Depletion Ameliorates Asthmatic Airway Inflammation by Modulating Macrophage Polarization. *Int Immunopharmacol* (2020) 83:106450. doi: 10.1016/j.intimp.2020.106450

67. Zhang Y, Li X, Wang C, Zhang M, Yang H, Lv K. IncRNA AK085865 Promotes Macrophage M2 Polarization in CVB3-Induced VM by Regulating IL2F-ILF Complex-Mediated miRNA-192Biosign. *Mol Ther Nucleic Acids* (2020) 21:441–51. doi: 10.1016/j.mtna.2020.06.017

68. Xue Y, Zhang S, Zheng C, Li Y, Zhang L, Su Q, et al. Long non-coding RNA ME3G3 Inhibits M2 Macrophage Polarization by Activating TRAF6 via microRNA-223 Down-Regulation in Viral Myocarditis. *J Cell Mol Med* (2020) 24:1234–54. doi: 10.1111/cmm.15720

69. Wang B, Li X, Hu W, Zhou Y, Yin D. Silencing of IncRNA SNHG20 Delays the Progression of Nonalcoholic Fatty Liver Disease to Hepatocellular Carcinoma via Regulating Liver Kupffer Cells Polarization. *IUBMB Life* (2019) 71:1952–61. doi: 10.1007/s12231-019-1237-y

70. Wang W, Guo Z-H. Downregulation of IncRNA NEAT1 Ameliorates LPS-Induced Inflammatory Responses by Promoting Macrophage M2 Polarization via miR-152-5p/TRAF6/TAK1 Axis. *Inflammation* (2020) 43:1548–60. doi: 10.1007/s10753-020-02131-y

71. Chen J, Zhou R, Liang Y, Fu X, Wang D, Wang C. Blockade of IncRNA-ASNCNsS088-long and Exosome Generation in M2 Macrophages by GW4869 Dampens the Effect of M2 Macrophages on Orchestrating Lipid Metabolism. *Macli2* (2019) 33:20190165. doi: 10.1016/j.maci.2020.08.008

72. Liu D, Wei Y, Liu Y, Wu T, Hu J, Liu H. The Long Non-Coding RNA NEAT1-miR-224-5p/IL-33 Axis Modulates Macrophage M2 Polarization and A1 Astrocyte Activation. *Mol Neurobiol* (2021) 58:4506–19. doi: 10.1007/s12035-021-02405-x

73. Ma W, Zhang W, Cui B, Gao J, Liu Q, Yao M, et al. Functional Delivery of IncRNA TUG1 by Endothelial Progenitor Cells Derived Extracellular Vesicles Confers Anti-Inflammatory Macrophage Polarization in Sepsis via Impairing miR-9-5p-Targeted SIRT1 Inhibition. *Cell Death Dis* (2019) 10:12036. doi: 10.1038/s41419-021-04177-5

74. Zhang P, Lu B, Zhang Q, Xu F, Zhang R, Wang C, et al. LncRNA NEAT1 Sponges MRNA-148a-3p to Suppress Choroidal Neovascularization and M2 Macrophage Polarization. *Mol Immunol* (2020) 127:212–22. doi: 10.1016/j.molimm.2020.08.008

75. Han Y-B, Tian M, Wang X-X, Fan D-H, Li W-Z, Wu F, et al. Berberine Ameliorates Obesity-Induced Chronic Inflammation Through Suppression of ER Stress and Promotion of Macrophage M2 Polarization at Least Partly via Downregulating IncRNA Gomafu. *Int Immunopharmacol* (2020) 86:106741. doi: 10.1016/j.intimp.2020.106741

76. Sun D, Yu Z, Fang X, Liu M, Pu Y, Shao Q, et al. Lnc RNA GAS 5 Inhibits Microglial M2 Polarization and Exacerbates Demyelination. *EMBO Rep* (2017) 18:1801–6. doi: 10.15252/embr.201643600

