Association of the Oncostatin M Receptor Gene Polymorphisms with Papillary Thyroid Cancer in the Korean Population

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INTRODUCTION

Papillary thyroid cancer (PTC) is the most common type of dif-

ferentiated thyroid carcinoma which accounts for at least 70% of all follicular-cell derived thyroid cancer, and its incidence has been increasing (1). Although the prognosis of PTC is generally good, up to 10% of patients would eventually die of the disease or face the morbidity of recurrence (2). Tumor staging, which is predictive of prognosis, is based on the size and extent of the primary tumor and the presence of lymph node or distant metastasis (2).

The oncostatin M receptor (OSMR) gene, located 5p13.1, encodes a protein called OSMRβ which heterodimerizes with interleukin (IL) 6 signal transducer (gp130) to form type II OSMR (3, 4). Once recruited, the receptor complexes allow the activation of Janus protein tyrosine kinase (JAK) and, subsequently, the activation of signal transducer and activator of transcription (STAT, mainly STAT3) and mitogen activated protein kinase (MAPK) (5-7). In melanoma or other solid tumors, the key role

Objectives. To investigate the association between papillary thyroid cancer (PTC) and single nucleotide polymorphisms (SNPs) of oncostatin M receptor (OSMR) in the Korean population.

Methods. Retrospective case-control study was done. Eighty-five patients with PTC and 287 controls were studied. One missense SNP (rs2278329, Asp553Asn) and one promoter SNP (rs2292016, -100 G/T) of the OSMR gene were genotyped by direct sequencing. Genetic data were analyzed using the SNPStats, Helixtree, and SNPAnalyzer Pro. PTC patients were dichotomized and compared with respect to the clinicopathologic characteristics.

Results. There was no association between genotypes and allele frequencies of OSMR SNPs (rs2278329 and rs2292016) and PTC susceptibility. SNP rs2278329 was significantly associated with tumor size (dominant model; \( P = 0.028 \); odds ratio [OR], 2.71; 95% confidence interval [CI], 1.12 to 6.57). The A allele was higher in sizes larger than 1 cm (32.5% vs. 16.7%; \( P = 0.018 \); OR, 2.41; 95% CI, 1.17 to 4.98). Regarding the number of tumors, we found no significant association with genotype, however, the A allele was higher in patients with multifocality (33.3% vs. 19.1%; \( P = 0.040 \); OR, 2.12; 95% CI, 1.03 to 4.34).

Conclusion. The results suggest that OSMR polymorphism rs2278329 is associated with clinicopathologic characteristics of the tumor growth and multifocality development.

Key Words. Papillary thyroid cancer, Oncostatin M receptor, Single nucleotide polymorphism, Clinicopathologic status
of STAT3 is to mediate the growth inhibitory effect of OSM (8).

The OSM is a member of the IL6 family which is now consid-
ered a multifunctional cytokine that is implicated in the activa-
tion, proliferation and/or differentiation of several cell types, such
as hepatocytes, osteoblasts and lung epithelial cells (7, 9, 10).
OSM is more active than IL6 in inhibiting the proliferation of
numerous solid tumor cell lines derived from breast or lung can-
cer, hepatoma, osteosarcoma and melanoma (9). In addition, it
was reported to stimulate AIDS-related Kaposi’s sarcoma, my-
eloma, plasmacytoma, and human prostate cancer (11-14). OSM
is a potent inhibitor of iodine metabolism and was show to de-
crease thyroid peroxidase mRNA levels in porcine thyroid cells
(4). Iodide oxidation and coupling activities of thyroid peroxi-
dase are significantly lower in PTC than in diffuse goiter and
beneign adenoma (15).

Although OSM and its interaction with OSMR are related to
PTC development and clinical characteristics, no genetic studies
of this interaction between OSMR and PTC have been conduct-

ed. Thus, in the present study, we investigated whether single
nucleotide polymorphisms (SNPs) of OSMR contribute to the
development of PTC. Also, we assessed the association of SNPs
of OSMR with clinicopathologic characteristics of PTC in the
Korean population.

MATERIALS AND METHODS

Subjects

Patients with PTC were recruited from the Kyung Hee Uni-
versity Hospital, Seoul, Korea. The PTC group included 85 patients
(23 males and 62 females; mean of age, 53.2 years). A diagnosis
of PTC and the presence of cervical regional lymph node me-
tastasis were both confirmed by pathologic examination. A total
of 287 normal controls (156 males and 131 females; mean of
age, 37.6 years) were included for comparison. None of the con-
trols were found to have any malignancy or thyroid disease at
enrollment. Written informed consent was obtained from all in-
dividuals according to the Declaration of Helsinki guidelines.
This study was approved by the Institutional Review Boards of
the Medical Research Institute, Kyung Hee University Medical
Center.

