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Analysis of the ARPC1A Gene in Patients Diagnosed with Periodontitis

Periodontitis Tanısı Konulan Hastalarda ARPC1A Geninin Analizi

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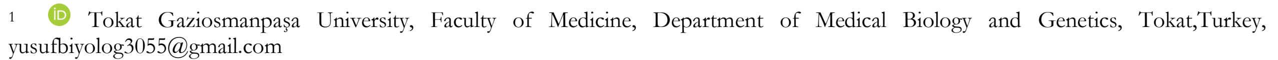
ABSTRACT

Periodontitis is a chronic inflammatory disease characterized by the progressive destruction of the tooth-supporting tissues and has a multifactorial etiology associated with the individual oral microbiota and host immune response. The development of targeted therapeutic approaches requires a comprehensive understanding of the molecular pathways underlying the etiology of the disease. Cell migration is essential for fundamental physiological processes such as development, tissue repair, and immune responses.The actin-related protein 2/3 (ARP2/3) complex is a critical regulator that controls the nucleation and branching of actin filaments within the cytoskeleton, which are necessary for cell motility, maintenance of cell shape, and membrane dynamics. Actin-related protein complex subunit 1A (ARPC1A) is a member of the ARP2/3 complex family. ARPC1A is involved in various cellular processes, including regulation of gene expression, intracellular transport, and cytoskeletal dynamics. Abnormalities in the cytoskeleton and its associated proteins are known to contribute to the pathogenesis of numerous diseases. Periodontitis is also considered to be associated with cytoskeletal alterations. In the present study, the mRNA expression level of the ARPC1A gene was analyzed using RT-PCR in tissue samples obtained from 20 patients diagnosed with periodontitis and in 20 healthy control tissues derived from the same individuals. Although a certain increase in ARPC1A gene expression was observed in both patient and control tissues, this increase was not found to be statistically significant.

ÖZET

Periodontitis, dişleri destekleyen dokuların ilerleyici yıkımı ile karakterize edilen, hastanın bireysel ağız mikrobiyotası ve bağışıklık yanıtı ile ilişkili multifaktöriyel etiyolojiye sahip kronik bir inflamatuvar hastalıktır. Hedefe yönelik tedavi yaklaşımlarının geliştirilmesi, hastalığın etiyolojisinin arkasındaki moleküler yolakların anlaşılmasını gerektirmektedir. Hücre göçü, gelişim, doku onarımı ve bağışıklık yanıtları gibi temel fizyolojik süreçler için hayati öneme sahiptir. Aktin protein 2/3 (ARP2/3) kompleksi, hücre hareketliliği, şekil korunumu ve membran dinamikleri için gerekli olan iskelet sistemindeki aktin filamentlerinin nükleasyonunu ve dallanmasını düzenleyen kritik bir düzenleyicidir. Aktin protein 2/3 kompleks alt birimi 1A (ARPC1A), ARP2/3 kompleks ailesinin bir üyesidir. ARPC1A; gen ekspresyonunun düzenlenmesi, hücre içi taşınma ve hücre iskeleti dinamikler gibi çeşitli hücresel süreçlerde rol oynamaktadır. Hücre iskeleti ve ona bağlı proteinlerdeki anormalliklerin birçok hastalığın patogenezinde rol oynadığı bilinmektedir. Periodontitisin de bu tür hücre iskeleti hastalıklardan biri olduğu düşünülmektedir. Bu çalışmada, ARPC1A geninin mRNA düzeyindeki ekspresyonu, periodontitis tanısı konulmuş 20 hastadan elde edilen dokular ile aynı bireylere ait 20 sağlıklı kontrol dokusunda RT-PCR yöntemi kullanılarak incelenmiştir. Hem hasta hem de kontrol dokularında ARPC1A geninde belirli bir artış gözlemlenmiş ancak bu artışın istatistiksel olarak anlamlı olmadığı saptanmıştır.

[*] Makale hakkında ek bilgiler / Additional information about the article.



