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SYSTEMIC LUPUS ERYTHEMATOSUS (G TSOKOS, SECTION EDITOR)

Genetic Versus Non-genetic Drivers of SLE: Implications of IRF5 Dysregulation in Both Roads Leading to SLE

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Abstract

Purpose of Review Systemic lupus erythematosus (SLE) is characterized by a breakdown of immune tolerance, resulting in inflammation and tissue destruction. While the primary causes of SLE are still obscure, the disorder is highly heritable. Genetic risk variants, on their own, are rarely causal or fully explain disease pathogenesis. We discuss the possibility that *IRF5*, a SLE susceptibility gene, has both genetic and non-genetic contributions to disease pathogenesis.

Recent Findings Genetic variants within and around *IRF5* robustly associate with SLE risk. In SLE blood cells, *IRF5* risk variants associate with elevated *IRF5* expression and IFN production. Whether the observed increase in expression is due to risk variants or other disease-associated factors is not clear. Data from $Irf5^{-/-}$ mice backcrossed to multiple models of murine lupus support that IRF5's role in disease pathogenesis is non-genetic.

Summary Studies of IRF5 expression and function in genotyped healthy donors will address the question of whether IRF5 dysregulation in SLE is driven by genetic or non-genetic factors.

Keywords Interferon regulatory factor · Lupus · Genotype · Interferon

Introduction

Members of the interferon (IFN) regulatory factor (IRF) family of transcription factors are critical regulators of immune cell development, differentiation, and response, with abnormalities in IRF expression and function increasingly linked to autoimmune diseases [1•, 2•]. Genetic variants within or near *IRF5* have been robustly associated with the autoimmune disease systemic lupus erythematosus (SLE) across every major ancestral group tested [3–7]. To date, four *IRF5* homozygous risk variants have been identified that strongly associate with SLE risk and make up the major *IRF5*-SLE risk haplotype in European Caucasians. These four variants occur at regions of transcriptional control—two are in the 5′ untranslated region (UTR) of *IRF5* (rs2004640 and a 5 bp CGGGG insertion/deletion (indel)) and one is in the 3′ UTR (rs10954213) [1•, 2•, 3–5]. The fourth one is 5 kb downstream of *IRF5* at rs10488631 [4–6] (Fig. 1). Subsequent studies identified an additional single nucleotide polymorphism (SNP) in the 5′ UTR of *IRF5* (rs4728142) that was suggested to explain all genetic risk from the four original variants; however, limited analysis has been performed in genotyped healthy donors and SLE patients that explain the functionality of this SNP [8]. Kottyan et al. reported that the risk allele of rs4728142 provided a site for increased binding of the transcription factor ZBTB3 in immortalized lymphoblastoid (B) cell lines [8]. Whether this SNP or ZBTB3 is directly functional leading to increased *IRF5* expression is not yet known. Nonetheless, SLE patients carrying the major *IRF5*-SLE homozygous risk haplotype (Fig. 1) were found to have elevated IRF5 expression, at both the transcript and protein level [3–7, 9, 10]. Further, Niewold et al. reported that SLE patients carrying an *IRF5* risk haplotype have elevated *IRF5* expression that correlates with elevated serum IFNα in patients positive for anti-dsDNA or -RBP autoantibodies [10, 11]. In efforts to identify the functional contribution of SNPs to the regulation of *IRF5* gene expression, many labs, including ours, have generated *IRF5* mini-genes that contain individual genetic variants, or combinations of each [4, 6, 7, 9, 12]. To our great

