Gene Expression Analysis of Tissue Remodeling in Chronic Rhinosinusitis: A Preliminary Investigation

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Abstract

Objective: This study aims to understand the pathophysiology of bone and tissue remodeling by demonstrating the gene expression profiles in the development of chronic rhinosinusitis (CRS).

Material and Methods: The study included patients who were operated with the diagnosis of CRS. The study group consisted of eight patients who underwent endoscopic sinus surgery with the diagnosis of CRS and had a history of chronic sinusitis as well as osteitic bone changes. The control group consisted of ethmoid bulla specimens of eight patients who had no history of sinusitis or sinus surgery with the diagnosis of acute sinusitis or antrochoanal polyp. In both bone and mucosal samples, RNA isolation was performed to identify and analyze genes that were upregulated and downregulated by whole-gene expression profiling using microarray technology.

Results: When the diseased and healthy bone samples were compared, a total of 1302 genes were detected in 1766, and the disease was intact. Four genes, CD36 (FC[Fold Change]=31.19), tenascin XB (FC=13.6), S100 calcium binding protein A12 (FC=9.4), and G0/G1 switch 2 (FC=9.3) up-regulated in both bone and mucosa.

Conclusion: Chronic rhinosinusitis is a disease that decreases both quality of life of the patient and the high cost of treatment. Gene expression analysis in tissue samples of patients with CRS and treatment-resistant CRS disease early can be used in the diagnosis of the period. With the understanding of the mechanisms involved in disease development, new treatment protocols can be established in the early period to prevent insufficiencies in medical and surgical treatment.

Keywords: Gene Expression, chronic rhinosinusitis CD36, tenascin XB, S100 calcium binding protein A12, G0/G1 switch 2

INTRODUCTION

Treatment-resistant chronic rhinosinusitis (CRS) reduces the quality of life and labor productivity requiring long-term medical treatments and recurrent surgical procedures (1). In the pathophysiology of this treatment-resistant form of CRS, tissue remodeling is being investigated. In CRS, tissue remodeling occurs in both the bone and mucosa. In this context, mucosal hypertrophy, fibrosis, osteitis, and basal membrane thickening are observed (2). Although many studies have been conducted on mucosal remodeling, bone remodeling (osteitis) became the focus of interest, and may play an important role in the pathophysiology of CRS (3). An osteitic bone is a source of inflammation and is thought to play a role in the chronicity of the disease. Although the definitive diagnosis of osteitis is made histopathologically, various measurement methods have been defined preoperatively via paranasal sinus tomography. In a patient whose osteitis cannot be detected radiologically, various degrees of osteitis can be diagnosed histopathologically (4). A gene expression analysis using the microarray method, which is a relatively new and revolutionary technique, has recently been used in human CRS tissue characterization. However, to the best of our knowledge, this technique has not yet been analyzed at the diseased bone tissue level.

In our study, we compared both the bone and mucosal gene expression profiles of the patients with CRS and compared them with healthy individuals. Thus, we tried to understand the pathophysiology of the disease. With these results, we can create diagnostic markers that can be used in the early diagnosis of treatment-resistant disease. On the

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other hand, we can create new medical treatment options by detecting the genes involved in the disease and/or their proteins. To the best of our knowledge, our study is the first study on this subject, and we believe that it will contribute to the literature on this issue.

