

Review Article

Reza Amiri, Poorya Najjari Nabi, Ahmad Fazilat, Fatemeh Roshani, Alireza Nouhi Kararoudi, Mohsen Hemmati-Dinarvand* and Mohammad Valilo*

Crosstalk between miRNAs and signaling pathways in the development of drug resistance in breast cancer

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Abstract: One of the biggest challenges of today's society is cancer, which imposes a significant financial, emotional and spiritual burden on human life. Breast cancer (BC) is one of the most common cancers that affects people in society, especially women, and due to advanced treatment strategies and primary prevention, it is still the second cause of cancer-related deaths in society. Various genetic and environmental factors are involved in the development of BC. MicroRNAs (miRNA)s are non-coding RNAs, that the degradation or inhibition of them plays an important role in the prevention or development of cancer by modulating many cellular pathways including apoptosis, drug resistance, and tumorigenesis. Drug resistance is one of the important defense mechanisms of cancer cells against anticancer drugs and is considered one of the main causes of cancer treatment failure. Different miRNAs, including mir-7, mir-21, mir-31, and mir-124 control different cell activities, including drug resistance, through different pathways, including PI3K/AKT/mTOR, TGF- β , STAT3, and NF- κ B. Therefore, cell signaling pathways are one of the important factors

that miRNAs control cellular activities. Hence, in this study, we decided to highlight an overview of the relationship between miRNAs and signaling pathways in the development of drug resistance in BC.

Keywords: breast cancer; drug resistance; miRNA; signaling pathways

Introduction

Contrary to the increasing prevalence of breast cancer (BC) in recent decades, the death rate from this cancer has decreased [1]. In the past few years, the prevalence of BC has statistically increased more than lung cancer. BC, which accounted for 11.7 % of all cancers in 2020, affected about 2.3 million individuals. Since the use of mammography, the rate of BC detection has increased, a trend that continues with the aging of the population. The death rate from BC is lower in developed countries than in developing countries. In developed countries, due to the improvements in technology, modern treatments, and diagnostic methods, the death rate from BC has declined [2, 3]. The mortality rate of BC in China is the highest among women aged 13–44 years. The average age at which BC is diagnosed in China is about 49 years, which is significantly different from that in the United States, which is about 60 years [4, 5]. The pathophysiology of BC is complex and not fully understood. Female gender and aging are the most important risk factors [6]. Among the key genetic mutations associated with BC are BRCA1-associated RING domain 1 [BARD1], BC1/2 [BRCA1/2], RAD51 homolog C [RAD51C], ATM, BRCA2 [PALB2], and checkpoint kinase 2 [CHEK2]. Premature menstruation, late menopause, a high body mass index (BMI), dense breasts, and hormone therapy after menopause are BC risk factors [7–9]. One of the most basic methods of BC treatment is surgery along with auxiliary treatments, such as chemotherapy, hormone therapy, radiotherapy, or a combination of these approaches. Cancer cells become resistant to drugs and treatment via various mechanisms that have been identified during treatment. Multiple drug resistance (MDR),

*Corresponding authors: Mohsen Hemmati-Dinarvand, Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran, E-mail: mohsenhemmati@gmail.com. <https://orcid.org/0000-0002-1726-370X>; and Mohammad Valilo, Department of Biochemistry, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran, E-mail: valilo.biomed@gmail.com. <https://orcid.org/0000-0002-7675-3995>

Reza Amiri, Nargund College of Pharmacy, Rajiv Gandhi University of Health Sciences, Bengaluru, Karnataka, India

Poorya Najjari Nabi, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

Ahmad Fazilat, Department of Genetics, Motamed Cancer Institute, ACECR, Tehran, Iran

Fatemeh Roshani, Department of Biology, Faculty of Natural Science, University of Tabriz, Tabriz, Iran

Alireza Nouhi Kararoudi, Department of Biology, Faculty of Sciences, Rasht Branch, Islamic Azad University, Rasht, Iran

