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Immunology Letters 156 (2013) 118–122

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Identification of the polymorphisms in *IFITM1* gene and their association in a Korean population with ulcerative colitis

Ji-Su Mo [1], Kyung-Sook Na [1], Ji-In Yu, Soo-Cheon Chae *

Department of Pathology, School of Medicine, Wonkwang University, Iksan, Chonbuk 570-749, South Korea

ARTICLE INFO

Article history:
Received 14 August 2013
Received in revised form
14 September 2013
Accepted 19 September 2013
Available online 10 October 2013

Keywords:
IFITM1
CD225
IBD
Ulcerative colitis
Polymorphism

ABSTRACT

Interferon inducible transmembrane protein (IFITM) family genes have been implicated in several cellular processes such as the homotypic cell adhesion functions of IFNs and cellular anti-proliferative activities. We previously showed that the *IFITM3* single nucleotide polymorphisms (SNPs) associated with susceptibility to ulcerative colitis (UC). The present study aimed to investigate whether the polymorphisms in the *IFITM1* gene are associated with susceptibility to UC. We also evaluated the expression levels in the putative functional promoter polymorphisms to determine the change of their activity. Gene expression profiles in the tissues obtained from human digestive tracts by RT-PCR, and the possible variation sites and SNPs of *IFITM1* were identified by direct sequencing method. Genotype analysis in the *IFITM1* SNPs was performed by high resolution melting and TaqMan probe analysis, and the haplotype frequencies of *IFITM1* SNPs for multiple loci were estimated using the expectation maximization (EM) algorithm. The expression levels in the putative functional promoter polymorphisms were evaluated by performing a luciferase reporter assay. We identified two SNPs and two variation sites, g.-1920G>A (rs77537847), g.-1547delA (novel) and g.-416C>G (rs11246062) in the promoter region, and g.364delA (rs200576757) in intron 1. The genotype and allele frequencies of the g.-1920G>A polymorphism of *IFITM1* gene in the UC patients were significantly different from those of the healthy controls ($P = 0.002$ and 0.042, respectively). These results suggest that the g.-1920G>A polymorphism in *IFITM1* may be associated with susceptibility to UC.

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1. Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) belong to the group of inflammatory bowel disease (IBD), which is a chronic inflammatory disease of the gastrointestinal tract of unknown etiology [1]. IBDs are complex and multifactorial involving genetic, environmental and microbial factors [2,3]. The balance between pro- and anti-inflammatory cytokines secreted by T cells is responsible for both initiation and perpetuation of IBD. Cytokine production in lamina propria $CD4^+$ T lymphocytes differs between CD and UC. Whereas CD is associated with increased production of T helper 1 cell (Th1) type cytokines, such as interferon-gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α), UC is associated with T cells that produce large amounts of the Th2 type cytokine IL-5, however, IFN-γ production is not affected [4–6]. Th1 and Th2 cells cross-regulate one another in their differentiation.

Interferon induced transmembrane protein 1 (IFITM1, also known as CD225, 9–27 or LEU13) is a member of the IFITM protein family, which mediates cellular processes, including the homotypic cell adhesion functions of IFNs. Expression levels of IFITM genes have been found to be up-regulated in gastric cancer cell and colorectal tumors [7,8]. The IFITM family potently inhibits human immunodeficiency virus type 1 (HIV-1) [9], SARS coronavirus [10], West Nile virus and dengue virus infections [11]. *IFITM1* was initially cloned from a human lymphoid cell cDNA library [12], and is located on chromosome 11p15.5 [13]. *IFITM1* proteins play separate roles in mouse primordial germ cell homing and repulsion [14], and also play an essential role in the anti-proliferative action of IFN-γ [15].

