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Endocrine Resistance in Breast Cancer: The Role of mTOR Signaling in Mediating Resistance to Selective Estrogen Receptor Modulators

Abstract

Selective estrogen receptor modulators (SERMs) are chemical compounds that demonstrate agonistic and or antagonistic effects on estrogen receptors, depending on the specific tissue they target. SERMs that are competitive inhibitors of hormonal estrogens have been widely prescribed and efficacious as a first-line endocrine therapy to treat estrogen receptor (ER)-positive breast cancer. The most widely used SERM in the treatment of breast cancer, tamoxifen, is a prodrug whose active form 4-hydroxytamoxifen (4-OHT) is anti-proliferative in breast tissue. Its widespread use has had a tremendous impact on reducing breast cancer mortality. 4-OHT represses the expression of estrogen-responsive genes involved in cancer growth. The binding of 4-OHT to estrogen receptors prevents the recruitment of coactivators to chromatin. Instead, 4-OHT promotes the recruitment of corepressors and histone deacetylases, thus inhibiting transcriptional activation of target genes. However, the issue of endocrine resistance remains a predominant problem with this therapy. Resistance can arise due to acquired mutations in ERα or dysregulations in the mTOR signaling pathway. By knocking down *YAP/TAZ* or *PSAT1* in the mTOR pathway, we can re-sensitize the breast cancer cells to SERM therapy. Despite this discovery, endocrine resistance remains an issue due to irregularities in additional pathways. Therefore, subsequent research is crucial to identify more targets that, when inactivated, enable re-sensitization of resistant cells, restoring full therapeutic ability of SERMs in afflicted women.

Introduction

The beginning of a woman's reproductive years is marked by the onset of ovulation and menstruation. This transition involves the production of endocrine hormones which stimulate the ovaries to produce a class of female sex hormones known as estrogens, with 17β-estradiol functioning as the predominant intracellular form. Estrogens play a vital role in the development of the female reproductive system, differentiation of healthy breast epithelium, and maintenance of bone density[1,2]. This ovarian hormone conducts its physiological effects in its target tissues through stimulation of the estrogen receptor (ER), which exists in two isoforms: ERα and ERβ[2]. Estrogen receptors are nuclear receptors and hormone regulated transcription factors. They control gene expression by binding cognate DNA motifs known as estrogen response elements, located in the regulatory regions of target genes[2]. A functionally relevant region of this receptor is the ligand binding domain (LBD), which is a region with a series of alpha helices that form a hydrophobic pocket enabling ligand binding[1]. Within the LBD is located the transcriptional activation function domain 2 (AF-2) which facilitates transcriptional activation of the target genes of the receptor in response to ligand binding by recruiting coactivators to its site[1]. As depicted in Figure 1A, following the binding of estrogen to the LBD, the receptor undergoes a conformational change[1]. As the estrogen adheres to the hydrophobic binding pocket of its receptor, helix 12 seals the estrogen into place leading to the exposure of the coactivator binding groove, AF-2, which can then recruit coactivator molecules[1,2]. The dimerization of the receptor then enables the binding of estrogen-response elements to the promoter region of target genes and thus the transcription of these genes[1,2]. This mechanism enables the transcription of estrogen-responsive genes essential for growth, development, and differentiation in the healthy female.

Although estrogen is an essential hormone for many tissues, the positive effects of estrogen are frequently overshadowed by its negative effects on female health. One of the most detrimental features of estrogen is its promotion of breast cancer. Breast cancer remains the leading cause of death from cancer in women worldwide[3]. Broadly speaking, breast cancer is pathologically classified into categories : Estrogen Receptor positive (ER+), Progesterone Receptor positive (PR+), Human Epidermal Growth Factor Receptor-2 positive (HER2+) and Triple-Negative, with ER/PR+ breast cancer making up around 70% of all breast cancers diagnosed[3]. ER+ breast cancers are dependent on active ER signaling which can stimulate proliferation of normal and malignant cells by inducing the activation of growth-regulatory genes. The upregulation of cell proliferation by estrogen increases the number of mistakes made by error-prone DNA repair machinery, resulting in mutation accumulation in the genome, as well as an increase in cancer growth[1]. Given this mechanism of cancer growth, ER+ breast cancer tumours are very dependent on estrogen, rendering ER a sought-after therapeutic target. Hormonal therapeutic antagonists of the ER have been successfully used for the last several decades by postoperative patients and by women at high risk of developing ER+ breast cancer to prevent the recurrence of the cancer post surgically, to reduce mortality due to the breast cancer, or to delay the need for chemotherapy[2].

