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A Review of the Molecular Mechanisms of EGFR and IGFR Receptors in Tamoxifen Resistance in Breast Cancer

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In 1980, tamoxifen was introduced as an effective adjuvant endocrine therapy for breast cancer, resulting in a significant increase in overall survival. Nevertheless, the development of acquired resistance limited the efficacy of tamoxifen therapy. Several molecular mechanisms have been proposed to explain the probable process of tamoxifen resistance. In vitro studies have suggested that alterations in the expression of cytoplasmic growth cascades such as insulin-like growth factor receptor (IGFR) and epidermal growth factor receptor (EGFR) along with associated downstream signaling pathways such as ERK1, ERK2, and ERK6 are the main cause of resistance to tamoxifen. In this review, we investigated the role of estrogen receptor-α (ER-α), EGFR, IGFR, and their downstream signaling pathways in tamoxifen resistance. The present study attempted to find out possible culprits of tamoxifen resistance to improve treatment efficacy in breast cancer patients.

INTRODUCTION

Tamoxifen has antiestrogenic properties that are helpful in chemoprophylaxis of ductal carcinoma in situ. This medication also plays the vital role in adjuvant therapy of ER-positive invasive ductal carcinoma [1]. Although tamoxifen is considered the gold standard in the adjuvant treatment of ER-positive breast cancer [2], approximately 30% of ER-positive tumors are naturally resistant to this anti-hormonal therapeutic agent [3]. Studies indicate that insulin-like growth factor-1 receptor (IGF-1R), estrogen receptor-alpha (ER-α), epidermal growth factor receptor (EGFR), and their downstream signaling pathways are the main reasons for this resistance [4-6]. Tamoxifen is widely used in both luminal A and luminal B subtypes of breast carcinoma, which are the most common (luminal A and B subtypes) [7-10]. In the following sections, we present an overview focusing on receptors and their potential signaling pathways in the context of tamoxifen resistance.

Estrogen Receptor-α66

In breast cancer, overexpression of Estrogen Receptor α-66 (ER-α66) is common and is observed in nearly 70% of tissues (cancerous breast cancer). This receptor and its downstream molecules are involved in the transcription of a variety of transcription factors that have the ability to bind to estrogen receptor elements (ERE) located upstream of target genes. ER-α66 expression is associated with

breast cancer progression. Thus, tumor cells lacking ER-α66 expression usually exhibit an aggressive phenotype [11]. Moreover, ER-α66 expression in tumor tissues is usually associated with a better prognosis with endocrine therapy. Different variants of the estrogen receptor may play a central role in tamoxifen resistance. Recent studies have further investigated the role of ER-α36 (a 36-kilodalton variant of the estrogen receptor) in independent cell growth and tamoxifen resistance. Studies revealed a triad between ER-α36, EGFR, and HER-2. These molecules can activate each other and phosphorylate and induce estrogen receptor-α in an estrogen-free manner [12-14]. Due to this interaction of ER-α66 and ER-α36, cells can become independent of the genomic pathway for proliferation, and when this occurs, tamoxifen sensitivity is not restored even when Receptor Tyrosine Kinase is inhibited [15]. Another form of ER, called the G protein-coupled estrogen receptor or GPER, is also associated with tamoxifen resistance. Studies show that this molecule is another variant of the estrogen receptor, located in the plasma membrane and activated by G-proteins. In the next step, it triggers EGFR and its downstream molecules such as AKT and MAPK [16-20]. According to Ignatov et al., migration of GPER from the cytoplasm to the plasma membrane has been linked to tamoxifen resistance by initiating crosstalk between GPER and the EGFR signaling pathway [17]. Moreover, GPER has a recognized anti-apoptotic effect by inhibiting pro-apoptotic proteins [20]. ERα exerts most of its pro-survival and mitogenic activities in cancerous breast tissue through a small fraction of ER and its interaction with various growth factor receptor components in tyrosine kinase signaling pathways [21, 22].

