Promoter Polymorphisms of ST3GAL4 and ST6GAL1 Genes and Associations with Risk of Premalignant and Malignant Lesions of the Cervix

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Abstract

Sialyltransferase gene expression is altered in several cancers, including examples in the cervix. Transcriptional regulation of the responsible genes depends on different promoters. We aimed to determine the association of single-nucleotide polymorphisms in the B3 promoter of the ST3GAL4 gene and the P1 promoter of the ST6GAL1 gene with cervical premalignant lesions or cervical cancer. A blood sample and/or cervical scrapes were obtained from 104 women with normal cytology, 154 with premalignant lesions and 100 with cervical cancer. We also included 119 blood samples of random donors. The polymorphisms were identified by sequencing from PCR products. For the B3 promoter, a fragment of 506 bp (from nucleotide -408 to +98) was analyzed, and for the P1 promoter a 490 bp (-326 to +164) fragment. The polymorphism analysis showed that at SNP rs10893506, genotypes CC and CT of the ST3GAL4 B3 promoter were associated with the presence of premalignant lesions (OR=2.89; 95%CI 1.72-4.85) and cervical cancer (OR=2.23; 95%CI 1.27-3.91). We detected only one allele of each polymorphism in the ST6GAL1 P1 promoter. We did not detect any genetic variability in the P1 promoter region in our study population. Our results suggest that the rs10893506 polymorphism -22C/T may increase susceptibility to premalignant and malignant lesions of the cervix

Keywords: SNPs, single-nucleotide polymorphism - sialyltransferase - cervical cancer - cervical neoplasia

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Introduction

Sialyltransferases are a family of enzymes that transfer sialic acid to glycoconjugates (Harduin-Lepers et al., 2001). In cervical cancer, increased mRNA levels of the sialyltransferase genes ST6GAL1 and ST3GAL3 have been reported. Higher levels of ST6GAL1 mRNA are associated with invasion to the stroma and lymphatic nodule (Wang et al., 2002). In premalignant lesions, higher levels of ST6GAL1, ST3GAL3 and ST3GAL4 mRNAs have been reported (López-Morales et al., 2009). Increased expression of sialic acid and also sialylated antigens, such as sLewis(x), have been reported in premalignant and malignant lesions of the cervix (Roy and Chakraborty, 2005; López-Morales et al., 2010; Velázquez-Márquez et al., 2012).

The gene ST6GAL1 codes for different mRNA isoforms, three of which are better characterized than the others. Isoform 1, also called isoform H, is increased in cervical cancer tissue (Aasheim et al., 1993; Wang et al., 1993; Wang et al., 2003). This isoform results from the activity of the P1 promoter, which has been characterized

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in the cervical cancer cell line C33A (Millfiores-Flores et al., 2012). Six mRNA isoforms have been reported for ST3GAL4: A1, A2, B1, B2, B3 and BX (Kitagawa et al., 1996; Taniguchi and Matsumoto, 1998). The B3 promoter shows greater activity in the cervical cancer cell line HeLa (Taniguchi and Matsumoto, 1999).

Single-nucleotide polymorphisms (SNPs) of different genes have been associated with the risk of cervical cancer (Stanczuk et al., 2001; Zhang et al., 2007; Yu et al., 2009; Jiang et al., 2010). No association studies of SNPs in sialyltransferase gene promoters and cervical cancer have been reported. Only for a few diseases, such as schizophrenia and IgG nephropathy, have promoter SNPs been associated with the disease and with change in the gene expression (Arai et al., 2006; Li et al., 2007). One polymorphism in the promoter of GALNT1 has been associated with decreased risk of ovarian cancer (Sellers et al., 2008). SNPs have excellent potential to be used as biomarkers for diagnosing genetic diseases, including cancer.

The objective of this work was to analyze the polymorphisms in the P1 promoter of ST6GALI and B3 promoter of ST3GAL4 and their associations with the presence of premalignant and malignant lesions of the cervix.