ATP-binding cassette (ABC) transporter, adaptive signaling pathways, unprogrammed apoptosis, and epigenetic changes are among the mechanisms that contribute to drug resistance in cancer cells [10]. miRNAs are a group of non-coding RNAs with approximately 20–25 nucleotides that bind to the 3' untranslated region (UTR) of mRNA through their 5' UTR and suppress gene expression after transcription. Gene expression is involved in metastasis, carcinogenesis, and cancer response. Growing studies have shown that the dysfunction of miRNAs is associated with drug resistance in cancer cells. miRNAs can affect the expression of hundreds of genes, or a target gene can be regulated by several different miRNAs. One of the most important factors that regulate the function of miRNAs are exosomes, which transfer miRNAs from donor cells to recipient cells in the tumor microenvironment [11–14]. On the other hand, various studies have revealed that miRNAs play a role in different cellular processes, including angiogenesis, apoptosis, cell growth, cell proliferation, and inflammation. miRNAs contribute to these cellular processes mostly through interaction with cellular signaling pathways [15]. Moreover, signaling pathways play a vital role in controlling cellular processes, including cell division, transcription, translation, cell cycle, cell growth and proliferation, and apoptosis [16, 17]. According to the above-mentioned findings, miRNAs are one of the main regulators of cellular processes, exerting their control mostly through interaction with signaling pathways. Therefore, in this review, we decided to clarify the relationship between miRNAs and signaling pathways in order to examine their role in the development and progression of BC, or conversely, in preventing the development and progression of this disease.

Methods

In the present study, we conducted literature search using the PubMed database, Semantic Scholar, and Google Scholar search engines. It is noteworthy that in this review, we identified articles that were related to our research topic and were written in English. In addition, the search for articles was conducted between November 2022 and December 2023. To find articles related to the topic, keywords including drug resistance, miRNAs, breast cancer, and signaling pathways were used. Moreover, in the review article, we were willing to examine the articles related to this topic from 2001 to 2023. Therefore, articles that were outside the specific time frame of our study or were in languages other than English were excluded.

BC

The second leading cause of cancer death among women is BC. One of the most effective methods to prevent BC is early detection. In developed countries, due to early detection, the survival rate of patients with BC is about 80 %. In recent years, significant progress has been made in understanding the pathogenesis of the disease, diagnostic methods, and drug resistance mechanisms through the study of BC stem cells (BCSCs) [18]. There are two main theories about the origin of BC: The random theory and the cancer stem cell theory. The random theory states that cancer originates from a single cell and various mutations can accumulate in this cell, leading to its transformation into a cancerous cell. Cancer stem cell theory suggests that stem cells are the origin of all tumor subtypes. Different genetic and epigenetic mutations in progenitor and stem cells lead to different cancer phenotypes [19]. BC is divided into different groups based on the presence of biomarkers, metastasis, tumor size, estrogen and progesterone receptors, and ERBB2 receptor. Stage zero BC, referred to as ductal carcinoma *in situ* (DCIS), is a non-invasive form of BC. Stages I, IIa, and IIb are the initial invasive stages, and stages IIIa and IIIb involve advanced local invasiveness. The fourth stage is the metastatic stage [20, 21]. DCIS involves the microcalcification of the ducts of the breast. Women with DCIS are treated with radiation therapy, lumpectomy, and mastectomy. Systemic treatments include immunotherapy with monoclonal antibodies, chemotherapy, radiation therapy, and endocrine treatments before and after surgery for non-metastatic BC. In the metastatic stage, BC metastasizes to the lungs, liver, and brain. Patients with metastasis can rarely be cured, and their survival rate is 2–3 years [22, 23].

However, treatments such as radiation therapy, chemotherapy, immunotherapy, and surgery are performed for purposes such as reducing the symptoms and improving patients' quality of life [24]. BC treatment faces many challenges. The emergence of miRNAs as biological biomarkers has provided a new perspective on the treatment and diagnosis of BC. In BC, miRNAs play a significant role in the growth and proliferation of cancer cells and tumorigenesis [25]. There are many similarities between the growth of cancerous cells and normal cells. In healthy humans, cell growth is controlled by complex signaling pathways that allow cells to communicate with their surrounding environment. However, this regulatory system is disrupted in cancer cells, causing them to escape from the mechanisms that control the growth, proliferation, and migration of cells. Therefore, the activating mutations of proto-oncogenes lead to the activation of more signaling pathways and the inactivation of tumor

suppressors, resulting in the elimination of negative regulators of signals [26, 27].