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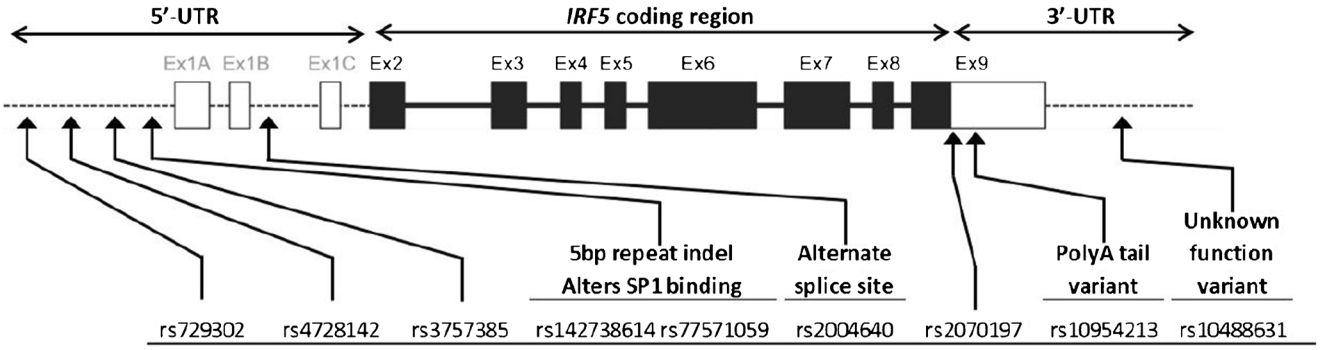

Fig. 1 Candidate causal SNPs associated with SLE are shown relative to the human *IRF5* gene. The four genetic variants that make up the homozygous *IRF5*-SLE risk haplotype in European Caucasians are shown with stated functionalities. Variants listed underneath the listed functionalities are those that are candidate causal or associated with SLE in GWAS, and thus proxies for the candidate causal variants

surprise, very few of these studies identified a significant functional role for individual variants in driving IRF5 expression. One possible explanation for this is that we have yet to identify the causal variant(s) that drives *IRF5* expression. However, this is unlikely given the extensive replication of *IRF5* genetic risk in multiple ethnic cohorts. A second possibility is that no single genetic variant is sufficient to drive risk and/or changes in IRF5 expression/function. Instead, alterations in IRF5 expression and function may require the full-risk haplotype [9, 10]. In support of this last thesis are findings from studies on SNP rs2004640. The risk allele of rs2004640 was originally identified (and functionally characterized) as supplying an alternative splice site that preferentially drives *IRF5* transcription from non-coding exon 1B [4]. Unfortunately, however, this finding has not been well-replicated by others [9, 12], and thus, its functionality with regard to regulating *IRF5* expression levels remains in question. However, numerous labs have reported changes in *IRF5* expression in immortalized lymphoblastoid cell lines and primary blood cells from SLE patients carrying the rs2004640 risk allele along with other *IRF5* risk variants [5–7, 9–11, 13, 14].

An additional alternate explanation, albeit more complex and intriguing, is the possibility that *IRF5* genetic risk does not actually confer changes in IRF5 expression levels and instead confers changes in IRF5 activity. We began considering this possibility when we detected a very significant increase in *IRF5* transcript levels in peripheral blood mononuclear cells (PBMCs) from SLE patients as compared to healthy donors that could not be explained by genotype alone (Fig. 2a) [9]. Stratification of IRF5 expression by SLE patients carrying either the homozygous risk or non-risk haplotype only provided a small association of elevated IRF5 expression with the *IRF5*-SLE risk haplotype [9]. These data were the first to suggest that there might be little contribution of the *IRF5*-SLE risk haplotype to elevated IRF5 expression. Instead, we postulated that other disease-associated factors, such as elevated levels of circulating immune complexes and/or type I IFNs, may be upregulating IRF5 expression [15]. Indeed, Niewold et al. reported that elevated IRF5 expression associated with elevated serum IFN activity in SLE patients carrying an *IRF5* risk haplotype [10]. However, since this was an association study rather than a functional study, it is not currently clear whether the *IRF5* risk haplotype is driving elevated IRF5 expression that leads to increased IFN activity, or the converse that increased IFN activity is inducing *IRF5* expression [15].