The predominant treatment strategy for these tumours has been to inhibit aspects of the ER pathway with different pharmacological agents. One of the many endocrine treatment strategies for ER+ breast cancer are SERMs which function as antiestrogens by directly binding to the ER and, consequently, blocking its signaling and activation of downstream target genes[2]. SERMs are chemical compounds that function as agonists or antagonists, or both simultaneously, depending on the target tissue. For instance, ta-

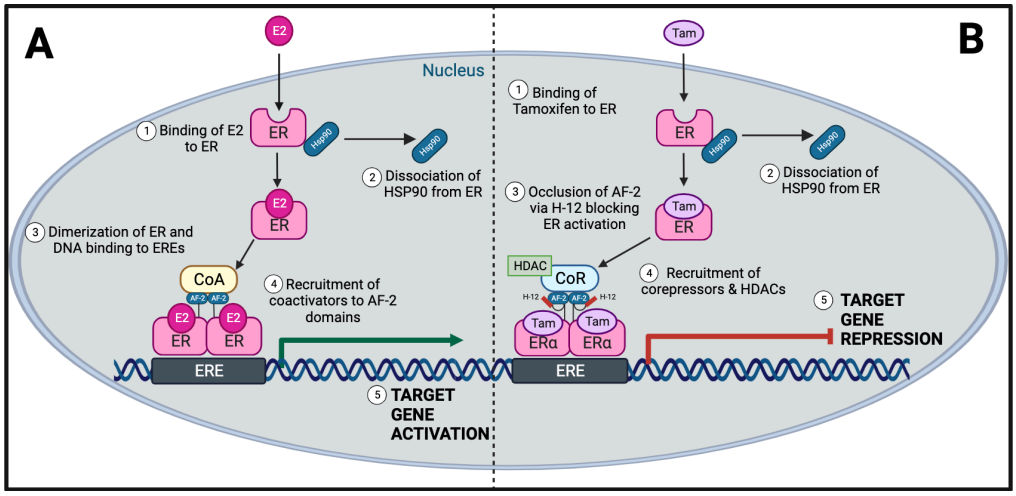

Figure 1. (A) The Mechanism of Action of Estrogen on the Estrogen Receptor[1]. Estrogen (E2) diffuses through the plasma membrane and binds to the estrogen receptor (ER). Binding of estrogen to its receptor induces a conformational change, resulting in the dissociation from heat shock protein 90 and dimerization of the receptor. The subsequent complex binds to estrogen-responsive elements (EREs) on the promoter region of estrogen's target genes. One of the ER's domains, AF-2, enables the recruitment of coactivators (CoA) to the transcriptional complex on the estrogen receptor and transcription of the target genes occurs. **(B)**. The Antagonistic Action of SERMs in tissues[1]. SERMs bind to the estrogen receptor (ER) and confer target gene repression by binding to the estrogen response elements (ERE) on target genes. The SERM will prevent the recruitment of coactivators on the AF-2 domain and instead facilitate the recruitment of corepressors (CoR) and histone deacetylases (HDAC) to the promoter of the genes which will inhibit their transcription.

