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Interferon and Apoptosis in Systemic Lupus Erythematosus

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1. Introduction

Systemic lupus erythematosus (SLE) is generally diagnosed long after the disease begins. This means that the cause of the disease is hard to find, buried in the past. In the search for the elusive causal agents for SLE, one candidate is the immune signaling molecule, interferon (IFN). Interferon is a secreted signaling protein, or cytokine, which is expressed at higher levels in SLE patients and has been associated with incidence and severity of the disease.

A combination of environmental triggers and genetic susceptibility combine to initiate SLE. Although there are many etiological components, they usually converge on a heightened state of activation for the immune system, with resultant increases in interferon production and interferon signaling. That is to say that interferon could be thought of as either a causative agent, a result of the disease, or both.

This chapter will discuss the basics of interferon function and how de-regulation of apoptosis can lead to interferon production due to immune complexes. We will then discuss how the functioning of the immune system changes in someone with SLE, the genes which are associated with risk for SLE, and clinical manifestations of interferon in SLE.

2. How interferon works in the context of SLE

Interferon is a signaling protein which is secreted to activate neighboring cells in response to viruses or other infections. It is a cytokine, or immune signaling molecule which allows communication between cells. When a cell is infected with a virus, interferon is produced and secreted as a warning to other cells to prepare for an infection. Interferons alpha (IFNα) and beta (IFNβ) are the type I interferons, and interferon gamma (IFNγ) is the type II interferon. Most of the cells in the human body have receptors for type I IFN, whereas certain immune cells express the receptor for type II IFN (Su, et al., 2004). The proteins are made by many different cells, but generally speaking, IFNα is of leukocyte origin, IFNβ is of fibroblast origin, and IFNγ is made by lymphocytes (Lucero, et al., 1982). Other less studied interferons also exist, and interferons are conserved among many species. This chapter will talk mostly about type I interferons, which are IFNα and IFNβ.

The main purpose of interferon is to shut down a cell before a virus can take it over, although it has many other jobs (Niewold, et al., 2010). Interferon signaling leads to increased apoptosis, which is a normal response to control viral spread or to decrease the

size of a tumor (Takaoka, et al., 2003). If one cell can undergo apoptosis before a virus can replicate and infect other cells, the infection is halted (Luker, et al., 2005).

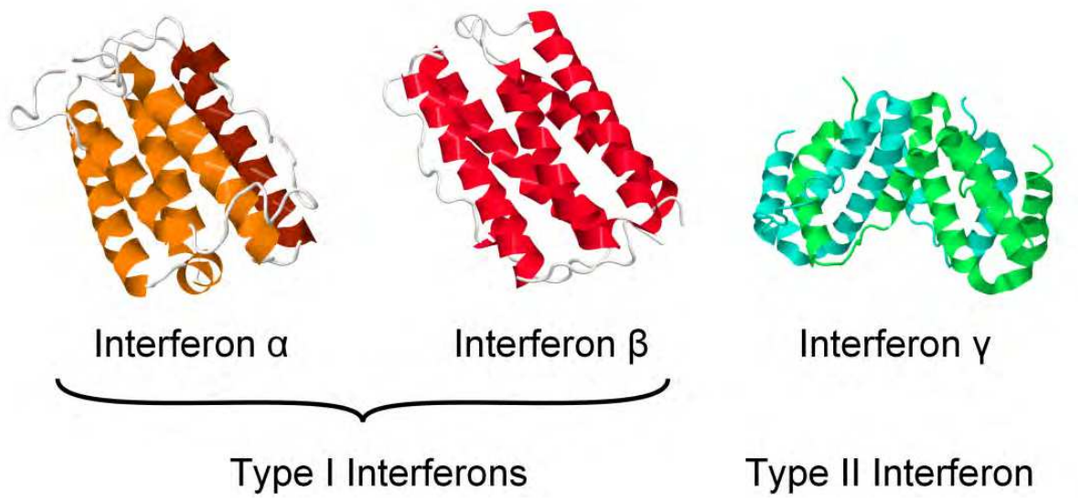


Fig. 1. Interferon protein structures. Interferons alpha and beta, the type I interferons, have a common structure composed mainly of five alpha helices (shown are IFNα2a and IFNβ1 based on PDB files 1itf and 1au1, respectively). Although the monomers of each are very similar in structure, the functional form of both is a dimer, and the two dimerize differently, IFNα2a along homologous surfaces and IFNβ1 on opposing sides of the protein (Karpusas, et al., 1997). IFNγ is show in its dimerized form, with the two colors representing two intertwined monomers (based on PDB file 1hig). Not shown to scale; figures drawn with Jmol (Jmol, 2011).

