Expression analysis of *ST3GAL4* transcripts in cervical cancer cells

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Abstract. *ST3GAL4* gene expression is altered in different cancer types, including cervical cancer. Several mRNA transcripts have been reported for this gene; however, their expression levels in cervical cancer have not been analyzed. *ST3GAL4* encodes for β-galactosidase α-2,3-sialyltransferase 4, involved in the biosynthesis of the tumour antigens sLe(x) and sulfo-sLe(x). The present study evaluated the presence of three mRNA variants (V1, V2 and V3) in cervical cancer cell lines, detecting the three variants. Additionally, the expression level of the V1 transcript of the *ST3GAL4* gene was determined by reverse transcription-quantitative polymerase chain reaction in cervical cell lines and in normal, premalignant and cervical cancer tissue. The V1 transcript of the *ST3GAL4* demonstrated significant decreased expression in premalignant and malignant cervical tissues. The results suggested that deregulation of this gene could occur prior to the presence of cancer and demonstrated the importance of evaluating the expression level of V1, and its association with disease progression.

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Introduction

The *ST3GAL4* gene encodes for β-galactoside α-2,3-sialyltransferase 4 (ST3Gal IV), enzyme that transfers sialic acid to the type 2 precursor (Galβ1,4GlcNAc). It is involved in the biosynthesis of the sLe(x) and sulfo-sLe(x) epitopes (1-3).

Alteration of sialyltransferase gene expression has been implicated in carcinogenesis. Specifically, expression of this gene is altered in different cancer types. *ST3GAL4* expression is decreased in renal cell carcinoma and cervical cancer (4,5), whereas it is increased in gastric cancer and in premalignant lesions of the cervix (6,7). For other cancer types, including colorectal cancer, the expression level of *ST3GAL4* does not demonstrate any changes (8).

Sialyltransferase genes are regulated in a tissue specific manner; that is, gene expression may be regulated by different promoters, and their alternative use can regulate gene expression in different tissues. Thus far, five different promoters have been reported for the *ST3GAL4* gene: pA, pB1, pB2, pB3 and pBx (9,10). Complexity of the gene expression increases since six mRNA isoforms have also been reported: A1, A2, B1, B2, B3 and B4 (1,11,12) and these may be produced by combinations of promoter utilization and alternative splicing.

The transcript isoforms (9,10) are now listed in GenBank (https://www.ncbi.nlm.nih.gov/genbank/) as variant transcripts. The expression of these variants has not been evaluated in cervical cancer cells. To better understand the mechanisms by which the expression of the *ST3GAL4* gene is regulated in cervical cancer, it is important to determine the transcript variants present in this tissue and how their expression is modified during tumour transformation.

Materials and methods

Alignment analysis of transcript variants of the ST3GAL4 gene. An alignment analysis was performed to compare the sequences of the transcript variants available in GenBank and the mRNA B isoforms of the *ST3GAL4* gene reported by Kitagawa *et al* in 1996 (11). The gene bank accession numbers for the ST3GAL4 isoforms are: V1 isoform: NM_006278; V2 isoform: NM_001254757; V3 isoform: NM_001254758 and V4 isoform: NM_001254759.

Cell culture. The human keratinocyte cell line HaCaT was obtained from the Centro de Investigación Biomédica de Occidente (Guadalajara, Mexico), and human cervical cell lines (SiHa, HeLa, C33A) were obtained from the Centro de Investigación Biomédica de Oriente (Puebla, Mexico). The cells were grown in monolayer culture in p25 cm^2 flasks and were maintained at 37˚C in an atmosphere of CO_2 in Dulbecco's modified Eagle's medium (Sigma-Aldrich; Merck KGaA, Darmstadt, Germany) with 10 mmol/l HEPES, which was supplemented with 10% fetal bovine serum, 100 IU/ml penicillin and 100 μg/ml streptomycin (Sigma-Aldrich; Merck KGaA). The culture medium was replaced every two days. Subconfluent adherent cells were harvested using a mixture of trypsin (0.025%) and EDTA (0.02%); (Sigma-Aldrich; Merck KGaA) and were washed with phosphate buffered saline.

Sample tissue. Cervical specimens were obtained at the Centro Médico Nacional sXXI (Mexico City, Mexico), between January 2013 and January 2014, from female patients (aged 18-65 years). Samples of squamous cell carcinoma of the cervix were obtained from women that underwent radical hysterectomy. Samples exhibiting premalignant lesions (low and high grade squamous intraepithelial lesions) were obtained from women who were treated by cervical conisation. Normal tissue was obtained from women undergoing hysterectomy for uterine miomatosis. Women with a clinical history of other cancer types, as well as samples with degraded RNA, were excluded from the present study. All data, including age and pathological results, were prospectively recorded. The present study was approved by the Ethics Committee of Instituto Mexicano del Seguro Social (Mexico City, Mexico; Number R-2012-785-061). All patients provided informed consent according to the guidelines of the Human Ethics Committee. In total, 8 normal samples, 7 samples of premalignant lesions and 8 samples of cervical cancer were included.

