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REGULATION OF MUCIN 1 AND MULTIDRUG RESISTANCE PROTEIN 1 BY NEURAMINIDASE 1 ALTERS THE CYTOTOXIC EFFECTS OF DOXORUBICIN IN BREAST CANCER CELLS

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ABSTRACT – *Objective:* Elevated expression of Multidrug Resistance Protein 1 (MRP1) has been associated with poor prognosis among breast cancer patients. Chemotherapeutic drugs such as doxorubicin (DOX) are substrates of MRP1 that efflux the drug, conferring drug resistance. Chemoresistance is associated with the upregulation of MRP1 via Mucin 1 (MUC1). Aberrant glycosylation of MUC1 promotes tumor associated changes involved in cancer progression. Sialylation, a form of glycosylation, is regulated by the enzyme Neuraminidase 1 (Neu1) which adds 9-carbon sialic acids on glycoproteins to control cancer growth. The objective of this study was to understand the relationship between Neu1, MUC1 and MRP1 in mammary carcinoma cells as related to improving the efficacy of DOX to suppress cell growth.

Materials and Methods: MDA-MB-231 and MCF-7 cells were treated with Oseltamivir Phosphate (OP) and/or DOX to assess cell viability using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay. Cells transfected with Neu1 siRNA or those overexpressed with Neu1 in the presence or absence of DOX were counted using trypan blue exclusion assay. Expression levels of MUC1 and MRP1 were detected using western blotting in cells treated with oseltamivir phosphate, cells transfected with Neu1 siRNA and cells overexpressing Neu1.

Results: In this study, we demonstrated that reducing the activity of Neu1 with OP or silencing Neu1 enhanced DOX-mediated growth suppression. In addition, OP or Neu1 siRNA suppressed the protein expression of MUC1 and MRP1 while the overexpression of Neu1 reversed this effect.

Conclusions: Based on these observations, Neu1 affects the expression levels of MUC1, which in turn regulates the expression of MRP1. Consequently, this affects DOX-mediated growth suppression.

KEYWORDS: MUC1, MRP1, Neu1, Drug resistance, Doxorubicin, Breast cancer cells.

INTRODUCTION

Multidrug resistance (MDR) to chemotherapy remains to be a major obstacle in cancer therapy. An important mechanism for drug resistance is the overexpression of ATP-binding cassette (ABC) transporters such as Multidrug Resistance Protein 1-9 (MRP 1-9) which contribute to the efflux of anticancer drugs[1,2]. MRP1 expression dictates poor clinical outcome with reports demonstrating the metastatic potential of cancer cells and decreased survival in colorectal cancer patients[3]. A positive relationship between

the overexpression of MRP1 and metastasis is observed in breast cancer lymph nodes[4]. High grade tumors have a pronounced expression of MRP1, which may be a reason for the observed differences in the clinical outcome with chemotherapy[5,6]. MRP1 extrudes a wide range of anticancer drugs, including doxorubicin (DOX), which cause patients to respond poorly to chemotherapy or develop MDR [7,8].

Oncogene Mucin 1 (MUC1) is well known to play an important role in inducing cellular properties that result in tumor progression [9] and is noted to be a useful prognostic marker in several cancers[10,11]. MUC1 is a heterodimer that contains the N-terminal (MUC1-N) and C-terminal (MUC1-C) subunits. The extracellular domain of MUC1-N is heavily glycosylated with moderate N-glycosylation, whereas MUC1-C contains a few O-linked glycosylation[12,13]. In response to an external stimuli, MUC1 initiates cell proliferation, migration, invasion, and anti-apoptotic effects by activating multiple signaling pathways[14]. In various cancer subtypes, MUC1 induces drug resistance and protects the tumors against the cytotoxic effects of chemotherapeutic agents[15,16]. While there are multiple ways by which cancer cells acquire drug resistance, one of the mechanisms is through the upregulation of MRP1[17,18]. Suppression of MUC1 in breast cancer cell lines downregulates the expression of MRP1, improving the efficacy of DOX-mediated growth suppression[18]. Similarly in pancreatic cell lines, MUC1 regulates MRP1 in an Akt-independent mechanism[19].