Interferon can be produced in response to infection, other cytokines, mitogens and several signaling pathways. Once produced it is secreted where it can be recognized by other cells, which is called paracrine signaling, or by the cell which produced it, called autocrine signaling. One type of cell, the plasmacytoid dendritic cell (pDC) is a natural IFN producer, and is able to make very large amounts of IFNα (Ronnblom & Alm, 2001).
When interferon ligates an interferon receptor, signaling pathways are activated. Interferon causes an increase in the expression of both major histocompatibility complexes (MHCI and MHCII) for presentation of viral peptides to T cells, which can then lead to activation of other cells in order to kill infected cells, and remove them (Fruh & Yang, 1999). Interferon also increases intracellular levels of protein kinase R (PKR) which recognizes viral nucleic acids and activates RNase L to degrade viral RNAs. PKR also slows protein synthesis by inactivating translational initiation factors, so that viral proteins synthesis is slowed (Pindel & Sadler, 2011). p53 is also activated, which is pro-apoptotic (Takaoka, 2003). Interferons activate immune cells, especially natural killer cells and macrophages (Murray, 1988). This activation cascade is normally "turned off" after an infection is cleared to prevent damage to uninfected cells. However this activation state is not reduced to the normal levels in individuals with SLE, where a higher level of interferon is present (T. Kim, et al., 1987; Ytterberg & Schnitzer, 1982). This higher amount of interferon is also measurable by an increase in the expression of interferon-stimulated genes seen in lupus patients, called the interferon response signature (Baechler, et al., 2003; Bennett, et al., 2003; Feng, et al., 2006).

This means that IFN is turned on and that it is actively affecting how other cells are functioning.

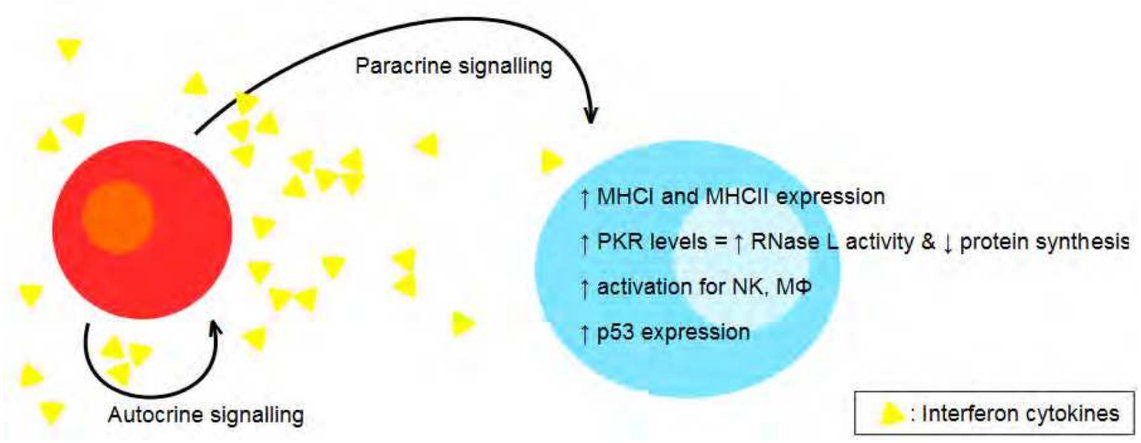


Fig. 2. Cell to cell IFN signaling and its effects. One cell produces interferon and either another cell (paracrine signaling) or the same cell (autocrine signaling) receives the signal. ↑: an increase, ↓: a decrease, MHC: major histocompatibility complex, PKR: protein kinase R, NK: natural killer cell, MΦ: macrophage

As a general feature of autoimmune diseases such as SLE, the immune system is in an "always on" state, which can lead to a breach in the body's natural tolerance to self. Once this self tolerance is lost, autoimmune disease can result. In addressing why the immune system generates an attack against one's own body, the over activation of the immune system, including the overproduction of interferon in SLE patients is a part of this picture.

3. Interferon leads to apoptosis, and the SLE-apoptosis connection

One effect of interferon production is the release of autoantigens due to increased cell death. This release is normally controlled by a process called efferocytosis, or apoptotic cell removal, where cell debris are processed by immune cells or neighboring cells which remove them by phagocytosis. Defects in apoptotic pathways have been noted in individuals with SLE (Gaipl, et al., 2006). Examples of why this occurs have been studied. For example, in SLE patients there is an overexpression of both soluble and membrane-bound Fas. Fas is a receptor which when ligated signals to a cell to undergo apoptosis. The levels of Fas also correlate with the amount of apoptotic lymphocytes and disease activity of SLE (Li, et al., 2009; Sahebari, et al., 2010). Mouse models of lupus commonly have genetic variations in apoptotic pathways such the Fas/Fas L pathway and interferon pathways.

Mouse as well as human SLE patients make antibodies to self antigens. This is likely because of over-exposure of potential autoantigens to the immune system. This could be due to an increased amount of apoptosis, or a decrease in the rate of clearance of apoptotic debris. Apoptosis, which can be induced by interferon, is also part of the natural cycle of cellular growth and death. Cells undergoing apoptosis are recognized as dead by other cells, so that they are cleared (Munoz, et al., 2010).

