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Interferon regulatory factor 5 in Rheumatoid arthritis and systemic lupus erythematosus

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Interferon regulatory factor 5 (IRF5) has been described as an important factor in regulating inflammatory response and a key transcription factor in the immune system. In antiviral response, IRF5 promotes the expression of type 1 interferon (IFN) and is also important in the differentiation of macrophages towards pro-inflammatory phenotypes, regulating B-cell maturity and antibody production. Some cancer patients treated with IFNα manifest symptoms resembling systemic lupus erythematosus (SLE). An important mechanism in this response is IRF5 that triggers apoptosis. Herein, we discuss the functional importance of IRF5 in rheumatoid arthritis (RA) and SLE in a setting of polymorphic mutations at the human *Irf5* locus. This paper describes murine models, the lessons of IRF functionality learned from these models, and the consequences of autoimmune diseases. It is hypothesized that modulation of IRF5 activity may be beneficial in autoimmune diseases therapies.

Keywords: Autoimmune disease, Interferon regulatory factor 5 (IRF5), Rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE)

Introduction

The interferon regulatory factor (IRF) family consists of nine members: IRF1, IRF2, IRF3, IRF4, IRF5, IRF6, IRF7, IRF8, and IRF9 [1]. In the 1980s, these proteins were described as transcriptional regulators of type I interferons (IFNs), including *Ifnb* and *Ifna* genes. The function of IRF and the production of IFNβ and IFNα form the first line of defense against viral infection. Type I IFN promotes degradation of viral DNA/RNA, inhibits viral replication and particle assembly, and enhances apoptosis in infected cells. It also enhances the differentiation of dendritic cells (DCs) and polarization of TH1 to enhance the antiviral immune response [2, 3]. The importance of these proteins is highlighted by the existence of viral-encoded IRF homologous of the host IRF, but with no function to circumvent the immune response [4-7]. The IRF protein binds to DNA by conserved N-terminal DNA binding domain, which is known as the interferon-stimulated response element (ISRE) [8]. The IRF also binds other transcription factors to enhance gene expression during the immune response.

The *Ifnb* enhancer includes regulatory elements designated as positive regulatory domains (PRD). The transcription proteins consist of four positive regulatory domains: 1 NFkB dimer (RelA/p50), 1 AP1 complex (ATF2/c-Jun), and 2 heterodimers or homodimers of IRF, and assemble at the *Ifnb* promoter and promotes gene expression [9-14]. Some immune cells such as plasma-cytoid dendritic cells are specialized to produce a large amount of IFNα. In this study, both IRF5 and IRF7 were expressed constitutively and played important roles in IFNα production [15]. In addition to antiviral immune response, IRF proteins could also play crucial roles in transcription regulations and the regulation of other immune responses. More importantly, IRF5 could be produced in different cell types such as macrophages, B cells, and DCs and has been associated with susceptibility to different autoimmune diseases [16].

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Because of its cytotoxic effects, IFNα was used in chemotherapy for cancer patients. However, this treatment resulted in some serious side effects, such as lupus-like symptoms [17]. Prolonged treatment may lead to autoimmune disorders including Grave's disease, autoimmune thyroiditis, autoimmune hepatitis, rheumatoid arthritis (RA), insulin-dependent diabetes mellitus (IDDM), vasculitis, and polymyositis [18, 19]. The IFNα signature was reported in various autoimmune disorders such as systemic lupus erythematosus (SLE) and RA [20]. One of the genes that control IFNα is IRF5, which is also upregulated and activated by IFNα in positive feedback and can induce the expression of apoptotic genes and inflammatory factors that result in autoimmunity [21, 22]. Tumor necrosis factor (TNF)-α is another important proinflammatory cytokine which is regulated by IRF5 [23, 24]. TNFα is described as the most important inflammatory cytokine in the RA joint that induces cartilage damage [25].

SLE is described as a heterogeneous autoimmune inflammatory disease that results in different clinical phenotypes in patients. The antinuclear antibodies (ANA) are detected in most patients and recognize the chromatin components such as double-stranded DNA, nucleosomes, and histones that break self-tolerance, resulting in autoimmune responses [26]. SLE patients also have an IFN signature that correlates with disease severity, and high levels of IFNα have been detected during the peak of the disease [27, 28].

