A General Sight about Linking PARP-1 and NFKB1 Variations to the Inflammatory Events

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polymorphisms of the promoter region (-410 C/T (rs2793378) and -1672 G/A (rs7527192)) in PARP-1 gene have been also investigating in the inflammatory situations [13,14].

We determined that, analyzing the studies about both of them may be a senseful and beneficial way to understand the interactions of these two genes in **inflammatory and autoimmune disorders.** In this brief review, we have summarized several supporting lines of evidence that PARP-1, NFKB1 and NFKBIA gene variants might have roles for pathogenesis of several related inflammatory and autoimmune diseases.

PARP-1

Poly (ADP-ribose) polymerase-1 (PARP-1) is the most celebrated and well–characterized member of the PARP family [15]. PARP-1 is involved in various cellular processes such as gene expression, amplification, malignant transformation, differentiation, division, DNA replication, mitochondrial function, DNA repair, chromatin replication, transcriptional regulation, cell death, and inflammatory response [16,17]. The human PARP-1 gene includes 23 exons spanning 43 kb and is located in 1q41–q43. The PARP-1 enzyme is a 116-kDa protein and contains three main domains: an N-terminal, DNA-binding domain (42 kDa) that contains a nuclear localization signal (NLS); a central automodification domain (16 kDa); and a C-terminal, catalytic domain (55 kDa). PARP-1 also enables various

NFKB1 and PARP-1 polymorphisms in relation to inflammatory diseases

Rheumatoid arthritis and systemic lupus erythematosus

RA and SLE are complex diseases characterized by chronic inflammation with contributions of systemic autoimmunity [10,70]. The PARP-1 and NFKB1 genes may be the suitable candidate genes for investigating autoimmune and inflammatory disorders such as RA and SLE as genetic aspect.

Our previously published data suggest, rs1136410, the polymorphic marker localized to the coding region of the PARP-1 gene, is not related to development of RA in Turkish population [10] (Tables 1 and 2). In other clinical study, AA (mutant) genotype in rs1136410 has shown to be related with arthritis in 350 Korean SLE patients and 330 healthy controls [71]. Ala allele of rs1136410, leading to decreased enzymatic activity of PARP-1, was described [19]. In addition, according to the study which included 213 Spanish RA patients and 242 healthy subjects as controls, CA microsatellite repeat and rs2793378, C1362T variants in the promoter region of the PARP-1 gene, found to be a risk factor for susceptibility to RA in the Spanish population [14].

Many researchers have also pointed that variations within the NFKB1 gene could potentially influence the function of NFKB protein and in turn the process of inflammation. Recently, it has been shown that NFKB has been activated in rheumatoid arthritis synovium and resembled in inflammation mediators from RA, suggesting a role in the control of inflammation [72]. According to Simmonds et al. the inhibition of the NFKB pathway is believed to have a potential as a therapeutic target in RA [42].

Wong et al. showed that, the activation of NFKB is decreased in SLE patients but not in RA patients [40]. According to Orozco et al. NFKB1 SNP rs28362491 did not play a role in the development of RA and SLE in Spain population including 272 RA patients, 181 SLE patients, and 264 healthy individuals [55]. However, homozygosity of del allele of rs28362491 has an increased risk of RA in Spain population [73]. Besides, del/ins genotype was found as a decreasing risk for SLE in 224 SLE patients and 256 control subjects Chinese population [70].

Hashimoto's thyroiditis

Hashimoto's Thyroiditis (HT) is a chronic inflammatory and autoimmune disease of thyroid gland affected by interaction of multiple genes and various cytokines. Human leukocyte antigen (HLA) and immune regulatory genes (i.e., CTLA-4 and others) have been studied as possible risk factors for HT for years [74]. PARP-1 gene becomes a candidate gene for searching immunity as well as HLA and CTLA-4.

As Wang et al. determined, PARP-1 SNP rs1136410 reduces the enzymatic activity of enzyme about 40%, so SNP rs1136410 becomes a considerable variant for understanding the relationship between this gene and inflammatory diseases [19]. In our study, enrolled with 141 HT patients and 150 controls in a group of women in Turkish population, heterozygous genotype (Val/Ala) and Ala allele of rs1136410 and heterozygous (GA) and A allele of rs7527192 were found to be as protective factors against HT [75] (Tables 1 and 2).

On the other hand, we also previously investigated the susceptibility of rs28362491 and rs696 in NFKB1 and NFKBIA genes in HT disease because of the significance of NFKB1 as an immune-related gene. There was no considerable differences in the frequency of genotypes and alleles of these two variants in single However, combining multiple variants resulted in greater predictive power of disease risk. As we analyzed the combined effects of NFKB1 and NFKBIA polymorphisms in 120 HT patients and 190 controls in Turkish population, we found that ins/ins/AG combined genotype had a protective role and this protectiveness was based on G allele of rs696. On the other hand, increasing IL-6 serum levels were accompanied with deletion of rs28362491 in NFKB1 [76] (Tables 1 and 2).