Cytosolic Components of Growth Signaling Pathways Phosphorylate ER-α66 At Ser118

According to a study by Qi et al., ER-α66 phosphorylation at Ser118 is one of the most important mechanisms for the acquisition of tamoxifen resistance. To investigate whether phosphorylation of ER-α66 at Ser118 is required for proteasomal degradation, wild-type and mutant ER-α66 proteins (differing in their Ser118 phosphorylation) were transfected into ER-negative cell lines. Interestingly, the amount of ER-α66 was not significantly different between the two groups. Nevertheless, transfection of MAPK resulted in a decrease in ER-α66 expression [4]. Thus, it was concluded that ER-α66 phosphorylation at Ser118 by the MAPK molecule is critical for proteasomal degradation. Another study performed on T47D cell lines transfected with p38γ MAPK showed that the MAPK molecule restricts the expression of ERα-driven classical genes. In contrast, non-classical gene pathways expressed through activation of c-JUN and AP-1 were not affected by p38γ MAPK, and expression of the end product of this pathway, cyclinD1, remained intact. Since p38γ mediates the switch from the classical to the non-classical ERα pathway, acquired tamoxifen resistance occurs [4]. The inhibitory effect of MAPK on the ERα may be justified via activation of downstream pathways of p38 MAPK [Inhibitory effects of 17β-estradiol or a resveratrol dimer on]. Classical gene expression pathway can be reversed in the presence of HER-2 and SRC3, enhancing the cross-links between HER-2 and ER-α. These cross-links, in turn, lead to ER-α phosphorylation via activation of downstream molecules of the HER-2 pathway, and in the end, ERα is activated in the absence of estrogen, resulting in tamoxifen resistance [23]. They are all illustrated in Figure 1.

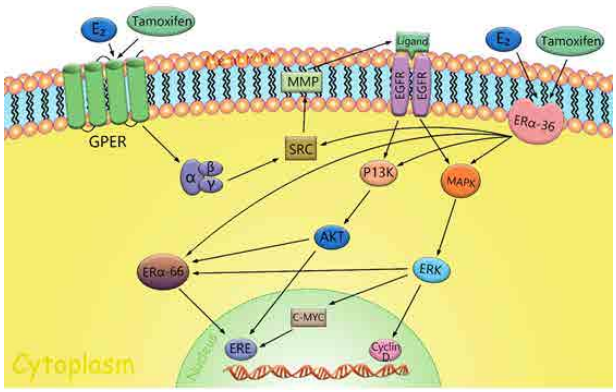

Figure 1: Different Variants of Estrogen Receptor May Play a Critical Role in Tamoxifen Resistance

As shown in Figure 1, Tamoxifen and Estrogen both have a stimulatory effect on these variants (ER-α36 and GPER). They, in turn, induce the growth pathways independently or in companion with Her2 or EGFR, leading to Tamoxifen resistance. To evaluate the role of the EGFR cascade on the phosphorylation of ER-α, EGFR-stimulating ligands such as EGF and

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heregulin (HRG; soluble secreted growth factor) were added to the medium of MCF7 cells ectopically expressing the HER-2 gene. Administration of estrogen, EGF, heregulin, and tamoxifen resulted in the phosphorylation of ER-α, ERK1, ERK2, AKT, and HER-2. Since tamoxifen was unable to act as an antiproliferative agent in this context, gefitinib was added as an inhibitor of heregulin and EGF. It reduced the active phosphorylated form of ER, HER-2, and their downstream molecules and restored the antiestrogenic effect of tamoxifen in these cells [24]. Degraffenried et al. showed that the administration of rapamycin, a potent mTOR inhibitor, decreased 118p-ERα via inhibiting AKT/mTOR activity [25]. On the other hand, some studies have shown that peptidylprolyl isomerase or Pin1 stabilizes 118p-ERα. This phenomenon in the presence of tamoxifen facilitates ER-α66 activity as a transcription factor [26-28]. This may explain the cause of the increase in 118p- ER-α in tamoxifen resistance.