RNA isolation from cells and biopsies. Total RNA was extracted from cell lines using a Nucleo Spin RNA II kit (Macherey-Nagel GmbH, Düren, Germany) according to the manufacturer's protocols.

Biopsies were maintained in RNAlater solution (Qiagen, Inc., Valencia, CA, USA), and 25 mg of tissue was disrupted with the TissueLyser II (Qiagen, Inc.) for 2 min. Subsequently, RNA was extracted with an RNeasy Plus Mini kit (Qiagen, Inc.) according to the manufacturer's protocols.

cDNA synthesis. First-strand cDNA synthesis was performed with a RevertAid H Minus First Strand cDNA Synthesis kit (Thermo Fisher Scientific, Inc., Waltham, MA, US) using the following concentrations: 1X of reaction buffer, 1 U/μl of Ribolock RNAse Inhibitor, 1 mM of dNTP mix, 10 U/μl of RevertAid H Minus M-MuLV Reverse Transcriptase, 5 μM of random primers and 1 μg of total RNA, in a final volume of 20 μl, according to the manufacturer's protocols. The reaction was incubated for 5 min at 25˚C followed by incubation for 60 min at 42˚C.

Reverse transcription-semi-quantitative polymerase chain reaction (RT-sqPCR) analysis. RT-sqPCR was performed on a 1000 Touch thermal cycler (Bio-Rad Laboratories, Inc., Hercules, CA, USA) in a final volume of 20 μl using the following: 10 μl of 2X PCR Master Mix (Promega Corporation, Madison, WI, USA), 1 μl of 10 μM forward and reverse primer, and 2 μl of cDNA. The primer sequences were as follows: V1 transcript forward 5'-gactgtgctggaggt gacag-3', reverse 5'-accatgtttctcagcaggca-3'; V2 forward 5'-gaaccgtgctgccccgcccc-3'; reverse 5'-gggacttgctgaccatgtt t-3'; V3 forward 5'-tttgtagtgtttcccgccca-3', reverse 5'-gctgac catgtttctcagca-3'. A positive control containing primers for hypoxanthine-guanine phosphoribosyltransferase (HPRT) (forward 5'-ccctggcgtcgtgattagtga-3'; reverse 5'-agcaagacg ttcagtcctgtcc-3') and a negative control (with no template) were added into each assay. The program cycle was: 95˚C for 2 min, 40 cycles of 95˚C for 30 sec, 56˚C for 1 min and 72˚C for 1 min. A total of 40 cycles were performed to ensure for the successful detection of RNA variants with a low copy number. The presence of the variants was confirmed, by performing the reactions twice. The amplification product was assessed on an agarose gel for low molecular weight fragments at a 2% concentration. The gels were stained with ethidium bromide (1 mg/ml), observed in an ultraviolet trans-illuminator, and then photographed using a digital camera (ELP110HS; Canon, Inc., Tokyo, Japan). To confirm that the amplified product corresponded to the variant transcript, direct sequencing of the PCR products was performed using the Sanger method in the Laboratory of Biodiversity and Genomics, CINVESTAV (Irapuato, Mexico).

RT quantitative (q)PCR validation. To prove that the efficiencies of the *ST3Gal 4* gene and HPRT amplification were similar and optimal, RT-qPCR was performed to validate the endogenous gene and to quantify the V1 transcription in cell lines and biopsies. Each reaction was performed in a final volume of 10 μl with the concentrations: 5 μl of 2X Maxima SYBR Green/Rox qPCR Master Mix (Thermo Fisher Scientific, Inc.), 1 μl of 10 mM forward and reverse primers for the V1 isoform of the *ST3GAL4* gene or HPRT, and cDNA from SiHa, HeLa, and C33A cell lines that had been previously synthesized, using the aforementioned procedure. A standard curve was determined with the concentrations: 2, 1, 0.5, 0.25, 0.125 and 0.0625 ng/μl. The reactions were performed in triplicate using a StepOne Real-Time PCR System (Applied Biosystems; Thermo Fisher Scientific, Inc.), and the conditions were as follows: 95˚C for 10 min, followed by 40 cycles of 95˚C for 10 sec, 30 sec at 60˚C, and 70˚C for 30 sec.

Relative quantification of the V1 transcript in cell lines and biopsies. Relative quantification was performed using the comparative CT method with the formula: $2^{-\Delta\Delta Cq}$ (13). The qPCR

Table I. Current status of *ST3GAL4* mRNA variant nomenclature previously reported by Kitagawa *et al* (11).