MATERIAL AND METHODS

Tissue samples for the microarray analysis were taken from a total of 16 patients. The study group consisted of 8 patients who underwent endoscopic sinus surgery with the diagnosis of CRS and who had osteitic bone changes, as well as signs of chronic sinusitis, on preoperative paranasal sinus tomography. The control group was taken from the ethmoid bulla samples of 8 patients who had not been diagnosed with CRS but underwent sinus surgery with the diagnosis of acute sinusitis or antrochoanal polyps. The medical history of the patients was questioned before the operation, and nasal endoscopic examination was performed. Oral and topical steroids were not used until at least 4 weeks before the operation. The osteitic bone detected in the paranasal sinus tomography, and the mucosa covering it was removed during the operation and saved for the study. The tissues removed during surgery were immediately protected to -80 degrees. Total RNA isolation from tissues to be used in mRNA profiling was achieved by using a combination of RNeasy Kit, commercial kit (Qiagen, Hilden, Germany), and TRIzol protocols. The concentration I purity of the obtained RNA samples were determined on Nano drops, Thermo Scientific instrument (Thermo Fisher Scientific, Waltham, USA) at 260/280 nm wavelengths. The absorbance ratios of RNA A260/A280 and A260/A230 were expected to be ≥1.8. The verification and confirmation of the degradation of RNA having a sufficient molecular weight was performed using the Agilent 2100 Bioanalyzer system (Agilent Technologies, Palo Alto, California) and the RNA 6000 Nano Assay Reagent Kit (Agilent Technologies, Palo Alto, California). The samples with an insufficient weight and degradation were excluded from the study and were not included in the labeling and hybridization steps. For double-stranded c-RNA synthesis, the Low Input Quick Amp Labeling Kit, One-Color Commercial Kit (Agilent Technologies, Palo Alto, California) (Agilent) was used. The hybridization of the microarray was carried out in a special hybridization oven (Agilent Hybridization Oven, Agilent). All reagents required for the hybridization were prepared according to the Agilent Gene Expression Hybridization Kit (Agilent) protocol. The Agilent Feature Extraction software was used for scanning images obtained for the data analysis. The normalization of the expression data during the analysis was performed according to the "quantile normalization" method (Bioinformatics 2003; 19: 185). Also, in this software program, gene calls values which evaluates the gene expression analysis and calls files were obtained via Robust Multichip Average algorithms (Nucleic Acids Res. 2003; 31: e15 and Biostatistic 2003; 4: 249).

In isolated samples of both the bone and mucosa, RNA was isolated, and the whole gene expression profiling via microarray detected up-regulated and down-regulated genes, after which they were analyzed. While the bone coverslips of patients with CRS were compared with bone coverslips of the healthy group, the mucosal samples of the patient group were compared with the mucosal samples of the healthy group.

The study was approved by the Non-Interventional Clinical Trials Ethics Committee of the Adnan Menderes University. Written consent was obtained from all patients.

RESULTS

The study group consisted of 5 female and 3 male patients with an average age of 47.63±12.86 years. The control group consisted of 5 female and 3 male patients with an average age of 39.38±16.63 years. During the analysis, the Fold Change (FC) was taken as 2. In other words, the genes that were 95% or more safe and show a two-fold or more expression difference were listed. Accordingly, when the diseased and healthy bone samples and the diseased and healthy mucosa samples were compared, 1766 and 1302 genes were detected, respectively. When the analysis interval was narrowed, and FC=5 was taken, 258 genes were found in the bone samples, and 273 genes were found in the mucosa samples. Among these, a total of 40 genes from the SOURCE gene bank, which were most up-regulated and down-regulated (20 each) were selected, the functions of which were described. These genes are listed in Tables 1 and 2. Among these genes, four common down-regulated genes were identified: CD36 (FC=31.19), tenascin XB (FC=13.6), S100 calcium-binding protein A12 (FC=9.4), and G0/G1 switch 2 (FC=9.3)

DISCUSSION

The microarray technology has revolutionized the field of genetic analysis, making it possible to measure the synthesis of thousands of genes simultaneously (5). There are several studies evaluating the gene expression in the sinonasal mucosa. These studies have demonstrated the expression of different genes in CRS patient groups. However, no studies have been conducted directly on the osteitic bone in the scanned publications. To the best of our knowledge, our study is the first study to compare the samples with those of healthy individuals by performing a gene analysis on both the bone in which we have radiologically detected osteitis and the mucosa covering it.

When the results were examined, four overexpressed genes were detected in both the bone and mucosa compared to healthy individuals. These are CD36, tenascin XB, S100 calcium-binding protein A12 and G0/G1 switch 2 genes. No common down-regulated gene was detected.

The CD36 molecule is known as a plasma membrane protein belonging to the Class B scavenger receptor family. It is released from many cells and tissues, including platelets, monocytes, macrophages, endothelial cells, fat east, skeletal muscles, and the heart (6). It has multiple functions, including the lipid metabolism and immune response (7). It is the main carrier of oxidized low-density lipoproteins and long-chain fatty acids (8). It plays a role in the Toll-like receptor (TLR) signaling pathway and apoptosis. This pathway controls the immune response against gram-positive bacteria, such as *S. aeurius*, and mycobacteria (8). There have been studies linking its proinflammatory effect to the suppression of immunoregulatory cytokines, such as IL-10 secreted during the apoptotic cell clearance (9).