moxifen was the first relevant SERM discovered for treatment in post-menopausal women suffering from ER+ breast cancer. The active form of this prodrug, 4-hydroxytamoxifen (4-OHT), is anti-proliferative in breast tissue, albeit agonistic in nature in the uterus. Tamoxifen was approved by the FDA in 1977 to treat women with advanced breast cancer following its success in decreasing breast cancer recurrence and the incidence of contralateral secondary tumours by 50% in breast cancer trials[1]. Later in 1999, the FDA approved tamoxifen as the first chemo preventative drug to prevent breast cancer in pre- and post-menopausal women[1]. While tamoxifen can act as an antiestrogen in the mammary gland, tamoxifen has estrogenic effects in other tissues, notably the uterus[4]. Thus, one of the negative side effects of tamoxifen is an elevated risk of endometrial cancer[4]. This led to the approval and use of another SERM for ER+ breast cancer therapy known as Raloxifene. Raloxifene acts as an antagonist in both breast and uterus tissue eliminating the risk of endometrial cancer[1,4]. Since then, there have been many SERMs approved for use, all of which differ in their agonist and antagonistic actions depending on the specific tissue they are operating in. Despite the relative efficacy and safety of the application of SERMs in the clinical setting, their successes have been limited by the development of endocrine resistance. Often, when the cancer returns, it may metastasize and become resistant to antiestrogen therapies that were previously effective. It is known that approximately one third of patients with ER+ breast cancer who undergo adjuvant therapy with SERMs develop resistance to the drugs[4].

As the search for novel targets to re-sensitize the cells to the SERM therapies remains a clinical struggle, this review will concentrate on some of the more recent mechanisms and targets discovered for potential treatment of endocrine resistance. To fully understand cellular resistance to hormonal therapies, the mechanism of action of SERMs in the breast cancer setting, accompanied by experimental evidence, will be provided. The primary focus will be the antagonistic action of tamoxifen on ER+ breast cancer tumours given that its discovery sparked immense research on the use of SERMs in breast cancer therapy.

SERMs and Their Antagonistic Mechanism of Action

SERMs function as antiestrogens by competing with estrogen for binding on the ER, altering its conformation and thus leading to a change in the coregulators that associate with the ER[2]. The binding of the antiestrogen to the ER differs from that of estrogen due to structural differences. Notably, due to the large side chains of the antagonist, helix 12 on the ER is prevented from sealing the ligand into the LBD which would typically occur following estrogen binding. This repositioning of helix 12 occludes the AF-2 coactivator binding groove, preventing the recruitment of coactivators to the site[1]. Many early studies on the antagonism of the ER characterized the repositioning of helix 12 following estrogen binding and noted that this is a prerequisite for transcriptional activation, as the repositioning of helix 12 generates a functional AF-2 domain crucial for coactivator recruitment[5]. Occluding the AF-2 domain through a repositioning of helix 12 is the way in which SERMs block the activation of the estrogen receptor[1,2].

Additionally, these antiestrogens inhibit the transcription of estrogen-responsive genes by inducing different conformational states of the receptor. These states facilitate the interaction of corepressors with the receptor, which serve to prevent the recruitment of transcriptional machinery to the genes' promoters, and thus represses transcription as portrayed in Figure 1B[1]. As previously discussed, the downstream effect of SERMs on ER signaling differs depending on the specific tissues they reside in. Notably, SERMs can act as estrogen agonists in some tissues via the AP-1 tethered pathway[1]. This has complicated the field of adjuvant endocrine therapy and has led to a need for more research on these agents. For this review, only the antagonistic ability of SERMs will be examined as the antagonism of SERMs represents a mechanism for impeding breast cancer growth.

Experimental Evidence on the Function of SERMs as Antiestrogens

Both the optimistic and unfavourable discoveries on these endocrine agents have encouraged a vast number of experiments, particularly on tamoxifen. The crystallization of the LBD of the ERα in the presence of estrogen, com-

pared to the domain bound to tamoxifen, provided evidence for side chain interference with the capping over of helix 12. This prevents necessary coactivator recruitment[6].