We have previously identified 7 single nucleotide polymorphisms (SNPs) and multiple variation regions in the *IFITM3* gene, another member of the IFITM family, and have suggested that *IFITM3* polymorphisms are associated with a susceptibility to UC [16]. However, other *IFITM* family including the *IFITM1* gene in the epipathogenesis of UC has not been elucidated. In an attempt to understand the genetic influences of *IFITM1* on UC, we have identified possible variation sites and SNPs through the two exons of *IFITM1* and their boundary intron sequences, including the ∼2.2 kb promoter regions. To determine whether or not these *IFITM1* SNPs are associated with susceptibility to UC, genotype and allele frequencies of *IFITM1* polymorphisms were analyzed on genomic

* Corresponding author. Tel.: +82 63 8506793; fax: +82 63 8522110.
E-mail address: chaesc@wku.ac.kr (S.-C. Chae).
[1] These authors equally contributed to this study.

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http://dx.doi.org/10.1016/j.imlet.2013.09.026

DNAs isolated from UC patients and healthy controls. Furthermore, we investigated haplotype frequencies constructed by these SNPs in both groups. We also evaluated the expression levels in the putative functional promoter polymorphisms by performing a luciferase reporter assay to determine the change of their activity.

2. Materials and methods

2.1. Patients and DNA samples

The DNA samples used in this study were provided by the Biobank of Wonkwang University Hospital, a member of the National Biobank of Korea, which is supported by the Ministry of Health and Welfare Affairs. On the basis of approval and informed consent from the institutional review board, we obtained the genomic DNAs from 126 UC patients (70 males and 56 females) and 529 healthy controls (332 males and 197 females). Mean ages of IBD patients and controls were 41.3 years and 40.8 years, respectively. Genomic DNA was extracted from peripheral blood leukocytes by using a standard phenol-chloroform method or by using a Genomic DNA Extraction kit (iNtRON Biotechnology, Korea) according to the manufacturer's directions. IBD patients were recruited from the outpatient clinic at Wonkwang University Hospital. Patients were classified into the IBD group according to clinical features, endoscopic findings, and histopathologic examinations. Healthy controls were recruited from the general population, and had received comprehensive medical testing at the Wonkwang University Hospital. All subjects in this study were Korean.

2.2. Polymerase chain reaction (PCR) and sequence analysis

The entire coding regions of the *IFITM1* gene, including the ~2.2 kb promoter regions, were partially amplified by PCR using the two primer pairs (Table 1). PCR reactions were prepared by previously described procedures [17]. Amplification was carried out in a GeneAmp PCR system 9700 thermocycler (PE Applied Biosystem, USA) at 95 °C for 5 min in order to pre-denature the template DNA, followed by 30 cycles of denaturation at 98 °C for 10 s, annealing at 68 °C for 30 s and extension at 72 °C for 2.0 or 2.5 min. The final extension was completed at 72 °C for 7 min. PCR products purified by use of a PCR purification kit (Millipore, USA) were used template DNA for sequencing analysis. Purified PCR products were sequenced using the ABI Prism BigDye Terminator cycle sequencing system (PE Applied Biosystems, USA) on the ABI 3100 automatic sequencer (PE Applied Biosystem). Both sense and antisense strands of PCR products were directly sequenced using the same primers used for the PCR amplification, and seven primers were additionally used to sequence the promoter and intron 1 region (Table 1). SNPs and variation sites of the *IFITM1* gene were detected by direct sequence analysis. The reference sequence for the *IFITM1* gene was based on the sequence of human chromosome 11, clone RP13-317D12.

2.3. mRNA expression level

The expression level of *IFITM1* mRNA in various tissues was determined using MTC multiple tissue cDNA panels (Clontech, CA, USA), and IFITM1-MF1 and IFITM1-MR1 primers were used for RT-PCR (Table 1). The image of RT-PCR was analyzed using ImageJ 1.4 (http://rsbweb.nih.gov/ij/).

