CD Gene Microarray Profiles of Bambusae Caulis in Liquamen in Human Mast Cell

Hoon Jeon*, Nan Joo Kang[1], Gyo Seok Kim[2]

Department of Pharmacy, Woosuk University, 1:Juksanbiotech Co. 2:Greenbiotech Co.

Bambusae Caulis in Liquamen(BCL) has been used to relieve the cough and asthma, and remove the phlegm in traditional Oriental medicine. In recent years, it was studied for its antiinflammatory, antiallergenic, immune-modulating, and anticarcinogenic capabilities. This experiment was performed to evaluate the microarray profiles of CD genes in human mast cells before and after BCL treatment. The results are as follows: The expression of 51 of the genes studied was up-regulated in the BCL-treated group; they include the genes coding L apoferritin, beta-2-microglobulin, ferritin light polypeptide, CD63, monocyte chemotactic and activating fact, heme oxygenase 1, CD140a, integrin alpha M, colony stimulating factor 2 receptor, eukaryotic translation elongation factor, CD37, interleukin 18, NADH dehydrogenase 1 beta, CD48, 5-lipoxygenase activating protein, interleukin 4, ribosomal protein L5, GABA(A) receptor-associated protein, beta-tubulin, Integrin beta 1, CD162, CD32, lymphotoxin beta, alpha-tublin, integrin alpha L, CD2, CD151, CD331, 90 kDa heat shock protein, CD59, CD3Z, microsomal glutathione S-transferase 2, CD33, CD162R, cyclophilinA, CD84, interleukin 9 receptor, interleukin 11, CD117, CD39-Like 2, and so forth. The expression of 7 of the genes studied was down-regulated in the BCL-treated group; they include the genes coding CD77, CD238, SCF, CD160, CD231, CD24, and CD130. Consequently, the treatment of BCL on the human mast cells increased the expression of 51 genes and decreased the expression of 7 genes. These data would provide a fundamental basis to the traditional applications of Bambusae Caulis in Liquamen.

Key words : Bambusae Caulis in Liquamen, Succus Bambusae, Phyllostachys nigra, microarray, CD, human mast cell

Introduction

Bambusae Caulis in Liquamen(BCL) has been used to relieve the cough and asthma, and remove the phlegm in traditional Oriental medicine. It is made by a burning procedure. Drops were falled at each side of bundles and collected from a bundle of trunks of Phyllostachys nigra. The collected juice was cooled and used for therapy. The effects of BCL are resolving slippery phlegm, reducing fever, nourishing Yin, expelling wind, and activating blood curculation. If it is used for phlegm-retention of stroke, it is accompanied with fresh ginger juice.[1,2] In recent years, it was studied for its antiinflammatory, anti-allergenic, and anti-fatigue capabilities[3]. Mast cells are key elements of the immune system. Mast cells play a central role in the pathogenesis of diseases such as allergic asthma, rhinoconjunctivitis, urticaria, anaphylaxis, and systemic mastocytosis. They are also thought to be important players in other chronic inflammatory disorders such as inflammatory bowel disease and rheumatoid arthritis[4,5]. Mast cells are also thought to participate in sterile inflammatory conditions exacerbated by stress, such as atopic dermatitis, interstitial cystitis, irritable bowel syndrome, migraines, and multiple sclerosis[5]. Basophils, the circulating "equivalent" of tissue mast cells, are now considered as important elements in the pathogenesis of late phase allergic reactions[6,7]. CDs(Cluster of Differentiation) are a distinct assortment of molecules on cell surfaces, many of which reflect either different stages of lineage-specific differentiation or different states of activation or inactivation. Leukocyte cell surface molecules, which include CDs, are routinely detected with anti-leukocyte monoclonal antibodies(mAbs). Using different combinations of mAbs, it is possible to chart the cell surface immunophenotypes of different leukocyte subpopulations, including the functionally distinct mature lymphocyte subpopulations of B-cells, helper T-cells(Th), cytotoxic T-cells(TC), and NK cells etc. Bacteria, mast cells[8], and mouse macrophages[9] are expressed CD48 which is the membrane receptor for detection of FimH. And hematopoietic lineage, particularly lymphocytes, monocytes and mast cells are also well known to have CD48[10]. In the present study, microarray hybridization was used to assess the

* To whom correspondence should be addressed at : Hoon Jeon, College of Pharmacy, Woosuk University, Chonbuk 565-701, Korea
E-mail: jeonh@core.woosuk.ac.kr, Tel: 063-290-1577

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expression of 384 genes coding CDs, cytokines, growth factors, and growth factor receptors. We demonstrate that human mast cells express a large variety of CDs, cytokines, growth factors, and growth factor receptors and that BCL regulates the expression of CDs and cytokines in these cells.

