The Dysregulation of Cytokine Networks in Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is an autoimmune disease associated with chronic immune activation and tissue damage. Organ damage in SLE results from the deposition of immune complexes and the infiltration of activated T cells into susceptible organs. Cytokines are intimately involved in every step of the SLE pathogenesis. Defective immune regulation and uncontrolled lymphocyte activation, as well as increased antigen presenting cell maturation are all influenced by cytokines. Moreover, expansion of local immune responses as well as tissue infiltration by pathogenic cells is instigated by cytokines. In this review, we describe the main cytokine abnormalities reported in SLE and discuss the mechanisms that drive their aberrant production as well as the pathogenic pathways that their presence promotes.

Introduction

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) is a multifactorial autoimmune disorder of complex pathogenesis and clinical presentation (Crispin and others 2010). It is the result of multiple predisposing genetic traits accumulating in an individual, upon which environmental stimuli are superimposed and ultimately cause disease. Every year in the United States, there are 1–10 new cases of lupus per 100,000 individuals, whereas the estimated prevalence of the disease is 20–150 per 100,000 individuals (Lawrence and others 1998; Pons-Estel and others 2010). SLE has a predilection for women of child-bearing age, as 9 out of 10 cases affect women. African-American, Asian, and Hispanic populations are more commonly and more severely affected (Duarte and others 2011).

After diagnosis, SLE follows a relapsing/remitting course, although full remissions are unusual without treatment. Patients with lupus exhibit a wide array of clinical manifestations, the most prominent of which are skin rash and photosensitivity, glomerulonephritis, polyarthritis, serositis (mainly pleuritis and pericarditis), central nervous system manifestations, leukopenia, anemia, and thrombocytopenia. Although the 11 revised SLE classification criteria of the American College of Rheumatology as well as the SLE disease activity index score are widely used for classification of patients in clinical studies, the diagnosis is usually based on the overall clinical profile of the patient, assisted by laboratory results and occasionally biopsies of affected organs. Patients with lupus are almost invariably positive for anti-nuclear antibodies, whereas autoantibodies against the Smith antigen and against double-stranded DNA have a very high

degree of specificity. To the clinical picture of a patient with lupus, one should also add the various side effects that derive from the common treatment options that are available for SLE, namely, corticosteroids, anti-malarial and various immunosuppressive agents.

Autoimmune manifestations arise when tolerance of the immune system against self-antigens fails. SLE is a classic example of an aberrant immune response characterized by the production of autoantibodies directed against self antigens, mainly nuclear, which results in immune complex (IC)-mediated systemic end-organ damage (Crispin and others 2010). Although the exact causes of SLE remain elusive, it is now accepted that various aspects of the immune system demonstrate abnormal behavior. SLE has classically been studied as an adaptive immune response dysregulation, involving T and B cell abnormalities; however, growing evidence implicates innate immunity as well, with dendritic cells, neutrophils, and macrophages contributing to disease pathogenesis. Cytokines are protein molecules that are secreted by the cells of adaptive and innate immunity and orchestrate the immune response. Each cytokine can have pleiotropic effects, whereas different cytokines can share the same action. Their effects can be stimulatory for the immune response, including proliferation, activation, and chemotaxis, but also can be suppressive, favoring the contraction of an inappropriate or no longer desirable immune response. As important key players of the immune system, cytokine abnormalities have been implicated in the pathogenesis of SLE, either as part of the pathogenetic core process of lupus or as secondary markers indicating immune dysregulation. In this communication, we will review the various aspects by which cytokine abnormalities contribute to pathogenesis and tissue

TABLE 1. MAJOR CYTOKINE ABNORMALITIES OBSERVED IN LUPUS PATIENTS AND MURINE MODELS

Cytokine	Cytokine abnormality in lupus
IL-1ra	Low levels associated with lupus nephritis High levels associated with flares
IL-2	Low levels in patients and mouse models
IL-4	Increased double-negative and NK T cell production
IL-10	Increased monocyte and B-cell production
IL-15	Elevated levels in lupus patients
IL-17A and IL17F	Elevated levels in patients and mouse models
IL-23	Increased mononuclear cell production
IFN α/β	Elevated levels in patients and mouse models Increased transcription of IFN-regulated genes (IFN signature)

IL, interleukin; IFN, interferon; NK, natural killer.

damage in lupus patients and the various murine models of lupus (Table 1).

Interleukin-2

Interleukin 2 (IL-2) is a T cell product important in various cell functions such as expansion, contraction, and homeostasis. A hallmark of SLE is decreased production of IL-2 from T cells of lupus patients (Alcocer-Varela and Alarcon-Segovia 1982). This most likely contributes to the reduced numbers of regulatory T (Treg) cells and decreased activation induced cell death observed in this disease (Lieberman and Tsokos 2010).

As observed in SLE patients, various murine lupus models also exhibit decreased levels of IL-2, as well as autoantibody production and proteinuria. MRL/*lpr* mice spontaneously develop lupus-like disease by 12 weeks of age and have decreased IL-2 production and responsiveness that continuously decreases as the mice age (Altman and others 1981). It has also been reported that BXSb/Yaa mice have defective IL-2 responses by 6 weeks of age, whereas NZBW F1 mice, which

develop lupus-like symptoms more slowly than the other murine models mentioned, only develop decreased IL-2 responsiveness at 7.5 months of age (Altman and others 1981).

Much has been learned from mice lacking IL-2 or IL-2 receptor (IL-2R). These mice develop a severe spontaneous autoimmune disease characterized by lymphoproliferation, splenomegaly, and anemia (Schorle and others 1991; Suzuki and others 1995). Lymphoproliferation observed in these mice results from a decreased number of peripheral Treg cells (Malek and others 2002). IL-2/IL-2R^{-/-} mice also have lymphadenopathy and elevated serum autoantibody titers, similar to what has been reported in SLE patients.

It is well established that there is defective IL-2 production in SLE patients, but the mechanism underlying this defect is poorly understood. Several transcription factors modulate the transcription of *IL2*. However, in patients with SLE an imbalance between cyclic AMP responsive element-binding protein (CREB) and -modulator (CREM) is particularly relevant. CREB and CREM compete for a binding site in the *IL2* promoter. CREB exerts a positive effect, whereas CREM is a negative regulator. In resting T cells, CREB occupies the binding site and upon activation it is phosphorylated, resulting in *IL2* transcription. Patients with SLE have lower levels of CREB and abnormally high levels of CREM (Solomou and others 2001) (Fig. 1). Increased CREM levels are caused by increased CREM transcription driven by abnormally increased amounts of the activated form of the transcription factor SP-1 (Juang and others 2011). Furthermore, circulating autoantibodies common in SLE patients and possibly autoantigens can activate the kinase CaMKIV (calcium/calmodulin-dependent protein kinase type IV), which phosphorylates CREM and enhances its DNA-binding effects (Juang and others 2005). Accordingly, inhibition of CaMKIV alleviates lupus disease progression in a murine model of SLE (Ichinose and others 2011). Additionally, SLE T cells have increased levels of the serine/threonine phosphatase PP2A (Katsiari and others 2005; Sunahori and others 2011). This phosphatase is responsible for the dephosphorylation of CREB, further contributing to the imbalance of CREB/CREM in SLE T cells. PP2A also dephosphorylates and activates SP-1, which, as

FIG. 1. Dysregulation of *IL2* transcription in SLE T cells. The levels of CREB and CREM dictate *IL-2* production by T cells. In healthy individuals, there is a natural balance of these molecules that leads to *IL-2* production as needed. In SLE T cells, CREM transcription is enhanced due to increased binding of SP-1 to the CREM promoter. This is facilitated by the dephosphorylation of SP-1 by PP2A, a phosphatase that is found at elevated levels in SLE T cells. SLE, systemic lupus erythematosus; IL, interleukin; CREB, cyclic AMP responsive element-binding protein; CREM, cyclic AMP responsive element modulator.

noted above, promotes *CREM* transcription (Juang and others 2011).