In a subsequent study, we found that IRF5 is constitutively activated, i.e., nuclear-localized, in immune cells from SLE patients (Fig. 2b, c) [16]. In unstimulated cells, or cells from healthy donors, IRF5 generally resides in the cytoplasm [15, 17–19]. Only after stimulation of cells with pathogenic stimuli (virus, Toll-like receptor ligands, etc.) or treatment with DNA damaging agents does IRF5 undergo post-translational modification leading to activation and nuclear translocation [17–23]. Currently, it is not known whether the observed increase in basal IRF5 activation in SLE immune cells is driven by the *IRF5*-SLE risk haplotype or simply due to the presence of elevated circulating "pathogenic" triggers since the *IRF5* genotype in these patients is not unknown (Fig. 2b, c) [16]. Thus, others and we have not yet excluded the possibility that the *IRF5*-SLE risk haplotype is driving IRF5 activation rather than elevated expression [16].

Given that *IRF5* exists as multiple alternatively spliced transcripts that encode for protein isoforms with distinct cellular localization, cell type-specific expression and function [15], it is entirely plausible that total *IRF5* expression levels could remain unchanged between risk and non-risk donors, yet IRF5 isoform expression is dramatically changed leading to altered IRF5 activity and/or function [24]. In support of this thesis, we previously found that the *IRF5*-SLE risk haplotype drives the abundance ranking of specific *IRF5* transcript variants that drive distinct functions [24]. While the total level of *IRF5* transcript expression was similar between risk and non-risk donors, the abundance ranking of individual transcripts was distinct between risk and non-risk donors that may indeed drive different IRF5 functionalities [24].

To date, the most well-replicated *IRF5* functional variant is the promoter CGGGG indel as four copies (4×) of it provide

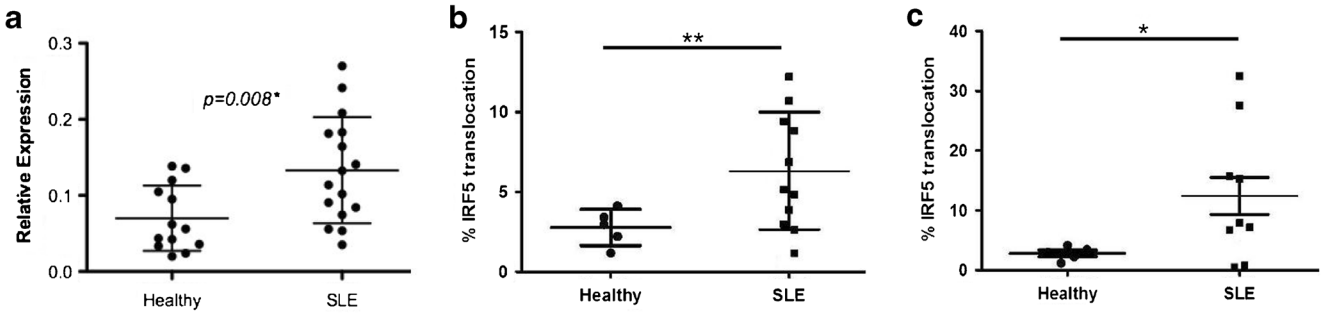

Fig. 2 IRF5 expression and activation are significantly elevated in SLE patients independent of genotype. **a** q-PCR analysis of *IRF5* expression in purified PBMC from healthy donors and SLE patients. Symbols represent independent donors. Relative expression was calculated by the ΔCt method. Lines show mean ± SD [9]. **b**, **c** IRF5 activation is significantly elevated in SLE monocytes (**b**) and B cells (**c**). IRF5 activation was determined with nuclear DRAQ5 staining by imaging flow cytometry [16]. $*p < 0.05$; $***p < 0.001$

