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Regulation of chemoresponsiveness in triple-negative breast cancer: androgen receptor, ABCG2, and microRNA (Review)

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Abstract

Breast cancer is a highly complex, diverse disease that is classified into several subtypes according to the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Such classification is critical as it determines the best therapeutic strategy for the disease. One subtype of breast cancer that lacks the expression of the three receptors is termed triple-negative breast cancer (TNBC). Consequently, TNBC patients do not benefit from therapies that target ER or HER2 and often require systemic therapy. TNBC represents about 15-20% of all newly diagnosed breast cancers and is responsible for about 5% of all cancer deaths annually. A subgroup of TNBCs expresses androgen receptor (AR), which is thought to be a potential therapeutic target. Published reports have indicated that the AR signaling pathway contributes to the growth and progression of this breast cancer subtype. In addition, AR-positive TNBCs have been reported to have a significantly lower rate of pathological complete response to neoadjuvant chemotherapy and are more chemotherapy-resistant. Targets of AR include the multi-drug resistance transporters such as breast cancer resistant protein (BCRP/ABCG2), a primary cause of resistance to chemotherapy. Interestingly, the *ABCG2* gene has also been shown to be targeted by specific microRNA molecules (miRNAs), which are also under the transcriptional regulation of AR. Herein, the roles of AR, ABCG2, and miRNAs in regulating chemoresponsiveness of breast cancer are presented with a proposal to utilize this knowledge in devising a novel therapeutic strategy of TNBC.

Keywords: Breast cancer, Triple negative breast cancer, Androgen receptor, MicroRNA, ABCG2

1. Introduction

Breast cancer is the most common type of cancer that afflicts women worldwide accounting for approximately 11.6% of all diagnosed cancer cases globally and is the leading cause of cancer death among women (Bray *et al*., 2018). In the USA, the 5-, 10-, and 15-year relative survival rates for breast cancer are 89%, 83%, and 78%, respectively (Miller *et al*., 2016). While breast cancer rates are higher among women in more developed regions, the disease is expected to cause the death of approximately 627,000 women worldwide, which is almost 15% of all cancer deaths among women (WHO, 2019). Data from the 2016 Annual Statistical Report of the Jordanian Ministry of Health indicated that cancer-associated deaths constitute about 16.2% of total mortality reported in 2012, making it the second leading cause of death in Jordan after cardiovascular diseases (representing 36.4%) (Annual Statistical Report of the Ministry of Health, 2016). Importantly, cancer cases are expected to increase reaching levels that will challenge public and private healthcare systems, potentially jeopardizing access of patients to life-saving treatment (Abdel-Razeq *et al*., 2015). In particular, breast cancer has been the most common cancer diagnosed in the Jordanian population overall throughout the years with 1067 cases recorded in 2013 and accounting for 19.7% of all cancer cases reported that year (Annual Statistical Report of the Ministry of Health, 2016).

Classification of Breast Cancer and TNBC

Breast cancer is a highly complex, heterogeneous disease in its histology, cellular origin, metastatic potential, mutations, disease progression, therapeutic response and clinical outcome (Ossovskaya *et al*., 2011). Accordingly, it can be classified into different distinguishable subtypes according to histological features in conjunction with the expression of biomarkers (Lv *et al*., 2011). The most prominent, classifying biomarkers are hormone receptors including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor-like receptor 2 (HER2). The four clinically important breast cancer classes are: (1) 'luminal A', which is ER- and PR-positive, but HER2-negative, (2) 'luminal B', which is ER-positive and/or PR-positive, and HER2- and Ki-67-positive, (3) HER2-enriched, a disease that is characterized by overexpression of HER2 and is ER- and PR-negative, and (4) 'triple-negative breast cancer' or TNBC where all three receptors are not expressed (ER-, PR-, and HER2-negative) (Rakha *et al*., 2007; Boyle, 2012; Brouckaert *et al*., 2013; Lam *et al*., 2014; Parise and Caggiano, 2014). The majority of TNBCs possess basal-like characteristics.