Treg cells are responsible for controlling T cell expansion and they help prevent autoimmunity. Expansion and homeostasis of these $CD4^+CD25^+Foxp3^+$ Treg cells is greatly dependent on IL-2, so it is not surprising that in low IL-2 states, such as lupus, the numbers of Treg cells are reduced (Malek and others 2002). In SLE patients, the number of Treg cells relates inversely to the disease severity (La Cava 2008).

IL-17, Its Role and the Balance Between Th17 and Treg Cells

IL-17A is an inflammatory cytokine that belongs to a group of cytokines called the IL-17 family, which also includes IL-17B, IL-17C, IL-17D, and IL-17F. It is produced rapidly and in large amounts by T cell receptor (TCR) $\gamma\delta$ and double-negative (DN) TCR $\alpha\beta$ T cells ($CD3^+CD4^-CD8^-$) (Crispin and others 2008; Rioll-Blanco and others 2010). These cells represent a first line of defense against certain extracellular bacterial infections (eg, *Listeria monocytogenes*) (Rioll-Blanco and others 2010). IL-17A is also the signature cytokine of a recently discovered subset of T helper cells, called Th17 cells (Harrington and others 2005; Park and others 2005), which also produce IL-17F, IL-21, and IL-22. Th17 T cells derive from naïve $CD4^+$ T cells primed in the presence of transforming growth factor (TGF)- β and proinflammatory cytokines, namely, IL-6, IL-21, and IL-1 β (Mangan and others 2006; Veldhoen and others 2006; Yang and others 2008). IL-23, produced by antigen presenting cells, is the major inducer of expansion of Th17 cells and although it seems not necessary for their generation, it is essential for their maintenance (Langrish and others 2005). IL-17 has various pro-inflammatory effects, including the production of IL-6, granulocyte monocyte-colony stimulating factor (GM-CSF), and G-CSF (Schwarzenberger and others 1998, 2000, 2001; Tan and others 2006; von Vietinghoff and Ley 2009). As a result, its release promotes monocyte and neutrophil recruitment leading to tissue inflammation and damage. IL-17, in conjunction with B cell activating factor, has also been shown to provide help to B cells, increasing B cell activation and proliferation as well as antibody production and class switching (Doreau and others 2009; Mitsdoerffer and others 2010).

There is growing evidence both in humans as well as in experimental models that implicates the above cytokines in the pathogenesis of lupus (Fig. 2). Lupus patients have increased serum levels of IL-17 (Wong and others 2000), and IL-17-producing cells appear with increased frequency in the peripheral blood of these patients (Crispin and others 2008; Shah and others 2009; Yang and others 2009). Additionally, the numbers of DN T cells are increased and represent a major source of IL-17 (Crispin and others 2008) in lupus patients. TCR $\alpha\beta$ DN cells derive from $CD8^+$ T cells (Crispin and Tsokos 2009) and play a central role in the tissue damage that accompanies lupus by exerting effector functions. They produce several proinflammatory mediators, including IL-17, interferon (IFN)- γ , IL-1 β , CXCL2, and CXCL3, and infiltrate the kidneys (Crispin and others 2008; Crispin and Tsokos 2009).

Th17 and Treg cells appear to be in homeostatic balance in patients with SLE (Yang and others 2009). This balance can change with disease activity. TGF- β promotes the generation of Treg cells by inducing *Foxp3* expression (Fontenot and others 2005), the signature transcription factor of Treg cells.

In this circumstance, Treg cells exert their suppressive function to keep autoimmune phenomena checked. However, in an inflammatory setting, TGF- β coupled with IL-6 promotes Th17 differentiation (Bettelli and others 2006). IL-6 effectively shuts down *Foxp3* expression and induces, along with TGF- β , expression of *Rorc*, which leads to IL-17A and IL-17F production (Bettelli and others 2006; Ivanov and others 2006). This is supported by the fact that patients with SLE have indeed increased levels of phosphorylated STAT3 (Harada and others 2007), a transcription factor activated by IL-6, IL-21, and IL-23, which is necessary for the development of Th17 cells. In addition to increased levels of pro-inflammatory cytokines, increased production of IL-17 has also been attributed to the reduced IL-2 production observed in SLE. IL-2 is necessary for Treg cell maintenance but has been shown to hinder *Il17a* expression and Th17 differentiation (Harada and others 2007; Laurence and others 2007).

Studies in lupus mouse models also illustrate the important role of IL-17 in SLE. MRL/*lpr* and B6/*lpr* mice develop a massive expansion of DN T cells (Igarashi and others 1988; Cohen and Eisenberg 1991). DN T cells are the main producers of IL-17 in MRL/*lpr* mice, where they infiltrate the kidneys propagating local inflammation (Wang and others 2009; Zhang and others 2009). The central role of IL-23 in the pathogenicity and expansion of IL-17-producing DN T cells was shown in B6/*lpr* mice deficient for the IL-23 receptor (Kytitaris and others 2010). These mice exhibit a drop in the number of DN T cells to normal levels and abrogation of the lupus-like manifestations.

SNF1 mice (SWR $\times$ NZB F1), another lupus-prone strain, is characterized by the development of autoantibodies and glomerulonephritis (Ghatak and others 1987). The addition of nucleosomes, which play a central role in lupus pathogenesis as autoantigens, into total spleen cell cultures from these mice leads to the production of high amounts of IL-17 (Kang and others 2007). Treatment with a tolerogenic regimen, either low-dose nucleosomal peptides (Kang and others 2005, 2007) or nasal administration of anti-CD3 (Wu and others 2008), ameliorates disease by inducing the expansion of Treg cells and by diminishing the numbers of Th17 cells and their infiltration into the kidneys.

The BXD2 strain represents a mouse model that spontaneously develops glomerulonephritis and erosive arthritis and demonstrates the contribution of IL-17 to B cell functions (Hsu and others 2006). In these mice, the immune system mounts a robust humoral response with production of pathogenic autoantibodies. However, before the appearance of autoantibodies, BXD2 mice produce high levels of IL-17 and exhibit spontaneous germinal center formation, where IL-17-producing T cells colocalize with IL-17R $^+$ B cells (Hsu and others 2008). Indeed, *Il17a* overexpression in these mice accelerates the formation of germinal centers, whereas mice lacking the IL-17R have reduced germinal center B cell development and humoral responses. This mouse model stresses the fact that IL-17-producing cells have alternative immune functions, since they have the ability to interact with B cells and aid them in the formation of germinal centers, as well as autoantibody production.

The IFN Signature

IFN was identified in 1957 (Isaacs and Lindenmann 1957), and in the next 50 years researchers have unveiled many

FIG. 2. The generation and effector functions of IL-17 producing T cells in SLE. TCR $\alpha\beta$ double-negative (DN) T cells and CD4⁺ Th17 T cells comprise the pool of IL-17-producing T cells in SLE. The generation of these 2 subsets is quite different: DN T cells derive from CD8⁺ T cells after sustained TCR activation, whereas the generation of Th17 T cells is favored in an inflammatory setting, where activated dendritic cells (DCs) provide inflammatory cytokines. This favors Th17 differentiation over production of regulatory T (Treg) cells. The decreased levels of IL-2 in SLE contribute further to the Th17/Treg imbalance. IL-17⁺ cells infiltrate the tissues, where they induce neutrophil recruitment, causing tissue inflammation, and damage. In addition, IL-17 induces autoantibody formation, by acting on B-cells. TCR, T cell receptor.

biological functions of type I IFNs (IFN α and IFN β), including antiviral, anti-proliferative, and immune modulator functions. Due to these immune modulator effects, type I IFNs are connected to several pathogenic pathways in various autoimmune diseases (Baccala and others 2005; Theofilopoulos and others 2005; Sozzani and others 2010), the most characteristic example of which is SLE (Crow 2007).

