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Interferon-inducible *Ifi200*-family genes as modifiers of lupus susceptibility

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Abstract

Both genetic and environmental factors contribute to the development and progression of systemic lupus erythematosus (SLE), a complex autoimmune disease. The disease exhibits a strong gender bias and develops predominantly in females. Additionally, most SLE patients exhibit increased serum levels of interferon-α (IFN-α) and the "IFN signature". Studies using the mouse models of lupus have identified several lupus susceptibility loci, including the New Zealand Black (NZB)-derived autoimmunity 2 (*Nba2*) interval on the chromosome 1. The interval, which is syntenic to the human chromosome 1q region, harbors the FcγR family, SLAM/CD2-family, and the IFN-inducible *Ifi200*-family genes (encoding for the p200-family proteins). Studies involving the B6.*Nba2* congenic mice revealed that the development of antinuclear autoantibodies (ANAs) depends on the age, gender, and activation of type I IFN-signaling. Interestingly, recent studies involving the generation of *Nba2* subcongenic mouse lines and generation of mice deficient for the *Fcgr2b* or *Aim2* gene within the interval have provided evidence that epistatic interactions among the *Nba2* genes contribute to increased lupus susceptibility. Given that the expression of some of the p200-family proteins is differentially regulated by sex hormones and these proteins differentially regulate cytosolic DNA-induced production of type I IFN and proinflammatory cytokines (IL-1β and IL-18), the major known contributors of SLE-associated inflammation, we discuss the recent advancements in our understanding of the role of p200-family proteins in lupus susceptibility modification. An improved understanding of the role of p200-family proteins in the development of autoimmunity is likely to identify new approaches to treat SLE patients.

Keywords

Lupus susceptibility; *Nba2* locus; Interferons; Sex hormones; *Ifi200*-family genes

1. Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease [1–6]. The disease is highly heterogeneous and has a potential to involve multiple organ systems. SLE in patients

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(and mouse models) is characterized by increased production of pathogenic anti-nuclear autoantibodies (ANAs), the presence of immune complexes containing nucleic acids that are bound to DNA-binding proteins, increased serum levels of interferon-α (IFN-α) and increased expression of a set of IFN-inducible genes (the "IFN-signature"), and increased serum levels of B cell activating factor (BAFF) [1–3].

The development of SLE involves immune dysregulation at the interface between the innate and adaptive immune systems [7, 8]. Studies have suggested that a defective clearance of cellular debris causes a loss of self-tolerance, autoantibody production, and the formation of immune complexes (ICs) [8]. ICs containing nucleic acids such as self DNA activate innate immune responses [8, 9]. Consequently, several clinical manifestations of SLE are thought to be the result of ICs deposition in tissues leading to secondary inflammatory responses and tissue damage [1, 2, 8, 9]. Therefore, ICs are thought to be the predominant cause of SLE-associated inflammation [1–3, 9].

SLE patients and certain mouse models exhibit a strong gender bias in the development of disease: develops at a female-to-male ratio of 9:1 [10–12]. Although, the etiology of human SLE remains unknown, there is considerable evidence that genetic, hormonal, and environmental factors contribute to the development and progression of lupus [1–3]. Correspondingly, multiple lupus susceptibility genes and pathways appear to be involved in lupus susceptibility [13, 14].

Genetic studies have identified polymorphisms within genes of the IFN pathway (and the IFN-regulated genes) that confer an increased risk for the development of SLE [15, 16]. Notably, the production of type IFNs *in vivo* is regulated by mechanisms that have the capacity to self-amplify upon recognition of IFN-inducing ligands (for example, ICs containing self DNA), thus, resulting in a feed-forward amplification loop of type I IFN production [17, 18]. Increased production of type I IFNs in SLE patients and certain mouse models is associated with organ and tissue damage [17–19].

Our overall understanding of the molecular mechanisms that contribute to the development of lupus disease and associated immunopathology has derived in part from studies involving mouse models [6, 20–22]. These models include the F_1 hybrid of the New Zealand Black (NZB) and New Zealand White (NZW) strains, the MRL/lpr, and BXSB/Yaa strains, which spontaneously develop the disease. Additionally, there are models that are derived from the hybrid mice (for example, NZM2328 and NZM2410). Generation of B6.*Nb2* congenic (congenic for the NZB-derived *Nba2* interval on the C57BL/6 genetic background) mice indicated that female mice spontaneously develop splenomegaly (due to increases in the number of B and T cells) and increased levels of a variety of ANAs (anti-dsDNA, anti-chromatin, and anti-histone) much earlier than the age-matched male mice [23, 24]. The development of ANAs was age (~6–7-month) dependent. Additionally, the B6.*Nba2* mice express increased levels of *Ifi202* (a member of the IFN-inducible *Ifi200*-family of genes) mRNA and protein in splenic B cells and non-T/non-B cells [23]. Although, B6.*Nba2* mice do not develop a kidney disease, however, (B6.*Nba2* x NZW)F_1 mice develop the disease like the (NZB x NZW)F_1 mice, indicating a cooperation between the *Nba2* interval genes and the NZW loci in the development of a kidney disease [23]. Interestingly, a deficiency of type I IFN-signaling in the B6.*Nba2* mice reduces lupus-like disease [25]. Accordingly, treatment of mice with polyI:C, which induces the production of IFN-α/β, accelerates the development of ANA phenotype and lupus-like nephritis in the (B6.*Nba2* x NZW)F_1 mice [26], indicating a role for the IFN-signaling in modifying the development and progression of lupus disease. Moreover, TLR9-deficient B6.*Nba2* mice, which express increased levels of TLR7, display increased production of ANAs and also develop lupus nephritis [27], suggesting opposing regulatory roles for the TLR7 and TLR9 in modifying the ANA