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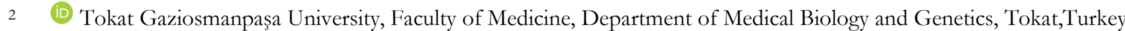

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1. Introduction

Periodontitis is a chronic, multifactorial inflammatory disease that begins with the accumulation of a dysbiotic biofilm on tooth surfaces, resulting in an immune-inflammatory host response that, if not treated appropriately, leads to progressive periodontal tissue destruction, tooth loss, and negatively impacts overall quality of life. The global prevalence of mild forms of periodontitis is estimated to be approximately 62% of the worldwide population, with severe forms of the disease affecting approximately 23.6% of them. Recent studies have shown that periodontal diseases are a potential risk factor for systemic diseases, strengthening the two-way relationship between oral and general systemic health. In particular, over the past few years, periodontitis has been associated with various systemic diseases, such as cardiovascular diseases, cancer, rheumatic diseases, diabetes, obesity, Alzheimer's disease, and increased risk of chronic lower respiratory tract diseases and peri-implantitis (Isola, Gaetano, et al., 2025; Ryder et al., 2021; Ramseier, 2024).

Although the factors causing periodontitis have been known for many years and significant progress has been made in this regard, the formation of the disease could not be prevented. One of these barriers is host sensitivity (Ebersole et al., 2016). Bacteria of periodontal origin and their virulence factors cause a systemic immunoinflammatory state either directly through the blood circulation or indirectly through the intense release of various inflammatory mediators (Francesch et al., 2017).

Actin is a family of cytoskeletal proteins expressed in nearly all eukaryotic cells and containing highly conserved sequences throughout evolution. This family of proteins is responsible for maintaining the shape and internal organization of the cell. Many cellular processes, including cell structure, cellular movement, intercellular interactions, endocytosis, cytokinesis, signal transduction, and cell activation, adhesion, and phagocytosis, require coordinated polymerization and depolymerization of the actin cytoskeleton. The Arp2/3 complex is an important actin core responsible for promoting the nucleation of microfilaments. Intracellular actin monomers form the cellular structure and play a role in the formation of cell-cell connections, the motility of pathogens and the transport of vesicles (Ma et al., 2019). ARPC1A is a member of the actin-related protein ARP2/3 complex family. The ARPC1A gene encodes the p41 subunit of the human Arp2/3 complex, which is involved in the control of actin polymerization in cells. Multiple versions of the p41 subunit have demonstrated that the complex can adapt its functions to different cell types or developmental stages (Oringer, 2002). Recent studies have shown that the Arp2/3 complex is critical for the formation of immune cell synapses, and loss of the Arp2/3 complex component predisposes to inflammatory disease (Giannopoulou et al., 2003).

As far as we have reviewed the literature, we have not found any study investigating the relationship between the ARPC1A gene and the development of periodontitis.

However, the N-WASP gene, which is in the same signaling pathway as the ARPC1A gene is associated with psoriasis, which has the same pathogenesis and risk factors as periodontitis. Considering that the development of periodontitis occurs as a result of bacterial infections; ARPC1A is involved in cell migration, signal transduction, cell polymerization and phagocytosis, it can be thought that the ARPC1A gene may be effective in tooth loss in the development of periodontitis.

In light of all this information, the hypothesis of our study is that there may be a relationship between periodontitis, a chronic inflammatory disease, and the ARPC1A gene, which has been shown to have an effect on inflammation and immune processes. Our aim in this study is to understand the effect of the ARPC1A actin cytoskeleton regulator on inflammatory responses in inflammatory autoimmune diseases such as periodontitis, which may benefit the development of new therapeutics for the diagnosis and treatment of other autoimmune/inflammatory diseases.

2. Materıals And Methods

We think that our study is important in terms of being the first study in the literature, which has been done in Turkish society and in the world, and to give an idea for new studies to be done.

This study included 20 patients (12 males, 8 females) diagnosed with periodontitis who applied to the Tokat Gaziosmanpaşa University Faculty of Dentistry Hospital Oral and Maxillofacial Surgery Department outpatient clinic for tooth extraction due to advanced tooth support tissue loss due to periodontitis. Patient group; after extraction of teeth with indications for tooth extraction from patients aged between 34-65 (mean = 51.15), 2 mm of attached gingival tissue samples with periodontitis were obtained from areas requiring soft tissue correction. For

the control group tissue samples, 2 mm healthy gingival samples were taken from the same patient in the presence of indications for resective gingival surgery (crown lengthening, dental implant healing cap application, etc.). The healthy gingival area was accepted as pocket probing depth ≤ 3mm and no bleeding on probing. The necessary permission for the study was obtained by the Tokat Gaziosmanpaşa University Clinical Research Ethics Committee at its meeting dated 18.02.2021 with the project number 21-KAEK-048.
Tissue samples taken during surgery were stored at -80°C for immediate study.