2.4. Genotype analysis by TaqMan probe

The assay reagents for g.-1920G>A (rs77537847) in the *IFITM1* gene was designed by Applied Biosystems (Applied Biosystems, USA). The reagents consisted of a 40X mix of un-labeled PCR primer and TaqMan MGB probes were labeled with the FAM dye and the other with the fluorescent VIC dye [18]. The reaction in 10 μl was optimized to work with 0.125 μl 40× reagents, 5 μl 2× TaqMan Genotyping Master mix (Applied Biosystems, USA), and 2 μl (50 ng) of genomic DNA. The PCR conditions were as follows: one cycle at 95°C for 15 min; 40 cycles at 95 °C for 15 s and 60 °C for 45 s. The PCR was performed in the Rotor-Gene thermal cycler RG6000 (Corbett Research, Australia). The samples were read and analyzed by using the Rotor-Gene 1.7.40 software (Corbett Research, Australia).

Table 1
Primer sequences used for PCR amplification, sequencing analysis and genotyping in this study.

Applications	Primers	Primer sequence (5′→3′)	Regions
PCR analysis	IFITM1-PF1	ATCCTCCAGCCGCGTGACTCCT	Promoter and exon 1
	IFITM1-PR1	ACACAAGTCCCCACCCCAGGCA	
	IFITM1-PF2	TGCGACAAGTGAGGTGAGGGCT	Exon 1, 2 and intron 1
	IFITM1-PR2	AGAGGAGGGATACGGCTGTGCA	
Sequencing analysis	IFITM1-SF1	TCAGGTAGGAAGGGGGCTTG	Promoter
	IFITM1-SF2	TCCTCGATGTCTCAGAGCACGCT	Promoter
	IFITM1-SF3	ACATGAACGTGAAAAGCATTTAGGCT	Promoter
	IFITM1-SF4	ACCCTCCAGGTCTCTCCTGCAT	Promoter
	IFITM1-SR1	AGCCTAAATGCTTTTCACGTTCATGTGA	Promoter
	IFITM1-SR2	AGCCGCGTGCTATGGCTCCGT	Intron 1
	IFITM1-SR3	TGTCTCAGGACTAGGCCGGGA	Exon 2
TaqMan analysis	IFITM1-TF1	TGCAAAGGTGGTTTCAGTTCCAT	g.-1920G>A
	IFITM1-TR1	AGAAACTGCAGGGCACAAGA	
	IFITM1-TVI1	TCAGAATCCTATCTCCC	
	IFITM1-TFA1	CAGAATCCTGTCTCCC	
PCR-RFLP	IFITM1-RF1	CTTATTAAAGATTCTACTTA	g.-1275C>T
	IFITM1-RR1	GCTCTGATTTTTCCTTTATG	
High resolution melt (HRM)	IFITM1-HF1	ACCCGCACAGAGCAGGACTGCA	g.-416C>G
	IFITM1-HR1	TCTGTCCACCCCAGGCCAGCA	
RT-PCR	IFITM1-MF1	TGAACTGGTGCTGTCTGGGCT	mRNA
	IFITM1-MR1	AGAGCCGAATACCAGTGACAGGA	
Luciferase assay	IFITM1-LF1	CAGGGTACCTCTCTCCAGATTAGTTTAGGC	Promoter
	IFITM1-LR1	CAGCTCGAGGGTTTGAGAAGTGTGGTTTTC	

2.5. Genotype analysis by high-resolution melting analysis

Genotype analysis was performed by high-resolution melting (HRM) analysis for the g.-416C>G (rs1124662) in the *IFITM1* gene. The 10 μl reaction mixture comprised 2 μl of genomic DNA (50 ng), 1 μl of primer mix (containing 5 pmol of the forward and reverse primers), 0.25 μl of EvaGreen solution (Biotium, Hayward, CA, USA) and 5 μl of a QuantiTect Probe PCR kit (Qiagen, Valencia, CA, USA). PCR cycling and HRM analysis were performed on the Gene^{TM} 6000 (Corbett Research). The PCR cycling conditions were as follows: 1 cycle at 95 °C for 15 min; 45 cycles at 95 °C for 5 s; annealing conditions at 60 °C for 10 s; and 72 °C for 30 s. After a completion of 45 cycles, melting curve data were generated by increasing the temperature from 77 to 95 °C at 0.1 °C/s and recording fluorescence. HRM curve analysis was performed using the Rotor-Gene 1.7.40 software and the HRM algorithm that was provided.

