

Silencing *SATB1* Gene Suppressed Expression of *mP53*, *S1004A* Genes and Increased Expression of β -catenin and *E-cadherin* Genes in Murine Mammary Cancer Cells in the Presence and Absence of Tocotrienol-Rich Fraction (TRF)

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Abstract

Tocotrienol-Rich Fraction (TRF), which is vitamin E from palm oil, has been reported to have anticancer effects. Previous studies have shown that TRF supplementation downregulates the expression of *special AT-rich sequence-binding protein 1 (SATB1)* gene in murine Breast Cancer cells (BC). *SATB1* is a unique AT-rich binding protein, which coordinates expression of a number of genes responsible for promoting metastasis in cancer cells. In this study, the *SATB1* gene was silenced in the 4T1 murine mammary cancer cell line using the small-interfering RNA (siRNA) approach. Treating the Wild-Type (WT) and *SATB1*-silenced 4T1 (*SATB1*–4T1) cells resulted in marked reduction of proliferation in the presence and absence of TRF. The expression of various tumour marker genes (*mP53*, *S1004A*) was reduced ($p < 0.05$) in the 4T1 cells that were cultured in the presence or absence of TRF. In addition, the expression of some tumour suppressor genes (β -catenin and *E-cadherin*) was increased ($p < 0.05$) in the 4T1 cells that were cultured in the presence or absence of TRF. The findings from this study show that *SATB1* gene plays a key role in carcinogenesis in this BC cell line.

Keywords: SiRNA, *SATB1*, breast cancer, siRNA, knockdown gene

Introduction

Breast cancer (BC) is a major health concern as it is the most common cause of cancer-related deaths in women worldwide. Despite recent developments in BC detection and treatment, there are almost 1.38 million women affected by this disease each year [1]. Some of the

challenges in developing effective BC therapies include the complexity of this disease and its ability to rapidly metastasise. Gene silencing is a technique that aims to reduce or eliminate production of a protein by disrupting the gene that is responsible for its expression [2]. There are various gene silencing methods currently employed in research. Some are also being evaluated for its potential

as therapeutic agents. Nearly all of these gene silencing approaches involve disabling the function of messenger RNA (mRNA) and prevent it from being translated into the corresponding protein. However, these approaches differ in design, molecule used to disrupt mRNA and the manner of mRNA breakdown [3].

New developments in gene therapy have highlighted the use of small interfering RNA (siRNA) technology as a possible tool to treat breast cancer (BC) and other types of cancers [4]. The siRNAs are small molecules, which are synthetically made double-stranded RNA (dsRNA) molecules designed to pair with specific mRNA [5]. Binding of siRNA to its target mRNAs will attract proteins that can result in degradation of the mRNA; thus, preventing the target mRNA from being translated into protein. For siRNA to be a useful therapeutic tool, siRNA-mediated transcriptional silencing has to be efficient, specific and can inhibit tumour growth [6]. Although the siRNA approach has some limitations, it nevertheless provides a broad potential as a promising tool that can be used to regulate disease-associated genes; including oncogenes and tumour suppressor genes.

Vitamin E from palm oil is known as Tocotrienol-Rich Fraction (TRF). Recently, we reported that the *SATB1* gene was downregulated in tumour tissue isolated from TRF supplemented mice induced with BC and treated with Dendritic Cell (DC) vaccine [10]. That was a novel finding, which showed the possible anti-cancer role of TRF as *SATB1* gene is reported to play a critical role in the growth and metastasis of BC. In the present study, we investigated the role of *SATB1* expression in 4T1 murine mammary cancer cells using the siRNA approach in the presence and absence of TRF. The objective of this study was to investigate the impact of silencing the *SATB1* gene on various genes reported to be related to cancer and/or metastasis in the presence and absence of TRF. The results of this study may be useful in developing future cancer therapy using siRNA-based treatment.

Materials and Methods

Cell Line

4T1 cells, which is a highly metastatic murine mammary cancer cell line was purchased from the American Type

Culture Collection (ATCC, USA) and cultured as recommended by the ATCC. The cells were cultured at 37°C in a humidified 5% CO₂ incubator (Heraeus, Germany) as described previously [7, 9 & 10].