Current nomenclature of mRNA variants and accession number[a]	Isoforms B reported by Kitagawa *et al* (11)	Transcript size (bases)	Protein isoform and accession number
V1 NM_006278	B1	2053 b	Isoform 1 NP_006269
V2 NM_001254757	BX	1854 b	Isoform 2 NP_001241686
V3 NM_001254758	-	1727 b	Isoform 2 NP_001241687
V4 NM_001254759	B3	1871 b	Isoform 3 NP_001241688
-	B2	-	-

[a]Information available in GenBank. The sequence of the isoform B2 is not available in GenBank. V3 transcript was not reported by Kitagawa *et al* (11).

reaction was performed with the StepOneReal-Time PCR System (Applied Biosytems; Thermo Fisher Scientific, Inc.). The final reaction volume of 10 μl included 1 μl of cDNA template (0.5 ng final concentration in cell lines and 12 ng in biopsies), 5 μl of 2X Maxima SYBR Green/Rox qPCR Master Mix (Thermo Fisher Scientific, Inc.), 0.5 μl of forward and reverse primers (0.5 μM final concentration) and 3 μl of RNase free water. RT-qPCR was performed under the following conditions: 1 cycle at 50˚C for 2 min, 95˚C for 10 min, 40 cycles of 95˚C for 15 sec, and 60˚C for 1 min. Triplicates of each sample were analysed, and negative controls with no cDNA template were included in each assay. Transcript levels were normalized against HPRT expression.

Statistical analysis. Statistical analysis was performed using the Graph Pad program (version 7; GraphPad Software, Inc., La Jolla, CA, USA). A one-way analysis of variance followed by Tukey's post-test was performed for multiple comparisons. Data are presented as mean ± standard error deviation. $P<0.05$ was considered to indicate a statistically significant difference. All experiments were repeated in triplicate.

Results

Alignment analysis of transcript variants of the ST3GAL4 gene. Since isoforms A1 and A2 are reported exclusively in testicle, ovary and placenta these isoforms were excluded from subsequent analysis. First, an alignment was performed among isoforms B1, B2, B3 and B4 reported by Kitagawa *et al* (11) with those transcript variants reported in GenBank to determine their correspondence and their sequence identity. Table I indicates the B isoforms whose sequence corresponded to the current nomenclature of transcript variants reported in GenBank and the protein isoform coded. Analysis demonstrated that B1 isoform corresponds to V1 variant, BX to V2 and B3 to V4. The B2 isoform sequence was not available in the GenBank data base, and the V3 transcript was not reported by Kitagawa *et al* (11) (Access date April 29, 2016).

Analysis of transcript variants in cervical cell lines. Next, the presence of the transcripts variants V1, V2 and V3 was evaluated in cervical cell lines. The RT-PCR analysis demonstrated that V1 and V2 transcripts were present in all the cervical cell lines, SiHa, HeLa, and C33A, and in the human keratinocyte cell line HaCaT; V3 transcript was present in SiHa, HeLa and HaCaT cell lines, however not in C33A (Fig. 1).

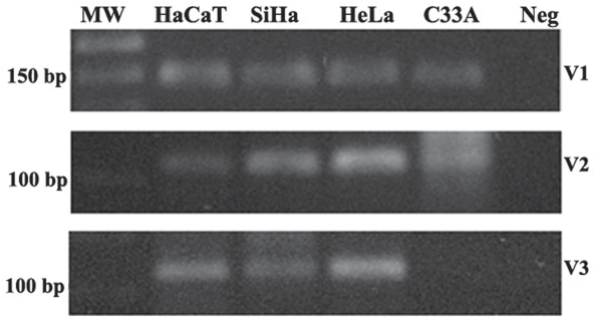

Figure 1. Agarose gel electrophoresis of polymerase chain reaction products of the V1 transcript (142 bp). Lanes show DNA marker, HaCaT, SiHa, HeLa, C33A cell lines and non-template control. The amplification product corresponded to a fragment of 142 bp. Bp, base pairs; MW, DNA marker; Neg, non-template control.

Relative quantification of the V1 variant in cervical cell lines. The expression level of the V1 transcript was determined in the cervical cell lines SiHa, HeLa and C33A. The $\Delta\Delta$Cq analysis demonstrated that SiHa cells exhibited the highest expression (Fig. 2) compared with HeLa, C33A and HaCaT. In every case, significant differences were identified.

Quantification of transcript variant 1 in patients. Next, the V1 transcript levels in biopsies were analysed to determine whether the V1 transcript modifies its expression in relation to cervical neoplasia grade. Relative quantification was performed by RT-qPCR using 8 samples of normal tissue, 7 samples of squamous intraepithelial lesions (low and high grade) and 8 samples of cervical cancer. Premalignant lesions and cervical cancer demonstrated a decreased level of V1 transcript compared with normal tissue (Fig. 3). In every case, significant differences were identified.