In the USA, TNBC represents about 15-20% of all newly diagnosed breast cancers, and is responsible for

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about 5% of all cancer deaths annually (Dent *et al*., 2007). In addition to its lack of expression of ER, PR and HER-2, this class of breast cancer is characterized by expression of genes usually found to be active in basal or myoepithelial cells of the normal breast (Rakha *et al*., 2007; Rakha *et al*., 2009). Initially, TNBC was further classified into six subtypes: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), immunomodulatory (IM), mesenchymal stem-like (MSL) and luminal androgen receptor (LAR) (Lehmann *et al*., 2011, Masuda *et al*., 2013). However, in a follow-up study, IM and MSL subtypes were found not to be true TNBC and were removed from this category (Lehmann *et al*., 2016). Furthermore, both Burstein *et al*. (2015) and Ding *et al* (2019) classified TNBC into basal-like, immune-activated (BLIA), basal-like immunosuppressed (BLIS), LAR, and MES subtypes. Recently, Jiang *et al*. (2019) classified TNBC into four transcriptome-based subtypes: LAR, IM, BLIS, and mesenchymal-like (MES).

Transcriptional signatures of each breast cancer subtype can be used to support therapeutic decisions, predict outcomes and assist in the management of individual breast cancer patients (Harris *et al*., 2016; Rakha 2017). In addition, ER, PR and HER-2 expressions not only play an important role in the biology of the tumors, but are also determinants of therapeutic strategy. For example, whereas ER-expressing tumors are treated by targeting the receptor with antagonists such as tamoxifen or with inhibitors of the estrogen-producing enzyme, aromatase, HER2-enriched tumors are treated with HER2 inhibitors such as Trastuzumab or Herceptin® (Lewis Phillips *et al*., 2008). There is no effective targeted therapy for TNBC due to the lack of expression of these receptors and TNBC patients, therefore, often require systemic anti-cancer therapy to manage the disease (Brady-West and McGrowder, 2011). TNBC is the most sensitive to chemotherapy amongst breast cancer subtypes (Anders and Carey, 2008; Khokher *et al*., 2013; Cetin and Topcul, 2014). However, TNBC is associated with a higher risk of disease recurrence at earlier times, worse prognosis after recurrence, and higher rates of central nervous system and visceral metastases (Carey *et al*., 2010). This has been referred to as the triple negative paradox (Carey *et al*., 2007). Interestingly, since TNBCs differ in their clinicopathologic characteristics, it has been reported that TNBC subtypes also differ in their response to standardized therapeutic efforts (Choi *et al*., 2012; Masuda *et al*., 2013).

Structure and Function of Androgen Receptor in Breast Cancer

Testosterone is produced by and released from Leydig cells of the male testes and theca cells of the female ovaries, while dehydroepiandrosterone is produced in the adrenal gland of both genders (Smith *et al*., 2013). Testosterone acts as both a hormone and a pro-hormone (Smith *et al*., 2013). It is converted to its more efficacious derivative dihydrotestosterone (DHT) by 5-α-reductase in peripheral tissues, skin, hair follicle, bone, prostate and liver, or by aromatase to the potent estrogen, 17β-estradiol in ovaries, bone, brain, adipose tissue and prostate (Ellem and Risbridger, 2010; Smith *et al*., 2013). The levels of circulating androgens decline with age in both men and women, which can affect bone and muscle integrity and sexual drive in addition to general wellbeing (Davison *et al*., 2005; Gooren 2010).

At the molecular level, the function of androgens is mediated by activation of androgen receptor (AR). DHT has two fold higher affinity for AR and a five-fold lower rate of dissociation when compared with testosterone (Grino *et al*., 1990; Tan *et al*., 2015). AR is a member of the steroid-hormone receptor family, which also includes receptors for estrogen, progesterone, glucocorticoids, and mineralocorticoids (Lubahn *et al*., 1989). The human *AR* gene is located on chromosome Xq11-12 and contains a highly polymorphic CAG repeat sequence within exon 1 (Lubahn *et al*., 1989; Chamberlain *et al*., 1994). The receptor is ubiquitously expressed in human tissues, with the highest levels reported in reproductive tissues (testes, prostate, uterus and ovaries) as well as liver, breast, adipose and muscle tissues (Bookout *et al*., 2006). AR-regulated signals are responsible for male sexual differentiation and reproductive development (Bruchovsky *et al*., 1976). In the absence of ligand, AR exists primarily in the cytoplasm, bound to chaperone proteins that stabilize the receptor in a conformational state that promotes ligand binding (Claessens *et al*., 2008). In the presence of androgens, in particular testosterone and DHT, AR undergoes a series of conformational changes, dissociates from chaperones, then forms a homodimer that translocates into the nucleus (Claessens *et al*., 2008). Inside the nucleus, the hormone-AR complex binds to androgen response elements and recruits co-regulatory activators resulting in the regulation of target gene transcription (Claessens *et al*., 2008). AR expression also has a role in a range of other conditions including acne, male pattern baldness and polycystic ovarian syndrome (Smith *et al*., 2013). Importantly, AR has been shown to play an important role in the development and progression of a number of cancers such as prostate, endometrial, bladder, kidney and breast (Hunter *et al*., 2018).