Silencing of SATB1 Gene

Four siRNA probes (Table 1) specific for murine 4T1 genes were designed and used to transfect 4T1 cells to silence the expression of the SATB1 gene. Transfection was performed using the Hi-Perfect Transfection kit (QIAGEN, Germany). Briefly, the 4T1 cells were seeded at 5×10^4 cells per well in a 24-well plate in 0.5 mL of complete medium (RPMI 1640 supplemented with 10% FBS, 1% glutamine and 1% penicillin/streptomycin). The cells were incubated at 37°C overnight in a humidified 5% CO₂ incubator. Three concentrations (20 nM, 30 nM and 40 nM) of each siRNA were evaluated for silencing efficiency, which were freshly prepared in 100 mL of culture medium without FBS before the transfection step. Then, 3 µL Hi-Perfect Transfection reagent was added to the freshly prepared siRNA and the contents were mixed by vortexing. The mixture was incubated for 10 min at room temperature to allow formation of transfection complexes. Following this, the transfection complex was added drop-wise onto the pre-seeded 4T1 cells. The plate was gently swirled to ensure uniform distribution of the transfection complex and the cells were incubated at 37°C overnight in a humidified 5% CO₂ for 72 hours. At the end of the culture period, the cells were harvested and RNA was extracted for quantitative PCR (qPCR) analysis to confirm that the SATB1 gene was silenced.

Gene Expression Studies

Total RNA was extracted from WT and SATB1-silenced (SATB1-siRNA) 4T1 cells using the Tri-reagent total RNA extraction kit (Molecular Research Centre, USA). The RNA samples were analysed using quantitative real-time PCR (qPCR) to confirm silencing of the *SATB1* gene in the 4T1 cells. The QuantiFast SYBR Green RT-PCR master mix (QIAGEN, Germany) used to prepare the RNA samples for qPCR analysis. The qPCR was performed using two-step cycling (Table 2) using a multicolour real-time PCR detection system (IQ5 Hercules, California, USA). The *SATB1* and *beta-actin* genes were purchased from a commercial source

(QIAGEN, Germany). The other primers used for qPCR analysis of murine *metastatin-1 (Mts-1 S100A4)*, *E-cadherin*, *B-catenin* and *mutant p53 (mP53)* genes

(Table 3) were synthesised using the First Base Sequencing system (Applied Biosystem Inc., USA).

Table 1: The siRNA premix sequence used for siRNA.

No.	FlexiTube siRNA Premix	Sequence	
1	Mm_Satb1_5	CCCGAAGTACACCATCATCAA	<i>All siRNA premix lyophilised pellets were diluted with RNase-free water to 625 μL to obtain the concentration of 20 μM</i>
2	Mm_Satb1_7	AAGGTGGTACAAACATTTCAA	
3	Mm_Satb1_6	CAGGAAATGAAGCGTGCTAAA	
4	Mm_Satb1_1	CACAGTTGCCCTAAACTAGAA	

Table 2: Conditions used for the real-time PCR.

Step	Time	Temperature	Ramp rate
Reverse transcription	10 min	50°C	
PCR initial activation step	5 min	95°C	Maximal/Fast mode
Two-step cycling			
Denaturation	10sec	95°C	Maximal/Fast mode
Combined/annealing/extension	30 sec	60°C	Maximal/Fast mode, perform fluorescence data collection
Number of cycles	40		
Last step	Infinite(∞)	10°C	Until take out from cycler. Kept all samples stable

Table 3: Primers used for the qRT-PCR.

Genes (Mouse)	Reverse /Forward primers	Reference
<i>Beta-actin</i>	5'-AACTCGAGTGCCATGGTAACCGTTGAGAC-3'	QIAGEN, Germany
	5'-AACTCGAGAGACTCCTCAGATGAAGTGTT-3'	
<i>S100A4 (mts1)</i>	5'-AACTCGAGTGCCATGGTAACCGTTGAGAC-3'	EL Naaman <i>et. al.</i> 2004 [11]
	5'-AACTCGAGAGACTCCTCAGATGAAGTGTT-3'	
<i>E-cadherin</i>	5'-AATGGCGGCAATGCAATCCCAAGA-3'	Criswell <i>et.al.</i> 2007 [13]
	5'-TGCCACAGACCGATTGTGGAGATA-3'	
<i>B-catenin</i>	5'-TTAAACTCCTGCACCCACCAT-3'	Rui Zhang <i>et. al.</i> 2007 [14]
	5'-AGGGCAAGGTTTCGAATCAA-3'	
<i>p53</i>	5'-AAAACCACTTGATGGAGAGTATTTCA-3'	Rui Zhang <i>et.al.</i> 2007 [14]
	5'-GCTCCCGGAACATCTCGAA-3'	
<i>SATB1</i>	5'-ACACAGCTCTGCTGCCCAAGCC-3'	QIAGEN, Germany
	5'-GACCAGCTGAGGACTGATCGG-3'	