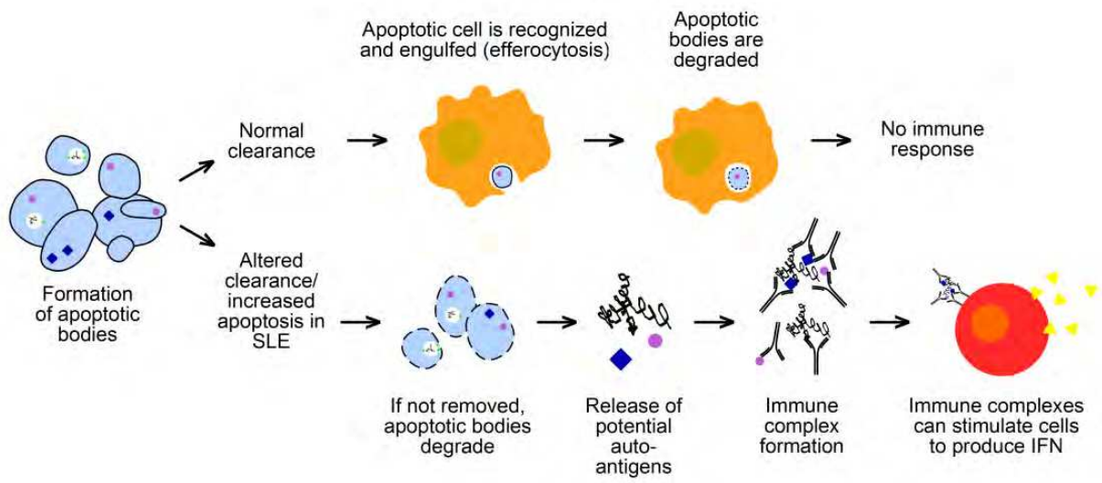


Fig. 3. Production of interferon can begin with defects in apoptosis. This can be due to either an increase in apoptosis or a decrease in clearance of apoptotic debris. If contents are released, they can form immune complexes with autoantibodies. These immune complexes can cause cells to produce interferon. Manipulating this pathway is also a common characteristic of mouse models of lupus.

3.1 Mouse models allow the study of IFN and apoptosis pathways

Mouse models have been very useful in understanding the etiology and pathogenesis of lupus. Two approaches to experimental mice have been used to generate information about the role of interferon in lupus. In the first approach, interferon-related genes are knocked out and the resulting effects on lupus are studied. For the second, established lupus mouse models are studied on a molecular level for differences in interferon pathways or interferon-related effects. These two approaches often overlap, as in cases where interferon-related genes are knocked out in lupus-prone mice. Several established lupus mouse models include the MRL/lpr mice, NZW/NZB, and others. These are mice that spontaneously develop lupus, and several of them have been investigated to understand the role of interferon in their pathogenesis. Although a complete description of the mouse models for lupus is beyond the scope of this or any one publication, a few illustrative examples represent the power of these model systems.

One mouse model that is especially relevant for the study of interferon in lupus is the BXSB/MpJ (BXSB) or Yaa mouse. These mice spontaneously develop lupus-like disease in a sex-linked fashion because of a duplication of the Toll-like receptor 7 (TLR7) gene on the Y chromosome (Izui, et al., 1994). TLR7 is responsible for inducing interferon in response to viral infection or autoantibody production.

Another interesting mouse for the study of interferon is the NZB/NZW mouse. These mice spontaneously develop a lupus-like autoimmune disease. They have been used to investigate the role of several interferon-related molecules and cells. For example, treating these mice with interferon accelerates disease in a T-cell like manner (Z. Liu, et al., 2010; Mathian, et al., 2005), while knocking out or inhibiting interferon-related genes slows or eliminates the development of lupus-like symptoms (Jorgensen, et al., 2007; Sharma, et al., 2005). These mice have been used to clarify the interactions between sex hormones and

interferon in lupus etiology (Bynote, et al., 2008; Panchanathan, et al., 2009; Panchanathan, et al., 2010), and they serve as an excellent all-around model for spontaneous development of lupus.

The role of several interferon-related molecules has been examined using a combination of mouse models. As an example, consider the gene interferon regulatory factor five (IRF5). This gene is an interferon-regulating gene which will be described in section 5.2 below. It was discovered that knockout of IRF5 prevents or inhibits the development of lupus in MRL/lpr mice, Fcγ-/- Yaa mice, and pristine-injected mice (Richez, et al., 2010; Savitsky, et al., 2010; Tada, et al., 2011).

Mouse models for lupus represent a powerful and flexible mechanism for investigating the role of multiple aspects of lupus. However, it must be remembered that the mutations or disease manifestations in these mice are not necessarily related to those seen in human lupus, and therefore the results observed must be interpreted with caution.

4. A cycle of autoantibody production

When it comes to SLE we may think of interferon production as a cycle, which begins when an environmental trigger, such as a viral infection, UV light damage or medical treatment activates the immune system to produce interferon.

Normally B cells which produce antibodies to self-antigens undergo negative selection, where they receive signals to die off or become inactivated if they make antibody against a self-antigen. This self-tolerance is breached in SLE (Cancro, et al., 2009), and the self-antigens released from damaged or apoptotic cells during or after initial triggering events become the targets of autoantibodies. When autoantibodies are produced, they are made by B cells as well as plasma cells, which are a mature differentiated form of B cells.

