Hindawi Publishing Corporation
Journal of Biomedicine and Biotechnology
Volume 2010, Article ID 676284, 5 pages
doi:10.1155/2010/676284

Review Article

Cytokine Networks in Systemic Lupus Erythematosus

Hooi-Ming Lee,[1] Hidehiko Sugino,[1] and Norihiro Nishimoto[1,2]

[1] *Graduate School of Frontier Biosciences, Osaka University, Suita, Osaka 565-0871, Japan*
[2] *Laboratory of Immune Regulation, Wakayama Medical University, 105 Saito Bio Innovation Center, 7-7-20 Saito-Asagi, Ibaraki, Osaka 567-0085, Japan*

Correspondence should be addressed to Norihiro Nishimoto, norichan@wakayama-med.ac.jp

Received 9 February 2010; Accepted 21 March 2010

Academic Editor: Brian Poole

Systemic lupus erythematosus (SLE) is an autoimmune disease more prominent in women and characterized by multiple organ damage. Imbalance in cytokine production and cytokine levels correlates with SLE progression, making the understanding of SLE cytokine networks very important for SLE treatment strategy and drug development. In this article, we review cytokine networks that may be involved in the pathogenesis of SLE by briefly describing abnormal cytokine production and serum cytokine levels in SLE patients. We also focus on the pathological roles of cytokines and their interactions in immunoregulatory networks and suggest how their disturbances may implicate in pathological conditions in SLE. Finally, we further discuss the influence of estrogen on these cytokine networks.

1. Introduction

Systemic lupus erythematosus (SLE) is a prototypical systemic autoimmune disease characterized by multiple organ damage, high titers of autoantibodies, and various clinical manifestations [1]. There is a 10–15 times higher frequency of SLE in women during childbearing years, probably due to an estrogen hormonal effect [2]. Aberrant biological activities by numerous cytokines have been described in patients with SLE. Despite concerted effort to unravel the pathological roles of individual cytokines in SLE, the considerable redundancy and pleiotropism of cytokine characteristics has kept their functions poorly understood. However, significant progress in microarray techniques as well as advances in biological databases has given us new perspective on autoimmune diseases in general including the complicated pathogenesis and heterogeneous manifestations like those seen in SLE. These breakthroughs show promise for the next great leap in understanding the immunoregulatory networks of autoimmune diseases that are influenced by multiple factors, with specific emphasis on cytokines and their interactions, in other words, cytokine networks.

In this article, we present current knowledge regarding abnormal cytokine networks that may be involved in the pathogenesis of SLE. First, we provide a brief description of the abnormal cytokine production and serum cytokine levels in patients with SLE. Subsequently, we focus on the pathological roles of cytokines, in particularly tumor necrosis factor (TNF) and interferon (IFN), as well as cytokine interactions in immunoregulatory networks and suggest how their disturbances may trigger SLE pathologies. Finally, we further discuss the influence of estrogen on cytokine networks.

2. Cytokine Productions and Cytokine Levels in Patients with SLE

It is thought that the balance between proinflammatory and anti-inflammatory cytokines influences the clinical manifestations in many inflammatory diseases such as SLE and rheumatoid arthritis (RA). These cytokines are mainly produced by helper T (Th) cells, which can be divided into several subsets according to their distinct profiles [3]. We review several relevant cytokines by discussing their production, serum levels, and roles in SLE below.

Several groups have studied individual cytokines that are produced differently between patients with SLE from

