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Functional variations of *NFKB1* and *NFKB1A* in inflammatory disorders and their implication for therapeutic approaches

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Abstract

Nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) is a sophisticated transcription factor that is particularly important in the inflammatory response, but it regulates more than 400 individual and dependent genes for parts of the apoptotic, angiogenic, and proliferative, differentiative, and cell adhesion pathways. NF-κB function is directly inhibited by the binding of inhibitor of κB (IκB), and the imbalance between NF-κB and IκB has been linked to the development and progression of cancer and a variety of inflammatory disorders. These observations might broaden the horizon of current knowledge, particularly on the pathogenesis of inflammatory diseases considering the roles of NF-κB and IκB. In this context, we focus this narrative review on a comparative discussion of our findings with other literature regarding variations of *NFKB1* and *NFKB1A* and their association with susceptibility to widespread inflammatory disorders (such as atherosclerosis, morbid obesity, Behçet syndrome, Graves disease, Hashimoto disease) and common cancers (such as gliomas).

Keywords: I-kappa B proteins; inflammation mediators; neoplasms; NF-kappa B; polymorphism; single nucleotide

Inflammation, a requisite process in the pathogenesis of several disorders, is coupled with the enhanced gene expression of the immune regulators [1]. Nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), a prominent pleiotropic transcription factor, organizes a broad range of genes required for the distinct processes of the inflammatory and immune responses by displaying critical roles in the development of autoimmunity [2]. The NF-κB family in mammals consists of five Rel homology domain-containing proteins in mammals, namely, p50/p105, p65/RelA, p52/p100, RelB, and c-Rel,

present in a homo- or heterodimerized formation. The most commonly observed heterodimer forms of NF-κB are the p50 and the p65 (also known as RelA), encoded by *NFKB1 and NFKB2, respectively. NFKB1*—having 24 exons, spanning 156 kb, and being strongly associated with inflammation and immunity—encodes the genes for the p50 and p105 NF-κB isoforms, which are always-ready transcription regulators remarkable for their association with the pathological states of many diseases [2, 3]. *NFKBIA* (NF-κB inhibitor, α), having 6 exons and located on chromosome 14q13, instead, encodes

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the alpha subunit of the inhibitor of κB (IκBα), a typical form of the IκB family that naturally sequesters the NF-κB proteins within the cytoplasm [4].

The variations present in the genes responsible for the synthesis of the NF-κB (*NFKB1*) and IκB proteins (*NFKB1A*) are thus considered to exist in inflammatory disorders and cancer pathogenesis. So far, the U.S. National Center for Biotechnology Information (NCBI) database has 25,820 single-nucleotide polymorphisms (SNPs) reports on *NFKB1* (accessed March 25, 2020). The most studied variation rs28362491 (−94 ins/del ATTG) is present within the promoter region of *NFKB1* (**Figure 1**). Owing to its presence between two essential promoter regulatory elements, only this variation (of the 6 variations is known to have a likely functional behavior modulating nuclear protein binding to the *NFKB1* promoter site [5].

IκBα, conversely, includes a number of polymorphisms. NFKBIA −881 A/G, −519 C/T, and −826 C/T variations, respectively located at putative binding sites for transcription factors retinoic acid-related orphan receptor α, CCAAT/enhancer-binding protein, and GATA binding protein 2, may regulate expression of the genes for IκBα and indirectly NF-κB activation [5, 6]. Another well-studied variant, namely, rs696 (3′ untranslated region [UTR] A→G polymorphism; **Figure 1**), alters NF-κB activity [7]. There is a general agreement on the involvement of an imbalance of IκB and NF-κB in a wide variety of diseases, yet, the mechanisms behind how functional changes within numerous genes are associated with disease development remain to be elucidated. We consider that evaluation of studies of *NFKB1* and *NFKB1A* polymorphisms may open a beneficial window to establish the connection between these two genes, if any, in inflammation-related diseases.

The present narrative review is based mainly on a comparative discussion of our findings with other literature regarding variations of *NFKB1* and *NFKB1A* and their association with susceptibility to widespread inflammatory disorders (such as atherosclerosis [AT, morbid obesity, Behçet syndrome, Graves disease, Hashimoto disease) and common cancers (such as gliomas).

