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Cytokines and Systemic Lupus Erythematosus

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1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by the production of numerous autoantibodies that typically involves multiple organ systems. As opposed to lupus in animal models, SLE in humans is heterogeneous and affects different individuals with a wide range of disease courses and manifestations. The pathogenesis is still unclear, a myriad of innate and adaptative immune system aberrations in SLE have been identified as major contributors of the disease.

Cytokines are a diverse group of soluble proteins and peptides, produced and released by immune system cells, that act as humoral regulators and modulate the functional activities of individual cells and tissues, playing a pivotal role in the differentiation, maturation, and activation of various immune and non-immune cells. Cytokine dysregulation is likely to play a role in the loss of immune tolerance that leads to SLE, and in the damage resulting from the disease. Many of the genes that are associated with risk for lupus are cytokines, regulators of cytokines, or downstream members of cytokine pathways.

Multiple cytokines have been implicated in the disease activity or organ involvement in SLE. Among these, IL-6, Interferon (IFN), B-lymphocyte stimulator (BlyS), IL-10, IL-17 is thought to play an important role in the creation of the characteristic milieu in SLE, which promotes B-cell survival and autoantibody production. On the other hand, also cytokines like IL-10, IL-1, TNF- α , IFN, are important in development of the autoimmune injury in renal and central nervous system, the most frequently observed causes of death in patients with SLE. Moreover, recent studies strongly suggest that the cytokines, at least in part, would be implicated in the pathogenesis of accelerated atherosclerosis associated with SLE.

The knowledge of cytokines not only provides new insight into pathogenesis of SLE, but also it has allowed the development of clinical applications such as monitoring of disease and as potential therapeutic targets with the use of several biologic agents, targeting different cytokines or their receptors. Consequently, many trials of anticytokine therapies for SLE are underway.

The focus of the present chapter is to summarize the cytokines which have significant implications in the pathogenesis of SLE, the potential clinical and therapeutic use will be reviewed.

2. SLE gender susceptibility and cytokines

One feature of lupus, which also occurs with other autoimmune diseases, is the influence of gender on disease susceptibility. In fact 90% of people affected by lupus are women (Masi &

Kaslow 1978). Immunological, epidemiological and clinical evidence suggest that female sex hormones play an important role in the etiology and pathophysiology of chronic immune diseases. Abundant studies have suggested that gender differences in susceptibility to SLE are mediated by sex hormones (Rider & Abdou 2001, Cohen-Solal et al 2006, Zandman et al 2007). The high female prevalence is most marked after puberty: while the pre-puberty female to male ratio is 3 : 1, this increases to 10 : 1 during the childbearing years and decreases again to 8 : 1 after menopause (Lahita et al 1999a). Pregnancy is frequently associated with activity and flares of the disease in SLE patients (Lahita 1999a). Also there is an increased risk of developing SLE in postmenopausal women who received estrogen hormone replacement therapy (Buyon et al 2007) and increased the risk of flares in postmenopausal patients (Straub 2007). Together these considerations indicate that estrogen may be proposed as candidates to explain the sexual dimorphism of SLE. Cytokines are intimately involved with sex hormones, as they regulate the level of sex hormones both systemically and locally, especially in the reproductive organs. The interactions between cytokines and estrogens affect important cellular activities as proliferation and apoptosis (Lahita 1999b).

Estrogens exert their effects by activation of intracellular receptors, the estrogen receptor alpha (ER α) and beta (ER β) (Green et al 1986). In addition to its intracellular receptors have also been reported membrane receptors that correspond to full-length isoforms of both ER α and ER β with extracellular functionality (Pedram et al 2006). Both receptors have been identified in the membrane of thymocytes and have a great importance in the proper development of the thymus (Stimson & Hunter 1980). Thus it seems that estrogen receptors influence the adequate development of T lymphocytes. It is well known that low doses of estrogen promote enhanced Th1 responses and increased cell-mediated immunity, while high doses of estrogen lead instead to increased Th2 responses and antibodies production (Maret et al 2003, Bao et al 2002). This effect of estrogens seems to be achieved through direct alteration in the Th cytokine profile from a proinflammatory (IL-2, IFN- γ) to an humoral direction (IL-4, IL-5, IL-9, IL-13). Besides the effect of estrogen on the profile of cytokines released by T cells, estrogen also increases the release of IL-1, IL-6 and TNF by monocytes/macrophages (Kramer et al 2004). SLE patients show immune-related disorders mediated through estrogens. In vitro peripheral blood mononuclear cells in SLE patients show an increase in anti-dsDNA and IL-10 in response to estrogen, and in vivo there are clear differences in hormonal and cytokine levels in SLE *vs* control pregnancies (Doria et al 2004). Although there is much indirect evidence for estrogen involvement in the lupus disease process, the direct role of estrogen/estrogen-receptor mediated pathways in regulating cytokine production in SLE patients has not as yet been clearly defined. The first evidence for a molecular marker of estrogen action in SLE was the estrogen dependent changes in lupus T-cells calcineurin that could alter cytokine regulation (Rider et al 1998). Calcineurin is the target of a class of drugs called calcineurin inhibitors, which includes cyclosporine, pimecrolimus and tacrolimus. Calcineurin induces different transcription factors as NFATs that are important in the transcription of cytokine genes. A recent study demonstrate that blocking estrogens receptor in vivo in SLE pre- menopausal women they reduced the expression of calcineurin in peripheral T cells (Abdou et al 2008). Another possible mechanism of the role of estrogen in gender susceptibility in lupus is the altered expression of its receptors. Peripheral cells of SLE patients showed increased expression of ER α mRNA and decreased expression of ER β (Iinui et al 2007). ERs are overexpressed in CD4+ and CD8+ cells while is decreased in B cells. The decline in ER β expression inversely

correlated with SLEDAI score. In conclusion, estrogen and its ability to influence on the profiles of cytokines release and immune system regulation is a very powerful factor in the gender susceptibility described in lupus.