Epidermal Growth Factor Receptor

Epidermal Growth Factor Receptor (EGFR) is a glycoprotein receptor on the surface of cells. It binds with its specific ligands, including epidermal growth factor (EGF), transforming growth factor-α (TGFα), heparin-binding EGF-like growth factor (HB-EGF), amphiregulin (AR), betacellulin (BTC), and epiregulin (EPR). All of these ligands can cause dimerization and autophosphorylation of the receptor, leading to induction of the p38 MAPK pathway, which, in turn, affects cell proliferation [29, 30]. Moreover, EGFR activation can induce breast cancer cell proliferation in response to various types of environmental factors and pro-inflammatory cytokines [29]. Overexpression of EGFR as a major factor in the development of tamoxifen resistance. Although EGFR expression is reduced in estrogen-containing media, its expression is slightly increased in tamoxifen-resistant cell lines. Moreover, EGFR expression was not increased in tamoxifen-resistant cell lines that developed resistance in estrogen-free media. Consequently, tamoxifen resistance could possibly be due to overexpression of EGFR due to the presence of tamoxifen in the culture media. It has been found that not only EGFR expression is increased in resistant cells but also the associated genes are overexpressed [17, 23, 31]. In contrast, there are still some studies showing that EGFR expression is decreased at both mRNA and protein levels in tamoxifen-resistant cell lines [3, 32]. Overall, EGFR overexpression correlates with tamoxifen resistance [33].

Administration of gefitinib, a potent EGFR inhibitor, was associated with a significant prolongation of overall survival in ER-positive tamoxifen-resistant breast cancer patients. Further investigation revealed that patients whose overall survival improved with gefitinib administration had a significant decrease in p-EGFR, p-ERK1, p-ERK2, p-MAPK, and Ki67 compared to the other patients. However, the levels of ER, PR, pAKT, HER-2, and IGF1-R were not significantly decreased in these cases [33]. Finally, increased EGFR expression in breast cancer patients treated with tamoxifen was associated with poor prognosis and lower disease-free survival rates [33, 34]. As previously mentioned, phosphorylated EGFR is significantly increased in the MCF7 cell line in estrogen-free media [35], causing a significant increase in the expression of some genes such as amphiregulin (AREG), betacellulin (BTC), epithelial mitogen homolog (EPGN), heparin-binding EGF-like growth factor (HBEGF), neuregulin2 (NRG2), and Neuregulin3 (NRG3)[36].

Enhanced Downstream ERK1,2 Activities in the Activated EGFR Pathway

Although EGFR is known to be overexpressed in tamoxifen-resistant cells, the status of its downstream molecules has not been fully elucidated. The estrogen receptor kinases ERK1 and ERK2 are two important cytosolic signaling molecules that are stimulated by EGFR activation and are responsible for the phosphorylation and activation of MAPK. Compared to the AKT/PI3K pathway, ERK1 and ERK2 play a greater role in the development of tamoxifen resistance and are responsible for the phosphorylation and activation of MAPK [37]. Although the study by Block et al., on tamoxifen-resistant MCF7 and T47D cell lines showed no changes in ERK1 and ERK2 expression levels, a significant increase in the amounts of phosphorylated ERK1 (p-ERK1) and ERK2 (p-ERK2) was observed. Moreover, p-ERK1 and p-ERK2 were found to be significantly higher in tamoxifen-resistant cell lines compared to sensitive cell lines [32]. Nevertheless, the question

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arises whether the expression levels of p-ERK1 and p-ERK2 are under the control of estrogen or not. It has been found that in the absence of estrogen or chronic tamoxifen exposure, the expression levels of p-ERK1 and p-ERK2 increase significantly, leading to acquired tamoxifen resistance [35]. On the other hand, studies on MCF-7 cell lines showed a direct correlation between elevated estrogen levels and p-ERK 1, 2. Furthermore, the effects of variable estrogen concentrations on tamoxifen-resistant cell lines showed that the expression of p-ERK1 and p-ERK2 reaches its maximum at an estrogen concentration of 10-14 M. However, in sensitive cells, the estrogen concentration must be higher (around 10-12 M)[38]. Interestingly, further studies showed that activation of Gαs (the alpha subunit of the stimulatory G protein) at low concentrations of tamoxifen led to the induction of p-ERK1 and p-ERK2 [39]. Qi et al., performed a study on MCF7 cell lines overexpressing the gene HER-2 and stated that estrogen-free or estrogen-only media could not increase p-ERK1 and p-ERK2 levels [4]. However, these levels were higher in estrogen-only media compared to estrogen-free media. Overall, not only are p-ERK1 and p-ERK2 levels increased in an estrogen-dependent manner, but low concentrations of tamoxifen also have agonistic effects on p-ERK1 and p-ERK2 expression via Gαs.