NFKB1 and *NFKB1A* variants and their relation to inflammatory disorders

As a widespread transcription factor in every mammalian cell dominating the gene expression of many acute-phase proteins such as cell adhesion molecules, chemokines, growth factors, and cytokines [8, 9], NF-κB manages the gene products required for both adaptive and innate immune responses. NF-κB is activated after intra- or extracellular stimuli, such as viral products, cytokines, and ultraviolet irradiation [10, 11]. In an unstimulated phase, NF-κB proteins are present within the cytoplasm in their sequestered homo- or heterodimer formation and interact with IκB inhibitors [12].
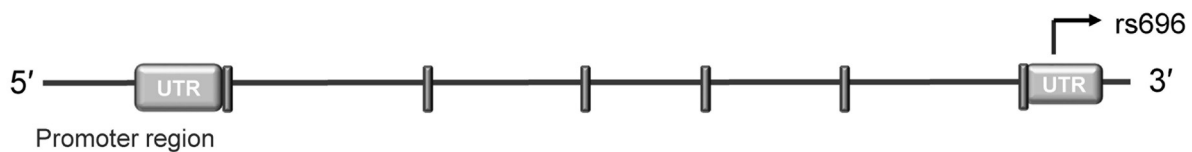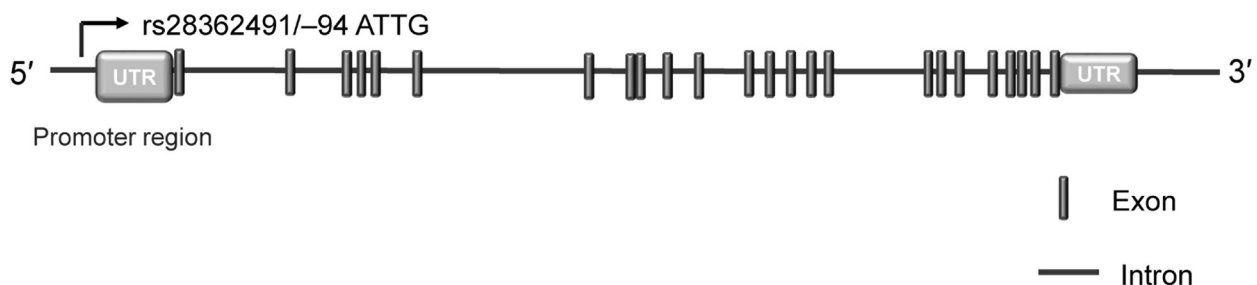
Figure 1. *NFKB1A* 3′-UTR (rs696) and *NFKB1* −94ATTG (rs28362491) polymorphisms. UTR, untranslated region.

NF-κB signaling is critically involved in both cancer development and inflammation pathways first by enhancing antiapoptosis, proliferation, and angiogenesis and, second, by repressing immune responses. NF-κB performs its unique roles using two distinct signaling pathways, i.e., noncanonical and canonical pathways. The noncanonical pathway has a completely different signaling process, such as involving variable signaling molecules and leading to p52/RelB dimer activation [2, 13]. By contrast, in the canonical pathway, the phosphorylation of two N-terminal serines of IκBα by IκB kinase (IKK) is followed by its ubiquitination and proteasomal degradation, finally leading to the nuclear translocation of dimerized p50/c-Rel and p50/RelA of NF-κB complexes. After activation, the NF-κB/RelA unit induces the transcription of several proinflammatory genes, displaying its prominent role through inflammation.

Although the purpose of this chapter is to review *NFKB1* and *NFKB1A* variants and their relation to specific inflammatory disorders, before proceeding, it is useful to mention the general relationship of *NFKB1* with some other diseases. In neurodegenerative diseases such as vascular cognitive impairment, NF-κB contribution may lead to demyelination, axonal loss, and memory impairment of astrocytes [14]. By contrast, in healing processes, elevated NF-κB activation through *NFKB1* deletion enriches aggregation of both myofibroblasts and macrophages, leading to enhanced collagen deposition [15]. This finding is in agreement with Stone's findings in a mouse model of multiple sclerosis, which showed NF-κB-associated protection of oligodendrocytes against inflammation [16].