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phenotype and progression of lupus disease in these mice. Furthermore, overexpression of B cell activating factor (BAFF) in B6.*Nba2*.BAFF transgenic mice as compared to age-matched non-transgenic or B6.BAFF mice accelerated the development of a kidney disease [28]. Given that B6.*Nba2* congenic mice exhibit a sex bias in the development of ANA phenotype [23, 29] and the development of the ANA phenotype requires the type I IFN-signaling [25, 26], this mouse model has emerged as a valuable model to investigate the potential role of sex hormones and IFN-signaling in the development of autoimmunity [12].

The *Nba2* interval (~90–97 cM; see Fig. 1), which is located on the distal portion of the NZB chromosome 1, has emerged as a major genetic contribution to the disease susceptibility in the (NZB x NZW)F_1 mice [20, 23, 30, 31]. The interval is syntenic to human lupus susceptibility region 1q and contains genes that encode for the Fcγ receptors (including the FcγRIIB receptor), Slam/CD2 family proteins, and p200-family proteins (encoded by the *Ifi200*-family genes) [30, 32, 33]. Interestingly, the generation of subcongenic mouse lines of the *Nba2* interval [34, 35] and generation of mice deficient for the *Fcgr2b* (encoding for the inhibitory FcγRIIB receptor) [36, 37] or *Aim2* (encoding for the Aim2 protein, a member of the p200-family) [38, 39] gene have provided important evidence that epistatic interactions among the *Nba2* interval genes contribute to an increased lupus susceptibility. In this review, we discuss the recent advancements in our understanding of the role of *Ifi200*-genes as modifiers of lupus susceptibility.

2. The interferon-inducible *Ifi200*-family genes as immune regulators

The *Ifi200*-family genes encode for structurally and functionally-related p200-family proteins [12, 32, 40–43]. The family includes murine (for example, *Ifi202a*, *Ifi202b*, *Ifi203*, *Ifi204*, and *Aim2*) and human (for example, *MNDA*, *IFIX*, *IFI16*, and *AIM2*) genes [32]. The *Ifi202a* and *Ifi202b* are highly homolgous genes and encode for p202a and p202b proteins [44]. Therefore, in this review, we refer both p202a and p202b proteins as p202 protein.

The p200-family proteins share a partially conserved repeat of 200-amino acids residues (also called HIN-200 domain). The HIN-200 domain allows binding to double-stranded DNA (dsDNA) in a sequence independent manner [45, 46]. Interestingly, the crystal structures of both HIN-A and HIN-B domains of IFI16 protein (encoded by the *IFI16* gene) revealed that each HIN domain is capable of enhancing p53-DNA complex formation and transcriptional activation [47]. However, both domains distinctly regulate the p53-mediated transcription: the HIN-A domain binds to the basic C terminus of p53 protein, whereas the HIN-B domain binds to the core DNA-binding region of p53. Notably, both protein-protein interactions are compatible with the DNA-bound state of p53. Except the p202a and p202b proteins, all p200-family proteins also share a homotypic protein-protein interaction pyrin domain (PYD) [39]. Most p200-family proteins (except the p202a and p202b proteins) contain both PYD and HIN-200 domain, therefore, these proteins are also called PYHIN-family proteins [48].

Most p200-family proteins (except the murine Aim2 and human AIM2 proteins), depending upon the cell type, are detected both in the cytoplasmic as well as in the nuclear fractions to some extents [39, 49]. Interestingly, activation of IFN-signaling in immune cells, which induces the expression of p200-family proteins, also potentiates the nuclear localization of certain proteins, including the p202 proteins [39, 50, 51].

