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# mRNA Expression of Somatostatin Receptors (1-5) in MCF7 and MDA-MB231 Breast Cancer Cells

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## ABSTRACT

**Background:** Breast cancer is one of the most common types of cancer and heterogeneous disease. Somatostatin receptors (SSTRs) are expressed in normal and tumour tissues including breast cancer cells.

**Objective:** The aim of this study to evaluate the expression of SSTRs subtypes 1 – 5 in MCF7 and MDA-MB231 human breast cancer cell lines and compare the levels between two cells.

**Methods:** The detection of mRNA expression levels of SSTRs in MCF7 and MDA-MB231 was performed using quantitative-polymerase chain reaction (qPCR).

**Results:** SSTR1, 2, 3 and 4 mRNA levels were significantly higher in MDA-MB-231 about MCF-7. The expression of SSTR 4 mRNA was highest in MDA-MB231 and MCF-7 cell lines, however, SSTR3 mRNA was least expressed in both cell lines.

**Conclusion:** SSTRs subtypes (1 – 5) were expressed in both MDA-MB231 and MCF7 cells. However, the levels of expression differ between both cell lines.

**Key Words:** Breast cancer, Cell lines, Somatostatin receptors and mRNA expression

## INTRODUCTION

Breast cancer is the most common type of cancer and the second leading cause of cancer-related deaths in women worldwide.<sup>1,2</sup> It is the most common cancer in both developed and developing countries,<sup>2</sup> but still diagnosed in late-stage due to lack of awareness and knowledge for most of risk factors, signs and symptoms of breast cancer.<sup>3</sup> Breast cancer is considered a heterogeneous disease because of the changes in the mammary epithelial cells leading to aggressive cell proliferation.<sup>4</sup> The three main biomarkers of interest in breast cancer include estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Currently, four molecular subtypes with different levels of expression of these receptors are luminal A, luminal B, HER2 enriched, and basal-like have been identified. Triple-negative breast cancer (TNBC), which is a part of the basal-like subgroup, is characterized by the lack of PR, ER, and HER2 expression.<sup>5</sup> Different breast cancer

subtypes extremely high mortality, poor drugs response and recurrence.<sup>6</sup> At the most advanced stage of breast cancer, in particular, the hormone-independent cancers develop resistance to therapy and leading to increasing cases of mortality. Breast cancer cure and control includes surgery, radiation therapy and chemotherapy as well as hormone therapy.<sup>7</sup> The peptide hormones are expressed in tumour tissues affected cellular process regulation and proliferation which causing therapy resistance.<sup>8</sup> Somatostatin (SST) is an endogenous peptide known to inhibit the cellular processes such as inhibits the motility and acid secretion of GI, it's effectively stopped bleeding in cases with acute upper GI bleeding,<sup>9</sup> neurotransmissions, hormonal secretion and cell proliferation as well as induced apoptosis through SSTRs subtypes (1-5) encoded by five distinct SSTR genes on chromosomes 14, 16, 17, 20 and 22, respectively.<sup>10</sup> Somatostatin receptors (SSTRs) are G-protein-coupled plasma membrane receptors, initially secreted as a long precursor molecule; it undergoes specific enzymatic degradation generation with