The AR signaling pathway has a role in breast cancer proliferation. Interestingly, both growth stimulatory and growth inhibitory impacts of androgens have been described in breast cancer cells lines (reviewed in Rahim and O'Regan, 2017). Mechanisms underlying these seemingly paradoxical effects are complex. However, the function of AR in breast cancer pathogenesis may depend on the molecular phenotype of the tumor, the relative coexpression of other hormone receptors, and the hormonal environment (Rahim and O'Regan, 2017). AR expression has been identified in 70-90% of breast tumors, similar to ER expression, and it is commonly found in breast tumors that express ER (Obeidat *et al*., 2018). The prevalence of AR expression in TNBCs is less frequently reported, ranging from 13.7% to 64.3% (Rakha *et al*., 2007; Luo *et al*., 2010; McNamara *et al*., 2013; Asano *et al*., 2017; Obeidat *et al*., 2018). This variability may be due to technical differences among the different studies or to the criteria used to define AR positivity (Rakha *et al*., 2007; Luo *et al*., 2010; McNamara *et al*., 2013; Obeidat *et al*., 2018).

Formerly, androgens, such as fluoxymesterone, testolactone, and calusterone were used for the treatment of advanced breast cancer, resulting in about 18-39% clinical responses (Gucalp and Traina, 2016). However, the undesirable masculinizing side effects of these agents have limited their routine use in the treatment of breast

cancer especially in the advent of newer, less toxic endocrine agents. Currently, there is renewed interest in targeting the AR signaling pathway, particularly in TNBC. In fact, AR-positive TNBC showed preserved androgenic signaling that can be used as a possible therapeutic target similar to ER-positive breast cancers (Lehmann *et al*., 2011; Gucalp *et al*., 2013). Several clinical trials currently underway have illustrated the efficiency of anti-androgen therapy for the treatment of AR-positive TNBC (Gucalp *et al*., 2013; Bonnefoi *et al*., 2016).

AR-positive TNBCs have different clinicopathologic characteristics than compared to AR-negative TNBCs. One such difference is reported in disease-free survival whereby AR-positive TNBC patients survive longer after recurrence than those with AR-negative TNBCs (Asano *et al*., 2017). In addition, patients with AR-positive TNBC have a better prognosis and delayed disease recurrence (Luo *et al*., 2010; Asano *et al*., 2017). Most AR-positive TNBCs could be categorized as the LAR subtype (Asano *et al*., 2017), associated with lower Ki-67 index (McNamara *et al*., 2013), postmenopausal status, positive nodal status (Luo *et al*., 2010), higher tumor grade, and development of distant metastasis (Rakha *et al*., 2007). It is also important to note that some studies have suggested positive correlations between AR positivity and progressive disease or poor prognosis (Hu *et al*., 2011). Thus, debate still exists concerning the clinical significance of AR expression in TNBC (Fioretti *et al*., 2014).

Reason(s) for the increased survival of patients with AR-positive TNBC have not been identified and might be due to differences in sensitivity to conventional treatments or to the innate nature of this tumor phenotype (Asano *et al*., 2017). AR-positive TNBCs have been reported to have a significantly lower rate of pathological complete response (pCR), of about 10%, to neoadjuvant chemotherapy (NAC) and are more chemotherapy-resistant (Asano *et al*., 2016; Lehmann *et al*., 2016). Therefore, it is hoped, as will be detailed in the next section, that the status of AR expression in TNBC may aid in determining the best strategy of breast cancer treatment and the use of AR-targeted therapy (Gucalp and Traina, 2016).

