Non-Coding RNAs in the Crosstalk between Breast Cancer Cells and Tumor-Associated Macrophages

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Abstract: Non-coding RNAs (ncRNAs) play a pivotal role in regulating the tumor microenvironment (TME) by controlling gene expression at multiple levels. In tumors, ncRNAs can mediate the crosstalk between cancer cells and other cells in the TME, such as immune cells, stromal cells, and endothelial cells, influencing tumor development and progression. Tumor-associated macrophages (TAMs) are among the most abundant inflammatory cells infiltrating solid cancers that promote tumorigenesis, and their infiltration correlates with a poor prognosis in many tumors. Cancer cells produce different ncRNAs that orchestrate TAM recruitment and polarization toward a tumor-promoting phenotype. Tumor-reprogrammed macrophages shape the TME by promoting angiogenesis and tissue remodeling, and suppressing the anti-tumor activity of adaptive immune cells. TAMs can also produce ncRNA molecules that boost cancer cell proliferation and direct their phenotype and metabolic changes facilitating cancer progression and metastasis. This review will focus on the crosstalk between cancer cells and TAMs mediated by microRNAs and long non-coding RNAs during breast cancer (BC) initiation and progression.

Keywords: tumor-associated macrophages; microRNA; long non-coding RNA; breast cancer

1. Introduction

The communication of cancer cells with the surrounding environment is crucial for tumor development and progression. Cancer cells direct the formation of a TME that sustains their nutrient demand by spreading through the blood to other organs, and the escape from immune surveillance [1–3]. The TME includes cancer cells, blood vessels, immune cells, and stromal cells with the adjacent extracellular matrix (ECM) [3,4]. TAMs represent one of the primary infiltrating myeloid cells that are part of the TME, and their presence correlates with tumor aggressiveness and bad prognosis in breast cancer and other tumors [5].

TAMs partly originate from tissue-resident macrophages, but they mostly derive from circulating monocytic precursors recruited to the tumor site by chemotactic signals released by cancer cells [6]. These chemotactic signals include cytokines such as CSF-1, and chemokines such as CCL-2 and CCL-5, which recruit inflammatory monocytes and direct TAM differentiation [6,7]. Although TAMs can support or inhibit cancer progression depending on their activation state and polarization, many studies have shown that they mostly polarize toward a tumor-promoting phenotype [6,7]. Macrophages can differentiate into the pro-inflammatory M1 phenotype or the anti-inflammatory M2 phenotype [8]. Classical M1 macrophages are driven by IFNγ and bacteria during TH1 (type I helper) responses against pathogens, and produce inflammatory cytokines and tissue-damaging factors [9]. M1-like macrophages exert an anti-tumor activity during tumor onset by distinguishing and killing malignant cells. However, in established tumors, cancer
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2. Role of Non-Coding RNAs in TAM Recruitment and Polarization in Breast Cancer

Non-coding RNAs produced by cancer cells may regulate monocyte recruitment to the tumor site and direct their differentiation into M1 or M2 macrophages by influencing the expression of pro-or anti-inflammatory genes in macrophages [30,31].

Monocyte recruitment is guided by chemotactic signals released by cancer cells. One of the most potent factors involved in this process is CCL2, upregulated in many cancers.
Recently, Frank et al. found that miR-375 induces CCL2 expression in breast cancer cells [34]. MiR-375 is released by apoptotic BC cells and stimulates the production of CCL2 in other cancer cells by unknown mechanisms. Furthermore, miR-375 binds to the macrophage CD36 receptor and is transferred to TAMs, where it directly binds and downregulates TNS3 and PXN, two migration-inhibitory proteins, increasing the macrophage’s ability to infiltrate the tumor, resulting in cancer progression [34]. CCL2 mediates macrophage recruitment also at metastatic sites [35]. LncRNA associated with breast cancer brain metastases (Inc-BM) is significantly upregulated in brain metastasis and influences TAM recruitment by inducing the production of CCL2 via JAK2/STAT3 pathway activation in cancer cells [36]. The cytokine colony-stimulating factor-1 (CSF1) stimulates macrophage recruitment and survival, and its expression is prognostic for mortality in breast cancer [37,38]. Mir-149 directly targets and inhibits CSF1 mRNA in breast cancer cells, limiting macrophage recruitment to the primary tumor. The reduced TAM infiltration has also been associated with decreased lung metastasis formation in a mouse model with orthotopically injected MDA-MB-231 cells [39]. Once in the tumor site, monocytes rapidly differentiate and are polarized into M1 or M2-like macrophages, depending on the stimuli from the TME [6,7]. MiR-149 suppresses the expression of two M2 markers in macrophages, the mannose receptor C-type 1 (MRc1) and arginase-1 (ARG1). Although the authors did not investigate the mechanism, miR-149 possibly acts in a paracrine manner by regulating the production of soluble factors secreted by BC cells that influence macrophage polarization [39].