2.6. Luciferase assay

The promoter region of the human *IFITM1* gene carrying either the g.-1920G or g.-1920A allele was inserted upstream of the firefly luciferase gene in the pGL3 basic plasmid vector (Promega, Madison, WI, USA) and this was verified by DNA sequencing. To make these constructs, we amplified the target sequence by PCR using a forward primer with *KpnI* and a reverse primer with *XhoI* (Table 1). These promoter plasmids were co-transfected into the SW480 cells (ATCC, USA) with a pRL-TK control vector (Promega), using Lipofectamin 2000 reagent (Invitrogen, Carlsbad, CA, USA), according to the manufacturer's instructions. The assays for firefly luciferase activity and Renilla luciferase activity were performed 24 h after the transfection of the cells using the Dual-Luciferase Reporter Assay System (Promega) with a microplate luminometer LB 96V (BERTHOLD, Australia). To normalize the transfection efficiency, the luminescence value of the pGL3-basic vector was standardized with the value of the pRL-TK vector. Each experiment was repeated three times, and each sample was studied in triplicate.

2.7. Statistic analysis

UC patients and healthy control groups were compared using case–control association analysis. The χ^2 test was used to estimate Hardy–Weinberg equilibrium (HWE). Allele frequency was defined as the percentage of individuals carrying the allele among the total number of individuals. Logistic regression analyses were used to calculate odds ratios (95% confidence interval) for SNP sites. Linkage disequilibrium (LD) analyses by pair-wise comparison of biallelic loci and haplotype frequencies of the *IFITM1* gene for multiple loci were estimated using the expectation maximization (EM) algorithm with SNPAlyze software (DYNACOM, Japan). A *P*-value of less than 0.05 was considered an indication of statistical significance.

3. Results

We examined expression patterns of *IFITM1* mRNA in the various tissues of the human digestive system (Fig. 1). Our results showed that the expression level of *IFITM1* mRNA was somewhat higher in tissues of the ileocecum than those in other tissues of the digestive system (Fig. 1). These results suggest that the expression level of *IFITM1* gene is stable in normal digestive system.

To determine the possible variation sites, in the entire coding regions, and the boundary intron sequences of *IFITM1* that include about 2.2 kb of the promoter region, we scanned the genomic DNAs isolated from 24 unrelated UC patients and 24 healthy controls. We identified two SNPs and two variation sites by direct sequencing methods, g.-1920G>A (rs77537847), g.-1547delA (novel) and g.-416C>G (rs11246062) in the promoter region, and g.364delA (rs200576757) in intron 1 (Fig. 2). The LD coefficients (|*D*′|) between

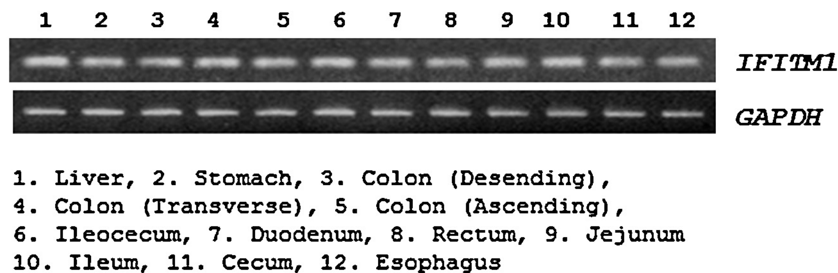

Fig. 1. Expression patterns of the *IFITM1* mRNA by RT-PCR in the tissues of human digestive system.