Materials and Methods

Study population

The study was carried out using cervical scrapes and peripheral blood of patients assigned to different clinics and hospitals of the Instituto Mexicano del Seguro Social. This study included cervical scrapes and/or peripheral blood of 104 specimens of from healthy women, 154 patients with a diagnosis of cervical lesions and 100 patients with cervical cancer. Additionally, we included 119 blood samples of donors in order to have a reference for the allelic distribution in the population. All samples were obtained according to the guidelines of the Human Ethics Committee of our Institute. The purpose and procedures of the study were explained to patients, and informed consent was obtained from all participants.

Collection of specimens

Two cervical samples were collected from the endo- and exocervix with a cytobrush and an Ayre spatula, respectively. The first sample was used for cytological diagnosis. Papnicolaou smears were evaluated by a pathologist according to the Bethesda diagnosis criteria. The second sample was used for the polymorphism analysis and was placed in a tube containing 3 mL of ice-cold phosphate-buffered saline (PBS). Blood samples were collected using a needle and placed in tubes containing 0.5 mL of EDTA buffer. All samples were stored at 4°C and processed within 24 h of their arrival at the laboratory. Samples of blood donors were obtained from the buffy coats from the blood bank of the UMAE No. 80, Instituto Mexicano del Seguro Social.

DNA extraction

Blood samples and cervical scrapes were centrifuged at 4000 rpm for 10 min at 4°C. The leukocytes and cervical cell pellets were used for DNA extraction. DNA was extracted according the protocol for purification of total DNA from animal blood or cells QIAamp DNA Mini Kit (QIAGEN, Hilden, Germany). DNA was dissolved in 100 μL DNase-free water and stored at -20°C until use. All samples were tested for the integrity of DNA by 1% agarose gel electrophoresis. DNA yield was determined spectrophotometrically.

PCR assays

The region -326 to +164 of the P1 promoter was amplified using the primers 5’-AGT AGA GAT GGA GTT TCA CC-3’ (forward primer) and 5’-CTC TAT CTG CTT CTG GCT AAT CC-3’ (reverse primer). All the amplifications were performed using 40 cycles of 1 min at 95°C, 45 s at 58°C and 1 min at 72°C, and this was followed by a single 7 min extension at 72°C. The region -408 to +98 of the B3 promoter was amplified with the primers 5’-GAGGACTCAAGCCCTCACAC-3’ (forward primer) and 5’-GGATGACACTCA C GGGACCTT-3’ (reverse primer). Amplifications were performed using 40 cycles of 1 min at 95°C, 45 s at 57°C and 1 min at 72°C, followed by a final extension of 7 min at 72°C. The PCR mixture consisted of 25 μL PCR Master Mix 2X (Promega, Madison, WI), 40-50 ng DNA template, and 0.2 μM of each primer, with distilled water added to a final volume of 50 μL. Reactions were run in a PTC-200 thermocycler (MJ Research, Watertown, MA). PCR products were electrophoresed, and the band was purified according the protocol of the Wizard SV gel and PCR clean-up system, DNA kit (Promega, Madison, WI).

SNP selection and genotyping

The SNPs analyzed in this study are found in the NCBI SNP database (http://www.ncbi.nlm.nih.gov/projects /SNP/). For the P1 promoter of the ST6GAL1 gene, the SNPs selected were rs141894607 (-306G/T), rs150796963 (-275C/T), rs116918425 (-259A/G), rs187589817 (-237G/ T), rs116705383 (-216C/T), rs139268780 (-208C/T), rs149979727 (-202A/G), and rs73071448 (-123C/T). For the B3 promoter of the ST3GAL4 gene, the SNPs were rs148809885 (-278T/C), rs2186716 (-267A/G), rs7933887 (-218A/C), rs141571632 (-215T/C), rs11603211 (-152A/G), rs115057909 (-57T/C), rs10893506 (-22C/T), rs190884962 (+24T/C) and rs184073997 (+25A/G).