Role of ABCG2 in Breast Cancer

Development of chemoresistance is a significant obstacle in the effective treatment of breast cancer. Overexpression of multi drug resistance (MDR) transporters is one of the most important causes of chemoresistance (Szakács *et al*., 2006) and members of the ABC transporter family members are the most widely studied MDR transporters (Gottesman and Ling, 2006). ABC transporters use ATP hydrolysis to control the absorption, distribution, and clearance of numerous substances, including hormones (e.g. folates and dihydrotestosterone), pharmaceutical agents, dietary carcinogens and conjugated metabolites (Huss *et al*., 2005; Vore and Leggas, 2008). In addition, they have similar trans-membrane domains that can pump chemotherapeutic drugs out of cancer cells against a concentration gradient in an ATP-dependent manner, thus reducing intracellular accumulation of such agents and sparing cancer cells from toxicity (Huss *et al*., 2005; Vore and Leggas, 2008).

To date, 48 ABC transporters have been identified in the human genome (Vasiliou *et al*., 2009), among which the most extensively characterized are P-glycoprotein (P-gp/ABCB1), multidrug resistance associated protein-1 (MRP1/ABCC1), and breast cancer resistant protein (BCRP/ABCG2) (Huang *et al*., 2014; An *et al*., 2017). ABCG2 is a 72 kDa protein that has many substrates, which include tyrosine kinase inhibitors (TKIs) (e.g. imatinib and gefitinib), anthracyclines (e.g. doxorubicin), camptothecin-derived topoisomerase I inhibitors, disease-modifying anti-rheumatic drugs (e.g. methotrexate), and cyclin-dependent kinase inhibitors (e.g. flavopiridols) (An *et al*., 2017). Recent studies have demonstrated that transcriptional factors and nuclear receptors and epigenetic factors play important roles in the regulation of *ABCG2* expression in different model systems (To *et al*., 2008a).

An ABCG2-expressing side population (SP) is present in normal and cancerous tissues (Mathew *et al*., 2009). ABCG2 expression and function are well studied in prostate cancer where expression is found in ~1% of cells in the basal compartment (Huss *et al*., 2005). ABCG2-expressing prostate tumor cells have been detected in tissue biopsies following androgen deprivation therapy (Huss *et al*., 2005) and ABCG2 expression is upregulated upon androgen blockade *in vitro* (Huss *et al*., 2005; Pfeiffer *et al*., 2011). Moreover, ABCG2-expressing SP cells in the prostate demonstrate multipotency and self-renewal properties, suggesting an enrichment of stem cells in this population (Huss *et al*., 2005; Foster *et al*., 2013). An earlier study has shown the ability of ABCG2 to efflux the AR antagonist bicalutamide in prostate cancer tissues (Colabufo *et al*., 2008). Another study has shown a link between AR signaling and ABCG2 at various levels where inhibition of ABCG2-mediated androgen efflux led to increased nuclear AR expression concomitant with induced expression of AR target genes, delayed cell growth response and cell differentiation mediated by AR, delayed tumor progression and increased overall survival *in vivo* (Sabnis *et al*., 2017).

In breast cancer, higher levels of ABCG2 were correlated with a reduced efficacy of chemotherapy and poorer outcome in breast cancer patients (Kim *et al*., 2013). ABCG2 has been described as a stemness marker for various histological breast cancer subtypes (Collina *et al*., 2015). Furthermore, it was suggested that ABCG2 alone can be considered a suitable marker for breast cancer, in particular for the TNBC phenotype, but this observation was limited to cellular models (Britton *et al*., 2012). Interestingly, ABCG2 has been shown to be down-regulated in androgen-treated breast cancer cells affecting chemoresistance to mitoxantrone, a topoisomerase II inhibitor (Chua *et al*., 2016). The last report suggests that AR activation may influence the chemoresponsiveness of breast cancers.

MicroRNA and Their Significance in Breast Cancer

The variable expression of specific genes in tumor cells, including cell surface receptor proteins, mutated genes, and microRNAs (miRNAs or miRs) has been shown to predict the likelihood of cancer progression. miRNAs have significant potential in clinical research since they have important regulatory biological roles, are detected in different tissue types including serum and are relatively stable in formalin-fixed paraffin-embedded

tissue samples, suggesting that they can be used as biomarkers (Sethi *et al*., 2014; An *et al*., 2017). MiRNAs are short, single-stranded, non-coding RNAs of 20–25 nucleotides in length, and are widely conserved among species (Christodoulatos and Dalamaga, 2014). Since their discovery in 1993, around 2600 unique mature human miRNAs have been identified and more are expected to be detected (miRBase version 20) (Kozomara and Griffiths-Jones, 2013). Most miRNAs are located in non-coding intronic regions, but some are located in exonic regions (Rutnam *et al*., 2013). The main function of miRNAs is post-transcriptional gene silencing via directly and specifically base-pairing of their conserved 5′-heptametrical seed sequence with the 3′ untranslated region (3′-UTR) of multiple target messenger RNAs (mRNAs). Consequently, they induce either mRNA degradation if base-pairing is perfect or decrease the rate of protein translation if the match is imperfect (Rutnam *et al*., 2013; Subtil *et al*., 2014). It is worth noting that miRNAs are not always associated with inhibitory or down regulatory effects. In rare circumstances, dependent on cell cycle phase and co-factor expression, miRNAs can activate mRNA translation, thus up regulating protein levels (Vasudevan *et al*., 2007).