Compared to non-transformed cells, aberrant protein glycosylation has been displayed in tumor cells which is a common feature of cancer initiation and progression[20]. Although glycosylation has been implicated in protein stability, destabilization of glycosylated proteins can occur due to conformational change[21]. Sialylation is a form of tumor glycosylation that attaches sialic acid to proteins[22]. Sialic acid plays a role in cell communication, adhesion, and protein targeting[22]. MUC1 is highly O-glycosylated and 90% of breast cancer patients have aberrant glycosylated pattern of MUC1, often with an increased expression of sialylated glycans, which are associated with malignant properties of tumor and ultimately drug resistance[23,24].

Protein glycosylation is a well-regulated post-translational modification process which uses specific enzymes to orchestrate the addition or removal of glycans. One such class of enzymes are Neuraminidases (Neus) that cleave terminal sialic acids from glycoproteins generally exposed on the cell surface or secreted in the extracellular matrix[25]. Neus play roles in cell proliferation, apoptosis, and differentiation in states such as cancer, cardiovascular disorders, microbial diseases, and neurodegenerative conditions[26]. Among this family, Neu1 is associated with the development of cancer and metabolic diseases[27]. Progression of hepatocellular carcinoma caused by the overexpression of Neu1[28], highlights the importance of Neu1 in cancer development. In terms of the role of Neu1 on drug resistance, chemoresistance in pancreatic cells was overcome by targeting the activity of Neu1 with Tamiflu/Oseltamivir Phosphate (OP)[29,30]. Previous study in breast cancer cell lines demonstrated the role of Neu1 in proliferation, cell death, and alteration of the epithelial-mesenchymal properties[31]. Furthermore, tumor growth was hampered in xenograft models of triple negative breast cancer cells (TNBCs) treated with OP[32]. Altogether, these findings suggest that Neu1 may be a therapeutic target in cancer, but the protein targets of Neu1 are unknown.

It is unknown whether changes associated with sialylation of MUC1 impacts its stability and consequently downregulates MRP1 expression, allowing the entry of DOX into the cells. In the present study, we decipher the crosstalk between Neu1-MUC1-MRP1 in mammary carcinoma cells and determine whether Neu1 participates in the regulation of MUC1 which modulates MRP1 expression. We report that reduced activity or downregulation of Neu1 suppresses MUC1 and MRP1, resulting in increased efficacy of DOX-mediated growth suppression. In corroboration with these findings, overexpression of Neu1 induces MUC1 and MRP1 expression, and thus overcoming the anti-cancer effects of DOX.

MATERIALS AND METHODS

Reagents

Antibodies against MRP1 were purchased from Abcam (Waltham, MA, USA) and GAPDH was obtained from Cell Signaling (Danvers, MA, USA). Neu1 and MUC1 antibody were acquired from Santa Cruz Biotechnology (Dallas, TX, USA). Bio-Rad Laboratories (Hercules, CA, USA) supplied anti-mouse and anti-rabbit immunoglobulin horseradish peroxidase-conjugated antibodies. Oseltamivir Phosphate (OP), DOX and the MTT reagent (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) were obtained from Sigma (St. Louis, MO, USA).

Cell Lines

Triple negative breast cancer cell line, MDA-MB-231 and luminal subtype, MCF-7 cells (Estrogen Receptor (ER) positive, Progesterone Receptor (PR) positive and Human Epidermal Growth Factor Receptor 2 (HER2) negative) purchased from ATCC (Manassas, VA, USA) were harvested in Dulbecco's Modified Eagle's Medium (DMEM) containing 10% Fetal Bovine Serum (FBS) (Atlanta Biologicals, Flowery Branch, GA, USA) and antibiotics-antimycotics (Atlanta Biologicals, Flowery Branch, GA, USA). The cells were maintained at 37°C in an incubator set at 5% CO_2.

Cell Viability Assays

MDA-MB-231 cells or MCF-7 cells were plated in a 96-well plate and treated with varying concentrations of OP in the presence or absence of 0.25 µM DOX for 48 hrs. Cell proliferation was performed using the MTT reagent. After treatment for 48 hrs, 50 µL of 5 µg/mL MTT was added directly to the medium and incubated for 3 hrs. After incubation, the media was removed, and the cells were re-suspended in 200 µL of 0.04 M HCl in isopropanol and the cells were placed in the incubator for 30 min. Absorbance was then measured at 570 nm which represented cell growth. The % cell proliferation was normalized against the control.