Atherosclerosis

Being described as immune activation within the arterial wall in the presence of inflammatory mediators, atherosclerosis (AT) is believed to be a chronic immunoinflammatory disease. As NF-κB is accepted as regulating the expression of a wide range of genes cooperating with the distinct aspects of atherosclerotic pathogenesis [17], *NFKB1* may be an appropriate candidate for investigating arterial wall inflammation-related disorders such as atherosclerosis and coronary artery disease (CAD) [18]. Özbilüm et al. [19] draw our attention to alveolar epithelial cells as a piece of evidence for the mechanism of the IκBα–NF-κB-dependent anti-inflammatory effect. Our results differed from those of Özbilüm et al.: we reported that rs28362491 polymorphism has no association with AT; however, the AA genotype of the rs696 polymorphism of *NFKB1A* gene was considerably elevated in atherosclerotic patients in a Turkish population. Moreover, the combined

genotype association of rs28362491 and rs696 polymorphisms with atherosclerosis was not statistically significant, suggesting that these two polymorphisms together play no role in the pathogenesis of atherosclerosis [20]. Although the findings represent *NFKB1A* rs696 polymorphism as a novel marker of susceptibility to atherosclerosis, the results from such analyses should be treated with caution because of the limited sample size.

NFKB1A −826 C/T promoter polymorphism was reported as a risk factor for susceptibility to CAD, but *NFKB1A* −297C/T and −881A/G polymorphisms had no associations, in a Turkish population [19], whereas Lai et al. [21] found that rs28362491 polymorphism had a critical role and was related to functional interleukin (IL)-6 expression in a Chinese Uygur population. In an Iranian subpopulation, *rs28362491* polymorphism, but not *NFKB1A* −826C/T polymorphism, was found to be significantly associated with the development and severity of CAD as an independent risk factor [22]. In research into an *NFKB1* promoter variant in coronary heart diseases (CHDs) of people of European ancestry, Vogel et al. [23] reported that a variant previously found to lead to partial depletion of NF-κB p50 is associated with CHD. The participation of rs28362491 polymorphism in CAD in Korean and Chinese populations was reported more recently [24, 25]. There is general agreement that inflammation occupies a pivotal role in both initiation and progression of coronary atherosclerosis is the necessarily condition for CHD. Jin et al. [25] concluded that the del/del genotype of rs28362491 is associated with the risk and the severity of the disease.

NF-κB is a good illustration of two sides of the same coin. While a majority of authors mention that NF-κB activation is associated with normal conditioning, Peterson et al. [26], using a murine model of Duchenne muscular dystrophy, report the importance of NF-κB blocking in normal cardiac function.

MicroRNAs (miRNAs) are noncoding, single-stranded RNAs around 20–22 nucleotides in length, which organize gene expression through posttranscriptional repression [27] and are members of a large array of remodification processes, such as cellular differentiation, proliferation, development, immunity, apoptosis, and angiogenesis [28–30], but these are linked to several chronic and acute diseases, such as heart diseases, cancer, acute organ injury, autoimmunity, and ischemic stroke, when they are dysregulated [31–34]. In a major advance for understanding inflammatory diseases, Taganov et al. [35] noted that an NF-κB-targeting actor, namely, mir-146a, enhances the inflammatory response by being used as a feedback inhibitor of NF-κB activation. Generally, the expression level of mature miRNA-146a may be regulated by SNPs of pre-miR-146a. An SNP located in the stem region, namely, rs2910164, may modify the transcription of genes involved

putatively in the pathogenesis of inflammation-related diseases, such as cardiovascular diseases, reducing the total amount of mature miRNA [36, 37].

More recently, literature has emerged that describes consistent findings for mir-146a SNP. Xiong et al. [38] reported that a G-to-C substitution in the precursor of mir-146a seems to lead to the enhanced expression of mature mir-146a. This is in agreement with findings by Guo et al. [39] that the function of TH-1 cells, which is necessary for the progression of acute coronary syndrome, is stimulated by increased mature mir-146a expression levels.

The following findings also seem to be consistent with this research, which found significant differences within atherosclerotic patients compared with control subjects, concerning pre-miR-146a rs2910164 polymorphism. The G allele and GG genotype were associated with an elevated risk for atherosclerosis thus pre-miR-146a rs2910164 is assumed to play a role as a novel marker for possible atherosclerosis susceptibility [20].