There is an ongoing dispute about the role of genetic predisposition and environmental factors in the initiation and progression of autoimmune diseases. The finding that high serum IFN α activity is a common heritable trait within SLE families in both healthy and SLE-affected members (Niewold and others 2007, 2008) indicates that the genetic control of the type I IFN system is important for the disease susceptibility, but the manifestation of clinical symptoms most likely needs to be triggered by environmental factors. Moreover, gene expression analysis of SLE peripheral blood

mononuclear cells (PBMCs) showed that up to 90% of the patients display the IFN signature, but only 40%–50% of the patients have significantly high serum IFN α activity. These discrepancies suggest that additional factors may play a role in the IFN α production or sensitivity to its signaling.

Activation of the type I IFN system is shown to be important in the initiation of the disease as well as in maintaining the clinical manifestations of SLE. These patients are characterized by increased serum levels of IFN α (Hooks and others 1979; Ytterberg and Schnitzer 1982), which correlates with disease activity (Dall'era and others 2005; Bauer and others 2006; Feng and others 2006). Moreover, administration of therapeutic IFN α can induce a lupus-like syndrome (Biggioggero and others 2010). Using genome-wide gene expression profiling, several research groups described highly upregulated expression levels of IFN-inducible genes in PBMCs of SLE patients (Baechler and others 2003; Bennett and others 2003;

Crow and Wohlgemuth 2003; Han and others 2003; Feng and others 2006). However, other diseases, such as systemic sclerosis (Coelho and others 2008) and Sjögren syndrome (Nordmark and others 2006), may also show this characteristic gene expression pattern. The IFN signature gene expression has been reported in lupus-affected tissues (eg, kidneys), suggesting that the phenomenon is important also for the clinical manifestations of the disease (Bennett and others 2003; Pascual and others 2003; Ronnblom and others 2009).

The role of the type I IFN system is further highlighted using murine models of lupus. For instance, treatment with IFN α accelerates disease and mortality in (NZB/W)-F1 mice (Mathian and others 2005) and treatment of NZB autoimmune mice with Toll-like receptor (TLR) 9 agonists induces high levels of serum IFN α (Lian and others 2004). Conversely, IFN receptor deficiency may protect lupus-prone mice from developing the disease (Agrawal and others 2009).

Plasmacytoid dendritic cells (pDCs) produce large amounts of IFN α in response to viral or bacterial infections (reviewed in Gilliet and others 2008). Sera from SLE patients have circulating ICs, containing autoantibodies and DNA with the capacity to activate pDCs (Vallin and others 1999; Ronnblom and others 2006). These nucleic acid-containing autoantigens in the IFN α -inducing ICs can be generated from apoptotic or necrotic cells (Lovgren and others 2004; Munoz and others 2008), or from neutrophil extracellular traps, a product of activated neutrophils rich in DNA and DNA-binding proteins (Garcia-Romo and others 2011; Lande and others 2011). In SLE, pDC numbers are markedly decreased in the peripheral blood of the patients (Blanco and others 2001; Blomberg and others 2003; Robak and others 2006) as they migrate to the tissues, where they appear with increased numbers and produce IFN α (Blomberg and others 2001; Farkas and others 2001; Ronnblom and Alm 2002; Tucci and others 2008).

IFN α promotes differentiation and maturation of DCs. Also, it stimulates the differentiation of activated B cells into antibody-secreting plasma cells. Through the formation of nucleic acid-containing ICs, a positive feedback loop is formed to enhance TLR7/9 activation and IFN α production. Importantly, IFN α upregulates the expression of TLR7, TLR9, and IRF7 in pDCs, myeloid DCs, and monocytes, thereby increasing the responsiveness to nucleic acid-containing ICs, with further augmentation of IFN α synthesis (Blanco and others 2005; Pascual and others 2006; Kis-Toth and Tsokos 2010; Obermoser and Pascual 2010). In addition, IFN α enhances autoreactive CD8⁺ T cell maturation contributing to tissue damage through perforin and granzyme release, thus generating novel autoantigens and further assisting IC-driven production of IFN α (Fig. 3).

IFN α seems to be a logical therapeutic target. Blocking type I IFN activity by using neutralizing anti-IFN antibodies or soluble IFN receptor-Fc constructs, or by inhibiting TLR ligation promises a better control of disease activity in SLE.

The IL-2 Superfamily: IL-15 and IL-21

IL-15 and IL-21 are part of the IL-2 superfamily, sharing structural as well as functional redundancy. The receptors of all 3 cytokines contain the common gamma chain (γ_c), and the IL-2R and IL-15R also share the IL-2R β , thereby sharing 2 out of 3 receptors. Similar to IL-2, IL-15 is involved in the expansion and homeostasis of T, natural killer (NK), and NKT cells. Furthermore, IL-15 promotes isotype switching in

B cells (Gabay and McInnes 2009). It has been reported that SLE patients have increased serum levels of IL-15 (Aringer and others 2001; Baranda and others 2005) and increased levels of IL-15 have been found in synovial joints of patients with rheumatoid arthritis contributing to the inflammation (McInnes and others 1996).

IL-21 is produced by T cells and binds γ_c and a novel receptor chain (IL-21R) found on T, NK, NKT, and B cells (Gabay and McInnes 2009). IL-21 plays a role in enhancing cytotoxicity of NKT cells and, unlike IL-2 or IL-15, IL-21 is involved in B cell activation and plasma cell differentiation, which likely contributes to autoimmune autoantibody production. IL-21 is involved in activation-induced death of expanded B cells (Ozaki and others 2004; Ettinger and others 2008) and a relationship has been identified between decreased *IL21R* expression on the peripheral B cells, high levels of autoantibody production and nephritis in SLE patients (Mitoma and others 2005). It has been reported that polymorphisms of the *IL21* and *IL21R* genes have been identified in SLE patients (Sawalha and others 2008; Webb and others 2009) and this may contribute to the pathogenesis of disease. IL-21 may be a good therapeutic target for alleviating SLE pathology, as it was reported that deletion of the *Il21r* gene in BXS^B/*Yaa* mice arrests disease progression (Bubier and others 2009).

The IL-12/IFN- γ Axis

IL-12 stimulates the differentiation of Th1 cells, which produce IFN- γ . In murine models of lupus, IFN- γ has a pro-pathogenic effect. Some strains of SLE-prone mice have elevated levels of IFN- γ (Prud'homme and others 1995) and deletion of the IFN- γ gene reduces lupus pathology (Balomenos and others 1998).

Expression of the IL-12R was examined, and while one study was unable to link IL-12RB polymorphisms to SLE (Sanchez and others 2005), a recent study reported that SLE patients have a higher copy number of the *IL12RB* gene as compared to the control population (Yu and others 2011). The IFN- γ R was also evaluated and the Val14Met polymorphism of the *IFNGR* was linked to SLE disease in one report (Tanaka and others 1999), but another study found no link between this polymorphism or the Gln64Arg variant within the population they tested (Yao and others 2007).

IL-27 is a new member of the IL-12 cytokine family that can synergize with IL-12 to increase IFN- γ production and it has been reported to induce both pro- or anti-inflammatory processes (Pflanz and others 2002; Awasthi and others 2007). It has been demonstrated that mice lacking the WSX-1 chain of the IL-27R have increased inflammation (Villarino and others 2003). The role of IL-27 in SLE pathogenesis is not clear. It has been reported that serum levels of IL-27 are lower in SLE patients than in healthy individuals (Li and others 2010). Overexpression of WSX-1 in MRL/*lpr* mice arrested glomerulonephritis development and decreased IFN- γ production, and these mice displayed prolonged survival (Sugiyama and others 2008). In addition, targeted expression of WSX-1 in T cells of MRL/*lpr* mice resulted in greatly reduced skin lesions compared with control mice (Kido and others 2011).

