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IRF-5 - A New Link to Autoimmune Diseases

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1. Introduction

Transcription factors of the interferon regulatory factor (IRF) family have a critical role in the activation of interferon (IFN) genes. All cellular IRFs share a region of homology in the amino terminus encompassing a highly conserved DNA binding motif characterized by five tryptophan repeats, but show variability in the carboxy (C-) terminal part of the IRF polypeptides. While some of these IRFs like IRF-3 and IRF-7 have a critical role in the antiviral response, the others like IRF-1, IRF-4 and IRF-8 have basic roles in the development and function of lymphoid cells. Recently, the importance of IRF-5 in the antiviral and inflammatory response *in vivo* has been clearly established, but it was also shown that this IRF has a basic function in apoptosis and B cells and macrophage differentiation. More interestingly, the role of IRF-5 pathogenicity in autoimmune diseases has been also established, as IRF-5 has been identified as one of the primary risk factors associated with Systemic Lupus Erythematosus (SLE) and other autoimmune diseases. This chapter will review the current knowledge of the mechanisms of IRF-5 activation by the TLR7 pathway and the genetic modifications of IRF-5 that may contribute to the dysregulation of the innate and adaptive immune response associated with the autoimmune disease. Furthermore we will summarize the contribution of the SLE mouse models to our understanding of the role of IRF-5 and TLR7 in the induction of the autoimmune diseases.

2. Type I IFN and SLE

Autoimmune diseases are characterized by a dysregulated expression of Type I IFN, hyper-reactivity of B cells and the production of auto-antibodies. Leukocytes from patients with different autoimmune disorders such as SLE, psoriasis, dermatomyositis and rheumatic arthritis all show overexpression of interferon-induced genes. Furthermore, clinical use of IFNα leads to development of autoimmune syndromes like type I diabetes, psoriasis and inflammatory arthritis (Gota and Calabrese 2003). Till date, it has not been determined whether the uncontrolled production of Type I IFN is a consequence of dysregulated function of the immune system or due to genetic variations of the factors involved in IFN induction or IFN signalling pathway. Type I IFNs are produced by all leucocytes in response to TLR7 or TLR9 activation and the plasmacytoid dendritic cells (pDC) are the most active producer of IFNα. pDCs represent only about 1% of the PBMCs, but they can secrete up to 10^9 IFNα molecules per cell within 12 hours (Fitzgerald-Bocarsly *et al.*, 2008).

SLE is a classical systemic autoimmune disease. The link between SLE and Type I IFN is indisputable, reviewed in (Crow 2009). The elevation of type I IFNs is the hallmark of autoimmune diseases. In SLE, there is a correlation between IFN levels and the presence of anti-ds (double-stranded) DNA antibodies and disease progression. Interferon-stimulated genes (ISG) signature is a marker for severity of the disease (Baechler *et al.*, 2003). Also the high levels of IFNα are a heritable risk for SLE (Niewold *et al.*, 2007).
Clinical findings show that elevated pDC populations along with higher IFN mRNA levels present in dermal lesions of SLE patients contribute to elevated IFN levels. (Blomberg *et al.*, 2001). pDCs also accumulate in active lupus nephritis and migrate to the glomeruli (Silvestris *et al.*, 2003). Immune complexes containing nucleic acid found in the serum from lupus patients are known to trigger a type I IFN response in pDCs (Bengtsson *et al.*, 2000). The IgG RNA/DNA complexes are internalized via receptors [fragment crystallizable gamma receptor IIa (FcγRIIa)] expressed on pDCs, and stimulate endosomic TLR7 or TLR9 followed by activation of IRF-5 and IRF-7 and IFNα production. Both TLR7 and TLR9 are expressed in pDCs. RNA-containing immune complexes signalling through TLR7 are especially efficient in inducing IFNα and there is a direct correlation between serum levels of IFNα and the presence of autoantibodies to RNA-protein complexes (Vollmer *et al.*, 2005). Autoantibodies reactive against RNA-containing autoantigens are detected in the cerebrospinal fluid of patients with cerebral lupus (Santer *et al.*, 2009). An indirect evidence for the role of IFNα in autoimmune disease is the observation showing that patients receiving anti-IFN therapy for other diseases (such as HCV-related hepatitis treated with IFNα) develop autoantibodies and SLE-like syndrome (Ho *et al.*, 2008). Another indirect observation is the induction of anti-dsDNA antibodies and full-blown SLE during a clinical anti-TNFα therapy in patients with rheumatoid arthritis (RA) (De Rycke *et al.*, 2005). *In vitro*, TNFα suppresses IFNα expression and thus suppression of TNFα in patients with arthritis, with the antibody treatment, may result in enhancement of IFNα production.