Once the structural properties of tamoxifen and its potential as an antiestrogen became of interest, many studies tested the ability of tamoxifen to prevent the transcription of estrogen-responsive genes. In a follow-up study, the effects of estrogen and tamoxifen in breast cancer tumours were supported through evidence of active recruitment of coactivator and corepressor proteins respectively[7]. Researchers used immunofluorescence staining to confirm the colocalization of these proteins with the ER. It was found that the steroid receptor coactivator-1 (SRC-1), which is known to enhance transcription, is expressed with the ER[6]. Additionally, the silencing mediator for retinoid and thyroid hormone receptor (SMRT), a corepressor, was also shown to be expressed with the ER[6]. The recruitment of this corepressor to the estrogen-responsive genes was thought to be the main driver for the antagonist activity of tamoxifen. To examine this, researchers used primary breast tumour cells extracted from patients as well as an MCF-7 breast tumour cell line. Immunoblotting was used to identify the coregulators recruited to the transcriptional DNA complex of the ER on the estrogen-responsive elements (ERE) of genes in the presence of β-estradiol and in the presence of 4-OHT[6]. In the presence of β-estradiol, coactivator SRC-1 expression was increased at the estrogen receptor-ERE complex, whereas there was no expression at the complex in the presence of 4-OHT[6]. In contrast, the expression of corepressor SMRT was increased at the complex in the presence of 4-OHT as compared to control and β-estradiol incubated breast cells[6]. Thus, the recruitment of corepressors was thought to be essential for full antagonistic activity of tamoxifen.

Consistent with many lines of evidence, Fleming et al. suggested that the corepressor proteins recruited to the ER exert their transcriptional silencing effects by recruiting many other regulatory proteins — notably histone deacetylases (HDACs)[8]. Research by Liu et al.[7] presented this evidence clearly in various experiments. In studying MCF-7 breast cancer cells and using reverse-transcriptase polymerase chain reaction, researchers first confirmed the effect of 4-OHT on the expression of estrogen-responsive genes, notably *pS2* and *C-MYC*[7]. pS2 protein is a prevailing expressed protein in human ER+ breast cancer and C-MYC protein is a master of cell metabolism and proliferation. These characteristics render both genes to be genes of interest in cancer growth research. The repressive ability of 4-OHT on these two estrogen-responsive genes in cancer cells is clearly shown by the reduction of *pS2* and *C-MYC* expression following its addition[7]. It is important to note that this experiment evidently confirmed that the tamoxifen induced recruitment of ER-α and NCoR corepressor to the estrogen-response elements on the promoter regions of *pS2* and *C-MYC* genes. This is consistent with the previously described mechanism of the ER complex binding to estrogen-response elements on target gene promoters. Estrogen-bound estrogen receptors recruit coactivator complexes containing histone acetyltransferases which facilitate the binding of transcription factors leading to gene activation. This raised the possibility that a similar mechanism occurs for tamoxifen-bound ER. Perhaps the previously discovered corepressors like SMRT that are recruited to the ER are also associated with HDACs and it is thanks to their local hypoacetylation on the target genes that tamoxifen functions as an antiestrogen. To explore the nature of this corepressor complex recruited to the tamoxifen-bound ER, researchers exposed MCF-7 breast cancer cells to either estrogen or 4-OHT and isolated the cross-linked chromatins[7]. Using serial chromatin immunoprecipitation and antibodies against two histone deacetylases, HDAC1 and HDAC3, the results demonstrated the following. In the presence of 4-OHT, both HDAC1 and HDAC3 were recruited to the genes' promoters. Furthermore, they found that other components of the NCoR-HDAC3 complex were recruited to the promoters, for instance transducing B-like protein 1 (TBL1)[7]. Further experiments demonstrated similar results for the HDAC1 complex. Histone deacetylases are transcriptional repressors that reduce acetylation of histones and repress the transcription of genes. Thus, it seems as though the antiestrogen effects of tamoxifen are, in part, due to the recruitment of deacetylases to estrogen-responsive regions[7].

In summary, the results of this study provide evidence that the silencing effects of tamoxifen on estrogen-responsive genes are thanks to the recruitment of a large transcriptional silencing complex. Their evidence elaborates on the results of the previous study that displayed 4-OHT dependent recruitment of SMRT, as they demonstrated that such corepressors exist in a multiprotein complex containing HDACs and other polypeptides. These HDACs are known to create a repressive chromatin conformation that prevents the interaction of transcription factors and RNA polymerase II — critical molecules for gene expression[7]. In addition, researchers concluded that the promoter-bound OHT-ER is associated with only one of the HDAC complexes at a time; a way to effectively repress target gene transcription via sequential association with the complexes[7]. All in all, it is the transcriptional repression of the ER and its recruited HDACs and corepressors that confers tamoxifen sensitivity to estrogen target genes, such as *MYC*[9]. As more research is undertaken, more ER corepressors are being identified as enhancing the antitumorigenic effects of tamoxifen[9].