Morbid obesity

The link between obesity and obesity-related disorders can be explained by inflammation, which is noticed as an elevation in circulating levels of C-reactive protein (CRP) with low-grade inflammation [40, 41]. The debate about the association of *NFKB1* with obesity has gained fresh prominence, with many arguing that NF-κB is weakly initiated in a nonobese murine model of type 1 diabetes [42], whereas NF-κB is directly correlated with pancreatic β-cell failure within diabetes [43]. However, we previously concluded that the ins allele of *NFKB1* rs28362491 and/or ins/ins genotype is related to morbid obesity in a Turkish population [44]. These findings are in contrast to those of Stegger et al. [45], who found no substantial interaction between rs28362491 and gluteofemoral, abdominal, and general obesity in a Danish population.

Morbid obesity is correlated with elevated circulating systemic acute-phase proteins, namely, CRP, and the expression of CRP is regulated by the p50 homodimer of *NFKB1*. We found that the rs28362491 deletion variant tends to decrease the p50 subunit level and that increased serum CRP levels are correlated with *NFKB1* rs28362491 polymorphism [46]. By modulating serum levels of CRP, this polymorphism may be correlated with morbid obesity.

There is good evidence for an association among toll-like receptor (*TLR*) polymorphisms, hepatic fat accumulation, and chronic inflammation, and the NF-κB gene appears to play a key role. We reported that *TLR2* variants, such as rs5743708

(G/G), and high levels of liver enzymes, such as alanine transaminase, alkaline phosphatase, aspartate transaminase, and γ-glutamyl transpeptidase, are associated with high levels of CRP [44]. These results are important for 2 main reasons. First, detecting the ins allele of rs28362491 and Arg753Gln allele of rs5743708, combined with a high level of CRP, may offer better treatments in the future. Second, *NFKB1* may be useful to monitor both the course and severity of liver disease, suggesting new trends of therapies for these conditions.

Male infertility

Male infertility accounts for approximately 50% of infertility cases, even though 60% of whole infertility cases are idiopathic [47]. Severe oligozoospermia or azoospermia is responsible for most idiopathic male infertility. The interaction between the egg and the sperm is a key point, but the molecular mechanisms of egg–sperm membrane protein binding and fusion reactions are not fully clarified.

NFKB1 is a candidate gene in spermatogenesis, whose failure may lead to male infertility [48, 49]. The relationship of the variants of the promoter sites of *NFKB1* with numerous diseases has been studied widely. Ranganathan et al. [50] have associated decreased *NFKB1* expression with poor sperm production.

The E-cadherin short interfering RNA (siRNA) is known to trigger the stimulation of NF-κB transcriptional activity [51]. α-Catenin and E-cadherin are validated to be good indices of infertility [52]. Hernandez Gifford et al. [53] proposed anti-catenin/anti-cadherin antibodies for male contraception, and Purohit et al. [54] reported the absence of E-cadherin on the head domain of spermatozoa from oligospermic individuals; however, as yet, the precise mechanisms of both recognition and fusion processes remain to be elucidated. We found increased risk of development of male infertility associated with the presence of the ins allele of *NFKB1*. Moreover, in the context of low E-cadherin expression, *NFKB1* rs28362491 ins/ins and del/del genotypes are likely to display an essential role in the case of susceptibility to oligospermic male infertility [55]. In other works, we were not able to find any correlation of rs28362491 within *NFKB1* or the rs696 polymorphisms within *NFKB1A* in cases of elevated apoptosis in oligospermia. However, we concluded that the rs28362491 heterozygosity is likely to play a protective role by altering oligospermia susceptibility [56]. Consistent with these findings, in the context of E-cadherin and fibronectin levels, we found that the insertion allele within the promoter region of *NFKB1* is presumably a key function in the susceptibility to normospermic male infertility [57].

There is other evidence to suggest that the NF-κB also contributes to female infertility. In a murine model, Wang et al. confirmed the idea that intrauterine adhesion results in impaired pregnancy and concluded that NF-κB activation is notably increased within the endometrial tissues of patients with Asherman syndrome [58].

Hashimoto disease

Hashimoto disease is a common chronic inflammation-based disorder present in the thyroid gland influenced by the interplay between various cytokines, and the potential risk factors for Hashimoto disease have been studied widely for decades [59].