3. Cytokines involved in SLE

3.1 Th1/Th2 balance in SLE

The Th1/Th2 balance hypothesis emerge from observations in mice of two subtypes of CD4 T-helper cells differing in cytokine secretion patterns and other functions (Mosmann et al 1986). The concept subsequently was applied to human immunity (Mosmann et al 1989). Th1 cells release significantly $\text{INF}\gamma$ and IL2, and through these mediators Th1- polarized responses are highly protective against infections especially the intracellular pathogens, because of the ability of Th1-type cytokines to activate phagocytes and enhance the cellular response. In contrast Th2 cells release mainly IL4, IL5 IL9 and IL13 and induce the *in situ* survival of eosinophils (through IL-5), promote the production by B lymphocytes of high amounts of antibodies, including IgE (through IL-4 and IL-13), as well as the growth and degranulation of mast cells and basophiles (through IL-4 and IL- 9). (figure 1)

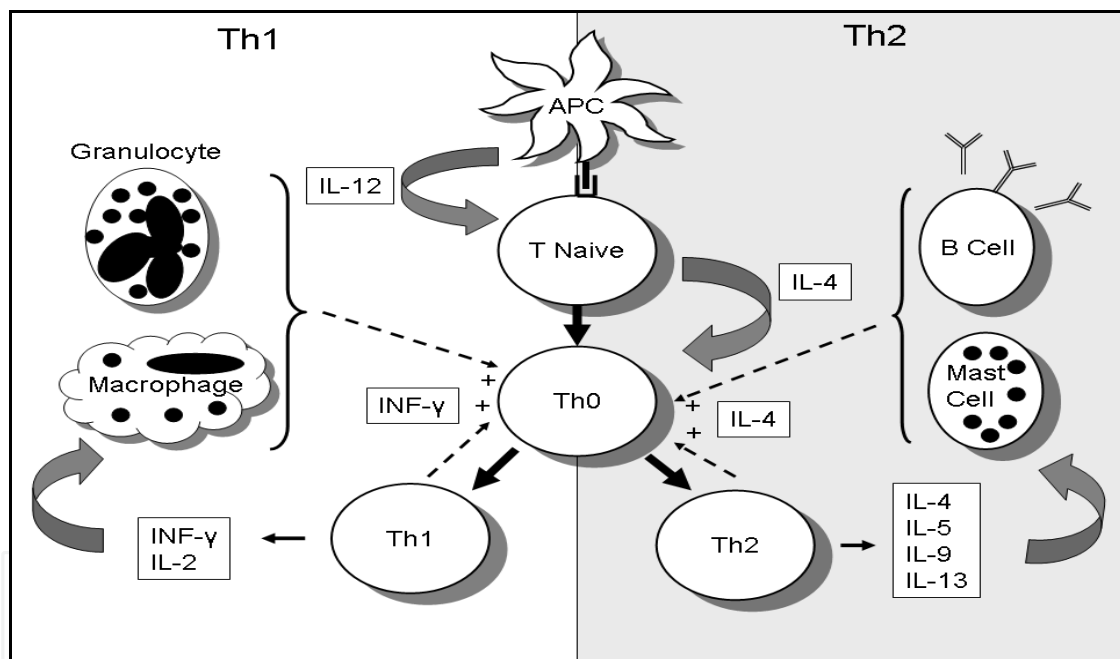


Fig. 1. Diagrammatic representation of the differentiation into Th1 or Th2 cells from naive cells.

Antigen-presenting cells interact with undifferentiated cells secreting specific cytokines that induce differentiation toward Th1 or Th2 cells. $\text{INF}\gamma$ released by Th1 cells and IL4 produced by Th2 cells act as their own growth factors and cross-regulate the other differentiation. Two features define the Th1/Th2 balance, first each cell subset produced cytokines that served as their own growth factor (autocrine effect) and second the two subsets released cytokines to cross regulate each other's development. Polarization to a subtype or another depends largely on the APC and experience on the antigen. This process is directed by the microenvironment of cytokines resulting in the antigen presentation of APC to T naive cells. A Th1/Th2 imbalance with excess of Th1 predominance appears in organ specific

inflammatory diseases as arthritis, multiple sclerosis and type 1 diabetes, and instead a predominance of Th2 response has been described in allergy and systemic autoimmune diseases (Abbas et al 1996).

The roles of Th1 and Th2 cytokines in the pathogenesis of SLE are controversial. In patients with SLE, Th2 cytokines are increased (Ogawa et al 1992), whereas Th1 cytokines are decreased (Klinman & Steinberg 1995). Thus, SLE was initially considered to be a Th2 predominant disease. However different results contradict this hypothesis like that IFN γ levels in the sera of patients with SLE are significantly elevated and that there is a correlation between the severity of SLE and the amount of IFN γ secreted (Al-Janadi et al 1993). All these findings suggest that the Th1 and Th2 responses are both important in the pathogenesis of lupus associated tissue injury. SLE is a disease involving a wide spectrum of cytokines. SLE patients with arthritis have higher IFN γ levels than the other patients, and conversely, patients with serositis or CNS involvement have higher IL-4 levels (Chang et al 2002). Furthermore SLE patients with nephritis have higher Th1 cytokines in serum and urine than non-nephritis patients (Chang et al 2006). Still more a significant difference in the Th1/Th2 balance in peripheral blood exists between WHO class IV and V lupus nephritis. Th1 cells are predominant in class IV but not in class V (Akahoshi et al 1999). In class V, the number of infiltrating cells was reduced, with a large percentage of CD4 T cells producing IL4 in the peripheral blood (Masutani et al 2001).