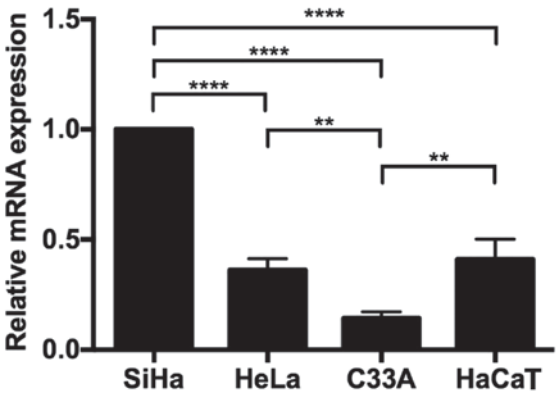

Figure 2. Expression levels of the V1 transcript in the cell lines SiHa, HeLa, C33A and HaCaT. Error bars represent the standard error of the mean for 3 independent experiments in the cell line analysis. The expression level was determined with reverse transcription-quantitative polymerase chain reaction using the comparative CT method. **P<0.01, ****P<0.0001.

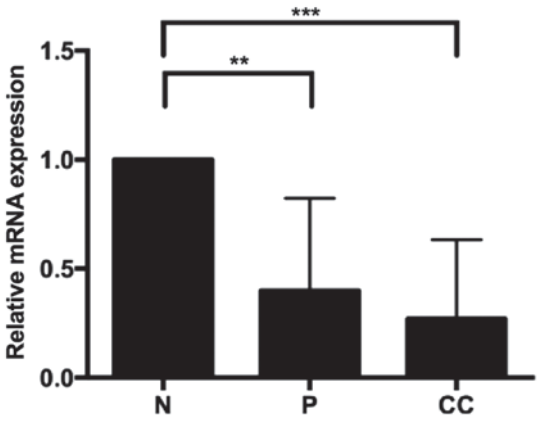

Figure 3. Expression levels of the V1 transcript in the cervical samples. The expression level was determined with reverse transcription-quantitative polymerase chain reaction using the comparative CT method. **P<0.01, ***P<0.001. N, normal tissue; P, premalignant lesions; CC, cervical cancer.

Discussion

The *ST3GAL4* gene encodes sialyltransferase ST3Gal IV. It produces at least 5 transcripts by alternative promoter utilization in combination with alternative splicing (1). This gene has been reported to have increased expression in pancreatic cancer (14). In contrast, *ST3GAL4* has decreased expression in renal cancer and is associated with malignant progression (4). Decreased expression has also been reported in cervical cancer (5). The present study detected the presence of the variants V1, V2 and V3 in cervical cell lines. The expression level of the V1 transcript in cervical cell lines and in cervical tissue with different neoplasia grades was analysed. The V1 transcript represents the longest transcript and encodes protein isoform 1. This transcript demonstrated decreased expression in premalignant and malignant tissues. These results demonstrated that glycosylation changes occur in previous stages of cancer, as has been reported for sialic acid and sialyltransferase expression (7,15,16). It is important to mention that *ST3GAL4* encodes the sialyltransferase that is involved in the synthesis of the sLe(x) antigen, which has been reported to increase in different cancer types including cervical cancer and premalignant lesions of the cervix (17,18). This suggests that other sialyltransferases could participate in the synthesis of the sLe(x) antigen, including ST3Gal III (19). The expression level of sLe(x) does not appear to be associated with the mRNA level reported in cervical cancer samples where a diminished expression of *ST3GAL4* has been detected. The increased level of sLewis(x) could be the result of an increased expression of *ST3GAL3* that may participate in the synthesis of these antigens, as has been reported previously (20). Increased expression of the *ST3GAL3* gene has been reported in cervical cancer and premalignant lesions, and this could explain the increased expression of the sLe(x) antigen (5,7,20,21).

Transcript variants of this and other glycogenes may be regulated in a different manner as a result of promoter utilization. Analysis of the transcript variants could help to elucidate the regulation mechanisms that could be participating in malignant transformation.

In conclusion, the V1 transcript of the *ST3GAL4* gene has decreased expression in premalignant and malignant tissues. The expression level analysis of this transcript may be utilized to develop diagnostic methods for the early detection of cervical tissue transformation.

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Authors' contributions

CGR, CGF, CRA and TAG were responsible for the recruitment of patients. LMF, NRM, COM, RMS, GSL, LRC, PMM, IMC, AAL and LJS performed the experiments. AAL, LJS, GSL JRL and VVR contributed to the study design, data analysis and the writing of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Instituto Mexicano del Seguro Social (Mexico City, Mexico; Number R-2012-785-061). All patients provided informed consent according to the guidelines of the Ethics Committee of Instituto Mexicano del Seguro Social.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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