Th2 Cytokines

IL-4, IL-5, IL-10, and IL-13 are all cytokines that play an important role in various B cell functions, including

FIG. 3. The contribution of IFN α to the disruption of peripheral immune tolerance in SLE. (1). IFN α augments differentiation of monocytes into DCs and from immature DCs to mature, autoantigen-presenting DCs. These DCs present autoantigens to T cells and B cells leading to survival, proliferation, and differentiation of autoreactive lymphocytes. (2). IFN α promotes the differentiation of activated B cells into antibody-secreting plasma cells and subsequent formation of immune complexes (ICs). (3). Through the formation of nucleic acid-containing ICs, a positive feedback loop is formed to enhance TLR7/9 activation and IFN α production in pDCs, myeloid DCs, and monocytes. (4). IFN α enhances autoreactive CD8 $^{+}$ T cell maturation contributing to tissue damage through perforin and granzyme release, thus generating novel autoantigens and further assisting IC-driven production of IFN α . IFN, interferon; TLR, Toll-like receptor; pDC, plasmacytoid dendritic cell.

proliferation, activation, and isotype switching. They also induce the differentiation of naïve T cells to Th2 T cells. Autoantibody formation is pivotal to the pathogenesis of SLE and any aberrations in this complex of B cell associated cytokines can contribute to disease. IL-4 has been shown to be produced in higher amounts by DN T cells (Dean and others 2002) and NKT cells in patients with SLE (Funauchi and others 1999). The frequency of IL-4-positive cells among PBMCs is increased in SLE compared with healthy controls (Funauchi and others 1998).

IL-10, although known to be closely associated with Treg cell functions, has also a well-characterized role in B cell responses (Briere and others 1994). Interestingly, in patients with SLE the major producers of IL-10 are monocytes and B lymphocytes (Llorente and others 1993), and these cells can

induce *in vitro* as well as *in vivo* immunoglobulin production in an IL-10-dependent manner (Llorente and others 1995). Furthermore, single-nucleotide polymorphisms known to regulate the IL-10 promoter function have been found in African-American patients with SLE, and this may contribute to the increased levels of IL-10 observed in these lupus patients (Gibson and others 2001). Hypomethylation of the *IL10* and *IL13* promoters, due to the established decrease of expression and activity of DNA methyltransferase 1 observed in SLE patients (Oelke and others 2004; Ballestar and others 2006; Sunahori and others 2009), may further contribute to increased production of these cytokines (Zhao and others 2010).

Antagonizing IL-10 actions has proved to be beneficial in the lupus mouse model NZB/NZW (Ishida and others 1994),

as well as in patients with SLE, in whom administration of IL-10 blocking antibodies attenuated joint and skin damage (Llorente and others 2000).

IL-1

The major source of IL-1 is activated mononuclear phagocytes. IL-1 exists in 2 forms, termed IL-1 α and IL-1 β , that share 30% homology. IL-1 α is initially produced as a 33 kD precursor, which is then proteolytically cleaved by caspase-1 after activation of the inflammasome to its active 17 kD form, whereas IL-1 β is active in both forms, the 33 kD precursor as well as the 17 kD mature form. Mononuclear phagocytes also produce an antagonist of IL-1, the IL-1 receptor antagonist (IL-1 α), which is structurally homologous to IL-1 but has no biological activity and thus blocks IL-1 functions.

In murine lupus models, recombinant IL-1 β administration has been shown to accelerate the onset and progression of arthritis in MRL/*lpr* mice (Hom and others 1990). However, in both MRL/*lpr* and NZB/NZW mouse models, macrophage-derived IL-1 production appears to be defective (Donnelly and others 1990; Fitzpatrick and others 1996; Levine and others 1998).

In lupus patients, studies of genetic variations in the genes of the IL-1 family members have shown that specific polymorphisms in the *il1a* and *il1b* genes are associated with increased risk for SLE (Parks and others 2004), whereas specific alleles of the *il1ra* gene have been associated with increased severity of the disease (Blakemore and others 1994). Measurement of serum levels of IL-1 α in lupus patients have shown that low levels are associated with kidney involvement, whereas flares in other organs correlate with increased levels of IL-1 α .

Conclusions

The factors that mediate lupus pathogenesis and tissue damage span the whole immune system. Thus, it is not surprising that the cytokine networks orchestrating immune cell functions appear dysregulated. In turn, the study of this aberrant regulation of cytokines provides 2 major windows of opportunity: first, the opportunity to modify these cytokine networks to modulate the disease progression in a way that will be beneficial for lupus patients; second, the study of the factors that underline the aberrant cytokine signaling in SLE will eventually allow us to identify novel biomarkers to classify lupus patients according to their prognosis and their differential response to treatment.

The IL-2 dysregulation is fundamental for lupus pathogenesis. IL-17 and the IFN signature play important roles both in the pathogenesis and more significantly in the tissue damage mediated by effector cells. Understanding and modulating these 3 main axes in lupus patients is of critical significance and currently one of the main goals in lupus research.

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References

- Agrawal H, Jacob N, Carreras E, Bajana S, Putterman C, Turner S, Neas B, Mathian A, Koss MN, Stohl W, Kovats S, Jacob CO. 2009. Deficiency of type I IFN receptor in lupus-prone New Zealand mixed 2328 mice decreases dendritic cell numbers and activation and protects from disease. *J Immunol* 183: 6021–6029.
- Alcocer-Varela J, Alarcon-Segovia D. 1982. Decreased production of and response to interleukin-2 by cultured lymphocytes from patients with systemic lupus erythematosus. *J Clin Invest* 69:1388–1392.
- Altman A, Theofilopoulos AN, Weiner R, Katz DH, Dixon FJ. 1981. Analysis of T cell function in autoimmune murine strains. Defects in production and responsiveness to interleukin 2. *J Exp Med* 154:791–808.
- Aringer M, Stummvoll GH, Steiner G, Koller M, Steiner CW, Hofler E, Hiesberger H, Smolen JS, Graninger WB. 2001. Serum interleukin-15 is elevated in systemic lupus erythematosus. *Rheumatology (Oxford)* 40:876–881.
- Awasthi A, Carrier Y, Peron JP, Bettelli E, Kamanaka M, Flavell RA, Kuchroo VK, Oukka M, Weiner HL. 2007. A dominant function for interleukin 27 in generating interleukin 10-producing anti-inflammatory T cells. *Nat Immunol* 8:1380–1389.
- Baccala R, Kono DH, Theofilopoulos AN. 2005. Interferons as pathogenic effectors in autoimmunity. *Immunol Rev* 204:9–26.
- Baechler EC, Batliwalla FM, Karypis G, Gaffney PM, Ortmann WA, Espe KJ, Shark KB, Grande WJ, Hughes KM, Kapur V, Gregersen PK, Behrens TW. 2003. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. *Proc Natl Acad Sci USA* 100:2610–2615.
- Ballestar E, Esteller M, Richardson BC. 2006. The epigenetic face of systemic lupus erythematosus. *J Immunol* 176:7143–7147.
- Balomenos D, Rumold R, Theofilopoulos AN. 1998. Interferon-gamma is required for lupus-like disease and lymphoaccumulation in MRL-*lpr* mice. *J Clin Invest* 101:364–371.
- Baranda L, de la FH, Layseca-Espinosa E, Portales-Perez D, Nino-Moreno P, Valencia-Pacheco G, Abud-Mendoza C, Alcocer-Varela J, Gonzalez-Amaro R. 2005. IL-15 and IL-15R in leucocytes from patients with systemic lupus erythematosus. *Rheumatology (Oxford)* 44:1507–1513.
- Bauer JW, Baechler EC, Petri M, Batliwalla FM, Crawford D, Ortmann WA, Espe KJ, Li W, Patel DD, Gregersen PK, Behrens TW. 2006. Elevated serum levels of interferon-regulated chemokines are biomarkers for active human systemic lupus erythematosus. *PLoS Med* 3:e491.
- Bennett L, Palucka AK, Arce E, Cantrell V, Borvak J, Banchereau J, Pascual V. 2003. Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. *J Exp Med* 197:711–723.
- Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, Weiner HL, Kuchroo VK. 2006. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature* 441:235–238.
- Biggioggero M, Gabbriellini L, Meroni PL. 2010. Type I interferon therapy and its role in autoimmunity. *Autoimmunity* 43:248–254.
- Blakemore AI, Tarlow JK, Cork MJ, Gordon C, Emery P, Duff GW. 1994. Interleukin-1 receptor antagonist gene polymorphism as a disease severity factor in systemic lupus erythematosus. *Arthritis Rheum* 37:1380–1385.
- Blanco P, Palucka AK, Gill M, Pascual V, Banchereau J. 2001. Induction of dendritic cell differentiation by IFN- α in systemic lupus erythematosus. *Science* 294:1540–1543.
- Blanco P, Viallard JF, Pellegrin JL, Moreau JF. 2005. Cytotoxic T lymphocytes and autoimmunity. *Curr Opin Rheumatol* 17:731–734.