Cell Transfection with siRNA

MDA-MB-231 and MCF-7 cells were plated in 6-well plates and transfected the following day with either 30 pmol control or 30 pmol Neu1 siRNA purchased from Santa Cruz Biotechnology (Dallas, TX, USA) using Lipofectamine RNAimax, according to the protocol from Invitrogen (Waltham, MA, USA). Briefly, the siRNA complexed with Lipofectamine RNAimax was added dropwise into the plates. The cells were incubated at 37°C for 48 hrs, and proteins from the cells were extracted and probed for the appropriate protein.

Trypan Blue Exclusion Assay

MDA-MB-231 and MCF-7 cells were transfected with Neu1 or control siRNA and treated with DOX for 48 hrs prior to counting the cells using trypan blue. Representation of viable cells are noted as cells/mL.

Overexpression of Neu1

MDA-MB-231 and MCF-7 cells were plated in 6-well plates and transfected the following day with 1.0 ug control or Neu1 expression plasmid (Origene, Rockville, MD, USA) using the MegaTran 2.0 reagent (Origene). Protein extracts were obtained 24 hrs after treatment and probed for MUC1 and MRP1 using western blotting. For cell counting, transfected cells with or without DOX were counted using the trypan blue exclusion assay. Live cells are represented as cells/mL

Western Blotting

Protein concentration was determined using the Bradford Assay (Bio-Rad Laboratories, (Hercules, CA, USA)). Using Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), cell lysates were resolved and probed with the appropriate antibody. GAPDH was used as a loading control. Odyssey Fc imaging system was the instrumentation used to capture bands.

Statistical Analysis

Calculation of the *p*-values were performed through the student's two tailed *t*-test. $p < 0.05$ was statistically significant.

RESULTS

Effect of Neu1 on the suppressive effects of DOX

MDA-MB-231 cells treated with varying concentrations of OP reduced growth in a dose-dependent manner[31]. To understand the role of Neu1 on the growth suppressive effects of DOX, MDA-MB-231 cells were treated with 0.25 µM of DOX in the presence or absence of 400 µg/mL of OP. Results showed DOX at a concentration of 0.25 µM did not inhibit cell growth, but in the presence of OP, DOX reduced cell viability when compared to DOX or OP alone (Figure 1A). Similarly, in MCF-7 cells OP enhanced DOX-mediated growth suppression (Figure 1B). Since OP is a non-specific inhibitor of Neu1, MDA-MB-231 cells were transfected with Neu1 siRNA to silence Neu1 protein expression in MDA-MB-231 cells, then treated with or without DOX (0.25 µM) for 48 hrs and viable cells were obtained using trypan blue. Silencing Neu1 increased the sensitivity of DOX to suppress growth in MDA-MB-231 cells (Figure 1C). Similarly, in MCF-7 cells, results showed knockdown of Neu1 improved the efficacy of DOX-mediated growth suppression (Figure 1D). These results indicate that Neu1 engages in sensitizing breast cancer cell lines to the growth suppressive effects of DOX.