Patients’ profile and clinical data

To determine the association between the SNPs of OSMR and
the clinicopathologic characteristics of PTC, patients were divid-
ed into subgroups according to size (≤1 cm vs. >1 cm), number
(unifocality vs. multifocality), bilaterality (unilateral vs. bilateral)
of tumors, presence or absence of extrathyroidal invasion, lymph
node metastasis and angiolymphatic invasion. The demographi-

c characteristics of PTC patients and controls are shown in Table 1.

| Characteristics                  | Values |
|---------------------------------|--------|
| Age (years)                     | 53.2±11.5 |
| Sex (male/female)               | 23/62  |
| Tumor size >1 cm                | 40 (47) |
| Multifocal                      | 30 (35) |
| Bilateral                       | 26 (31) |
| Extrathyroidal invasion         | 43 (51) |
| Cervical lymph node metastasis  | 24 (28) |
| Angiolymphatic invasion         | 5 (6)   |

Values are presented as mean±SD or number (%).

SNP selection and genotyping

The SNPs of the OSMR gene were selected using the database
found at http://ncbi.nlm.nih.gov/SNP, dbSNP BUILD 131. Of the
SNPs in the OSMR coding region, SNPs with low heterozygos-
ity (below 0.1; rs16867807, rs35207712, rs35117676, rs35727755,
rs34324145, rs35546805, rs2289925, rs2290926, rs35739767,
rs3749737, and rs34080825), without Asian population
(rs34675408), and without genotype information (rs10941412)
were excluded. In the promoter region, SNPs with low hetero-
yzosity (below 0.1; rs76020575), a low minor allele frequency
(below 0.05; rs540558), a mono genotype (rs5867434), and
without genotype information (rs79913282, rs3763098, and
rs13359039), were excluded. Finally, we selected the SNPs
rs2278329 (missense, Asp553Asn) and rs2292016 (promoter,
-100 G/T) and their heterozygosities were 0.226 and 0.242, re-
spectively. Blood samples for DNA extraction from each subject
were collected in EDTA tube and then stored in a -80°C refrig-
erator. Genomic DNA was extracted using a QIAamp DNA
mini kit (QIAGEN, Valencia, CA, USA). SNP genotyping was
determined by direct sequencing. Genomic DNA was amplified
using the following primers: rs2278329 (sense, 5′-GCACCTGT
AACT AT-3′; 346 bp), rs2292016 (sense, 5′-GCACCTGT
AACT AT-3′; 461 bp), rs13359039, were excluded. Finally, we selected the SNPs
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using the following primers: rs2278329 (sense, 5′- GCACCTGT
AACT AT-3′; antisense, 5′- CTATAACCCCATGCT-GATTTG
G-3′; 461 bp), rs2292016 (sense, 5′-GGACTTCTCTT-
GCTGAGATT-3′; antisense, 5′- AGGAATCTCCCTCTTCA
GTC-3′; 347 bp). Polymerase chain reaction products were se-
quenced using an ABI Prism 3730XL analyzer (PE Applied Bio-
systems, Carlsbad, CA, USA). Sequence data were analyzed using
SeqManII software (DNAStar Inc., Madison, WI, USA).

Statistics

For all SNPs, Hardy-Weinberg equilibrium was assessed using
SPNStats software (http://bioinfo.iconcologia.net/index.php?
module=Snpsstats). Helixtree (Golden Helix Inc., Bozeman, MT,
USA) and SNPAnalyzer Pro (ISTECH Inc., Goyang, Korea) were
used to analyze the genetic data. Multiple logistic regression
models (codominant, dominant, and recessive) were performed,
after adjustment for sex and age, for odds ratios (ORs), 95% confi-
dence intervals (CIs), and corresponding P-values. Linkage
disequilibrium (LD) block of polymorphisms was tested using
Table 2. Genotype and allele frequencies of oncostatin M receptor (OSMR) polymorphisms in patients with papillary thyroid cancer and in controls