SLE is known to be a heterogeneous disease in which a wide range of cytokines are involved, it seems the most likely that Th1 or Th2 dominance depends on the stage of the disease and involvement. The Th2 response would be related to the development and production of autoantibodies, and Th1 with immune-mediated inflammatory activity.

3.2 B-lymphocytic Stimulator (BLyS)

BlyS a member of the TNF family, is also known as the B cell-activating factor (BAFF) and appears to play an important role in the differentiation and survival of B cells (Mackay et al 2002). BlyS can be released in a soluble form or can be expressed as a transmembrane protein on a wide variety of cell types, including monocytes, activated neutrophils, T cells, and DCs and its release is upregulated by IFN- γ , IL-10, G-CSF and CD40L (Nardelli et al 2001, Moore et al 1999, Litinskiy et al 2002, Harigay et al 2008).

BLyS binds to 3 receptors, BAFF-R (BAFF receptor), TACI (transmembrane activator and calcium modulator and cyclophilin ligand antereceptor), and BCMA (B-cell maturation antigen), that are differentially expressed during B cell ontogeny (Bossen & Schneider 2006, Bossen et al 2008). The stimulation of all three receptors promotes B-cell differentiation and proliferation. BLyS is the sole ligand for BAFF-R, whereas TACI and BCMA each can bind either BLyS or another TNF family ligand known as a proliferation-inducing ligand (APRIL) (Bossen et al 2008).

After maturation in the bone marrow, newly formed B cells migrate to the secondary lymphoid organs (spleen and lymph nodes). These B cells do not possess all the characteristics of fully mature B cells, and they are referred to as transitional B cells. This transitional stage is an elastic checkpoint where thresholds for negative selection are homeostatically adjusted by free BLyS concentration. At this point an upregulation of BLyS expression can result in the rescue of self-reactive B cells from elimination. This effect explains, at least in part, the greatly increased levels of autoantibody production and associated autoimmune manifestations observed in transgenic mice that overexpress BlyS (Cancro et al 2009, MacKay et al 2007, Zheng et al 2005, Miller et al 2006, Thien et al 2004)

Elevated BlyS serum levels are often observed in SLE patients and correlate with disease activity (Petri et al 2008). Experiments in mice, have been demonstrated causality between BlyS over expression and development of SLE, on the other hand, also had been documented the amelioration of clinical disease in SLE mice following treatment with BlyS antagonist (Mackay et al 1999, Petri et al 2008, Jacob et al 2006)

The primary source of BlyS secretion in SLE remains speculative, a secretion by DCs (dendritic cells), a profoundly dysregulated IFNs in SLE or an increased levels of BlyS resulting from the presentation of self antigens (derived of an defective clearance of apoptotic bodies) to innate immune cells (which express BlyS upon antigenic stimulation) are potentially mechanisms implicated (Cancro et al 2009).

Because BlyS may figure prominently in the development of SLE and it could be a valid target for SLE, therapy with BlyS antagonists have been developed. Belimumab, a fully human monoclonal Ab (IgG1) that binds soluble BlyS and inhibits its binding to TACI, BCMA, and BR3, and Atacicept (TACI-Ig) a soluble, recombinant fusion protein of the human IgG1 Fc and the extracellular domain of the TACI receptor that binds BlyS and APRIL, have been tested in clinical trials. Results from phase III trials have demonstrated the safety profile and efficacy of belimumab in controlling SLE in a broad range of patients (Navarra et al 2011).

3.3 Interferon- α

Interferon alpha (INF- α) is produced mainly by plasmacytoid dendritic cells (PDC) in response to viral infection. INF- α is not one protein, but rather a family of highly related proteins encoded on the short arm of chromosome 9, and called type I INFs. Studies in which cellular mRNAs are screened against thousands of gene sequences have demonstrated that in SLE patients the INF- α induced genes are the most overexpressed of all those assayed (Baechler et al 2003). Evidence of the effect of INF- α in SLE comes from observations on the therapeutic administration of INF- α in various types of malignancies and hepatitis C infection. Case reports emerged describing the development of lupus associated autoantibodies and even clinical lupus (Niewold & Swedler 2005). Discontinuation of INF- α typically resulted in remission of SLE symptoms, supporting a causal relationship with INF- α . Only a minority of patients treated with INF- α develop SLE (<1% of patients), these data support the idea that INF- α can be sufficient to induce SLE in some genetically designed individuals. In addition, SLE patients commonly harbor anti INF- α autoantibodies. Anti INF- α antibodies-positive patients have lower levels of serum type I IFN bioactivity and evidence for reduced downstream IFN-pathway and disease activity.

A very strong correlation is consistently observed between the presence of SLE-associated autoantibodies that recognize nucleic acid structures or RNA-containing protein, such as anti-Ro, anti-La, anti-Sm, anti-RNP, and anti-dsDNA and high production of INF- α (Kirou et al 2005). Also lupus patients with high serum INF- α had a significantly higher prevalence of cutaneous and renal disease in most studies (Dall'era et al 2005). It is interesting that both of these clinical manifestations share an association with a particular serology (rash with anti-Ro and nephritis with anti-dsDNA).