Materials and Methods

1. Materials

BCL was purchased from Juksan biotech.(Damyang, Jeonnam, Korea) and Green biotech.(Eumsug, Chungbuk, Korea), and DMEM, PBS, and FBS were purchased from GibcoBRL(Grand Island, NY, USA). The microarray chip(CREA HI380) was purchased from CreaGene Co. (Yusung-Gu, Taejon, Korea). A complete list of the genes is available on the CreaGene web site(http://www.creagene.com/Ncreagene/human_gene_list.htm). Each of the cDNAs printed on the array has been sequenced and verified by the company.

2. Cell culture

Human mast cell line(HMC-1), a growth factor-irresponsive cell line, was obtained from Dr. Chad Oh of Harbor-UCLA medical center. This cell line expresses a continuously activated c-kit receptor, and it does not express Fc ε RI, a high-affinity receptor for IgE. Cells were cultured in Iscove's Modified Dulbecco's Medium(IMDM, GibcoBRL, Grand Island, NY, USA) with 10% fetal bovine serum (GibcoBRL, Grand Island, NY, USA), 2mM L-glutamine, 1.2mM alpha-thioglycerol(Sigma Chemical Co., St. Louis, MO, USA), 100U/ml penicillin, and 100μg/ml streptomycin (GibcoBRL, Grand Island, NY, USA) at 37℃, in 5% CO_2 atmosphere. Subcultures were made every 3-4 days.

3. Sample treatment and RNA isolation

HMC-1 cells were first cultured to a density of 5 x 10^5/ml. BCL was then applied at a final concentration of 0.1% for a day prior to RNA isolation. Cells of the control group were given equivalent amounts of a vehicle. Total ribonucleic acid(RNA) was isolated from the cells with the TRIzol reagent(GibcoBRL, Grand Island, NY, USA) as per the manufacturer's instructions. In brief, cells were collected from culture bottles, sedimented by centrifugation at 200 x g for 5 min, 1㎖ of TRIzol reagent, a monophasic solution of phenol and guanidinium isothiocyanate, was added to the cell pellets, and the cells were lysed by repetitive pipetting. After incubation at room temperature for 5 min, chloroform (0.2㎖ /1.0㎖ of TRIzol reagent) was added, and samples were capped and shaken vigorously by hand and then centrifuged at 13,000 x g for 15 min. The colorless upper aqueous phase was transferred to a fresh tube, and 0.5㎖ of isopropyl alcohol was added to precipitate the RNA. Following centrifugation at 13,000 x g for 10 min, total RNA pellet was obtained, and it was washed once with 75% ethanol and dissolved in DEPC-treated water. RNA yields were measured by measuring the absorbance of the final solution at 260nm.

4. Synthesis of fluorescence probe

100μg of total RNA in a volume of 22$\mu\ell$ and 2$\mu\ell$ of oligo dT at a concentration of 500μg/㎖ were mixed together and incubated at 70℃ for 10 min. The mixture was cooled immediately after incubation on ice. 10$\mu\ell$ of 5 x reaction buffer, 0.1M DTT, 5$\mu\ell$ of 10 x dNTP(5mM d(ACG)TP and 2mM TTP), 2 $\mu\ell$ of fluorescent nucleotide(1mM Cy3-dUTP for the control group and Cy5-dUTP for the BCL-treated group), 1.5$\mu\ell$ of RNAsin, and 2.5$\mu\ell$ of superscript II reverse transcriptase (200U/ $\mu\ell$) were added to the mixture, which was then incubated at 37℃ for 2 hours. Afterwards, 6$\mu\ell$ of 3N NaOH was added to the reaction mixture to eliminate the RNA. 20$\mu\ell$ of 1M Tris HCl(pH 7.5) and 12$\mu\ell$ of 1N HCl were added to neutralize the NaOH. The reaction mixture was loaded into Biospin 6 columns, centrifuged at 1,000 x g for 4 min, loaded into Microcon 30 tubes, and centrifuged at 12,000 x g for another 3 min.

5. Prehybridization of slide

For preparation of hybridization, prehybridization buffer (6 x SSC, 0.2% SDS, 5 x Denhardt's solution, 1㎎/㎖ salmon sperm solution) was sprayed on the array under a 22 mm x 22 mm glass coverslip, sealed with glue, and left for 2 hours at room temperature. Slides were then unsealed, washed by 2 x SSC, 0.2 x SSC, and spun dry by centrifugation for 2 min in a 50㎖ tube at 3,000 rpm.

