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A vicious circle in breast cancer: The interplay between inflammation, reactive oxygen species, and microRNAs

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Breast cancer (BC) is the most common cancer in women worldwide. This highly heterogeneous disease is molecularly stratified into luminal A, luminal B, HER2, triple-negative/basal-like, and normal-like subtypes. An important aspect in BC progression is the activation of inflammatory processes. The activation of CD8+/Th1, NK, and M1 tumor associated macrophages (TAMs), leads to tumor destruction. In contrast, an anti-inflammatory response mediated by CD4+/Th2 and M2 TAMs will favor tumor progression. Inflammation also stimulates the production of inflammatory mediators like reactive oxygen species (ROS). In chronic inflammation, ROS activates oxidative stress and endothelial dysfunction. In cancer, ROS plays a dual role with anti-tumorigenic and pro-tumorigenic effects in cell signaling pathways that control proliferation, survival, apoptosis, and inflammation. MicroRNAs (miRNAs), which are known to be involved in BC progression and inflammation, can be regulated by ROS. At the same time, miRNAs regulate the expression of genes modulating oxidative stress. In this review, we will discuss the interplay between inflammation, ROS, and miRNAs as anticancer and tumor promoter molecules in BC. A clear understanding of the role of miRNAs in the regulation of ROS production and inflammation, may lead to new opportunities for therapy in BC.

KEYWORDS

inflammation, ROS, microRNAs, breast cancer, regulation

Introduction

In women, breast cancer (BC) is the most diagnosed cancer with an estimated incidence of 2.3 million new cases (11.7% of all cancer cases) and it is the leading global cause of cancer since 2020. Although the mortality of BC patients has decreased in the last decade, it remains the leading cause of cancer death in women, and it is the fifth leading cause of cancer mortality worldwide, with around 685,000 deaths per year (1). Most BC are sporadic (~90%), and their increasing incidence has been related to the alteration of risk factors such as prolonged exposure to endogenous estrogens, age, sedentary lifestyle, alcohol consumption, obesity, exposure to ionizing radiation, and hormone replacement therapy (especially the combination of estrogens and progestogens) (2, 3).

The majority of BCs start in the lobes or in the ducts that connect the lobes to the nipple (4). The mammary epithelial cells acquire the ability to grow “abnormally” for years while remaining within the ducts or breast lobes (5). Once leaving the ducts or lobes, cancerous cells can metastasize through the blood or lymphatic system to distant organs such as the lungs, liver, brain or bones. During metastasis, cell migration and invasion occurs through a cascade of molecular events directed by genetic mutations and altered gene expression (6).

Inflammation is a mechanism of the immune system that responds to external or internal stimuli, removes the aggressor, and restores homeostasis. When chronic inflammation appears, diseases can develop, including BC (7). BC progression requires the participation of growth signaling pathways, as well as supportive signals from immune cells, proinflammatory cytokines, and growth factors present in an inflammatory tumor microenvironment (TME) (8–10) are necessary. Additionally, inflammation is important in cancer development and metastasis (11). Inflammation also promotes the production of reactive oxygen species (ROS), which are free radicals, ions, or molecules with a single unpaired electron (12). ROS have a dual role, they can act beneficially as signaling molecules when they are produced at low levels, but when ROS is elevated, they can induce damage, resulting in genetic instability and tumorigenesis (13–15). ROS can influence different processes that induce cancer progression, including BC, in association with the inflammatory TME (16).

ROS participate in complex regulatory pathways with other molecules involved in inflammation and oncological processes including the microRNA (miRNAs) (17). MiRNAs are small non-coding RNA molecules that participate in gene regulation (18). Their mechanism of action depends on the complementarity of base pairs with the target messenger RNA (mRNA): if it is total, a degradation of the mRNA occurs; if it is partial, it causes a decrease in mRNA translation (19). The deregulation of miRNAs has been reported in multiple types of cancer, including BC, and has been associated with the

progression of this disease (20). Interestingly, miRNA deregulation has a direct connection with ROS regulation, and ROS levels are also key in the regulation of multiple miRNAs, highlighting the connection between the regulatory networks of both molecules in BC (21, 22). A better understanding of the relationship between both molecules will allow the development of novel therapeutic approaches.

Breast cancer subtypes

BC is a highly heterogeneous disease with molecular, biological, and morphological variations, and thus has different behavior and responses to treatment. BC classification is based on its histological and molecular features, which can be used for prognosis or to predict treatment response and overall survival (23, 24). Histologic classification evaluates different parameters like tumor cell type, extracellular secretions, structural features, immunohistochemical profile as well as the pathological growth pattern and anatomical origin (25, 26). The histological differentiation is a good prognostic factor and it is used to make better clinical decisions (27). TNM staging, on the other hand, uses clinical and pathologic information of tumor size (T), the status of regional lymph nodes (N), and distant metastases (M). The staging combines these factors and stratifies the disease into five stages (0, I, II, III, and IV) (28).

Modern genomic techniques have confirmed an association between the natural history of BC with a particular gene expression profile of the tumor (29). This molecular classification is more effective than the anatomical criteria, and allows for prognosis and treatment options to be defined individually (30). Under this classification BC is divided into five molecular subtypes according to a combination of gene expression profiles and immunochemistry information: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2), basal-like BC, and normal-like tumors. This molecular classification is based on the presence of hormone receptors and HER2 status (Table 1) (31).

Luminal breast cancers are associated with estrogen receptor (ER) activation and they are divided into two subgroups according to the expression of proliferation-related genes (37). Luminal A is the most common molecular subtype, and it is considered of low grade, with the best prognosis among all subtypes. It has positive hormone receptors, like ER and progesterone receptor (PR), and negative HER2, as well as a low expression of proliferation-related genes (38, 39). In contrast, luminal B tumors tend to be of higher grade and have a worse prognosis, lower expression of ER-related genes, variable HER2 expression, and high expression of proliferation-related genes (40). Because of their characteristics, luminal A tumors show a good response to hormonal therapy, whereas luminal B tumors may be candidates for chemotherapy because

TABLE 1 Breast Cancer Molecular Subtypes.

Subtype	IHC Phenotype	Prognosis	Characteristics	References
Luminal A	ER+, PR ≥ 20%, HER2-, Ki67 low	Good	Most common subtype Lower-grade tumor Diagnosed at early stages	(31–33)
Luminal B	ER+, PR < 20%, HER2+/-, Ki67 high	Intermediate	Higher grade tumor	(31–33)
HER2	ER-, PR-, HER2+, Ki67 high	Poor	Less common subtype Higher grade tumor Highly aggressive	(31–34)
Basal like	ER-, PR-, HER2-, Ki67 high	Poor	Most aggressive subtype High invasiveness High metastatic potential	(31–33, 35)
Normal-like	ER+, PR+, HER2-, Ki67 low	Intermediate	Resembling the normal breast profiling	(36)

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; Ki67, proliferation index.

of their high proliferation rates (23, 31). The Ki67 index, also known as a proliferation biomarker, is an independent prognostic factor in BC and it is used to evaluate the risk of recurrence and BC survival; higher Ki67 correlates with tumor grade and poor prognosis (32, 41–43). This marker is also used to differentiate luminal A from B tumors (44).

ER-negative cancers are also divided into two subgroups: HER2-enriched and basal-like/triple negative BC. The HER2-enriched group is distinguished by HER2 overexpression and genes associated with HER2 signaling (37). These HER2-overexpressing tumors are generally high-grade, ER-, PR-, and are clinically aggressive. However, they are very sensitive to anti-HER2 targeted therapy. Most tumors within this subgroup are HER2+, but a small number of HER2+ cancers co-express ER and are classified as luminal B (39, 45).