Endocrine Resistance to SERMs: How Can We Re-sensitize the Cells?

Although the exact mechanism by which cancer recurrence due to endocrine resistance occurs is unknown, over the years, many studies have uncovered several possibilities behind the eventual relapse that most patients face. Importantly, most ER+ breast cancer tumours maintain expression of a functional ER, suggesting mechanisms other than receptor loss[3]. Several other mechanisms of endocrine resistance include acquired mutations of the ERα, alterations in the ER pathway, amplification of epidermal growth factor receptors, and activation of various growth factor pathways, cell cycle pathways, or apoptosis pathways[2]. This variability has made the battle against endocrine resistance to SERMs a challenging feat. The following analysis will focus on the phosphatidylinositol 3-kinase/activated protein kinase B (PI3K/AKT) signaling pathway and its mediation in conferring estrogen-independent growth properties to ER+ breast cancer cells, leading to endocrine resistance[10]. Given that the PI3K/AKT pathway is involved in the promotion of cell proliferation, cell growth, and the inhibition of apoptosis, the pathway has been a predominant therapeutic target for research on re-sensitization mechanisms[11].

A way in which ER signaling is altered, and thus endocrine resistance arises, is by ligand-independent ER activation. The PI3K/AKT pathway can protect breast tumour cells from tamoxifen-induced apoptosis since AKT can activate the ER in a ligand-independent manner[10]. AKT has been found to inhibit apoptosis and stimulate cell growth, thus contributing highly to the oncogenic transformation of cells[10]. The PI3K/AKT pathway functions to upregulate the expression of genes involved in cell proliferation, cell survival, angiogenesis, and tumorigenesis[12]. Upon activation of the receptor tyrosine kinase of this pathway by diverse stimuli, the activation of PI3K will occur[11]. PI3K is highly implicated in cancer and enables the production of phosphatidylinositol (3,4,5)-tris-phosphate (PIP_3) which leads to the translocation and binding of AKT to the plasma membrane[11]. At the membrane, AKT will become partially phosphorylated by phosphoinositide-dependent kinase 1 (PDK1). However, full activation of AKT requires additional phosphorylation from mammalian target of rapamycin (mTOR)[10,11]. When coupled to its regulatory-associated protein, Raptor, mTOR denoted Raptor, will form the mammalian target of rapamycin complex 1 (mTORC1) which functions to regulate protein synthesis and cell proliferation[12]. Protein synthesis is a requirement for cells to be able to divide and grow, thus mTOR signalling is highly implicated in

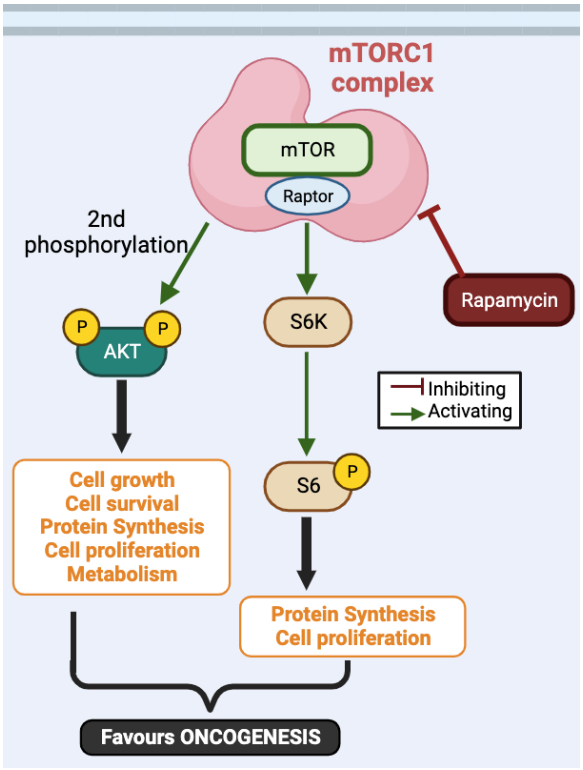

Figure 2. mTORC1 and AKT on the Regulation of Cellular Mechanisms, Favouring Oncogenesis[11–13].