2.1. qPCR İnstrument Screen

Real-time PCR is used to estimate the differential mRNA expression profile of genes. It is the quantitative expression of a set of genes from cDNA. The basic principle behind the technique is the stepwise recording of PCR-based DNA amplification by continuously recording changes in fluorescence. The qPCR technique may include fluorescent dyes such as SYBR Green, Eva Green, or Taqman probing (Pal, 2021). These dyes fluoresce when bound to the minor groove of DNA. While the primer binds to the double-stranded DNA and elongation occurs, the fluorescent dye also binds to the grooves. The increase in both DNA amount and fluorescence amount proportionally during the amplification process can be followed on the RTPCR device screen (Günel, 2007). RNAs were obtained by applying the RNA isolation kit (Thermo, Lot: 01125929, Lithuania) protocol in tissue samples of the patient and control groups. Reverse transcription of isolated RNA samples into cDNA was performed using Applied Biosystems Thermo Fisher Scientific brand High Capacity cDNA Reverse Transcription Kit (lot; 01152470). In the synthesis process, the manufacturer's kit protocol was used. Qubit® 2.0 fluorometer device was used for cDNA measurements. Invitrogen brand Qubit™ 1X dsDNA HS Assay Kit (lot 2346191) was used for Qubit. The amount of cDNA was calculated as 60 ng per reaction and the amount of cDNA added to the reaction was calculated separately for each sample. By converting the isolated RNAs to cDNA, the stage of detecting gene expression with real time PCR was started. At this stage, β-Actin was used as the control primer with control and study groups for the target ARPC1A gene. AMPLIQON RealQ Plus 2X qPZR SYBR-Green MasterMix (High ROXTM) (Cat no: A325402) was used as the reaction mixture. Total cDNA (3 µl) was performed in a final volume of 25 µl containing primers dH_2O, ARPC1A and β-Actin. For ARPC1A and reference (β-Actin), serial dilutions were made by preparing cDNA samples "Serial dilutions of cDNA samples were prepared at 1:10, 1:100, 1:1000, and 1:10,000 ratios." at different concentrations. In the study, as a reference (control) gene; β-Actin gene: as negative control; Real Time mixed sample without cDNA template was used. The PCR cycle consists of one cycle; to begin with (50 °C, 1 cycle, 20 seconds), denaturation (95 °C, 1 cycle, 10 minutes), annealing (95 °C, 40 cycles, 15 seconds elongation and (55 °C, 40 cycles, 1 minute) sec. The β-Actin gene was used as a reference for normalization. The qRT-PCR results of ARPC1A and β-Actin genes were quantified with step one plus software v2.3. Ct (Cycle Threshold) values of ARPC1A and β-Actin genes were used to calculate $2^{-\Delta\Delta Ct}$ values.

Table 1. Primers for ARPC1A and β-actin used in qRT-PCR

Beta-Actin / ARPC1A Base Sequence	
β-Actin	5'-GCATGGGTCAGAAGGATTCC-3' 5'-CACGCAGCTCATTGTAGAAGG-3'
ARPC1A	5' AACTCAAGGAGCACAACGG 3'
ARPC1A Reverse	5' ATCAGCAACAGACACGGTG 3'