Cell Proliferation

The 4T1 cells were treated with the concentration of the siRNA complex that caused the highest silencing of the *SATB1* gene expression in the 4T1 cells. Transfection was performed in 10 mm Upcell Nunc dish (Nunc, Germany). Following incubation of the 4T1 cells with the siRNA complex and Hi-Perfect transfection reagent, the cells were washed with sterile PBS solution and recovered by centrifugation (1500 rpm for 5 min). The cells were seeded at 0.5×10^4 cells/well in complete medium and cultured at 37°C in a humidified 5% CO₂ incubator (Heraceus, Germany) overnight. The next day, the culture medium was removed and replaced with a fresh medium, which contained different concentrations (4, 8 or 12 µg/mL) of TRF. Similarly treated WT 4T1 cells were used as controls. The cells were cultured for 72 hours at 37°C in a humidified 5% CO₂ incubator (Heraceus, Germany). Following 72 hours, the WT and SATB1-silenced 4T1 cells were washed with RNA-free PBS and RNA was extracted from these cells. The extracted RNA was used for qPCR analysis to check for expression of SATB1 gene and other genes that play a role in carcinogenesis of BC.

Statistical Analysis

Statistical analysis was done using the student T-test and SPSS version 9.12 for most of the data and data represent mean value with \pm S.E.M of triplicate measurements for qPCR experiments. Results were considered statistically significant when $p < 0.05$.

Results

Optimal conditions for using short interfering RNA approach in 4T1 cells

The 4T1 cells exposed to 20 nM siRNA3 showed the most potent inhibition of *SATB1* expression (relative fold expression: 0.14) compared to siRNA 1 (relative fold expression: 0.3) and siRNA4 (relative fold expression: 0.24) (Figure 1). However, only the inhibition observed with siRNA1 was found to be statistically significant ($p < 0.05$) when compared with wild-type (control). The relative expression fold when 30 nM siRNA was used were 0.66; 0.64; 0.28 and 0.15 for siRNA1, 2, 3 and 4, respectively (Figure 1). In addition, the inhibition

observed with siRNA3 and siRNA4 were found to be statistically significant ($p < 0.05$) when compared with wild-type (control). When 40 nM siRNA was used, the relative expression fold was 0.29; 1.0; 0.55 and 0.24 for siRNA1, 2, 3 and 4, respectively (Figure 1). In addition, the inhibition observed with siRNA1, siRNA3 and siRNA4 were found to be statistically significant ($p < 0.05$) when compared with wild-type (control). From the optimisation step, siRNA 4 at 30nM concentration was found to have the most significant ($p < 0.05$) reduction of the *SATB1* gene expression in the 4T1 cells. So, for the next few studies, 30 nM of siRNA 4 was used to silence the expression of the *SATB1* gene the 4T1 cells.

Viability of SATB1-silenced 4T1 cells treated with TRF

The viability of the SATB1-silenced 4T1 cells was lower (84.1%) when compared to WT 4T1 cells (100%) (Figure 2). In addition, exposure to various concentrations of TRF caused significant reduction ($p < 0.05$) in the viability of the WT and the SATB1-silenced 4T1 (Figure 2). Cell viability reduced when higher concentrations of TRF were used, suggesting that the effects observed were dose-dependent. Overall, the viability of the SATB1-silenced 4T1 cells appears to be lower than the WT 4T1 cells at all concentrations tested.

Expression of SATB1

In the siRNA-treated 4T1 cells, there was a marked ($p < 0.05$) down-regulation of the *SATB1* gene regardless of exposure to TRF (Figure 3). There were minimal differences observed between each TRF treatments in the SATB1-silenced cells, possibly due to the extremely low expression of the *SATB1* gene.

Expression of S1004A and mutant P53

S1004A gene is a metastasis inducer, which is an important regulator of BC progression [16]. This *S1004A* gene was reported as a *SATB1*-dependent gene in BC cells [16]. Treating WT 4T1 cells with TRF, down-regulated the expression of the *S1004A* gene in a dose-dependent manner (Figure 4a). A similar inhibition of the *S1004A* gene expression was also observed in SATB1-silenced 4T1. Mutant p53 (mP53) is reported to contribute to various stages of tumour progression as well as cause increased

resistance to anti-cancer treatments [17]. The expression of the *mP53* gene was reduced in WT treated with TRF and the SATB1-silenced 4T1 cells (Figure 4b). Highest level of suppression of the *mP53* gene was observed when

12 µg/mL (relative fold expression: 0.31 fold) was used. This was followed by 8 µg/mL (relative fold expression: 0.55 fold) and 4 µg/mL (relative fold expression: 0.59 fold) of TRF (Figure 4b).