The principal mechanism through which INF- α is produced in SLE is through Toll-like receptors (TLR). TLR receptors is a family of receptors present in a variety of cells and that recognize characteristics ligand present in pathogens. Some TLR recognize RNA and DNA sequences of single or double chain. A quality of many cases of lupus is the production of

autoantibodies against RNA or DNA containing protein complexes such as Sm, RNP, Ro, and La. Autoantibodies specific for these lupus-associated riboproteins can bind with antigens derived from apoptotic cells. The RNA/DNA found in these complexes are capable of promoting the production of $\text{INF-}\alpha$ through the stimulation of TLR. Because some TLR is located in the endosomes, RNA or DNA containing complexes must access the interior of the cell before they are able to act as activators. The Fc portions of the immune complexes are recognized and internalized by cells with Fc receptors in their surface, providing a route of entry for RNA or DNA to reach TLR, resulting in interferon alpha production (Figure 2). This process is especially well established in PDCs on TLR7 and TLR9 (Båve et al 2003).

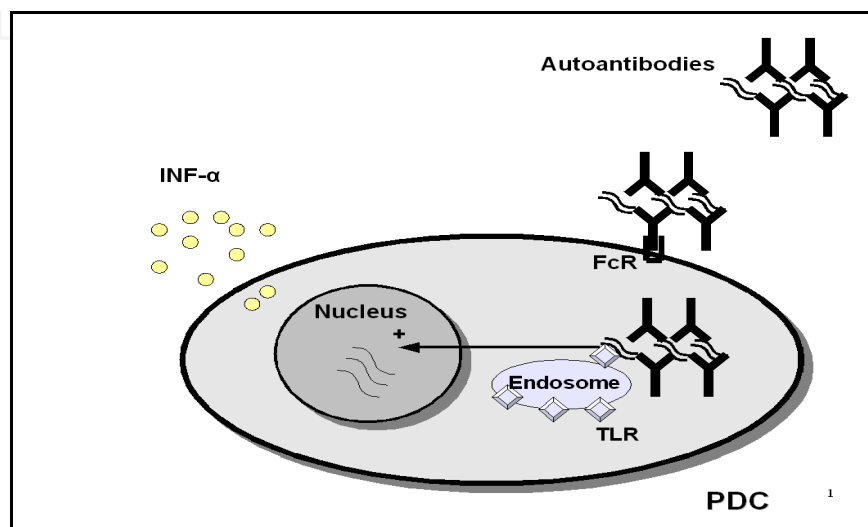


Fig. 2. Induction of $\text{INF-}\alpha$ in lupus. RNA/DNA containing immune complexes access the interior of the cell through recognition of Fc portion by Fc receptors in PDC membrane. Inside cell the RNA/DNA specific ligands are recognized by Toll-like receptors (TLR). TLR dependent signals reach to the cell nucleus and induce transcription of IFN genes.

$\text{INF-}\alpha$ generates an effective antigen-presenting cell state by mediating maturation of dendritic cells. Thus $\text{INF-}\alpha$ primes the immune system for augmented sensitivity to subsequent stimuli. The activated antigen-presenting cell state may also be characterized by an augmented capacity to generate a peripheral T-cell repertoire enriched in autoreactive cells. Dendritic cells are primary activators of T-cells and affect both tolerance and activation, depending on the state of dendritic cells. Dendritic cells from lupus patients are able to present self-antigens to T-cells in a stimulatory rather than regulatory manner, a process which is $\text{INF-}\alpha$ dependent (Blanco et al 2001). Moreover, PDCs significantly enhance autoreactive B cell proliferation, autoantibody production, and survival in response to TLR activation (Ding et al 2009). Recently it has been reported that activation of the IFN signaling pathway may be linked to the risk of atherosclerosis by affecting plaque formation in patients with SLE (Li et al 2011).

In conclusion, in SLE patients, some autoantibodies are able to induce the production of $\text{INF-}\alpha$. $\text{INF-}\alpha$ enhances the autoimmunity and immune response.

3.4 Tumor necrosis factor- α (TNF- α)

TNF- α is a pleiotropic cytokine produced by a variety of cell types including monocytes, lymphocytes and non-immunological cell types in response to inflammation, infection and

other environmental challenges. There are controversial results about the role of TNF in mice lupus strains. In NZB/W strain diminished production of TNF- α has been reported demonstrating the protective effect of TNF- α (Jacob & McDevitt 1988). In other strains of murine lupus an increased production of TNF- α has been described. In addition, TNF- α concentration correlates with the severity of the illness and anti-TNF therapy is profitable (Boswell et al 1988). Overall, these results show a duality in the role of TNF in lupus, one beneficial and one detrimental.

TNF- α contributes to avoiding the development of autoimmunity and autoantibody production. When introducing inhibitory TNF- α therapies in patients with diseases such as arthritis, spondyloarthropathies or Crohn disease shows the appearance of antinuclear antibodies and anti-ds DNA antibodies (De Ricke et al 2003, Garcia-Planella et al 2003). Normally these antibodies are not pathological, but in a few patients autoantibodies are associated with a SLE-like activity. TNF- α blocker induced lupus is usually benign and the symptoms resolve after TNF blockade stopped (Ramos-Casal et al 2007). It should be noted that these patients do not have the genetic background that makes them susceptible to SLE developing. When using anti-TNF therapy in SLE patients it has been found an elevation of antinuclear and anticardiolipin antibodies in most patients (Aringer et al 2007). This elevation was transient and did not produce complement consumption or lupus flare.