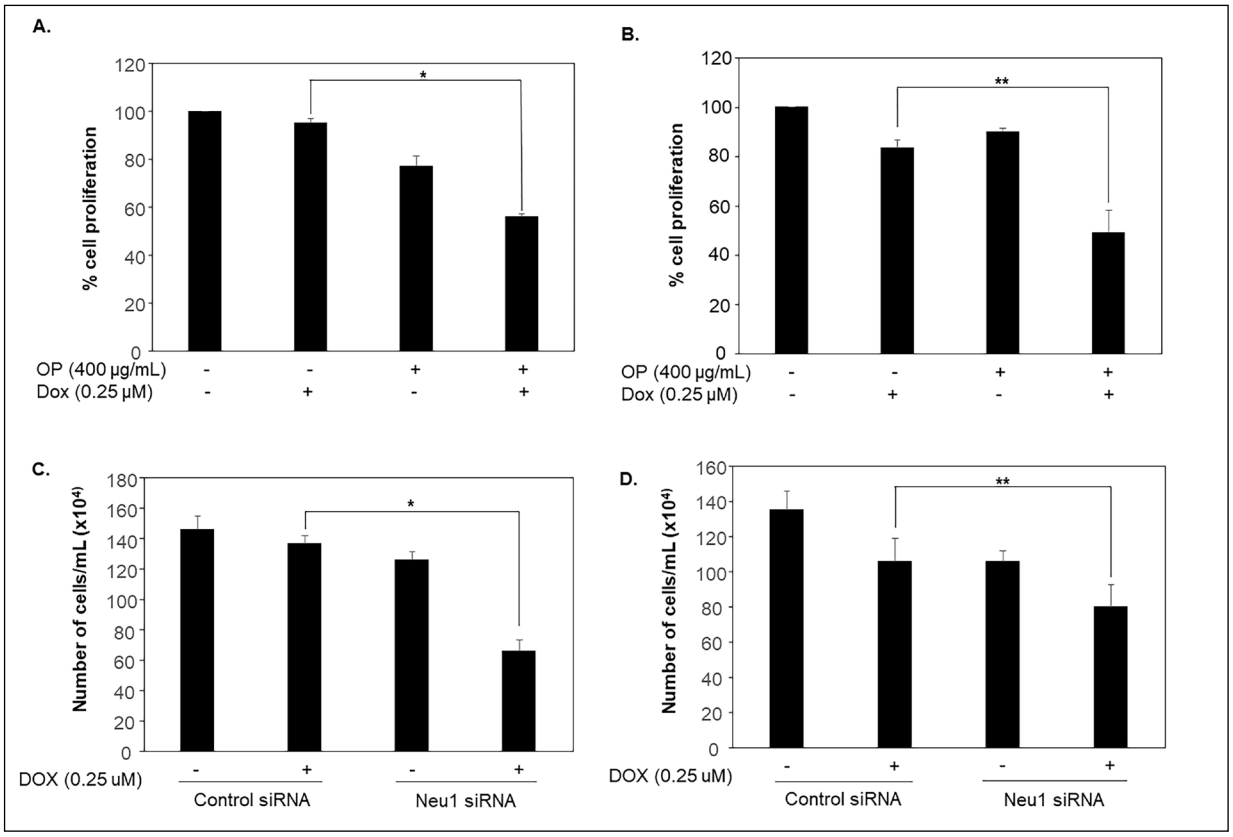

Figure 1. Blocking the activity or expression of Neu1 enhances the anticancer effects of DOX. MDA-MB-231 (*A*) and MCF-7 (*B*) cells were treated with OP (400 ug/ml) in the presence or absence of DOX (0.25 uM) for 48 hrs. Cell viability was assessed using the MTT assay. Data are mean of ± SE (n=4). *, p=0.001 **, p=0.01. MDA-MB-231 (*C*) and MCF-7 (*D*) cells were transfected with control or Neu1 siRNA with or without the presence 0.25 uM DOX, and viable cells were obtained using trypan blue. Data are mean of ± SE (n=3). *, p=0.03 **, p=-0.001.

Evaluating the regulation of Neu1 on MUC1 and MRP1 expressions

In a previous study, it was shown that MUC1 regulates MRP1 and suppression of MUC1 enhances the efficacy of DOX-mediated growth suppression[18]. By decreasing Neu1 activity with OP in MDA-MB-231 cells, the protein expression of MUC1 is reduced, suggesting Neu1 regulates MUC1 (Figure 2A). We also examined MUC1 expression after transfection with Neu1 siRNA in MDA-MB-231 cells and as shown in Figure 2B, reduction of MUC1 protein levels was observed in Neu1 silenced cells. Using MCF-7, we also