More than 50% of all translated human genes are regulated by miRNAs and this type of gene regulation controls many facets of cell signaling pathways in both normal and tumor tissues (Rutnam *et al*., 2013; Subtil *et al*., 2014). Moreover, each miRNA can regulate numerous target genes, and the same target gene can be regulated by multiple miRNAs, creating a complex network of molecular interactions (Esteller 2011; Mendell and Olson, 2012; Spizzo *et al*., 2012). The inherent complexity of this regulatory system allows miRNAs to control the global activity of the cell including cell differentiation, proliferation, stress response, metabolism, cell cycle, apoptosis, and angiogenesis (Gebert and MacRae, 2019). Comparison of human plasma or tissue samples from cancer patients *vs.* cancer-free individuals by miRNA microarray has revealed evidence of deregulation of several miRNAs in many cancers including breast cancer (Sethi *et al*., 2014; An *et al*., 2017). Different miRNA expression profiles between cancerous cells and paired normal tissues from the same organ have been documented in a number of studies (Lu *et al*., 2005; Zhu *et al*., 2014). As such, it is proposed that miRNAs influence cancer development, metastasis, angiogenesis and drug resistance (Liang and He, 2011; An *et al*., 2017).

MiRNAs are reported to be aberrantly expressed in human breast cancers compared with normal breast tissue, with affected miRNAs having tumor suppressing or oncogenic effects. Furthermore, several studies have demonstrated that diverse cancer types at different developmental stages display unique miRNA expression profiles (Puppin *et al*., 2014). Down-regulated miRNAs include miR-10b, miR-125b and miR-145 (Iorio *et al*., 2005), and the re-introduction of under-expressed miRNAs has been shown to reduce the viability of cancer cells, suggesting tumor-suppressor functions and antiproliferative and /or pro-apoptotic roles (Lu *et al*., 2005; Zhu *et al*., 2014). In contrast, oncogenic miRNAs (oncomiRs) display antiapoptotic activities and are over-expressed in cancer cells (Nugent 2014). An example is miR-21, which was found to be overexpressed in breast tumors compared to matched normal breast tissues (Si *et al*., 2007). Inhibition of miR-21 resulted in cell growth inhibition in association with increased apoptosis and decreased cell proliferation (Si *et al*., 2007). Expression of miR-21 was also found to be associated with specific features of breast cancer such as expression of ER and PR, tumor stage, vascular invasion, and proliferation (Yan *et al*., 2008).

Changes in the expression of miRNAs and/or their functional roles in TNBC, particularly, have also been investigated. Differential expression of some miRNAs have been proposed as prognostic biomarkers such as miR-9, miR-15, miR-588 (Jang *et al*. 2017; Nama *et al*., 2019). Several circulating miRNAs were identified in the sera of early-stage TNBC patients (miR-126-5p and miR-34a) (Kahraman *et al*., 2018). In addition, numerous published studies have elucidated the association of miRNAs with TNBC progression or suppression (Piasecka *et al*., 2018). One example is miR-20a-5p that promotes the growth of triple-negative breast cancer cells through targeting RUNX3 (Bai *et al*., 2018). MiR-9 was also been shown to exhibit a suppressor-like activity in metastatic TNBC cells by direct targeting of NOTCH1 (Mohammadi-Yeganeh *et al*., 2015). Migration and invasion of TNBC have been proven to be affected by several miRNAs. Examples include miR-124, which regulates epithelial-to-mesenchymal transition (EMT) via targeting ZEB2, thereby inhibiting invasion and metastasis in TNBC (Ji *et al*., 2019). It was reported that Let-7 miRNA controls metastasis and stemness of TNBC cells by regulating the JAK-STAT3 and cMyc pathways (Lyu *et al*., 2014). Furthermore, the role of miR-10a in suppressing breast cancer progression via the PI3K/Akt/mTOR pathway was illustrated (Ke and Lou, 2017).