Tamoxifen Resistance as a Result of Interaction Between ERK 1,2 And MED1

ERK1 and ERK2 may also lead to tamoxifen resistance in other ways via phosphorylation of TRAP /MED1 in HER-2/EGFR overexpressing cells. MED1 is a nuclear protein that acts as a co-activator for ER-α and several other transcription factors. While ERK1 and 2 activate MED1, it induces ER-α (via phosphorylation at serine-118) to transcribe from the HER-2 gene complex, which repeatedly leads to overexpression of EGFR/HER-2 cascade proteins [40-43]. It has also been reported that AG825_as HER-2 inhibitor_ and PD98059_as MAPK inhibitor_ can dramatically reduce p-MED1 [17]. As mentioned earlier, stronger expression of SRC3 leads tamoxifen to have agonistic effects on ER-α with the same mechanisms [44, 45]. In contrast, Brandt et al. showed an inverse relationship between SRC3 and ER-α expression levels [46]. The interaction between HOXB7, ER-α, and MED1 is summarized in Figure 2.

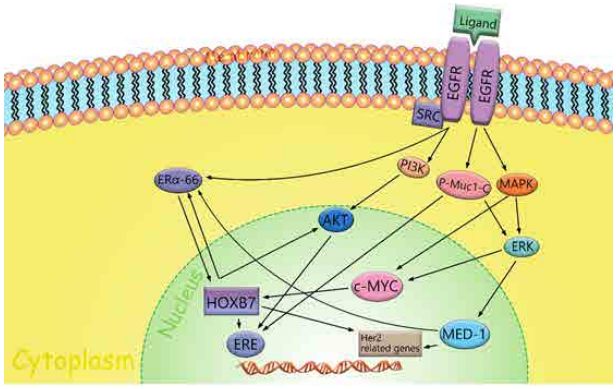

Figure 2: EGFR and Its Major Molecular Interactions

Interactions Between EGFR and MUC1-C

Some tumor cells showed increased expression of MUC1 protein. These cells are at higher risk of tamoxifen resistance. This is due to the role of the proto-oncogene MUC1-C and its interactions with EGFR. MUC1-C is the complex of 72 amino acid residues located at the C-terminus of the MUC1 protein. Studies have confirmed that EGFR can phosphorylate the MUC1-C protein and that MUC1-C, in turn, induces other non-genomic growth pathways. It can also bind to the DNA-binding domain of the estrogen receptor and induce genomic pathways. In this way, the expression of the MUC1 protein is increased [47-49]. Increased expression and activity of ERK-6 (p38-γ) in tamoxifen resistance overexpression of p38MAPK has been demonstrated in many studies [50]. P38-γ and p38-α are two isoforms of p38MAPK that act in opposite ways [51]. Similar to ERK1 and ERK2, p38-γ or ERK-6 also has mitogenic activity. It also has specific kinase activity in response to stressors [6, 52]. Numerous studies have shown that p38-γ is overexpressed in cell lines with EGFR overexpression [36, 53]. MCF7 cell lines transfected with EGFR-containing vectors showed a significant increase in p-AKT and ERK-6 levels. Therefore, tumor cell proliferation was not significantly affected by the presence of tamoxifen [24]. Interestingly, the expression of ERE (Estrogen Response Elements) was not suppressed in transfected cell lines in the presence of tamoxifen, suggesting that exogenous EGFR does not alter the inhibitory effects of tamoxifen. Further studies on the relationship between EGFR expression and

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acquired tamoxifen resistance have shown that inhibition of p38-γ in transfected cell lines treated with estradiol and EGF failed to desensitize the cells to tamoxifen. Consequently, it appears that p38-γ is not the only mediator of the EGFR-dependent mechanism of acquired resistance [1]. Studies in MCF7, 293T, and T47D cell lines, which differ in the level of expression of HER-2, have shown that MAPK activation, ERK1 and ERK2 activation led to phosphorylation of ER-α at the serine 118 residue (Ser118), which, in turn, leads to enhanced ER-α proteasomal degradation via E6AP activation. Based on current evidence, ERK-6 appears to be enhanced in ER-negative cells in contrast to ER-positive cells. Consequently, there is an inverse relationship between ER-α and ERK-6. Of note, overexpression of ERK-6 occurs in approximately 70% of breast cancers [4, 36].