Recent studies have indicated that certain p200-family proteins can sense cytosolic DNA in innate immune cells (macrophage and dendritic cells) [52–56]. Upon sensing cytosolic DNA in bone marrow-derived macrophages, the p202 protein (possibly both p202a and p202b) does not initiate an innate immune response [46]. However, PYHIN proteins such as p204

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[52], Aim2 and AIM2 [53–55], and IFI16 [52] can initiate innate immune responses after sensing cytosolic DNA in monocytes or macrophages. Interestingly, Aim2 and AIM2 proteins form inflammasomes [46, 53–55], which through activation of caspase-1, increase the secretion of proinflammatory cytokines, such as IL-1β and IL-18. Additionally, the activation of an inflammasome also induces cell death by pyroptosis (caspase-1-dependent death) in macrophages [46]. In contrast to the Aim2/AIM2 proteins, upon sensing dsDNA, the p204 and IFI16 proteins were reported to recruit stimulator of interferon genes (STING) protein to stimulate the expression of IFN-β through the activation of interferon-regulated factor 3 (IRF3) and NF-κB [52]. Consistent with the above role for the p200-family proteins in innate immune responses, a recent study has noted that IFI16 protein may play an important role in sensing intracellular dsDNA in human monocyte-derived DCs as well as primary DCs [56]. Importantly, the study reported that human dsDNA-activated DCs, rather than LPS- or inflammatory cytokine mixture-activated DCs, represent the most potent inducers of naive $CD4^+$ T cells to promote Th1-type cytokine production and generate $CD4^+$ and $CD8^+$ cytotoxic T cells. These studies clearly indicate an important role for the p200-family proteins in the initiation of innate immune responses upon sensing cytosolic DNA.

Overexpression of *Ifi202* gene enhances the LPS-induced IL-12p40 and NF-κB promoter activities in a murine macrophage cell line (RAW 264.7) [57]. In addition, forced expression of *Ifi202* gene enhances IL-12p40 mRNA induction in NZW bone marrow-derived dendritic cells (BMDCs) [57]. This observation raises the possibility that increased levels of the p202 protein in macrophages regulate the expression of IL-12p40, which is required for the production of IL-12 and IL-23. Increased expression of both IL-12 and IL-23 is important for T_H1 and T_H17 differentiation [58].

In addition, there is emerging evidence that p200-family proteins also participate in the regulation of adaptive immune responses through regulating the production of cytokines, including the type I IFN, which regulate cell proliferation, survival, and differentiation of immune cells, including B and T cells [23, 59–63]. Treatment of splenic B and T cells with IFN-α or their stimulation up-regulates the expression of p202 protein [62]. Increased levels of p202 protein in splenic B cells from lupus-prone B6.*Nba2* female mice (see below) are associated with defects in the expression of target genes for E2F1 [64] and p53 [65] transcription factors that encode for pro-apoptotic proteins. Moreover, increased levels of the p202 protein in B cells are associated with defects in apoptosis after an *in vitro* ligation with anti-IgM [23].

p202 protein also inhibits the transcriptional activities of AP-1 [66] and c-Myc [67] in a variety of cell types. Moreover, p202 protein modulates the transcriptional activity of NF-κB, a potent regulator of immunoregulatory genes, in a cell-type dependent manner [57, 66, 68]. These observations raise the possibility that increased levels of the p202 protein in immune cells, including B and T cells, promote survival of autoreactive cells through transcriptional modulation of genes that promote cell survival.

2.1 Identification of Ifi202 as a candidate lupus susceptibility gene within the Nba2 interval

Generation of B6.*Nba2* congenic mice allowed screening for candidate lupus susceptibility genes within the *Nba2* interval through gene expression analyses [23]. The analyses, which involved pair-wise comparisons of gene expression between C57BL/6 (B6) and B6.*Nba2* female mice (age ~4-mo), identified two genes (*Ifi202* and *Ifi203*), expression of which was altered significantly. Splenic cells from the congenic mice had 10–100-fold higher steady-state levels of *Ifi202* mRNA and lower levels of *Ifi203* mRNA [23]. However, the expression pattern was opposite in the B6 cells. Considering that the lupus phenotype in SLE patients and mouse models is associated with multiple genes [4, 5], identification of only two genes with differential expression between B6 and B6.*Nba2* mice in the above