Basal-like BC is associated with high expression of high-molecular-weight cytokeratins, P-cadherin, and the epidermal growth factor receptor in normal myoepithelial and basal mammary cells (39). This subtype of BC also exhibits overexpression of genes related with proliferation, but they do not express ER, PR or HER2. Histologically, they are high grade, with a high proliferation index, and a triple negative phenotype (45). BC that carries the *BRCA1* mutation mostly belong to the basal-like subtype. Although, the terms basal-like and triple negative BC have been used indistinctly, not all triple negative breast cancers are of the basal-like subtype (23). Triple negative BC has different molecular features and fluctuating clinical outcomes and responses to treatment, and have therefore been divided in 6 subgroups (46–48). The aggressiveness of this subtype is best exemplified by the fact that the peak risk of recurrence is between the first and third years after the initial diagnosis. Most of the deaths occur in the first 5 years following therapy (49).

Normal-like tumors are characterized by the expression of genes identical to normal mammary epithelium and shares similar immunohistochemical status with the luminal A subtype, which is ER+, PR+, HER2-, and Ki67 low. In

addition, this type of tumors exhibit high expression of adipose and myoepithelium-associated genes, and low expression of luminal genes and clusters with fibroadenoma and normal breast tissue (5, 37). However, the existence of this BC subtype is controversial because the normal epithelial cell is “contaminated” with low content of malignant cells (50). In addition, the gene expression pattern of the normal breast is typified by the high expression of genes of basal epithelial and adipose cells, and the low expression of genes, characteristic of luminal epithelial cells (37).

In addition to the five BC subtypes, there is a rare and very aggressive type of BC known as inflammatory breast cancer (IBC) (51). The term inflammatory is not due to the participation of inflammatory signaling pathways (52) but for its clinical characteristics, such as the inflamed appearance of the skin. IBC is characterized by a low hormone receptor expression and is associated with a more aggressive clinical course and decreased survival (53). The aggressiveness of this disease is attributed to the alteration in key signaling pathways leading to a rapid growth and early metastasis, as well as the development of tumor emboli, which invade and block local lymphatic vessels, provoking tissue damage and immune infiltration, and also generating tumor growth (54). The clinical characteristics of IBC are diffuse induration of the skin with an erysipeloid edge, and most of the times without a dominant tumor mass (55). This behavior occurs because groups of cells are infiltrated in the stroma and they are grouped together forming clusters (56), which have characteristics of progenitor cells with CD44+ CD24-, ALDH1+, or CD133+ profiles (57).

Together, both histological and molecular systems are complementary to each other and, in combination with the TNM system, play an important role in BC diagnosis, prognosis, and therapy (23). In the next sections we will discuss the involvement of inflammatory process in the progress of BC and how this inflammation is correlated with the ROS and miRNAs production.

Breast cancer as an inflammatory process

Inflammation is a conserved mechanism that protects from pathogens, repairs injured tissues, and eliminates damaged cells, leading to the homeostasis of the organisms (58). Acute inflammatory processes should be carefully regulated to prevent excessive tissue damage (58, 59). When acute inflammation is not resolved, it becomes chronic, causing the destruction of tissues and the disturbance of the homeostasis, leading to clinical consequences (60). Chronic inflammation is associated with the risk of developing different types of cancer, including BC (61). BC generally arise in an inflammatory environment, characterized by chronic inflammation accompanied by the presence of immune cells, proinflammatory cytokines, growth factors, and mediator proteins (8, 9).

The tumor microenvironment (TME) consists of different types of cells, including cancer cells, stromal cells, immune cells, and the extracellular matrix. The interaction among components of the TME makes it a complex system that facilitates tumorigenesis and metastasis (62). The most common immune cells found in the TME are monocytes that differentiate to tumor-associated macrophages (TAMs). TAMs have the ability to promote tumor growth and they are present during angiogenesis, invasion and metastasis; high presence of TAMs generally correlates with poor prognosis (63, 64). TAMs show strong plasticity, and they can polarize into two different populations, M1 and M2, in response to the stimuli of the microenvironment (65).

M1 macrophages are polarized by cytokines like tumor necrosis factor- α (TNF- α), interferon- γ (IFN- γ), IL-1, IL-6, and IL-17, and they can produce and secrete high levels of pro-inflammatory cytokines such as IL-1 α , IL-1 β , IL-6, IL-12, IL-23, and cyclooxygenase-2 (COX-2). These macrophages elicit anti-tumor activity, mediate ROS-induced damage, and impair tissue regeneration and wound healing (66–68). M2 macrophages are polarized by anti-inflammatory cytokines including IL-4, IL-10, and IL-13 by the activation of signal transducer and activator of transcription 6 (STAT6) through the IL-4 receptor alpha (IL-4R α); or by the activation of signal transducer and activator of transcription 3 (STAT3) through the IL-10 receptor (IL-10R) (69). M2 macrophages exhibit an anti-inflammatory profile, producing low levels of IL-12, high levels of IL-10, and transforming growth factor- β (TGF- β). These macrophages have pro-angiogenic properties and potent phagocytosis capacity that promote tissue repair and wound healing (65, 69). M2 macrophages participate also in tumor progression, immunoregulation, and angiogenesis (70–72), as they secrete factors to produce an immunosuppressive TME. It is known that BC tumors possess a high density of M2 macrophages that are associated with poor patient prognosis (73).

In addition to the M1/M2 macrophage polarization, Malyshev et al. showed that there is a third phenotype of macrophages, known as the M3 phenotype or the switching phenotype (74). They observed an imbalance in the M1/M2 alveolar macrophage phenotype, suggesting the formation of M3 phenotype. These M3 macrophages are found in lung-related conditions including bronchial asthma and chronic obstructive pulmonary disease (COPD), and during the administration of anti-inflammatory treatments like inhaled glucocorticosteroids (74–77). This M3 phenotype is characterized by the upregulation of anti-inflammatory cytokines in response to the programming factor (RF)-M1 resulting in the reprogramming to the M2 phenotype (M1/M2 phenotype). Opposite, the upregulation of pro-inflammatory cytokines in response to RF-M2 induces the reprogramming to the M1 phenotype (M2/M1 phenotype) (74). There are few reports studying the M3 macrophage population. Jackaman et al. found a mixed of IL-10⁺TNF- α ⁺CD206⁻CX3CR1⁺ M1/M2 (M3) macrophage subset dominating the mesothelioma microenvironment. This observation, support the hypothesis about the transition of M1 cells to M3 cells during tumor proliferation (78). Kalish et al. reported that the M3 phenotype exhibited an antiproliferative antitumor effect *in vitro*, and prolonged the survival time of mice with Ehrlich ascites carcinoma (79). Nevertheless, more studies are needed to fully characterize and understand the activity of the M3 macrophages.

An immune cell population present also in the TME are the neutrophils. These cells constitute the first line of defense against microbial pathogens infection and tissue damage (80). In the context of TME, neutrophils are known as tumor-associated neutrophils (TANs). Depending on the stage of development of the tumor or on the tumor type, TANs could induce tumor-suppressive (N1) or tumor-promoting (N2) phenotypes (81, 82). In early stages of the tumor, neutrophils are recruited to the TME through the release of cytokines and ROS by tumor and stromal cells (83), promoting apoptosis. However, during tumor progression, neutrophils could promote angiogenesis and invasion, by modifying the extracellular matrix (ECM). TANs exerted these effects by releasing factors like proteases, reactive nitrogen species (RNS) (84), MMP9, ROS, and growth factors (i.e. VEGF) (81, 85, 86). It is reported that the chemokine receptor CXCR2 and their ligands CXCL1-3 and CXCL5-8 are in charge to attract neutrophils to the tumor and develop an inflammatory response (87). CXCR2 chemokines are produced by tumor cells, immune cells, and cancer-associated fibroblasts (CAFs) (88). It has been shown that when neutrophils are co-cultured with human BC cells, they released oncostatin M (OSM), a member of the IL-6 superfamily, promoting tumor progression, angiogenesis, and metastasis through the expression of VEGF (89). Also, the IL-17-CXCR2 axis facilitates the recruitment of neutrophils to the tumor site, promoting BC progression (90).