77. Li N, Liu Y, Cai J. LncRNA MIR155HG Regulates M1/M2 Macrophage Polarization in Chronic Obstructive Pulmonary Disease. *BioMed Pharmacother* (2019) 117:109015. doi: 10.1016/j.biopha.2019.109015
96. Sica A, Larghi P, Mancino A, Rubino L, Porta C, Totaro MG, et al. Macrophage Polarization in Tumour Progression. *Semin Cancer Biol* (2008) 18:349–55. doi: 10.1016/j.semcancer.2008.03.004

98. Hou L, Heilbronner U, Degenhardt F, Adli M, Akiyama K, Akula N, et al. Noncoding RNAs Regulate Polarization of Macrophages. *Nature Rev Cancer* (2017) 17:339–49. doi: 10.1038/nrc.2017.170

101. Previdi MC, Carotenuto P, Zito D, Pandolfo R, Braconi C. Noncoding RNAs Contribute to Macrophage Polarization and Promotes Lung Inflammation and Injury by Activating the JNK Pathway. *J Immunol* (2015) 194:1239–51. doi: 10.4049/jimmunol.1402088

105. Oishi Y, Manabe I. Macrophages in Age-Related Chronic Inflammatory Diseases. *NPI Aging Mech Dis* (2016) 2:16018. doi: 10.1038/njnm.2016.18

109. Westendorf JI, Carayon P, LaFrentz D, Redick RJ, Allen B, Datta S, et al. M2/M1 Macrophage Polarity and Response to Inflammation. *Semin Immunol* (2012) 24:1004. doi: 10.1016/j.smim.2012.12.015

113. Pirlog R, Cismaru A, Nutu A, Berindan-Neagoe I. Field Cancerization in NSCLC: A New Perspective on MicroRNAs in Macrophage Polarization. *Int J Mol Sci* (2017) 18:1037. doi: 10.3390/ijms18051037

118. Ying H, Kang Y, Zhang H, Zhao D, Xia J, Lu Z, et al. MiR-127 Modulates Macrophage Polarization and Promotes Lung Inflammation and Injury by Activating the JNK Pathway. *J Immunol* (2015) 194:1239–51. doi: 10.4049/jimmunol.1402088

120. Arranz A, Doxaki C, Vergadi E, Martinez de la Torre Y, Vapordi K, Lagoudaki ED, et al. Akt1 and Akt2 Protein Kinases Differentially Contribute to Macrophage Polarization. *Proc Natl Acad Sci* (2012) 109:9517–22. doi: 10.1073/pnas.1119038109

122. Burdo TH, Walker J, Williams KC. Macrophage Polarization in AIDs: Dynamic Interface Between Anti-Viral and Anti-Inflammatory Macrophages During Acute and Chronic Infection. *J Clin Cell Immunol* (2015) 6:633.

123. Li S, Reddy MA, Cai Q, Meng L, Yuan H, Lanting L, et al. Enhanced Proinflammatory Responses in Macrophages and Vascular Smooth Muscle Cells Derived From Diabetic Db/Dk Mice. *Diabetes* (2006) 55:2611–9. doi: 10.2337/db06-0164

126. Miron VE, Boyd A, Zhao J-W, Yuen TJ, Ruckh JM, Shadrach JL, et al. M2 Macrophages in Tumour Microenvironments and the Progression of Tumors. *Future Oncol* (2012) 2012:1. doi: 10.2217/fon.12.1

129. Gordon S. Alternative Activation of Macrophages. *Immunity* (2006) 24:1004. doi: 10.1016/j.immuni.2006.03.004

131. Gordon S. Alternative Activation of Macrophages. *Nature Rev Immunol* (2003) 3:23–35. doi: 10.1038/nri878

135. Miron VE, Boyd A, Zhao J-W, Yuen TJ, Ruckh JM, Shadrach JL, et al. M2 Macrophages Drive Oligodendrocyte Differentiation During CNS Remyelination. *Nat Neurosci* (2013) 16:1211–8. doi: 10.1038/nn.3469

136. Griffin TM, Scanzello CR. Inflammatory Immune and Synovial Macrophages in Osteoarthritis Pathophysiology. *Clin Exp Rheumatol* (2019) 37 Suppl 12657–63.