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gene expression analyses was consistent with the inclusion of limited (only ~11,000) number of genes in microarray gene expression analysis. Of note, several observations provided support for the potential role of the *Ifi202* gene in the *Nba2* interval-associated phenotype (ANA production). Firstly, we identified promoter polymorphisms in the *Ifi202* gene between B6 and NZB strain of mice, which are associated with increased basal and induced expression of *Ifi202* gene in the B6.*Nba2* congenic mice [23, 24, 32]. Secondly, several studies involving other mouse models of SLE provided evidence for a role for the *Ifi202* gene in the development of autoimmunity [32]. Thirdly, nuclear localization of p202 protein modulates the transcriptional activity of immunoregulatory factors, including the NF-κB and AP-1, in a cell type-dependent manner [66, 68]. Thus, raising the possibility that mouse strain-dependent increased nuclear levels of the p202 protein contribute to autoimmunity through modulating the transcription of immunomodulatory genes [24, 32]. Fourthly, expression of *Ifi202* gene is differentially regulated by sex hormones: the female sex hormone estrogen (17β-estradiole) up-regulates the expression, whereas the male hormone androgen (dihydrotestosterone) suppresses the expression [69]. Interestingly, our observations that a deficiency of type I IFN-signaling in NZB female mice [70], which reduced lupus disease, did not decrease levels of the p202 protein raised the possibility that other cytokines could regulate the expression of *Ifi202* gene in B6.*Nba2* mice. Accordingly, we noted that IL-6 signaling through STAT3 activation can up-regulate the expression of *Ifi202* gene in the B6.*Nba2* mice [71]. Given that p202 protein's nuclear localization (thus, its ability to modulate the expression of immunoregulatory genes) is potentiated by an activation of type I IFN-signaling [50, 51] and a deficiency in type I IFN-signaling in the B6.*Nba2* mice reduced lupus disease [25], these observations make it likely that increased nuclear levels of the p202 protein in immune cells enhance the ANA phenotype in B6.*Nba2* female mice in part through transcriptional modulation of the *Nba2* interval genes.

2.2. p202 proteins and their regulation

Both p202a and p202b proteins are highly similar proteins [44]. Interestingly, *Ifi202a*-deficiency in mice and in embryonic fibroblasts increases levels of the p202b protein by a posttranscriptional mechanism [44]. Given that p202a and p202b proteins differ by only seven amino acid residues in the N-terminus, a compensatory increase in the levels of p202b protein in *Ifi202a*-deficient mice (and cells) could account for a lack of phenotype [44].

Steady-state levels of p202 protein are regulated by both transcriptional and post-transcriptional mechanisms [72]. These mechanisms include stabilization of *Ifi202* mRNA in IFN-treated cells. Consistent with the above observations, the 3′-untraslated region in the *Ifi202* mRNA contains three APyTGA-like regulatory elements, which are known to stabilize mRNAs after estrogen treatment of cells [73]. Importantly, a 50% increase (or decrease) in the levels of p202 protein in a variety of cultured cell lines and splenic B cells inhibits cell cycle progression and also modulates cell survival [32, 72].

The amino acid sequence of p202 protein contains a potential mitochondrial targeting sequence (MTS) in the N-terminus [50]. Consistent with the presence of an MTS in the p202 protein, a fraction of the p202 in the cytoplasm is detected in the mitochondria [50, 51]. Because p202 protein lacks a classical nuclear localization signal (NLS) and a nuclear export signal (NES) [72] and activation of IFN-signaling potentiates the nuclear localization in B6.*Nba2* MEFs [50] and B cells [35], these observations support the idea that nucleo-cytoplasmic distribution of p202 protein in immune cells depends on the p202-binding proteins.

p202 is a phosphoprotein [45, 51] and dephosphorylation of p202 protein increases its ability to bind DNA *in vitro* [45]. Although, protein kinases that phosphorylate p202 protein remain unknown, the protein is predicted to be phosphorylated by several protein kinases.

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These kinases include the cyclin-dependent kinase-5 (Cdk-5) on Thr-46, Cdk-1 on Thr-46, PKC-epsilon on Ser-85 and Ser-436, PKC-delta on Ser-436, PKC-zeta on Ser-185 and Ser-275, DNA-PK on Ser-346, casein kinase 1 on Thr-168, and casein kinase 2 on Ser-344 and Ser-345. Because the unphosphorylated p202 protein binds to DNA tightly[45] and p202 protein also associates with the chromatin *in vivo* [51], these observations support the idea that phosphorylation of p202 protein regulates its nuclear levels.

Like other members of the p200-family proteins, p202 appears to homo- and heterodimerize [74]. Moreover, homodimerization of p202 protein depends on a motif MFHATVAT, which is conserved among the p200-family proteins. Notably, a substitution of His residue in the motif with a Phe residue abrogated the p202-mediated inhibition of the transcriptional activity of AP-1 [75]. Importantly, there are indications that p202 protein heterodimerizes with p204 protein [72, 76]. These observations are consistent with the idea that heterodimerization of p202 with other p200-family proteins in immune cells may regulate its nucleocytoplasmic distribution and functions.