Increased HOXB7 Expression Is Associated With EGFR Overexpression

In 2018, Farahmand et al., indicated that stem cell acquisition is one of the major mechanisms of drug resistance in breast cancer cells. EGFR and other Receptor Tyrosine Kinases (RTKs) can lead to overexpression of stem cell genes and proteins, which result in uncontrolled cell proliferation [54]. One of these proteins is HOXB7. This protein is one of the members of the HOX family, which is known to be one of the most potent transcription factors in cell development, proliferation, and differentiation [55-57]. MCF7-B7 cell lines expressing high levels of HOXB7 protein are more invasive in vitro than normal MCF7 cell lines [58, 59]. Moreover, MCF7-B7 cells were able to survive in estrogen-free media. In the presence of tamoxifen, MCF7 cell lines concomitantly exhibit a gradual increase in HOXB7 expression. In support of this observation, HOXB7 siRNAs (small interfering RNAs) were added to the media to repress the HOXB7 gene. Interestingly, the siRNAs effectively desensitized the tamoxifen- resistant cells. Moreover, MCF7-B7 cancer cells treated with 1 µg tamoxifen for thirty minutes showed a significant increase in EGFR autophosphorylation and phosphorylation of ER-α at Ser118. It has been shown that HOXB7 in the presence of tamoxifen leads to overexpression of EGFR and consequently enhances the response to EGFR-specific ligands such as TGF-β and HB-EGF. It has been shown that ER-α is the major mediator required for HOXB7 function. Thus, inhibition of ER-α reduces the effects of HOXB7. ER-α coupling with HOXB7 leads to HER-2 and overexpression of estrogen receptor-related genes.

Interactions Between Mirna, HOXB7 and C-MYC

miR-196α is a microRNA that has shown regulatory effects on HOX gene expression. This molecule is regulated by ER-α, and activation of ER can lead to higher expression of miR-196α. Studies indicated the positive correlation between higher levels of miR-196 and tamoxifen resistance. The family of MYC oncogenes is also known as super transcription factors, which are responsible for the transcription of approximately 15% of the entire human genome. The related proteins are c-myc (MYC), n-myc, and l-myc. They all play critical roles in cell differentiation, proliferation, and survival [60-64]. It appears that suppression of miR-196α significantly increases HOXB7 expression and tamoxifen resistance. Overexpression of MYC due to activation of HER-2 further increased HOXB7 levels by miR-196α inhibition. Thus, it appears that a positive feedback loop is due to HER-2 activation, MYC overexpression, and HOXB7 elevation [65].
In this Figure, the interactions between HOXB7, c-myc, and MED1 are shown, all of which are activated via downstream EGFR molecules. Moreover, non-genomic pathways of the estrogen receptor can also be activated. The ligand in this Figure can denote different molecules such as EGF, HB-EGF, TGFβ, etc.

Insulin Growth Factor Receptor Signaling Cascade

IGFR, another receptor tyrosine kinase, is activated by insulin and IGF-1. It can induce p38 MAPK and PI3K/AKT signaling pathways with similar downstream molecules as EGFR. In the remainder of this article, we will examine some of them in more detail.

IGFR/EGFR and IGFR/HER-2 Dimerization, a Novel Strategy for Inhibitor Inactivation

IGFR can induce EGFR activation by dimerization with EGFR or direct coupling with ER-α [5]. It has been suggested that IGFR heterodimerization with HER-2 in the presence of trastuzumab is a contributing factor to resistance to trastuzumab [66].