3. Induction of innate antiviral response

Almost all nucleated cells respond to viral infections by producing Type I IFNs. Type I IFNs (IFNα and IFNβ) are an essential part of the antiviral response; however, their unregulated production is associated with pathology. Virus mediated Type I IFN induction is a classical example of transcriptional regulation. Virus infection induces activation of two families of transcriptional factors, NFκB and IRF family. The IRF proteins possess a common DNA binding domain at the N terminus characterized by a helix-turn-helix motif. The motif is rich in tryptophan residues and binds the GAAA and AANNGAAA domains in the virus responsive element (VRE) of Type I IFN promoters. The C-terminal regions of IRFs are distinct and contain IRF-associated domains (IADs) which are required for protein-protein interactions: either with other IRFs or other transcriptional factors. Two members of the IRF family, IRF-3 and IRF-7 are the major players in the induction of Type I IFN (Au *et al.*, 1998; Au *et al.*, 1995; Marie *et al.*, 1998; Ronco *et al.*, 1998). In the uninfected cell, they are localized to the cytoplasm, but in response to a viral infection, they are phosphorylated and translocate to the nucleus where they associate with the co-activator CREB-binding protein and stimulate transcription of *IfnA* and *IfnB* genes. While IRF-3 alone is sufficient for induction of *IfnB* gene, IRF-7 expression is essential for expression of the entire battery of *IfnA* genes, reviewed in (Pitha and Kunzi 2007). Both IRFs can be activated by a signalling pathway that initiates upon binding of viral dsRNA to membrane Toll-like Receptors, TLR3

and TL4, or cytoplasmic receptors, Retinoic acid-Inducible Gene (RIG)-I or Melanoma Differentiation-Associated gene (MDA)-5. Recent data, however, shows that IRF-3 can be also activated by binding of the viral DNA to the cytoplasmic receptor, Absent In Melanoma (AIM)-2 (Ishikawa and Barber 2011).

4. Role of IRF-5 in the induction of an antiviral response

Another IRF, IRF-5 also stimulates Type I IFN production in infected cells. IRF-5 differs from IRF-3 and IRF-7 in activation and function. While IRF-3 and IRF-7 are induced by TLR3, TLR4 or RIG-I/MDA5 pathways, IRF-5 is activated only by TLR7 and TLR9 in a Myeloid Differentiation factor 88 (MyD88)-dependent pathway and consequently, only certain viral infections (Newcastle disease virus, NDV; VSV; and HSV) can activate IRF-5 (Barnes *et al.*, 2001). The activation of IRF-5 results in the transcription of nine differently alternatively spliced IRF-5 mRNAs, these isoforms are cell-type specific and have distinct functions (Mancl *et al.*, 2005).

Ectopic expression of IRF-5 induces several IFNα subtypes; however, the subtypes induced by IRF-5 and IRF-7 are distinct, *e.g*. IRF-7 induces mostly *IfnA1* while the major subtype induced by IRF-5 is *IfnA8* (Barnes *et al.*, 2001).

5. Downstream effectors of IFNs

The Type I IFN system is well characterized and well-studied. Type I IFNs mediate their action by engaging the ubiquitously expressed IFNα receptor (IFNAR) complex which has two units, IFNAR1 and IFNAR2, reviewed in (Uze *et al.*, 2007). On binding to their respective receptors, IFNs exert their multiple effects through receptor-mediated signalling pathways, resulting in the induction of IFN-stimulated genes (ISGs). The major signalling pathway is the JAK-STAT pathway; beginning from the Janus kinases (JAK1 and Tyk2) and followed by tyrosine phosphorylation of pre-existing signal transducer and activator of transcription (STAT). On phosphorylation, STAT1 and STAT2 assemble together, associate with interferon regulatory factor 9 (IRF-9) and form a multimeric complex (ISGF3) that translocates to the nucleus, where it interacts with interferon-responsive elements (ISRE) present in the 5′ flanking region of ISG (Improta *et al.*, 1994; Levy and Darnell 2002). While ISGF3 seems to be the main transcription factor regulating transcription of ISGs, Type I IFN also stimulates formation of STAT1 homodimers that bind to a slightly different DNA domain, the IFNγ activated site (GAS), present in the promoters of ISG that can be induced both by Type I IFN and IFNγ. The signalling by Type I IFN is not limited to the JAK–STAT pathway as this receptor can also activate both the Mitogen-Activated Protein kinase (MAPK) and Phosphoinositide 3-kinase (PI3K) pathways (Platanias 2005). Activation of IFNs through the IFNARs followed by amplification of the signal via downstream pathways results in activation of more than 300 ISGs. The function of the majority of ISGs has yet to be determined; however, the antiviral function of several of the ISG have been recently characterized, and the proteins described (Samuel 2001; Schoggins *et al.*, 2011).