RA is also a chronic autoimmune inflammatory disease that primarily targets the synovial joints. RA joints are characterized by a massive infiltration of leukocytes in synovium that result in chronic inflammation and joint damage due to cartilage destruction [29, 30]. RA synovium contains a variety of activated leukocytes and a wide range of inflammatory molecules such as proinflammatory cytokines including interleukin (IL)-1b, TNFα, and IL-6 that result in chronic inflammation [31]. IRF5 is one of the most important regulatory factors in TNF-α and IFN-α production and is also important in the pathogenesis of both RA and SLE.

This paper discusses the function and regulation of IRF5 in autoimmunity as well as the role of single nucleotide polymorphisms (SNPs) at the *Irf5* gene locus in the context of rheumatoid arthritis and systemic lupus erythematosus. These SNPs could enhance IRF5 expression which also regulates and induces inflammatory responses in autoimmune diseases. The therapeutic strategies based on IRF5 targeting were also analyzed.

IRF5 Gene structure, processing, and regulation

IRF5 is located on chromosome 7q32 which includes 9 coding exons plus 1 noncoding exon in the 5′ untranslated region (UTR). The IRF5 gene has 3 variants of exon 1 (1A, 1B, 1C) that encode alternative promoters (P-V1, P-V2, P-V3) upstream of the start codon in exon 2. The IRF5 transcript splicing with 3 alternative transcript start sites and different variants with multiple exon combinations lead to 9 IRF5 transcript variants with different expression states in various cell types. IRF5-v1, IRF5-v2, and IRF5-v3/v4 are expressed in plasmacytoid dendritic cells and macrophages; however, IRF5-v5 and IRF5-v6 are expressed in human primary peripheral blood mononuclear cells (PBMCs). Other variants are only detected by polymerase chain reaction (PCR) analysis in cancer cell lines [32]. Different variant combinations were detected in autoimmune disease compared with healthy donors, which highlights the importance of gene expression and processing in such diseases [33]. As a result of the alternative splicing pattern, IRF5 transcript variants exhibit distinctive insertion/deletion patterns in exon 6. Because of two constitutively active 3′ acceptor splice sites, 48 bp insertion in exon 6 (known as SV-16) consists of IRF5-v1 and v5. In addition, v1, v3, and v4 have other forms of in-frame deletion (known as indel-10) in exon 6. However, these indels could be at risk in autoimmune diseases by altering the functional activity of IRF5 [34]. The IRF5 proteins also need phosphorylation events to obtain an active form [35]. The IRF5-v3 transcript has an IRF-binding site that binds IRF9 and implies the regulation of IRF5 by other IRF family members [32]. IRF5 expression also induces after granulocyte macrophage-colony stimulating factor (GM-CSF) stimulation in vitro, which reveals the signal transducer and activator of the transcription (STAT) regulation procedure in IRF expression [23, 36, 37]. Other different transcription factors, including PU.1, AP1, PAX5, TCF12, p53, EBF, Myc, IRF4, and NFkB, could also regulate IRF5 expression [38]. Consisting of CpG islands that span the IRF5 promoter region is another important regulatory factor in IRF5 gene expression [39]. The CpG islands are enriched for the Sp1 binding site; in turn, Sp1 also recruits other proteins that are needed for transcription [40]. The CpG islands produce a basal level of transcription and offer an opportunity for rapid expression in immune responses [41]. Methylation of this region leads to the silencing of IRF5 expression in some contexts, such as T cells during immune responses [16]. The epigenetic alteration was seemingly unimportant in such autoimmune disease, but more studies are need in this field [42, 43].

Polymorphism of IRF5 gene

Genome-wide association studies (GWASs) are useful tools for comparing genome sequences in healthy persons and patients to identify gene mutations that alter the risk of diseases. Various SNPs in the IRF5 gene have been reported, and in some cases functional differences or different expression levels were also reported [44, 45]. In many GWASs, the association between IRF5 polymorphisms and predisposition to various autoimmune diseases has been reported. For example, rs2004640 and rs2280714 SNPs were reported to be risk factors for systemic sclerosis [46, 47], rs77571059 is associated with Sjögren's syndrome [48], and rs3807306 and rs4728142 SNPs are associated with MS [49]. These SNPs are correlated with poor pharmacologic responses in MS patients [50]. The rs2004640 and rs3757385 SNPs are associated with RA pathogenesis [51-53]. The rs2004640, rs10488631, rs77571059, and rs10954213 were associated with increased risk of SLE in patients [54]. Most of these alleles could regulate the differentiation of T cells

toward TH1/17/2, are responsible for immune-related disorders, and also highlight again the function of IRF5 in inflammation and autoimmunity [55].