Asthma

Asthma is a common and heterogeneous respiratory disease featured by lasting airway inflammation with bronchial hyper-responsiveness increase and reversible airway obstruction. Epidemiological and twin studies have shown that genetic and environmental factors are both responsible for this disease [77]. It has been suggested that numerous genetic factors are related to the susceptibility for asthma. PARP-1 experiments and therapeutic studies with PARP-1 inhibitors have indicated that an increasing inflammation in various situations such as asthma, pointing PARP-1 as a candidate gene. The protective effect of PARP-1 against asthma development may be related with its decreased enzymatic activity due to Ala 762 variant of Val762Ala polymorphism. It may affect expression of genes involved in inflammatory response. Our findings suggested that, Val allele had 5 times risk for developing asthma in comparison to the patients without the allele. We also found that PARP-1 762 Val/Ala and Ala/Ala genotypes had decreasing risk ability of adult asthma with respect to their wild-type homozygotes by univariate regression analysis model. Therefore, in a Turkish population of 180 controls and 112 patients with asthma, we provide evidence that, an amino acid substitution in a variant of PARP-1 gene had a protective role for asthma [77] (Tables 1 and 2).

Inflammatory airway diseases in humans have been associated with adhesion molecule expression and cytokine, correlating with the activation of NFKB in bronchial biopsies from asthma patients. Park et al. found that, rs2233407 A→T promoter polymorphism in NFKBIA gene was associated with development of atopic asthma by regulation of gene expression at the transcriptional level in 598 asthma patients and 183 controls in a Korean population [78].

Allergic rhinitis

Another chronic inflammatory disease is allergic rhinitis (AR) characterized by mucosal inflammation. The pathogenesis of AR and other allergic diseases are developed by the exposure to irritating complex substances and in response to respiratory allergens [79].

PARP-1 is the probable candidate gene as therapeutic approaches using PARP-1 inhibitors, indicates an improvement of systemic or tissue inflammation. We did not find any differences in allele or genotype frequencies of PARP-1 C410T (rs2793378) and Val762Ala (rs1136410) polymorphisms. However, heterozygote genotype of the promoter polymorphism G1672A (rs 7527192) was significantly found to be associated with the susceptibility to 110 AR patients compared with 130 controls. In haplotype analysis, PARP-1 C410T, G1672A and Val762Ala polymorphisms were not associated with an increased risk for AR. These results proved that the promoter G1672A

Graves' Disease (GD) is an organ specific autoimmune thyroid disorder characterized by diffuse goiter, hyperthyroidism, dermopathy, and an ocular disorder. GD is an autoimmune disorder. Hence it may be affected by a co-operation of multiple genes such as NFKB1, NFKBIA, PARP-1 and cytokines like IL-1β, IL-6, and TNF-α. It has been found as high as 79% contribution of genetic factors in GD development. We suggest that, PARP-1 and NFKB1 gene polymorphisms may be risk factors for developing GD and ophthalmopathy [80].

We found that, by means of rs7527192, patients with GG genotype and carriers of G allele were in a risk group of having GD. Patients with GG genotype and G allele have an increased risk of having the disease by 2.4 and 1.5 fold, respectively. We did not find any significant relationships or differences in patient and control groups for rs2793378, but found n ł ᴬᵐM find any
significant relationships or differe" m P Patients

Grave's Disease							
rs28362491	50 (33.3)	80 (53.3)	20 (13.3)	40 (33.3)	63 (52.6)	17 (14.1)	>0.05
rs696	18 (12)	100 (66.7)	32 (21.3)	14 (11.6)	77 (64.2)	29 (24.2)	

Behcet's Disease					
rs28362491	ins,213 (56)	del,167 (44)	ins,124 (70)	del,54 (30)	0.004
rs696	A,180 (48)	G,198 (52)	A,72 (42)	G,104 (58)	>0.05

Table 2: Allele assessment of SNPs rs1136410, rs7527192, rs2793378, rs28362491, and rs696 in PARP-1 and NFKB1 genes in autoimmune diseases in Turkish population.

NFKB1 and PARP-1 as a Therapeutic Target for Diseases

Researchers have gained new insights into the relationship of DNA damage and autoimmune and inflammatory diseases regarding immune-related genetic factors. PARP-1 is included in the list of most important genetic factors for better is!

polymorphisms, angiographically verified coronary artery disease and myocardial infarction in South Indian patients with type 2 diabetes mellitus. Thromb Res 130: e259-65.

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