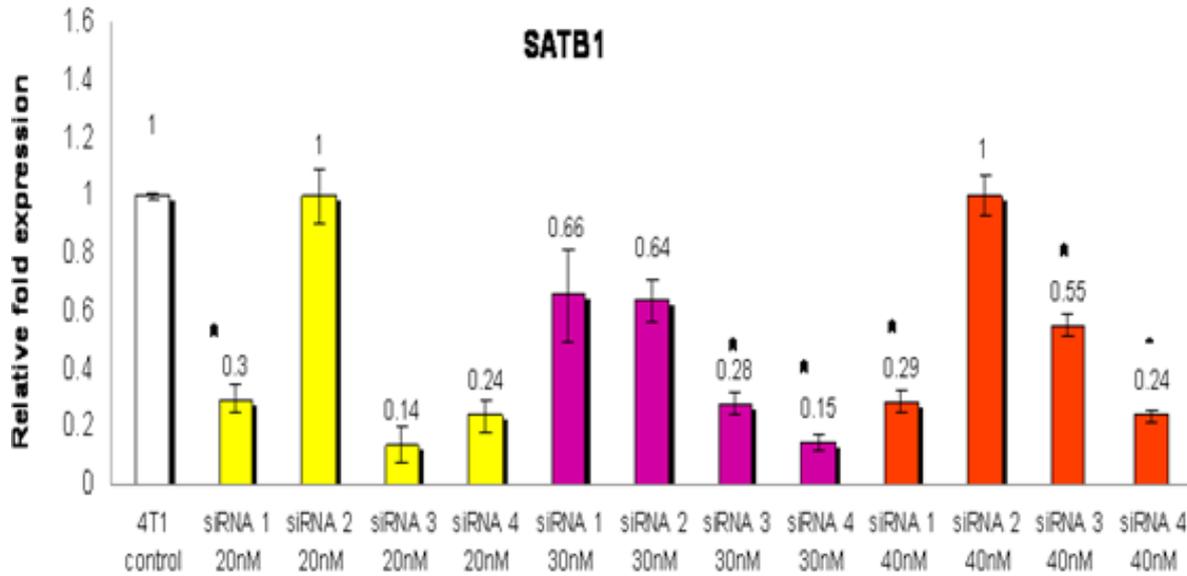


Figure 1: The 4T1 cells were treated with four types of siRNA (siRNA 1, siRNA 2, siRNA 3 or siRNA 4) to silence the expression of the SATB1 gene. For each type of siRNA, three different concentrations (20, 30 or 40 nM) of the siRNA were used to identify the siRNA and optimal concentration that gave the highest inhibition of the SATB1 gene expression in the 4T1 cells. RNA from wild-type (WT) 4T1 cells were used as control. Each data point represents mean ± SEM of triplicate samples. [* significantly different from control (p<0.05)]