As NF-κB is at the center of all autoimmune diseases, and since inflammation is inevitable, we have previously analyzed the associations of polymorphisms of rs28362491 within *NFKB1* and rs696 within *NFKBIA* with susceptibility to Hashimoto disease. There was no significant association between the frequency of the alleles of these two variants and the genotypes. In a combined genotype analysis of *NFKB1* and *NFKBIA* polymorphisms, instead, the ins/ins/AG combined genotype was negatively associated with Hashimoto disease, which predominantly depends on the G allele of rs696 in the Turkish population. In the presence of at least one G allele, the IL-6 levels were also higher in patients with the del/del genotype [60]. Elevated serum IL-6 levels were correlated with the del allele of rs2836249. Therefore, polymorphism of the functional *NFKB1* rs28362491 promoter was significantly associated with modulated IL-6 levels in the population with Hashimoto disease [61].

Graves disease

Graves disease is classified as a distinctive organ-specific inflammatory and autoimmunity-based disease of the thyroid, defined by dermopathy, hyperthyroidism, an ocular disorder, and especially diffuse goiter. At least 79% of genetic factors are involved in this disorder; cooperation between several inflammation-related genes, such as *NFKB1* and *NFKBIA*, and cytokines, may have an impact on the development of Graves disease. An association study within a Turkish population found that the rs28362491 del/ins genotype is a possible candidate variation for the development of Graves disease, whereas the ins/ins genotype is likely to play a protective role in this disorder. By contrast, in the case of rs696, there were no statistical differences between the groups [62]. The levels of cytokines IL-1β, IL-6, and tumor necrosis factor (TNF)-α showed remarkable associations with variations in *NFKB1* rs28362491. Kurylowicz et al. [63] found that susceptibility to Graves disease is associated with *NFKB1* rs28362491 polymorphism within a Polish population.

Behçet syndrome

Behçet syndrome is both a systemic autoimmune disorder and a chronic inflammatory disease defined by ocular inflammation, recurrent vasculitis, oral and genital ulcers, and skin lesions [64]. Although there is some evidence for the involvement of both environmental and genetic factors, Behçet syndrome remains classified as a disease of unknown origin. *NFKB1* and its inhibitor, *NFKBIA*, are important actors in the inflammatory cascade of Behçet syndrome.

The promoter region polymorphisms of *NFKB1* in Behçet syndrome could lead to modified *NFKB1* expression, which then promotes altered inflammatory cytokine transcription and might clarify the elevated expression and serum concentrations of these cytokines. In an association study in a Turkish population, the association of *NFKB1* rs28362491 polymorphism with the ins allele and ins/ins genotype of rs28362491 is found to increase susceptibility to Behçet syndrome by 1.8- and 2.5-fold, respectively [65] (**Tables 1 and 2**). There appears to be no doubt that NF-κB inhibition is caused by binding of an inhibitor (IKBα) that is encoded by *NFKBIA,* and any instability of this binding may lead to progression of inflammatory diseases. Hung et al. [67], in their study of Behçet syndrome, found an association with *NFKBIA* promoter polymorphisms, including –826 T/T, –826 C/T, 519C/T, and –881A/G, and –550A/T, and reported a correlation with the –826 T/T genotype and characteristic skin lesions. Consistent with these studies, we observed an rs696 AA genotype within *NFKBIA* as a factor that leads to a 2.5-times-increased risk for development of Behçet syndrome [65]. By contrast, assuming them as variations, Kaustio et al. [68] associated *NFKB1* mutations, such as I553M and H67R, with Behçet syndrome-like phenotypes.

Glioma

Elevated NF-κB activation has also been related to cancer progression [69]. In cancer, the process that controls gene expression in response to inflammatory stimuli combines its survival with both its phenotype and function with the rest of the tissue [70]. This is generally apparent in strictly compromised regulation of NF-κB activity, which enables abnormal cohorts of the NF-κB target gene expression in cancer cells [71]. The conclusion is not only that the cells of surrounding

Table 1. Genotype assessment of SNPs rs28362491 within *NFKB1A* and rs696 within *NFKB1* in inflammatory disorders and glioma in the Turkish population