The miR-200 tumor suppressor family are well-known negative regulators of Epithelial-mesenchymal transition (EMT), and their expression is downregulated in many aggressive cancers, including breast cancer [40]. Williams et al. reported that the restoration of miR-200c expression in BC cells stimulates GM-CSF secretion, which induces M1-macrophage polarization as demonstrated by the upregulation of the M1 marker Nos2 and the downregulation of the M2 marker Arg1 [41]. Indeed, GM-CSF is an important regulator of the pro-inflammatory M1 phenotype [42]. On the contrary, other studies have shown that miR-200 expression is associated with poor prognosis in breast cancer patients [43,44]. Accordingly, Meng et al. reported that miR-200c upregulates PAI-2 expression in BC cells and promotes the secretion of the anti-inflammatory cytokine IL-10, which directly stimulates M2-like polarization [45].

Several cell types present in the TME, such as cancer cells, fibroblasts, and immune cells, produce a high level of IL-6 cytokine, which correlates with low survival rates in breast cancer [46]. IL-6 produced by breast cancer cells can induce M2-macrophage polarization by leading to the inhibition of miR-19a-3p expression in TAMs. Mechanistically, the downregulation of miR-19a-3p releases its inhibitory activity on the Fra1 gene, activating the downstream STAT3 pathway which drives M2-polarization [47]. Wang et al. reported that miR-100 is highly expressed in TAMs from breast cancer and in the surrounding cancer tissue. High expression of miR-100 in TAMs favors M2 TAM polarization by inhibiting the mTOR pathway and leading to the upregulation of the M2 marker CD206 [48].

Tao et al. showed that the expression of the lncRNA linc00514 in breast cancer tissues correlates with tumor aggressiveness and controls TAM polarization via Notch signaling activation [49]. In BC cells, linc00514 induces a STAT3-mediated increase in Jagged1, promoting the secretion of the anti-inflammatory cytokines IL-4 and IL-6, which facilitate M2 polarization by increasing the expression of the M2 markers CD206 and CD163 in TAMs [49].

Xist is a tumor-suppressor and poorly expresses lncRNA in BC cells [50]. Recently, Zhao et al. showed that Xist is also expressed in macrophages, and it participates in M1-phenotype maintenance. Xist functions as a sponge for miR-101, which inhibits the expression of C/EBPα and KLF6, two regulators of M1 macrophage polarization. The knockdown of Xist in M1 macrophages promotes the switch to the M2 phenotype, as demonstrated by the upregulation of the M2 marker CD206, confirming its tumor-suppressor
role not only in BC cells but also in TAMs [51]. Several studies have reported the oncogenic function of miR-181 in breast cancer [52]. MiR-181 can be released into BC cell-derived exosomes, and promotes the generation of an immunosuppressive environment by enhancing the infiltration of myeloid-derived suppressor cells, which play a crucial role in cancer immune escape [53]. In TAMs, miR-181a suppresses the expression of C/EBPβ and KLF6, promoting M2-polarization and increasing TAM pro-tumoral behavior [54].

The lncRNA GNAS-AS1 is upregulated in ER+ breast cancer tissues and TAMs from BC tissues. The overexpression of GNAS-AS1 facilitates M2 macrophage polarization in vitro by directly sponging miR-433-3p, a negative regulator of GATA3, which induces M2-macrophage polarization and promotes anti-inflammatory activity [55]. GATA3 is also targeted and inhibited by miR-720, an anti-oncogenic miRNA downregulated in TAMs from metastatic breast cancer patients. The restoration of miR-720 expression in M2-macrophages drastically reduces the production of anti-inflammatory cytokines and the ability of macrophages to stimulate BC cell migration [56].

NcRNAs have also been studied as drugs to re-educate TAMs in vivo [57]. Huang et al. constructed a nanoparticle loaded with miRNA mimic let-7b, which can bind to the TLR7 on TAM membrane. In vitro, let-7b acts as an agonist of TLR7 and inhibits the secretion of IL-10, a potent immunosuppressive cytokine that induces M2-like polarization. Once delivered in vivo in a mouse model of breast cancer, the let-7b-complex is released in the tumor acidic microenvironment and limits tumor growth by reversing M2-like TAM phenotypes. Moreover, let-7b can also activate the TAM-induced Th1 response in the treated mice, restoring the anti-tumor immune response [58]. Figure 1 and Table 1 and Table 2 recapitulate the role of miRNAs and lncRNAs in TAM recruitment and polarization in breast cancer.