either healthy individuals or those suffering from rheumatic diseases, like RA [4, 5]. Patients with active SLE have been reported to have significantly higher levels of serum proinflammatory cytokines, tumor necrosis factor (TNF), and interleukin (IL)-6 [6–8]. However, one study found that serum TNF concentrations did not differ from controls, instead observing that increased levels of soluble TNF receptor (TNF-sR) correlated positively with the degree of disease activity [9]. TNF-sR is an antagonist to TNF and therefore decreases TNF activity. Elevated serum IL-6 levels may be due to environmental factors since exposure to UV light has been shown stimulate the monocyte/macrophage fraction of peripheral blood mononuclear cells (PBMCs) taken from patients with SLE to produce IL-6 [10]. Elevation of serum IL-10 concentration and its correlation with disease activity has also been described in SLE patients [11–13]. Both constitutive and stimulated levels of the anti-inflammatory cytokine transforming growth factor (TGF)β have been reported to be lower in patients with SLE, probably because high levels of IL-10 should suppress TGFβ production by natural killer (NK) cells [14]. The high immunoglobulin (Ig)G production seen in SLE patients may be a consequence of low TGFβ levels, as TGFβ suppresses B lymphocyte secretion of IgG via CD8+ cells in presence of IL-2 [15]. A recent pilot clinical study showed that Tocilizumab, an IL-6 receptor inhibitor, decreased IgG levels in SLE patients, suggesting that high levels of IL-6 may also contribute to high IgG [16]. TGFβ converts naive T cells into regulatory T cells, which can then prevent autoimmunity. However, in the presence of IL-6, TGFβ also promotes the differentiation of naive T lymphocytes into proinflammatory IL-17-producing Th17 cells, resulting in autoimmunity and inflammation [3]. Despite many reports showing the pathological role of IL-17 in RA, few have made this connection in SLE [17–19], although increased plasma IL-17 levels have been reported [20].

Furthermore, type I IFN and type II IFN have both been implicated in the pathogenesis of SLE. High IFN-α and IFN-γ serum levels have been reported in SLE [4, 21–24]. Patients with active SLE often present flu-like symptoms such as fever and fatigue, both of which reflect high serum IFN-α levels and are relevant to disease activity and severity [25–27]. The major producer of IFN-α is the cell subset plasmacytoid dendritic cells (pDCs) [28]. Two groups have identified large numbers of IFN-producing pDCs in cutaneous LE skin lesions [29, 30]. Decreased numbers in peripheral blood have also been reported, suggesting the potential ability of pDCs to migrate toward peripheral tissues [31–34]. Although our previous report did not identify any overexpression of the IFN-α gene in peripheral blood cells from SLE patients [35], we have found the overexpression of several IFN-inducible (IFI) genes, which agrees with other reports showing that peripheral blood from SLE patients has remarkably homogeneous gene expression patterns including an overexpression of IFI genes, implying IFN involvement in SLE [36–40].

Finally, in the cerebrospinal fluid (CSF) of SLE patients with central nervous system (CNS) pathologies, elevated concentrations of TNF, IL-1, IL-6, and IL-10 have been reported [41, 42]. IL-6 and IFN-γ have also been found in kidney biopsy specimens from patients with lupus nephritis [32, 43].

3. Interactions Among IFN-α, IFN-β, and TNF in the Immunoregulatory Networks of SLE

Aberrant regulations or interactions among immune response molecules have been reported in our previous study [35]. TNF and IFN-γ have been observed to play central roles in the immunoregulatory networks of SLE, which mainly include IFI molecules. Studies on the effect of interactions between IFN-α and one of TNF or IFN-γ on the expression of IFI molecules found that TNF has a repressive effect while IFN-γ mainly has a synergistic effect on the regulation of IFI gene expressions induced by IFN-α in vitro. Although the exact function of IFI molecules in SLE pathogenesis is still obscure, we suspect that the increased serum TNF level in SLE compensates for the immune system balance altered by IFN-α in SLE. More than 10 years ago, SLE patients with "low" PBMC TNF production were found to be more likely to develop nephritis [44]. In addition, patients with RA or Crohn's disease can develop autoantibodies to nuclear antigens when under TNF blocking therapies [45]. It has also been reported that patients on anti-TNF therapy display increased transcription of IFN-α-regulated genes and that TNF inhibits virus-induced IFN-α release by both healthy and SLE PBMCs [46]. All these evidences further implicate that a strong TNF response is protective against lupus nephritis and that therapeutic TNF blockaders could exacerbate SLE or provoke lupus-like manifestations. With regards to IFN-γ, SLE patients have been found to have genetic deficiencies and abnormal overexpression in the affected organs [32, 43, 47–51]. IFN-γ receptor knockout lupus prone mouse strain has suggested that IFN-γ is essential for the development of nephritis in mice and that increasing IFN-γ during disease activation may cause an increase in IgG [52]. A recent study has also described activation of the IFN-γ signaling pathway in the PBMCs of patients with SLE [53], supporting the notion that IFN-γ has a pathological role in SLE development. Although the mechanisms of increased IFN-γ serum levels in SLE are still unknown, together with our results, the synergistic effect of IFN-γ with IFN-α seems to accelerate SLE disease development.