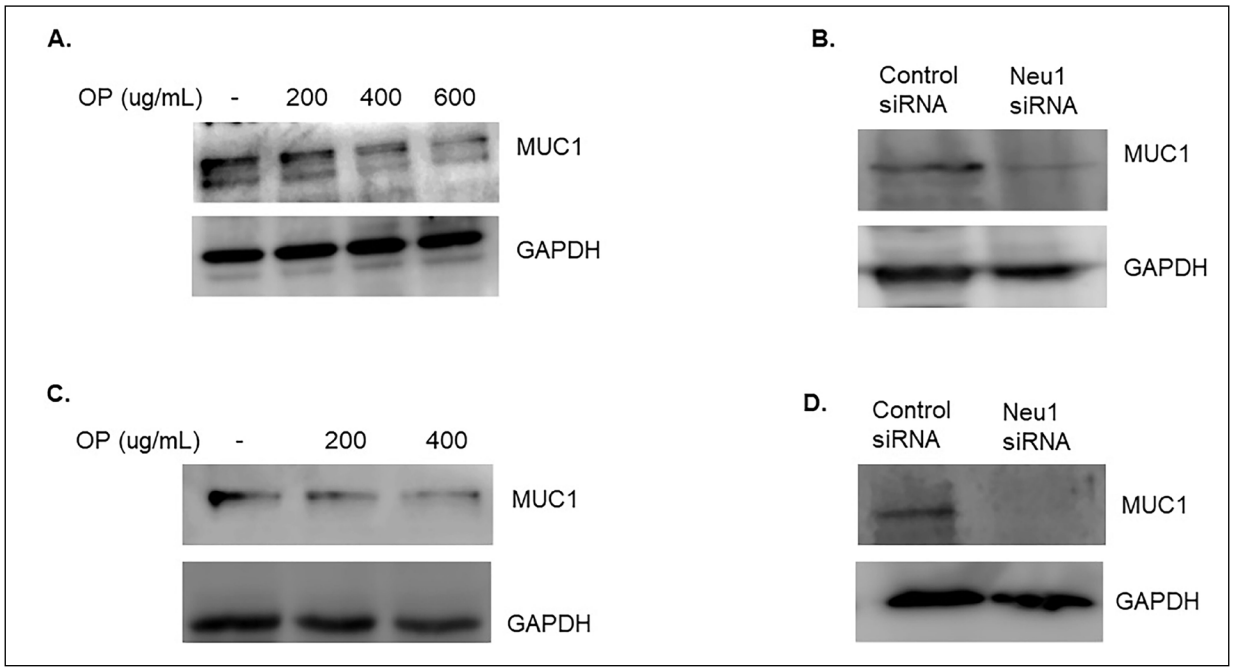

Figure 2. Oseltamivir phosphate reduced the protein expression of MUC1 in Neu1 silenced breast cancer cells. The protein extracted from MDA-MB-231 (*A*) and MCF-7 (*C*) treated with varying concentrations of OP for 24 hrs was probed for MUC1 protein through SDS-PAGE. Loading control: GAPDH. MDA-MB-231 (*B*) and MCF-7 cells (*D*) were transfected with control or Neu1 siRNA, protein lysates separated by SDS-PAGE and immunoblotted against MUC1. The loading control used was GAPDH.

observed reducing Neu1 activity or silencing Neu1 protein expression suppressed MUC1 protein levels (Figure 2C and D). These results suggest Neu1 regulates the expression of MUC1 in two subtypes of breast cancer cell lines and it may be a global effect among mammary carcinoma cells.

DOX is a substrate of MRP1 and overexpression of MRP1 in cells prevent the entry of DOX[33]. Since silencing Neu1 improves the potency of DOX in MDA-MB-231 and MCF-7 cells (Figure 1C and D), we sought to examine whether Neu1 regulates MRP1 protein expression in these cells. As observed in Figure 3A, reducing Neu1 activity with varying concentrations of OP reduced the expression of MRP1 in MDA-MB-231 cells. Corroborating these findings, knockdown of Neu1 protein reduced the expression of MRP1 in MDA-MB-231 cells (Figure 3B). To determine whether Neu1-MRP1 signaling is a global effect among mammary carcinoma cells, MCF-7 cells were also used to study the crosstalk between Neu1 and MRP1. Correspondingly, OP also reduced the protein expression of MRP1 in MCF-7 cells (Figure 3C). The expression of MRP1 protein levels was also downregulated when Neu1 was silenced in MCF-7 cells (Figure 3D). Between the two different classifications of breast cancer cell lines, these results demonstrate Neu1 regulates MRP1, and the interaction between Neu1 and MRP1 is a common mechanism among mammary carcinoma cells. Based on the findings that Neu1 regulates MUC1 in the breast cancer cell lines, this in turn affects the downstream target, MRP1. Consequently, this improves the efficacy of DOX and enhances the anti-cancer effects of this agent to reduce cell growth.

Examining the requirement of MUC1 on the regulation of MRP1 by Neu1

To further explore the Neu1-MUC1-MRP1 crosstalk, MDA-MB-231 cells and MCF-7 cells were transfected with pCMV empty vector or pCMV-Neu1, and protein expression was verified (Figure 4A and 4B). Overexpression of Neu1 induced the expression of MUC1 and MRP1 in both MDA-MB-231 and MCF-7 cells (Figure 4A and B). Exploring the effects of Neu1 in the presence or absence of DOX on cell growth indicated that Neu1 enhanced cell growth compared to control and overexpression of Neu1 desensitized MDA-MB-231 and MCF-7 cells to DOX (Figure 4A and 4B). As shown in our work, MUC1 directly regulates MRP1 in mammary carcinoma cells [18]. This present data demonstrates that Neu1 induces MUC1 and MRP1 which overcomes the growth suppressive effects of DOX.