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Werner et al. were the first group to introduce IGFR as a cancer biomarker due to its overexpression in several breast cancer cell lines [67]. Moreover, the agonistic activity of IGFR in breast cancer cells showed that it is one of the major causes of tamoxifen resistance. Recent studies suggest that the agonistic activities of tamoxifen at the lower doses may be the result of IGFR effects [2].

The Maintenance of Survival, Enhancement of Proliferation, and Inhibition of Apoptosis as a Result of Interaction of IGFR Networks With Other Molecules

IGFR has been shown to promote cell maintenance and metastasis of cancer cells [5]. It can also effectively inhibit tamoxifen-induced apoptosis in cancer cells. Schoenlein et al., reported that co-administration of tamoxifen and mifepristone can induce apoptosis in MCF7 cancer cell lines. Nevertheless, administration of IGF-1 under physiological concentrations can alter cell fate. Further studies have shown that co-administration of tamoxifen and mifepristone can trigger cell death via increased hyperphosphorylation of retinoblastoma 110 (RB110), an important protein involved in the induction of apoptosis [68, 69]. On the other hand, concomitant administration of IGF1/tamoxifen or IGF1/mifepristone significantly reduces the expression of RB100, poly ADP-ribose polymerase (PARP), lamin A, Reactive Oxygen Species (ROS), and other proteins involved in the apoptosis cascade [70].

Activation and Overexpression of IGFR

Tamoxifen-resistant and tamoxifen-sensitive cancer cells differ in the expression of IGFR. Several studies indicated overexpression of phosphorylated IGFR in tamoxifen-resistant cells compared to sensitive cells, suggesting the role of IGFR in tamoxifen resistance [31]. Inhibition of IGFR expression has no significant effect on sensitivity to tamoxifen and mifepristone in either resistant or sensitive cells. According to Periyasamy et al., although the addition of IGF-1 to the media leads to the development of resistance to mifepristone and tamoxifen, the acquired resistance is much more evident in cell lines in which IGFR expression is inhibited [70]. This indicates that IGFR activity in resistant cells is dependent on extracellular stimulators rather than EGFR. Conversely, Chong et al. found that IGF-1 mRNA levels were reduced in resistant cancer cells in contrast to sensitive cell lines, and increased IGF-1 expression was associated with better prognosis in breast cancer patients; however, there was no established association between IGFR levels and prognostic status [23]. Overall, although the role of IGFR in acquired tamoxifen resistance has not been fully elucidated, it appears that its increased activity, as well as other mediators, including growth signaling systems may lead to the development of tamoxifen resistance.

CONCLUSIONS

Proliferation of breast cancer cells may occur as a result of uncontrolled overactivity of cytosolic growth pathways. Among these, estrogen with its associated receptor in the nucleus appears to be the most important factor in controlling proliferation of a majority of breast cancer cells. In recent studies, estrogen surprisingly showed both proliferative and anti-proliferative properties. Remarkably, estrogen led to apoptosis in the experiment conducted with the tamoxifen-resistant long-term cell line Estrogen Deprived (LTED-R). Neither RTK inhibitors nor tamoxifen succeeded in inducing programmed cell death. This was a crucial difference between simple tamoxifen-resistant cell lines (Tam-R) and LTED-R cell lines [71]. Tamoxifen has been identified as a selective estrogen receptor modulator. This drug is used in prevention and treatment of estrogen receptor (ER)-positive breast cancer. The differential antagonistic or agonistic effects of tamoxifen on ERα are explained through the tissue-specific expression profiles of receptor coactivators as well as activators [72, 73]. In cases of metastatic breast cancer with ERα positive, at the beginning of treatment with tamoxifen, the mechanism is such that the mitogenic activity of estrogens is initially blocked by tamoxifen, which causes tumor regression. Like previous studies, some breast cancers had primary resistance to tamoxifen in the study. In the treatment process, cancers (breast cancer) that respond well at the beginning through different mechanisms (including the expression of G-protein coupled estrogen receptor 1: GPER1), which mediates the stimulating action in fulvestrant and tamoxifen, become resistant to tamoxifen [74]. Tamoxifen can act as an agonist or antagonist through the ERα

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pathway, depending on cellular differences in co-repressors or co-activators. Meanwhile, Tamoxifen can be introduced as an estrogen agonist that acts through GPER-1. GPER-1 has a higher expression level in breast cancer cells (with primary or secondary resistance to tamoxifen)[75].