Figure 1. miRNAs and lncRNAs involved in TAM recruitment and polarization in breast cancer. The expression of miRNAs and lncRNAs in BC cells influences TAM recruitment by regulating the secretion of cytokines and chemokines in the TME. MiR-149 inhibits monocyte recruitment, whereas miR-375 and Inc-BM promote monocyte recruitment. Once in the tumor site, monocytes can differentiate into anti-tumoral (M1-like) or pro-tumoral (M2-like) macrophages. The expression of miR-200c, miR-100, miR-101, IncRNA-Xist, miR-720 and lncRNA Xist, miR-181 and lncRNA GNAS-AS1 in BC cells or TAMs promotes the differentiation into the M2-like phenotype. Conversely, the expression of miR-149, miR-200c, miR-19a-3p, IncRNA Xist, miR-720, and miR-let-7b in BC cells or TAMs promotes the differentiation into the M1-like phenotype.
**Table 1. miRNAs involved in BC cells-TAM crosstalk during BC progression.**

| microRNA | Expression | Regulated Pathways                                      | Biological Function                                                                 | Reference |
|----------|------------|---------------------------------------------------------|-------------------------------------------------------------------------------------|-----------|
| miR-375  | Transferred from apoptotic BC cells to TAMs            | Induces CCL2 secretion in BC cells and TNS3 and PXN downregulation in TAMs          | Promotes TAM migration and recruitment                                              | [34]      |
| miR-149  | Brain metastatic BC cells                              | Directly targets and inhibits CSF1                                                  | Limits TAM recruitment and lung metastasis; promotes M1 polarization                | [39]      |
| miR-200c | BC cells                                             | Induces GM-CSF secretion                                                            | Induces M1 polarization                                                             | [41]      |
| miR-200c | BC cells                                             | Induces nPAI-2-mediated IL-10 secretion                                              | Induces M2 polarization                                                             | [45]      |
| miR-19a-3p| TAMs                                                 | Inhibits Frl1/STAT3 pathway                                                           | Inhibits M2 polarization                                                             | [47]      |
| miR-100  | TAMs                                                 | Inhibits mTOR and induces STAT5-mediated IL1-ra secretion and metastasis and chemoresistance | Induces M2 polarization, lung metastasis and chemoresistance                      | [48]      |
| miR-181a | TAMs                                                 | Inhibits C/EBPα and KLF6 expression                                                  | Induces M2 polarization                                                             | [54]      |
| miR-720  | TAMs                                                 | Directly targets and inhibits GATA3                                                  | Inhibits M2 polarization                                                             | [56]      |
| Let-7b   | Ectopically administered                              | Acts as an agonist of TLR7 in TAMs and inhibits IL-10 secretion                      | Inhibits M2 polarization                                                             | [58]      |
| miR-375  | Transferred from BC cells to TAMs                     | Inhibits LDHB expression and induces SREBP2 activation                              | Induces aerobic glycolysis and lactate production                                   | [59]      |
| miR-503-3p| Transferred from TAMs cells to BC cells               | Activates Wnt/β-catenin pathway by directly targeting DACT2                         | Induces glycolysis and inhibits OXPHOS                                              | [60]      |
| miR-33   | Ectopically administered                              | Stimulates M1-related cytokine production                                           | Inhibits M1 polarization. induces glycolysis and inhibits FAO                       | [61]      |
| miR-29b  | TAMs                                                 | Inhibits STAT3 pathway                                                               | Inhibits M2 polarization                                                             | [62]      |
| miR-122  | BC cells                                             | PK downregulation                                                                    | Increases glucose availability in the pre-metastatic niche for cancer cells          | [63]      |
| miR-107  | TAMs                                                 | Inhibits HIF1 and GRN expression                                                    | Inhibits TAM pro-angiogenic functions                                               | [64]      |
| miR-15b  | TAMs                                                 | Inhibits VEGF secretion by downregulating Akt3                                      | Inhibits angiogenesis                                                               | [65]      |
| miR-29b  | BC cells                                             | Inhibits VEGF secretion by downregulating Akt3                                      | Inhibits angiogenesis                                                               | [66]      |
| miR-155  | BC cells/TAMs                                        | Directly targets and inhibits VHL                                                    | Induces angiogenesis                                                               | [67]      |
| miR-21   | TAMs                                                 | Inhibits Pdcd4, Spry1, Timp3, Col4a2, and Sparc expression                          | Induces TAM pro-angiogenic reprogramming                                            | [68]      |
| miR-29a  | TAMs                                                 | Directly targets and inhibits PPP2CA inducing NFkB activation                      | Promotes the formation of a pro-inflammatory TME and induces lung metastasis        | [69]      |
| miR-183-5p| Transferred from BC cells to TAMs                    | Inhibits KDM6B histone demethylase                                                   | Induces M2 polarization and promotes lung metastasis                                |           |
Table 2. IncRNAs involved in BC cells-TAM crosstalk during BC progression.