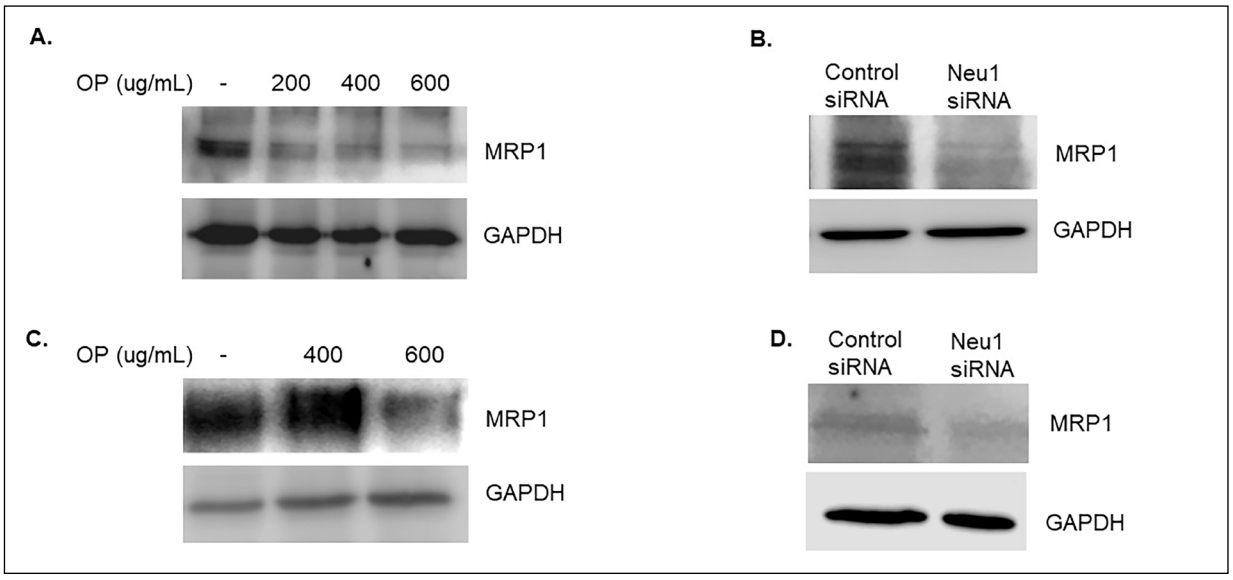

Figure 3. Oseltamivir phosphate reduced the protein expression of MRP1 in Neu1 silenced breast cancer cells. MDA-MB-231 (*A*) and MCF-7 (*C*) cells were treated with varying concentrations of OP for 24 hrs and protein extracts were probed for MRP1. Loading control: GAPDH. Protein lysates from control or Neu1 transfected MDA-MB-231 (*B*) and MCF-7 cells (*D*) were isolated to probe for MRP1 protein expression, with GAPDH as a loading control, through immunoblotting.