3. The NZB-derived *Ifi200*-family genes are insufficient in the development of autoimmunity

To assess the relative genetic contributions of the *Nba2* interval genes in ANA phenotype, subcongenic mice (B6.*Nba2*-A, B6.*Nba2*-B, B6.*Nba2*-A′B, B6.*Nba2*-BC, and B6.*Nba2*-C) have been generated [34]. Comparisons of these subcongenic strains of female mice with the parental strains (B6 and NZB) and congenic B6.*Nba2* (mice indicated as the B6.*Nba2*-ABC) female mice with respect to the ANA phenotype and type I IFN production revealed that the B6.*Nba2*-A female mice (mice harboring the subinterval A that comprises the *FcγRs* genes; see Fig. 1) and B6.*Nba2*-B female mice (mice harboring the subinterval B that comprises the *Slam*-family genes) develop detectable levels of certain ANAs. However, levels of ANA were much higher in the B6.*Nba2*-A′B mice (mice harboring both *FcγRs* and *Slam*-familygenes), thus, indicating that the *FcγR* interval and *Slam* interval genes cooperate with each other to influence the autoantibody production [34]. Additionally, increased ANA levels in the B6.*Nba2*-A′B mice were associated with increased production of type I IFN. Moreover, the study revealed that B6.*Nba2*-C female mice (harboring subinterval C that comprises the *Ifi200*-family genes) do not develop ANAs and produce type I IFN. Together, these observations demonstrated that the *Ifi200*-family genes are not sufficient to break the tolerance in the B6.*Nba2*-C subcongenic mice [34]. Given that expression of most of *Ifi200*-family genes is up-regulated by type I IFNs [32], the lack of ANA phenotype in the B6.*Nba2*-C subcongenic mice is consistent with a reduced expression of these genes in the absence of type I IFN production (Table 1). Moreover, because type I IFN-induced signaling potentiates the nuclear localization (and nuclear functions) of the p202 protein [50, 51], the lack of type I IFN production in B6.*Nba2*-C subcongenic mice reduced the nuclear localization of the p202 protein in splenic B cells (Table 1). Interestingly, the study revealed that epistatic interactions between the *Ifi200*-family genes and *Fcgr2b* gene may down-regulate the expression of the *Fcgr2b* gene, resulting in an inhibition of the FcγRIIB-induced apoptosis [34].

4. The *Fcγr2b* gene is a lupus susceptibility modifier gene within the *Nba2* interval

As noted above, the *Nba2* subinterval-A harbors genes that encode for Fc receptors for IgG [77, 78]. These receptors regulate innate and adaptive immune responses. Four Fcγ receptors have been reported in mice [77, 78]. Upon stimulation by immune complexes, the FcγRI and FcγRIII receptors initiate a stimulatory response through the FcRγ chain. The

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chain contains an intracellular immunoreceptor tyrosine-based activating motif (ITAM). In contrast to the stimulatory receptors, the FcγRIIB receptor (encoded by the *Fcgr2b* gene) transduces inhibitory signals via intracellular immunoreceptor tyrosine-based inhibitory motif (ITIMs). Because FcγRIIB receptor is the only Fcγ receptor, which is expressed by B cells, its expression is regulated tightly [78]. In humans and mice, isoforms of the inhibitory FcγRIIB receptor have been reported [79, 80]. The FcγRIIB1 isoform is predominantly expressed by B cells, whereas FcγRIIB2 isoform is predominantly expressed by myeloid-derived cells [78, 80]. Expression of FcγRIIB receptor in immune cells inhibits the functions of the activating Fcγ receptors [78]. These functions include phagocytosis and pro-inflammatory cytokine release. Consequently, the FcγRIIB receptor regulates several immune responses [78].

4.1 Epistatic interactions involving the Fcgr2b gene in the ANA phenotype

A deficiency of FcγRIIB receptor in mice of certain genetic background results in the development of autoimmunity [36, 81–83]. For example, *Fcgr2b*-deficient mice on the mixed (mice indicated as $\text{Fc}\gamma\text{RIIB}_{129}{}^{-/-}$; embryonic stem cells derived from the 129 strain of mice) genetic background develop autoimmunity [36, 81]. However, *Fcgr2b*-deficent mice on the B6 genetic background (mice indicated as $\text{Fc}\gamma\text{RIIB}_{\text{B6}}{}^{-/-}$; mice generated from the B6 embryonic stem cells) do not develop autoimmunity [36]. The development of autoimmunity in the $\text{Fc}\gamma\text{RIIB}_{129}{}^{-/-}$ mice has been attributed to epistatic interactions between 129-derived *Sle16* locus (the locus contains the *Nba2* interval genes) and B6 genes [36]. Interestingly, splenic cells from the lupus-prone $\text{Fc}\gamma\text{RIIB}_{129}{}^{-/-}$ female mice exhibit activation of an IFN-response and express increased levels of the p202 protein [37, 84]. Similarly, a blockade of the inhibitory FcγRIIB receptor in human innate immune cells (dendritic cells and monocytes) induces a type I IFN response, activates phosphorylation of STAT1, and induces expression of certain IFN-inducible genes, including the IFI16 and AIM2 p200-family proteins [85]. These observations provided evidence for epistatic interactions involving the *Fcgr2b* gene with other genes, including the *Nba2* interval genes, in the modification of *Nba2* interval-associated ANA phenotype through activation of an IFN response.