It has also recently been found that CD36 regulates the TLR4-TLR6 heterodimer assembly. This complex is responsible for the activation of proinflammatory cytokines, such as IL-1β and the production of nitric oxide. This inflammatory response is involved in many serious diseases, such as atherosclerosis, Alzheimer's disease, metabolic syndromes, and insulin resistance (10).

To date, to the best of our knowledge, no studies have been conducted on the relationship between CRS and CD36. In our study group, a significant overexpression in patients with CRS in both bone and mucosa compared to the healthy group strengthens the opinion that CD36 may play a role in the development of CRS. This effect may be through *S. aerius*, which has been shown as effective in the pathogenesis of nasal polyposis.

Table 1. Significantly up- regulated and significantly down-regulated (negative value) genes 257 of the bone in chronic rhinosinusitis are shown by gene name and gene bank number

Gene name	Gene bank Accession number	Ontology/function	Fold Change
Olfactory receptor, family 2, subfamily Y, member 1	NM_001001657	Olfactory receptors interact with odorant molecules in the nose, to initiate a neuronal response that triggers the perception of a smell. The olfactory receptor proteins are members of a large family of G-protein-coupled receptors (GPCR) arising from single coding-exon genes.	91.2
Chloride intracellular channel 4	NM_013943	**Voltage-gated chloride channel activity** Chloride channels are a diverse group of proteins that regulate fundamental cellular processes including stabilization of cell membrane potential, transepithelial transport, maintenance of intracellular pH, and regulation of cell volume.	15.6
Macrophage expressed 1	NM_001039396	**Integral component of membrane**	11.1
Colony stimulating factor 1 receptor	NM_001288705	**Cytokine binding** The protein encoded by this gene is the receptor for colony stimulating factor 1, a cytokine which controls the production, differentiation, and function of macrophages. This receptor mediates most if not all of the biological effects of this cytokine.	8.7
Ficolin (collagen/ fibrinogen domain containing) 1	NM_002003	**Calcium ion binding/Antigen binding** The ficolinfamily of proteins are characterized by the presence of a leader peptide, a short N-terminal segment, followed by a collagen-like region, and a C-terminal fibrinogen-like domain. The collagen-like and the fibrinogen-like domains are also found separately in other proteins such as complement protein C1q, C-type lectins known as collectins, and tenascins	8.6
Lectin, galactoside-binding, soluble, 2	NM_006498	**galactoside binding** The protein encoded by this gene is a soluble beta-galactoside binding lectin. its physiological function is not yet known	8.3
Heat shock transcription factor family member 5	NM_001080439	**Sulfotransferase activity** Sulfonation, an important step in the metabolism of many drugs, xenobiotics, hormones, and neurotransmitters, is catalyzed by sulfotransferases.	-58.8
Ras suppressor protein 1	NM_012425	Protein binding/ Positive regulation of neural precursor cell proliferation This gene encodes a protein that is involved in the Ras signal transduction pathway, growth inhibition, and nerve-growth factor induced differentiation processes, as determined in mouse and human cell line studies.	-58.8
Ribosomal protein S4, Y-linked 2	NM_001039567	**Structural constituent of ribosome** The protein encoded by this gene is a ribosomal protein that is highly similar to RPS4Y1.	-55.6
DEAD (Asp-Glu-Ala-Asp) box helicase 3, Y-linked	NM_001122665	**ATP catabolic process** The protein encoded by this gene is a member of the DEAD-box RNA helicase family, characterized by nine conserved motifs, included the conserved Asp-Glu-Ala-Asp (DEAD) motif. These motifs are thought to be involved in ATP binding, hydrolysis, RNA binding, and inthe formation of intramolecular interactions.	-55.6
Mahogunin ring finger 1, E3 ubiquitin protein ligase	NM_001142289	**Ubiquitin-protein transferase activity** Mahogunin (MGRN1) is a C3HC4 RING-containing protein with E3 ubiquitin ligase activity in vitro.	-50.0
Zinc finger, DBF-type containing 2	NM_001285549	**Zinc ion binding, Nucleid Acid binding**	-50.0
Taxilin gamma pseudogene, Y-linked	NM_001005852	**Syntaxin binding**	-47.6
Ribosomal protein S4, Y-linked 1	NM_001008	**Structural constituent of ribosome/RNA binding** Ribosomal protein S4 is the only ribosomal protein known to be encoded by more than one gene, namely this gene and ribosomal protein S4, X-linked (RPS4X). The 2 isoforms encoded by these genes are not identical, but are functionally equivalent.	-41.7
Galactose-3-O-sulfotransferase 1	NM_004861	**Sulfotransferase activity** Sulfonation, an important step in the metabolism of many drugs, xenobiotics, hormones, and neurotransmitters, is catalyzed by sulfotransferases.	-23,8
HECT and RLD domain containing E3 ubiquitin protein ligase 3	NM_001271602	**Ubiquitin-protein transferase activity** This gene encodes a member the HERC ubiquitin ligase family. The encoded protein is located in the cytosol and binds ubiquitin via a HECT domain. Mutations in this gene have been associated with colorectal and gastric carcinomas.	-22.7