3. Results

3.1. Statistical Analysis of ARPC1A *qPCR* Results

The expression of ARPC1A gene at RNA level in periodontitis and control tissues was performed using qRT-PCR. The ***qPCR*** results of ARPC1A and β-actin genes were quantified using the step one plus software v2.3 program. ARPC1A gene data were standardized with the β-actin. In determining the expression level, the Ct values of ARPC1A and β-actin genes were used to calculate $2^{-\Delta\Delta Ct}$ values. The reference range of the values obtained is accepted as 0.9-1.1. According to these results, ARPC1A expression in tissues decreases from the range of 0.9, and it means that the expression level of ARPC1A decreases in the range of 0.9-1.1, and it means that it is ideal

expression and that it is high expression when it is above 1.1. The obtained data were then statistically analyzed. Descriptive analyses were performed in order to provide information about the general characteristics of the study groups. Data for continuous variables are given as mean ± SD; data for categorical variables are given as n (%). When comparing the means of quantitative variables between groups, the Student's t-test and one-way ANOVA are used. Cross tables and chi-square tests are used to evaluate whether there is a relationship between qualitative variables. P values <0.05 were considered statistically significant. SPSS statistical software was used in the calculations (SPSS 22.0 Chicago, IL, USA).
The results were calculated with the $2^{-\Delta\Delta Ct}$ method (13). ΔCt (periodontitis tissue)=ARPC1A Gene (Ct mean)- Actin Gene (Ct mean) Ct (control tissue) = ARPC1A Gene (Ct mean)-Actin Gene (Ct mean) = $2^{-\Delta\Delta Ct}$ (periodontitis tissue)- ΔCt (control group)

Table 2. $2^{-\Delta\Delta Ct}$ Distribution of Values According to Qualitative Variables

Variables		Average	Standard deviation	*t*	*P*
Group	Diseased	1,15	0,82	0,628	0,433
	Control	1,00	0,00		

Significance test of the difference between two means
t: Test for the mean of two groups
P: Probability that the result occurred by chance
ΔCt: Normalized gene expression value

The significance test of the difference between two means was used in the distribution of qualitative variables according to the group. In the study, when the expression level of the ARPC1A gene in periodontitis tissue was compared to normal tissue, an increase was observed in periodontitis tissue; however, this increase ($p = 0.433$, $p > 0.05$) was not found to be statistically significant (Figure1) (Table 2).

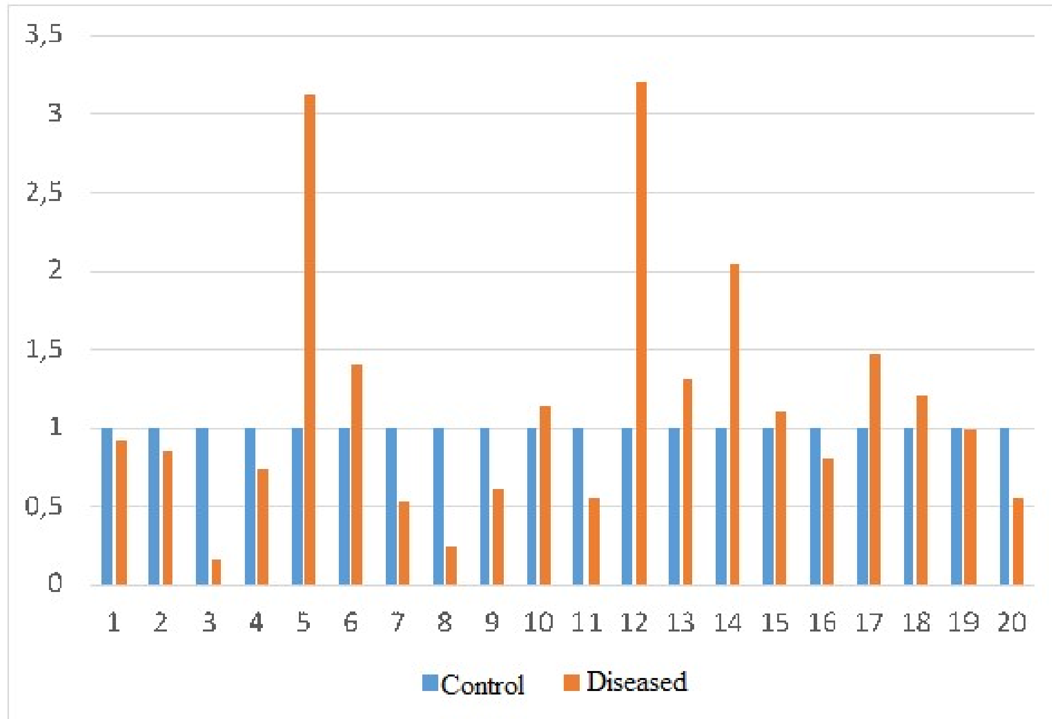

Figure 1: Control/Diseased Tissue Group Gene Expression by $2^{-\Delta\Delta Ct}$ Value of ARPC1A
According to our study results, it was found that expression level was low in 10 patients, ideal expression was found in 1 patient, and high expression was found in 9 patients. Gingival recession is also high in patients with high ARPC1A expression.