increasing mRNA translation through regulation of its substrates[11,12]. Notably, mTORC1 will stimulate ribosomal protein S6kinase (S6K), as portrayed in Figure 2, which in turn will phosphorylate ribosomal protein S6 (S6)[12,13]. These downstream effects on the targets of mTORC1 will promote mRNA translation and cellular proliferation. Once AKT is fully activated by the upstream PI3K and the downstream mTOR, AKT will then go on to phosphorylate many proteins involved in translation, cell growth, proliferation, metabolism, and survival, providing an ideal state for oncogenesis[11]. Many studies have revealed that high levels of AKT confer resistance to radiotherapy and hormonal therapy and thus survivability to the ER+ breast cancer.

Given that the aberrant signaling of this pathway promotes breast cancer tumorigenesis by inhibiting cell apoptosis, overriding cell cycle control, and upregulating the production of survival factors, preclinical studies have been carried out to study how the inhibition of critical components of this pathway could affect endocrine sensitivity[10]. It was consistently found in the field that this inhibition could, in turn, restore hormone sensitivity. Notably, one study by deGraffenried and colleagues explored the effect of the antibiotic rapamycin on inhibiting mTOR to sensitize resistant cancer cells to tamoxifen[10]. Rapamycin has been found to induce G1 cell cycle arrest, anti-proliferative effects, and apoptosis in many cancer models with high AKT activity and restore its sensitivity[10]. Thus, to elaborate on the implication of rapamycin in breast cancer, the study developed MCF-7 breast cancer cells with high and low AKT activity[10]. To explore whether the inhibition of downstream AKT targets with rapamycin could restore sensitivity to tamoxifen in breast cancer cells, researchers treated MCF-7 cells with low and high levels of phosphorylated AKT with increasing amounts of 4-OHT and measured their relative percentage of growth[10]. The MCF-7 cells with low expression levels of phosphorylated AKT and the control MCF-7 cells had a dose-dependent decrease to tamoxifen in terms of their growth[10]. However, the MCF-7 cells with high AKT activity experienced no growth inhibition indicating resistance to the tamoxifen[10]. Next, the researchers cotreated the 3 groups of MCF-7 cells with the mTOR inhibitor rapamycin, along with 4-OHT. Interestingly, the MCF-7 cells with low AKT activity showed an even greater decrease in growth due to tamoxifen following the addition of the mTOR inhibitor[10]. Successfully, the cotreatment of the high AKT activity MCF-7 cells with rapamycin restored sensitivity to tamoxifen as seen by the great reduction in growth percentage[10]. This indicates that the mTOR signaling plays an important role in mediating the resistance to tamoxifen and suggests that by inhibiting mTOR signaling with rapamycin, previously resistant breast cancer cells to tamoxifen can be re-sensitized.

Many studies have continued to investigate the role of PI3K/AKT/mTOR pathway in endocrine resistance. In a study from 2022, investigators found that by targeting transcriptional activators that are elevated in tamoxifen-resistant breast cancer cells, the cells can be re-sensitized via a suppression of components of the mTOR pathway[4]. Prior to the execution of this study, it was known that transcriptional regulators Yes-associated protein (YAP) and transcriptional coactivators with PDZ-binding motif (TAZ) are elevated in many cancers. They are known to reprogram the cancer cells into cancer stem cells by inducing expression of target genes involved in cancer initiation, proliferation, and metastasis[14]. Thus, they were appealing targets to study in the realm of endocrine resistance. To confirm the elevated levels of YAP and TAZ coactivators in tamoxifen-resistant breast cancer cells, researchers measured growth and cell viability of MCF-7 breast cancer cells and MCF-7 tamoxifen-resistant cells. Using varying doses of 4-OHT, the results showed that the 4-OHT caused a dose-dependent decrease in the viability of the MCF-7 breast cancer cells. However, it had a weak inhibitory effect on the viability of the resistant cells, notably less than a 15% decrease in viability after treatment with 4-OHT, as seen in Figure 3A[4]. To demonstrate that these cells are resistant to cell death, the researchers used the cleavage of poly-ADP ribose polymerase 1 (PARP), a hallmark of cell apoptosis, to measure the cell death induced by 4-OHT[4]. As expected, the resistant MCF-7 breast cancer cells experienced no significant cell death when faced with the SERM, as portrayed in Figure 3B[4]. Given the elevated levels of YAP and TAZ coactivators, the researchers used small interfering RNA machinery to create a knockdown of *YAP* and *TAZ*[4]. Using measures for cell viability and apoptosis, they found that this knockdown induced increased PARP cleavage and reduced cell viability in the resistant cells, as seen in Figure 3C when comparing lane 3 to lane 1. This indicates that more cell death of these resistant cells was occurring[4]. When they added 4-OHT to the cells, they found an exacerbation of the previous results, notably there was a larger increase in PARP cleavage and a larger decrease in cell viability[4]. This suggests that by suppressing expression of YAP and TAZ coactivators, the breast cancer cells' sensitivity to tamoxifen increases.