On the other hand numerous studies have shown that TNF blockade in SLE patients suffering from arthritis, nephritis and skin lesions were clinically effective in open clinic trials (Aringer et al 2004, Hayat el al 2007). It has found expression of TNF- α in inflamed tissue biopsies in patients with lupus, which does not occur in healthy individuals (Herrera-Esparza et al 1998), and TNF- α expression is associated with high histological disease activity (Zha et al 2009).

TNF- α performs two major functions: one as an immunoregulatory cytokine and the other as a potent mediator of inflammation. Among the immunoregulatory functions TNF- α induces the release of antiapoptotic molecules, TNF blockade may lead to increased apoptosis (Aringer et al 2007). The resulting increase in apoptotic material could explain why the emerging antibodies appear to exclusively target nuclear antigens and phospholipids, both of which are expressed on apoptotic bodies (Utz et al 1997). In addition, TNF blockade hampers the elimination of autoimmune B lymphocytes by cytotoxic T cells (Via et al 2001). All together could explain the pathways to increased lupus autoantibodies under TNF- α blockade.

The immunecomplexes generated by autoantibodies are deposited in tissues and organs. The deposit of immunecomplexes mediated inflammatory process triggered largely by TNF- α . The expression of TNF- α activates the local inflammation and tissue damage. TNF- α is the most important proinflammatory cytokine and a harbinger of tissue destruction, and it is at the top of a pro-inflammatory "cascade" leading to tissue damage. In contrast to the complex role of TNF- α in apoptosis and in immune regulation, its powerful proinflammatory effects are unequivocal. At the tissue level, TNF blockade induces remission of inflammation and hence tissue recovery. Anyway in the use of anti-TNF therapy is important to note the dual activity of this cytokine.

3.5 IL-6

IL6 is a pleiotropic cytokine, structurally, it shares homology with other cytokines: oncostatin M, IL11, leukaemia inhibitory factor, ciliary neurotrophic factor and cardiotrophin (Hirano, 1998). It was known initially as B-cell stimulatory factor 2 because it

stimulates B cell growth and maturation to antibody-producing plasma cells. It is produced by a wide range of cell types including, monocytes, T cells, fibroblasts, synoviocytes and endothelial cells. IL-6 beyond his capacity of B cell activation and promotion of Ig production, play an important role in governing inflammation process (Ishihara et al., 2002).

IL-6 responses are transmitted through gp130, which serves as the universal signal-transducing receptor subunit for all IL-6-related cytokines. Although this classically occurs through IL-6 binding to its membrane-bound receptor (IL-6R), it is clear that a soluble form of the cognate IL-6 receptor (sIL-6R) affords IL-6 with an alternative mechanism of gp130 activation. This additional mode of cell activation is termed IL-6 trans-signaling and results from formation of a sIL-6R_IL-6 complex, which can directly bind cellular gp130. Because gp130 is ubiquitously expressed within tissue, trans-signaling provides IL-6 with the capacity to activate cells that would not intrinsically respond to IL-6 itself (Hibi et al., 1990; Hirano et al., 1994; McLoughlin et al., 2005). Therefore, IL-6 and gp130 signaling plays a critical role in the inflammatory process and tissue injury (Nechemia-Arbely et al., 2008).

An association between IL-6 and progression of lupus has been published for several murine models of SLE. The direct role of IL-6 in controlling autoantibody production has been demonstrated in the pristane induced model of lupus (Richards et al., 1998). On the other hand the administration of recombinant IL-6 to female NZB/W mice exacerbates the progression of glomerulonephritis (Ryffel et al., 1994). Anti IL-6 monoclonal antibody given in MRL lpr lupus prone mice, has been shown to cause a decrease in renal damage and a temporary reduction in levels of anti-dsDNA antibody production (Kiberd 1993).

Elevated levels of IL-6 have been found in the serum and in the urine of active SLE patients (Chun et al., 2007; Grondal et al., 2000; Horii et al., 1993). Raised expression of gp130, has been found in patients with active SLE, while an important reduction in the gp130 expression on B lymphocytes was observed when the activity of the disease had disappeared after readjusting its immunosuppressive treatment (De La Torre et al., 2009). Therefore, monitoring the frequency of gp130, could provide a useful tool in the diagnosis and monitoring of disease activity in patients with lupus.

Beyond the ability of IL-6 to stimulate B-lymphocyte differentiation into immunoglobulin secreting cells, IL-6 in concert with TGF- β is a critical cofactor for Th17 development, whereas the absence of IL-6 induces Foxp3, thereby specifying Treg development (Weaver et al., 2006). The two T-cell subsets play prominent roles in immune functions: Th17 cell is a key player in the pathogenesis of autoimmune diseases and protection against bacterial infections, while Treg functions to restrain excessive effector T-cell responses (Kimura et al., 2010).

Factors leading to the constitutive expression of IL-6 in SLE have not been elucidated yet, they may involve other regulator cytokines, like IL-10, or may be due, at least in part, to genetic differences (Linker et al., 1999; Tackey et al., 2004).

Recently, tocilizumab, a humanized monoclonal antibody against the α -chain of the IL-6 receptor, which prevents the binding of IL-6 to membrane bound and soluble IL-6 receptor, has been tested in SLE patients, with promising results (Illei et al., 2010).

3.6 IL-2

The cytokine IL-2 is a multifactorial cytokine. It was initially identified as a potent T cell growth factor, however, more recent data strongly indicate that IL-2 is essential for immune tolerance (Humrich et al., 2010). IL-2 constitutes a key element in the maintenance of the

homeostasis between a proliferative immune response and the induction of tolerance, which supports the involvement of this cytokine in diverse autoimmunity disorders, such as SLE (Sharma et al., 2011). Predominantly produced by activated CD4⁺ and CD8⁺ T cells, IL-2 exerts its functions through the interaction with its receptor (IL-2R) (Kammer, 2005).