Another cells found in the TME are myeloid-derived suppressor cells (MDSCs), a heterogeneous group of monocytic and polymorphonuclear immature myeloid cells that are produced under inflammation (91). MDSCs participate in premetastatic niche formation and promote tumor cell metastasis and angiogenesis by secreting TGF- β , VEGF, and MMP9 (92, 93). MDSCs can also inhibit immune function to accelerate tumor progression (92, 93), increase tumor cell stemness and angiogenesis, as well as promoting EMT through IL-6 secretion (94). In cancer patients, the expansion of MDSCs promotes cell growth and metastasis, and decrease the immunotherapy effectiveness (91). It has been reported that high levels of MDSCs in BC correlates with advanced stages of the disease and increased rates of recurrence and metastasis (95). It has been observed that in the lung tissues of BC patients, CCL2 can recruit MDSCs to promote BC metastasis (96).

T cells are also found in the TME, and they are classified into CD8+ cytotoxic T cells and CD4+ helper T cells, including Th1, Th2, Th17, T regulatory cells, as well as natural killer T cells. Importantly, T cells have tumor-suppressive and tumor-promoting capabilities (97, 98). In addition, the $\gamma\delta$ T cells are also found in the TME, they are known as nonconventional lymphocytes and characterized by the expression of specific receptor of the V γ and V δ chains (99). The presence of $\gamma\delta$ T cells in the TME is associated with poor prognosis in different types of cancer, including BC. Chabab et al. observed that in human BC tumors, $\gamma\delta$ T cells were present in the late stages of the disease (100). Around ~20% of the $\gamma\delta$ T cells expressed CD37, and exhibited immunosuppressive functions through the expression of IL-8, IL-10, and adenosine (100).

CAFs are also part of the BC stromal compartment and are recruited and activated by different mediators, including TGF- β , platelet-derived growth factor (PDGF), fibroblast growth factor 2 (FGF-2), and ROS (101). CAFs are able to secrete proteases, inflammatory molecules and growth factors. These proteases and inflammatory molecules increase the ability of CAFs to migrate and remodel the ECM, and recruit other inflammatory cells at neoplastic sites (102, 103). The growth factors also stimulate cancer cells to produce and secrete TGF- β , MMP9 and MMP13 which contribute to the proliferation and angiogenesis of the tumor (104). In BC, high levels of MMP9 are associated with cancer development and tumor progression, while in TNBC MMP9 promotes angiogenesis and metastasis (105, 106).

The TME also includes cancer-associated adipocytes (CAAs). CAAs are smaller than normal adipocytes, and also differs in metabolic activity and adipokine expression (107). CAAs secrete adipokines, inflammatory chemokines, and interleukins and are implicated in tumor progression, metastasis, and therapy resistance (108). For instance, it has been shown that high secretion of leptin by CAAs promote cell proliferation and angiogenesis in BC by the upregulation

of the enzyme lysyl hydroxylase (109). Leptin in CAAs also activates ER pathways, JAK/STAT3, PI3K/AKT and SRC-1 signaling pathways and increases cyclin D1 and vascular endothelial growth factor (VEGF)/VEGFR expression (108, 109). Increased levels of STAT3 and JAK phosphorylation in CAAs may lead to the production of IL-6, which promotes cancer cell survival, immune suppression, and drug resistance (110).

Mediators of the immune response and inflammatory mediators such as ROS, cytokines, chemokines, prostaglandins, and growth factors can regulate cancer progression (111), and participate in all the stages of carcinogenesis, including initiation, promotion, cell proliferation, angiogenesis, and metastasis (11, 112, 113). TGF- β is a cytokine that also promotes metastasis in BC and it is crucial during epithelial-mesenchymal transition (EMT), invasion, and progression of BC (114). TNF- α is known as a multifunctional cytokine that contributes to cancer development and also participates in different signaling pathways connected to inflammation, proliferation, survival, invasion, and migration in BC (115). The effects of TNF- α are mediated through its receptors, TNFR1 and TNFR2 (116). The binding of TNF- α to its receptors activates the p42/p48 MAPK, PI3K/AKT and p38/MAPK pathways which activate the expression of proliferation-related genes mediated by NF- κ B, STAT3, and AP-1 transcription factors (117). Resistin, another inflammatory cytokine, is released in the inflammatory TME, promote tumor cell growth and aggressiveness, and it is elevated in BC patients (118, 119). High levels of resistin positively correlated with breast tumor size and stage, lymph node metastasis, and estrogen receptor status, and negatively correlated with the overall survival in BC patients (120).

Some ILs as IL-1, IL-6, IL-8, IL-11, and IL-23 also promote an inflammatory microenvironment, and some of them are involved in tumor progression (121). IL-6, a pleiotropic cytokine that regulates multiple biological activities is the most studied cytokine in the pathogenesis of BC (122). It is speculated that IL-6 can inhibit apoptosis by regulating the expression of antiapoptotic proteins, such as B-cell lymphoma-extra-large (BCL-XL) and B-cell lymphoma 2 (BCL-2) (123). IL-6 also promotes cell survival, immune suppression, and drug resistance through STAT3 dependent pathway and JAK phosphorylation (123, 124). The JAK/STAT3 signaling pathway is induced by the overexpression of IL-6 released from TAMs, causing the translocation of phospho-STAT3 into the nucleus and transactivation of proteins, inducing the processes of proliferation, differentiation, and survival (125, 126). Another cytokine involved in inflammation and cancer progression is IL-17. This cytokine protects the body against infections. IL-17 promotes inflammation by inducing inflammatory mediators such as IL-6, CXCL1 and G-CSF (127), recruiting dysfunctional myeloid cells and establishing a suppressive

and proangiogenic immune response in the TME (128). Dysregulation of IL-17 production or in its signaling pathway causes an unresolved inflammation, resulting in tissue damage. The chronic activation of IL-17 generates a pro tumor microenvironment, since IL-17 induces inflammatory mediators to promote tumor progression (128).

Other mediators of inflammation in the TME are the chemokines and their receptors. These molecules are implicated in diverse processes, including wound healing, angiogenesis, inflammatory diseases, tumor growth, and metastasis (129, 130). The chemokine CCL20 and its receptor CCR6 promotes cancer progression by increasing the proliferation and migration of cancer cells (131). CCL20 has been associated with poor prognosis in BC patients, Lee et al. reported that patients with high expression of CCL20 showed significantly lower overall survival and metastasis-free survival, in addition to increase cell invasion and secretion of MMP2 and MMP9 in TNBC cells (132). The chemokine CXCL8 and their chemokine receptors CXCR1/2 are also fundamental in the activation and trafficking of inflammatory mediators, and tumor progression as well as metastasis (133). It has been reported that in BC the chemokine CXCL8 induces EMT (134), and participates in angiogenesis, cell invasion, and migration of TNBC cells (135). The chemokine receptors CXCR2, CXCR3, CXCR4, CCR6, and CCR7 and their cognate ligands are associated to BC metastasis (130, 136, 137).