- Blomberg S, Eloranta ML, Cederblad B, Nordlin K, Alm GV, Ronnblom L. 2001. Presence of cutaneous interferon-alpha producing cells in patients with systemic lupus erythematosus. *Lupus* 10:484-490.
- Blomberg S, Eloranta ML, Magnusson M, Alm GV, Ronnblom L. 2003. Expression of the markers BDCA-2 and BDCA-4 and production of interferon-alpha by plasmacytoid dendritic cells in systemic lupus erythematosus. *Arthritis Rheum* 48:2524-2532.
- Briere F, Servet-Delprat C, Bridon JM, Saint-Remy JM, Banchereau J. 1994. Human interleukin 10 induces naive surface immunoglobulin D+ (sIgD+) B cells to secrete IgG1 and IgG3. *J Exp Med* 179:757-762.
- Bubier JA, Sproule TJ, Foreman O, Spolski R, Shaffer DJ, Morse HC, III, Leonard WJ, Roopenian DC. 2009. A critical role for IL-21 receptor signaling in the pathogenesis of systemic lupus erythematosus in BXSb-Yaa mice. *Proc Natl Acad Sci USA* 106:1518-1523.
- Coelho LF, de Oliveira JG, Kroon EG. 2008. Interferons and scleroderma-a new clue to understanding the pathogenesis of scleroderma? *Immunol Lett* 118:110-115.
- Cohen PL, Eisenberg RA. 1991. Lpr and gld: single gene models of systemic autoimmunity and lymphoproliferative disease. *Annu Rev Immunol* 9:243-269.
- Crispin JC, Liossis SN, Kis-Toth K, Lieberman LA, Kyttaris VC, Juang YT, Tsokos GC. 2010. Pathogenesis of human systemic lupus erythematosus: recent advances. *Trends Mol Med* 16:47-57.
- Crispin JC, Oukka M, Bayliss G, Cohen RA, Van Beek CA, Stillman IE, Kyttaris VC, Juang YT, Tsokos GC. 2008. Expanded double negative T cells in patients with systemic lupus erythematosus produce IL-17 and infiltrate the kidneys. *J Immunol* 181:8761-8766.
- Crispin JC, Tsokos GC. 2009. Human TCR- $\alpha\beta^+$ CD4⁻ CD8⁻ T cells can derive from CD8⁺ T cells and display an inflammatory effector phenotype. *J Immunol* 183:4675-4681.
- Crow MK. 2007. Type I interferon in systemic lupus erythematosus. *Curr Top Microbiol Immunol* 316:359-386.
- Crow MK, Wohlgemuth J. 2003. Microarray analysis of gene expression in lupus. *Arthritis Res Ther* 5:279-287.
- Dall'era MC, Cardarelli PM, Preston BT, Witte A, Davis JC, Jr. 2005. Type I interferon correlates with serological and clinical manifestations of SLE. *Ann Rheum Dis* 64:1692-1697.
- Dean GS, Anand A, Blofeld A, Isenberg DA, Lydyard PM. 2002. Characterization of CD3⁺ CD4⁻ CD8⁻ (double negative) T cells in patients with systemic lupus erythematosus: production of IL-4. *Lupus* 11:501-507.
- Donnelly RP, Levine J, Hartwell DQ, Frenzl G, Fenton MJ, Beller DI. 1990. Aberrant regulation of IL-1 expression in macrophages from young autoimmune-prone mice. *J Immunol* 145:3231-3239.
- Doreau A, Belot A, Bastid J, Riche B, Trescol-Biemont MC, Ranchin B, Fabien N, Cochat P, Pouteil-Noble C, Trolliet P, Durieu I, Tebib J, Kassai B, Ansieau S, Puisieux A, Eliaou JF, Bonnefoy-Berard N. 2009. Interleukin 17 acts in synergy with B cell-activating factor to influence B cell biology and the pathophysiology of systemic lupus erythematosus. *Nat Immunol* 10:778-785.
- Duarte C, Couto M, Ines L, Liang MH. 2011. Epidemiology of systemic lupus erythematosus. In: Lahita RG, Tsokos GC, Buyon JP, Koike T, eds. *Systemic lupus erythematosus*, 5th ed. London: Elsevier. pp 673-696.
- Ettinger R, Kuchen S, Lipsky PE. 2008. The role of IL-21 in regulating B-cell function in health and disease. *Immunol Rev* 223:60-86.
- Farkas L, Beiske K, Lund-Johansen F, Brandtzaeg P, Jahnsen FL. 2001. Plasmacytoid dendritic cells (natural interferon- α /beta-producing cells) accumulate in cutaneous lupus erythematosus lesions. *Am J Pathol* 159:237-243.
- Feng X, Wu H, Grossman JM, Hanvivadhanakul P, FitzGerald JD, Park GS, Dong X, Chen W, Kim MH, Weng HH, Furst DE, Gorn A, McMahon M, Taylor M, Brahn E, Hahn BH, Tsao BP. 2006. Association of increased interferon-inducible gene expression with disease activity and lupus nephritis in patients with systemic lupus erythematosus. *Arthritis Rheum* 54:2951-2962.
- Fitzpatrick JM, Koh JS, Hartwell D, Beller DI, Levine JS. 1996. Dysregulated cytokine expression *in vivo* in prediseased and diseased autoimmune-prone MRL mice. *Autoimmunity* 23:217-229.
- Fontenot JD, Rasmussen JP, Williams LM, Dooley JL, Farr AG, Rudensky AY. 2005. Regulatory T cell lineage specification by the forkhead transcription factor foxp3. *Immunity* 22:329-341.
- Funauchi M, Ikoma S, Enomoto H, Horiuchi A. 1998. Decreased Th1-like and increased Th2-like cells in systemic lupus erythematosus. *Scand J Rheumatol* 27:219-224.
- Funauchi M, Yu H, Sugiyama M, Ikoma S, Ohno M, Kinoshita K, Hamada K, Kanamaru A. 1999. Increased interleukin-4 production by NK T cells in systemic lupus erythematosus. *Clin Immunol* 92:197-202.
- Gabay C, McInnes IB. 2009. The biological and clinical importance of the 'new generation' cytokines in rheumatic diseases. *Arthritis Res Ther* 11:230.
- Garcia-Romo GS, Caielli S, Vega B, Connolly J, Allantaz F, Xu Z, Punaro M, Baisch J, Guiducci C, Coffman RL, Barrat FJ, Banchereau J, Pascual V. 2011. Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. *Sci Transl Med* 3:73ra20.
- Ghatak S, Sainis K, Owen FL, Datta SK. 1987. T-cell-receptor beta- and I-A beta-chain genes of normal SWR mice are linked with the development of lupus nephritis in NZB x SWR crosses. *Proc Natl Acad Sci USA* 84:6850-6853.
- Gibson AW, Edberg JC, Wu J, Westendorp RG, Huizinga TW, Kimberly RP. 2001. Novel single nucleotide polymorphisms in the distal IL-10 promoter affect IL-10 production and enhance the risk of systemic lupus erythematosus. *J Immunol* 166:3915-3922.
- Gilliet M, Cao W, Liu YJ. 2008. Plasmacytoid dendritic cells: sensing nucleic acids in viral infection and autoimmune diseases. *Nat Rev Immunol* 8:594-606.
- Han GM, Chen SL, Shen N, Ye S, Bao CD, Gu YY. 2003. Analysis of gene expression profiles in human systemic lupus erythematosus using oligonucleotide microarray. *Genes Immun* 4:177-186.
- Harada T, Kyttaris V, Li Y, Juang YT, Wang Y, Tsokos GC. 2007. Increased expression of STAT3 in SLE T cells contributes to enhanced chemokine-mediated cell migration. *Autoimmunity* 40:1-8.
- Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, Weaver CT. 2005. Interleukin 17-producing CD4⁺ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat Immunol* 6:1123-1132.
- Hom JT, Cole H, Bendele AM. 1990. Interleukin 1 enhances the development of spontaneous arthritis in MRL/lpr mice. *Clin Immunol Immunopathol* 55:109-119.
- Hooks JJ, Moutsopoulos HM, Geis SA, Stahl NI, Decker JL, Notkins AL. 1979. Immune interferon in the circulation of patients with autoimmune disease. *N Engl J Med* 301:5-8.
- Hsu HC, Yang P, Wang J, Wu Q, Myers R, Chen J, Yi J, Guentert T, Tousson A, Stanus AL, Le TV, Lorenz RG, Xu H, Kolls JK,