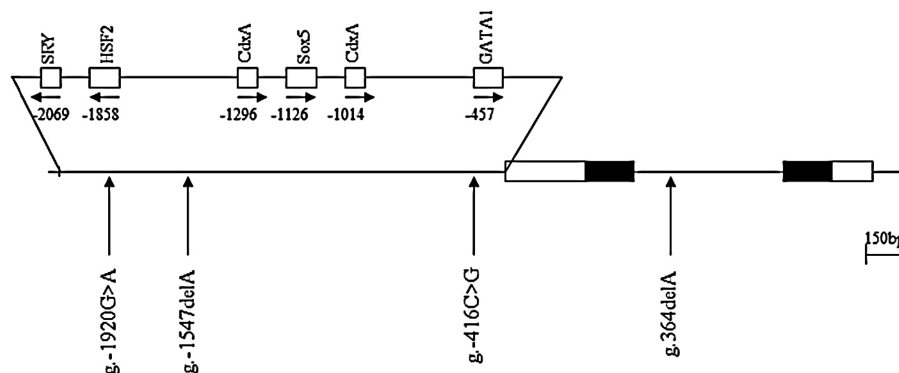

Fig. 2. Locations of each single nucleotide polymorphisms (SNPs) and variation sites in *IFITM1*. Coding exons are marked by black blocks and 5′- and 3′-UTR by white blocks. The positions of SNPs were calculated from the translation start site. Putative transcription factor sites were searched at http://www.cbrc.jp/research/db/TFSEARCH.html. The reference sequence for *IFITM1* was based on the sequence of human chromosome 11, clone RP13-317D12.

Table 2
Genotype and allele analyses of the *IFITM1* gene polymorphisms in the UC patients and the healthy controls.

Position[a]	Genotype/allele	Control n (%)	UC n (%)	Odds ratio[b] (95% CI)	P[c]
g.-1920G>A (rs77537847)	AA	198 (38.8)	46 (36.8)	1.00	0.002
	AG	248 (48.6)	48 (38.4)	0.83 (0.53–1.30)	
	GG	64 (12.5)	31 (24.8)	2.09 (1.22–3.56)	
	A	644 (63.1)	140 (56.0)	1.00	0.04
	G	376 (36.9)	110 (44.0)	1.35 (1.02–1.78)	
g.-416C>G (rs11246062)	CC	322 (64.1)	69 (59.5)	1.00	0.35
	CG	180 (35.9)	47 (40.5)	1.22 (0.81–1.84)	
	GG	0 (0.0)	0 (0.0)	–	
	C	824 (82.1)	185 (79.7)	1.00	0.40
	G	180 (17.9)	47 (20.3)	1.16 (0.81–1.66)	

[a] Calculated from the translation start site.
[b] Logistic regression analyses were used for calculating OR (95% CI; confidence interval).
[c] Value was determined by Fisher's exact test or χ^2 test from a 2 × 2 contingency table.

Table 3
Haplotype frequencies between UC patients and healthy controls in *IFITM1* SNPs.

Haplotype		Frequency[a]		Chi-square	P[b]
rs77537847	rs11246062	Control	UC		
A	C	0.621	0.578	1.389	0.239
G	C	0.197	0.222	0.722	0.396
G	G	0.177	0.200	0.644	0.422
Others		0.005	0.000	–	–

[a] Values were constructed by EM algorithm with genotyped SNPs.
[b] Values were analyzed by Chi-square.

all SNP pairs were calculated, and there was no absolute LD (|D′| = 1 and r^2 = 1) among the SNPs of the *IFITM1* gene (data not shown). Among the identified polymorphisms, two SNPs (g.-1920G>A and g.-416C>G) were selected for large sample genotyping. The SNP, g.-1275C>T (rs79441268, but not detected in our study), from the NCBI SNP database, was also genotype analyzed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. However, when 192 samples were analyzed, there was only a genotype. These results indicate that the g.-1275C>T (rs79441268) of *IFITM1* might be a very rare polymorphism or monomorphism in the Korean population.