4.2 Epistatic interactions between the Ifi202 and Fcgr2b genes

Certain polymorphisms involving short deletions in the promoter and intronic regions of the murine *Fcgr2b* gene are associated with reduced steady-state levels of mRNA in germinal center B cells and plasma cells in certain lupus-prone strains of female mice (including the NZB mice) [78–80]. However, the observation that epistatic interactions between Fcγ receptor genes and p200-family genes may contribute to reduced expression of the *Fcgr2b* gene in the B6.*Nba2* mice [34, 35] (independent of known polymorphisms) served as a basis to investigate whether IFNs or IFN-inducible p202 protein could down-regulate the expression of the *Fcgr2b* gene. The investigation revealed that activation of IFN-signaling in splenic cells by IFN-α or IFN-γ significantly decreases levels of the FcgRIIB mRNA and protein [84]. Furthermore, increased expression of p202 protein in cells, which increased the expression IFN-β and activated an IFN response, suppressed the expression of the *Fcgr2b* gene [84]. These observations provided further evidence for epistatic interactions between the *Ifi202* and the *Fcgr2b* genes in increased production of ANAs in the B6.*Nba2* mice.

5. Epistatic interactions between the *Slam*-family and *Ifi200*-family genes

Genetic studies have implicated the signaling lymphocytic activation molecule (SLAM) family of cell surface receptors in the modulation of immune cell functions [86–88]. The family consists of nine transmembrane proteins (for example, the SLAMF1 to SLAMF9) that are differentially expressed on lymphoid and myeloid cells [87, 88]. Interestingly,

studies have indicated that increased expression of SLAMF3 and SLAMF6 in human SLE T cells promotes Th17 differentiation [89]. Similarly, increased expression of *Ly108.1* (or *Slamf6*) in immature B cells from lupus-prone B6.*Sle1z* mice is associated with the development of lupus phenotype [90]. Additionally, the SLAMF6-driven co-stimulation of peripheral T cells was found to be defective in human SLE T cells [91].

SLAMF1 (or CD150) is a self-ligand cell surface glycoprotein (~75 kDa), which is expressed on T, B, macrophages, and dendritic cells [86, 87]. *Slamf1*-deficient T cells ($CD4^+$) produce increased levels of interferon-γ [92]. Moreover, *Slam*-deficient mice on the C57BL/6 genetic background develop a lupus-like disease [93]. Cross-linking of the Slamf1 receptor on $CD4^+$ T cells induces rapid serine phosphorylation of the Akt/PKB protein kinase [94]. Given that the AKT kinase inactivates MDM2 protein (a negative regulator of the p53) through phosphorylation [95] and the activation of the p53 represses the transcription of a number genes, including the *Ifi202* gene [96], it is likely that the Slamf1 receptor regulates T-cell proliferation and survival through suppression of the *Ifi202* gene. Accordingly, in a NOD mouse line, which is congenic for the B6-derived *Nkt1* locus (which includes the *Slam* and the *Ifi200*-family genes), the increased expression of *Slamf1* gene was inversely correlated with the *Ifi202* gene [97]. Moreover, increased expression of *Slamf1* gene was associated with an increased expression of the *Ifi203* gene. These observations predict that epistatic interactions between the *Ifi200*-family genes and *Slam*-family genes could contribute to ANA phenotype in the B6.*Nba2* mice. Therefore, further studies are needed to investigate the potential role of the interactions between *Ifi200*-family genes and *Slam*-family genes (*Slamf1-9*) in the *Nba2* interval-associated phenotype.

6. Interactions among the *Ifi200*-family genes

Steady-state levels of *Ifi202* mRNA in B6.*Nba2* splenic cells are inversely correlated with levels of *Ifi203* mRNA [23]. Furthermore, overexpression of p202 protein in RAW264.7 macrophage cells decreases levels of the p203 protein [98]. These observations suggested a mutual regulation of gene expression by the p200-family proteins.

6.1 Interactions between Ifi202 and Aim2 genes in the Nba2 interval-associated phenotype

Generation of *Aim2*-deficeint mice on the C57BL/6 genetic background (ES cells derived from the B6 mice; mice indicated as $Aim2_{B6}^{-/-}$) [99] and the mixed genetic background (ES cells from the 129 strain of mice; mice indicated as $Aim2_{129}^{-/-}$) [38] and their characterization indicated that Aim2 protein expression is not required for the production of type I IFN upon infections with certain bacteria or viruses. Interestingly, the deficiency of the *Aim2* gene in mice (both $Aim2_{B6}^{-/-}$ and $Aim2_{129}^{-/-}$) increased constitutive as well as induced (induced by infection by pathogens or transfection of DNA) levels of IFN-β [38, 98, 99]. These observations raised the possibility that Aim2 expression in immune cells suppresses the expression of IFN-β. Accordingly, we noted that *Aim2*-deficiency in the $Aim2_{129}^{-/-}$ mice was associated with activation of type I IFN response: increased expression of IFN-β, activation of IFN-signaling, and an induction of the IFN-inducible proteins, including the p202 protein [98]. Moreover, levels of the inhibitory receptor FcγRIIB were decreased [84]. These observations, which indicated that expression of Aim2 protein in immune cells suppresses the type I IFN response and the expression of p202 protein, served as a basis to investigate whether increased levels of p202 protein in innate immune cells activate an IFN response. Surprisingly, increased expression of p202 protein in macrophage cell line RAW264.7 activated an IFN response and suppressed the expression of both Aim2 and FcγRIIB receptor [84]. Accordingly, increased levels of p202 protein in splenic cells from lupus-prone B6.*Nba2* female mice as compared to age-matched B6 females were associated with activation of an IFN response and reduced levels of Aim and FcγRIIB receptor [84]. Given that expression of Aim2 protein is up-regulated by male sex