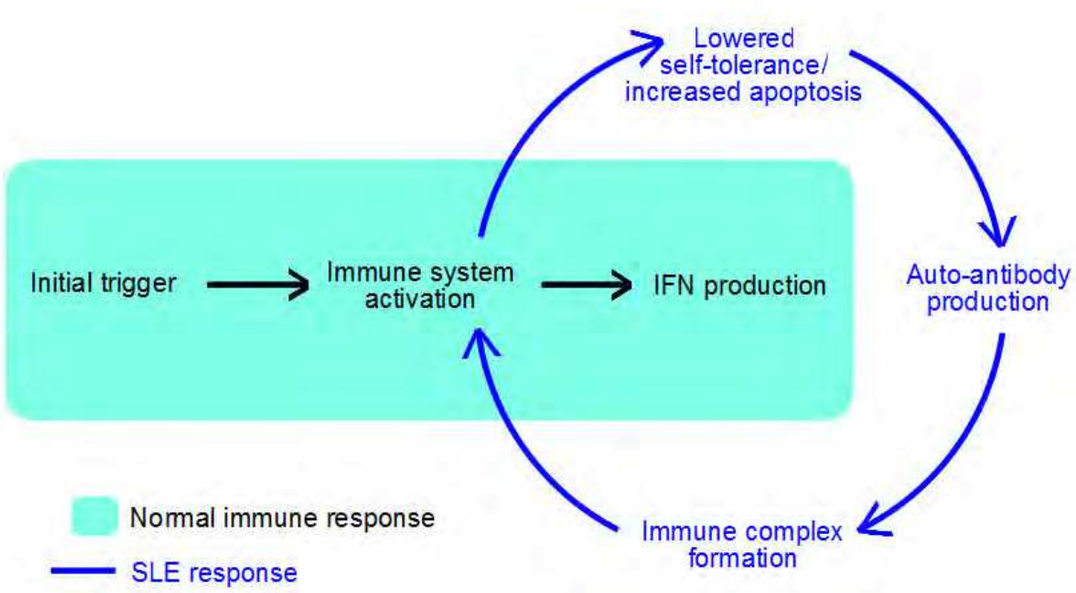


Fig. 4. The altered immune response in SLE generates a cycle. In blue is a cycle which exists in SLE, amplifying the amount of IFN present. This cycle needs a trigger, but once it begins, it can leave the immune system in an "always on" state.

Autoantibodies lead to the production of interferon by forming immune complexes which are immunostimulatory (Ronnblom, et al., 2011). Immune complexes are composed of aggregates of antibody and antigen molecules which are processed by the body. These immune complexes are a main source of SLE pathology, as they obstruct small passages in areas of the body such as the kidneys and joints (Crispin, et al., 2010).

Immune complexes may include the common SLE autoantigens such as RNA-containing protein complexes like Sm, RNPs, Ro, and La. Having a combination of both nucleic acids and protein complexed with antibody means many pathways can be turned on. For example, antibody can stimulate an immune cell through an Fc receptor, nucleic acids can stimulate cells through Toll-like receptors (TLRs), and proteins can be recognized by other antibodies.

Immune cells are activated by immune complexes and the cycle continues. Interferon production is instigated by immune cells which recognize part of the complex, be it the antibody, the antigen, or other associated molecules.

5. SLE genetic risk screens identify genes in interferon signaling pathways

We have looked at the disease state of SLE, and how the immune system functions improperly to instigate disease. Things begin when an environmental trigger works on the genetic background of varying degrees of susceptibility. Genetic susceptibility is thought to account for at least 20% of the risk for SLE (Deapen, et al., 1992). To find the actual genes involved, studies are performed to determine the linkage or association of a variation in the genome to a particular disease.

One important method is called a genome wide association study (GWAS). These GWA studies genotype thousands of individuals, grouped into SLE patients and non-patients comparing them at thousands of single nucleotide polymorphisms (SNPs). These studies reveal the genomic regions which contain disease-associated genes, because the variations are more common in people with the disease. Individual genes or gene pathways are pinpointed, and can ultimately lead to treatment strategies. Many genes have been identified that contain SNPs which confer risk to SLE.

These studies are especially useful for diseases with unknown or complex genetic components. The genome is examined for sets of single nucleotide polymorphisms (SNPs). When sets of SNPs are usually inherited together in a group it is called a haplotype. When a haplotype is more common in the disease group than in the unaffected group, it can be assumed that it is associated with the disease. Although specific genes are sometimes found which may predict a disease, it is more likely that the information will reveal molecular pathways associated with the disease. Association of genes or pathways to diseases such as heart disease, asthma, diabetes and others have been found using this method (Stranger, et al., 2011). The amount of effect is measured as an odds ratio (OR), which is a measure of the strength of association of the disease with a haplotype. A median OR value is around 1.3, with some genes having much higher association ORs. For example, one of the lupus-associated haplotypes TREX1, has a published OR of 25 (Lee-Kirsch, et al., 2007). In such cases, the genetic risk is almost certainly associated with the disease.

An important caveat to these tests is that they answer the question, “What?” but not the question, “How?” That is, they identify genetic loci which confer risk to SLE, but then further studies are needed to show what functional changes affect people with a risk haplotype. For most of the genes, we do not know what functional role they play. However

it is promising to note that the genes are within certain pathways, some of which are already associated with lupus.