Given that it has been reported that YAP and TAZ induce the expression of an enzyme known as phosphoserine aminotransferase 1 (PSAT1), the next thing researchers wanted to study was whether the knockdown of *YAP* and *TAZ* suppresses the expression of *PSAT* in tamoxifen-resistant breast cancer cells[4]. PSAT1 is an enzyme associated with cell proliferation and chemoresistance, thus it was expected to see the elevation of PSAT1 in the tamoxifen-resistant breast cancer cells. Consistent with their predicted outcome, researchers found that the knockdown of *YAP* and *TAZ* resulted in a reduction in both the mRNA and protein levels of PSAT1[4]. Furthermore, researchers wished to explore the effects of PSAT1 suppression on the resistant cells' survival. The results from the *PSAT1* knockdown showed sensitization of the tamoxifen-resistant cells to tamoxifen given by the reduction in cell viability and increase in cell apoptosis of the MCF-7 resistant cells. Building on the finding of the previous study on the re-sensitization of refractory breast cancer cells to tamoxifen via mTOR inhibition, researchers investigated whether the knockdown of *YAP/TAZ* or of *PSAT1* was resolving the endocrine resistance issue by specifically modulating the mTOR pathway. As previously reported, high AKT activity is proven to be responsible for the cancer growth and is dependent on the phosphorylation by mTOR and PDK1[10]. Thus, by inhibiting the activation of mTOR, the AKT should remain partially unphosphorylated and there-