| IncRNA   | Expression          | Regulated Pathways                           | Biological Function                                      | References |
|----------|---------------------|-----------------------------------------------|----------------------------------------------------------|------------|
| Inc-BM   | Brain metastatic BC cells | Upregulates JAK2/STAT3 pathway                | Promotes TAM recruitment and brain metastasis formation    | [36]       |
| linc-00514 | BC cells          | Induces STAT3-mediated Jagged1 up-regulation | Promotes M2 polarization                                  | [49]       |
| Inc-Xist | TAMs               | Sponges miR-101 and induces C/EBPα and KLF6 expression | Promotes M1 polarization                                  | [51]       |
| Inc-GNAS-AS1 | BC cells/TAMs    | Sponges miR-433-3p and induces GATA3 expression | Promotes M2 polarization                                  | [55]       |
| Inc-Hisla | Transferred from TAMs to BC cells | Upregulates HIF1α expression by inhibiting PHD2 | Induces aerobic glycolysis                                | [77]       |
| Inc-PCAT6 | BC cells          | Inhibits VEGFR2 degradation                   | Induces angiogenesis                                      | [78]       |
| Inc-IRENA | TAMs              | Induces PKR-mediated NFkB pathway activation | Induces BC chemoresistance                               | [79]       |
| linc-00337 | BC cells          | Promotes CCL12, IL-13, M-CSF secretion         | Induces chemoresistance, and M2 polarization             | [80]       |

3. Non-Coding RNAs in the Regulation of BC Cells and TAM Metabolic Reprogramming

Cancer cells profoundly alter their metabolism to cope with the high biosynthetic demand of proliferating cells and adopt aerobic glycolysis, also known as the Warburg effect, to enhance glucose uptake and utilization [81]. In aerobic glycolysis, glucose is processed into lactate even in the presence of oxygen, providing ATP and building blocks very quickly to support tumor cell survival and proliferation [81,82]. In this context, TAM metabolism is also reprogrammed to sustain the newly developed tumor microenvironment [83,84]. Despite TAM phenotype changes over time during tumor progression, M1-like macrophages generally display a highly glycolytic metabolism associated with lactate secretion and ROS production. Instead, M2-like macrophages typically rely on oxidative phosphorylation and fatty acid oxidation [83,84]. Cancer cells and TAMs establish a mutual metabolic communication, with cancer cells promoting the M2-like phenotype through the secretion of lactate, and TAMs increasing glucose availability for tumor cells [84]. Non-coding RNAs are crucial mediators of this interplay [85,86].
Cancer cells increase HIF-1α protein levels in response to hypoxia to counteract cellular stress. HIF-1α is well known for its ability to modify cancer cell metabolism by inducing the overexpression of different glycolytic enzymes [87]. In healthy cells, PHD2 rapidly hydroxylates and degrades HIF-1α through the ubiquitin/proteasome pathway [88]. However, in cancer cells, HIF-1α degradation is prevented, leading to cancer cell metabolic switch and tumor progression [89]. Chen et al. demonstrated that TAMs isolated from breast cancer tissue release extracellular vesicles (EVs) containing the lncRNA HISLA, which enters tumor cells and stabilizes HIF-1α leading to aerobic glycolysis upregulation. Mechanistically, HISLA functions by directly interacting with PHD2 and inhibiting its hydroxylase activity on HIF-1α, leading to its stabilization [77].

Lactate dehydrogenase B (LDHB) is a glycolysis-related enzyme that catalyzes the interconversion of pyruvate and lactate, whose function in macrophages has been poorly investigated [59]. Frank et al. demonstrated that miR-375 derived from breast cancer cells is captured by TAMs, where it reduces LDHB expression levels, likely by directly targeting its transcript. The decrease in LDHB leads to the upregulation of aerobic glycolysis and lactate production in TAMs. The downregulation of LDHB also results in the activation of SREBP2, an enzyme that regulates cholesterol synthesis. The increased production of lactate and sterol by TAMs in the TME boosts tumor progression by stimulating cancer cell proliferation and survival. Therefore, miR-375 can be a promising target to selectively interfere with TAM tumor-promoting functions by reverting their metabolic status [59].

MiR-503-3p is an miRNA upregulated in breast cancer patients with a poor prognosis [90]. Huang et al. reported that exosomal miR-503-3p secreted by TAMs directly targets DACT2 transcript, a tumor suppressor gene acting as an antagonist of β-catenin in BC cells. The inhibition of miR-503-3p upregulates DACT2 and inhibits Wnt/β-catenin pathway in BC cells, resulting in glycolysis suppression and mitochondrial oxidative phosphorylation increase [60].