Significant changes in miRNA expression profiles have been observed in drug-resistant cancer cells in comparison with parental drug-sensitive cancer cells (Fojo 2007). Evidence pointing to the role of miRNAs in determining drug sensitivity and MDR is emerging (Wang *et al*., 2015). One example is miRNA-451 whose expression correlates with an increased sensitivity of MCF-7 cells towards doxorubicin (Kovalchuk *et al*., 2008). The dysregulation of miRNA expression profiles in cancer cells can lead to resistance towards anti-cancer drugs by abnormally modulating the expression of genes involved in MDR action such as genes encoding ABC transporters, apoptosis and autophagy regulators, regulators of drug metabolism, and genes associated with redox systems (Wang *et al*., 2015). Therefore, miRNAs may drive tumorigenesis or may be used as diagnostic and prognostic biomarkers, and can potentially be targeted in order to improve treatment responses.

Dysregulation of numerous miRNAs has been linked to the chemoresponsiveness of TNBC (Rizzo *et al*., 2017; Ouyang *et al*., 2014). For example, upregulating miR-33a-5p significantly increased cell sensitivity toward doxorubicin in TNBC, but not other breast cancer types (Guan *et al*., 2019). Downregulation of miR-27b-3p also desensitized cells to tamoxifen in TNBC by increasing NR5A2 and CREB1 expression (Zhu *et al*., 2016). Interestingly, tamoxifen has also been shown to reverse EMT in TNBC as well as their metastatic capability by down-regulating miR-200 (Wang *et al*., 2017). One mechanism by which miRNA can affect

chemoresponsiveness of cells is via manipulating DNA repair efficiency as shown for miR-302b (Cataldo *et al*. 2016). Another mechanism has also been illustrated for miR-5195-3p, which enhances the sensitivity of paclitaxel-resistant TNBC cells by down-regulating EIF4A2, a helicase upregulated in proliferating cells (Liu *et al*., 2019). These findings, and others, strongly implicate the possibility of alternative therapeutic strategies for the disease.

Androgen Regulation of MiRNA in Breast Cancer

Published studies have predominantly focused on the association of AR with miRNA expression in prostate cancer. A few studies, however, have analyzed the regulation of miRNA expression by androgens in breast cancer. For example, Nakano *et al*. (2013) showed that five miRNAs were dysregulated in MCF-7 cells using PCR microarray. Lyu *et al*. (2014) showed that expression of four miRNAs, let-7a, b, c and d was up-regulated in androgen-treated MDA-MB-453 cells while other 7 miRNAs were downregulated. The regulation of miRNA expression by androgens in MDA-MB-453 cells has also been studied using PCR arrays by Ahram *et al*. (2017) reporting the differential expression of 20 miRNAs. Interestingly, only three microRNAs, let-7a, b, and d were found to be commonly altered in the former two studies but with a different trend where Lyu *et al*. (2014) reported their up-regulation, whereas they were down-regulated by the study of Ahram *et al*. (2017). Ahram *et al*. (2017) also analyzed the regulation of miRNA expression by androgens in MCF-7 and T47D cells. However, none of the reported changes were common with those reported by Nakano *et al*. (2013). These discrepancies in the results could be due to the type and concentration of agonist used, the duration of experiments, and/or passage number of cells. Further work by our group has identified a number of miRNAs, including miR-328-3p, whose expression was up-regulated upon androgen treatment of the TNBC MDA-MB-231 cells (Al-Othman *et al*., 2018). The general experimental conditions and results of these studies are summarized in Figure. 1.