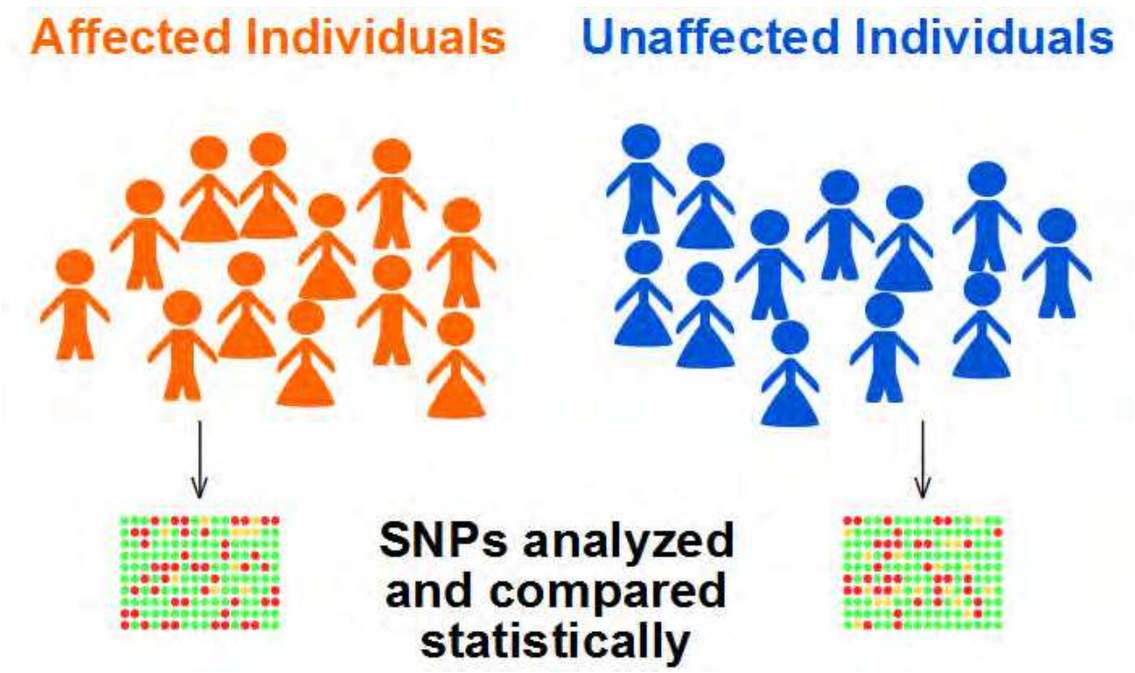


Fig. 5. Genome wide association studies (GWAS). Genome-wide association studies aim to discover the genetic risk component of a disease by finding differences in a group with the disease compared to a group of unaffected control individuals.

Several review articles have reviewed the findings of many lupus GWAS with varying degrees of certainty (R.R. Graham, et al., 2009; I.T.W. Harley, et al., 2009; Moser, et al., 2009; Rhodes & Vyse, 2008; Sebastiani & Galeazzi, 2009). In some cases the indicated susceptibility genes are common in many ethnicities and populations, while others are specific to certain groups. The statistical significance of many of these genes is well established, while others are novel and need to be replicated by other groups. An important finding is that most of the genes that have been identified in GWA studies can be grouped into several functional pathways. We will focus on the genes in the IFN pathway and the pathways involving clearing of apoptotic cells and immune complexes.

5.1 Interferon production pathways

Intracellular signaling pathways which control interferon production include the production of type I interferons by interferon regulatory factors (IRFs), and the production of type II interferon by STAT4. IRFs are activated by TLRs, which are extracellular or endosomal pattern recognition molecules. TLRs 7, 8, and 9 recognize nucleic acids and are endosomal. Maintaining these TLRs in the endosome instead of the cell surface is an important barrier to too frequent TLR activation. Once the nucleic acids are brought into the cells through endocytosis, the TLRs become activated to turn on IRFs. TLR 8 and TLR 9 have both been identified as lupus risk genes (Armstrong, et al., 2009; Xu, et al., 2009).

TLRs begin a signaling cascade through a MyD88 signaling complex. MyD88 activates another confirmed locus of SLE risk, the gene which encodes IL1 receptor-associated kinase 1

(IRAK1). In Sle1 and Sle3 mouse models of lupus, IRAK deficiency eliminated most lupus symptoms (Jacob, et al., 2009), which highlights the importance of IRAK1. Since this gene is on the X chromosome, it could help explain why lupus is more common among women. The MyD88 complex can be affected by osteopontin (OPN). It regulates IFNα production in plasmacytoid dendritic cells, which are the body's main IFNα producer cell (Cao & Liu, 2006). The lupus-risk variant of OPN was tied to high IFNα levels in certain lupus patients (Kariuki, et al., 2009b).