6. Microarray hybridization and scanning

28.2$\mu\ell$ of the fluorescence probe, 1$\mu\ell$ of poly(dA)(4㎎/㎖ in TE), 1$\mu\ell$ of yeast tRNA(4㎎/㎖), 1$\mu\ell$ of human Cot I DNA(Amersham Pharmacia Biotech Inc. Piscataway, NJ, USA)(10㎎/㎖), 0.8$\mu\ell$ of 10% SDS, and 8$\mu\ell$ of 20 x SSC were added together and mixed. The mixture was incubated at 99℃ for 5 min. After staying for 5 min. at room temperature, the mixture was centrifuged at 12,000 x g for 2 min. The mixture was then sprayed on the microarray, and the microarray was incubated at 62℃ overnight. The hybridized microarray was washed with 1 x SSC, 0.1% SDS solution. The microarray was washed with a 0.1 x SSC/0.1% SDS solution at 50 ℃ for 10 min, and then in a 0.1 x SSC solution for another 10 min.

7. Array quantification and data processing

Following hybridization, arrays were scanned using a confocal laser-scanning microscope(Scan Array 5000, Affymetrix, Santa Clara, CA, USA) at 543nm(Cy3, GHeNe laser) and 632nm(Cy5, RHeNe laser). Each spot was defined by manual positioning of a grid of circle over the array image. For each fluorescent image, the average pixel intensity within each circle was determined, and the local background beyond a 3-pixel buffer range from the circle was computed for each spot. Net signal was determined by subtraction of this local background from the average intensity of each spot. Signal intensities between the two fluorescent images were normalized by the intensities of the house-keeping genes provided on the arrays.

8. Data Analysis

Signal intensities of the fluorescent images for Cy3 and Cy5 were considered significant when they were more than twice the average intensity of the negative control signals. Genes with consistently low signals in subsequent repetition of the experiment were omitted from the analysis.

Results

The following results show that BCL regulates the expression of CDs in human mast cells. The whole experiments were repeated twice.

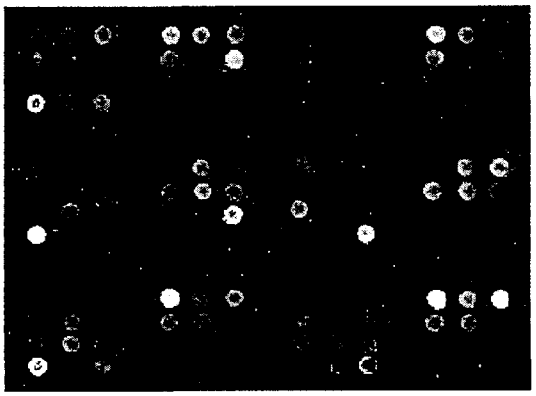

Fig. 1. Two-color image of an HMC-1 cDNA microarray. The array consists of PCR-amplified cDNA clones printed on glass; the diameter of each spot is 500 μ m. A sample mixture consisting of Cy3-labelled mRNA from untreated cells and Cy5-labelled mRNA from Bambusae Caulis in Liquamen-treated cells was added. After scanning for each fluorescent dye false colour images(red for Cy3, green for Cy5) were superimposed. Yellow dots represent genes that show no change in expression. The hybridized microarray was scanned with the confocal laser scanner Scan Array 5000(General Scanning) at 543 nm (Cy3, GHeNe laser) and 632 nm(Cy5, RHeNe laser). Two independent experiments were performed.

1. Cyanine dye-labelled HMC-1 cDNA was hybridized to the microarray

A two-color image of an HMC-1 cDNA microarray is shown in Fig. 1. Red dots represent Cy3, and green dots represent Cy5. After scanning for each fluorescent dye false colour images were superimposed. Red dots or green dots represent genes that show altered expression, and yellow dots represent genes that show no change in expression. Total gene index of the microarray is available at the CreaGene web site (http://www.creagene.com/Ncreagene/human_gene_list.htm).