One of the most common polymorphisms in the IRF5 gene locus is rs2004640 in the promoter region of IRF5 and 2bp downstream of exon 1B. Here, the T risk allele causes the splicing of exon 1B to exon 2. When the protective G allele exists, the splice junction is not recognized, and that leads to nonsense-mediated decay [56, 57]. This SNP enhances the expression of v2 and v9, whereas exon 1A is prominent, as usual. The SNPs could increase the risk of autoimmunity by producing greater amounts of IRF5 and IFNα [54, 58]. It has been revealed that some immune cells such as DCs and macrophages that have this SNP produce more inflammatory cytokines, including IL-12p40, TNFα, IL-8, and IL-1β [59]. The other common SNP is rs77571059 which is located 64 bp upstream of exon 1A and described as the CGGGG indel. This polymorphism resulted in an extra binding site for Sp1 which leads to more expression of IRF5 [52]. The functional rs10954213 is also reported in autoimmune diseases. The A risk allele causes polyA site creation, resulting in a shorter 3′UTR and long half-life of IRF5 [60]. The rs10488631 SNP that seems to be more related in autoimmune diseases is located 4 kb upstream of the 3′end of *Irf5* locus [61]. The C risk allele results in IRF5 upregulation and more IFNα production [54, 58]. However, the contribution of this SNP in autoimmune diseases needs to be more closely investigated (Table 1).

IRF5 target genes

The cDNA microarray was used to detect different genes regulated by IRF5 [62]. IRF5 induces various important inflammatory genes during the immune response, including IFNα and IFNβ genes, cytokine and chemokine genes like CCL3 (chemokine (C-C motif) ligand 3), CCL4, CCL5, CCL6, MIP-1α (macrophage inflammatory proteins), and MIP-1β. The genes which participate in cell cycle regulation, cell adhesion, ubiquitin-dependent pathway of degradation, and some pro-apoptotic genes were upregulated by IRF5. IRF5 enhances the expression level of different transcription factors and RNA binding proteins such as poly(A) poly-merase, poly(C)-binding protein, KH domain RNA-binding protein, helicase DEAE box 18, fragile X mental retardation gene, PAI-1 (plasminogen activator inhibitor-1), STAT1 (signal transducer and activator of transcription 1), STAT3, STAT5b, and also other members of IRF like IRF1 and IRF8, gene encoding cellular chaperones like heat shock proteins that are important in antiviral and stress immune responses [15, 62-66]. IRF5 could induce the potent monocyte chemoattractant such as MCP-1, I-309 and initiate the macrophage inflammatory response [66].

Dysregulation of these cytokines is reported in many inflammatory disorders and autoimmune diseases such as SLE, RA, Sjogren's syndrome, and multiple sclerosis (MS) [67-72]. Thus, upregulation of IRF5 may result in inflammation and the development of such disorders.

IRF5 and immune receptor signaling

Toll-like receptors (TLRs) play important roles in immune responses. Stimulatory molecules such as pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) presented by bacteria, fungi, protozoa, viruses, and damaged cells including lipopolysaccharides (LPS), flagellin, peptidoglycans (PGN), lipopeptides, unmethylated CpGs, ssRNA, and dsRNA could activate TLRs and initiate the immune response. Many adaptor proteins are activated in the downstream signaling of TLRs. Eleven members of this family have been recognized in mammals [73, 74]. Various types of TLRs could recognize different PAMPs and DAMPs, but all of them activate three major downstream pathways, i.e. the NF-κB, MAPK, and IRF pathways [63, 75]. Stimulation of TLR3, TLR5, TLR7, and TLR9 with their ligands on DCs and macrophages leads to IRF5 expression and activation [63, 76]. In viral immune responses, pDCs produce a large amount of IFNα due to constitutively high expression levels of TLR7 and TLR9 which are correlated with IRF5 expression. The silencing of IRF5 by siRNAs disrupts TLRs signaling and reduces the expression of IFNα/β and other pro-inflammatory molecules such as TNFα, IkBζ, CXCL2, IL-6, and IL-12p40 [15, 63, 77-79]. In addition to TLR signaling, other immune receptors could enhance IRF5 signaling in immune cells. Fas and TNF-related apoptosis-inducing ligand (TRAIL) stimulation also activates IRF5, which leads to apoptosis and is more specific to activated dendritic cells [80]. Signaling from intracellular receptors such as nucleotide-binding oligomerization domain-containing protein (NOD)2, a member of NOD-like receptors (NLRs), through the ligands muramyl dipeptide (MDP) or PGN could promote IRF5 expression [81]. The other immune receptor, such as Dectin-1, also induce IRF5 signaling after stimulation with b1,3-glucans in immune cells against intracellular bacterial and fungal pathogens [82] (Figure 1).