To determine whether the *IFITM1* SNPs identified are associated with UC susceptibility, the genotypes of the *IFITM1* polymorphisms were analyzed by the HRM or TaqMan probe method, and the genotype and allelic frequencies between the groups were compared. Although the genotype and allelic frequencies of the *IFITM1* g.-416C>G in the UC patient group were not significantly different from those of the healthy control group, the genotype and allelic frequencies of the *IFITM1* g.-1920G>A between the UC patients group and the healthy controls group were significantly different (Table 2, P = 0.002 and 0.04, respectively). These results suggest that the g.-1920G>A identified in *IFITM1* appear to be associated with UC susceptibility. To determine the possible correlation between the haplotypes associated with g.-1920G>A and g.-416C>G of the *IFITM1* gene and UC susceptibility, we further analyzed haplotype frequencies of the SNPs in the UC patients and the healthy controls (Table 3). While the major (AC) haplotypes explaining more than 62.1% of the distributions were identified in the healthy controls, the AC haplotypes (57.8%), out of four possible haplotypes, were identified in the UC patients. However there are no significant differences between the groups (P = 0.239). These results suggest that the haplotype frequency of *IFITM1* polymorphisms might be not associated with UC susceptibility.

To evaluate the putative functional polymorphisms, we assessed actual promoter activity with the luciferase reporter assay (Fig. 3). We prepared two reporter constructs that contained the A or G allele of the human *IFITM1* gene g.-1920G>A polymorphisms. In the SW480 cells, the luciferase activity in the cells with the A allele in the *IFITM1* g.-1920G>A polymorphism was significantly higher than that in the cells with the G allele (P = 0.05). This result suggests that the g.-1920A allele might affect the increased transcriptional activity of the *IFITM1* gene in vivo.

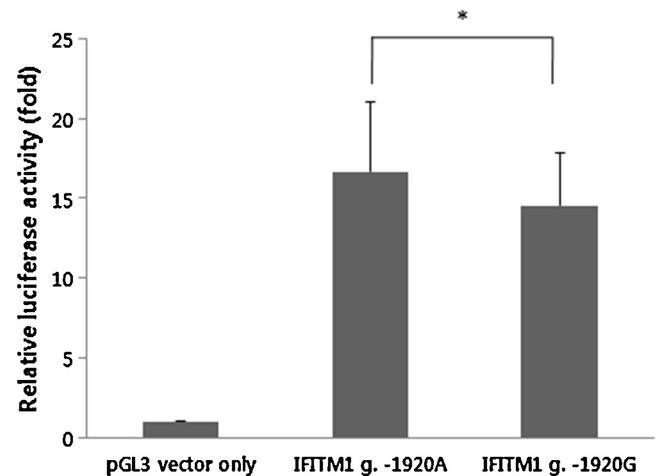

Fig. 3. Relative luciferase activities between the A allele and the G allele of the *IFITM1* g.-1920G>A. *IFITM1* g.-1920A and *IFITM1* g.-1920G represent luciferase activities in two constructs with a major allele (g.-1920A) and a minor allele (g.-1920G), respectively. Control represents luciferase activity without polymorphism as a standard (pGL3). Data were obtained from multiple independent experiments and are represented as the mean ± standard deviation. *P = 0.05.

4. Discussion

IBD is a chronic disease that is frequently encountered in the gastrointestinal tract and it can profoundly affect the quality of life. Although great advances have been made in the management of IBD with the introduction of immune-modulators and monoclonal antibodies, the precise etiology of IBD is unclear. However, IBD is thought to be the result of an aberrant intestinal immune response to bacterial microflora and this occurs in genetically susceptible individuals. Multiple IBD susceptibility loci (referred to as *IBD 1–9*) have been implicated in genomic studies in human. The most extensively studied genetic region, associated with IBD, among these loci is the *IBD1* locus (16p13.1–16q12.2). The *NOD2* gene, which has been widely shown to influence both the susceptibility and phenotype of patients with CD, is located at the *IBD1* locus [19–21]. Most studies have shown an association between *NOD2* mutations and the susceptibility to CD, but not to UC. We previously reported that an exon 4 variation of the *Tim-1* gene and the SNPs of the

IL27, *TNFRSF17* and *EED* genes were associated with UC in a Korean population [18,22–24].