2. Genes up-regulated in the BCL-treated group

51 genes, including those coding for L apoferritin, beta-2-microglobulin, ferritin light polypeptide, CD63, monocyte chemotactic and activating fact, heme oxygenase 1, CD140a, integrin alpha M, colony stimulating factor 2 receptor, eukaryotic translation elongation factor, CD37, interleukin 18, NADH dehydrogenase 1 beta, CD48, 5-lipoxygenase activating protein, interleukin 4, ribosomal protein L5, GABA(A) receptor-associated protein, beta-tubulin, integrin beta 1, CD162, CD32, lymphotoxin beta, alpha-tublin, integrin alpha L, CD2, CD151, CD331, 90 kDa heat shock protein, CD59, CD3Z, microsomal glutathione S-transferase 2, CD33, CD162R, cyclophilinA, CD84, interleukin 9 receptor, interleukin 11, CD117, CD39-Like 2, colony stimulating factor 3, interleukin 1 beta, protein tyrosine phosphatase, CD47R, CD68, CD107, L19, CD44, interferon alpha 2, LPS-induced TNF-alpha factor, and CD98, were up-regulated in BCL-treated HMC-1 cells(Table I).

Table 1. Genes upregulated in Bambusae Caulis in Liquamen(BCL)-treated HMC-1 cells

Gene	ID	Normalized Ratio of Medians
L apoferritin	hak285	22.80
beta-2-microglobulin	hak330	13.85
ferritin, light polypeptide	hak301	11.88
CD63	kribb119	10.97
monocyte chemotactic and activating fact	hak328	10.76
heme oxygenase 1	kribb15	10.69
CD140a	hak102	7.27
integrin, alpha M	kribb63	6.49
colony stimulating factor 2 receptor	kribb22	6.41
eukaryotic translation elongation factor	hak334	6.25
CD37	kribb2	6.22
interleukin 18	kribb39	6.10
NADH dehydrogenase 1 beta	kribb90	5.84
CD48	kribb92	5.54
5-lipoxygenase activating protein	hak326	5.53
interleukin 4	kribb35	5.41
ribosomal protein L5	hak341	4.77
GABA(A) receptor-associated protein	hak311	4.66
beta-tubulin	hak307	4.62
integrin, beta 1	kribb38	4.49
CD162	hak115	4.45

Gene	ID	Normalized Ratio of Medians
CD32	Ahn12	4.37
lymphotoxin beta	kribb41	4.36
alpha-tublin	hak247	4.11
integrin, alpha L	kribb20	3.86
CD2	kribb24	3.79
CD151	kribb78	3.79
CD331	kribb14	3.72
90 kDa heat shock protein	hak272	3.69
CD59	kribb37	3.62
CD3Z	kribb9	3.61
microsomal glutathione S-transferase 2	hak309	3.58
CD33	kribb31	3.51
CD162R	hak125	3.48
cyclophilinA	hak251	3.48
CD84	kribb28	3.40
interleukin 9 receptor	kribb88	3.18
interleukin 11	kribb34	2.93
CD117	Ahn45	2.91
CD39-Like 2	kribb82	2.88
colony stimulating factor 3	kribb81	2.86
interleukin 1, beta	kribb46	2.75
protein tyrosine phosphatase	kribb70	2.70
CD47R	hak178	2.66
CD68	kribb66	2.60
CD107	Ahn41	2.60
L19	hak249	2.48
CD44	kribb89	2.47
interferon, alpha 2	kribb29	2.43
LPS-induced TNF-alpha factor	kribb76	2.22
CD98	hak83	2.15

ID is the name given to each gene in the Stanford Genome Database. Web Database: http://www.creagene.com/Ncreagene/human_gene_list.htm. Cy3-labelled mRNA came from HMC-1 cells before BCL treatment, and Cy5-labelled mRNA from BCL-treated HMC-1 cells.. Normalized ratios of medians were calculated as Cy5 dividing Cy3 and the ratios more than 2.0 are shown in this table.

3. Genes down-regulated in the BCL-treated group

7 genes, including those coding for CD77, CD238, SCF, CD160, CD231, CD24, and CD130, were down-regulated in BCL-treated HMC-1 cells(Table 2).

Table 2. Genes downregulated in Bambusae Caulis in Liquamen (BCL)-treated HMC-1 cells

Gene	ID	Normalized Ratio of Medians
CD77	Ahn27	0.43
CD238	hak170	0.43
SCF	hak246	0.43
CD160	hak124	0.45
CD231	hak163	0.49
CD24	kribb101	0.49
CD130	hak97	0.49

ID is the name given to each gene in the Stanford Genome Database. Web Database: http://www.creagene.com/Ncreagene/human_gene_list.htm. Cy3-labelled mRNA came from HMC-1 cells before BCL treatment, and Cy5-labelled mRNA from BCL-treated HMC-1 cells. Normalized ratios of medians were calculated as Cy5 dividing Cy3 and the ratios less than 0.5 are shown in this table.