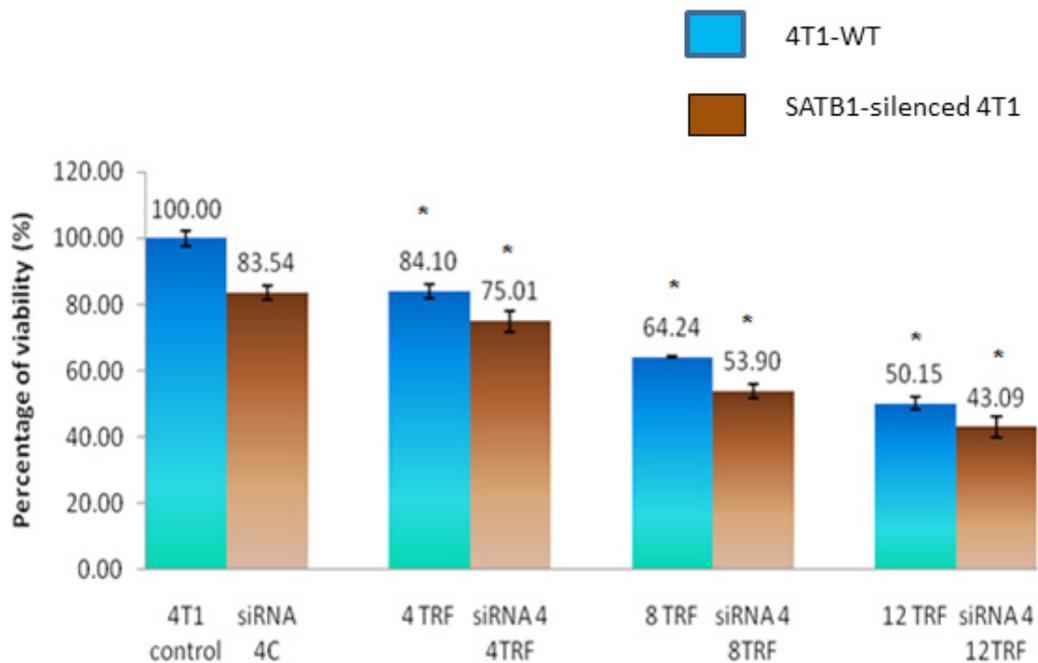


Figure 2: Wild-type (WT) or SATB1-silenced 4T1 cells (siRNA 4) cells were cultured in the presence or absence of TRF (0, 4, 8 or 12 mg/mL) for 72 hours at 37°C in a humidified 5% CO₂ incubator. Cell viability was quantified using the MTT assay. Results are expressed as percentage of cell viability based on untreated controls. Each data point represents mean ± SEM of triplicate samples. [* significantly different from control (p<0.05)]

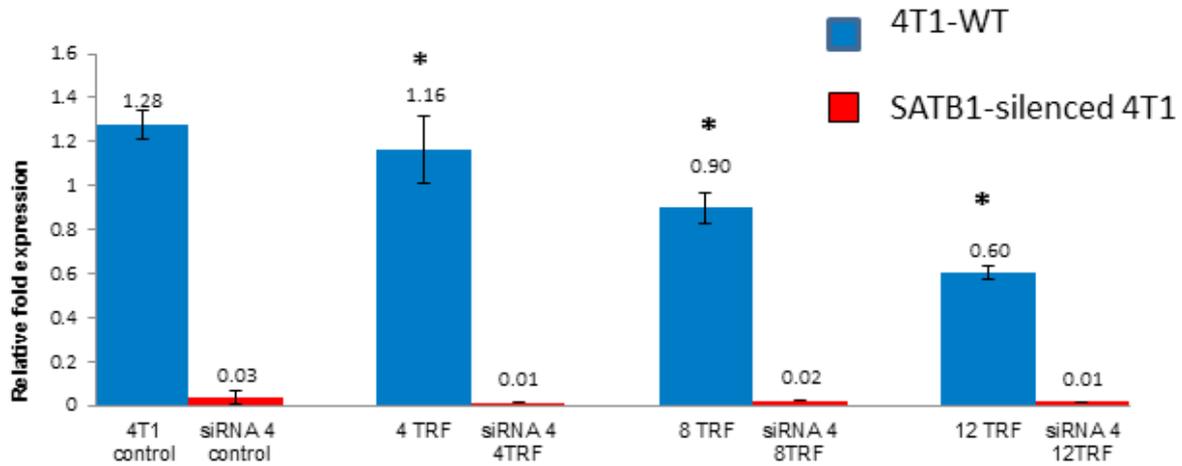
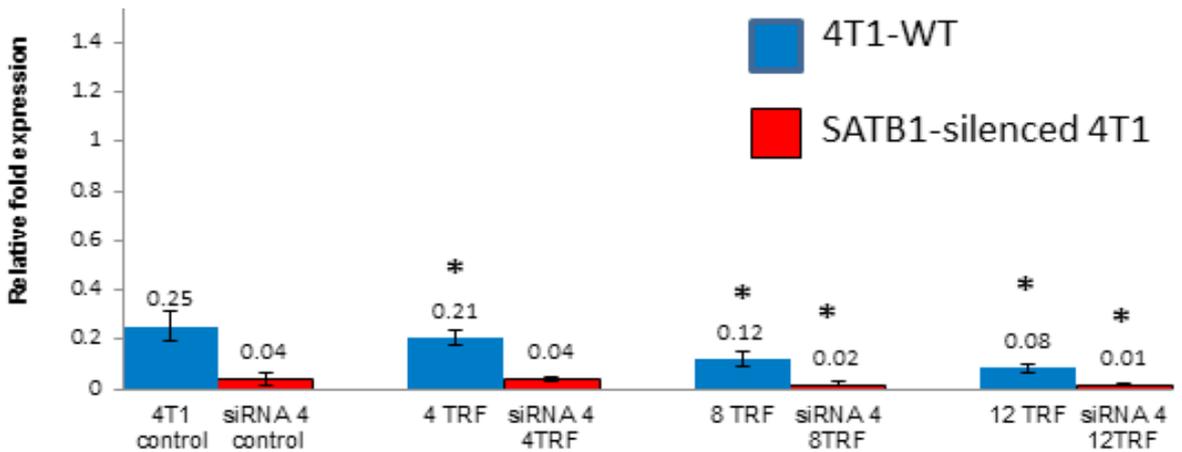