The 258 gene function derived the SOURCE gene data bank are presented in the third column

Table 2. Significantly up- regulated and significantly down-regulated (negative value) genes of the mucosa in chronic rhinosinusitis when compared healty samples are shown by gene name and gene bank number

	Mucosa		
Gene name	**Gene bank Accession number**	**Ontology/function**	**Fold change**
Myeloid cell nuclear differentiation antigen	NM_002432	**Protein binding** The myeloid cell nuclear differentiation antigen (MNDA) is detected only in nuclei of cells of the granulocyte-monocyte lineage.	76.7
CD36 molecule (thrombospondin receptor)	NM_000072		68.38
TNXB (tenascin XB)	NM_019105		57.0
S100 calcium binding protein A12	NM_005621		52.72
LIM domain only 2 (rhombotin-like 1)	NM_001142315	**Chromatin binding** LMO2 encodes a cysteine-rich, two LIM-domain protein that is required for yolk sac erythropoiesis. The LMO2 protein has a central and crucial role in hematopoietic development and is highly conserved	48.5
Macrophage expressed 1	NM_001039396	Integral component of membrane	44.0
FES proto-oncogene, tyrosine kinase	NM_001143783	**Non-membrane spanning protein tyrosine kinase activity** This gene encodes the human cellular counterpart of a feline sarcoma retrovirus protein with transforming capabilities. The gene product has tyrosine-specific protein kinase activity and that activity is required for maintenance of cellular transformation.	37.5
G0/G1 switch 2	NM_015714		35.62
Phospholipase B domain containing 1	NM_024829	**Hydrolase activity** it has been proposed that it may act as an amidase or a peptidase (by similarity). exhibits a weak phospholipase activity, acting on various phospholipids, including phosphatidylcholine, phosphatidylinositol, phosphatidylethanolamine and lysophospholipids.	31.6
Threonine synthase-like 2 (S. cerevisiae)	NM_001244676	**Cytokine activity** This gene encodes a threonine synthase-like protein. This protein also has phospho-lyase activity on both gamma and beta phosphorylated substrates. In mouse an alternatively spliced form of this protein has been shown to act as a cytokine and can induce the production of the inflammatory cytokine IL6 in osteoblasts.	-13.3
Ferrochelatase	NM_000140	**Ferrochelatase activity** The protein encoded by this gene is localized to the mitochondrion, where it catalyzes the insertion of the ferrous form of iron into protoporphyrin IX in the heme synthesis pathway	-13.3
Katanin p60 subunit A-like 2	NM_031303	**ATP binding** severs microtubules in vitro in an atp-dependent manner. this activity may promote rapid reorganization of cellular microtubule arrays.	-14.7
Nebulin	NM_001164507	**Structural constituent of muscle** This gene encodes nebulin, a giant protein component of the cytoskeletal matrix that coexists with the thick and thin filaments within the sarcomeres of skeletal muscle. In most vertebrates, nebulin accounts for 3 to 4% of the total myofibrillar protein.	-15.6
Sodium channel, voltage gated, type VIII, alpha subunit	NM_001177984	**Voltage-gated sodium channel activity** This gene encodes a member of the sodium channel alpha subunit gene family. The encoded protein forms the ion pore region of the voltage-gated sodium channel. This protein is essential for the rapid membrane depolarization that occurs during the formation of the action potential in excitable neurons.	-15.6
Renalase, FAD-dependent amine oxidase	NM_001031709	**Oxidoreductase activity** Renalase is a flavin adenine dinucleotide-dependent amine oxidase that is secreted into the blood from the kidney	-15.9
Histone deacetylase 6	NM_006044	**Protein binding protein** Histones play a critical role in transcriptional regulation, cell cycle progression, and developmental events. Histone acetylation/deacetylation alters chromosome structure and affects transcription factor access to DNA.	-25.0
Calcium binding protein 7	NM_182527	**Calcium ion binding**	-38.5
Zinc finger protein 77	NM_021217	**Metal ion binding** may be involved in transcriptional regulation.	-100.0
Hyaluronan and proteoglycan link protein 2	NM_021817	**Extracellular matrix structural constituent** mediates a firm binding of versican v2 to hyaluronic acid. may play a pivotal role in the formation of the hyaluronan- associated matrix in the central nervous system (cns) which facilitates neuronal conduction and general structural stabilization.	-131.6