As a member of the selective estrogen receptor modulator (SERM) family, tamoxifen selectively couples to ER-α66 in the nucleus and inhibits the transcription of specific genes. Nevertheless, cytosolic growth pathways also play a vital role in promoting the cell cycle in an estrogen-independent manner. Cells have been shown to proliferate independently of the estrogen pathway and its inhibitors such as tamoxifen when these pathways, including EGFR and IGFR are overactivated. As described in detail in this review, EGFR and IGFR are activated by binding to their most specific ligands, EGF and IGF, respectively and, in turn, trigger the downstream signaling cascades ERK1, ERK2, and ERK6. Overall, studies in breast cancer patients and cell lines show that overexpression and/or overactivation of EGFR [17, 23, 31, 35], ERK 1, 2 [24, 32, 35, 37, 39], EGFR ligands including amphiregulin (AREG), Betacellulin (BTC), Epithelial Mitogen Homolog (EPGN), Heparin-binding EGF-like growth factor (HBEGF), Neuregulin2 (NRG2), NRG3 in tamoxifen-resistant cells [36], and HOXB7 [56] are among the major contributors to the development of tamoxifen resistance. In addition, overexpression and/or activity of IGFR [31, 40, 69, 70] and its coupling with the receptors HER-2 and EGFR [31, 66], together with the agonistic effects of tamoxifen (via IGFR), may also induce tamoxifen resistance [2]. Therefore, it is of utmost importance for future studies to describe the role of these agents in resensitizing cells to tamoxifen.

Since the introduction of gefitinib as an effective EGFR inhibitor, numerous studies have investigated the efficacy of this drug in resensitizing tamoxifen-resistant cells. Most of them have been performed in vitro, and there are few clinical trials. The study by Gutteridge et al. is an example of a clinical trial that compared the beneficial effects of gefitinib administration on resensitization of ER-positive patients [33]. Since there are numerous interactions between ER-α, HER-2, and the EGFR pathway, administration of a dual HER-2 and EGFR inhibitor, such as lapatinib in combination with tamoxifen, may resensitize cancer cells to tamoxifen. In addition, the phase III clinical trial (EGF30008) studied 1286 patients to compare the results of co-administration of lapatinib and letrozole with the control group receiving letrozole alone. Interestingly, the results indicated that concurrent treatment with lapatinib prolonged disease-free survival from 3 months in the control group to 8 months in the case group receiving concurrent letrozole and lapatinib [76].

Therefore, it is critical for future studies to further elucidate the molecular relationships between estrogen-dependent and-independent pathways and the subsequent development of tamoxifen resistance. Crosstalk between ERα and HER-2 and EGFR are the major molecular pathways contributing to tamoxifen resistance. Activation of MAPK and AKT triggers the subsequent phosphorylation of MAPK, AKT, and ER-α at Ser118 and Ser167. In addition, ERα and HOXB7 would lead to overexpression of EGFR and HER-2 [65]. There is a need to investigate how certain patients develop tamoxifen resistance, especially given the complex networks of molecular interactions that may result from chronic tamoxifen exposure. However, this question remains unclear, as some patients never develop resistance despite the molecular pathways mentioned above. Therefore, certain unknown signaling pathways may contribute to the activation of the EGFR/IGFR cascade and promote the development of cell resistance. The cross-talk between estrogen-dependent and -independent signaling pathways associated with acquired tamoxifen resistance has led researchers to search for molecules involved in altering the cellular response to tamoxifen, which requires further study and investigation.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

ETHICS APPROVAL

This project was in accordance with the national norms, the ethical principles and standards for conducting medical research in Iran and evaluated

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by Motamed Cancer Institute-Academic Centre for Education, Culture and Research. This institution performed its reviews based on United States Public Health Service (USPHS) regulations and applicable federal and local laws.

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