Among these, ISG15 is one of the very early induced ISGs that influence a panoply of cellular functions; ISG15 is a ubiquitin homologue which is covalently attached to lysine residues (ISGylation) of the targeted proteins. Recent evidence indicates the existence of cross-talk between ubiquitinylation and ISGylation. Since ubiquitinylation is a component of many cellular and stress induced signalling pathway, ISGylation can effectively interfere

with these pathways. Activation of ISGylation proceeds by similar enzymatic pathways as used for ubiquitinylation, and interestingly, all enzymes required for ISGylation are induced by IFN. Similar to ubiquitinylation, the ISGylation process is reversible and de-ISGYlating enzymes provide an additional level of control over the entire process. More than a hundred ISG15 targets have been identified, and some of these genes such as RIG-I, JAK1, Protein Kinase R (PKR) and STAT-1 are part of the IFN response system while others have different cellular functions. However, unlike the degradation-driven ubiquitinylation, ISGylation in many cases inhibits ubiquitinylation, reviewed in (Skaug and Chen 2010).

Another IFN induced gene with multiple functions is a constitutively expressed dsRNA dependent PKR whose expression is enhanced by Type I IFN. The inactive monomers of PKR are activated by viral RNA, PKR is phosphorylated and forms active dimers. Activated PKR catalyzes phosphorylation of several substrates including the α subunit of the initiation factor eIF-2 (eIF-2α) (Samuel 1993), as well as the transcription factor inhibitor IκB (Kumar *et al.*, 1994). Thus PKR affects both viral replication and many cellular functions, reviewed in (Pindel and Sadler 2011).

Other ISGs such as cytidine deaminases of the APOBEC family and adenosine deaminase ADAR1 have been recently characterized but their cellular functions are yet to be determined (Chiu and Greene 2008; George *et al.*, 2011; Schoggins *et al.*, 2011). Also interesting is a recent finding from the Rice group (Schoggins *et al.*, 2011) which shows that IRF-1, induced by both IFNγ and Type I IFN has antiviral activity against a large group of distinct viruses and that this antiviral activity is not IFN-mediated. This group also identified large number of novel antiviral ISGs and showed that a number of these proteins function at the translational level.

In addition, there are reports of host-produced antiviral micro-RNAs (miRNAs) in response to IFNs (Hansen *et al.*, 2010; Lagos *et al.*, 2010; O'Connell *et al.*, 2007; Pedersen *et al.*, 2007). Even though first identified in fishes and invertebrates, it was assumed that miRNAs were not elicited as a first line of defence in mammals. However, microarray analysis of general IFNα/β response identified a few candidate miRNAs which are increased or attenuated in response to IFNα/β. Some of these target IFNB mRNA and thus serve as negative regulators of the IFN system, while others are induced during the innate antiviral response. Therefore it seems that IFN-induced cellular miRNAs may represent fine-tuning of the IFN system.

6. Role of IRF-5 in the innate immune response

The transcription factor IRF-5 plays a key role in the innate antiviral and inflammatory response. *In vitro* studies had initially indicated that IRF-5 may be involved in the antiviral response (Barnes *et al.*, 2001), and when genetically modified *Irf-5*$^{-/-}$ mice became available, the importance of IRF-5 in the antiviral and inflammatory response *in vivo* was also demonstrated (Paun *et al.*, 2008; Takaoka *et al.*, 2005). *Irf-5*$^{-/-}$ mice exhibit high susceptibility to viral infection and show reductions in serum levels of Type I IFN as well as inflammatory cytokines such as IL-6 and TNFα. IRF-5 shows a cell type specific expression in B cells, DC, monocytes and macrophages. In contrast to IRF-3 and IRF-7, IRF-5 is activated only by TLR7 and TLR9 MyD88 dependent pathway and unlike IRF-3 and IRF-7, not by TLR3 or RIG I pathways (Schoenemeyer *et al.*, 2005). The MyD88 mediated activation of IRF-5 involves the formation of a tertiary complex consisting of MyD88 and tetramers of IRAK1, IRAK4, TRAF6 and IRF-5 and IRF-7. It was shown that both K63 ubiquitinylation by TRAF6 and phosphorylation are necessary for activation and translocation of IRF-5 to the nucleus, but

the kinase that activates IRF-5 has not yet been identified (Balkhi *et al.*, 2008). Activated IRF-5 forms homodimers and heterodimers with IRF-3 and IRF-7, but while the IRF-5 synergizes with IRF-3 activation, it inhibits the transcriptional activity of IRF-7 (Barnes *et al.*, 2004). In addition to its role in the early inflammatory response, IRF-5 also has pro-apoptotic functions.