Figure 3: The expression of the SATB1 gene in the wild type (Control) and SATB1-silenced (siRNA 4) 4T1 cells cultured in the presence or absence of TRF (0, 4, 8 or 12 mg/ml) for 72 hours at 37°C in a humidified 5% CO₂ incubator was quantified using quantitative PCR. Triplicate preparations were used for each sample. [* significantly different from control ($p < 0.05$)]

(a) *S1004A* gene



(b) mutant *P53* (mP53) gene

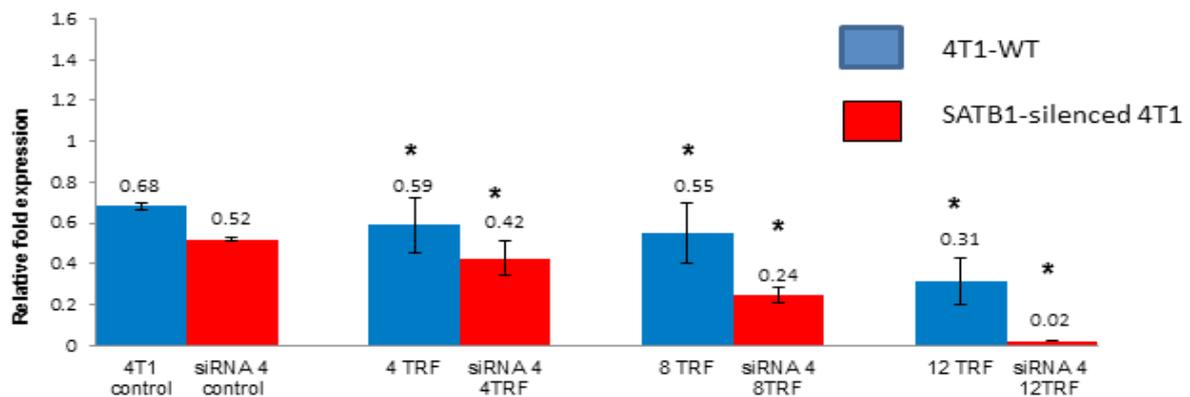


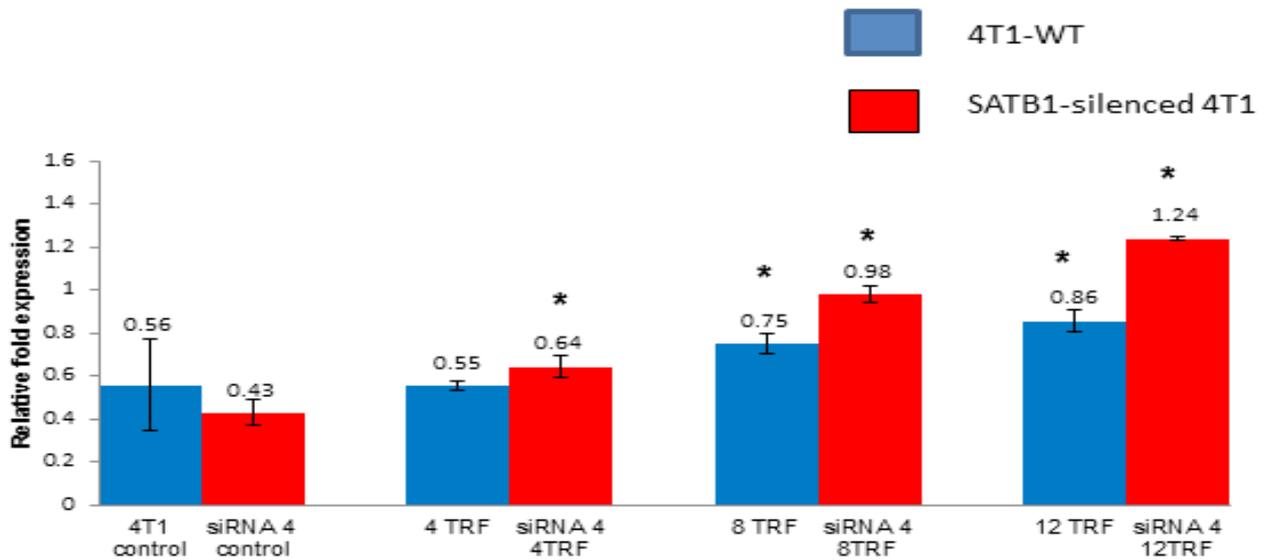
Figure 4: Expression of (A) *S1004A* and (B) mutant *P53* (mP53) genes in the wild-type (4T1-WT) and SATB1-silenced 4T1 cells treated with TRF (0, 4, 8 or 12 mg/ml) at 37°C for 72 hours in a humidified 5% CO₂ incubator was determined using real-time PCR. Results are expressed as relative fold expression of untreated 4T1 cells (Control). *Significantly different from control ($p < 0.05$)