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hormone androgen in immune cells [62], the above observations suggest that an inverse expression correlation between the Aim2 and p202 proteins in the B6.*Nba2* female mice contributes to increased production of autoantibodies, up-regulation of type I IFN production, and activation of an IFN response.

7. Distinct regulation of the *Nba2* genes by IRF5, a positive regulator of IFN expression

Genome-wide association studies (GWAS) have identified human *IRF5* gene (encoding for the IFN-regulatory IRF5 transcription factor) and its down stream target gene, PRDM1 (encoding for Blimp-1 transcriptional repressor) in lupus susceptibility [15]. Similarly, studies involving mouse models of SLE have provided evidence for murine *Irf5* and *Prdm1* genes in lupus susceptibility [100]. The murine IRF5, which is a member of the IRF family [101], is primarily expressed in the B220$^+$ mature B cells and levels of IRF5 protein decrease in CD138$^+$ plasma cells [102]. The activated IRF5 induces the transcription of a number of genes in cell type-dependent manner. These genes include the type I IFN and the *Prdm1* gene [102]. Blimp-1 is a master regulator of the B cell differentiation [103]. The *Irf5*$^{-/-}$ female mice show reduced serum levels of type I IFNs and develop an age-related splenomegaly that is associated with an accumulation of CD19$^+$ B220$^-$ B cells [102]. Moreover, splenic cells from *Irf5*$^{-/-}$ female mice exhibit a decrease in the number of plasma cells and down-regulation of Blimp-1 expression. IRF5 contributes to murine SLE-like disease through its direct regulation of class-switch recombination of the γ2a locus in B cells [104]. Because *Nba2* interval includes the IFN-regulated genes such as *Ifi202*, *Aim2* and *Fcgr2b* genes, we investigated whether the IRF5/Blimp-1 axis could regulate the expression of these genes. Our study revealed that IRF5 up-regulates the expression of p202 protein [63]. However, IRF5 expression down-regulates the expression of Aim2 and FcγRIIB receptor in immune cells. Given that expression of IRF5 is up-regulated by the female sex hormone estrogen in immune cells [105], the above observations provide further evidence for sex-dependent epistatic interactions among the *Nba2* interval genes in increased production of autoantibodies in the female B6. *Nba2* mice.

8. Interactions between *IFI16* and *AIM2* genes in autoimmunity

Studies have indicated a role for IFI16 protein in the development of autoimmune diseases [106–108]. Accordingly, increased levels of IFI16 mRNA have been reported in peripheral blood mononuclear cells isolated from SLE patients as compared to healthy donors [108]. Given that the expression of IFI16 and AIM2 proteins is inversely correlated in a variety of cells [109] and decreased levels of the AIM2 mRNA have been reported in SLE patients [110, 111], it is likely that increased levels of the IFI16 protein in innate immune cells contribute to increased production of type I IFN in SLE patients. Therefore, further studies are needed to understand the potential role of IFI16 and AIM2 proteins in innate and adaptive immune responses that are associated with the human SLE.

9. Conclusions

Recent studies have revealed sex hormone-dependent epistatic interactions among the *Nba2* interval genes in the modification of autoantibody production and type I IFN production. These interactions involve the IFN-inducible *Ifi200*-family genes. Therefore, understanding of the molecular mechanisms through which IFN-inducible p200-family proteins regulate innate and adaptive innate immune responses in sex-dependent manner will serve as a basis to understand the molecular mechanisms that contribute to immune dysregulation in the development and progression of human SLE. Consequently, an improved understanding of

the regulation and role of the p200-family proteins in the modification of SLE is needed to identify new approaches to effectively treat SLE patients.