In addition to cytokines and chemokines, lipid mediators, derived from polyunsaturated fatty acids (i.e. arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid) that are synthesized during normal cell homeostasis, they are also over-produced under stress conditions, and contribute to the inflammation and tumor progression (138, 139). Prostaglandins are derived from arachidonic acid and are catalyzed by cyclooxygenases (COX) (139). Evidence indicates that prostaglandin E₂ (PGE₂), the most abundant prostaglandin, participates in several carcinogenesis-related processes including cell growth, apoptosis escape, EMT, and angiogenesis (140, 141). PGE₂ is able to bind to four G-protein-coupled EP receptors, EP1-EP4. EP4 is frequently upregulated in cancer cells where it promotes proliferation, migration, invasion, and metastasis (142). In murine pulmonary endothelial cells, PGE₂ enhanced tumor metastasis by promoting release of VEGF through the EP2 receptor pathway (143). EP4 stimulation increased proliferation, invasion, and metastasis of SUM149 IBC tumor cells, and was correlated with aggressive BC subtypes (144, 145).

Besides the role in TME, inflammation also promotes the overproduction of ROS which contribute to BC progression. The interactions between inflammation and ROS in the context of BC is discussed in the next section.

Interplay between inflammation and ROS production in breast cancer

ROS are free radicals, ions or molecules with a single unpaired electron (12); these oxygen-containing molecules are small, short-lived and highly reactive (146). There are more than 20 types of ROS classified into two groups, free oxygen radicals and non-radical ROS (147, 148). The most studied ROS associated with cancer are superoxide anions and hydroxyl radicals of the free oxygen radical group, and hydrogen peroxide of the non-radical ROS group (146).

Intracellular ROS are mainly originated by the mitochondria's electron transport chain. The endoplasmic reticulum, lysosomes, and peroxisomes also produce considerable amounts of ROS (149). ROS have a dual role; at low levels, ROS are signaling molecules in different physiological events including cell growth and survival, apoptosis, and immune response (13, 14). When ROS levels are elevated, for example during a chronic inflammatory event, they induce damage to the DNA, proteins, and lipids. DNA damage results in genetic instability, tumorigenesis and aging (147).

During an inflammatory process associated with the initiation and progression of BC, macrophages and mast cells of the TME produce inflammatory mediators that increase vascular permeability, allowing the migration of leukocytes to the site of damage (150). ROS participate in this process by regulating the expression of molecules such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), P- and E-selectin that are expressed in the endothelial surface and interact with leukocytes, favoring their migration (151). Other molecules that induce cell migration and adhesion are cytokines such as TNF, platelet-derived growth factor, angiopoietin-1, and VEGF. The binding of these chemoattractants and growth factors to cell surface receptors triggers nicotinamide adenine dinucleotide phosphate (NADPH) oxidases to form ROS (152, 153). Additionally, ROS can induce the activation and synthesis of factors responsible of the inflammatory response including hypoxia-inducible factor-1 alpha (HIF-1 α), β -catenin/Wnt, activator protein 1, NF- κ B, peroxisome proliferator-activated receptor gamma, growth factors, and pro-inflammatory cytokines (154–157).

ROS overproduction plays also important role in EMT. During EMT, epithelial cells lose their junctions and their polarity, a cytoskeleton reorganization occurs, and a reprogramming of gene expression that promote mesenchymal properties including cell motility and invasive phenotypes (158, 159). The TGF- β signaling pathway play an important role in EMT and higher levels of TGF- β 1 and TGF- β receptor type II (T β RII) have been observed in BC cells. The pathway through which TGF- β drives EMT and cellular migration in breast epithelial normal and tumor cells partially rely on the NADPH oxidase 4 (NOX4) (160, 161), an enzyme, that is a major source of intracellular ROS (162). Zhang et al. reported that

in the BC cells 4T1, TGF- β induced ROS production and enhanced cell migration (160). These TGF- β -associated effects were mediated by NOX4 because an NOX4 chemical inhibitor and RNAi-mediated NOX4 knockdown significantly decreased TGF- β -dependent cell migration (160). Tobar et al. co-cultured RMF-EG mammary stromal cells and MCF-7 cells to observe the migratory ability of the breast cancer cells. Pre-treatment of RMF-EG cells with TGF- β 1 enhanced the migratory ability by elevating NOX4 expression and intracellular ROS production. These effects were abolished by knocking down NOX4 in RMF-EG cells with small interfering RNA (siRNA) (163). Other reports indicate that TGF- β 1 regulates uPA (Urokinase type Plasminogen Activator) and matrix metalloproteinase 9 (MMP-9) using ROS-dependent mechanisms (164, 165). Additionally, in MCF-7 cells ROS increased tumor migration by inducing MMPs-mediated hypoxia and cathepsin expression (166, 167).

In general, the high levels of ROS, generated by increased mitochondrial metabolic and energetic activity, by alterations in the electron transport chain, by HIF-1 α expression, and/or during a chronic inflammation (168), are responsible for increasing the activation of the PI3K/AKT and MAPK/ERK signaling pathway and cell proliferation (147). Incubation of MDA-MB-231 BC cells with deferoxamine (DFO) increased ROS levels, activated the ERK signaling pathway, increased HIF-1 α expression, and promoted cell migration and invasion of these cells (169). A study by Han et al. found that high levels of epidermal growth factor (EGF) promoted the production of hydrogen peroxide (H₂O₂), and activated p70S6K1 via the PI3K/AKT. This signaling pathway promoted also the VEGF and HIF-1 α production in MCF-7 cells (170). In another report, copper, which in excess is a potent oxidant causing the production of ROS in cells (171, 172), through the EGFR/ERK/c-Fos pathway, increased the expression of VEGF, HIF-1 α , and G-protein estrogen receptor (GPER) in the SKBR3 BC cells (173, 174). Also, in MCF-7 cells ROS activated the PI3K/AKT signaling pathway and increased the expression of HIF-1 α and angiogenesis (175). Together, ROS stimulate growth factors, cytokines, and molecules such as HIF-1 α and VEGF, which induce migration and proliferation of BC cells (176–178). These ROS-dependent signaling pathways activate the PI3K/AKT/mTOR pathway, increasing VEGF production by HIF-1 α dependent and independent mechanisms.

Opposite, ROS are able to induce apoptosis by destabilizing the mitochondrial membrane and opening the mitochondrial permeability transition pore. These events alter the electron transport chain and releases cytochrome-c that, in conjunction with apoptotic peptidase activating factor 1 and procaspase-9 forms apoptosomes. Apoptosomes activate caspase-9, and then caspase-3 which executes the last steps of the apoptosis cascade in the nucleus (179–182). As apoptosis is a desirable mechanism to eliminate undesirable cells, the generation of ROS could be beneficial to eradicate cancer cells in tumors (183–185). Some anticancer agents, such as the natural polyphenol resveratrol,

promotes apoptosis of MCF-7 cells through the accumulation of H₂O₂ in the mitochondria (186).

Together, ROS have a central role in the growth and proliferation of cancerous cells as well as in the TME as mediators of the oxidative stress conditions, and in the inflammatory responses. ROS are not the only molecules involved in these meaningful processes as miRNAs are also able to regulate ROS production. In the next section, we will discuss the interconnection between miRNAs in ROS production during BC progression.

Interplay between miRNAs and ROS in breast cancer

Deregulation of miRNAs in breast cancer

Although only 2% of the human genome is composed of protein coding genes, more than 90% of the DNA is transcribed into RNA (187). RNA molecules that are not translated into proteins are called non-coding RNAs (ncRNAs), whose biological and regulatory functions are still under investigation (188, 189). The first report that ncRNA participate in the regulation of gene expression occurred in 1984 by Mizuno et al. who observed that the *Escherichia coli micF* gene has its own promoter and encodes a small ncRNA that can inhibit translation of *ompF* mRNA by base pairing (190, 191). In the subsequent years it became evident that ncRNAs are a key piece in the regulation of gene expression.