Expressions of β -catenin and E-cadherin

Mutant *β-catenin* gene has been implicated in the pathogenesis of several cancers [18, 19] and *β-catenin* was reported to be down-regulated by *SATB1* gene (18, 19). The expression of the *β-catenin* gene was increased in both wild-type and SATB1-silenced 4T1 cells treated with different concentrations of TRF (Figure 5a). The expression of the *β-catenin* gene increased ($p < 0.05$) in

SATB1-silenced 4T1 cells when treated with 4 mg/mL (relative fold change: 0.64 fold), 8 mg/mL (relative fold change: 0.98) and 12 mg/mL (relative fold change: 1.24) TRF compared to untreated controls. In the WT 4T1 cells, exposure to TRF also increased ($p < 0.05$) expression of the *β-catenin* gene [8 mg/mL (relative fold change: 0.75) and 12 mg/mL (relative fold change: 0.86)] of TRF (Figure 5a).

(a) *beta-catenin*



(b) *E-cadherin*

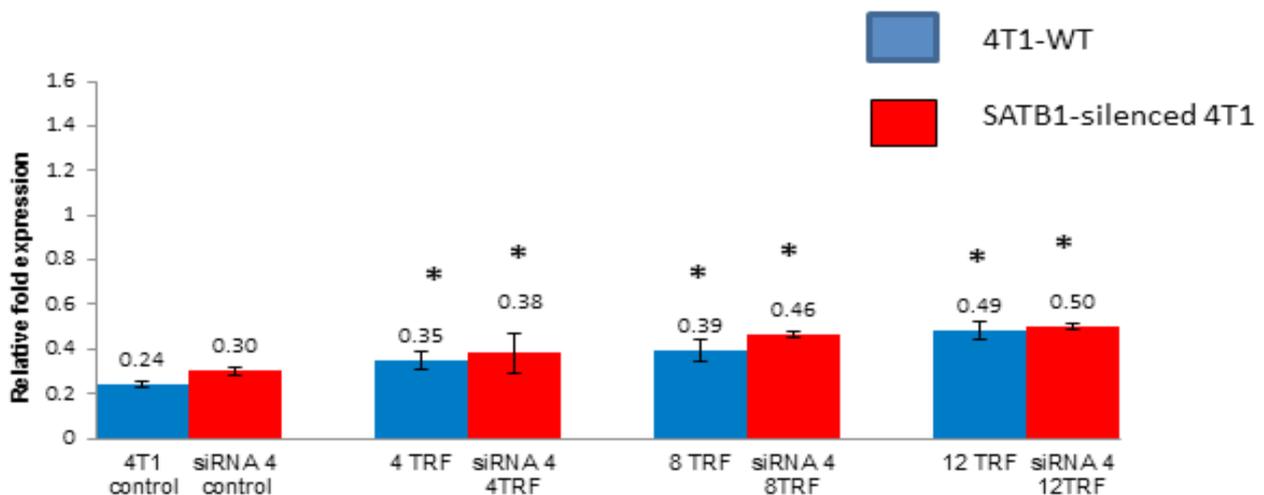


Figure 5: The expression of (a) *beta-catenin* and (b) *E-cadherin* genes in the 4T1 wild-type (4T1-WT) and *SATB1* gene silenced through the silencing RNA (siRNA) 4T1 approach cultured in the presence or absence of TRF (0, 4, 8 or 12 mg/mL) for 72 hours at 37°C in a humidified 5% CO₂ incubator was determined using real time PCR. Results are expressed as relative fold expression of untreated 4T1 cells (Control). *Significantly different from control ($p < 0.05$)