Two interacting proteins involved in inflammation, TNFα-induced protein 3 (TNFAIP3) and TNFAIP3-interacting protein 1 (TNIP1), are also lupus risk loci (Gateva, et al., 2009; Musone, et al., 2008). TNFAIP3 encodes the protein A20, which abrogates NFκB after an inflammatory response, and lupus-risk variants of this gene are associated with blood and kidney manifestations (Bates, et al., 2009). TNIP1 interacts with TNFAIP3 as well as affecting several other signal transduction pathways.

Interferon regulatory factors are activated next, downstream of TLRs; they are transcription factors which travel to the nucleus to bind DNA to initiate transcription. IRF5 binds to a sequence-specific region of DNA to induce IFN production. It has been confirmed as a risk factor for SLE in among several ethnicities (Kawasaki, et al., 2008; Kelly, et al., 2008; Lee & Song, 2009; Reddy, et al., 2007; Shimane, et al., 2009). There are three main genetic variants within IRF5, one copy number variant with either two or four copies of a 30-bp sequence, and two SNPs (R.R. Graham, et al., 2007b). The rs2004640 SNP changes the first exon, although this exon does not encode protein. The other SNP, rs10954213, creates an early polyadenylation sequence, which yields shorter more stable mRNA (D.S.C. Graham, et al., 2007a). Work has shown that these variants increase the amount of IFN in the presence of SLE autoantibodies (Niewold, et al., 2008; Salloum, et al., 2009).

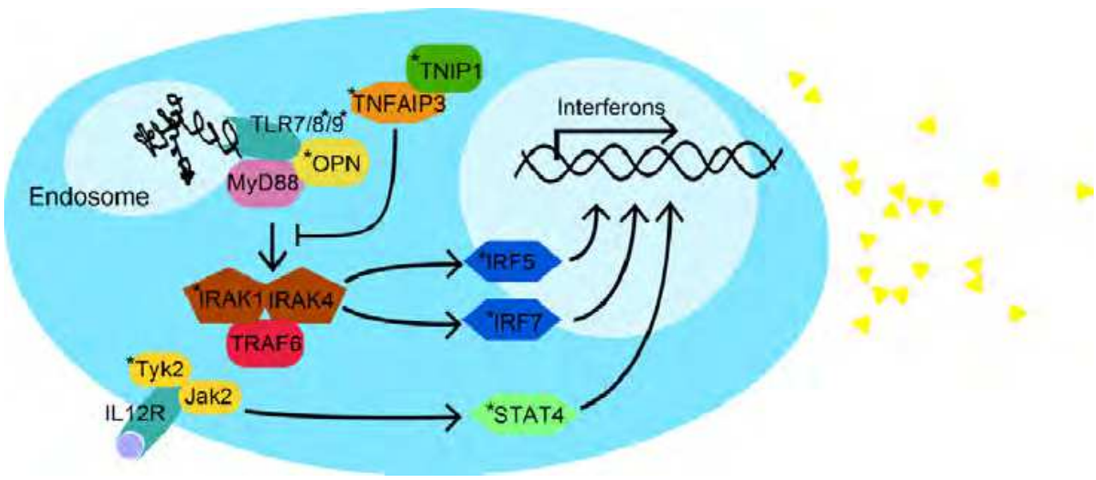


Fig. 6. Interferon production pathways are affected by lupus-risk genes. The * represents genes which have been identified as having risk for lupus. The endosomal TLRs (7, 8, and 9) can bind to autoantigenic nucleic acids and signal through a MyD88 complex which can be affected by association with osteopontin (OPN). If it is not blocked by TNFAIP3, this activates an IRAK signaling complex to phosphorylate the IRF5 and IRF7 transcription factors to produce type I IFN. IL-12 or IL-23 signal through Tyk2/Jak2 to activate the STAT4 transcription factor to produce type II IFN, commonly in T helper cells (Watford, et al., 2004).

IRF7 is associated with SLE risk by its proximity to SNPs in the IRF7/KIAA1542 locus (J.B. Harley, et al., 2008; Suarez-Gestal, et al., 2009). IRF7 SNPs have been shown to lead to increased IFNα levels and alter of which autoantibodies are made (Salloum, et al., 2009).
Signal transducer and activator of transcription 4 (STAT4) is also associated with risk for SLE. It is a transcription factor which activates genes in proliferation, differentiation and apoptosis pathways. Two STAT4 SNPs have been examined, rs7574865 increases sensitivity to IFNα (Kariuki, et al., 2009a), and rs3821236 causes STAT4 to be transcribed at higher levels and is additive with IRF5 risk loci so that when both are present, the risk to SLE is multiplied (Abelson, et al., 2009; Sigurdsson, et al., 2008).

5.2 Genes associated with apoptosis and immune complexes

Another set of risk genes can be placed into a functional group of apoptosis-associated genes. As we read earlier in the chapter, defects in apoptosis can lead to the presence of potential autoantigens. For example, a cell undergoes apoptosis and instead of being cleared by other cells, its contents are released. The cellular contents can contain things like nucleic acids, RNA binding proteins, and others which are common lupus autoantigens. If antibodies bind to these antigens, a complex of multiple antibodies and multiple antigens can aggregate. The resultant immune complexes can be broken down through reactions with complement components, which are commonly found at low levels in SLE patients (C.C. Liu & Ahearn, 2009). If they are not broken down, they reach areas such as the kidneys or joints, which can be damaged by these immune complexes. This is how organ damage usually occurs in lupus patients.