- Carter RH, Chaplin DD, Williams RW, Mountz JD. 2008. Interleukin 17-producing T helper cells and interleukin 17 orchestrate autoreactive germinal center development in autoimmune BXD2 mice. *Nat Immunol* 9:166–175.
- Hsu HC, Zhou T, Kim H, Barnes S, Yang P, Wu Q, Zhou J, Freeman BA, Luo M, Mountz JD. 2006. Production of a novel class of polyreactive pathogenic autoantibodies in BXD2 mice causes glomerulonephritis and arthritis. *Arthritis Rheum* 54:343–355.
- Ichinose K, Juang YT, Crispin JC, Kis-Toth K, Tsokos GC. 2011. Suppression of autoimmunity and organ pathology in lupus-prone mice upon inhibition of calcium/calmodulin-dependent protein kinase type IV. *Arthritis Rheum* 63:523–529.
- Igarashi S, Takiguchi M, Kariyone A, Kano K. 1988. Phenotypic and functional analyses on T-cell subsets in lymph nodes of MRL/Mp-lpr/lpr mice. *Int Arch Allergy Appl Immunol* 86:249–255.
- Isaacs A, Lindenmann J. 1957. Virus interference. I. The interferon. *Proc R Soc Lond B Biol Sci* 147:258–267.
- Ishida H, Muchamuel T, Sakaguchi S, Andrade S, Menon S, Howard M. 1994. Continuous administration of anti-interleukin 10 antibodies delays onset of autoimmunity in NZB/W F1 mice. *J Exp Med* 179:305–310.
- Ivanov IL, McKenzie BS, Zhou L, Tadokoro CE, Lepelley A, Lafaille JJ, Cua DJ, Littman DR. 2006. The orphan nuclear receptor ROR γ directs the differentiation program of proinflammatory IL-17+ T helper cells. *Cell* 126:1121–1133.
- Juang YT, Rauen T, Wang Y, Ichinose K, Benedyk K, Tenbrock K, Tsokos GC. 2011. Transcriptional activation of the cAMP-responsive modulator promoter in human T cells is regulated by protein phosphatase 2A-mediated dephosphorylation of SP-1 and reflects disease activity in patients with systemic lupus erythematosus. *J Biol Chem* 286:1795–1801.
- Juang YT, Wang Y, Solomou EE, Li Y, Mawrin C, Tenbrock K, Kyttaris VC, Tsokos GC. 2005. Systemic lupus erythematosus serum IgG increases CREM binding to the IL-2 promoter and suppresses IL-2 production through CaMKIV. *J Clin Invest* 115:996–1005.
- Kang HK, Liu M, Datta SK. 2007. Low-dose peptide tolerance therapy of lupus generates plasmacytoid dendritic cells that cause expansion of autoantigen-specific regulatory T cells and contraction of inflammatory Th17 cells. *J Immunol* 178:7849–7858.
- Kang HK, Michaels MA, Berner BR, Datta SK. 2005. Very low-dose tolerance with nucleosomal peptides controls lupus and induces potent regulatory T cell subsets. *J Immunol* 174:3247–3255.
- Katsiari CG, Kyttaris VC, Juang YT, Tsokos GC. 2005. Protein phosphatase 2A is a negative regulator of IL-2 production in patients with systemic lupus erythematosus. *J Clin Invest* 115:3193–3204.
- Kido M, Takeuchi S, Sugiyama N, Esaki H, Nakashima H, Yoshida H, Furue M. 2011. T cell-specific overexpression of interleukin-27 receptor α -subunit (WSX-1) prevents spontaneous skin inflammation in MRL/lpr mice. *Br J Dermatol* 164:1214–1220.
- Kis-Toth K, Tsokos GC. 2010. Dendritic cell function in lupus: independent contributors or victims of aberrant immune regulation. *Autoimmunity* 43:121–130.
- Kyttaris VC, Zhang Z, Kuchroo VK, Oukka M, Tsokos GC. 2010. Cutting edge: IL-23 receptor deficiency prevents the development of lupus nephritis in C57BL/6-lpr/lpr mice. *J Immunol* 184:4605–4609.
- La Cava A. 2008. T-regulatory cells in systemic lupus erythematosus. *Lupus* 17:421–425.
- Lande R, Ganguly D, Facchinetti V, Frasca L, Conrad C, Gregorio J, Meller S, Chamilos G, Sebasigari R, Ricciari V, Bassett R, Amuro H, Fukuhara S, Ito T, Liu YJ, Gilliet M. 2011. Neutrophils activate plasmacytoid dendritic cells by releasing self-DNA-peptide complexes in systemic lupus erythematosus. *Sci Transl Med* 3:73ra19.
- Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD, McClanahan T, Kastelein RA, Cua DJ. 2005. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J Exp Med* 201:233–240.
- Laurence A, Tato CM, Davidson TS, Kanno Y, Chen Z, Yao Z, Blank RB, Meylan F, Siegel R, Hennighausen L, Shevach EM, O'Shea JJ. 2007. Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. *Immunity* 26:371–381.
- Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, Heyse SP, Hirsch R, Hochberg MC, Hunder GG, Liang MH, Pillemer SR, Steen VD, Wolfe F. 1998. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 41:778–799.
- Levine JS, Koh JS, Hartwell D, Beller DI. 1998. Adhesion elicits an intrinsic defect in interleukin-1 expression by macrophages from autoimmune-prone MRL mice. *J Autoimmun* 11:141–150.
- Li TT, Zhang T, Chen GM, Zhu QQ, Tao JH, Pan HF, Ye DQ. 2010. Low level of serum interleukin 27 in patients with systemic lupus erythematosus. *J Investig Med* 58:737–739.
- Lian ZX, Kikuchi K, Yang GX, Ansari AA, Ikehara S, Gershwin ME. 2004. Expansion of bone marrow IFN- α -producing dendritic cells in New Zealand Black (NZB) mice: high level expression of TLR9 and secretion of IFN- α in NZB bone marrow. *J Immunol* 173:5283–5289.
- Lieberman LA, Tsokos GC. 2010. The IL-2 defect in systemic lupus erythematosus disease has an expansive effect on host immunity. *J Biomed Biotechnol* 2010:740619.
- Llorente L, Richaud-Patin Y, Garcia-Padilla C, Claret E, Jakez-Ocampo J, Cardiel MH, Cacer-Varela J, Grangeot-Keros L, Arcon-Segovia D, Wijdenes J, Galanaud P, Emilie D. 2000. Clinical and biologic effects of anti-interleukin-10 monoclonal antibody administration in systemic lupus erythematosus. *Arthritis Rheum* 43:1790–1800.
- Llorente L, Richaud-Patin Y, Wijdenes J, cacer-Varela J, Maillot MC, Durand-Gasselin I, Fourrier BM, Galanaud P, Emilie D. 1993. Spontaneous production of interleukin-10 by B lymphocytes and monocytes in systemic lupus erythematosus. *Eur Cytokine Netw* 4:421–427.
- Llorente L, Zou W, Levy Y, Richaud-Patin Y, Wijdenes J, cacer-Varela J, Morel-Fourrier B, Brouet JC, arcon-Segovia D, Galanaud P, Emilie D. 1995. Role of interleukin 10 in the B lymphocyte hyperactivity and autoantibody production of human systemic lupus erythematosus. *J Exp Med* 181:839–844.
- Lovgren T, Eloranta ML, Bave U, Alm GV, Ronnblom L. 2004. Induction of interferon- α production in plasmacytoid dendritic cells by immune complexes containing nucleic acid released by necrotic or late apoptotic cells and lupus IgG. *Arthritis Rheum* 50:1861–1872.
- Malek TR, Yu A, Vincek V, Scibelli P, Kong L. 2002. CD4 regulatory T cells prevent lethal autoimmunity in IL-2R β -deficient mice. Implications for the nonredundant function of IL-2. *Immunity* 17:167–178.
- Mangan PR, Harrington LE, O'Quinn DB, Helms WS, Bullard DC, Elson CO, Hatton RD, Wahl SM, Schoeb TR, Weaver CT. 2006. Transforming growth factor- β induces development of the T(H)17 lineage. *Nature* 441:231–234.