The human *IFITM1* gene, a member of the IFITM family, consists of two exons and one intron. IFITM proteins were first discovered in T98G neuroblastoma cells that express the proteins in response to interferon stimulation [25]. We have previously identified 7 SNPs in *IFITM3* and have suggested that the *IFITM3* polymorphism is associated with a susceptibility to UC [16]. The *IFITM1* gene was selected as a candidate gene for UC by our cDNA microarray analysis (our unpublished data) because the expression level of the *IFITM1* gene was more increased in the UC mouse model than that of the healthy control mouse. These results were led us to determine whether or not the *IFITM1* SNPs are associated with susceptibility to UC in this study.

We showed that the expression level of *IFITM1* mRNA was stable in the human digestive system (Fig. 1), and identified a total of four polymorphisms (two SNPs and two variations) in the *IFITM1* gene (Fig. 2). The genotype frequency of g.-1920G>A polymorphisms in UC patients was significantly different from that of the healthy control group (Table 2). This result strongly suggests that SNPs of *IFITM1* may be associated with susceptibility to UC. These results led us to think it is interesting to know that *IFITM1* gene polymorphism (g.-1920G>A) may have some influence on the susceptibility to UC. This may happen because the polymorphisms within the binding site of the promoter region may influence the expression level by suppression or activation of binding between the specific transcriptional binding site and transcription factor. Due to its implication, we decided to investigate the role of the g.-1920G>A polymorphism in the *IFITM1* by luciferase reporter assay. Our result shows that the luciferase activity for the A allele with g.-1920G>A polymorphism was higher than that for the G allele in the SW480 cells (Fig. 3). This result indicates that the g.-1920G allele might affect the decreased transcriptional activity level of the *IFITM1* gene in vivo, and it might have an influence on the susceptibility to UC.

There are several limitations to our study. We did not check the expression levels of *IFITM1* in UC patients and did not show the clinical impact of *IFITM1* SNPs on UC. It will be also interesting to show the expression levels of the *IFITM1* in the colon tissues of UC patients by further studies. Our results suggest a possibility that *IFITM1* SNPs may be involved in inflammation by an unknown pathway in UC pathogenesis.

In conclusion, the results of this study suggest that the *IFITM1* gene might be a candidate gene associated with the pathogenesis of UC. Although it is not clear how the *IFITM1* polymorphisms are related to the susceptibility of UC, our results provide useful information for further functional studies of the *IFITM1* gene or IFITM gene family, and gastrointestinal disease such as colorectal cancer and inflammatory responses.

Acknowledgements

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (NRF-2010-0002842).