It has been reported that production of IL-2 is decreased in patients with SLE (Sharma et al., 2011). Transcriptional regulators responsible for the transcription or suppression of IL-2 production are imbalanced in SLE T cells and this explains the reduced IL-2 levels found in SLE patients (Solomou et al., 2001). The decreased production of IL-2 in SLE patients most likely contributes to various immune defects such as decreased Treg production, decreased activation-induced cell death (AICD), and potentially decreased cytotoxic T lymphocytes (Lieberman & Tsokos 2010).

IL-2 signals are critical for the outcome of a CD8⁺ T cell response. Recently it was discovered that a strong IL-2 signal promotes the progressive acquisition of effector T cell functions (such as perforin and granzyme B expression, the hallmarks of CD8⁺ T cell cytotoxicity) but decreases the capacity to generate cells with memory features. By contrast, in conditions of weak IL-2 signaling, T cells fail to acquire the full program of effectors differentiation. (Pipkin et al., 2010)

IL-2 module activation-induced cell death (AICD). The activation of AICD is a mechanism of self tolerance in which apoptosis of autoreactive lymphocytes is induced after repeated stimulation. The deficiency in activation induced cell death might be related to the persistence of autoreactive T cell clones that eventually may lead to the activation of B cell subsets, with the subsequent production of autoantibodies and the development of autoimmune disorders (Gómez-Martín et al., 2009).

IL-2 is also required for the expansion and conversion of CD4⁺foxp3⁺T cells into CD4⁺foxp3⁺ cells or regulatory T cells (Treg) (Setoguchi et al., 2005; Zheng et al., 2007;). Tregs cells, are necessary for maintaining tolerance to self antigens and they are able to do is by suppressing self-reactive T cells (Buckner , 2010). It has been well recognized that a decline in Tregs as a critical event in the development of systemic autoimmunity both mice and SLE patients (Valencia et al., 2007; Suzuki et al., 1995). On the other hand, recently IL-2 signaling has been shown to play a role in inhibiting the development of Th17 cells (Tato et al., 2007; Ma et al., 2010). Thus, the effects of IL-2 on Treg and Th17 cells may serve to promote auto-reactivity while at the same time inhibiting a counter regulatory response (discussed later).

3.7 IL-17

Interleukin 17 (IL-17) is a proinflammatory cytokine that is involved in defending the host against extracellular, some intracellular pathogens and fungi (Bettelli et al., 2008; Khader et al., 2010). IL-17 promote inflammation on several levels, as their receptors are expressed on both hematopoietic cells and non hematopoietic cells. IL-17 exerts its effects through the recruitment of monocytes and neutrophils by increasing the local production of chemokines. IL-17 can also stimulate B-cell antibody production (Hsu et al., 2008; Mitsdoerffer et al., 2010).

Recent studies have reported that production of IL-17 is abnormally high in patients with SLE. Its levels are increased in SLE sera and correlate with SLE disease activity. Moreover, the frequency of IL-17-producing T cells is increased in the peripheral blood of patients with SLE (Crispín & Toscos, 2010; Shah et al., 2010). Recent evidence indicates that a significant fraction of the IL-17 produced in SLE derives from Th17 cells and CD3⁺CD4⁺CD8⁻ (double negative or DN) T cells (Nalbandian et al., 2009).

The identification of Th17-lineage-specific transcription factors, established Th17 cells as an independent T-cell subset. Differentiation of naïve T cells into Th17 cells depends on TGF- β and IL-6, being IL-23 essential for expansion and maintenance of pathogenic Th17 cells (Jäger & Kuchroo, 2010). Interestingly, the participation of TGF- β in the differentiation of Th17 cells places the Th17 lineage in close relationship with CD4⁺CD25⁺Foxp3⁺ regulatory T cells (Tregs), as TGF- β also induces differentiation of naïve T cells into Foxp3⁺ Tregs in the peripheral immune compartment (Korn et al., 2009).

In light of this knowledge, now is the general notion that there is a reciprocal relationship between pro-inflammatory IL-17-producing Th17 cells and protective Foxp3⁺ Tregs. The presence of pro-inflammatory cytokines like IL-6, which is induced during infection, inflammation or injury, inhibited the induction of Foxp3⁺ Tregs and simultaneously promoted Th17-cell differentiation (Bettelli et al., 2006). On the other hand, tolerance induction was associated with decreased IL-6 production and increased TGF- β production that paralleled a reduction in the fraction of IL-17-producing T cells and a reciprocal increase in regulatory T cells (Kang et al., 2007). Therefore, some authors support the notion that therapeutic intervention in SLE should focus on therapeutic agents that can regulate the immune balance between Th17 and Treg cells rather than on those that exclusively regulate Th17 cells or a specific cytokine (Yang et al., 2011).

3.8 IL-10

Interleukin (IL)-10 is one of the most important cytokine with anti-inflammatory properties. Today it is known that the ability to synthesize IL-10 is not limited to certain T cells subsets, but is characteristic of almost all leukocytes. Very important sources *in vivo* appear to be mainly monocytes and macrophages as well as Th cells (Sabat et al., 2010).

IL-10 is a potent inhibitor of antigen presentation. The other profound effect of IL-10 is to inhibit the production of proinflammatory cytokines and mediators from macrophages and DCs. The major inflammatory cytokines, IL-1, IL-6, IL-12, and tumor necrosis factor (TNF), are all dramatically repressed following exposure to IL-10. On the other hand, IL-10 can costimulate B-cell activation, prolong B-cell survival, and contribute to class switching in B cells (Mosser & Zhang, 2008).