- Mathian A, Weinberg A, Gallegos M, Banchereau J, Koutouzov S. 2005. IFN- α induces early lethal lupus in preauto-immune (New Zealand Black x New Zealand White) F1 but not in BALB/c mice. *J Immunol* 174:2499–2506.
- McInnes IB, al-Mughales J, Field M, Leung BP, Huang FP, Dixon R, Sturrock RD, Wilkinson PC, Liew FY. 1996. The role of interleukin-15 in T-cell migration and activation in rheumatoid arthritis. *Nat Med* 2:175–182.
- Mitoma H, Horiuchi T, Kimoto Y, Tsukamoto H, Uchino A, Tamimoto Y, Miyagi Y, Harada M. 2005. Decreased expression of interleukin-21 receptor on peripheral B lymphocytes in systemic lupus erythematosus. *Int J Mol Med* 16:609–615.
- Mitsdoerffer M, Lee Y, Jager A, Kim HJ, Korn T, Kolls JK, Cantor H, Bettelli E, Kuchroo VK. 2010. Proinflammatory T helper type 17 cells are effective B-cell helpers. *Proc Natl Acad Sci USA* 107:14292–14297.
- Munoz LE, van Bavel C, Franz S, Berden J, Herrmann M, van der Vlag J. 2008. Apoptosis in the pathogenesis of systemic lupus erythematosus. *Lupus* 17:371–375.
- Niewold TB, Adler JE, Glenn SB, Lehman TJ, Harley JB, Crow MK. 2008. Age- and sex-related patterns of serum interferon- α activity in lupus families. *Arthritis Rheum* 58:2113–2119.
- Niewold TB, Hua J, Lehman TJ, Harley JB, Crow MK. 2007. High serum IFN- α activity is a heritable risk factor for systemic lupus erythematosus. *Genes Immun* 8:492–502.
- Nordmark G, Alm GV, Ronnblom L. 2006. Mechanisms of disease: primary Sjogren's syndrome and the type I interferon system. *Nat Clin Pract Rheumatol* 2:262–269.
- Obermoser G, Pascual V. 2010. The interferon- α signature of systemic lupus erythematosus. *Lupus* 19:1012–1019.
- Oelke K, Lu Q, Richardson D, Wu A, Deng C, Hanash S, Richardson B. 2004. Overexpression of CD70 and overstimulation of IgG synthesis by lupus T cells and T cells treated with DNA methylation inhibitors. *Arthritis Rheum* 50:1850–1860.
- Ozaki K, Spolski R, Ettinger R, Kim HP, Wang G, Qi CF, Hwu P, Shaffer DJ, Akilesh S, Roopenian DC, Morse HC, III, Lipsky PE, Leonard WJ. 2004. Regulation of B cell differentiation and plasma cell generation by IL-21, a novel inducer of Blimp-1 and Bcl-6. *J Immunol* 173:5361–5371.
- Park H, Li Z, Yang XO, Chang SH, Nurieva R, Wang YH, Wang Y, Hood L, Zhu Z, Tian Q, Dong C. 2005. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nat Immunol* 6:1133–1141.
- Parks CG, Cooper GS, Dooley MA, Treadwell EL, St Clair EW, Gilkeson GS, Pandey JP. 2004. Systemic lupus erythematosus and genetic variation in the interleukin 1 gene cluster: a population based study in the southeastern United States. *Ann Rheum Dis* 63:91–94.
- Pascual V, Banchereau J, Palucka AK. 2003. The central role of dendritic cells and interferon- α in SLE. *Curr Opin Rheumatol* 15:548–556.
- Pascual V, Farkas L, Banchereau J. 2006. Systemic lupus erythematosus: all roads lead to type I interferons. *Curr Opin Immunol* 18:676–682.
- Pflanz S, Timans JC, Cheung J, Rosales R, Kanzler H, Gilbert J, Hibbert L, Churakova T, Travis M, Vaisberg E, Blumenschein WM, Mattson JD, Wagner JL, To W, Zurawski S, McClanahan TK, Gorman DM, Bazan JF, de Waal MR, Rennick D, Kastelein RA. 2002. IL-27, a heterodimeric cytokine composed of EBI3 and p28 protein, induces proliferation of naive CD4(+) T cells. *Immunity* 16:779–790.
- Pons-Estel GJ, Alarcon GS, Scofield L, Reinlib L, Cooper GS. 2010. Understanding the epidemiology and progression of systemic lupus erythematosus. *Semin Arthritis Rheum* 39:257–268.
- Prud'homme GJ, Kono DH, Theofilopoulos AN. 1995. Quantitative polymerase chain reaction analysis reveals marked overexpression of interleukin-1 β , interleukin-1 and interferon- γ mRNA in the lymph nodes of lupus-prone mice. *Mol Immunol* 32:495–503.
- Riol-Blanco L, Lazarevic V, Awasthi A, Mitsdoerffer M, Wilson BS, Croxford A, Waisman A, Kuchroo VK, Glimcher LH, Oukka M. 2010. IL-23 receptor regulates unconventional IL-17-producing T cells that control bacterial infections. *J Immunol* 184:1710–1720.
- Robak E, Sysa-Jedrzejowska A, Robak T, Smolewski P. 2006. Peripheral blood lymphocyte apoptosis and circulating dendritic cells in patients with systemic lupus erythematosus: correlation with immunological status and disease-related symptoms. *Clin Rheumatol* 25:225–233.
- Ronnblom L, Alm GV. 2002. The natural interferon- α producing cells in systemic lupus erythematosus. *Hum Immunol* 63:1181–1193.
- Ronnblom L, Alm GV, Eloranta ML. 2009. Type I interferon and lupus. *Curr Opin Rheumatol* 21:471–477.
- Ronnblom L, Eloranta ML, Alm GV. 2006. The type I interferon system in systemic lupus erythematosus. *Arthritis Rheum* 54:408–420.
- Sanchez E, Morales S, Paco L, Lopez-Nevot MA, Hidalgo C, Jimenez-Alonso J, Torres B, Gonzalez-Gay MA, Callejas JL, Ortego-Centeno N, Sanchez-Roman J, Gonzalez-Escribano MF, Martin J. 2005. Interleukin 12 (IL12B), interleukin 12 receptor (IL12RB1) and interleukin 23 (IL23A) gene polymorphism in systemic lupus erythematosus. *Rheumatology (Oxford)* 44:1136–1139.
- Sawalha AH, Kaufman KM, Kelly JA, Adler AJ, Aberle T, Kilpatrick J, Wakeland EK, Li QZ, Wandstrat AE, Karp DR, James JA, Merrill JT, Lipsky P, Harley JB. 2008. Genetic association of interleukin-21 polymorphisms with systemic lupus erythematosus. *Ann Rheum Dis* 67:458–461.
- Schorle H, Holtschke T, Hunig T, Schimpl A, Horak I. 1991. Development and function of T cells in mice rendered interleukin-2 deficient by gene targeting. *Nature* 352:621–624.
- Schwarzenberger P, Huang W, Oliver P, Byrne P, La Russa V, Zhang Z, Kolls JK. 2001. IL-17 mobilizes peripheral blood stem cells with short- and long-term repopulating ability in mice. *J Immunol* 167:2081–2086.
- Schwarzenberger P, Huang W, Ye P, Oliver P, Manuel M, Zhang Z, Bagby G, Nelson S, Kolls JK. 2000. Requirement of endogenous stem cell factor and granulocyte-colony-stimulating factor for IL-17-mediated granulopoiesis. *J Immunol* 164:4783–4789.
- Schwarzenberger P, La Russa V, Miller A, Ye P, Huang W, Zieske A, Nelson S, Bagby GJ, Stoltz D, Mynatt RL, Spriggs M, Kolls JK. 1998. IL-17 stimulates granulopoiesis in mice: use of an alternate, novel gene therapy-derived method for *in vivo* evaluation of cytokines. *J Immunol* 161:6383–6389.
- Shah K, Lee WW, Kang SW, Kim SH, Lee SH, Craft J, Kang I. 2009. Dysregulated balance of Th17 and Th1 cells in systemic lupus erythematosus. *Arthritis Res Ther* 12: R53.
- Solomou EE, Juang YT, Gourley MF, Kammer GM, Tsokos GC. 2001. Molecular basis of deficient IL-2 production in T cells from patients with systemic lupus erythematosus. *J Immunol* 166:4216–4222.
- Sozzani S, Bosisio D, Scarsi M, Tincani A. 2010. Type I interferons in systemic autoimmunity. *Autoimmunity* 43:196–203.
- Sugiyama N, Nakashima H, Yoshimura T, Sadanaga A, Shimizu S, Masutani K, Igawa T, Akahoshi M, Miyake K, Takeda A,