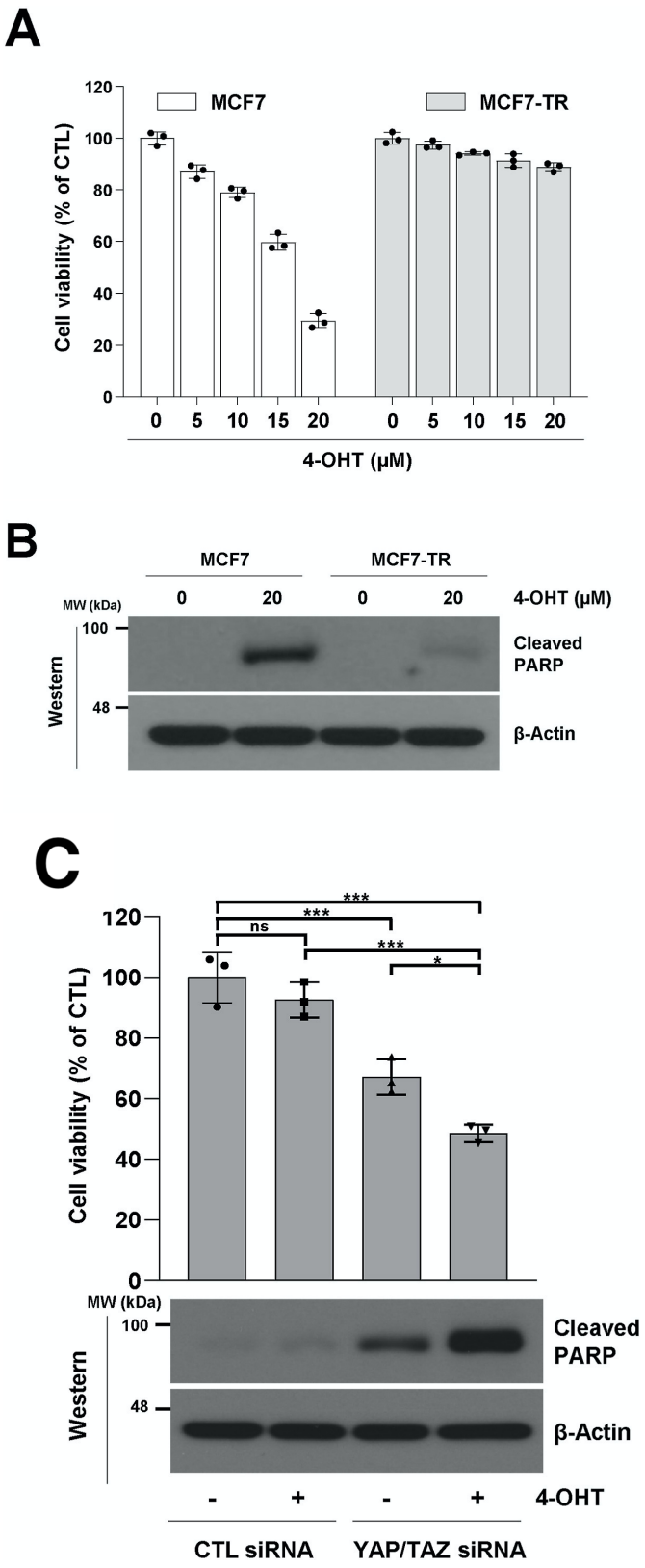

Figure 3. (A) Cell viability of MCF-7 cells and MCF-7 Tamoxifen resistant cells (MCF7-TR) in response to increasing doses of 4-hydroxytamoxifen (4-OHT). Measured using an MTT assay[4]. **(B)** Assessment of cell death of MCF-7 control cells and MCF-7 tamoxifen resistant cells (MCF7-TR) based on PARP cleavage[4]. **(C)** Assessment of cell viability and cell death in the control (CTL) siRNA cells and the cells with the YAP/TAZ knockdown (YAP/TAZ siRNA). Additional assessment of the effect of 4-hydroxytamoxifen (4-OHT) treatment to the cells[4].

fore be unable to induce genes, such as survivin, involved in destructive oncogenic processes. Given the previous results outlined, the researchers speculated that a knockdown in *YAP/TAZ* and *PSAT1* would induce a disruption in mTOR activation, which is characterized by a decrease in S6 and S6K phosphorylation. This speculation was correct as both knockdowns caused a decrease in survivin protein expression following treatment of 4-OHT, which is expected considering a lack of mTOR activation results in less AKT activity and thus less target gene expression. Considering survivin expression is a marker for radiation resistance, these results suggest that by knocking down *YAP/TAZ* or *PSAT1* in resistant breast cancer cells, which in turn reduce the expression of genes involved in endocrine resistance, a re-sensitization to tamoxifen can occur. Re-sensitization through this mechanism may be possible because the knockdowns cause a decrease in mTOR activity and survivin expression which are crucial for cancer progression and endocrine resistance. Both analyzed studies suggest that a downregulation of the components of the PI3K/AKT/mTOR pathway is one mechanism by which tamoxifen-resistant breast cancer cells can be re-sensitized to SERM therapy given that one of the causes is indeed aberrant signaling of this pathway. Follow-up studies on this approach will be necessary to finalize a potential treatment that will be able to conquer this issue.

Conclusion

In summation, SERMs have had a significant impact on breast cancer treatment. While they offer a promising pharmacological profile in reducing breast cancer progression and mortality, many women continue to experience resistance to these agents. In response to this problem, mTOR inhibitors have demonstrated efficacy in restoring sensitivity in resistant cells. However, multiple pathways contribute to endocrine resistance and thus continued research is needed to identify more targets that will counteract this resistance and advance the fight against this formidable disease.

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