The inhibition of miR-33 regulates macrophage metabolism and M2-polarization by reducing glycolysis and promoting Fatty Acid Oxidation (FAO) in atherosclerosis [91]. Moradi-Chaleshtori et al. employed the delivery of 4T1 BC cell-derived exosomes containing miR-33 to macrophages to regulate their polarization. MiR-33 delivery resulted in macrophage polarization switch from M2 to M1 phenotype, and the upregulation of the M1 markers Nos2, Irf5, CD86, TNF-α, and IL-1β. The delivery of miR-33 induces M1 macrophage polarization also by regulating TAM metabolism. These M1-reprogrammed macrophages acquired the ability to inhibit 4T1 cell migration and invasion, identifying miR-33 delivery as a potential drug treatment for breast cancer [61].

Adipocyte/macrophage fatty acid-binding proteins (FABPs) are lipid chaperons that integrate inflammatory and metabolic responses in macrophages [92]. The upregulation of FABPs increases the pro-tumoral activity of a subtype of TAMs (CD11b+F4/80+Ly6C-MHCII-CD11c-) by upregulating the IL-6/STAT3 pathway via the modulation of NFkB/miR-29b. Mechanistically, FABPs downregulate miR-29b in TAMs via an increased NFkB activity, releasing the inhibitory effect of miR-29b on the pro-tumoral factor STAT3 and inducing macrophage M2 polarization. Therefore, the authors proposed FABPs as new prognostic markers and potential therapeutic targets in breast cancers [62].

Breast cancer cells secrete miR-122, which suppresses glucose metabolism by reducing the glycolytic enzyme pyruvate kinase expression in the premetastatic niche. In this manner, miR-122 prepares the environment for the tumor cell arrival by increasing glucose availability and thus favoring cancer cell proliferation and dissemination. Indeed, the authors showed that miR-122 secreted from the primary tumor could affect glucose metabolism in the lungs and brain before metastases onset [63]. In this context, miR-122 may also influence macrophage metabolism and affect their pro-tumoral phenotype in the premetastatic niche. Figure 2, Table 1, and Table 2 summarize the role of miRNAs and lncRNAs in TAM and BC cell metabolic reprogramming during cancer progression.
Figure 2. miRNAs and lncRNAs involved in TAM-BC crosstalk during metabolism reprogramming. LncRNA Hisla and miR-503-3p are secreted from TAMs and collected by BC cells, where they promote aerobic glycolysis and suppress OXPHOS. Instead, miR-375, miR-33 and miR-122 are secreted by BC cells and promote glycolysis upregulation and FAO inhibition in TAMs.

4. Non-Coding RNAs in the Regulation of TAM-Induced Angiogenesis

The formation of new blood vessels is indispensable for the successful growth of tumor cells, which require a considerable supply of nutrients, oxygen, and other factors to sustain a high growth rate [93,94]. The increased blood vessel density in the tumor environment allows cancer cells to intravasate and enter circulation, the primary event for metastasis formation [93,94]. The direct correlation between TAM presence and a pro-angiogenic environment has been extensively documented in breast cancer [95,96]. In this context, cancer cells reprogram TAMs to a pro-angiogenic phenotype to support all the stages for blood vessel formation. Indeed, TAMs promote ECM remodeling through metalloproteinase secretion and stimulate endothelial cell proliferation and migration by secreting growth factors such as EGF, VEGF, and pro-angiogenic cytokines such as TNFα, CCL8, and IL-8 [95,97]. NcRNAs control TAM and BC cell angiogenic properties by regulating the expression of growth factors and the release of cytokines in the TME [97,98].

Our group recently demonstrated that ID4 expression in breast cancer cells drives TAM reprogramming by increasing the expression of two pro-angiogenic factors, granulin (GRN) and HIF. We demonstrated that ID4 expression in BC cells mediates the release of VEGF, which acts in a paracrine manner and promotes the downregulation of the anti-angiogenic miR-107, miR-15b, and miR-195 in macrophages. The downregulation of these miRNAs leads to GRN and HIF-1 expression in macrophages, promoting their pro-angiogenic abilities and breast cancer progression [64,99,100].

M2 macrophages also secrete factors that regulate BC cell pro-angiogenic activity. Dong et al. demonstrated that VEGF secreted by M2 macrophages induces the upregulation of the lncRNA PCAF in human BC cells. PCAF induces the expression of VEGFR2, leading to the activation of the Akt/mTOR pathway. Mechanistically, PCAF recruits the ubiquitin protease USP14 on VEGFR2 inhibiting its proteasome-mediated degradation. The activation of the Akt/mTOR pathway in BC cells triggers a pro-angiogenic response, both in vivo and in vitro, facilitating their tumorigenic behavior [78].