We analyzed whether the alleles of the reported SNPs were part of the consensus binding sequence of any transcription factor using the Transcription Element Search System (www.cbil.upenn.edu/cgi-bin/tess/ tess). Genotyping was performed by direct sequencing of the PCR products of all samples using the Sanger method in the Laboratory of Biodiversity and Genomics, CINVESTAV, Irapuato, México.

Statistics

Hardy-Weinberg equilibrium (HWE) was tested with the χ² goodness-of-fit test. Before statistical analysis, we determined each SNP’s allelic and genotype frequencies according to the formula $F = PAA/PA + PAa/Pa - 1$, where PAA and Paa are the respective genotype frequencies.
for homozygotes and pA and pa the respective allele frequencies. The χ² test (2-tailed probability) was used to analyze the difference between genotypes. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by unconditional logistic regression analysis. IBM SPSS 20 was used for statistical analysis (SPSS Inc., Chicago, IL); p<0.05 was considered statistically significant.

**Results**

**SNP sequence analysis of promoter P1 of the ST6GAL1 gene**

The database of SNPs (dbSNP, http://www.ncbi.nlm.nih.gov/snp) reported 8 SNPs for the P1 promoter fragment analyzed in this study. To determine if the presence of certain alleles of the SNPs could generate transcription factor binding sites, we used the Transcription Element Search System (www.cbil.upenn.edu/cgi-bin/tess/tess) and found that only some of the alleles of the SNPs rs141894607, rs150796963, rs187589817 and rs116705383 could generate consensus binding sequences for transcription factors (Table 1).

**Analysis of SNPs of the P1 promoter in normal and cervical cancer groups**

The P1 promoter fragment (-326 bp to +164 bp) was sequenced to identify the SNPs present in the P1 promoter of the normal and cervical cancer groups. We analyzed 100 samples of women with normal cytology and 100 with cervical cancer. The SNP sequence analysis showed that all the samples were homozygous for every SNP in the P1 promoter, and the allele identified for all the SNPs was the major allele reported in dbSNP, which was the ancestral allele (Table 1).

**Analysis of SNPs of the B3 promoter of ST3GAL4**

In the B3 promoter region of the ST3GAL4 gene, dbSNP reported 9 SNPS, rs148809885, rs2186716, rs7933887, rs141571632, rs11603211, rs115057909, rs10893506, rs190884962 and rs184073997. The analyses with the Transcription Element Search System (www.cbil.upenn.edu/cgi-bin/tess/tess), showed that several consensus sequences for transcription factors could be generated depending of the allele present (Table 2).

**Association of SNPs from the B3 promoter with cervical premalignant lesions and cervical cancer**

The sequence of the B3 promoter of the ST3GAL4 gene was analyzed in 104 samples of women with normal

**Table 1. Information about SNPs in the P1 Promoter of the ST6GAL1 Gene According to dbSNP**

| ID         | Position | Alleles | Ancestor allele | Putative transcription factor binding site | Genotype identified in normal and cervical groups |
|------------|----------|---------|-----------------|--------------------------------------------|-------------------------------------------------|
| rs141894607| -306     | G       |                 | c-Myc                                      | GG                                              |
| rs150796963| -275     | C       |                 | PR                                         | CC                                              |
| rs116918425| -259     | A       |                 | G                                          | ------                                          |
| rs187589817| -237     | G       |                 | G                                          | ------                                          |
| rs116705383| -216     | C       |                 | ------                                     | ------                                          |
| rs139268780| -208     | C       |                 | ------                                     | ------                                          |
| rs149979727| -202     | A       |                 | ------                                     | ------                                          |
| rs73071448 | -123     | C       |                 | ------                                     | ------                                          |

*The position is given relative to the transcription start site. Shown are the alleles of each polymorphism, the ancestral (major) allele, the putative transcription factor binding site depending on the allele present and the only genotype identified in the normal and cervical cancer groups.