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Highlights

- Recent studies have revealed sex-dependent epistatic interactions among the *Nba2* interval genes in modification of lupus susceptibility
- The interferon-inducible *Ifi200*-family genes within *Nba2* interval regulate innate and adaptive immune responses
- Epistatic interactions between *Ifi200*-family genes and *Fcgr2b* gene contribute to increased IFN-α production
- p202 protein increase autoantibody production in part by activating an interferon response that regulate survival of autoreactive B and T cells
- p202 protein is a cell type-dependent transcriptional modulator for NF-κB and AP-1 transcription factors

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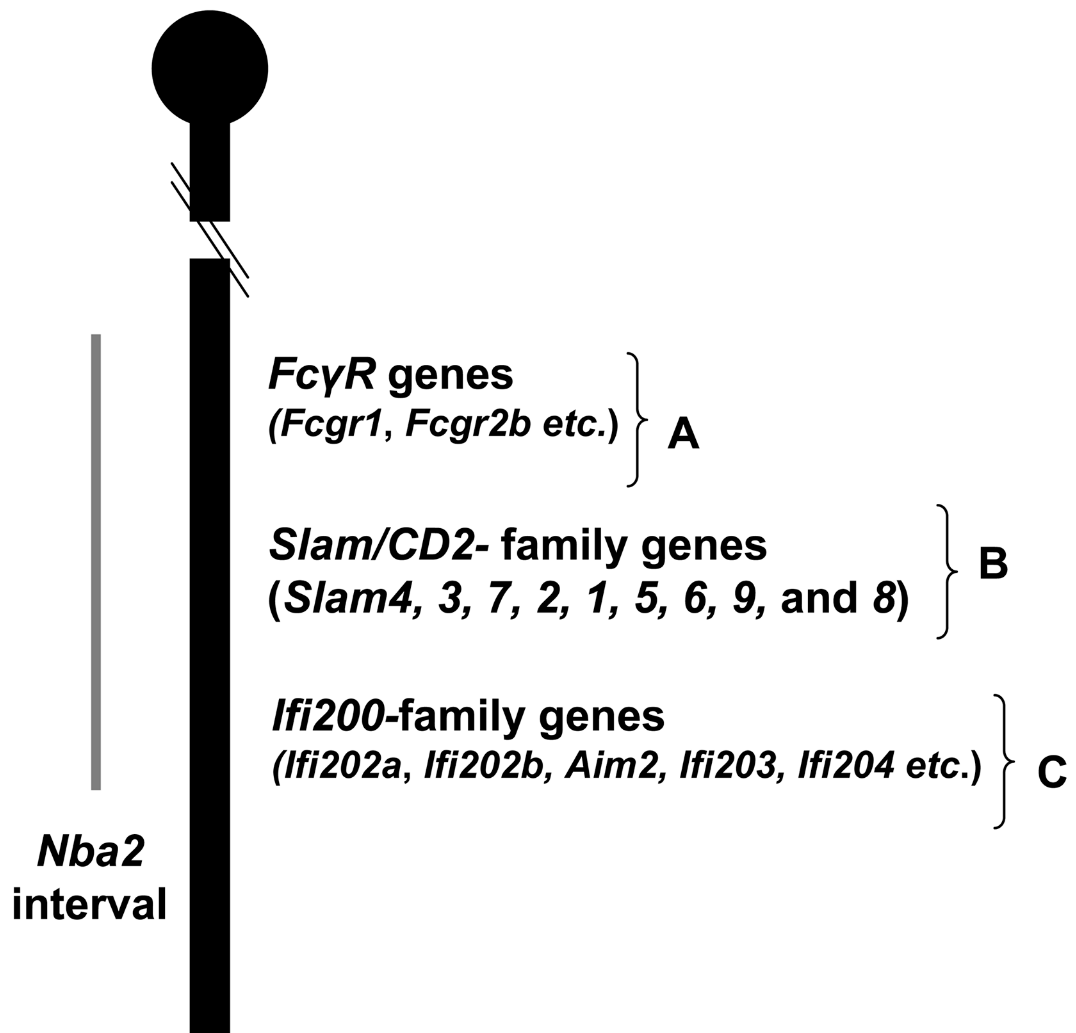

Fig. 1.

Schematic map of the distal end of murine chromosome 1 encompassing the *Nba2* interval (indicated by a gray line). The map includes the relative locations of the cluster of genes within the interval that encode for the Fcγreceptors, Slam/CD2 -familyreceptors, and p200-family proteins. Some of the genes that are discussed in this review are indicated.

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Table-1

Increased p202 protein levels and its nuclear localization are associated with the production of ANAs and IFN-α, and reduced levels of the FcγRIIB and Slamf1 receptors.

Mouse strain	*Nba2* genes	IFN-α levels[a]	Protein levels FcγRIIB	Protein levels Slamf1	Protein levels p202	ANAs[b]
B6	None	Not detected	+++	+++	+ (C)	Not detected
B6.*Nba2*-ABC	*FcγRs*, *Slam*, and *Ifi200*	Detectable	+	+	+++ (N)	Yes (+++)
B6.*Nba2*-A′B	*FcγRs*, *Slam*	Detectable	?	?	+ (?)	Yes (++)
B6.*Nba2*-C	*Ifi200*	Not detected	+++	+++	–	Not detected

[a]Serum levels of IFN-α at the age of 7–8 months;

[b]ANAs against chromatin, histones, and dsDNA;

C, cytoplasmic; N, Nuclear.