References

[1] Blumberg RS, Saubermann LJ, Strober W. Animal models of mucosal inflammation and their relation to human inflammatory bowel disease. Curr Opin Immunol 1999;11:648–56.
[2] Fiocchi C. Inflammatory bowel disease: etiology and pathogenesis. Gastroenterology 1998;115:182–205.
[3] Podolsky DK. Inflammatory bowel disease. N Engl J Med 2002;347:417–29.
[4] Fuss IJ, Neurath M, Boirivant M, Klein JS, de la Motte C, Strong SA, et al. Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease, Crohn's disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. J Immunol 1996;157:1261–70.
[5] Plevy SE, Landers CJ, Prehn J, Carramanzana NM, Deem RL, Shealy D, et al. A role for TNF-alpha and mucosal T helper-1 cytokines in the pathogenesis of Crohn's disease. J Immunol 1997;159:6276–82.
[6] Targan SR, Deem RL, Liu M, Wang S, Nel A. Definition of a lamina propria T cell responsive state. Enhanced cytokine responsiveness of T cells stimulated through the CD2 pathway. J Immunol 1995;154:664–75.
[7] Yang Y, Lee JH, Kim KY, Song HK, Kim JK, Yoon SR, et al. The interferon-inducible 9-27 gene modulates the susceptibility to natural killer cells and the invasiveness of gastric cancer cells. Cancer Lett 2005;221:191–200.
[8] Andreu P, Colnot S, Godard C, Laurent Puig P, Lamarque D, Kahn A, et al. Identification of the IFITM family as a new molecular marker in human colorectal tumors. Cancer Res 2006;66:1949–55.
[9] Lu J, Pan Q, Rong L, He W, Liu SL, Liang C. The IFITM proteins inhibit HIV-1 infection. J Virol 2011;85:2126–37.
[10] Huang IC, Bailey CC, Weyer JL, Radoshitzky SR, Becker MM, Chiang JJ, et al. Distinct patterns of IFITM-mediated restriction of filoviruses, SARS coronavirus, and influenza A virus. PLoS Pathog 2011;7(1):e1001258.
[11] Brass AL, Huang IC, Benita Y, John SP, Krishnan MN, Feeley EM, et al. The IFITM proteins mediate cellular resistance to influenza A H1N1 virus, West Nile virus, and dengue virus. Cell 2009;139:1243–54.
[12] Lewin AR, Reid LE, McMahon M, Stark GR, Kerr IM. Molecular analysis of a human interferon-inducible gene family. Eur J Biochem 1991;199:417–23.
[13] Lange UC, Saitou M, Western PS, Barton SC, Surani MA. The fragilis interferon-inducible gene family of transmembrane proteins is associated with germ cell specification in mice. BMC Dev Biol 2003;3:1.
[14] Tanaka SS, Yamaguchi YL, Tsoi B, Lickert H, Tam PP. IFITM/Mil/fragilis family proteins IFITM1 and IFITM3 play distinct roles in mouse primordial germ cell homing and repulsion. Dev Cell 2005;9:745–56.
[15] Yang G, Xu Y, Chen X, Hu G. IFITM1 plays an essential role in the antiproliferative action of interferon-gamma. Oncogene 2007;26(4):594–603.
[16] Seo GS, Lee JK, Yu JI, Yun KJ, Chae SC, Choi SC. Identification of the polymorphisms in *IFITM3* gene and their association in a Korean population with ulcerative colitis. Exp Mol Med 2010;42:99–104.
[17] Chae SC, Song JH, Pounsambath P, Yuan HY, Lee JH, Kim JJ, et al. Molecular variations in Th1-specific cell surface gene Tim-3. Exp Mol Med 2004;36:274–8.
[18] Chae SC, Yu JI, Oh GJ, Choi CS, Choi SC, Yang YS, et al. Identification of single nucleotide polymorphisms in the *TNFRSF17* gene and their association with gastrointestinal disorders. Mol Cells 2010;29:21–8.
[19] Hampe J, Cuthbert A, Croucher PJ, Mirza MM, Mascheretti S, Fisher S, et al. Association between insertion mutation in NOD2 gene and Crohn's disease in German and British populations. Lancet 2001;357:1925–8.
[20] Hugot JP, Chamaillard M, Zouali H, Lesage S, Cézard JP, Belaiche J, et al. Association of NOD2 leucinerich repeat variants with susceptibility to Crohn's disease. Nature 2001;411:599–603.
[21] Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, et al. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 2001;411:603–6.
[22] Li CS, Zhang Q, Lee KJ, Cho SW, Lee KM, Chae SC, et al. Interleukin 27 polymorphisms are associated with inflammatory bowel diseases in a Korean population. J Gastroenterol Hepatol 2009;24:1692–6.
[23] Park YR, Choi SC, Lee ST, Kim KS, Chae SC, Chung HT. The association of eotaxin-2 and eotaxin-3 gene polymorphisms in a Korean population with ulcerative colitis. Exp Mol Med 2005;37:553–8.
[24] Yu JI, Kang IH, Seo GS, Choi SC, Yun KJ, Chae SC. Promoter polymorphism of the EED gene is associated with the susceptibility to ulcerative colitis. Dig Dis Sci 2012;57(6):1537–43.
[25] Friedman RL, Manly SP, McMahon M, Kerr IM, Stark GR. Transcriptional and posttranscriptional regulation of interferon-induced gene expression in human cells. Cell 1984;38:745–55.