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two forms of SST peptides, SS-14 and SS-28, as their natural ligands.<sup>11</sup> SSTRs 1-5 expressed in normal and tumour tissues depending on cell type. In normal tissues, SSTRs are found mainly in the brain, pancreas, stomach and kidney, while in tumour tissues their expression depending on the type of tumour and biological characteristics.<sup>12</sup> SSTRs have direct and indirect effects on tumour biology. The direct effect includes the inhibition of tumour proliferation and induction of pro-apoptotic pathways including both intrinsic and extrinsic apoptosis pathway.<sup>13,14</sup> Meanwhile, the indirect effects include the inhibition of hormones and growth factors.<sup>15,16</sup> SSTRs mediate signal transduction pathways via inhibition of adenylyl cyclase (AC) and guanylyl cyclase (GC), protein phosphorylation and activation of mitogen-activated protein kinase (MAPK).<sup>17,18</sup> However, the activation of signalling pathways affected cell cycle arrest through activation of cyclin-dependent kinase inhibitor (p27Kip1) and apoptosis. Cancer cells with positive SSTRs are less malignant with higher survival whereas the lack of SSTRs expression has been associated with the poorly differentiated and invasive tumour. However, several effects demonstrated subtype selectivity, and subtype-specific signalling has been reported.<sup>19</sup> SSTR1, 2, 4 and 5 frequently interfere with the mitogen-activate protein kinase pathway to modulate cell proliferation, whereas SSTR3 was indicated to have an increased potential to induce apoptosis.<sup>4</sup> Furthermore, SSTR2 is considered a prognosis factor because it is associated with low proliferative and invasive breast cancer. Also, SSTRs being frequently expressed in the same cell, and the existence of ligand-induced dimerization proposed for G-protein-coupled receptors.<sup>12</sup> Therefore, somatostatin analogues (SSAs) have been used in the treatment of SSTR-positive tumours.<sup>14</sup> However, the therapeutic results of SSAs treatment varied due to different SSTR expression patterns and reasons that are not understood.<sup>20</sup> SSTRs levels have been investigated in different kinds of human cancer such as hepatocellular carcinoma, pancreatic cancer and breast cancer.<sup>21</sup> SSTRs are highly expressed in neuroendocrine tumours but their levels of expression in breast cancer are not well documented.<sup>22</sup> However, in breast cancer, SSTRs are expressed in different levels and are correlated with various histological markers in a receptor-specific manner.<sup>23</sup> Previous studies reported that of SSTRs expressed variety in tumour tissues and cancer cell lines.<sup>24</sup> In the present study, MCF-7 (estrogen-receptor-positive breast cancer cell line) and MDA-MB231 (estrogen receptor-negative breast cancer cell line) have been used in vitro as common breast cancer models to determine the expression of these receptors. The MCF7 cell line characterised by differentiated mammary epithelium including the ability to process estradiol via cytoplasmic estrogen receptors. While, MDA-MB231 is a highly aggressive, invasive but poorly differentiated triple-negative breast cancer (TNBC) cell line that lacks receptors

for estrogen (ER) and progesterone (PR) expression, as well as human epidermal growth factor receptor 2 (HER2) amplification,<sup>25</sup> and is known to be resistant to several anti-cancer agents.<sup>26</sup> The aim of this study was, therefore, to evaluate the mRNA expression for SSTRs (1-5) in human breast cancer cell lines MCF7 and MDA-MB231 using quantitative real-time polymerase chain reaction (qRT-PCR).

## MATERIALS AND METHODS

### Cell culture

MCF7 and MDA-MB231 human breast cancer cell lines were kindly donated by the National Cancer Institute Regina Elena Rome, Italy. Both cells were purchased from the American Type Culture Collection (Manassas, VA, USA). MCF7 and MDA-MB231 cells were grown in a humidified 37°C incubator in 5% CO<sub>2</sub> and cultured in Dulbeccos modified essential medium /F12 complete media supplemented with 10% fetal bovine serum, 1% penicillin/streptomycin and 1% L-glutamine.

### RNA extraction

Total RNA from MCF7 and MDA-MB231 cell lines was extracted by using EXIQON kit. The concentrations of total RNA were quantified by Nanodrop 2000 (Thermo Scientific, Hvidovre, Denmark), and all samples were stored at -20°C until analysis.

### Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR)

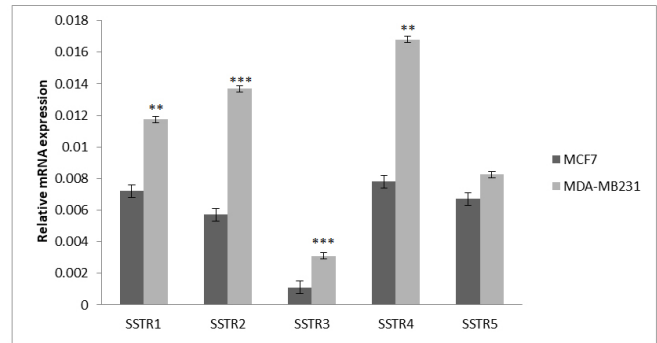
RNA was converted into complementary DNA (cDNA) by reverse transcriptase process according to the manufacturer's instruction. After addition oligo (dT), samples were incubated at 42°C for 1 hour in a thermal.