Depending on their function, ncRNAs are classified into two major groups (192). The first group are the housekeeping ncRNAs, which regulate essential cellular functions and includes ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear RNA (snRNA), small nucleolar RNA (snorRNA), and telomerase RNA (TERC) (193). The second group are the regulatory ncRNAs, which regulate gene expression at virtually every level (194). Depending on their size, regulatory ncRNAs are subclassified into small ncRNAs (sncRNAs) which are less than 200 nt in length, and long ncRNAs (lncRNAs) with more than 200 nt of length (193). Regulatory sncRNAs include, tRNA-Derived Fragments (tRE), halves tRNA (tiRNA), siRNA, piwi-interacting RNA (piRNA), enhancer RNA (eRNA), circular RNA (circRNA), Y RNA, and miRNAs. MiRNAs are the most studied sncRNAs due their critical role in the regulation of gene expression (188).

MiRNAs are small non-coding RNAs of about 22 nucleotides in length that regulate gene expression at the posttranscriptional level (18). Most miRNAs are transcribed by RNA polymerase II/III to generate a primary transcript (pri-miRNA) which is processed by microprocessor complex formed by Drosha-DiGeorge syndrome critical region gene 8 (DGCR8) to produce an RNA stem-loop pre-miRNA of ~80 nucleotides in length. Pre-miRNAs are transported into the cytoplasm by RanGTP/exportin 5 (XPO5), where Dicer together with the

transactivation response RNA binding protein (TRBP) generate a mature miRNA duplex. The duplex is loaded into Argonaute (AGO) proteins to form the RNA-induced silencing complex (RISC). RISC promotes miRNA molecules to bind their target mRNA. The ability to regulate gene expression depends on their degree of complementarity between the miRNA and the 3'UTR region of the mRNA target. A total complementary between mRNA and miRNA leads to RNA degradation but, incomplete complementarity causes a partial repression of translation (19).

Deregulation of miRNAs is a phenomenon observed in most cancers, including BC, and has been linked with all steps of carcinogenesis and drug resistance (20). Many deregulated miRNAs have been proposed as diagnostic or prognostic markers and/or as targets for BC therapy (20). In cancerous cells, upregulated miRNAs are known as oncomiRs and generally reduce the expression of genes with tumor suppressor capabilities. Opposite, downregulated miRNAs are known as tumor suppressor miRNAs and due to their absence, their target genes are upregulated acting as oncogenes (19). For instance, miR-145 promotes TNF- α -induced apoptosis in triple negative BC by facilitating the formation of RIP1-FADD/caspase-8 complex (195). On the other hand, miR-146b inhibits apoptosis in BC cells by inhibiting STAT3 and reducing IL-6 production in a NF- κ B dependent manner (196). Moreover, TGF- β can cause an increase in the expression of miR-106b, which promotes tumor growth and metastasis in BC (197).

As it was above mentioned, inflammation plays a fundamental role in BC progression (198). However, the role of miRNAs in this process is still not fully understood. A decade ago, O'Neill et al. described that immune cell populations expressed miRNAs that act on target genes involved in the regulation of the inflammatory process. Such miRNAs act on mRNA of inflammatory-related molecules, including: (i) receptors such as Toll-like receptor 4 (TLR4) (miR-223, let-7i, let-7e), TLR3 (miR-223), TLR2 (miR-105), (ii) signaling molecules such as myeloid differentiation primary-response protein 88 (miR-155), MYD88 adaptor-like protein (miR-145), IL-1R-associated kinase 1 and 2 (miR-146), TNFR-associated factor 6 (miR-146), (iii) transcription factors such as nuclear factor- κ B1 (miR-9), forkhead box P3 (miR-155), p300 (miR-132), (iv) cytokines such as IL-6 (let-7), TNF (miR-16, miR-155, miR-125b, miR-579, miR-369-3), IL-10 (miR-106, miR-466l), IL-12p35 (miR-21), and (v) regulator proteins such as acetylcholinesterase (miR-132), programmed cell death 4 (miR-21), Src homology 2 (SH2) domain-containing inositol-5'-phosphatase 1 (miR-155), and suppressor of cytokine signaling 1 (miR-155) (199, 200). Later, it was recognized that there is a feedback between miRNAs and the immune system to regulate the inflammatory responses and to protect the host from inflammation (201).

Depending on the type and differentiation stage of cells and tissues, a particular miRNA is expressed at different magnitudes.

Also, a miRNA, could be regulated through different mechanisms in normal vs. malignant cells. The innate immune system has the ability to regulate the expression of multiple miRNAs (202). During an inflammatory response, various proinflammatory, signaling pathways, and transcription factors are activated. For example, activation of NF- κ B in macrophages, DCs, and THP-1 cells, upregulates miR-21, miR-146a, and miR-155 (203–205). Enzymes related to inflammatory processes including adenosine deaminase RNA Specific (ADAR1) and Polyribonucleotide Nucleotidyltransferase 1 (PNPT1) are involved in the processing of pri-miRNAs (202).

In some populations of the innate immune system, miRNAs play important roles. Diverse technologies have been used for the analysis of miRNAs and their relationship with the immune system. For instance, Ishii et al. used a NanoString miRNA array to measure the miRNA expression levels in Gr-1+CD11b+ human myeloid cells and found that miR-130a and miR-145 can reprogram tumor-associated myeloid cells by modifying the cytokine milieu and the metastatic microenvironment. These two miRNAs regulate TGF- β receptor II production that results in an enhanced antitumor immune response (206). Chiodoni et al. used Bead array technology (Illumina), to assess whether circulating miRNAs from bone marrow samples were involved in the communication between the nascent cancer and the bone marrow. They identified 80 miRNAs differentially expressed between NeuT mice and the control group. Some of these miRNAs could be responsible for transcriptional alterations in the bone marrow that favor an environment of immune suppression during cancer development. These results provide evidence that deregulated miRNAs alters the immune system in response to the carcinogenesis process (207). Qing et al. found that Kaposi's sarcoma-associated herpesvirus encodes two miRNAs: miR-K12-3 and miR-K12-7. These two miRNAs bind to the 3'UTR of the basic region/leucine zipper motif transcription factor C/EBP and regulate its expression. Upregulation of C/EBP increased IL-6 and IL-10 expression in infected macrophages which resulted in suppression of antitumor immune responses, promotion of tumor cell growth, suppression the T cells activation, and increased angiogenesis (208).

Another effect of miRNAs on the immune response is their regulatory effect on IL-17. Seif et al. found that overexpression of miR-490-5p and miR-490-3p in peripheral blood mononuclear cells (PBMC) and plasma from BC patients led to the production of Th17 lymphocytes and IL-17-producing regulatory T cells (Tregs). This immune response reduced the levels of *CD3d*, *IL-2*, *IL-2 receptor chain alpha*, *forkhead box O1 (FOXO1)*, and *nuclear factor of activated T cells 5 (NFAT5)*; a micro environment that supports tumor progression (209). Soheilifar et al. reported that overexpression of miR-182-5p and miR-182-3p suppresses the FOXO1, NFATs, and IL-2/IL-2RA signaling pathways. On the other hand, these two miRNAs increased the expression of FOXP3, TGF- β , and IL-17 in tumor tissues

engender IL-17-producing Tregs that exert immunosuppressive functions in BC (210).