The observations discussed above show an important role for IRF-5 in the regulation of early inflammatory cytokines and chemokines' expression, as well as Type I IFN genes. The function of IRF-5 was also examined *in vivo* using the genetically modified *Irf-5*$^{-/-}$ mouse model. These mice exhibit an increased susceptibility to viral infection and reductions in serum levels of type I IFNs as well as inflammatory cytokines such as interleukin-6 and tumor necrosis factor alpha (TNFα) (Paun *et al.*, 2008; Takaoka *et al.*, 2005). Examination of the cells type in which expression of inflammatory cytokines and IFN depends on IRF-5 show that IRF-5 is required for the TLR9 mediated induction of IFN β in DC, but not in peritoneal macrophages, while the stimulation of inflammatory cytokines expression was dependent on IRF-5 in both cell types. These data indicate that the function of IRF-5 may be cell type specific.

Unexpectedly, approximately 80% of *Irf-5*$^{-/-}$ mice, (94% C57BL/6) developed an age-related splenomegaly, associated with a dramatic accumulation of $CD19^{+}B220^{-}$ B cells (Lien *et al.*, 2010). The age-related splenomegaly was dependent on genotype, and developed in mice with the mixture of 129 and C57BL/6 genotype, but did not occur in mice that were 98% of C57BL/6 background (unpublished data). Interestingly, the *Irf-5*$^{-/-}$ C57BL6 mice have attenuated responses to T-cell dependent (TD) and T-cell independent (TI) antigens (unpublished data), with a marked down-regulation of serum levels of antigen specific IgG2a and IgG2c. The Taniguchi group (Savitsky *et al.*, 2010) has shown that the down-regulation of IgG2a production occurred also in *in vitro* cultured IRF-5 knockout DC cells stimulated with CpG oligodeoxynucleotides. The synthesis of IL-6 and TNFα was also down-regulated in IRF-5 knockout B cell stimulated with TLR 9 ligand, indicating that the function of these cells is impaired (Lien *et al.*, 2010).

7. Role of IRF-5 in autoimmune diseases

The demonstration that IRF-5 is important not only for the induction of Type I IFN genes, but also for the inflammatory cytokines gave new insights into the regulation of the innate inflammatory response. However, there is also accumulating evidence that IRF-5 may play an important role in the dysregulation of the immune system leading to autoimmune diseases. Several distinctly spliced human IRF-5 isoforms (designated variants 1-10), which show cell type-specific expression and distinct cellular localization, were identified (Mancl *et al.*, 2005). The most common variations are insertions or deletions in exon 6. The majority of IRF-5 isotypes do not differ in their DNA binding sites, but differ in the interaction domain. The transcription of IRF-5 is started at one of the three different promoters. Transcript initiated at exon 1A and 1B are expressed constitutively in B cells and pDC, while transcript 1c is induced by IFN. It should be however noted that spliced variants of IRF-5 were identified only in human cells, while in inbred strains of mice, *IRF-5* encodes for a dominant unspliced transcript.

It has been known for a long time that the autoimmune disease SLE exhibits genetic predisposition, which was later mapped to a specific region on human chromosome 6. When the sequence of the human genome became available, it was found that the genomic

region associated with predisposition to SLE showed the presence of several genes associated with the Type I IFN induction and signalling pathway. One of these genes is IRF-5 and a common SNP haplotype in IRF-5 (rs 2004640T) was identified in Scandinavian cohorts as a risk factor for SLE. Interestingly, the same SNP haplotype of IRF-5 has been shown later to be associated with numerous other autoimmune disorders, such as rheumatoid arthritis (RA) (Sigurdsson *et al.*, 2007) and others (Kozyrev and Alarcon-Riquelme 2007). Three specific functional alleles of IRF-5 were identified that define risk factors for SLE (Graham et al., 2006). The rs 2004640 G allele expresses isotypes initiated from exon 1A and 1C, while the rs 2004640T allele expresses transcripts from exon 1B, which provides a stronger promoter and increases the expression of IRF-5. The second SNP is the in-frame insertion- of 30 bp in exon 6 that alters the proline, glutamic acid and serine rich regions and encodes a protein that is similar to unspliced isotype IRF-5v5. The third SNP introduces a variation in the poly A termination site that makes the 3'UTR shorter which leads to an increased stability of IRF-5 mRNA (Graham *et al.*, 2006). All together, these modifications in the *IRF-5* gene result in elevated levels of IRF-5 protein which is larger than the proteins encoded by the spliced IRF- transcripts. Many additional SNPs in IRF-5 have been later identified and are reviewed in (Kozyrev and Alarcon-Riquelme 2007). The high levels of lupus associated IRF-5 expression have been detected in PBMCs of Lupus patients (Feng *et al.*, 2010). Dysregulated expression of Type I IFN is associated with SLE pathogenesis (Niewold *et al.*, 2007) and gene array analysis of PMBCs from SLE patients has revealed elevated expression of IFN-stimulated genes (Crow *et al.*, 2003). Thus, the connection between expression of specific IRF-5 haplotypes and dysregulated production of Type I IFN has been emerging. Interestingly neither IRF-3 or IRF-7 or other members of IRF family were found to be associated with predisposition to autoimmune disease. Thus IRF-5 is possibly the most important factor in the predisposition to the inflammatory diseases.