Discussion

Bamboo has been used as a source of therapeutic drugs for thousands of years in Oriental societies. It is well known that Phyllostachys nigra and P. edulis have various benefit effects as antioxidant activity and been used for the prevention of immune diseases and cancer development. BCL comes from the plant P. nigra or P. edulis, which contain structural isomeric chlorogenic acid derivatives: 3-O-(3'-methylcaffeoyl)-quinic acid, 5-O-caffeoyl-4-methylquinic acid, and 3-O-caffeoyl--1-methylquinic acid which have antioxidant properties.[11-13] In the human, mast cells play a role in the pathogenesis of immunological diseases such as allergic asthma, rhinoconjunctivitis, urticaria, anaphylaxis, and systemic mastocytosis. They are also thought to be important players in other chronic inflammatory disorders such as inflammatory bowel disease and rheumatoid arthritis[4,5]. Mast cells are also thought to participate in sterile inflammatory conditions exacerbated by stress, such as atopic dermatitis, interstitial cystitis, irritable bowel syndrome, migraines, and multiple sclerosis[5]. Basophils, the circulating "equivalent" of tissue mast cells, are also considered to be important elements in the pathogenesis of late phase allergic reactions[6,7]. Leukocyte cell surface molecules are routinely detected with anti-leukocyte monoclonal antibodies(mAbs). These molecules include CDs, which indicate either different stages of lineage-specific differentiation or different states of activation or inactivation. In this experiment, we made the microarray profiles of CD expression in human mast cells before and after BCL treatment. Genes up-regulated in BCL-treated HMC-1 cells included those coding for L apoferritin, beta-2-microglobulin, ferritin light polypeptide, CD63, monocyte chemotactic and activating fact, heme oxygenase 1, CD140a, integrin alpha M, colony stimulating factor 2 receptor, eukaryotic translation elongation factor, CD37, interleukin 18, NADH dehydrogenase 1 beta, CD48, 5-lipoxygenase activating protein, interleukin 4, ribosomal protein L5, GABA(A) receptor-associated protein, beta-tubulin, integrin beta 1, CD162, CD32, lymphotoxin beta, alpha-tublin, integrin alpha L, CD2, CD151, CD331, 90 kDa heat shock protein, CD59, CD3Z, microsomal glutathione S-transferase 2, CD33, CD162R, cyclophilinA, CD84, interleukin 9 receptor, interleukin 11, CD117, CD39-Like 2, colony stimulating factor 3, interleukin 1 beta, protein tyrosine phosphatase, CD47R, CD68, CD107, L19, CD44, interferon alpha 2, LPS-induced TNF-alpha factor, and CD98. Of the above genes, heme oxygenase play an important role in the inhibition of the cell surface expression of CD11b and CD66b on human neutrophils, which causes seasonal intermittent

allergic rhinitis[14]. CD59 antigen p18-20 plays an important role in host defense via the complement system. On the other hand, CD39, the ATP diphosphohydrolase (ATPDase) expressed on quiescent vascular endothelium, modulates platelet purinoreceptor activity by sequential hydrolysis of extracellular ATP or ADP to AMP.[15,16] Integrin beta-1 is essential for epithelial-mesenchymal interactions.[17] Tumor necrosis factor(TNF) and lymphotoxin-beta activate TNF receptor types 1 and 2, which are broadly expressed by most cell types.[18] TNF receptor-mediated immune reactions are critically important in the pathogenesis and control of a variety of infections caused by bacteria, viruses, protozoa, and fungi. IL-18, a novel cytokine with potent IFN-gamma-inducing action, plays an important role in Th1-mediated immune response in collaboration with IL-12. It is a member of the IL-1 family. The IL-18 receptor system and its signal transduction pathway are analogous to those of IL-1. Studies with IL-18-deficient mice have demonstrated its critical role in natural killer cell activity and in vivo Th1 response.[19] Genes down-regulated in BCL-treated HMC-1 cells include those coding for CD77, CD238, SCF(stem cell factor), CD160, CD231, CD24, and CD130. Of these, CD130 shows elevated expression in basophilic granulocytes of allergic subjects, compared with those in healthy persons.[20] And SCF is known to induce airway-hyperreactivity via leukotriene production.[21] The results of the present study cannot fully explain the effects of BCL on mast cells, but they provide fundamental data for the involvement of human mast cells in immune-regulation. Moreover the data provides some insight into the mechanisms mediating the effects of BCL on immune system.

Acknowledgments

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