140. Gagné, L., Warren P., Wroma EA, Fisher MR, Freytes D.O. Macrophages’ Role in Tissue Disease and Regeneration. In: M Kloc, editor. *Macrophages. Results and Problems in Cell Differentiation*. Cham: Springer International Publishing (2017). p. 245–71. doi: 10.1007/978-3-319-54900-0_10

145. Neumann, F.M., Haemig S., Feinberg MW. *LncRNAs in Vascular Biology and Disease. Vascular Pharmacol* (2019) 114:145–56. doi: 10.1016/j.vph.2018.01.003

149. Cayla, S., Giffard R.G., Yanari MA. Endotoxin-Activated Microglia Injure Brain Derived Endothelial Cells via NF-xb, JAK-STAT and JNK Stress Kinase Pathways. *J Inflamm* (2011) 8:7. doi: 10.1186/1477-9255-8:7

153. Boon RA, Jaë N, Holdt L, Dimmerle S. Long Noncoding RNAs. *J Am Coll Cardiol* (2016) 67:1214–26. doi: 10.1016/j.jacc.2015.12.051

157. Fattahi S, Kosari-Monfare M, Golpour M, Emami Z, Ghasemiyan M, Nouri M, et al. LncRNAs Are Potential Diagnostic and Prognostic Biomarkers in Ovarian Cancer: A Novel Approach to Personalized Medicine. *J Cell Physiol* (2020) 235:3189–206. doi: 10.1002/jcp.29260

161. Litwin MS, Tan H-J. The Diagnosis and Treatment of Prostate Cancer. *A Review.* *JAMA* (2017) 317:2532. doi: 10.1001/jama.2017.7248

165. Tedesco S, Bolego C, Toniolo A, Nasi A, Fadini GP, Locati M, et al. Phenotypic Activation and Pharmacological Outcomes of Spontaneously Differentiated Human Monocyte-Derived Macrophages. *Immunobiology* (2015) 220:545–54. doi: 10.1007/s00438-014-1208-8

169. Liu M-L, Zhang Q, Yuan X, Jin L, Wang L-L, Fang T-T, et al. Long Noncoding RNA RP4 Functions as a Competing Endogenous RNA Through miR-7-5p Sponge Activity in Colorectal Cancer. *World J Gastroenterol* (2018) 24:1004–12. doi: 10.3748/wjg.v24.i9.1004

173. Pirlog R, Cisarau A, Nutu A, Berindan-Neagoe I. Field Cancerization in NSCLC: A New Perspective on MicroRNAs in Macrophage Polarization. *Int J Mol Sci* (2021) 22:476. doi: 10.3390/ijms22020476

177. Oishi Y, Manabe I. Macrophages in Inflammation, Repair and Regeneration. *Int Immunol* (2018) 30(11):511–28. doi: 10.1093/intimm/dzy054

181. Oishi Y, Manabe I. Macrophages in Age-Related Chronic Inflammatory Diseases. *NPI Aging Mech Dis* (2016) 2:16018. doi: 10.1038/njnm.2016.18

185. Neumann, F.M., Haemig S., Feinberg MW. *LncRNAs in Vascular Biology and Disease. Vascular Pharmacol* (2019) 114:145–56. doi: 10.1016/j.vph.2018.01.003

191. Masoumi, F., Ghorbani S., Talebi F., Branton WG., Rajai S., Power C., et al. Malati Long Noncoding RNA regulates inflammation and leukocyte differentiation in experimental autoimmune encephalomyelitis. *J Neuroimmun* (2019) 328:50–9. doi: 10.1016/j.jneuroim.2018.11.013

195. Hlavova Y, Popova R, Skrabanek P. Macrophage Polarization in Tumour Progression. *Int J Mol Sci* (2019) 20:15578. doi: 10.3390/ijms201515578

199. Westendorf JI, Carayon P, LaFrentz D, Redick RJ, Allen B, Datta S, et al. M2 Macrophages Drive Oligodendrocyte Differentiation During CNS Remyelination. *Nat Neurosci* (2013) 16:1211–8. doi: 10.1038/nn.3469

203. Franco R., Fernández-Suárez D. Alternatifly Activated Microglia and Macrophages in the Central Nervous System. *Prog Neurobiol* (2015) 131:65–86. doi: 10.1016/j.pneurobiol.2015.05.003

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Jiang and Li. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.