An effect of miRNAs on some inflammatory mediators such as PGE2 has been reported (211). Kim et al. found that miR-155 is involved in the metabolism of prostaglandins, as this miRNA up-regulates PGE2-producing enzymes (PTGE S/PTGES2) and down-regulates PGD2-producing enzymes (PTGDS). The correlation between high levels of miR-155 and overexpression of PGE2/prostaglandin D2 (PGD2), confirm the importance of this miRNA in the regulation of inflammation during carcinogenesis (211). COX-2 overexpression has been also related to the expression of miRNAs such as miR-526b and miR-655 in an MCF-7-COX2 BC cell line (212, 213). Overexpression of both miRNAs induced stem-like cell phenotypes, and stimulated angiogenesis (212, 214). Furthermore, Hunter et al. reported that the overexpression of miR-526b and miR-655 promoted the expression of angiogenic markers such as VEGF and EP4 receptors (215, 216).

As mentioned above, multiple cytokines and chemokines (TNF- α , TGF- β , granulocyte-macrophage colony-stimulating factor (GM-CSF)), as well as transcription factors (AP-1, NF- κ B, STAT3, HIF-1 α), participate in inflammatory responses during cancer progression. MiRNAs posttranscriptionally regulate the expression of those molecules. For example, miR-421 (targets: *FXR*, *DPC4/SMAD4*, *ATM*), miR-503 (target: *CCND1*), miR-24-3p (targets: *p27*, *p16*), miR-29a (targets: *PTEN*, *GSK3 β* , *TET1*) and miR-451 (targets: *MIF*, *YWHAZ*) play a critical role in the proliferation, migration, invasion, and metastasis of BC. Additionally, miRNAs have a direct effect on ROS regulation, as will be seen in the next section (217–219).

MiRNAs alter ROS production in breast cancer

Deregulation of miRNAs contributes to the production of ROS and therefore to BC progression. For example, Moi et al. reported that the nuclear transcription factor erythroid-derived factor 2-like 2 (Nrf2) and its Kelch-like inhibitor ECH-associated protein 1 (Keap1) (220) are regulators of the oxidative stress responses (221, 222). Under basal conditions of oxidative stress, Nrf2 is sequestered by Keap1 and directed to the proteasome (223). However, if ROS levels increase the Nrf2/Keap1 complex separate and Nrf2 is transferred to the nucleus, where it promotes the expression of encoding antioxidative-related genes such as proteins involved in redox balancing factors, detoxifying enzymes, stress response proteins and metabolic enzymes (223). This mechanism keeps cancer cells from entering apoptosis and favors tumorigenesis (224, 225). Interestingly, Singh et al. reported that Nrf2 is downregulated by miR-93 (226). The overexpression of miR-93 in breast epithelial cells decreases

apoptosis and increased colony formation, mammosphere formation, cell migration, and DNA damage. Opposite effects were observed after miR-93 reduction with vitamin C, an agent that reduce the intracellular levels of ROS (226). Yang et al. found a negative relationship between the expression levels of miR-28 and Nrf2. MiR-28 regulate the expression of Nrf2 in a Keap1-independent manner (227). Eades et al. reported that miR-200a binds to *KEAP1* mRNA, which increase the expression of Nrf2 in BC (228). Yi et al. reported that miR-101 inhibits Nrf2 expression and suppressed the proliferation of BC cells, making them more sensitive to oxidative stress (229). Overexpression of miR-153 reduced Nrf2, inhibited apoptosis and increased colony formation in BC cells (230). The Table 2 summarizes the reported miRNAs that regulate genes involved in the redox signaling pathway in BC (Table 2) (228).

MiRNAs also regulate diverse mitochondrial genes that encode proteins involved in cellular redox homeostasis (see Table 2). Singh et al. overexpressed miR-195 in MCF-7 and MDA-MB-231 BC and performed a gene expression profile. They observed mitochondrial dysfunction due to alterations in fatty acid metabolism or xenobiotic metabolism (236). There was also a reduced expression of various miR-195 target genes including *ACACA*, *FASN*, *HMGCR*, and *CYP27B1* (236). Additionally, they observed a reduction in cell proliferation, invasion, and migration, a reduction in mesenchymal markers, and an increasing in epithelial markers (236). Lou et al. found that both miR-485-3p and miR-485-5p act on peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1 α), a key element in regulation of cellular energy metabolism (237). The absence of this miRNA increased BC migration, invasion, and metastasis (237). Eastlack et al. found that increasing the miR-27b expression inhibited pyruvate dehydrogenase protein X (PDHX) in BC, which leads to altered levels of pyruvate, lactate, and citrate. Increased levels of miR-27a also reduced mitochondrial oxidation and promoted extracellular acidification and cell proliferation (238). More recently, Peng et al. reported that the overexpression of miR-3677 induced proliferation, migration, and metastasis in BC. In this setting, miR-3677 downregulates the expression of transducin-like enhancer of Split3 (TLE3), a transcriptional co-repressor involved in cell proliferation, metabolism regulation, and tumorigenesis (239). This observation suggest that miR-3677 acts as oncomiR in BC by increasing ROS levels (239). On the other hand, during oxidative stress conditions, miR-4485 could be translocated into the mitochondria where it binds to 16S rRNA, leading to an accumulation of ROS and mitochondrial dysfunction. In the mitochondria, miR-4485 regulated the activity of mitochondrial complex I, altered ATP production, activated caspase-3/7, and induced apoptosis. Because miR-4485 is downregulated in BC, its overexpression has been associated with suppression of tumorigenesis (240).

TABLE 2 miRNAs involved in ROS regulation in Breast Cancer.

Pathway	MiRNA	Action	Effect	Reference
Nrf2/Keap1	miR-93	Nrf2 downregulation	Decreases apoptosis, promotes colony and mammosphere formation, increases cell migration and DNA damage	(226)
	miR-28	Nrf2 downregulation	Increases colony formation	(227)
	miR-200a	Keap 1 downregulation		(228)
	miR-101	Nrf2 downregulation	Suppresses cell proliferation	(229)
	miR-153	Nrf2 downregulation	Decreases apoptosis and increases colony formation	(230)
NF- κ B	miR-520/373	NF- κ B, TGF- β	Tumor suppression	(231)
	miR-31	PKCe	Sensitizes to apoptosis	(232)
	miR-30c-2-3p	TNFR/NF- κ B	Reduce proliferaci3n e invasion	(233)
	miR-1246	PKA/PP2A	NF- κ B pro-inflammatory signaling	(234)
	miR-221/222	PTEN	Promote stem-like properties and tumor growth	(235)
Mitochondria and metabolism	miR-195	Acts on <i>ACACA</i> , <i>FASN</i> , <i>HMGCR</i> , <i>CYP27B1</i>	Decreases proliferation, invasion, and migration	(236)
	miR-485-3p miR-485-5p	Act on peroxisome proliferator-activated receptor-gamma Coactivator-1 alpha (PGC-1 α)	Inhibits migration, invasion, and metastasis	(237)
	miR-27b	Suppress PDHX	Promotes cell proliferation	(238)
	miR-3677	TLE3 downregulation	Induces proliferation, migration, and metastasis	(239)
	miR-4485	Acts on 16S Rrna	ROS accumulation	(240)
	miR-342-3p	MCT1	Disrupt energetic fluxes	(241)
	miR-155/miR-143	C/EBP β	HKII expression	(242)
	miR-204-5p	PIK3CB	Regulates growth, metastasis, and immune microenvironment remodeling	(243)
Hypoxia	miR-153	HIF-1 α	Inhibits migration, proliferation, and angiogenesis	(244)
	miR-191	TGF- β	More aggressive tumor	(245)
	miR-18a	HIF-1 α	Reduces metastasis	(246)
	miR-497	HIF-1 α , VEGF	Reduces tumor growth and angiogenesis	(247)
Other	miR-509	Inhibits SOD2	Inhibits proliferation, migration, and angiogenesis	(248)
	miR-500a-5p	TXNRD1 and NFE2L downregulation	Promotes the progression of BC	(249)
	miR-139-5p	Decreases MAT2A	Synergy with radiotherapy, increases ROS production	(250)
	miR-526b miR-655	<i>TCF21</i> and <i>PBRM1</i>	TXNRD1 upregulation	(251)

Many other miRNAs can alter the oxidative stress conditions inside cells. Song et al. found that miR-509 overexpression inhibits proliferation, migration, and angiogenesis in BC cells by downregulating superoxide dismutase 2 (SOD2), a central protein involved in ROS production (248). MiR-500a-5p overexpressed under conditions of oxidative stress, downregulates thioredoxin reductase 1 (TXNRD1) and nuclear factor erythroid 2-like 2 (NFE2L2), two proteins involved in stress responses, whose reduction is related to poor prognosis in BC (249). Transfection of MCF-7 cells with a miR-139-5p mimic followed by radiation increased ROS production and induced apoptosis in BC due to its action on methionine adenosyltransferase 2A (MAT2A). On the other hand, mice treated with a miR-139-5p mimic, completely eliminated the implanted tumor and they remained tumor-free (250).