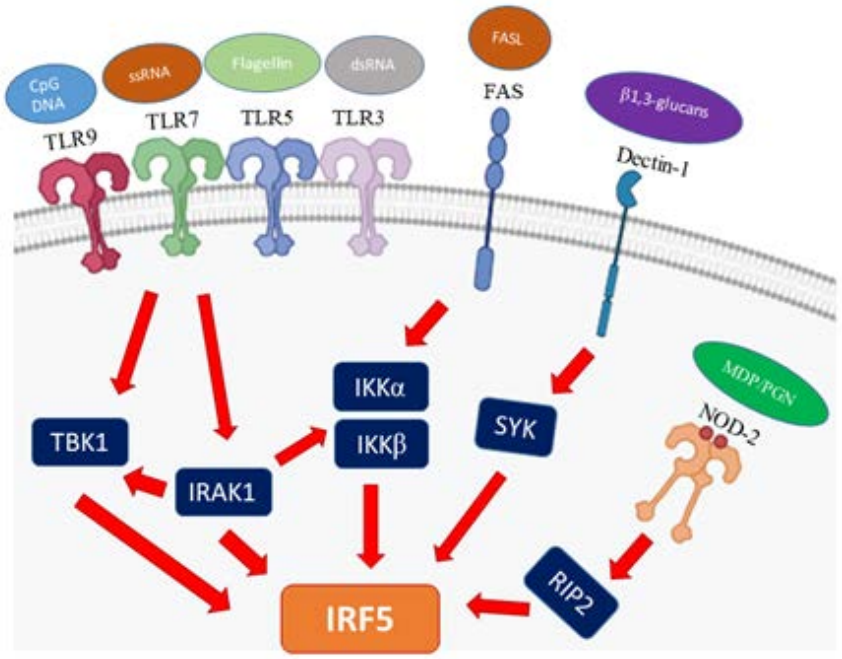

Figure 1. Signal transduction pathways that employ interferon regulatory factor 5 (IRF5).

MDP, Muramyl dipeptide; PGN, peptidoglycan; TLRs, Toll-like receptors; IKKs, IkB kinases; RIPs, Ribosome-inactivating proteins; IRAKs, interleukin-1 receptor associated kinase; TBKs, TANK-binding kinase 1; CpG, Cytosine-phosphate-guanosine-deoxynucleotides.

IRF5 and apoptosis regulation

Many studies have revealed the importance of apoptosis in the initiation and maintenance of SLE. Increased apoptosis rates have been reported in various SLE cells such as lymphocytes, neutrophils, and monocytes [83-85]. Under normal conditions, apoptotic debris is removed by phagocytosis, but an increased rate of apoptosis could impair this mechanism and release nuclear antigens that may lead to an autoimmune response, especially in SLE [86]. Increased apoptosis promotes the inflammatory response, releases cytokines and chemokines, and triggers more inflammation in these patients [87-89].