Drug resistance

One of the main problems in cancer treatment is the drug resistance that develops in cancer cells when exposed to drugs and chemicals. This complex mechanism operates via correlation with complicated signaling pathways. Cells usually develop drug resistance via increasing uptake and decreasing efflux through ABC drug transporters, the glutathione S-transferase π (GST π) gene, tumor microenvironment regulation, evasion from apoptosis, and the BC resistance protein (BCRP) gene. One of the most important members of the ABC transporter group is P-glycoprotein (P-gp), which is encoded by the MDR1 gene. Overexpression of P-gp causes resistance to anticancer drugs including tamoxifen, anthracyclines, platinum-based drugs, plant alkaloids, and taxanes. According to previous studies, changes in the structure and function of the estrogen receptor (ER), including ER gene mutations, reduction or loss of ER expression, abnormality of ER activators, post-translational modification of ER, and interference between ER and phosphoinositide 3-kinase (PI3K)/AKT/mTOR, HER2, mitogen-activated protein kinase (MAPK) pathways/ERK and HER2 are among the most important endocrine resistance mechanisms [28]. One of the factors controlling P-gp is miRNAs, which modulate the drug resistance of cancer cells [29, 30]. As an example, in drug-resistant MCF-7, the expressions of miR-345 and miR-326 are suppressed. Increasing the levels of these miRNAs directly by decreasing MRP enhances the sensitivity of MCF-7 cells to chemotherapy drugs [31]. In one study, miR-19 expression was reduced in the sensitive MCF-7 cell line contrary to three MDR BC cell lines (BCRP, MRP-1, and over-expressing MDR-1). miR-19 decreased the sensitivity of cells to chemotherapeutic drugs in MDR cells through modulating PTEN [32]. This paraclinical evidence indicates that miRNAs modulate the drug resistance of BC cells through different mechanisms, particularly signaling pathways.

miRNAs

miRNAs, which are non-coding RNAs about 22 nucleotides in length, are transcribed by RNA polymerases II and III. The pre-miRNAs produced by Drosha and DGCR8 are processed and generate 70-nucleotide RNAs. Pre-miRNAs are transported to the cytoplasm by exportin 5 and separated by Dicer, producing 22-nucleotide RNAs. Then these mature

miRNAs interact with Argonautes and complexes with other proteins to form the RNA-induced silencing complex (miR-ISC), which combines with target mRNAs and causes the degradation or inhibition of mRNA functions [33, 34]. Transcription factors involved in mRNA transcription also control the transcription of miRNAs. In addition to the transcription factor that plays a crucial role in the biogenesis of miRNAs, the expression of miRNAs can also be regulated by other factors, such as DNA methylation. The miRNA binds to the 3' UTR of the target mRNA through its 5' UTR. If the miRNA is fully complementary to the target mRNA, the target mRNA undergoes degradation; however, if the miRNA is complementary to the mRNA in only a limited number of nucleotides, the target mRNA is inhibited [35, 36] (Figure 1). Growing studies have revealed that miRNAs significantly contribute to tumor progression. miRNAs are differentially expressed based on the tumor subtype, and tumors can be classified based on the expression profile of miRNAs. Tumor suppressor miRNAs are mostly located in fragile chromosomal regions; therefore, mutation or damage to these regions leads to the disruption of tumor suppressor genes and causes the upregulation of oncogenes. Moreover, the proliferation of chromosomal regions encoding oncogenic miRNAs that suppress tumor suppressor genes plays a key role in cancer development [37–39]. According to the literature, miRNAs can affect self-renewal and drug resistance by regulating the characteristics of cancer stem cells, such as tumorigenesis. Therefore, many miRNAs are known as oncogenes or tumor suppressors in BC and regulate tumor initiation, drug resistance, and metastasis [40, 41]. By targeting ABC, miRNAs increase the chemosensitivity of cells to chemical drugs. Additionally, miRNAs are associated with drug resistance via other mechanisms. For example, miRNAs cause drug resistance by regulating proteins and signaling pathways that control important cellular processes, such as cell cycle and drug resistance [42]. Mir-452 causes the resistance of MCF-7 BC cells to adriamycin (ADR) by expressing insulin-like growth factor 1 receptor (IGF-1R) [43, 44]. The study by Zhang et al. revealed that miR-3646 leads to the resistance of MCF-7 cells to docetaxel chemotherapy by inhibiting the expression of glycogen synthase kinase 3 β (GSK-3 β) and the subsequent induction of the GSK-3 β /beta-catenin pathway [45] (Table 1).