8. IRF-5 functions in uninfected cells

Another unique feature of IRF-5 is that it is also induced upon DNA damage by p53 (Mori *et al.*, 2002). This establishes the connection between IRF-5 and p53-apoptotic pathways and identifies its possible role in tumor suppression. However, IRF-5 induces apoptosis in p53 independent manner (Barnes *et al.*, 2003). *Irf-5*$^{-/-}$ Mouse Embryonic Fibroblasts (MEFs) expressing c-Ras do not undergo apoptosis even under DNA damage and can efficiently form tumors in mice. These MEFs are also resistant to viral induced apoptosis even though their IFN and cytokine profiles are normal (Yanai *et al.*, 2007). However, there are several indications that IRF-5 and p53 pro-apoptotic function are independent. Several p53 targets are activated in *Irf-5*$^{-/-}$ cells and overexpression of IRF-5 can stop the growth of B cell tumor lymphoma in the absence of p53 (Barnes *et al.*, 2003). Ectopic expression of IRF-5 induces DNA damage-induced apoptosis in p53-deficient colon cancer cells (Hu *et al.*, 2005). IRF-5 is also involved in Fas/CD95-induced apoptosis, a p53 independent phenomenon (Couzinet *et al.*, 2008). IRF-5 stimulates the cyclin-dependent kinase inhibitor p21, but it also stimulates the expression of the pro-apoptotic genes *Bak1*, *Bax*, caspase 8, and DAP kinase 2, thus indicating its ability to promote cell cycle arrest and apoptosis independently of p53 (Barnes *et al.*, 2003).

Udalova and colleagues have also identified IRF-5 as a lineage-defining factor for macrophages (Krausgruber *et al.*, 2011). Their work shows, for the first time, that IRF-5 can be both a transcription activator and repressor. Macrophages differentiate into two

functionally opposite types depending on the differentiation stimulus. When bone marrow macrophages are grown with granulocyte–macrophage colony stimulating factor (GM-CSF), they differentiate into M1 type, classical pro-inflammatory macrophages which secrete cytokines like IL-12. However, when they are differentiated with M-CSF, they differentiate to the M2 type, which secretes anti-inflammatory cytokines like IL-10. The authors show that differentiation to M1 macrophages is accompanied by an increase in IRF-5 levels. Overexpression of IRF-5 in M2 macrophages forces them to express a pro-inflammatory profile of cytokines and lowers IL-10 levels, basically making the M2 macrophages functionally similar to M1. Conversely, knockdown of IRF-5 levels in M1 macrophages converts M1 macrophages to the M2 expression profile, producing high levels of IL-10 and low levels of proinflammatory cytokines. Thus IRF-5 is a determinant of macrophage plasticity. The authors also demonstrate that in macrophages, IRF-5 functions as a negative regulator of IL-10. These results open the field to many other questions such as possible cell type specificity of the suppression of IL-10 transcription, or how many other genes are negatively regulated by IRF-5. The analysis of the IRF-5 signature profile in human B cell line BJAB identifies large number of both up-regulated and down regulated genes (Barnes *et al.*, 2004).

9. Activation of IRF-5 by the TLR7 pathway

TLR7 and TLR9 recognize viral ss (single stranded)-RNA or a B form of dsDNA respectively. The recognition is dependent on endosomal internalization and acidification. The TLR7/9 signalling pathway is mediated by an adaptor molecule MyD88 (Kawai *et al.*, 1999; Muzio *et al.*, 1997). MyD88 has two domains: a C-terminal Toll/IL-1 Receptor (TIR) domain that is required for the interaction with the TLRs and an amino terminal death domain (DD) that interacts with members of the IL-1 receptor associated kinase (IRAK) family (Martin and Wesche 2002). This association between IRAK1 and MyD88 results in self-phosphorylation of IRAK-1, as well as phosphorylation by the related kinase, IRAK-4 (Cao *et al.*, 1996; Li *et al.*, 2002). After phosphorylation, IRAK1 dissociates from MyD88 and now binds to TRAF6 (TNF receptor-associated factor 6) (Burns *et al.*, 2000). TRAF6-mediated K63-linked ubiquitinylation is required for IRF-5 nuclear translocation in TLR7/9-MyD88-dependent signalling (Balkhi *et al.*, 2008). IRF-5 homo-dimerizes upon phosphorylation of serine/ threonine residues at the C-terminal end by a still undefined kinase and translocates to the nucleus (Chen *et al.*, 2008). Thus, both ubiquitinylation and phosphorylation of IRF-5 are required for nuclear translocation. IRF-5 also associates with Ikkα kinase, but that results in degradation of IRF-5-rather than activation (Balkhi *et al.*, 2010). It should be noted that TLR 7 and TL9 are the only know pathways that lead to the activation of IRF-5. Unlike IRF-3 or IRF-7, IRF-5 is not activated by TLR3 or TLR 4 via TIR-domain-containing adapter-inducing IFNβ (Trif) pathways or by the RIG-I/MAV IPS-1 pathways.