Recent studies have revealed that IRF5 can regulate cell growth and apoptosis [64]. Increased apoptosis induction has also been reported in other members of the IRF family, including IRF1 and IRF3 [90-93]. IRF5 is upregulated by tumor suppressor gene P53 in response to DNA damage and triggers apoptosis [94]. Some other proteins such as cyclin-dependent kinase inhibitor $p21^{cip1/waf1}$ and pro-apoptotic genes including Bax, Bak1, caspase 8, and DAP kinase-2 are upregulated in response to IRF5 and lead to apoptosis in damaged cells. However, anti-apoptotic proteins like cyclin B1 and CDK1, which prolonged cell life, were suppressed by IRF5 [64]. After IFNα stimulation, IRF5 was upregulated, leading to P21 upregulation and cell cycle arrest. Overexpression of IRF5 leads to cell cycle arrest and apoptosis in B cell lymphoma independent of P53 [62]. IFNα is used in chemotherapy in cancer patients to arrest the cell cycle and trigger apoptosis. Such cytotoxic effects could be triggered by the upregulation of IRF5 in these cells.

IRF5 and rheumatoid arthritis (RA)

RA is a chronic autoimmune disease with more incidence in women and at older ages [95]. The target tissue in these patients is the synovial joints. RA joints are characterized by leukocyte infiltration and chronic inflammation, which lead to irreversible joint damage [29, 30]. Multiple genetic and epigenetic factors play important roles in a person's predisposition to RA. The human leukocyte antigen (HLA) is one of the important genes in the immune response. The HLA-DRB1*01 and *04 alleles strongly increase the risk of RA and are also associated with greater bone damage and disease severity [96, 97].

In addition to *HLA*, multiple polymorphisms in *Irf5* locus have been associated with RA severity. The rs2004640 and rs3757385 SNPs have been reported in RA patients [51-53]. However, some studies have reported that the correlation between bone erosion and IRF5 SNPs is not clear [51, 98]. It is possible that IRF5 SNPs enhance acute inflammation in the early disease stage rather than systemic inflammation in RA. The inflamed synovium consists of activated immune cells including macrophages, T cells, B cells, and DCs. Resident tissue cells such as chondrocytes, synovial fibroblasts, and osteoclasts produce inflammatory cytokines and play pivotal roles in joint destruction [99]. RA synovial fluid consists of a large number of inflammatory cytokines including IL-1b, TNF, IL-6, matrix metalloproteases MMP-1, -3, -9, -13, and chem-okines such as IL-8, IP-10, MCP-1, and RANTES which result in persistent inflammation [31]. TNF is the most important mediator in inflamed RA joint because of its function in osteoclast activation and the degradation of

bones and cartilages [25, 100]. TNF blockade also inhibits the production of IL-6, IL-8, and GM-CSF in inflammatory conditions [101, 102].

IRF5 plays an important role in the production and prolonged TNF production by inflammatory macrophages [23, 37]. IRF5 also regulates many inflammatory genes by cooperating with NF-κB [103]. In mice whose *Irf5* gene has been removed (*Irf5*$^{-/-}$), impaired production of serum cytokines and resistance against lethal endotoxin shock have been reported [104]. In acute antigen-induced arthritis (AIA) in (*Irf5*$^{-/-}$) mice, IRF5 deficiency leads to decreased neut-rophil infiltration and reduction of TH1/TH17 and Tγδ IL-17^{+} cells in inflamed joints. However, a collagen-induced arthritis (CIA) model in (*Irf5*$^{-/-}$) mice exhibited no difference compared to the wild type [105]. Both AIA and CIA are antigen-induced arthritis models, but AIA is an acute form in contrast to CIA that is a more systemic form of arthritis [106, 107]. These results imply the more effective role of IRF5 in the early stage of autoimmunity. IRF5 plays crucial roles in macrophages, and its expression increases during differentiation into the inflammatory phenotype (M1) [36, 37]. The *Irf5*$^{-/-}$ macrophages differentiate into anti-inflammatory phenotype (M2) and in *Irf5*$^{-/-}$ mice immune responses shift toward TH2 cells instead of TH1 and TH17 cells, which induces strong inflammatory immune responses [37, 106]. The ectopic expression of IRF5 in M2 macrophages enforces the expression of M1 markers such as IL-12 and IL-23 [37].

In the context of autoimmunity and the results of mice models, IRF5 expression could result in RA severity and more inflammation in joints. The importance of macro-phages and inflammatory cytokines in RA joints suggests that dampening of IRF5 could be beneficial and advise new avenues for the development of RA-targeted therapies.