Tumor microenvironment in drug resistance of BC

The tumor microenvironment (TME), which is made of connective tissue, consists of different cells and a network of glycoprotein, proteoglycan and collagen called the extracellular

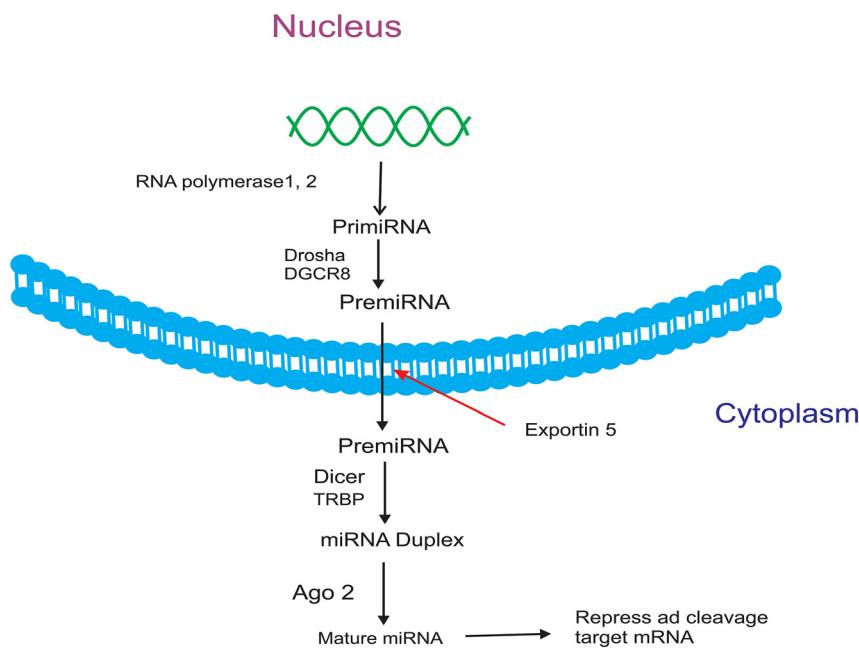


Figure 1: miRNA biosynthesis.

Table 1: miRNAs that regulate drug resistance in breast cancer.

Drug	miRNA	Ref
Anastrozole	miR-125b or miR-205, miR-424	[75]
Capivasertib	miR-4649-5p	[76]
Fulvestrant	microRNA-221/222, miR-3188, miR-21, miR-149	[77–79]
Lapatinib ditosylate	miR-630	[80]
Letrozole	miR-128a, miRNA181a, miRNA22	[81, 82]
Olaparib	miRNAs-181a/b	[83]
Palbociclib	miRNA-3613-3p, miR-29b-3p, miR-223, miR-432-5p, miR-106b, miR-432-5p	[84–88]
Pertuzumab	miRNA-150, miR-146a-5p	[89, 90]
Trastuzumab	miRNA-542-3p, miR-21, miR-23b-3p, miR-195-5p, miR-656-5p, miR-340-5p, miR-1246, miR-155	[91–95]
Tamoxifen	miR-221, miR-222, miR-15a, miR-16, miR-200b, miR-200c, miR-375, miR-301, miRNA-27b-3p, miR-342	[96–101]
Doxorubicin	miR-200c, miR-298, miR-221-3p, miR-451, miR-145, miR-124-3p, miR-134, miR-140-5p, miR-128, miR-519a	[102–106]
Adriamycin	mir-452, mir-29a, mir-221, mir-222, miR-7	[107–111]
Cisplatin	Let-7i, miR-569, miR-214, miR-146a, miR-10a, mir-221/222, mir-345, mir-200b, mir-200c	[31, 112]