Shin et al. found that overexpression of miR-526b and miR-655 in MCF-7 cells increased the expression of TXNRD1, and promoted ROS production, for this reason, it could be involved in the tumor growth and metastasis in BC (251). MiR-526b targets *TCF21* whereas miR-655 targets *PBRM1*. Both, *TCF21* and *PBRM1* are negative regulators of TXNRD1, since they inhibit the TXNRD1 expression (Table 2). Furthermore, MCF-7 cells treatment with H₂O₂ promoted the overexpression of these two miRNAs, ratifying that oxidative stress are able to induce the expression of miRNAs (251).

Together, miRNAs are important regulators of ROS and BC progression. The close relationship between miRNAs and ROS is essential to maintain cellular homeostasis. Alterations in miRNA and/or ROS levels could promote BC progression (Figure 1).

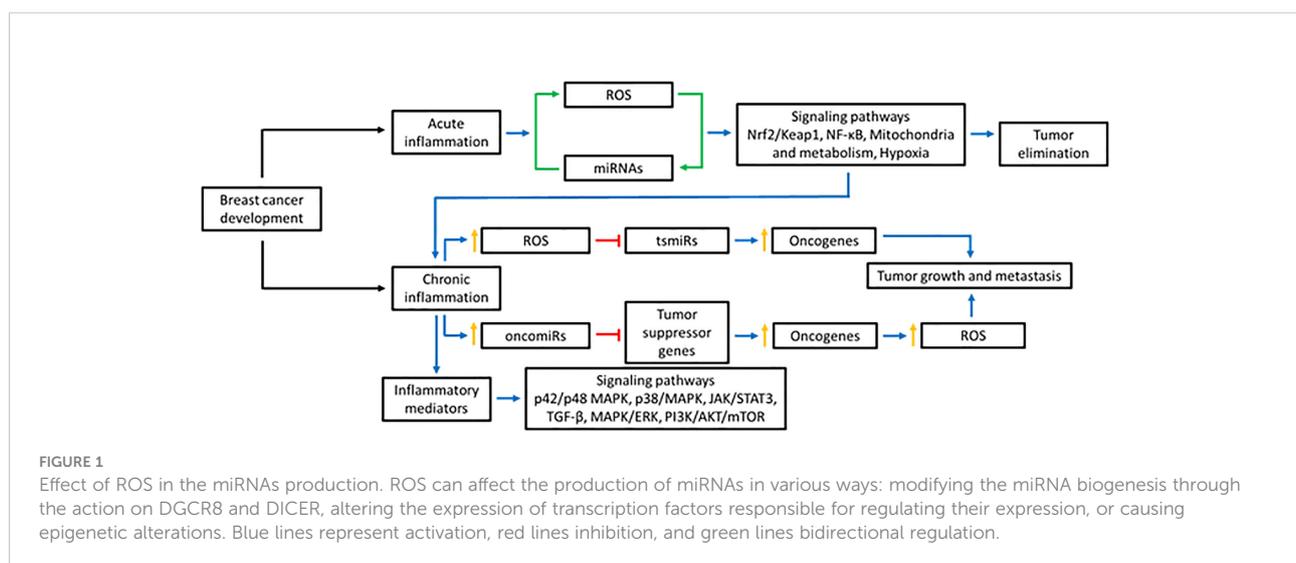
ROS alter miRNAs in breast cancer

Excess of ROS production alters the levels and function of virtually all biomolecules in cells, including miRNAs (22). Early evidence showed alterations in miRNA expression in response to radiation or H₂O₂ in cultured normal human fibroblasts (252). This effect was prevented using cysteine, which acts as a scavenger of free radicals (252). Oxidative stress can induce or decrease the expression of miRNAs through different mechanisms including the alteration of the biogenesis process, deregulation of transcription factors, or inducing epigenetic alterations (253) (Figure 2). For instance, ROS acts on heme groups linked to the heme-binding motif of DGCR8, causing a conformational change that suppresses pri-miRNA processing activity (254–256). Another protein downregulated by ROS is Dicer, which is overexpressed by the action of Nrf2 and had a direct effect on the synthesis of mature miRNAs (257). Let-7, a miRNA overexpressed under oxidative stress conditions, has the ability to suppress the action of Dicer, which is one of its target genes (258). Moreover, it has been reported that aging and ROS alter Dicer expression in cerebrovascular endothelial cells. Exposition of these cells to H₂O₂ reduced Dicer expression and downregulate miRNAs synthesis in around 89% when analyzing the miRNAs expression levels by RT-qPCR (259). Dicer could also work as a negative regulator of ROS production, a mechanism used to maintain redox balance (260). On the other hand, human microvascular endothelial cells with Dicer knockdown exhibited increased levels of HMG-Box Transcription Factor 1 (HBP1). HBP1 acts on p47phox, a subunit of NADPH oxidase, causing a decrease in ROS production and affecting angiogenesis in endothelial cells (260).

Interestingly, ROS are also capable of modifying mature-miRNAs. For example, under oxidative stress conditions, miR-184 suffers an oxidation process that allows it to interact with the 3'UTR region of anti-apoptotic proteins such as BCL-XL and B-cell lymphoma-w (BCL-W). Under normal conditions, genes encoding these proteins are not targets of miR-184 (261).

The expression of miRNAs is regulated by transcription factors such as NF-κB, cellular myelocytomatosis oncogene (c-Myc), AP-1, and HIF-1α, among others. The expression of many of these transcription factors is at the same time altered under oxidative stress conditions (254). For instance, reduced levels of miR-148a and miR-152 caused an increase in the expression of NF-κB (262). By a feedback loop, increased levels of NF-κB increased the levels of those miRNAs which could promote the growth and angiogenesis in BC (262). A CuO nanowire fabricated with folic acid (CuO-Nw-FA) caused a reduction in the NF-κB levels that reduced the expression of miR-425 and caused the overexpression of *PTEN*, a miR-425 target gene (263).