The administration of ncRNAs has emerged as a potential therapeutic strategy to stop tumor progression through angiogenesis suppression [101]. MiR-29b is a tumor suppressor miRNA in many cancers, where it regulates cell proliferation, apoptosis, and differentiation, and its expression also decreases in breast cancer tissue compared with normal mammary tissue [65]. Li et al. showed that the systemic administration of miR-29b in a mouse model of breast cancer significantly suppresses tumor growth by reducing angiogenesis. In BC cells, miR-29b downregulates Akt3 protein expression, which is known to
induce VEGF and to promote angiogenesis. At the same time, the authors observed that the TAM infiltration was significantly reduced after miR-29b administration, indicating that miR-29b directly or indirectly acts on macrophage recruitment. The reduced number of TAMs further mitigates the secretion of pro-angiogenic factors in the TME [65].

MiR-155 is a well-known oncomiRNA induced by hypoxia and VEGF, which can promote TAM recruitment in breast cancer [102]. Kong et al. reported that the overexpression of miR-155 induces angiogenesis in a mouse model of breast cancer by directly targeting VHL mRNA. VHL targets the members of HIFα family; thus, its downregulation results in HIF1α and HIF2α expression and the induction of angiogenesis. In addition, miR-155 overexpression results in a massive TAM infiltration, although the mechanisms regulating this process have not been clarified yet [66]. TAMs can, in turn, produce miR-155 and miR-155-stimulating factors, such as VEGF, causing a positive feedback loop that boosts angiogenesis [103,104].

MiR-21 and miR-29a are two potent pro-angiogenic factors involved in TAM reprogramming. Mathsyaraja et al. showed that these factors are upregulated in a CSF1-ETS2-dependent pathway in infiltrating myeloid cells from a metastatic model of murine breast cancer. MiR-21 and miR-29a mediate the pro-angiogenic switch in TAMs by downregulating the expression of the anti-angiogenic genes Pdcd4, Spry1, Timp3 Col4a2, and Sparc. The expression of miR-21 and miR-29a also correlates with the upregulation of M2 markers in macrophages and with an increased TAM pro-tumoral potential [103,104]. Tables 1 and 2 outline the roles of miRNAs and lncRNAs in TAM and BC cell pro-angiogenic activity during breast cancer progression.

5. Non-Coding RNAs in the Crosstalk between TAMs and BC Cells during Metastasis Formation

The metastatic spreading of cancer cells requires the cooperation between cancer cells and the TME [1]. Before metastasis onset, cancer cells acquire a motile mesenchymal phenotype by undergoing EMT, entering blood vessels, and finally extravasating and invading other tissues where they need to find a favorable niche to grow [105]. TAMs foster metastasis formation by promoting cancer cell EMT, angiogenesis and ECM remodeling, increasing the chances for cancer cells to extravasate and enter the circulation. Furthermore, TAMs provide factors to limit the immune response in the pre-metastatic niche to prepare the microenvironment for the arrival of metastatic cancer cells. Sanchez-Gonzalez et al. showed that miR-149 downregulation in BC cells promotes the secretion of CSF1, a cytokine that stimulates the secretion of EGFR ligands by TAMs. EGFR ligands then bind to the receptor expressed by cancer cells and activate the EGFR pathway, increasing BC cells’ malignant behavior and resulting in lung metastasis formation in an SCID mouse orthotopically injected with human BC cells. MiR-149 downregulation also favors tumor progression by increasing TAM recruitment to the tumor site [39]. MiR-100 expression in TAMs increases IL-1ra secretion via the modulation of the mTOR-Stat5a pathway. The authors showed that IL-1ra increases cancer cell invasive ability and stemness by inducing the activation of the Hedgehog signal pathway. In vivo experiments finally showed that miR-100 inhibition significantly reduced lung metastasis formation in a 4T1 BC mouse model [48]. Long noncoding RNA associated with breast cancer brain metastasis (lnc-BM) is upregulated in metastatic cells where it induces the expression of CCL2 via the activation of the JAK2/STAT3 pathway. The secretion of CCL2 recruits TAMs, which secrete oncostatin M (OSM) and IL-6, inducing an additional activation of the JAK2/STAT3 pathway, activating a positive feedback loop. The activation of the JAK/STAT pathway in cancer cells facilitates cell adhesion to capillaries and extravasation to the brain through the upregulation of the endothelial adhesive molecule ICAM. The treatment of a mouse xenograft model of BC with nanoparticles carrying lnc-BM siRNA inhibited brain metastasis formation [36].