Study	Controls, n (%)			Patients, n (%)			*P*
	WW	WD	DD	WW	WD	DD	
Atherosclerosis [39]							
rs28362491	46 (32)	74 (51)	25 (17)	49 (33)	65 (43)	36 (24)	>0.05
rs696	20 (14)	82 (56)	43 (30)	33 (22)	65 (43)	52 (35)	0.02
Morbid obesity [46]							
rs28362491	73 (35)	108 (52)	26 (13)	92 (46.5)	86 (43.5)	20 (10)	0.03
Male infertility [57]							
rs28362491	45 (30)	83 (55)	22 (15)	59 (39)	63 (42)	28 (19)	0.03
rs696	25 (16.7)	84 (56)	41 (27.3)	24 (16)	94 (63)	32 (21)	>0.05
Hashimoto disease [61]							
rs28362491	50 (27)	113 (69)	27 (14)	26 (22)	76 (63)	18 (16)	>0.05
rs696	26 (14)	130 (68)	34 (18)	23 (19)	74 (62)	23 (19)	>0.05
Graves disease [62]							
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)	>0.05
Behçet syndrome [65]							
rs28362491	50 (27)	113 (59)	27 (14)	43 (48)	38 (43)	8 (9)	0.003
rs696	25 (14)	130 (68)	34 (18)	18 (20)	38 (43)	33 (37)	0.033
Glioma [66]							
rs28362491	52 (24)	149 (66.2)	22 (9.7)	48 (40)	63 (52.5)	9 (7.5)	0.003

SNP, single-nucleotide polymorphism; WW, wild homozygote (ins-ins for rs28362491, AA for rs696); WD, heterozygote (ins-del for rs28362491, AG for rs696); DD, mutant homozygote (del-del for rs28362491, GG for rs696).

tissue change their function and fail to support the organism exclusively, but also that the cancer cells function abnormally. Instability of NF-κB and IκB interactions have been observed generally in several diseases; however, the mechanisms behind the association between certain variations within different genes and cancer development remain elusive.

Glioblastoma (glioblastoma multiforme), accounting for less than 2% of all human cancers, is the most malignant primary brain tumor in the adult nervous system [72, 73]. Although the origin of glioblastoma development is still unknown, some genetic modifications that lead to aberrant activity of pathways, such as proliferation, apoptosis, and cell cycle regulation, are considered to contribute to their pathogenesis [74, 75].

Deregulated NF-κB activity has become a central issue in the development of most human cancers [76, 77]. NF-κB organizes cancer aggressiveness and development by increasing angiogenesis, antiapoptosis, and tumor proliferation and by reducing the immune response and thus managing pathogenetic regulation [78].

Numerous studies advocate the idea that several malignant tumor types, including glioblastomas, have strong connections with NF-κB cascades [5, 79]. We have evaluated 120 glioma samples and 225 controls. There are significant associations between insertion allele carriers and elevated risk of gliomas [66] (**Tables 1** and **2**). Previous studies reported conflicting results. Meta-analyses such as those conducted by Sun et al. [80] and Yu et al. [81], for instance, concluded that the deletion allele is both a risk and a protection against cancer susceptibility in populations with European or Asian ancestry. The rs28362491 del/del genotype appears related to bladder, prostate, oral, and ovarian cancers but not with hepatocellular carcinoma [82]. Concetti and Wilson reviewed the status of this polymorphism and concluded that rs28362491 polymorphism is disadvantageous for colorectal, gastric, liver, bladder, and thyroid cancers but advantageous for prostate, ovarian, and cervical cancers [83]. Similarly, rs28362491 polymorphism was found to be associated with decreased cancer risk [84], as well as the development of head and neck cancer [85], and rs696 polymorphism was found to be associated with colorectal cancer risk [86].

Various *NFKB1* variations in specific pathways are associated with cancer progression, but blocking a signaling pathway in multifactorial diseases such as cancer may not be

Table 2. Assessment of SNP alleles rs28362491 within *NFKB1A* and rs696 within *NFKB1* in inflammatory disorders and glioma in the Turkish population

Study	Controls		Patients		P
	Allele, n (%)		Allele, n (%)		
Atherosclerosis [39]					
rs28362491	ins, 166 (57)	del, 124 (43)	ins, 163 (54)	del, 137 (46)	>0.05
rs696	A, 122 (42)	G, 168 (58)	A, 131 (44)	G, 169 (56)	>0.05
Morbid obesity [46]					
rs28362491	ins, 254 (61)	del, 160 (39)	ins, 270 (68)	del, 126 (32)	<0.05
Male infertility [57]					
rs28362491	ins, 173 (58)	del, 127 (42)	ins, 181 (60)	del, 119 (40)	>0.05
rs696	A, 142 (47)	G, 158 (53)	A, 134 (44.7)	G, 166 (55.3)	>0.05
Hashimoto disease [61]					
rs28362491	ins, 213 (56)	del, 167 (44)	ins, 128 (53)	del, 112 (47)	>0.05
rs696	A, 180 (48)	G, 198 (52)	A, 120 (50)	G, 120 (50)	>0.05
Graves disease [62]					
rs28362491	ins, 180 (60)	del, 120 (40)	ins, 143 (59.6)	del, 97 (40.4)	>0.05
rs696	A, 136 (45.3)	G, 164 (54.7)	A, 105 (43.8)	G135 (56.3)	>0.05
Behçet syndrome [65]					
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
Glioma [66]					
rs28362491	ins, 257 (57.1)	del, 193 (42.9)	ins, 159 (66.3)	del, 81 (33.7)	0.01
rs696	A, 180 (48)	G, 198 (52)	A, 72 (42)	G, 104 (58)	>0.05