matrix. Cellular components include endothelial cells, immune cells, fat cells, and fibroblasts. Each of the cells plays its role in the microenvironment according to its nature. Mutations in the stroma or epithelium lead to mutagenesis. Healthy stromal cells are affected by factors secreted from malignant cells, including transforming growth factor-beta TGF- β , fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), epidermal (EGF), and vascular endothelial growth factor (VEGF) or microvesicles such as exosomes are placed to get the characteristics similar to them [46–48]. In BC, TME plays a fundamental role in tumor treatment response, tumor behavior, and pathological examination for treatment management [49]. Cancer cells with metastatic property had a tendency to migrate to the desired places and grow. The seed and soil theory was

first presented by Stephen Paget. In this theory, metastatic cells are considered as seeds and the place of growth is considered as soil, and it points to the role of TME in cancer metastasis [50, 51]. TME leads to chemoresistance to chemotherapy drugs through an acquired mechanism or *de novo* pathway. Expression of ABCs, expression of tumor suppressor genes, and oncogenes are involved in acquired MDR through cell-to-TME matrix communication and cell-cell interaction. In the path of drug resistance that is created *de novo*, cancer cells after being exposed to treatment, the stromal tissue inside the TME shelters the cancer cells and induces stem formation in them, causing chemical resistance. On the other hand, cancer cells that have previously been exposed to drugs change their phenotype leading to resistance to subsequent treatments [52–54].

miRNAs and breast CSCs

Growing evidence shows that many cancers are curable after they grow and metastasize to other organs, although early-stage cancers are easier and more cost-effective to treat. However, by treating cancers in the early stages, a number of cancer source cells remain that can grow later and cause cancer recurrence and metastasis. These stem cells are said to be found in every stage of cancer and are similar to stem cells and are known as CSCs. It is believed that the activity of CSCs is mostly seen in malignant and solid cancers including breast, lung, liver, and brain cancer [28, 55]. CSCs show resistance to chemotherapy and cause cancer resistance [56]. It is said that the normal homeostasis of cancer stem cells is controlled by signaling pathways. Nevertheless, it is not far-fetched to expect that these signaling pathways are activated or suppressed in breast CSCs. Among these pathways, β -catenin, JAK/STAT, Notch, phosphoinositide 3-kinase (PI3K)/Akt, TGF- β , and NF- κ B pathways are involved in CSC homeostasis [57, 58]. Since CSCs cause drug and chemical resistance, therefore, targeting CSCs is one of the ways to treat cancers, including breast cancer. One of the treatment methods is to target the signaling pathways of CSCs. Targeting the surface markers of CSCs by monoclonal antibodies is one of the new treatment methods. But this method of treatment is because: 1). Similarity of markers of CSCs with normal SCs and other CSCs, 2). Lack of some markers to classify CSCs, 3). The very small presence of CSCs in cancer faces challenges. On the other hand, miRNAs are another treatment option that can be used alone or together with other treatment methods for CSCs. One of the basic problems in the use of miRNAs is the methods of providing miRNAs. The most basic delivery system is non-viral systems, which due to their low efficiency compared to viral systems, recently many efforts have been made to increase their efficiency by enlarging the size of the particles or increasing their surface area [59–63].

Interaction between signaling pathways and miRNAs in BC

PTEN induces tumor suppression by inhibiting the PI3K signaling pathway. PTEN, which is a phosphatase upstream of Akt, converts phosphatidyl-inositol-3,4,5-triphosphate (PIP3) to phosphatidyl-inositol-4,5-bisphosphate (PIP2), thus inhibiting the PI3K pathway. Various studies have been conducted on the relationship between the PTEN pathway and miRNAs in the development of drug resistance in BC cells. The study by Yuan et al. indicated that miR-130b in MCF-7 and MCF-7/ADR cells causes resistance to ADR and increases proliferation by targeting the PTEN-PI3K/Akt pathway. In addition, in BC cells, miR-130b increases the expression of p-Akt308 and p-Akt473. Interestingly, the effect of miR-130b on p-Akt308 and p-Akt473 is reduced by increasing the expression of PTEN. Overall, this finding revealed that miR-130b, by acting on PTEN through the PI3K/Akt pathway, increases the drug resistance and growth of BC cells [64–66]. Manxin et al. found that the expression of miR-132/212 through the PTEN pathway enhanced the resistance of BC cells [67]. A study on the relationship between miRNA-200c and drug resistance in MCF-7 cancer cells showed that miRNA-200c increases the sensitivity of MCF-7 cells to ADR by promoting the expression of PTEN and E-cadherin while decreasing the expression of Akt and ZEB1 [68]. In the study by Shen et al., it was revealed that miR-155 suppresses SOCS6 mRNA and protein. By reducing miR-155, SOCS6 levels are elevated, which can inhibit STAT3 through miR-155 and cause cell growth [69]. The results of a study in 2021 indicated that exosomal miR-205 causes resistance to tamoxifen, proliferation, and migration by targeting E2F transcription factor 1 (E2F1) in BC cells and suppresses apoptosis by phosphorylating Akt and activating the caspase pathway. On the other hand, the overexpression of E2F1 or the knockdown of miRNA-205 reverses this result [70]. Experiments on LINC00968 in BC showed that its expression