The gene function derived the SOURCE gene data bank are presented in the third column

Tenascain XB is one of the four members of the tenascin family of the extracellular matrix glycoproteins. This gene is located on chromosome 6 in the major histocompatibility complex Class III region. Its main function is to provide cell–matrix interactions. It is effective in the matrix maturation and wound healing. It has been reported to be expressed in the connective tissues, such as the dermis, blood vessels, and epimysium in adults and embryos (11). The studies have shown that the down-regulation of TNX supports invasion and metastasis of some tumors by increasing the matrix metalloproteinase production (12). The most studied in this family is tenascin C. The studies have shown that TGF-beta1 and eosinophils induce the TNC expression in nasal epithelial cells (13, 14). In their microarray study, Payne et al. found that the TNC expression was increased 10-fold in NP patients with fibrotic stroma. They explained that TNC, which regulates fibroblast migration in acute tissue trauma and inflammation, causes NP with fibrotic appearance by creating a continuous perception of inflammation in the NP tissue (15). However, there are no studies demonstrating the relationship between TNXB and CRS. Our study demonstrated that TNXB may play a role in the CRS tissue remodeling. Future studies are required that would show the mechanism by which TNXB causes tissue changes.

S100A12 is a gene located on chromosome 1q21.3 that encodes the same-name calcium and zinc-binding protein (16). This protein plays an important role in the inflammation and immune response and is overexpressed during inflammation. The proinflammatory activity is achieved by neutrophil chemotaxis, cytokine, and chemokine production, monocyte adhesion, and migration. It is predominantly released from monocytes, neutrophils, and active macrophages (17). This effect has been demonstrated *in vivo* and *in vitro*. It is claimed to support the monocyte activation by activating TLR4. Extracellular S100A12 is part of the immune response to microorganisms. In addition, it has been detected at a high rate in many inflammatory diseases, such as inflamed joint synovial fluid, atherosclerotic lesions, bronchial fluid in inflammatory lung diseases, and in the blood and skin in psoriatic skin lesions. Due to these properties, it has been suggested that it can be used as a diagnostic marker in inflammatory diseases (16, 18).

G0S2 was discovered in cultured mononuclear cells during the transition from the G0 to G1 phase during a drug-induced cell cycle. This protein is known to play a role in apoptosis, carcinogenesis, and inflammation (19). Again, this protein is a pro-apoptotic factor induced by TNF-α and NF kappa beta and secreted from neutrophil granulocytes. This gene is regulated during adipogenesis, and the overexpression of G0S2 reduces the effect of TNF-α on lipolysis (20). G0S2 was found to be a possible tumor suppressor gene in squamous cell lung and head-and-neck cancers. In the light of these findings, G0S2 may affect CRS via TNF-α or the apoptotic way.

CONCLUSION

Chronic rhinosinusitis is associated with tissue remodeling, including the paranasal sinus bones and mucosa. However, the underlying pathophysiology of this disease is unclear and multifactorial. This study is the first step in investigating tissue remodeling in CRS patients with osteitis. Unfortunately, there are some limitations to this study. The patient population consists of a heterogeneous CRS group. We plan to further investigate these preliminary data on the CRS subtypes in the future. As a result, these genes and proteins involved in the pathogenesis of CRS may serve new medical treatment options. We believe that our study contributes to the literature in this respect.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Adnan Menderes University (11/11/2013).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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