an additional binding site for the Sp1 transcription factor that may play a role in the regulation of *IRF5* expression and/or function [6, 25•]. Similar to SNP rs2004640, the CGGGG indel has its own controversies as well since some reports indicated no effect on *IRF5* expression [25•], while others found gender-dependent effects [26]. Others yet reported decreased IFN-α production in plasmacytoid dendritic cells (pDCs) from donors carrying the CGGGG risk indel [27]. One possible explanation for the observed differences could be cell type-specific effects, as some of the studies were performed in B cells, while others were done in monocytes or pDCs [6, 25•, 26, 27]. As stated above for the rs2004640 risk allele, another possible explanation could be that even though a particular study may focus on one specific genetic variant, in this case the CGGGG indel, donors are likely to carry other risk variants that may be contributing to the observed phenotype [8]. It is extremely rare for an individual to carry only one *IRF5* risk variant. Interestingly, a recent study by Calise et al. found no change in *IRF5* expression levels between healthy donors carrying the 4× (risk) or 3× (non-risk) CGGGG repeat, and instead detected an increased susceptibility of myeloid cells (monocytes) from risk carriers to undergo DNA-damage-induced apoptosis [25•]. To date, the most studied functions for IRF5 are its role in regulating pro-inflammatory cytokine expression and cellular apoptosis [17–23, 28–30]. Important, however, is the fact that increased IRF5 expression is insufficient on its own to induce either of these functions [21–23, 25•]. Instead, IRF5 must be activated, which may or may not be a result of genetic risk [17–19, 28]. Studies by Hedl et al. found that monocyte-derived macrophages from healthy donors carrying SNP rs2004640 and the CGGGG risk indel produced significantly more pro-inflammatory cytokines when stimulated with a variety of TLR ligands [13, 14]. Unfortunately, it was not reported whether there was a change in basal IRF5 expression and/or activation in donor samples before stimulation [13, 14]. Altogether, these data support the premise that *IRF5* genetic risk may confer changes in IRF5 activity/function rather than expression.

In line with this idea and driving the differential premise that the contribution of IRF5 to SLE susceptibility may be genotype-independent is based in part on our original finding that IRF5 expression (transcript and protein) and activation (nuclear translocation) were significantly elevated in immune cells from SLE patients as compared to healthy donors, which could not be fully explained by the *IRF5*-SLE risk haplotype [9, 16] (Fig. 2b, c). The observed dysregulation of IRF5 in SLE immune cells could instead be a result of circulating antigenic triggers that include apoptotic debris, immune complexes, and type I IFNs, resulting in upregulated IRF5 expression and activation [15, 16]. This idea is further supported by findings in multiple lupus-prone strains of mice that have been backcrossed to $Irf5^{-/-}$ mice and show significant attenuation of disease onset and severity [31–38]. Each of these mouse strains ($Fc\gamma RIIB^{-/-}$, $Fc\gamma RIIB^{-/-}Yaa$, MRL/lpr, pristane-induced (Balb/c and C57Bl/6)) has distinct genetic backgrounds with distinct mechanisms that drive murine lupus and thus replicate much of the heterogeneity seen in human SLE. To our knowledge, none of these mouse strains/models have polymorphisms in the murine *Irf5* gene, yet loss of *Irf5* expression and function protects mice from disease onset and severity [31–38]. Other than attenuating disease onset and severity, however, very few, if any, of these studies has informed us of the exact role that Irf5 is playing in driving disease development. What we do know from these studies, though, is that when $Irf5^{-/-}$ mice are backcrossed to any strain of lupus-prone mice, the mice are protected from disease [31–38]. Importantly, protection was also seen in mice with reduced *Irf5* expression ($Irf5^{+/-}$) supporting a gene-dosage effect [31, 33, 37]. These data support the direct targeting of IRF5 inhibition in SLE, as a therapeutic effect would be expected even if we are unable to inhibit all cellular IRF5.

Thus, based on findings from mouse studies thus far, we have learned that a global (whole-body) loss of *Irf5* expression results in poor lymphocyte activation, a Th2 phenotype, reduced cytokine and chemokine expression, reduced monocyte trafficking, reduced immunoglobulin G (IgG) class switching, reduced levels of anti-nuclear antibodies (ANA), and reduced

plasma cell maturation [31–38]. While findings from these studies are important for the clinical validation of targeting IRF5 inhibition therapeutically, they also support that IRF5 is playing a role in lupus disease development through a mechanism that is independent of *IRF5* genetics. Further studies in murine models of lupus that characterize Irf5 expression, activation, and function in the context of disease development—before clinical onset (negative for ANA(−) and proteinuria), during early onset (ANA+), and late-stages of disease (ANA+ and proteinuria)—will significantly aid in our understanding of how Irf5 becomes dysregulated in lupus, as well as providing insight into what might be driving its dysregulation.