| Genotypes         | PTC      | Control   | Model     | OR (95% CI) | P-value |
|-------------------|----------|-----------|-----------|-------------|---------|
| rs2278329         |          |           |           |             |         |
| Genotypes         |          |           |           |             |         |
| G/G               | 49 (57.6)| 138 (48.2)| Codominant1 | 1.64 (0.59–4.58) | 0.342   |
| missense          |          |           |           |             |         |
| A/G               | 31 (36.5)| 117 (40.9)| Codominant2 | 2.20 (0.81–5.98) | 0.122   |
| (Asp553Asn)       |          |           |           |             |         |
| A/A               | 5 (5.9)  | 31 (10.8) | Dominant  | 1.95 (0.73–5.17) | 0.182   |
| Alleles           | G        | 129 (75.9)| 393 (68.7) | 1.43 (0.97–2.12) | 0.073   |
|                   | A        | 41 (24.1) | 179 (31.3) | 1           |         |
| rs2292016         |          |           |           |             |         |
| Genotypes         |          |           |           |             |         |
| G/G               | 48 (57.1)| 126 (46.1)| Codominant1 | 0.97 (0.41–2.34) | 0.953   |
| promoter (-100 G/T)| T/G     | 28 (33.3)| 115 (42.1) | Codominant2 | 1.52 (0.66–3.54) | 0.327   |
|                   | T/T     | 8 (9.5)  | 32 (11.7)  | Dominant    | 1.26 (0.56–2.85) | 0.577   |
| Alleles           | G        | 124 (73.8)| 367 (67.2) | 1.38 (0.93–2.03) | 0.108   |
|                   | T        | 44 (26.2) | 179 (32.8) | 1           |         |

P-values were from logistic regression analyses with the codominant1 (A/A vs. A/G), codominant2 (A/A vs. G/G), dominant, and recessive models controlling age and gender as covariates. Values are presented as number (%). PTC: papillary thyroid cancer; OR: odds ratio; CI: confidence interval.

RESULTS

Genotypic and allelic frequency of rs2278329 and rs2292016

The genotypic and allelic frequencies of rs2278329 and rs2292016 in PTC patients and controls are given in Table 2. The observed genotype distributions of the SNPs were in Hardy-Weinberg equilibrium (P>0.05, data not shown).

No association between the genotype and allele frequencies of rs2278329 and rs2292016 were observed in the 85 PTC patients and 287 control subjects (Table 2). In the measurement of LD, no LD block was identified by the Gabriel method (16).

Association between rs2278329 and rs2292016 and clinicopathologic characteristics

We analyzed the association of the OSMR gene polymorphisms with the clinicopathologic status of size (larger or smaller than 1 cm), number (unifocality or multifocality), and bilaterality (unilateral or bilateral) of tumors, and the presence or absence of lymph node metastasis, extrathyroidal invasion and lymphovascular invasion. For rs2278329, we found a significant association between PTC and tumor size (dominant model, G/G vs. A/G and A/A; P=0.028; OR, 2.71; 95% CI, 1.12 to 6.57) (Table 3). The frequencies of the G/G, A/G, and A/A genotypes were 68.9%, 28.9%, and 2.2% in sizes smaller than 1 cm, respectively; and 45%, 45%, and 10% in sizes larger than 1 cm, respectively. Additionally, there was a significant difference in the allele frequency: the A allele was higher in sizes larger than 1 cm (32.5% vs. 16.7%; P=0.018; OR, 2.41; 95% CI, 1.17 to 4.98). Regarding the number of tumors, we found no significant association with genotypes: however, there was a significant difference in allele frequency: the A allele was higher in patients with the multifocality (33.3% vs. 19.1%; P=0.040; OR, 2.12; 95% CI, 1.03 to 4.34) (Table 3). However, we found no significant association with PTC in terms of bilaterality of tumors and presence of lymph node metastasis, extrathyroidal invasion and lymphovascular invasion.

We calculated the sample power to verify our data (http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html). In this study, the sample powers of each SNPs were 0.837 (rs2278329; number of cases for 80% power, 77) and 0.837 (rs2292016; number of cases for 80% power, 77), respectively. Accordingly, our results were acceptable.

We attempted to determine whether the promoter SNP rs2292016 affects transcription factors using the online program AliBaba2.1. The T-containing sequences can bind with ICSBF transcription factor, but IRF-I substitutes for ICSBF in G-containing sequences. Assuming the change of transcript factor binds according to variants of SNP, this promoter SNP may affect the gene expression of OSMR.

DISCUSSION

We found no association between the SNPs rs2278329 (missense, Asp553Asn) and rs2292016 (promoter, -100 G/T) of the OSMR gene and PTC susceptibility. However, we found an association between rs2278329 and clinicopathologic characteristics, such as the size and number of tumors.

OSMR is a specific receptor OSM which is a member of the IL6 family (4). OSM, produced mainly by activated monocytes...
and lymphocytes, is well recognized as a cytostatic cytokine for some types of tumor cell derived from melanoma (17), breast cancer (18), colorectal cancer (19), and glioma cells (20). In contrast, OSM stimulates the growth of AIDS-related Kaposi’s sarcoma (12), myeloma (13), and plasmacytoma (14). It promotes the growth of DU145 human prostate cancer cells through the signaling of the OSM specific receptor (11).