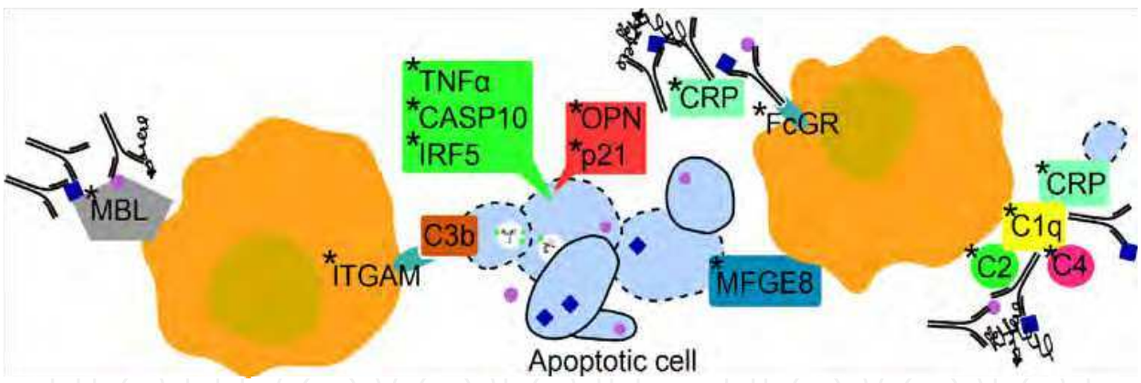


Fig. 7. Genes associated with risk for lupus in the apoptosis pathway. The * represents genes which have been identified as having risk for lupus. TNFα, CASP10 and IRF5 are pro-apoptotic whereas OPN and p21 are anti-apoptotic. These genes all have a role in how much apoptosis is occurring. Once apoptosis has transpired, the cell must be cleared. Parts of apoptotic cells or immune complexes can be recognized by other cells to facilitate their removal. This is aided by recognition molecules such as the complement components shown here.

The problem of creating autoantibodies could stem from too much apoptosis or too little clearance of apoptotic debris. Genes identified in GWA studies that could alter the amount of apoptosis include TNFα, caspase 10, IRF5, osteopontin and p21.
TNFα was identified as a risk factor for lupus in certain ethnicities (Jimenez-Morales, et al., 2009; Lin, et al., 2009). TNFα is a cytokine which is produced and secreted to signal to

other cells and is found at high levels in the serum of lupus patients (Davas, et al., 1999; Emilie, et al., 1996; Sabry, et al., 2006). Part of its function is to induce apoptosis—when a cell binds TNFα, it activates the caspase cascade. Caspases are proteases which are activated under certain conditions and are a hallmark of apoptosis. They cleave other caspases as well, and the combined proteolytic activity of several different activated caspases breaks down cellular components as the cell prepares to die. Caspase 10 is part of this cascade and is another lupus susceptibility gene (Armstrong, et al., 2009). Caspase 8, is activated by TNF signaling, and cleaves caspase 10, which then cleaves caspases 3 and 7. IRF5, as well as being a transcription factor which helps produce IFN, is also a tumor suppressor gene which is commonly inactivated in cancers. This is because of IRF5's pro-apoptotic function.

Osteopontin (OPN) and p21 are also lupus risk genes, both anti-apoptotic. OPN promotes proliferation, as well as prevention of death under apoptotic stimuli (Standal, et al., 2004). A mimic of p21 was used in the treatment of murine lupus in the NZB/NZW mouse, and it was found to dramatically reduce the disease (Goulvestre, et al., 2005).

So, there are genes which dysregulate the amount of apoptosis, and they are associated with risk for lupus. But this is only half of the picture; the other part is the clearance of apoptotic cells or immune complexes. Several SLE susceptibility genes in this pathway have been identified as well. Active SLE can be assessed when low levels of complement proteins are found in circulation. Complement can function against microbes during an infection, but can also help to degrade immune complexes. Once attached, they can help cells recognize and degrade them. Other proteins function to bind apoptotic cells or immune complexes to facilitate their uptake by other cells.

Integrin αM (ITGAM) has been convincingly associated to SLE (Nath, et al., 2008). Risk variants of ITGAM have been associated with certain clinical manifestations of lupus (Kim-Howard, et al., 2010). It is a cell receptor which binds to OPN or to complement C3b. C3b binds to apoptotic cells or immune complexes.

SLE association with complement components C1q, C2, C4a and C4b have large OR values, meaning that the risk haplotypes of these genes are causing a large effect. When C1q is expressed at low levels it can lead to lupus, and it was shown to increase the amount the of IFN produced due to immune complexes (Lood, et al., 2009). Complement components function by binding immune complexes by the Fc region of antibody or by binding to other parts of apoptotic cells, which can opsonize them for easier uptake by other cells. Cells can then remove the immune complex or apoptotic debris by endocytosis. Receptors for the Fc region of antibody have also been implicated in SLE risk (Lee-Kirsch, et al., 2007). These receptors can bind to antibody within an immune complex.