Multiple studies have reported high levels of IL-10 in SLE patients and in murine models of lupus, and this increase correlated with disease activity (Capper et al., 2004; Hagiwara et al., 1996; Houssiau et al., 1995; Park et al., 1998). However, the specificity of these findings is unclear. A recent study that investigated the role of IL-10 in a novel congenic model of lupus, B6.Sle1.Sle2.Sle3 (B6.TC) showed, that although B6.TC mice produced higher IL-10 levels than nonautoimmune control mice, an overexpression of IL-10 decreased T-cell activation, auto-antibody production and autoimmune pathogenesis (Blenman et al., 2006). Interestingly, other study has recently been shown that the presence of immune complexes and IFN α a cytokine implicated in the pathogenesis of SLE, decreases the capacity of IL-10 to suppress inflammation, limiting therefore the anti-inflammatory effect of this cytokine (Yuan et al., 2011). These results reinforce the notion that IL-10 exerts multiple functions and we must be cautious in equating high levels of IL-10 and increased pathogenesis in systemic autoimmunity (Blenman et al., 2006).

4. Cytokines in organ damage

4.1 Cutaneous lupus and cytokines

Cutaneous lupus erythematosus represents an autoimmune disease characterized by photosensitivity, apoptosis of keratinocytes and an inflammatory infiltrate in superficial

and/or deep compartments of the skin. Skin disease is the second most common manifestation in SLE patients. Although clearly there is a link between the skin and systemic manifestations of SLE, often the skin may flare independently or patients may have SLE without skin disease. Treatments also may improve the skin, systemic disease, or both, suggesting that there are differences pathogenetically between skin and systemic findings in cutaneous lupus.

UV-irradiation is a well-known trigger of apoptosis in keratinocytes and there is accumulating evidence that abnormalities in the generation and clearance of apoptotic material is an important source of antigens in autoimmune diseases (Caricchio et al 2003). Phototesting studies suggest that both UVB and UVA are potentially pathogenic wavelengths, although it is clear that UVA induction requires higher doses of light relative to UVB. UV light can induce the binding of autoantibodies to selected nuclear antigens located on blebs or apoptotic bodies of skin. It has been suggested that these bleb-associated antigens may then be phagocytosed, packaged, and presented to lymphocytes, thereby stimulating autoimmune responses (Casciola-Rosen & Rosen 1997). The high presence of anti-Ro antibodies in cutaneous involvement in lupus might be explained because anti-Ro antibodies might interfere with protection from UV damage as genetic knock-out of 60kD Ro resulted in an SLE-like illness in multiple strains of mice that were susceptible to UV damage (Xue et al 2003).

Exposure of keratinocytes to UVB results in the synthesis of many pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α), interleukin-1 α (IL-1 α), IL-6, IL-8, and IL-10 (Brink et al 2000). TNF- α is not only involved in the mediation of local inflammatory reactions within the epidermis, but may also enter the circulation and cause systemic effects. There is an association of subacute cutaneous LE with the extended HLA haplotype DRB1*03-B*08. Contained within this haplotype is the TNF2 allele, a TNF α promoter polymorphism, associated with increased TNF α production (Werth et al 2000).

UV induced injury trigger the initial chemokine production and release results in a first wave of skin-homing memory T cells and plasmacytoid dendritic cells (PDCs) via chemokine driven pathways. DNA, RNA, and immune complexes, present in skin containing apoptotic material, can serve as IFN- α inducers in PDCs. There is a higher frequency of PDCs in skin compared to the blood of patients with SLE, suggesting that PDCs migrate from the circulation into the skin. Under normal conditions PDCs are not able to respond to self nucleic acids, but in lupus PDCs became activated to produce IFN- α by self nucleic acids in complex with autoantibodies to DNA or nucleoproteins. These immuno-complexes trigger innate activation of PDC through TLR7 and 9 and lead to sustained production of IFN- α (show Figure 2) that may induce an unabated maturation of dendritic cells and the activation of autoreactive T cells. Enhanced type I IFN signaling promotes Th1-biased inflammation in cutaneous lupus. IFN- α can amplify cutaneous inflammation via the induction of chemokines that recruit potentially auto-reactive T cells into the skin. For example, IFN- α induces the production of chemokines, CXCL9, CXCL10, and CXCL11, which recruit chemokine receptor CXCR3 expressing lymphocytes, including Th1 cells and CD8+ T cells, from peripheral blood into inflamed skin (Wenzel et al 2005). Large numbers of CXCR3+ lymphocytes are detected in cutaneous lupus skin lesions. The majority of these infiltrating cells are memory T CD4+ lymphocytes. Among memory T cell subsets, CXCR3 is predominantly expressed on the surface of IFN- γ -producing Th1 cells, generating a proinflammatory effector response (Meller et al 2005). Hence, UV-irradiation may induce chemokine production and release, subsequently recruiting a first wave of skin-homing memory T cells and PDCs to sites of UV-injury which produce cytokine-mediated inflammation and tissue damage.

4.2 Neuropsychiatric SLE

Neuropsychiatric systemic lupus erythematosus (NPSLE) involves neurological manifestations seen in the central, peripheral, and autonomic nervous systems as well as psychiatric disorders in patients with SLE in which other causes have been excluded. NPSLE may occur at any time during the course of the disease, and symptoms are extremely diverse, ranging from depression, psychosis, and seizures to stroke (Committee on Neuropsychiatric Lupus Nomenclature 1999). Though the pathophysiology of NPSLE has not yet been elucidated, two mechanisms of damage, specifically those produced by autoantibodies, and inflammatory mediators, are implicated in NPSLE. The most common neuropathologic features are multifocal microinfarcts many of them due to the effect of anti-cardiolipin antibodies (Hanly et al 1992).