SNP, single-nucleotide polymorphism.

appropriate because the polymorphisms can be advantageous for the individual.

NF-κB as a therapeutic target for inflammatory diseases and cancer

Abnormal activation of NF-κB is commonly noticed in several inflammatory diseases and cancers. Thus, to advance therapeutic applications in cancer and inflammatory diseases, there has been increased interest in inhibiting NF-κB signaling. Many natural products used for their alleged anti-inflammatory and cancer-preventing activities have been found to inhibit NF-κB; therefore, dysregulations in NF-κB signaling may potentially be connected to certain cancers and inflammatory diseases [87, 88]. Characterization of these natural products is warranted.

In lymphoid, colon, breast, skin, and prostate cancers, prior persistent activation of NF-κB signaling is found; hence, the therapeutic inhibition of NF-κB signaling in malignant cells may provide a strategy for anticancer drug development.

Miller et al. screened approximately 2,800 clinically approved drugs to identify small molecule inhibitors of NF-κB signaling. Drugs such as bithionol, emetine, tribromsalan, metformin, lestaurtinib, sunitinib malate, and narasin were observed to inhibit NF-κB signaling through inhibition of IκBα phosphorylation, whereas bortezomib, chromomycin A3, and ecteinascidin 743 act through other mechanisms [89]. According to these findings, many currently approved pharmaceuticals have unpredictable impacts on the NF-κB signaling cascade; therefore, more detailed characterization of approved drugs might broaden the horizon of knowledge of their molecular mechanisms. Yamamoto et al. [90] highlighted a type of drug utilized in the treatment of inflammatory disease, which has an impact on NF-κB activity, which, in turn, leads to numerous therapeutic strategies aimed at blocking NF-κB activity.

According to a survey conducted by Tak and Firestein [91], the mode of action of corticosteroids, preferred in the treatment of psoriasis, asthma, rheumatoid arthritis, and inflammatory bowel disease, for instance, is presumably modulated by inhibiting NF-κB activation. Similarly,

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nonsteroidal anti-inflammatory drugs, such as leflunomide and sulfasalazine, inhibit nuclear translocation of NF-κB by inhibiting IκBα degradation [91]. The most preferable NF-κB-related inhibitors are selective IκB kinase inhibitors that block the catalytic activity of IκB kinase; and hence the IκBα phosphorylation; proteasome inhibitors; inhibitors that prevent nuclear translocation of NF-κB subunits; and drugs that block the DNA-binding activity of NF-κB. Kiliccioglu et al. [92], e.g., reported the importance of NF-κB and Hsp-27 inhibition, along with therapies for inhibition of androgen receptor variant-7. However, because of the lack of specificity of these drugs, relatively high concentrations were required to achieve strong inhibition of NF-κB.

We concluded in an in vitro study that metformin serves as a potential agent for breast cancer treatment in a dose-dependent manner. We observed that metformin blocked NF-κB through the prevention of the latter's nuclear translocation and reduced the expression of proteins such as matrix metalloproteinase (MMP)-2 and MMP-9, which are required for the invasion in breast cancer [93]. Metformin might have a protective function against breast cancer by regulating NF-κB.

Conclusion

There are differences between mechanisms of regulating *NFKB1* and *NFKB1A* and the autoimmune diseases discussed. We sought to supply a general update on the association of *NFKB1* and *NFKB1A* variations with their inhibitory effects on inflammatory diseases, as blocking NF-κB activation may open a path to new therapies. Despite its exploratory nature, the analysis of these polymorphisms undertaken here offers some insight into new therapies for, and has extended our knowledge of, the genetic variation in inflammation-related disorders.

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