The expression of the *E-cadherin* gene was increased ($p < 0.05$) in the TRF-treated wild-type and *SATB1*-silenced 4T1 cells (Figure 5b). Approximately 0.25 relative fold difference was observed when the expression of the *E-cadherin* gene between control (relative fold change: 0.24) and the same cells exposed to 12 $\mu\text{g/mL}$ TRF (relative fold change: 0.49 fold) while a 0.20-fold difference increase was recorded when compared between the *SATB1*-silenced untreated 4T1 cells (relative fold change: 0.30 fold) with those that had been exposed to 12 $\mu\text{g/mL}$ TRF (relative fold change: 0.50 fold). Overall, there was an increased *E-cadherin* in the *SATB1*-silenced 4T1 cells compared to wild-type cells. Higher expression of the *E-cadherin* gene was also observed when these cells were exposed to higher concentrations of TRF.

Discussion

Tocotrienol-rich fraction (4 to 12 $\mu\text{g/mL}$) inhibited proliferation of wild-type (WT) and *SATB1*-silenced 4T1 cells. The level inhibition observed in the *SATB1*-silenced 4T1 cells was observed to be greater than the WT cells. The expression of *mP53* and *S100A4* genes were markedly down-regulated in the *SATB1*-silenced 4T1 cells compared to WT cells.

The *mP53* gene contributes to various stages of tumour progressions. This gene is reported to be associated with increased resistance to some of the anti-cancer treatments [17]. In a transgenic mouse model, over-expression of *mP53* in certain tissues revealed a variety of manifestations of this gene such as cooperation with additional oncogenic events that accelerate tumour development and make the tumours to be more invasive and aggressive [17].

The *S100A4* gene is also known as *Mts-1* (*metastatin-1*), which is a member of the S100 family of calcium-binding proteins [16]. It is a metastasis inducer, making it an important regulator for BC progression [21]. The *S100A4* gene was also reported to be a *SATB1*-dependent gene in breast cancer cells [21]. This gene is highly expressed in various metastatic cells and its expression correlates with poor prognosis in some cancer [16, 22 & 23]. Studies with mouse models have shown that the *S100A4* gene itself is not tumorigenic, but once a tumour is formed, it enhances tumour invasiveness and metastasis [16, 22 & 23]. The most likely reason for this pattern of expression

in the *SATB1*-silenced 4T1 is because the *S100A4* gene may be a *SATB1*-dependent gene in the 4T1 cells. With TRF treatment and/or silencing of the *SATB1* gene in the 4T1 cancer cells, we found that these approached can reduce tumour growth as well as down-regulate the expression of some genes that are responsible for cancer growth and development such as *mP53* and *S100A4*.

Wild-type human BC cells (e.g. MDA-MD 231) are reported to express high levels of the *SATB1* gene [16]. Studies have shown that the expression of *β-catenin* and *E-cadherin* genes are down-regulated in MDA-MD 231 human BC cells due to the expression of the *SATB1* gene [20, 21 & 24]. The *β-catenin* is a member of the canonical *Wnt* pathway where a network of proteins that are normally involved in embryogenesis and cancer [20, 21 & 24]. *E-cadherins* are known as a tumour suppressor genes and abnormal expression of this gene has been associated with the development of metastases in BC patients [20]. The finding from the present study corroborates with previous findings that *SATB1* plays a role in the inhibiting expression of *β-catenin* and *E-cadherin* genes [16, 21] and silencing *SATB1* gene appear to increase the expression of both these genes. In addition, exposure to TRF also appears to inhibit *SATB1* expression, which in turn increases expression of both of *β-catenin* and *E-cadherin* genes.

Conclusion

In order to evaluate the importance of the *SATB1* expressions in BC cells, we generated *SATB1*-silenced 4T1 cells using the siRNA technique. The viability of the *SATB1*-silenced 4T1 cells decreased when these cells were exposed to TRF. Further analysis showed that in *SATB1*-silenced 4T1 cells treated with TRF, there was marked down-regulation of the *mP53* and *S100A4* genes, which are responsible for tumour progression as well as up-regulation of the *β-catenin* and *E-cadherin* genes.

Author's Contribution

Conceptualization, A.R.; methodology, A.R and S.C.; software, S.R and S.C.; validation, A.R., S.C. and S.R.; formal analysis, A.R., S.C. and S.R.; investigation, S.R.;

resources, A.R., S.C. and S.R.; writing—original draft preparation, S.R.; writing—review and editing, A.R and S.C.; visualization, A.R. and S.R.; supervision, A.R and S.C. All authors have read and agreed to the published version of the manuscript. All authors have read and agreed to the published version of the manuscript.

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