IL6 was shown to be related to aggressive behavior in thyroid cancer (21). Thyroid tumor cells originating from undifferentiated carcinomas express cytokines such as IL6, leukemia inhibitory factor, thyroid transcription factor-1, and paired box gene 8 (22). OSM is a potent inhibitor of iodine metabolism in thyroid cells and is thought to be one of the principal cytokines that counter thyroid dysfunction under severe illness such as sepsis (4). In this study, we found the association between the tumor size and SNP rs2278329 of the OSMR gene. Tumor size is related to the prognosis of PTC. Many studies have concluded that PTC ≤ 1 cm diameter has an excellent prognosis and very low mortality rate, even though debate has centered on the clinical significance of PTC ≤ 1 cm (23-26). We also found the association between the multifocality and SNP rs2278329 of the OSMR gene. The relevance and importance of multifocality on prognosis are still obscure. According to Antonaci et al. (27), multifocal PTC showed aggressive biological and clinical features. In contrast, multifocality was not considered a prognostic determinant for the categorization of tumors as low risk or high risk in the study of Hay et al. (28). Although the relevance of the multifocality is debated, it is associated with indications for completion of thyroidectomy after lobectomy and for postoperative radioactive iodine ablation.

A missense mutation was identified in the OSMR gene in three families of familial primary localized cutaneous amyloidosis (FPLCA) (3). FPLCA is an autosomal dominant disorder associated with chronic skin itching and deposition of epidermal keratinocytes. IL6 was shown to be related to aggressive behavior in thyroid cancer (21). Thyroid tumor cells originating from undifferentiated carcinomas express cytokines such as IL6, leukemia inhibitory factor, thyroid transcription factor-1, and paired box gene 8 (22). OSM is a potent inhibitor of iodine metabolism in thyroid cells and is thought to be one of the principal cytokines that counter thyroid dysfunction under severe illness such as sepsis (4). In this study, we found the association between the tumor size and SNP rs2278329 of the OSMR gene. Tumor size is related to the prognosis of PTC. Many studies have concluded that PTC ≤ 1 cm diameter has an excellent prognosis and very low mortality rate, even though debate has centered on the clinical significance of PTC ≤ 1 cm (23-26). We also found the association between the multifocality and SNP rs2278329 of the OSMR gene. The relevance and importance of multifocality on prognosis are still obscure. According to Antonaci et al. (27), multifocal PTC showed aggressive biological and clinical features. In contrast, multifocality was not considered a prognostic determinant for the categorization of tumors as low risk or high risk in the study of Hay et al. (28). Although the relevance of the multifocality is debated, it is associated with indications for completion of thyroidectomy after lobectomy and for postoperative radioactive iodine ablation.

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tin filament-associated amyloid material in the dermis (3). FPL-CA keratinocytes showed reduced activation of the JAD/STAT, MAPK, and p13K/Akt pathways after stimulation with OSM or the cytokine IL31 stimulation. The 2 pathogenic amino acid substitutions, 2072T-C transition (Ile691Thr substitution) and 1853G-C transversion (Gly618Ala) were located within the extracellular fibronectin type III like domains regions critical to receptor dimerization and function.

The human SNP database (dbSNP BUILD131) presents frequencies of genotype for rs2278329 (G/G:G/A:A/A; Chinese, 0.533:0.333:0.133; Japanese, 0.600:0.378:0.022; Korean in this study, 0.482:0.409:0.108) and rs2292016 (G/G:G/T:T/T; Chinese, 0.359:0.513:0.128; Japanese, 0.535:0.395:0.070; Korean in this study, 0.461:0.421:0.117). The allele frequencies of rs2278329 in the Korean population in this study (G, 0.687; A, 0.313) were similar to those observed in Chinese (G, 0.700; A, 0.300) and Japanese (G, 0.789; A, 0.211) populations. The allele frequencies of rs2292016 in the Korean population in this study (G, 0.672; T, 0.328) were also similar to those observed in Chinese (G, 0.615; T, 0.385) and Japanese (G, 0.733; T, 0.267) populations.

Our study has some limitations. First, sex ratio and mean age of controls differ in comparison with cases. However, the results, though the statistic power for analysis was reliable, so a further study with large number of patients should be performed.

In conclusion, the OSMR polymorphism is associated with clinicopathologic characteristics of tumor growth and multifocality development.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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