Several ligands can activate TLR7. TLR7 recognizes viral ssRNA , but IFN production can be also induced in response to imiquimod and resiquimod (Hemmi *et al.*, 2002). In addition, several other guanine nucleoside analogs are recognized exclusively via TLR7 (Lee and Kim 2007). Of physiological ligands, guanosine and uridine-rich ssRNA oligonucleotides derived from HIV-1, stimulate DCs and macrophages to secrete IFNα and other pro-inflammatory cytokines via murine TLR7 (Heil *et al.*, 2004). TLR7 also responds to ssRNA (polyU) or ssRNA derived from wild-type influenza virus (Diebold *et al.*, 2004). Since these sequences can originate from viral as well as endogenous RNA, TLR7 may be unable to discriminate between self and non-self RNA and see the self RNA as sensors of endogenous danger

signals. Accordingly, small nuclear ribonucleoproteins (snRNPs), a major component of the immune complexes associated with SLE can activate human pDCs by TLR7 induced signaling pathway and stimulate production of Type I IFNs and other proinflammatory cytokines. Interestingly, the TLR7 pathway can also be activated by nuclear ribonucleoprotein complexes (Savarese *et al.*, 2006).

10. Mouse models of SLE

The mouse model of SLE provides additional information on the mechanism of SLE pathogenicity. NZB mice develop spontaneous lupus, produce autoantibodies and develop glomerulonephritis. Duplication of TLR7 and transposition of the TLR7 gene as seen in the *Yaa* mutation promotes the SLE like symptoms. The B cells of murine lupus model also show an accelerated class switching, which is controlled by the genotype (Vyse *et al.*, 1996). Our results showed that in addition to a decreased production of Type I IFN and inflammatory cytokines, *Irf-5*$^{-/-}$ mice exhibit an alteration of the B cells phenotype, associated with age related expansion of $CD19^{+}B220^{-}$ group of B cells, decrease in plasma cells and splenomegaly (Lien *et al.*, 2010). However, the mechanism by which IRF-5 controls B cells differentiation to plasma cells is not known. *Irf-5*$^{-/-}$ mice have also decreased levels of natural antibodies and T cells dependent antigenic stimulation leads to profound decrease in serum IgG2a (Savitsky *et al.*, 2010). Finally the requirement of IRF-5 for the development of lupus like disease was demonstrated in *FcγRIIB*$^{-/-}$ mice, where IRF-5 deficiency profoundly decreased the manifestation of the disease (Richez *et al.*, 2010). Two other IRFs, IRF-4 and IRF-8 have critical functions in the B cell differentiation program. B cells development is blocked at the pre-B cells stage in IRF-4 and IRF-8 compound null mice (Lu *et al.*, 2003). IRF-4 also functions in late B cells development regulating IgG class switching and plasma cell development (Sciammas *et al.*, 2006). IRF-8 has a role in germinal centre transcription program (Lee *et al.*, 2006). Altogether, these data indicate that several members of the IRF family can affect B-cell development, however the strong genetic association between IRF-5 and autoimmune disease point out to a unique functions of IRF-5 in the immune system.

11. Induction of autoimmunity by IFNs

How the IFNs contribute to SLE and its progress remains to be fully explained. The presence of immunogenic complexes leads to dendritic cell activation and thus there is a greater antigen presentation and more IFNs are secreted. IFNα increases the expression of autoantigens such as Ro52 and also induces apoptosis via translocation of Ro52 to the nucleus (Baechler *et al.*, 2004; Bennett *et al.*, 2003). Type I IFNs also induce the maturation and activation of dendritic cells, along with upregulation of MHC Class I and II molecules (Baccala *et al.*, 2007). This promotes the development of helper T cells (Th1). In addition, Type I IFNs also enhance antibody production and class switching, decrease the selectivity of B cells for CpG-rich DNA, and permit stimulation by even non-CpG DNA and thereby promote an autoimmune response (Jego *et al.*, 2003; Le Bon *et al.*, 2006). How does IRF-5 contribute to this picture?