Tumors are often characterized by a persistent and non-resolutive inflammation that correlates with a poor prognosis [107]. Guo et al. demonstrated that the delivery of miR-
miR-183-5p from 4T1 BC cells to macrophages mediated by exosomes increases the secretion of pro-inflammatory cytokines IL-1b, IL-6, and TNF-α from macrophages. Mechanistically, miR-183-5p targets PPP2CA in TAMs, leading to the upregulation of the NF-κB pathway, which is responsible for the activation of the pro-inflammatory pathway. The release of pro-inflammatory cytokines in the TME is detrimental and results in tumor progression and lung metastasis. The authors finally showed that the injection of BC cells with downregulated miR-183-5p in a mouse model results in a significant reduction in lung metastasis [68]. Another study showed that exosomal miR-183-5p transmission from BC cells to TAMs targets and inhibits the H3K27 histone demethylase KDM6B, inhibiting the expression of M1-related pro-inflammatory genes. The co-administration of BC cells and TAMs pre-treated with exosomes from cells overexpressing miR-183-5p promoted lung metastasis in vivo, highlighting the ability of this miRNA to induce TAM-mediated metastasis formation [69].

Progranulin (PGRN) is a secreted glycoprotein upregulated in many human cancers [108]. Recently, it has been shown that TAMs isolated from PGRN-/- mice harboring breast cancer release exosomes that can affect BC cell behavior by reducing EMT and invasive ability. These TAM-released exosomes contained high levels of miR-5100, which could be taken up by BC cells targeting CXCL12, a chemokine known to promote BC cell invasiveness [70]. In an in vivo model of PY8119 breast cancer, the absence of PGRN resulted in a reduced grade of TAM infiltration and reduced lung metastasis formation [109].

TAMs are a primary source of CCL18, a chemokine associated with breast cancer progression and poor prognosis [110]. Lin et al. demonstrated that CCL18 decreases miR-98 expression in BC cells via Lin28b/NF-κB activation, promoting the activation of the EMT pathway. To investigate the role of CCL18 on metastasis formation, the authors injected CCL18 in a mouse model harboring a breast tumor derived from MDA-MB-231 cells and observed an induction of lung and liver metastasis formation, together with the downregulation of miR-98 [71]. Another study showed that the ectopic overexpression of miR-181b in TAMs could counteract the pro-tumoral effects of TAM-released CCL18 by inactivating the NF-κB pathway in BC cells in vitro [72]. Let-7a is a downregulated miRNA in breast cancer that can inhibit the effects of CCL18 in BC cells by downregulating Lin28 expression. Therefore, let-7a delivery in BC tissue could be a potential strategy to limit the detrimental effects of TAMs [111]. Figure 3, Table 1, and Table 2 summarize the role of miRNAs and lncRNAs in TAM-induced breast cancer metastasis.

**Figure 3.** miRNAs and lncRNAs regulating TAM-induced breast cancer metastasis. Lnc-BM, miR-183-5p, and miR-100 promote TAM ability to stimulate breast cancer metastasis, while miR-149, miR-5100, miR-98, miR-181b and let-7a inhibit TAM-mediated metastasis formation.
6. The Role of miRNAs and lncRNAs in TAM-Induced Chemoresistance in Breast Cancer

Drug resistance is the leading cause of relapse and death in cancer [112]. TAMs may play a significant role in response to chemotherapy by accumulating in the tumor tissue and mediating the pro-regenerative and anti-apoptotic responses that confer resistance to therapies to cancer cells [113]. In a recent study, Liu et al. reported that IRENA is the most upregulated lncRNA in TAMs after neoadjuvant chemotherapy in breast cancer patients. The authors demonstrated that chemotherapy activates the inflammatory response and upregulates the Jak1-STAT1-induced IRENA lncRNA. IRENA then induces the pro-inflammatory NF-κB pathway in TAMs by promoting the dimerization and phosphorylation of PKR, a protein that activates several inflammatory-related pathways [114]. Although inflammatory M1 macrophages are often associated with antitumor activity, the activation of the NF-κB pathway in the context of a chemotherapeutic treatment promoted TAM-mediated cancer cell chemoresistance. The authors showed that the IRENA knockdown in the PyMT murine model of breast cancer improved the cancer response to chemotherapy treatment [79].

MiR-770 is selectively overexpressed in chemo-sensitive breast cancer tissues and mediates doxorubicin sensitivity by regulating gene expression in BC cells and interfering with the TME. First, miR-770 promotes BC cells apoptosis after treatment with doxorubicin and reduces metastasis formation by directly targeting STMN1 mRNA and inhibiting the EMT pathway. Secondly, BC cells can transfer miR-770 to TAMs, where it upregulates the M1 markers MCP-1, iNOS and CD80 while decreasing the expression of M2-macrophage markers. The M1-reprogrammed macrophages helped to reverse the BC cell’s resistance to doxorubicin and sensitize them to cell death, underlining the importance of the TME in the chemoresistance process [73].