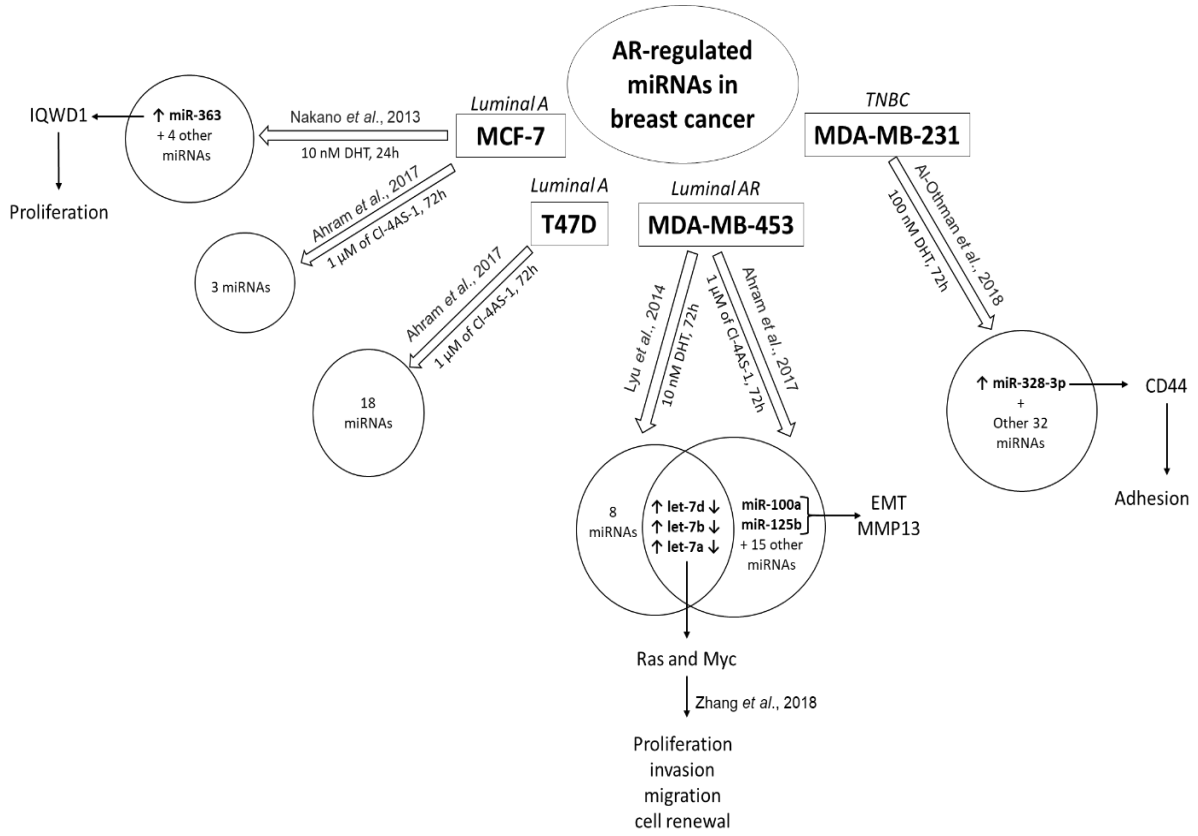

Figure 1. Androgen regulation of miRNAs in breast cancer and their cellular effects

MiRNAs Regulate ABCG2 Levels

A number of miRNAs have been shown to regulate the expression of proteins involved in the chemoresponsivness of cancer (Pan *et al*., 2009; Bockhorn *et al*., 2013; Wang *et al*., 2019). ABCG2/BCRP was the first MDR transporter found to be regulated by miRNA (To *et al*., 2008b). To date, several miRNAs have been shown to regulate ABCG2 expression, including miR-328, which has been shown to increase mitoxantrone sensitivity by negatively regulating ABCG2 protein expression via binding to target sites in the *ABCG2* gene 3'-UTR (Pan *et al*., 2009; Li *et al*., 2010; Li *et al*., 2011). Restoration of miR-328 expression as a therapy could therefore improve treatment outcomes, particularly responsiveness to doxorubicin and mitoxantrone, both of which are two substrates for ABCG2 (Pan *et al*., 2009; Li *et al*., 2010). Other miRNAs have similar negative regulatory effects on ABCG2 expression including miR-519, miR-520h, miR-212, miR-181a, and miR-487a (Li *et al*., 2011; Turrini *et al*., 2012; Jiao *et al*., 2013; Ma *et al*., 2013).

2. Conclusion

AR is an important regulator of breast cancer growth and has been proposed to be a potential therapeutic target.

The observations that AR can control cancer chemoresponsiveness can be highly significant in the clinical setting. However, the molecular mechanisms by which it can do so are incompletely characterized. One interesting mechanism is via miRNA molecules that regulate the expression of transporters involved in drug efflux such as ABCG2. Findings that AR can regulate both ABCG2 and its targeting miRNAs constitute an intriguing mechanism of regulation. Understanding of these molecular mechanisms may lead to novel and more effective therapeutic strategies of TNBC based on AR targeting of both ABCG2 and ABCG2-regulating miRNA.

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