Conclusions

In conclusion, numerous questions relevant to IRF5 and SLE disease pathogenesis still remain unanswered. These include the following: (1) What exactly is the contribution of *IRF5* genetic risk to disease susceptibility? (2) Is genetic risk cell lineage-specific and are we looking in the right cells? (3) If *IRF5* genetic risk confers elevated IRF5 activity that is independent of transcription levels, what is driving the activation? (4) Or, is dysregulated IRF5 activity simply driven by elevated levels of circulating antigenic triggers? And (5) conversely, if IRF5 activation is driven by risk variants, is it only then driving disease onset? In order to address many of these questions, a comprehensive analysis of immune-phenotypes from multiple independent cohorts of healthy donors that carry the major homozygous *IRF5*-SLE risk haplotype, as well as donors that carry individual risk and combinations of different risk alleles, will be required to understand the contribution of *IRF5* genetic risk to SLE susceptibility. Independent of the manner in which IRF5 dysregulation contributes to SLE susceptibility, whether genetic- or non-genetic-based, compelling data from multiple labs now support that therapeutic strategies targeting IRF5 inhibition may prevent disease onset, as well as protect patients from the mortality associated with SLE.

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Compliance with Ethical Standards

Conflict of Interest Dr. Barnes reports grants from Lupus Research Alliance and grants from DoD CDMRP Lupus Research Program, during the conduct of the study. In addition, Dr. Barnes has a patent WO2017/044855A2 issued.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance

1.• Matta B, Song S, Li D, Barnes BJ. Interferon regulatory factor signaling in autoimmune disease. Cytokine. 2017;98:15–26 **This review highlights the critical role of IRF5 in both human and mouse autoimmune disease pathogenesis**.
2.• Negishi H, Taniguchi T, Yanai H. The interferon (IFN) class of cytokines and the IFN regulatory factor (IRF) transcription factor family. Cold Spring Harb Perspect Biol. 2017;**10**. https://doi.org/10.1101/cshperspect.a028423. **This is the most recent, up-to-date review on the IRF family of transcription factors**.
3. Sigurdsson S, Nordmark G, Goring HH, Lindroos K, Wilman AC, Sturfelt G, et al. Polymorphisms in the tyrosine kinase 2 and interferon regulatory factor 5 genes are associated with systemic lupus erythematosus. Am J Hum Genet. 2005;76:528–37.
4. Graham RR, Kozrev SV, Baechler EC, Reddy MV, Plenge RM, Bauer JW, et al. A common haplotype of interferon regulatory factor 5 (IRF5) regulates splicing and expression and is associated with increased risk of systemic lupus erythematosus. Nat Genet. 2006;38:550–5.
5. Graham RR, Kyogoku C, Sigurdsson S, Vlasova IA, Davies LR, Baechler EC, et al. Three functional variants of IFN regulatory factor 5 (IRF5) define risk and protective haplotypes for human lupus. Proc Natl Acad Sci U S A. 2007;104:6758–63.
6. Sigurdsson S, Goring HH, Kristjansdottir G, Milani L, Nordmark G, Sandling JK, et al. Comprehensive evaluation of the genetic variants of interferon regulatory factor 5 (IRF5) reveals a novel 5 bp length polymorphism as strong risk factor for systemic lupus erythematosu. Hum Mol Genet. 2008;17:872–81.
7. Lofgren SE, Yin H, Delgado-Vega AM, Sanchez E, Lewen S, Pons-Estel BA, et al. Promoter insertion/deletion in the IRF5 gene is highly associated with susceptibility to systemic lupus erythematosus in distinct populations, but exerts a modest effect on gene expression in peripheral blood mononuclear cells. J Rheumatol. 2010;37:574–8.
8. Kottyan LC, Zoller EE, Bene J, Lu X, Kelly JA, Rupert AM, et al. The *IRF5-TNPO3* assocation with systemic lupus erythematosus has two components that other autoimmune disorders variably share. Hum Mol Gen. 2015;24:582–96.
9. Feng D, Stone RC, Eloranta ML, Sangster-Guity N, Normark G, Sigurdsson S, et al. Genetic variants and disease-associated factors contribute to enhanced interferon regulatory factor 5 expression in blood cells of patients with systemic lupus erythematosus. Arthritis Rheum. 2010;62:562–73.
10. Niewold TB, Kelly JA, Flesch MH, Espinoza LR, Harley JB, Crow MK. Association of the IRF5 risk haplotype with high serum interferon-alpha activity in systemic lupus erythematosus patients. Arthritis Rheum. 2008;58:2481–7.
11. Niewold TB, Kelly JA, Kariuki SN, Franek BS, Kumar AA, Kaufman KM, et al. IRF5 haplotypes demonstrate diverse serological associations which predict serum interferon alpha activity and explain the majority of the genetic association with systemic lupus erythematosus. Ann Rheum Dis. 2012;71:463–8.
12. Kozyrev SV, Lewén S, Reddy PM, Pons-Estel B; Argentine Collaborative Group, Witte T; German Collaborative Group,