Cytokines and chemokines have been implicated in the pathophysiology of NPSLE. Of the different cytokines studied, interleukin-6 (IL-6) has been shown to have the strongest positive association with NPSLE (Fragoso-Loyo et al 2007). IL-6 is a cytokine with high proinflammatory activity. IL-6 level in the CSF of NPSLE was reported to be elevated without damage of the blood-brain barrier, demonstrating an intrathecal synthesis of IL-6. In addition, the expression of IL-6 mRNA was elevated in the hippocampus and cerebral cortex, suggesting that IL-6 expression was increased within the entire CNS of NPSLE (Hirohata & Hayakawa 1999). Furthermore, when IL-6 activity was followed throughout symptom remission, they noted a decrease in CSF IL-6 activity measured indirectly, but not in serum IL-6 activity (Hirohata & Miyamoto 1990). A recent study has shown that the sensitivity and specificity of CSF IL-6 for diagnosis of lupus psychosis was 87.5% and 92.3%, respectively, indicating that CSF IL-6 might be an effective marker for the diagnosis of lupus psychosis (Hirohata et al 2009). Although some cytokines are important biomarkers of NPSLE, the mechanism for the elevated levels of cytokines is thus far unknown. Immune complexes in SLE can stimulate IFN- α and there is strong evidence in humans and in mice that IFN- α can cause neuropsychiatric manifestations. It has recently described using a bioassay containing plasmacytoid dendritic cells, that NPSLE CSF induced significantly higher IFN- α compared with CSF from patients with multiple sclerosis or other autoimmune disease controls. NPSLE CSF was 800-fold more potent at inducing IFN- α compared with paired serum, due to inhibitors present in serum (Santer et al 2009). Further immunological studies are expected to show how autoantibodies in SLE patients work to promote the cytokine storm associated with the pathophysiology of NPSLE.

4.3 Cytokines role in lupus nephropathy

Renal involvement in SLE is present in over 50% of patient with active SLE and remains a major cause of end-stage renal disease and it is associated with a greater than four-fold increase in mortality in recent series (Bernatsky et al., 2006; Boumpas et al., 1995). The pathologic manifestations of lupus nephritis (LN) are extremely diverse and may affect any or all renal compartments. The complexity of renal manifestations can be most easily approached using the World Health Organization Classification revised and updated in 2004 (Weening et al., 2004).

The picture of cytokines present in LN is already complex and no single-cell population or cytokine has been decisively identified as a key mediator. Elevated circulating levels and/or tissue mRNA transcripts for several cytokines are reported in lupus patients and mice. On the other hand, the data regarding the relative importance of Th1-type versus Th2-type cytokines are inconsistent (Foster, 2005; Theofilopoulos et al., 2001).

The development of laser-manipulated micro dissection (LMD) from clinical biopsy specimens, together with messenger RNA (mRNA) expression analysis in the targeted glomeruli or specific regions of interest, using real-time quantitative PCR, has allowed to explore the single-cell cytokine profile of the samples from the LN patients. Interestingly a recent study, using LMD and PCR analysis of renal biopsy samples from LN patients has showed a negative correlation between the level of IL-2 and renal damage while a positive correlation between IL-17 and renal damage was evidenced. Indicating that IL-2 and IL-17 play opposite roles in SLE development, suggesting that IL-2 may play a role in protecting against SLE development, while IL-17 might have a reverse effect (Wang et al., 2010). On the other hand, recent studies have highlighted the potential importance of the Th17 immune response in renal inflammatory disease. These include the identification and characterization of IL-17-producing T cells in nephritic kidneys of mice and humans, as well as evidence for the contribution of IL-17 and the IL-23/Th17 axis to renal tissue injury in LN (Turner et al., 2010; Zhang et al., 2009).

5. Conclusions

This chapter has focused in the new insights about the role of cytokine in the pathogenesis of Systemic Lupus Erythematosus. The imbalance in the levels of cytokines and their receptors found in SLE is clearly crucial to the development of the pathology of the disease. The cytokines are actively involved in both favoring the production of auto-antibodies as generating inflammation in affected tissues. Interactions between the cytokine milieus are complex and the attenuation of one cytokine would need to be approached with caution, considering effects on the cytokine network as a whole. There are still many facets of immunopathology of SLE elicited by cytokines to be elucidated. A more in-depth understanding of these cytokines may be of clinical significance in the context of devising biomarkers or therapeutic agents. Cytokine therapy, is highly probable that, in the future will take a relevant place in the therapeutic armamentarium of autoimmune disorders.

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7. References

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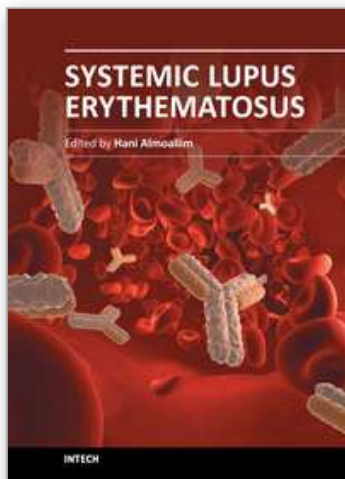
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This book provides a comprehensive overview of the basic and clinical sciences of Systemic Lupus Erythematosus. It is suitable for basic scientists looking for detailed coverage of their areas of interest. It describes how advances in molecular biology 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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