12. Genetic association studies and SLE

Genetic and population association studies provide a more comprehensive picture of the role of IFNs in SLE, reviewed in (Delgado-Vega *et al.*, 2010). Of the entire battery of genes

identified by genome wide association studies, most of the genes are involved in innate and adaptive immune responses. These can be divided into the following groups: (1) genes implicated in processing and presentation of immune complexes, (2) genes involved in the IFN-inducing pathways, and (3) genes involved in the Type I IFN signalling pathway. Of the first group, the MHC region shows up as a prime candidate in correlation studies, but is challenging to study since the region has hundreds of potential candidate genes (Deng and Tsao 2010; Sestak *et al.*, 2011). In the IFN-inducing pathways, transcription factor IRF-5 was the first identified gene directly to be associated with increased risk of lupus (Graham *et al.*, 2006; Sigurdsson *et al.*, 2005). IRF-5 allele variants with the highest probability of being causal were identified and shown to affect IRF-5 expression. Patients with a risk haplotype of IRF-5 show higher serum IFN activity, when compared to patients lacking this risk genotype. Finally, in the IFN signalling pathway, STAT4, a downstream interacting protein of IFNAR, is also strongly associated with lupus (Kariuki *et al.*, 2009). STAT4 is associated with increased sensitivity to IFNα and the presence of anti-dsDNA autoantibodies. In addition, polymorphisms in the Janus kinase tyrosine kinase 2 (TYK2), which binds to IFNAR, and is part of the initiation of the JAK-STAT pathway, was also found to be associated with lupus and strengthen the link between IFNα expression and SLE. Several other gene products that are part of the IFN signalling pathway, such as TNFAIP3, TYK2, and TREX1, have been also associated with susceptibility to SLE (Adrianto *et al.*, 2011; Fan *et al.*, 2011; Hellquist *et al.*, 2009). Recently identified SNPs in IRF7 also seem to be associated with SLE. (Fu *et al.*, 2011). It is unlikely that the alteration of the function of a single master gene will be responsible for the pathogenesis of SLE; rather it may be combination of malfunction of several genes. Without doubt there is still the potential of finding new genes that contribute to the development of SLE.

13. IRF-5 polymorphisms and association with SLE

IRF-5 was identified as a risk factor for SLE in two very important association studies. Sigurdsson *et al.* looked at sets of lupus patients from Sweden, Finland and Iceland and analyzed 4 SNPs of IRF-5 (Sigurdsson *et al.*, 2005). Graham *et al.* (Graham *et al.*, 2007) describe two functional SNPs within the IRF-5 gene which are a risk haplotype for SLE. One SNP, rs2004640, creates a donor splice site in intron 1 of IRF-5 and the isoform expresses an alternative of untranslated exon 1B. A second SNP is located about 5 kb downstream of IRF-5 and could not be tied to functional importance but is used as a haplotype tag (Graham *et al.*, 2007). Later, several groups identified a second polymorphism that has more easily identifiable functional roles. rs10954213 alters the polyadenylation site of IRF-5 and the resultant mRNA cal be correlated to higher levels of IRF-5 seen in SLE (Sigurdsson *et al.*, 2008). The A allele of this SNP leads to a shorter and more stable mRNA. Finally, an insertion- deletion is found in the 6th exon of IRF-5 that can potentially change the protein isoforms expressed IRF-5 by 10 amino acids (Kozyrev *et al.*, 2007). The deletion results in expression of the isoforms V1 and V4, while the insertion give rise to isoforms V5 and V6. The lupus risk haplotype, TCA, includes the insertion TCA and thus individuals with lupus are expected to express the corresponding isoforms (V5 and V6). The sequence added by the insertion/deletion gives rise to a proline-rich region which can be potentially recruited for additional protein –protein interactions and/or protein stability by altering the degradation rate of the resulting protein.

Even though the genetic association of lupus and IRF-5 has been consistent, the initial studies dealt with an overwhelmingly European population and there are some suggestions that the association factors might be population specific. Studies in Asian populations have identified new susceptibility genes for lupus, while some of the previously known ones have been discounted (Kawasaki *et al.*, 2008; Li *et al.*, 2011; Shimane *et al.*, 2009; Shin *et al.*, 2008; Siu *et al.*, 2008), reviewed in (Kim *et al.*, 2009). Given that the majority of lupus patients are women, genetic imprinting remains yet an unexplored topic. However very interesting is a recent finding showing that IRF-5 is expressed at higher levels in female than in male mice and that the IRF-5 promoter is under hormonal regulation (Shen *et al.*, 2010).