Another oxidative stress-related protein involved in the regulation of miRNAs expression is the endogenous protein kallistatin. Kallistatin promotes the expression of genes with antioxidant activity by at least two reported ways (264). First, kallistatin reduces the expression of TGF-β, through its active site and promotes the synthesis of endothelial nitric oxide synthase (eNOS), reducing oxidative stress, a powerful inducer of EMT process (264). Equally, TGF-β decreases the levels of miR-21, a well-known oncomiRNA, that targets *PTEN*, promoting chemoresistance and invasion (264, 265). Second, kallistatin through its active site stimulated the synthesis of eNOS/Sirt1/FoxO1, a pathway essential to regulate the oxidative stress conditions inside cells (264). Chao et al. found that kallistatin also stimulates the expression of miR-34a and



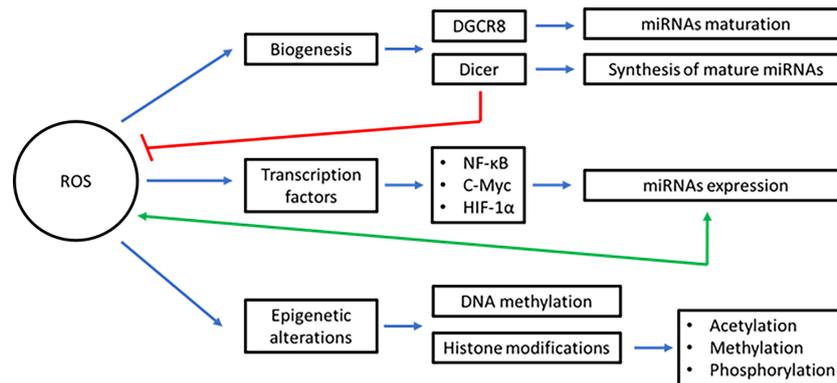


FIGURE 2

Interplay between inflammation, ROS, and miRNAs in BC. To prevent the development/progression of BC, acute inflammation must be resolved. ROS and miRNAs play a key role in this inflammatory mechanism. Instead, during tumor development and tumor maintenance, chronic inflammation occurs. In this process, several inflammatory mediators are generated that deregulate ROS and miRNAs. Furthermore, the production of ROS and miRNAs are interconnected each other and with the inflammatory mediators during all steps of the carcinogenesis process in BC. Blue lines represent activation, red lines inhibition, green lines bidirectional regulation, and orange lines overexpression. (oncomiRs: oncogenic miRNAs, tsmiRs: tumor suppressor miRNAs).

p53, both inhibits the miR-21/AKT/BCL-2 pathway, leading to apoptosis in BC cells (266).

In addition to the effect of ROS on miRNA biogenesis, miRNAs are regulated by ROS at the epigenetic level (254). Some of the epigenetic alterations contributing to the miRNA dysregulation in cancer include DNA methylation and histone modifications (acetylation, methylation, and phosphorylation) (267). DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) are two of the major enzymes epigenetically modifying DNA and histones, respectively (254). Han et al. measured the expression of miRNAs in cell lines that were knockout for DNMT1 and DNMT2 and found that the expression of about 10% of miRNAs are dependent on the DNA methylation status (268). Methylation of CpG regions is also important in the regulation of the expression of miRNAs, where the participation of DNMT3A and DNMT3B has been seen, by not allowing the expression of some regions of the genome (269). Oxidative stress may lead to HDACs degradation, causing changes in the miRNAs expression pattern (270, 271). Oxidative stress caused by glucose deprivation in mouse cells (B/CMBA.Ov) inhibited HDAC2 and induced the acetylation of the promoter region of miR-466h-5p and increasing its expression. These cells exhibited apoptotic features, because miR-466h-5p reduced the expression of some target genes with anti-apoptotic activity such as *bcl212*, *dad1*, *smo*, *birc6* and *stat5a* (270, 272).

To summarize, there is an intricate interconnection between miRNAs and ROS as together they form complex bidirectional regulatory pathways that must be properly regulated to maintain cell homeostasis. Alterations in these pathways can lead to the progression of BC.

Opportunities for therapy

Due to the multiple feedback loops between ROS, miRNAs, and inflammation in the progression and tumor maintenance of BC cells, both ROS and miRNAs have been proposed as targets for therapy (273). First, several miRNAs posttranscriptionally regulate genes associated with ROS production and inflammation. Thus, by regulating certain miRNAs we could reduce ROS and inflammation (274). Second, increased ROS levels could beneficial effects by activating apoptosis in response to chemical drugs or ionized radiation (275). In this line, ROS activates p53 and p38 MAPK making cancer cells more susceptible to treatment (275). Therefore, the use of drugs that promote the controlled formation of ROS could increase the efficacy of conventional therapies such as chemotherapy and radiotherapy (276).

A study of Temiz et al. reported that it is possible to decrease the expression of Chaperonin Containing TCP1 Subunit 3 (CCT3, protein essential in the folding of proteins involved in cell division, proliferation, and apoptosis) by transfecting mimics of miR-24-3p, miR-128-3p, and miR-149-5p in the BC cell line CRL-2329. The mimics promoted apoptosis by causing an imbalance in the intracellular ROS levels (277). Recently, Shang et al. transfected MDA-MB-231 cells with nanoparticles composed of chlorin e6 (Ce6)-anti-miR-21, Ce6-anti-miR-155 and zeolitic imidazolate framework-90 (ZIF-90) and observed a reduction of both miR-21 and miR-155, whereas the photosensitizer Ce6 induced the formation of ROS (278).

The development of resistance to chemotherapy is quite common in BC, and miRNAs are involved in this process. For example, the overexpression of miR-302b reduces cell viability and cell proliferation, making BC cells more sensitive to

cisplatin. This miRNA regulates E2F transcription factor 1 (E2F1), a controller of the G1/S transition (279). Also, miR-125b regulates the resistance to doxorubicin by decreasing the mitochondrial membrane potential (MMP), downregulating the HS-1-associated protein X-1 (HAX-1), and releasing ROS from the mitochondria into the cytoplasm (280). On the other hand, overexpression of miR-24 induces resistance to cisplatin by regulating BCL2 like 11 (BimL), a pro-apoptotic factor in BC cells (281). In addition, miR-24 binds to the mRNA of *FIH1* and reduce its expression. Reduction of *FIH1* increased the expression of HIF-1 α , growth of breast cancer stem cells, and promoted the chemotherapy resistance (281). MiR-668 is overexpressed in BC cells that are resistant to radiotherapy. This miRNA acts on $\text{I}\kappa\text{B}\alpha$, promoting the activation of NF- κB (282). The expression of miR-223 in conjunction with TNF-related apoptosis-inducing ligand (TRAIL) in the MDA-MB-231 cell line caused an increase in ROS levels due to its action on the proto-oncogene *HAX-1*, making the cells more sensitive to doxorubicin and cisplatin (283). Yadav et al. found that the overexpression of miR-5096 downregulates the Solute Carrier Family Seven Number 11 (SLC7A11), a protein related to reducing ROS levels, in the MDA-MB-231 cell line, suggesting that miR-5096 has tumor suppressive roles (284). Wu et al. performed RNA and miRNAs sequencing studies with RNA extracted of healthy and tumor tissues of the breast, and by using bioinformatics found 219 miRNAs related to the ferroptosis, an iron-dependent cell death mechanism, characterized by the intracellular accumulation of ROS (285). All of these miRNAs could be used as targets for BC therapy. Reduced levels of these miRNAs will increase their targets genes, will reduce the ROS production, and will reduce the inflammation associated with BC progression.

Conclusion

The production and regulation of ROS and miRNAs are interconnected each other, both being key regulators of inflammatory processes. Deregulation of these pathways promotes carcinogenesis in most cancer types, including BC. When conditions for oxidative stress exist, ROS overproduction can disturb the levels of various miRNAs. At the same time, deregulated miRNAs will alter ROS production. Alterations in cell homeostasis triggered by inflammatory processes facilitate the progression of BC by inducing processes such as migration, invasion, angiogenesis, drug resistance and/or inhibition of apoptosis. Better knowledge of the mechanisms involved in the

regulation of these molecules it will allow to explore new approaches in the treatment of BC.

Author contributions

Conceptualization PV-M and VG-V. Equal contribution and first authorship: VV-G and JE-J wrote the manuscript draft and elaborated the figures and tables. Review and editing: JV-G, DR-P, PV-M, and VG-V. All authors have read and agreed to the final version of the manuscript.

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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.

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