**Table 2. Minor Allelic Frequencies of SNPs in the B3 Promoter of ST3GAL4 in the Different Study Groups**

| ID         | Position | Alleles | Putative transcription factor binding site | Ancestor allele | Genotype identified MAF dbSNP | MAF Control lesions | MAF Premalignant cancer | MAF Cervical cancer |
|------------|----------|---------|--------------------------------------------|-----------------|------------------------------|---------------------|-------------------------|---------------------|
| rs148809885| -278     | T       | -----                                       | C               | CC                           | 0.0018               | -----                   | -----               |
| rs2186716  | -267     | A       | -----                                       | G               | GAG                          | 0.056                | 0.02                    | 0.03                | 0.04                |
| rs7933887  | -218     | A       | -----                                       | G               | GAT2                         | 0.1791               | 0.03                    | 0.04                | 0.06                |
| rs141571632| -215     | T       | -----                                       | C               | REL                         | 0.0014               | -----                   | -----               |
| rs11603211 | -152     | A       | -----                                       | C               | SP1                          | 0.0955               | 0.02                    | 0.03                | 0.04                |
| rs115057909| -57      | T       | -----                                       | C               | ETS1                         | 0.0087               | -----                   | -----               |
| rs10893506 | -22      | C       | -----                                       | T               | AP2                          | 0.4853               | 0.23                    | 0.42                | 0.37                |
| rs190884962| 24       | T       | -----                                       | C               | Myc                          | 0.0023               | -----                   | 0.009               | 0.005               |
| rs184073997| 25       | A       | -----                                       | G               | BCRA1                        | 0.0005               | -----                   | -----               |

*The position is given relative to the transcription start site. Shown are the alleles of each polymorphism, the ancestral (major) allele, the putative transcription factor binding site depending on the allele present and the only genotype identified in the study population.
The analysis compared the results of premalignant cervical cancer groups to the normal group. All comparisons were made using the χ² test (Table 3).

Table 3. Magnitudes of Associations (Odds Ratio; OR) of SNP rs10893506 (-22C/T) with Pre-Malignant Cervical Lesions and Cervical Cancer

| ID dbSNP | Genotype | Normal group n=104 | Premalignant group n=154 | χ² (95% CI) p value | Normal group n=104 | Cervical Cancer group n=100 | χ² (95% CI) p value |
|----------|----------|------------------|---------------------------|-------------------------|------------------|-----------------------------|-------------------------|
| rs2186716 | GG       | 100 (96.2)       | 144 (93.5)                | 0.41 (100 (96.2)       | 91 (91)          | 1.48                        |                         |
|          | -267     | GA               | 4 (3.8)                   | p=0.521                  | 4 (3.8)          | 9 (9)                       | p=0.222                 |
|          | AA       | 0 (0)            | 0 (0)                     |                         | 0 (0)            |                            |                         |
| rs7933887 | CC       | 98 (94.2)        | 142 (92.2)                | 0.142 (98 (94.2)       | 96 (96)          | 3.03                        |                         |
|          | -218     | AC               | 5 (4.8)                   | p=0.706                  | 5 (4.8)          | 13 (13)                     | p=0.081                 |
|          | AA       | 1 (1)            | 1 (0.65)                  |                         | 1 (1)            |                            |                         |
| rs11603211| GG       | 100 (96.2)       | 144 (93.5)                | 0.4 (100 (96.2)        | 91 (91)          | 1.48                        |                         |
|          | -152     | GA               | 4 (3.8)                   | p=0.521                  | 4 (3.8)          | 9 (9)                       | p=0.222                 |
|          | AA       | 0 (0)            | 0 (0)                     |                         | 0 (0)            |                            |                         |
| rs10893506| TT       | 59 (56.7)        | 48 (31.2)                 | 15.67 (59 (56.7)       | 37 (37)          | 7.19                        |                         |
|          | CC       | 9 (8.6)          | 24 (15.6)                 |                         | 9 (8.6)          | 12 (12)                     |                         |

The Hardy Weinberg (HWE) equilibrium was calculated only for the SNPs -218 and -22 because these SNPs presented the genotype heterozygous and both genotypes homozygous.