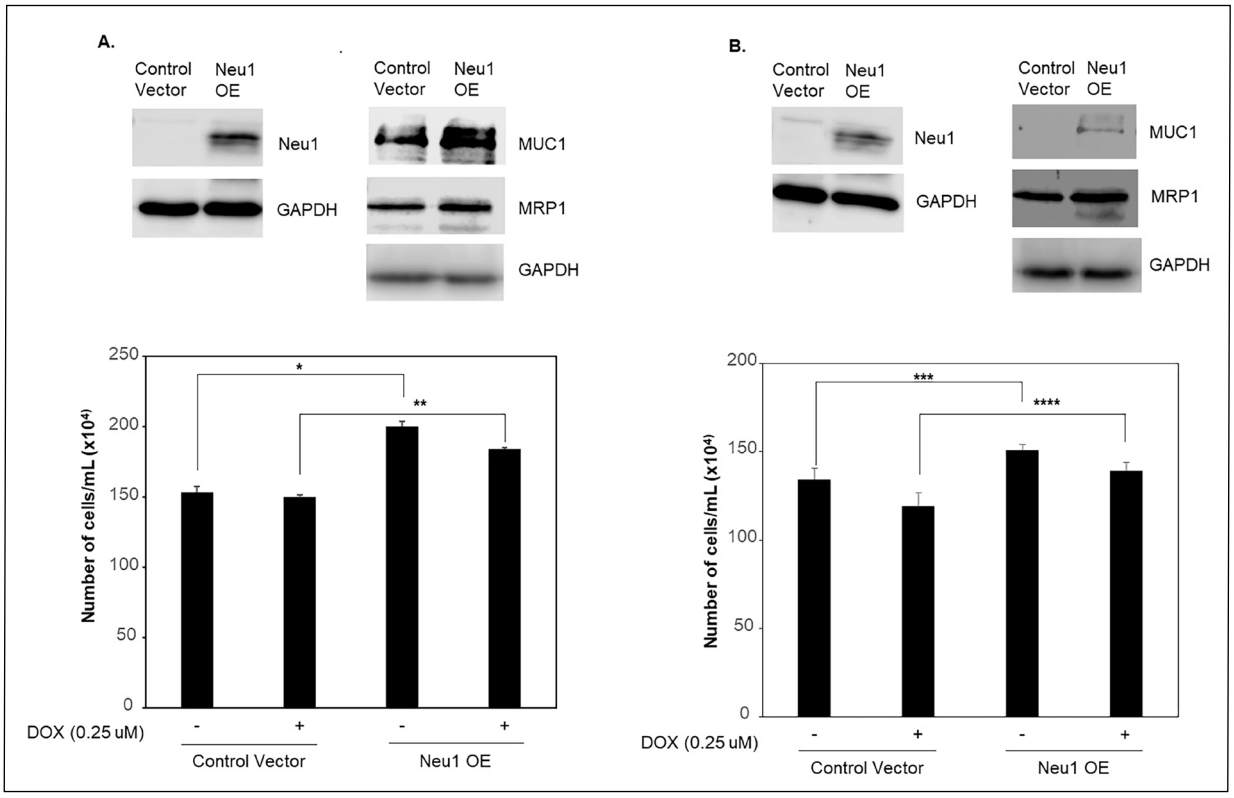

Figure 4. Overexpression of Neu1 induced MUC1 and MRP1 expression. MDA-MB-231 (*A*) and MCF-7 cells (*B*) were transfected with control or Neu1 overexpression (OE) plasmid and overexpression of Neu1 was verified in these cells by immunoblotting against Neu1. The loading control used was GAPDH. Overexpression of Neu1 in MDA-MB-231 (*A*) and MCF-7 cells (*B*) was assessed for MUC1 and MRP1 protein expression. MDA-MB-231 (*A*) and MCF-7 cells (*B*) were transfected with control or Neu1 OE plasmid in the presence or absence of DOX, and the cells were counted using trypan blue. Data are mean of ± SE (n=3). *, p=0.02 **, p=-0.002. *** p=0.04, **** p=0.03.

DISCUSSION

Challenges that lead to failure in the treatment of cancer are chemotherapeutic resistance that occur due to prolonged exposure to these agents, as well as metastasis. Accumulating evidence suggests a direct link between drug resistance and the metastatic characteristics associated with cancer progression. Even with progress made in cancer therapy, these factors remain to be driving forces and targeting these cellular mechanisms may be of interest in developing effective therapeutics.

One such protein target of therapeutic interest is the glycosylated MUC1, amplified in carcinoma cells derived from epithelial cells such as breast and prostate. Its overexpression is associated with poor prognosis. MUC1 is a heterodimer that contains the N-terminal (MUC1-N) and C-terminal (MUC1-C) subunits. The extracellular domain of MUC1-N is heavily glycosylated with moderate N-glycosylation. MUC1 drives chemoresistance in pancreatic and breast cancer cells by altering MRP1 expression[17,18], while in renal carcinomas, MUC1 modulates the expression of several class of the ABC transporters[34]. These studies have demonstrated that MUC1 participates in the regulation of multidrug resistant proteins, and consequently confers cancer drug resistance.