14. Conclusions and future perspectives

Identification of the IRF-5 gene as a genetic risk factor for SLE helps to dissect its role in the IFNα pathway in pathogenesis of SLE. The SNP, rs10954213, that affects the levels of IRF-5 expression through increasing the stability of its mRNA, has a great impact on function and expression of protein, but has not found to be strongly associated as a risk haplotype. Thus many questions remain. Higher levels of IRF-5 might result not only in continued production of type I IFN but also of the proinflammatory cytokines. Are these cytokines responsible for the activation of the immune cells such as B cells? Hyper activation of B cells is one of the markers of SLE and the results in mice indicate that IRF-5 has an important role in cell differentiation and induction of IgG2a subtype, which is an important subtype for the induction of autoimmunity. In humans, the IgG2a isotype corresponds to IgG1, which is the dominant subclass of serum autoantibodies in SLE (Manolova *et al.*, 2002). The biological role of IRF-5 isoforms remains to be determined. Presently we do not know whether TCA haplotype IRF-5 has a distinct function from the other IRF-5 variants or whether it induces different group of the inflammatory genes or IFN A variants. It would be of great interest to learn about the roles of the IRF-5 induced genes and their variation in SLE patients. Now

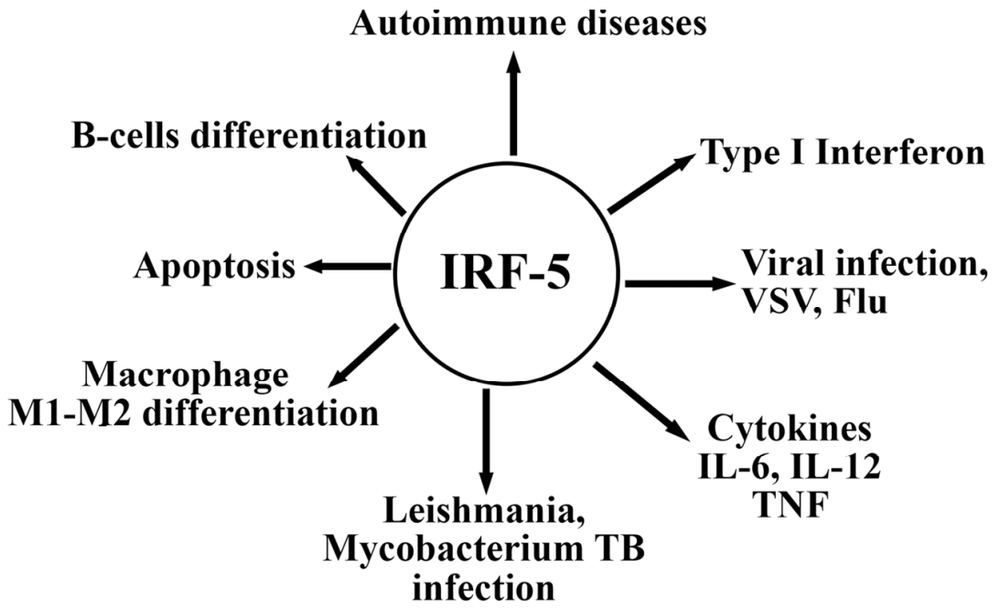


Fig. 1. Various roles of IRF-5 in immunity and autoimmune diseases.

that IRF-5 has been identified as an important factor in induction of type IFN in lupus, it will be important to determine which of the other IRF-5 regulated genes contribute to the pathogenicity of the disease. A recent observation that EBV might also be implicated in the activation of Type I IFN in SLE patients (Yadav *et al.*, 2011) might be an important link in dissecting the cross-talk between genetic predisposition or risk factors and environmental stimuli. Is there any cross talk between IRF-5 and some of the other gene products that were also identified to be associated with Lupus disease? Many of these questions remain yet to be explored to understand the impact of IRF-5 in SLE biology (Figure 1).

15. Acknowledgement

This work was supported by the NIAID grant R01 AI067632-05 to PMP.

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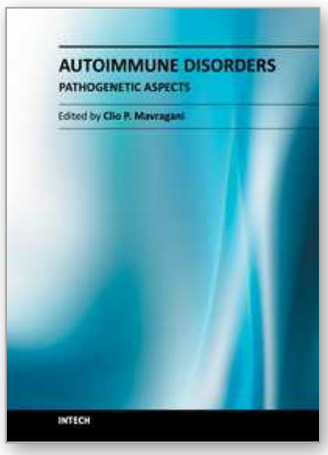
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Autoimmune Disorders - Pathogenetic Aspects

Edited by Dr. Clio Mavragani

ISBN 978-953-307-643-0
Hard cover, 508 pages
Publisher InTech
Published online 26, October, 2011
Published in print edition October, 2011

The present edition entitled "Autoimmune disorders - Pathogenetic aspects" aims to present the current available evidence of etiopathogenetic insights of both systemic and organ specific autoimmune disorders, the crossover interactions among autoimmunity, cardiovascular morbidity and malignancy as well as novel findings in the exciting fields of osteoimmunology and immunology of pregnancy.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Sujayita Roy and Paula M. Pitha (2011). IRF-5 - A New Link to Autoimmune Diseases, Autoimmune Disorders - Pathogenetic Aspects, Dr. Clio Mavragani (Ed.), ISBN: 978-953-307-643-0, InTech, Available from: http://www.intechopen.com/books/autoimmune-disorders-pathogenetic-aspects/irf-5-a-new-link-to-autoimmune-diseases

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