The genotype proportions observed for the SNPs -218 in the study groups: normal cytology (χ²=6.919 p=0.031), premalignant lesions (χ²=2.146 p=0.142), and cervical cancer (χ²=2.784 p=0.248), are in agreement with the expected proportions for the HWE in Mexican population (χ²=2.146 p=0.142), respectively (Table 2). We observed a homozygous genotype for the SNPs rs2186716 A/G, rs7933887 A/C, rs11603211 A/G, rs10893506 C/T and rs190884962 T/C. The MAFs obtained for this SNP were 0.009 and 0.005, respectively (Table 2).

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ST6GAL1 have distinct promoters that confer different tissue expression and also different levels of expression (Appenheimer et al., 2003; Taniguchi et al., 2003).

The presence of certain promoter activity-modifying SNPs in promoters of sialyltransferase genes has been associated with schizophrenia and IgG nephropathy. One SNP in the ST6GALNT gene has been associated with decreased risk of ovarian cancer (Seller et al., 2008).

The aim of the present study was to determine whether SNPs in the P1 promoter of ST6GAL1 and B3 promoter of ST3GAL4 are associated with premalignant lesions and cervical cancer. Database of dbSNP reports 8 SNPs for the P1 promoter region. Our analysis of these SNPs in both normal and cervical cancer groups showed the presence of only one of the two reported alleles for each of these SNPs, the major allele, which in each case was also the ancestral allele. The analysis of the SNPs of this promoter suggest that the Mexican population is monomorphic, but to confirm this, is necessary to increase the sample size.

For the B3 promoter of the ST3GAL4 gene, we analyzed a fragment of 506 bp (-408 to +98). dbSNP reports 9 SNPs in this promoter, only five of which included both alleles in our population (rs2186716 A/G, rs7933887 A/C, rs11603211 A/G, rs10893506 C/T and rs190884962 T/C). For these SNPs, the minor allele in our population was the minor allele reported in dbSNP. SNP rs10893506 (-22C/T) was significantly associated with premalignant lesions of the cervix and cervical cancer. The presence of allele C of SNP 10893506 was associated with the risk to developing premalignant lesions and cervical cancer.

The *in silico* analysis of the rs10893506 promoter sequence and the detection of the different SNP alleles using the Transcription Element Search System showed that the presence of the -22C allele of the B3 promoter generates a consensus binding sequence for the transcriptional factor AP2. By contrast, when the T allele is present, no transcription factor binding sequence is generated. The presence of a binding site for AP2 could modify the promoter activity. AP2 activates the transcription of cellular and viral genes (Williams and Tjian, 1991; Hilger-Eversheim et al., 2000; Zhao et al., 2001). Therefore, the presence of the C allele could be related to increased expression of ST3GAL4. But further studies of this promoter activity and the resultant mRNA levels should be performed to determine the effect of the C allele.

Genotype CC of SNP rs190884962 (+24) was only identified in the premalignant and cervical cancer groups. The presence of this allele generates a BRCA1 binding site. BRCA1 can modulate the transcription of several genes through its association with sequence-specific transcription factors, BRCA1 helps to repair damaged DNA, therefore, play a role in ensuring the stability of the cell’s genetic material (Mullan et al., 2006). The analysis of this SNP in a larger sample size could be of interest to determine its possible association with premalignant and malignant cervical lesions.

One limitation of our study is the sample size. To confirm whether the Mexican population is monomorphic for the P1 promoter, is necessary to analyze a larger sample. The second limitation is that ST3GAL4 expression data are lacking for the study population. Such expression data could confirm that the presence of the C allele in SNP rs10893506 modifies the expression of the gene.

In conclusion, the present study has reported the first association between a sialyltransferase gene promoter SNP and the presence of premalignant and cervical cancer. SNP -22C/T of the B3 promoter of the ST3GAL4 gene was associated with the presence of premalignant lesions and cervical cancer.

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