### Quantitative Real-time Polymerase Chain Reaction (qRT-PCR)

qRT-PCR was performed using q RT-PCR Systems (Bio-Rad) to detect the expression of SSTRs 1-5 levels in MCF7 and MDA-MB231 breast cancer cell lines. qRT-PCR was performed using 2 µg of retro-transcribed RNA and normalized with GADPH. The quantity of mRNA relative to the reference gene was calculated by 2<sup>-ΔC<sub>t</sub></sup> methods, the analysis type is Singleplex, and RQ min/max confidence level is 95.0. Samples were analysed using SYBR Green Supermix (Bio-Rad) according to the manufacturer's instructions. The sample analysis was performed in triplicate and the experiments have been repeated in different batches of cell lines. Primer sequences were obtained from thermo-fisher used for SSTRs (1-5) are shown in Table 1.

**Table 1: Primer sequences used for mRNA SSTRs (1-5)**

Receptor	Primer sequences
SSTR 1	Primer: 5'- CACATTTCT-CATGGGCTTCCT-3' Reverse: 5'- ACAAACATCACCAC-CATC-3'
SSTR 2	Primer: 5'- GGCATGTTTGACTTTGTG-GTG-3' Reverse: 5'- GTCTCATTAGCCGG-GATT-3'
SSTR 3	Primer: 5'- TGCCTTCTTTGGGCTC-TACTT-3' Reverse: 5'- ATCCTCCTC-CTCAGTCTTCTCC-3'
SSTR 4	Primer: 5'- CGTGGTCGTCTTTGT-GCTCT-3' Reverse: 5'- AAGGATCGGCGGAAGTT-GT-3'
SSTR 5	Primer: 5'- CTGGTGTGTTGCGGGAT-GTT-3" Reverse: 5'- GAAGCTCTGGCGGAA-GTTGT-3'



**Figure 1: mRNA expression levels of SSTRs (1-5) in human breast cancer cell lines.**

\*\*p<0.05, \*\*\*p<0.001 vs MCF7 group

**Table 2: Analysis of relative mRNA expression of SSTRs (1-5) in MCF7 and MDA-MB231 cell lines**

SSTRs Subtypes	MCF7	MDA-MB231
SSTR1	++	++
SSTR2	++	+++
SSTR3	+	+
SSTR4	++	+++
SSTR5	++	++

Low level +, Moderate level ++, High level +++

**Statistical analysis**

The SPSS software version 22 (IBM®) was used for the analysis. The mean and standard deviation of SSTRs expression levels in MCF7 and MDA-MB231 cell lines were compared using a T-test. P-values of < 0.05 were considered statistically significant.

**RESULTS**

SSTR1-5 mRNA expression was determined in both MCF-7 and MDA-MB-231 breast cancer human cell lines (Figure 1) and the overall expression levels differ between the two cell lines. The SSTR1, 2, 3 and 4 mRNA levels were significantly higher in MDA-MB231 cell line in relation to MCF-7 cell line (P=0.02, 0.002, 0.001, 0.01) respectively. While no different significant of SSTR5 in MCF7 compared to MDA-MB231 (P=0.2). The expression of SSTR4 mRNA was highest in the MDA-MB231 cell line followed by SSTR2, SSTR1, SSTR5 and SSTR3 mRNA. In the MCF7 cell line, SSTR4 has the highest expression levels, followed by SSTR1, SSTR5, SSTR2 and SSTR3. SSTR3 mRNA was least expressed in both cell lines, while SSTR4 has highly expressed in both cell lines too. An arbitrary score was adopted to summarize the expression levels of SSTRs as in (Table 2).