IRF5 AND systemic lupus erythematosus (SLE)

SLE is an autoimmune disease with a wide range of clinical manifestations. SLE could be a facial butterfly rash (malar rash) or a systemic life-threatening clinical pheno-type such as nephritis [108]. SLEs like RA have more incidence in women, and most patients have ANA that recognizes self-double-stranded DNA, nucleosomes, and histones, which could break self-tolerance as an important mechanism in autoimmune diseases. ANA has also been detected in a variety of autoimmune disorders such as Sjögren's syndrome, systemic sclerosis, and RA [26]. In addition to ANA, SLE patients have an IFN signature which correlates with disease severity, and the serum levels of IFNα are increased during the peak of the disease [26, 27]. IFNα-associated genes also have increased expression in PBMCs of SLE patients [20].

Genetic factors also play important roles in SLE predisposition. Several genes such as *HLA*, *Ptpn22*, *Stat4*, and importantly *Irf5* gene locus, have been reported in the context of SLE. The rs2004640 SNP has been shown to have the strongest association with SLE risk in worldwide cohorts [57, 61, 109, 110]. Some other studies have revealed a significant association between rs77571059 promoter indel upstream of exon 1A and SLE risk in patients [52, 109]. The rs10488631 SNP located 4 kb downstream of gene locus has also been associated with SLE risk in patients [61]. rs2004640, rs10488631, rs77571059, and rs10954213 increase the risk of SLE by elevating the level of IRF5 expression in patient monocytes [54]. IRF5 expression correlates with IFNα expression as a key characteristic of SLE. Monocytes derived from SLE patients express more pro-inflammatory cytokines such as IFN, IL-6, and TNF. These cytokines are important in SLE pathogenicity [111].

The important roles of IRF5 in SLE risk could be highlighted by mice models of SLE, in which the lymphocyte activation was decreased and more differen-tiation toward TH2 rather than TH1 was seen. That correlates with decreased expression levels of IL-12, IL-23, and IFNα, which leads to SLE disease pathogenesis [112]. Downregulation of chemokine receptors CXCR4 and CCR2 was a key element in monocyte attraction observed in these models [113]. The SLE (*Irf5*$^{-/-}$) mice models also showed reduced immunoglobulin G (IgG) class switching in B cells, which correlates with SLE pathogenesis [114]. The SLE (*Irf5*$^{-/-}$) mice experienced a low level of B cell maturation and plasma cell differen-tiation due to decreased *Prdm1* (BLIMP1) expression as a key regulator of plasma cell commitment factor and IRF5 targeted genes [115]. Reduced levels of mature B cells and antibody-producing cells lead to a low level of antibody production and ANA immune complex formation which have an important impact on the etiology and pathology of SLE.

In conclusion, SNP in IRF5 seems to increase the expression level of IRF5 and its target genes, including IFNα, which was a key factor in SLE pathogenesis. IRF5-targeted therapy could be one of the beneficial tools to control SLE severity in patients.

Current therapies in IRF5 inhibition

IRF5 is a key regulator of macrophage activation which could lead to the polarization of macrophages towards the M1 phenotype [24]. Because upregulation of IRF5 results in M1 phenotype, lipidoid nanoparticles loaded by siRNA were delivered to silence IRF5 in infiltrated macrophages in spinal cord injury wounds. IRF5 downregulation results in changing M1 to M2 phenotype, which leads to decreased inflammation, reduced demyelination and neurofilament loss, and better locomotor function [116]. In another study, siRNA silencing led to decreased post-MI heart failure in coronary ligation [117]. In the severe acute pancreatitis mouse model, high expression levels of IRF5, iNOS, TNFα, and IL10 have been shown in M1 macrophages. The siRNA could have repolarized the macrophages to M2 phenotype and decreased the inflammation in the pancreas environment [118]. In a mouse model of neuropathic pain, using gene therapy with homing peptide siRNA-IRF5 com-plexes in microglia cells resulted in decreased neuropathic pain [119]. Another interesting method for inhibiting IRF5 expression is using an AAG-rich microsatellite DNA-mimicking oligodeoxynucleotide designated as MS19, which results in the downregulation of iNOS, IL6, and TNFα along with the inhibition of IRF5 nuclear

translocation in cells [120]. Another study used the natural polyphenol mangiferin that is a component of Mangifera indica Linn. This product resulted in a reduction of IRF5 and pro-inflammatory cytokines, but the exact mechanism was not clear [121].