- Yoshimura A, Hamano S, Yoshida H. 2008. Amelioration of human lupus-like phenotypes in MRL/lpr mice by over-expression of interleukin 27 receptor alpha (WSX-1). *Ann Rheum Dis* 67:1461–1467.
- Sunahori K, Juang YT, Kyttaris VC, Tsokos GC. 2011. Promoter hypomethylation results in increased expression of protein phosphatase 2A in T cells from patients with systemic lupus erythematosus. *J Immunol* 186:4508–4517.
- Sunahori K, Juang YT, Tsokos GC. 2009. Methylation status of CpG islands flanking a cAMP response element motif on the protein phosphatase 2A alpha promoter determines CREB binding and activity. *J Immunol* 182:1500–1508.
- Suzuki H, Kundig TM, Furlonger C, Wakeham A, Timms E, Matsuyama T, Schmits R, Simard JJ, Ohashi PS, Griesser H. 1995. Deregulated T cell activation and autoimmunity in mice lacking interleukin-2 receptor beta. *Science* 268:1472–1476.
- Tan W, Huang W, Zhong Q, Schwarzenberger P. 2006. IL-17 receptor knockout mice have enhanced myelotoxicity and impaired hemopoietic recovery following gamma irradiation. *J Immunol* 176:6186–6193.
- Tanaka Y, Nakashima H, Hisano C, Kohsaka T, Nemoto Y, Niino H, Otsuka T, Otsuka T, Imamura T, Niho Y. 1999. Association of the interferon-gamma receptor variant (Val14Met) with systemic lupus erythematosus. *Immunogenetics* 49:266–271.
- Theofilopoulos AN, Baccala R, Beutler B, Kono DH. 2005. Type I interferons (alpha/beta) in immunity and autoimmunity. *Annu Rev Immunol* 23:307–336.
- Tucci M, Quatraro C, Lombardi L, Pellegrino C, Dammacco F, Silvestris F. 2008. Glomerular accumulation of plasmacytoid dendritic cells in active lupus nephritis: role of interleukin-18. *Arthritis Rheum* 58:251–262.
- Vallin H, Perers A, Alm GV, Ronnblom L. 1999. Anti-double-stranded DNA antibodies and immunostimulatory plasmid DNA in combination mimic the endogenous IFN-alpha inducer in systemic lupus erythematosus. *J Immunol* 163:6306–6313.
- Veldhoen M, Hocking RJ, Atkins CJ, Locksley RM, Stockinger B. 2006. TGFbeta in the context of an inflammatory cytokine milieu supports *de novo* differentiation of IL-17-producing T cells. *Immunity* 24:179–189.
- Villarino A, Hibbert L, Lieberman L, Wilson E, Mak T, Yoshida H, Kastelein RA, Saris C, Hunter CA. 2003. The IL-27R (WSX-1) is required to suppress T cell hyperactivity during infection. *Immunity* 19:645–655.
- von Vietinghoff S, Ley K. 2009. IL-17A controls IL-17F production and maintains blood neutrophil counts in mice. *J Immunol* 183:865–873.
- Wang Y, Ito S, Chino Y, Goto D, Matsumoto I, Murata H, Tsutsumi A, Hayashi T, Uchida K, Usui J, Yamagata K, Sumida T. 2009. Laser microdissection-based analysis of cytokine balance in the kidneys of patients with lupus nephritis. *Clin Exp Immunol* 159:1–10.
- Webb R, Merrill JT, Kelly JA, Sestak A, Kaufman KM, Langefeld CD, Ziegler J, Kimberly RP, Edberg JC, Ramsey-Goldman R, Petri M, Reveille JD, Alarcon GS, Vila LM, arcon-Riquelme ME, James JA, Gilkeson GS, Jacob CO, Moser KL, Gaffney PM, Vyse TJ, Nath SK, Lipsky P, Harley JB, Sawalha AH. 2009. A polymorphism within IL21R confers risk for systemic lupus erythematosus. *Arthritis Rheum* 60:2402–2407.
- Wong CK, Ho CY, Li EK, Lam CW. 2000. Elevation of pro-inflammatory cytokine (IL-18, IL-17, IL-12) and Th2 cytokine (IL-4) concentrations in patients with systemic lupus erythematosus. *Lupus* 9:589–593.
- Wu HY, Quintana FJ, Weiner HL. 2008. Nasal anti-CD3 antibody ameliorates lupus by inducing an IL-10-secreting CD4+. *J Immunol* 181:6038–6050.
- Yang J, Chu Y, Yang X, Gao D, Zhu L, Yang X, Wan L, Li M. 2009. Th17 and natural Treg cell population dynamics in systemic lupus erythematosus. *Arthritis Rheum* 60:1472–1483.
- Yang L, Anderson DE, Baecher-Allan C, Hastings WD, Bettelli E, Oukka M, Kuchroo VK, Hafler DA. 2008. IL-21 and TGF-beta are required for differentiation of human T(H)17 cells. *Nature* 454:350–352.
- Yao X, Chen ZQ, Gong JQ, Chen M, Li AS, Liu J. 2007. The interferon-gamma receptor gene polymorphisms (Val14Met and Gln64Arg) are not associated with systemic lupus erythematosus in Chinese patients. *Arch Dermatol Res* 299:367–371.
- Ytterberg SR, Schnitzer TJ. 1982. Serum interferon levels in patients with systemic lupus erythematosus. *Arthritis Rheum* 25:401–406.
- Yu B, Shao Y, Yue X, Zhang J, Guan M, Wan J, Zhang W. 2011. Copy number variations of Interleukin-12B and T-bet are associated with systemic lupus erythematosus. *Rheumatology (Oxford)* 50:1201–1205.
- Zhang Z, Kyttaris VC, Tsokos GC. 2009. The role of IL-23/IL-17 axis in lupus nephritis. *J Immunol* 183:3160–3169.
- Zhao M, Tang J, Gao F, Wu X, Liang Y, Yin H, Lu Q. 2010. Hypomethylation of IL10 and IL13 promoters in CD4+ T cells of patients with systemic lupus erythematosus. *J Biomed Biotechnol* 2010:931018.

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