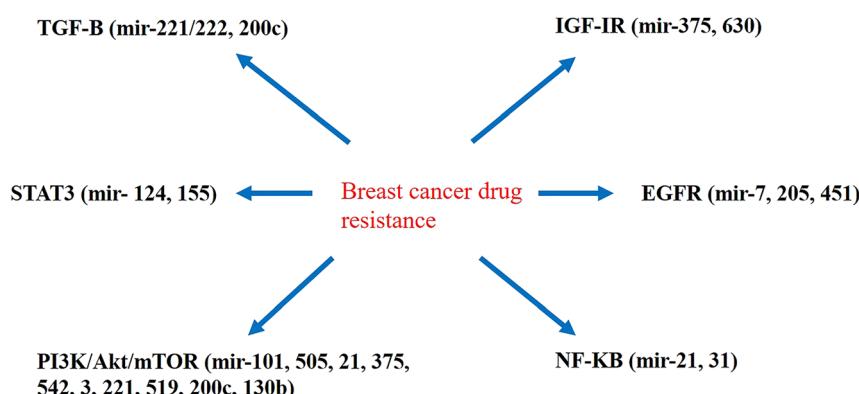


Figure 2: The interference of miRNAs with signalling pathways associated with drug resistance in breast cancer cells

in BC is low, while the expression of WNT2 is higher. *In vitro* and animal studies have shown that the overexpression of LINC00968 reduces drug resistance by silencing WNT2 through the recruitment of HEY1 and inhibiting the Wnt2/β-catenin signaling pathway [71]. A study on the relationship between LncRNA-HOX transcript antisense RNA (HOTAIR) and resistance to doxorubicin (DOX) in BC cells showed that lncRNA-HOTAIR reduces DOX resistance in these cells through the PI3K/AKT/mTOR signaling pathway. It also promotes apoptosis in MCF-7 cells and the DOX-resistant BC cell line (DOXR-MCF-7) and can be a therapeutic target in BC [72]. miR-124 causes BCSC sensitivity to DOX by interfering with HIF-1 and STAT3 signaling pathways in DOX-resistant BCSCs [73]. The research conducted by Bergamaschi et al. showed that miR-451 increases the sensitivity of BC cells to chemotherapy drugs by suppressing the epidermal growth factor receptor (EGFR) and increases apoptosis by targeting 14-3-3ζ [74] (Figure 2). Hence, considering the emerging data, there is substantial evidence elucidating that some miRNAs contribute to drug resistance in BC through signaling pathways. However, more studies are required in this field.

Conclusion

Initially, it was believed that miRNAs had no role in controlling the functions of the body and cells. However, subsequent research revealed that miRNAs play a pivotal role in controlling various cellular activities. Some miRNAs prevent cancer development and the growth of cancer cells by controlling cell pathways, and on the contrary, other miRNAs cause cell growth, invasion, and progression. Our findings demonstrated that miRNAs increase or eliminate drug resistance in BC cells through different mechanisms, particularly signaling pathways. According to the findings in this field, drug resistance, which is one of the strategies cancer cells use to escape from treatment, can be mediated through miRNA interference in cancer cells, which either increases or decreases their sensitivity to drugs. Therefore, more studies in this field are required to shed light on the function of miRNAs in the development of drug resistance in BC cells via interference with signaling pathways.

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