Other proteins such as milk fat globule EGF factor 8 (MFG-E8) and C-reactive protein (CRP) can bind to apoptotic cells by recognizing phospholipids on their membranes. MFG-E8 binds to phosphatidylserine, an "eat me" signal which is expressed on apoptotic cells. The MFG-E8 knockout mouse gets SLE because of failure to remove apoptotic cells (Yamaguchi, et al., 2010). CRP binds to phosphocholine, which is present on dying or damaged cells. Both MFG-E8 and CRP are lupus risk genes (Batuca & Alves, 2009; Hu, et al., 2009; H.A. Kim, et al., 2009). Low mannose-binding lectin (MBL) levels can lead to higher levels of apoptosis is this lupus-risk associated gene (Pradhan, et al., 2010).

The number of genes associated with risk for SLE will likely increase, though we have an interesting pool of genes already that point to certain pathways associated with the disease. The interferon and apoptosis pathways are certainly important in SLE etiopathogenesis.

6. Clinical component of interferon and SLE

Many researchers have sought to determine if higher levels of IFN, which is common in lupus patients, is a cause of lupus or an effect of lupus. An interesting occurrence can happen when someone undergoes treatment with IFNα. The presence of increased levels of IFN leads to lupus or a lupus-like syndrome (Gota & Calabrese, 2003; Ioannou & Isenberg, 2000; Niewold & Swedler, 2005). Because the lupus symptoms usually disappear after IFN treatment ends, this connection suggests that IFN may be more of a cause than an effect. In a small number of cases, some patients also develop SLE as a result of these IFN treatments. Furthermore, within a family, the levels of interferon among all members correlate, suggesting that this is a heritable trait (Niewold, et al., 2007). That is, even the siblings of a lupus patient with high IFN levels are more likely to have higher IFN levels. This also supports a causal role for IFN.

Clinically, disease activity can be measured and correlated to other observations to determine the cause of the different levels of activity. One item linked to SLE activity is interferon, where higher levels of IFN in the serum correlated with more severe disease in most cases (Bauer, et al., 2009; Dall'Era, et al., 2005; Feng, et al., 2006; Landolt-Marticorena, et al., 2009; Petri, et al., 2009; Zhuang, et al., 2005).

Common autoantibodies also correlate with IFN levels. A very strong correlation is consistently observed between IFNα levels and the presence of antibodies to common SLE autoantigens like Ro, La, Sm, RNP, and dsDNA (Kirou, et al., 2005).

Another set of findings has to do with properties of main producer of IFNα, the plasmacytoid dendritic cells (pDCs). High numbers of IFN-producing pDCs have been observed in lupus skin lesions (Blomberg, et al., 2001; Farkas, et al., 2001). Since the cells are present at the scene of the crime, the increased interferon could have to do with the pathology in these cases.

At the time of writing, two clinical drug trials for SLE are being conducted, Sifalimumab is in Phase II, and Rontalizumab is in Phase I. Both are antibodies, designed to block interferon alpha signaling by binding it to prevent its recognition by neighboring cells (Clinical Trials, 2011). If these drugs are found to be effective, it will show that IFN plays a critical role in the pathogenesis of lupus. In addition, the United States Food and Drug Administration recently approved an antibody to B lymphocyte stimulator (BLyS) to treat SLE called Belimumab (Sanz, et al., 2011). This should help control the selective apoptosis and autoantibody production to some degree.

7. Conclusions

Several themes have been examined in this chapter. Specifically that the production of interferon is tied to lupus and that apoptosis, clearance of apoptotic cells, and the formation of immune complexes are events that can augment the production of interferon. Exciting findings about the actual genetic causes of SLE are being examined which will lead to better treatments for this complex disease. Although most of the data discussed in this chapter are inferential, there is a large body of evidence in support of the hypothesis that increased interferon signaling promotes an autoimmune state in those genetically prone to SLE.

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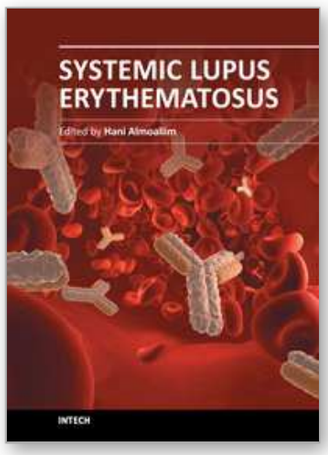
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This book provides a comprehensive overview of the basic and clinical sciences of Systemic Lupus Erythematosus. It is suitable for basic scientists looking for detailed coverage of their areas of interest. It describes how advances in molecular biology have increased our understanding of this disease. It is a valuable clinical resource for practicing clinicians from different disciplines including rheumatologists, rheumatology fellows and residents. This book provides convenient access to information you need about cytokines, genetics, Fas pathway, toll like receptors and atherogenesis in SLE. Animal models have been reviewed as well. How to avoid delay in SLE diagnosis and management, in addition to various clinical manifestations including pregnancy and SLE have all been explained thoroughly in this book.

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