The subject of Neu1 on cancer progression has been controversial with its function based on the type of cancer in study. *In vitro*, Neu1 has been implicated in cell growth, anti-apoptosis, and epithelial-mesenchymal transition in breast cancer cells[31], while *in vivo*, blocking the activity of Neu1 impairs breast tumor growth[32]. In addition, Neu1 has been associated with hepatocellular carcinoma growth[28], while reducing the activity of Neu1 promoted pancreatic cancer cells to become sensitive to chemotherapeutic agents [29]. Contrary to these works, overexpression of Neu1 in colon adenocarcinoma reduced invasion and migration[35], and similarly in bladder cancer cells, a negative correlation was associated between Neu1 and cellular processes such as proliferation and apoptosis [36]. Despite opposing effects of Neu1 in cancer subtypes, Neu1 could be a target to treat certain cancers.

Herein, we propose that MUC1 is a substrate for Neu1 in mammary carcinoma cells and destabilization of the protein expression of MUC1 leads to the downregulation of MRP1. This in turn improves the efficacy of DOX to suppress mammary carcinoma cell growth. Results of this study showed the key role of active Neu1 in upregulating the expression of MUC1 and MRP1 in two different breast cancer cell types. Based on previous findings that MUC1 directly regulates MRP1[18], we conclude from this study that the crosstalk between Neu1 and MRP1 is dependent on changes in MUC1 protein expression.

Glycosylation is the most abundant form of post-translational modification of proteins affecting stability and functional activity[37]. Altered protein glycosylation is a common feature of cancer initiation and progression. Although glycosylation has been implicated in protein stability, destabilization of glycosylated proteins can occur due to conformational change[21]. MUC1 is highly O-glycosylated (ser/thr) and has 5 potential sites of N-glycosylation (asn)[38]. Furthermore, a hallmark of cancer progression is increased sialylation of both O-linked and N-linked epitopes. Aberrant O-linked glycosylation of MUC1 is observed in 90% of breast cancer patients, often with an increased expression of sialylated glycans[24], predictive of tumor growth, and ultimately drug resistance.

The multifaceted role of glycosylation implicated in diseases prompts the need to dissect the composition of the glycosylated residues and differential expression of glycans on glycoproteins as it related to protein stability. Although glycosylation has been characterized in aiding in protein folding and stability, the function of proteins is determined by the glycan patterns[21,39,40]. Conformational changes that occur due to N-glycan alters thermodynamic stability of proteins and this could significantly impact the folding of the protein [21,41]. In this study, we focused on the protein expression of MUC1 as it is related to Neu1 function, and we did not delineate between the MUC1-C and MUC1-N domains of MUC1. However, previous studies have demonstrated the relationship between the efficacy of cancer therapeutics and protein glycosylation, and such studies provide strategies to develop effective anticancer therapeutics based on protein glycosylation. For instance, O-linked glycosylation specifically of MUC1-N reduced sensitivity to chemotherapy, with a specific focus on examining the glycosylated patterns of MUC1 in designing targeted antibody therapy[42,43]. For example, radiation causes considerable changes in both the O-linked and N-linked glycosylated proteins with cell adhesion properties[44]. Moreover, blocking N-glycosylation increased the efficacy of radiotherapy by regulating the gene expression of the receptor tyrosine kinase[45], while disrupting O-linked glycosylation reversed the resistance of laryngeal carcinoma to radiotherapy[46].

While a detailed investigation on how aberrant glycosylation of MUC1 can cause protein instability in models that lack Neu1 expression is outside the scope of this study, it is a compelling approach for future research. In addition, it is imperative to understand how the individual domains of MUC1 are

important in promoting drug sensitivity by altering the glycosylation residues. While this study focused on whether Neu1 destabilized the protein expression of MUC1 and MRP1, further studies to investigate how glycosylation causes the instability of these proteins could provide an avenue for the development of more effective targeted therapy.

CONCLUSIONS

This study demonstrated the existence of a crosstalk between Neu1, MUC1, and MRP1 in mammary carcinoma cells. The findings from this research highlighted that Neu1 regulates the protein expression of MUC1, which in turn influences the protein expression of MRP1. As a result, this impacts the cytotoxic effects of DOX. Studies to delineate the role of how glycan moieties on these proteins contribute to their stability are aims for future work.

Authors Contributions:

PT, KK, and AW collected and analyzed data. PT wrote the manuscript. KK and AW reviewed and revised the manuscript. All authors read and approved of the final manuscript.

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Conflict of interests:

The authors declare that they have no conflict of interest.

Data availability statement:

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval:

The Institutional Biosafety Committee at the University of South Alabama approved this study.

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Informed consent:

None required.

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