New strategies in IRF5 targeting

Some other members of IRF could regulate the expression of others such as IRF-1/IRF2 and IRF4/IRF5 [32, 122-126]. It is clear that IRF4 can bind the same region of MyD88 as IRF5 does [127]. In an *Irf4*$^{-/-}$ mice model, IRF5 dependent genes were upregulated after TLR stimulation. However, the alteration of an individual member of IRF could be nonspecific because of the cell type-dependent expression pattern of IRF members. Some studies have used this method to regulate IRF expression. In cancer cells, upregulation of IRF1 (an antagonist of IRF2) results in the downregulation of IRF2 [128]. Similarly, the upregulation of IRF4 could decrease the expression of IRF5 which leads to switching pro-inflammatory conditions to anti-inflammatory ones. However, this change could impact other signaling pathways based on cell type and results in the development of other diseases. The important challenge to this therapy is cell type-specific manner targeting [124, 127, 129]. SIK2 has been reported as a negative regulator of IL-12 and TNFα with an unknown mechanism that can reduce inflammation. Herein, SIK2 is a negative regulator of IRF5 that can induce an anti-inflammatory response. Thus, it may be defined as a candidate for the inhibition of inflammation and autoimmunity [130]. The other positive regulatory proteins are IKKβ, IRAK1/4, and TRAF6 which could be targeted to inhibit IRF5 activity. These enzymes could be easy targets for a therapeutic strategy, because all enzymes have an activity site and are more accessible for low molecular weight compounds to inhibit the activation. Another manner is targeting phosphatases such as alkaline phosphatase or A20 molecules, which would result in the deactivation of IRF5 [131, 132]. However, the inhibition of kinases, phosphatases, and ligases is note specific for IRF5 and could make a global change in cellular behavior and protein expression. The same hypothesis is also true about using co-activators that interact with IRF5, including CBP/p300 and GCN/PCAF that they are not specific for only IRF5 protein. Some viruses encode the viral proteins that are homologous to IRF (vIRF), such as Kaposi's sarcoma-associated herpesvirus and rhesus monkey rhadinovirus [124, 133, 134]. These viral proteins act as antagonists of IRF and inhibit the immune response. Some of these proteins do not have a DNA binding domain and, after homo- or hetero-dimerization with wild-type IRF, inhibit their interaction with DNA and inhibit the activity of IRF. However, C-terminal deletion mutants directly bind DNA and inhibit wild-type IRF [129, 135]. Other viral proteins also inhibit IRF by inducing its degradation [136]. These proteins or a specific sequence of them could be helpful in inhibiting IRF in a therapeutic target.

Some strategies have been developed based on these findings. The novel peptide inhibitors have been developed using specific sequences within the IRF5 gene. These peptides target the sequence inside the endogenous IRF and inhibit dimerization with other proteins as well as the full activation of IRF [137]. Other peptides which are cell-permeable, bind to the full-length IRF, and inhibit its function and cytokine production have also been developed [138]. These new strategies provide specific ways for IRF5 targeting which enhance the inhibition of IRF5 function and introduce the therapeutic method independent of cell types and pathway of activation.

Conclusion

Identification of the *IRF5* gene as an important factor in proinflammatory cytokine production and immune response regulation has driven studies to investigate this factor as a genetic risk factor in autoimmune diseases and inflammatory disorders. Any mechanisms that lead to a higher level of IRF5 expression can induce the expression of cytokines such as IL-6, IL-12, and TNFα that results in the activation of the immune response. Beyond this understanding, IRF5-based therapy is a beneficial strategy, and specific targeting of this transcription factor could overcome the problems related to off-target effects of treatments. One off-target and general therapy is anti-TNF that is useful in autoimmunity. However, blocking TNF activity is not a completely curative therapy, and it has many unwanted effects, because the immune system needs this agent as an important factor in the immune response. Although complete blocking of IRF5 as a transcription factor is challenging in disease treatment, IRF5 regulation might reduce the immune response in autoimmune diseases.

In conclusion, more studies are needed to investigate the IRF5 targeting therapy in inflammation and autoimmunity as a new specific therapy.

Acknowledgments

None.

Conflict of interest

The authors declare no potential conflicts of interest.

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