Junker P, Laustrup H, Gutiérrez C, Suárez A, Francisca González-Escribano M, Martín J; Spanish Collaborative Group, Alarcón-Riquelme ME. Structural insertion/deletion variation in IRF5 is associated with a risk haplotype and defines the precise IRF5 isoforms expressed in systemic lupus erythematosus. Arthritis Rheum 2007;56:1234–1241.

13. Hedl M, Abraham C. IRF5 risk polymorphisms contribute to interindividual variance in pattern recognition receptor-mediated cytokine secretion in human monocyte-derived cells. J Immunol. 2012;188:5348–56.
14. Hedl M, Yan J, Abraham C. IRF5 and IRF5 disease-risk variants increase glycolysis and human M1 macrophage polarization by regulating proximal signaling and Akt2 activation. Cell Rep. 2016;16:2442–55.
15. Mancl ME, Hu G, Sangster-Guity N, Olshalsky SL, Hoops K, Fitzgerald-Bocarsly P, et al. Two discrete promoters regulate the alternatively spliced human interferon regulatory factor-5 isoforms. Multiple isoforms with distinct cell type-specific expression, localization, regulation, and function. J Biol Chem. 2005;280:21078–90.
16. Stone RC, Feng D, Deng J, Singh S, Yang L, Fitzgerald-Bocarsly P, et al. Interferon regulatory factor 5 activation in monocytes of systemic lupus erythematosus patients is triggered by circulating autoantigens independent of type I interferons. Arthritis Rheum. 2012;64:788–98.
17. Schoenemeyer A, Barnes BJ, Mancl ME, Latz E, Goutagny N, Pitha PM, et al. The interferon regulatory factor, IRF-5, is a central mediator of toll-like receptor 7 signaling. J Biol Chem. 2005;280:17005–12.
18. Barnes BJ, Moore PA, Pitha PM. Virus-specific activation of a novel interferon regulatory factor, IRF-5, results in the induction of distinct interferon alpha genes. J Biol Chem. 2001;276:23382–90.
19. Barnes BJ, Kellum MJ, Field AE, Pitha PM. Multiple regulatory domains of IRF-5 control activation, cellular localization and induction of chemokines that mediate T-lymphocyte recruitment. Mol Cell Biol. 2002;22:5721–40.
20. Barnes BJ, Kellum MJ, Pinder KE, Frisancho JA, Pitha PM. Interferon regulatory factor 5, a novel mediator of cell cycle arrest and cell death. Cancer Res. 2003;63:6424–31.
21. Hu G, Mancl M, Barnes BJ. Signaling through IFN regulatory factor-5 sensitizes p53-deficient tumors to DNA damage-induced apoptosis and cell death. Cancer Res. 2005;65:7403–12.
22. Hu G, Barnes BJ. IRF-5 is a critical mediator of the death receptor-induced apoptotic signaling pathway. J Biol Chem. 2009;284:2767–77.
23. Couzinet A, Tamura K, Chen HM, Nishimura K, Wang ZC, Morishita T, et al. A cell-type-specific requirement for IFN regulatory factor 5 (IRF5) in Fas-induced apoptosis. Proc Natl Acad Sci U S A. 2008;105:2556–61.
24. Stone RC, Du P, Feng D, Dhawan K, Ronnblom L, Eloranta ML, et al. RNA-Seq for enrichment and analysis of IRF5 transcript expression in SLE. PLoS One. 2013;8:e54487.