**DISCUSSION**

In this study, our data showed that all the SSTRs1-5 were expressed in both MCF-7 and MDA-MB-231 breast cancer cell lines. Similar findings have been reported that all the SSTR subtypes were expressed in both MCF7 and MDA-MB231 and SSTR3 mRNA being the least expressed in both cell lines. SSTR4 was found to be express highly in MDA-MB231 cell lines while it is often reported that SSTR2 is predominant on breast cancer cells,<sup>27</sup> however, our somatostatin receptors’ expression levels differ from the literature, but several other studies were in agreement with our results.<sup>7</sup> The expression of SSRT2, SSTR3 and SSTR4 were significantly higher in the MDA-MB231 cell line.<sup>28</sup> The association between SSTRs and ER/PR positive receptors, it might be suggested that SSTR were overly expressed in MDA-MB231 cell lines that were correlated with poorly differentiated cancer cells. STTR1, 2, 3 and 4 have a key role in blocking tumour growth by inhibiting cell cycle progression and inducing apoptosis. Furthermore, SSA antagonist may have more clinical benefits for ER and PR negative tumours. The highly expressed SSTR4 and low expressed SSTR3 agreed with earlier reports.<sup>29,30</sup> The high expression of SSTR3 and SSTR2 or SSTR4 in MCF7 cell lines were associated with apoptosis. Meanwhile, SST enhanced cytotoxicity via SSTR2 and SSTR3.<sup>31</sup> The low-level expression of SSTR3 has made it a target for breast cancer therapy.

The activation of SSTR3 in MCF7 and MDA-MB231 breast cancer cell lines by SST for cancer treatment is now been explored.<sup>31,32</sup> However, the mechanism of SSTR3 in apoptosis and cell cycle arrest is still unclear.<sup>30</sup> Besides, estrogen and progesterone receptors in MCF7 are important in breast cancer prognosis and development<sup>33</sup>, and the positive estrogen effect on SSTR2 expression on regulation in breast cancer cells development has been documented.<sup>34</sup> Furthermore, many SST analogues have been synthesized for activation SSTRs while SST agonist is currently under development to control cancer cell proliferation.<sup>35,36</sup> Several studies demonstrated that SSTRs expression in breast cancer is down-regulated either in more aggressive and less differentiated tumours<sup>37</sup> or in anti-estrogen agents.<sup>38</sup> In this study, the high levels of SSTRs expression were documented in aggressive tumours and thus, MDA-MB231 may be considered as a target for therapeutic strategy. Meanwhile, the activation of the expression levels of SSTR1, SSTR2, SSTR3 and or SSTR4 might enhance apoptotic activity in MCF7 cells. Several previous studies have investigated that SSTR expression may be able to be explored for further insights into the therapeutic of breast cancer. Besides, the anti-proliferative role of SST and its analogues have also been demonstrated. Several *in vitro* studies have investigated the anti-proliferative effect of somatostatin analogues in breast cancer cells. Previous studies have also shown that SSTR2 overexpression produces an anti-proliferative role in the estrogen-dependent MCF-7 cells by inducing apoptosis and decreasing EGFR expression.<sup>12</sup> These results highlighted the SSTRs -targeted therapy in which the evaluation that SSTR1-5 is expressed in both breast cancer cell lines MCF7 and MDA-MB231. These findings recommended more understanding of the role of SSTRs functions in breast tumour biology to improve therapy in estrogen receptors positive and estrogen receptors negative breast cancers.

## CONCLUSION

SSTRs (1-5) were expressed in both MDA-MB231 and MCF7 cell lines, but the level of expression differed between both cell lines. The activation of SSTRs receptors in ER+, PR+ tumour may be considered. SSTRs overexpression in aggressive tumours (ER-, PR-) may be considered as a target for therapeutic strategy. Future research is warranted to study the functions of SSTRs.

## Abbreviations

SSTRs: Somatostatin receptors; qRT-PCR: Quantitative polymerase chain reaction; mRNA: Messenger RNA; ER: Estrogen receptors; PR: Progesterone receptors.

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### Conflict of interest

Nothing to report

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### Conflicts of interest

The authors have no conflict of interest.

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