The expression of the oncomiRNA miR-21 has been associated with trastuzumab and chemotherapy resistance in HER2-positive breast cancers [74]. MiR-21 mediates chemoresistance by acting in BC cells and TAM recruitment. In BC cells, miR-21 promotes survival by targeting PTEN and PDCD. In the TME, PTEN downregulation increased the secretion of IL-6 from BC cells, which correlated with higher TAM infiltration that contributed to the acquisition of chemoresistance in BC cells [74].

Tan et al. uncovered the role of miR-708 in chemoresistant breast cancer stem cells. MiR-708 is downregulated in chemoresistant stem cells, where it inhibits self-renewal by targeting the CD47. The overexpression of miR-708 in BC cells with increased chemosensitivity to docetaxel and increased macrophage phagocytic activity, restoring the immune-mediated elimination of chemoresistant cells [75].

MiR-100 expression in TAMs increases IL-1ra secretion via the mTOR-Stat5a pathway. The release of IL-1ra in the TME facilitates cancer stem cell development via the activation of the Hedgehog pathway and promotes resistance to cisplatin treatment. The inhibition of miR-100 in a 4T1 breast cancer model significantly improved the cisplatin response, resulting in reduced metastasis formation [48].

Breast cancer cells resistant to Adriamycin secrete exosomes containing miR-222, which are captured by macrophages, promoting M2 polarization by targeting PTEN and inducing the Akt pathway. By inducing M2 macrophages, chemo-resistant cells modify the TME to sustain tumor growth and metastasis formation [76].

The lncRNA LINC00337 is upregulated in breast cancer cells and promotes paclitaxel resistance by affecting the TAM phenotype. LINC00337 promotes CCL2, IL-13, and M-CSF secretion inducing macrophage recruitment and M2 polarization, as demonstrated by the upregulation of the M2 markers CD163 and ARG1 macrophages, which then increase the malignant behavior of chemo-resistant cancer cells by promoting their survival and migratory abilities [80]. Tables 1 and 2 recapitulate the role of ncRNAs in TAM-induced breast cancer chemoresistance.
7. Conclusions

Breast cancer is the most common tumor in women worldwide and a very heterogeneous disease [115]. Although the prognosis of non-metastatic breast cancer is generally favorable, the most aggressive forms remain incurable, and, in the case of chemo-resistant breast cancers, the treatments may alleviate the symptoms rather than eradicate the disease [115]. Therefore, new therapeutic approaches considering the molecular heterogeneities of the different breast cancer subtypes are needed to improve patients’ life expectancies [116]. The immunosuppressive and tumor-promoting tumor microenvironment allows cancer cells to escape the immune-mediated killing mechanisms and provides pro-survival signals, laying the foundations for metastasis formation and chemoresistance [1,117]. TAMs represent one of the primary cell populations in the TME that contribute to each stage of cancer progression [7,118]. Deregulated ncRNAs in BC cells promote TAM recruitment and polarization to the M2 phenotype and educate TAMs to promote cancer progression. At the same time, ncRNA alteration in TAMs affects BC cell behavior [98]. This crosstalk can be mediated by ncRNAs secreted in the TME and collected by nearby cells or by factors released in the TME that control ncRNA expression in other cells. Different studies showed that targeting TAMs is beneficial for breast cancer. Therapies under investigation involve blocking TAM recruitment, eliminating TAMs already present in the TME, or interfering with their polarization status [119].

TAM elimination is challenging, as the drugs used for this purpose may not be selective for macrophages. The manipulation of ncRNA expression could be a potential strategy to interfere with TAM recruitment or to reprogram M2-polarized macrophages [119]. NcRNAs are often released inside exosomes, so one possibility is the use of antibodies to target exosomes from cancer cells that can be recognized for the expression of particular proteins [120]. Another possibility involves the use of small molecules such as Antisense Oligonucleotides (ASOs) or small interfering RNA (siRNA) that inhibit or degrade ncRNA molecules [121]. On the contrary, the delivery of anti-oncogenic ncRNAs through exosomes or nanoparticles might restore altered molecular pathways in cancer [120,122]. Today, the use of RNA-based therapies for cancer treatment is still premature, due to the difficulties in drug delivery and the risk of off-target effects. However, in the future, the manipulation of ncRNA expression, alone or in combination with other treatments, could be a promising therapeutic approach to interfere with TAM pro-tumoral functions in breast cancer and other cancers.

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