25.• Calise J, Marquez Renteria S, Gregersen PK, Diamond B. Lineage-specific functionality of an interferon regulatory factor 5 lupus risk haplotype: lack of B cell intrinsic effects. Front Immunol. 2018;9:996 **This is the first study to document no effect of an *IRF5* risk haplotype on *IRF5* mRNA expression in genotyped healthy donors**.
26. Griesbeck M, Ziegler S, Laffont S, Smith N, Chauveau L, Tomezsko P, et al. Sex differences in plasmacytoid dendritic cell levels of IRF5 drive higher IFN-α production in women. J Immunol. 2015;195:5327–36.
27. Berggren O, Alexsson A, Morris DL, Tandre K, Weber G, Vyse TJ, et al. IFN-α production by plasmacytoid dendritic cell associations with polymorphisms in gene loci related to autoimmune and inflammatory diseases. Hum Mol Genet. 2015;24:3571–81.
28. Takaoka A, Yanai H, Kondo S, Duncan G, Negishi H, Mizutani T, et al. Integral role of IRF-5 in the gene induction programme activated by toll-like receptors. Nature. 2005;434:243–9.
29. Yanai H, Chen HM, Inuzuka T, Kondo S, Mak TW, Takaoka A, et al. Role of IFN regulatory factor 5 transcription factor in antiviral immunity and tumor suppression. Proc Natl Acad Sci U S A. 2007;104:3402–7.
30. Krausgruber T, Blazek K, Smallie T, Alzabin S, Lockstone H, Sahgal N, et al. IRF5 promotes inflammatory macrophage polarization and TH1-TH17 responses. Nat Immunol. 2011;12:231–8.
31. Richez C, Yasuda K, Bonegio RG, Watkins AA, Aprahamian T, Busto P, et al. IFN regulatory factor 5 is required for disease development in the FcgammaRIIB−/-Yaa and FcgammaRIIB−/− mouse models of systemic lupus erythematosus. J Immunol. 2010;184:796–806.
32. Tada Y, Kondo S, Aoki S, Koarada S, Inoue H, Suematsu R, et al. Interferon regulatory factor 5 is critical for the development of lupus in MRL/lpr mice. Arthritis Rheum. 2011;63:738–48.
33. Feng D, Yang L, Bi X, Stone RC, Patel P, Barnes BJ. Irf5-deficient mice are protected from pristane-induced lupus via increased Th2 cytokines and altered IgG class switching. Eur J Immunol. 2012;42:1477–87.
34. Xu Y, Lee PY, Li Y, Liu C, Zhuang H, Han S, et al. Pleiotropic IFN-dependent and -independent effects of IRF5 on the pathogenesis of experimental lupus. J Immunol. 2012;188:4113–21.
35. Yasuda K, Watkins AA, Kochar GS, Wilson GE, Laskow B, Richez C, et al. Interferon regulatory factor-5 deficiency ameliorates disease severity in the MRL/lpr mouse model of lupus in the absence of a mutation in DOCK2. PLoS One. 2014;9:e103478.
36. Watkins AA, Yasuda K, Wilson GE, Aprahamian T, Xie Y, Maganto-Garcia E, et al. IRF5 deficiency ameliorates lupus but promotes atherosclerosis and metabolic dysfunction in a mouse model of lupus-associated atherosclerosis. J Immunol. 2015;194:1467–79.
37. Savitsky DA, Yanai H, Tamura T, Taniguchi T, Honda K. Contribution of IRF5 in B cells to the development of murine SLE-like disease through its transcriptional control of the IgG2a locus. Proc Natl Acad Sci U S A. 2010;107:10154–9.
38. Yang L, Feng D, Bi X, Stone RC, Barnes BJ. Monocytes from Irf5 −/− mice have an intrinsic defect in their response to pristane-induced lupus. J Immunol. 2012;189:3741–50.