4. Discussion

Although the main etiological factor for periodontal diseases is microbial dental plaque, the factor that causes destruction of periodontal tissues is the complex interaction between pathogen bacteria in microbial dental plaque and host tissue defense mechanism. In addition to the direct pathological effects of bacteria, destruction occurs largely through indirect mechanisms caused by bacterial host interaction. Today, studies on the physiopathology and etiopathology of periodontal diseases have been replaced by the understanding of indirect mechanisms that play a role in the pathogenesis of periodontal diseases (Schmittgen & Livak, 2008). Clinical parameters such as probing depth, attachment level, bleeding on probing, plaque index, and radiographic measurement of alveolar bone loss provide important information about the severity of periodontal disease (Ozmeric, 2004). In periodontal diagnosis, in cases where hard tissue loss has not yet occurred or the change in the existing loss over time cannot be observed, it is necessary to analyze the host tissue response with laboratory methods (Heilmann et al., 2015). This requirement has revealed the necessity of investigating the biochemical and immunological signs of periodontal diseases.

Today, while periodontal and systemic health phenomena are defined as the most important indicator of quality of life (International, 1997). Increased mortality and morbidity rates associated with chronic diseases in developed and developing countries have led researchers to prevent periodontal and systemic disease with the role of genetic factors in chronic disease and gene modulation strategies (Laurila et al., 2009). In this study, we analyzed the ARPC1A gene, a member of the actin-related ARP2/3 complex family, in periodontitis tissue.

ARPC1A serves crucial roles in various cellular activities regulating cell motility, an important player in actin polymerization. Reassembly of the actin cytoskeleton is essential for invasive cell migration. The cytoskeleton is particularly important for cells of the immune system, as many essential actions, including migration, phagocytosis, activation, secretion, and cell-cell interaction, depend on cytoskeletal mobilization. In recent studies, insufficient or abnormal expression of proteins involved in the regulation of the actin cytoskeleton has been increasingly associated with immunodeficiency or autoimmune/inflammatory diseases (Lafouresse et al., 2013).

In studies, inadequate or abnormal expression of proteins involved in the regulation of the actin cytoskeleton has been increasingly associated with immune and/or autoimmune/inflammatory diseases. N-WASP, which shares the same pathogenesis with periodontitis, is associated with psoriasis. Psoriasis has the same risk factors and inflammatory processes as periodontitis. N-WASP regulates the actin cytoskeleton through the activation of the Arp2/3 complex and is involved in the same signaling pathway as ARPC1A. By evaluating all these data, we analyzed the ARPC1A gene, a member of the ARP2/3 complex family, in periodontitis tissue. In our study, when the expression level of ARPC1A gene in periodontitis tissue was compared with normal tissue, it was found that there was an increase in periodontitis tissue, but this increase ($p=0.433$, value $p>0.05$) was not statistically significant. Although no statistically significant difference was observed in the study, the expression level of the ARPC1A gene in periodontitis tissues was found to be lower in some diseased samples and higher in others compared to controls. These variations may be attributable to the presence of unidentified systemic conditions in certain patients. We believe that studies with many more parameters such as age, plaque formation, bleeding score and gingival recession in patients and with an increased number of patients will contribute to the understanding of the pathogenesis of the disease. Our results can be supported by further studies with an increased number of patients.

5. Conclusions

This study provides a molecular basis for the link between periodontitis and ARPC1A. At the same time, we believe that understanding the molecular mechanism of an inflammatory autoimmune disease such as periodontitis will be beneficial for the diagnosis and treatment of other diseases that develop with the same processes. The absence of a specific study investigating the relationship between the ARPC1A gene and the development of periodontitis makes our study unique. We believe that our study will fill this gap in the literature and form a basis for other studies. We believe that our study results can shed light on more specific supportive studies and provide a molecular basis for personalized treatment options to be performed with advanced technological methods.

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