4. Influence of Estrogen in Cytokine Networks

Several studies have suggested that gender differences in lupus susceptibility are mediated by sex hormones, consistent with the fact that 90% of SLE sufferers are female [54–56]. For example, there is an increased risk of developing SLE in postmenopausal women who received estrogen hormone replacement therapy [57]. The role of estrogen in cytokine networks has been well investigated in pregnant women. Cytokines are intimately involved with sex hormones, as they regulate the level of sex hormones both systemically and locally, especially in the reproductive organs. Complicated interactions in cytokine-steroid networks affect cell activities

such as proliferation and apoptosis [58]. It has been reported that a shift in the Th1 to Th2 ratio impacts immunological changes in maternal circulation during gestation due to the progressive increase of estrogens that reach peak level during the third trimester of pregnancy. It seems that estrogens inhibit cell-mediated immune response (Th1 cytokines), whereas they induce antibody production (Th2 cytokines) [59]. However, it has been shown that serum levels of estrogens are lower in SLE patients in the third trimester of pregnancy compared to healthy controls and that this may be due to compromised placental activities [60]. On the other hand, IL-6 progressively increases in maternal circulation in healthy individuals during pregnancy, but low levels of IL-6 have also been reported during the third trimester of pregnancy in SLE patients [61]. Therefore, low levels of estrogens and IL-6 are thought to be responsible for lower activation of the humoral immune response, which then leads to the lower disease activity observed over the same period in SLE patients [59]. Our previous report also shows that beta-estradiol plays a significant role in the immunoregulatory networks of SLE, although the in vitro results did not show any strong evidence for a functional interaction between estradiol and IFN-α on the expression of IFI genes [35]. Taken together, beta-estradiol too plays a significant role in the pathophysiology of SLE. Ultimately, we can see that complex interactions between hormones and cytokines have a strong effect on autoimmune diseases, but the details are still poorly grasped.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

The authors would like to thank Dr. Peter Karagiannis for advice on preparing manuscript. They also thank Ms. Ozawa for excellent secretarial support.

References

[1] B. L. Kotzin, "Systemic lupus erythematosus," *Cell*, vol. 85, no. 3, pp. 303–306, 1996.

[2] M. J. Rood, E. A. van der Velde, R. Ten Cate, F. C. Breedveld, and T. W J Huizinga, "Female sex hormones at the onset of systemic lupus erythematosus affect survival," *British Journal of Rheumatology*, vol. 37, no. 9, pp. 1008–1010, 1998.

[3] L. Steinman, "A brief history of T_H17, the first major revision in the T_H1/T_H2 hypothesis of T cell-mediated tissue damage," *Nature Medicine*, vol. 13, no. 2, pp. 139–145, 2007.

[4] M. Al-Janadi, S. Al-Balla, A. Al-Dalaan, and S. Raziuddin, "Cytokine profile in systemic lupus erythematosus, rheumatoid arthritis, and other rheumatic diseases," *Journal of Clinical Immunology*, vol. 13, no. 1, pp. 58–67, 1993.

[5] G. S. Dean, J. Tyrrell-Price, E. Crawley, and D. A. Isenberg, "Cytokines and systemic lupus erythematosus," *Annals of the Rheumatic Diseases*, vol. 59, no. 4, pp. 243–251, 2000.

[6] D. Emilie, L. Llorente, and P. Galanaud, "Cytokines and systemic lupus erythematosus," *Annales de Medecine Interne*, vol. 147, no. 7, pp. 480–484, 1996.

[7] E. M. Davas, A. Tsirogianni, I. Kappou, D. Karamitsos, I. Economidou, and P. C. Dantis, "Serum IL-6, TNFα, p55 srTNFα, p75 srTNFα, srIL-2α levels and disease activity in systemic lupus erythematosus," *Clinical Rheumatology*, vol. 18, no. 1, pp. 17–22, 1999.

[8] A. Sabry, H. Sheashaa, A. El-Husseini, et al., "Proinflammatory cytokines (TNF-α and IL-6) in Egyptian patients with SLE: its correlation with disease activity," *Cytokine*, vol. 35, no. 3-4, pp. 148–153, 2006.

[9] C. Gabay, N. Cakir, F. Moral, et al., "Circulating levels of tumor necrosis factor soluble receptors in systemic lupus erythematosus are significantly higher than in other rheumatic diseases and correlate with disease activity," *The Journal of Rheumatology*, vol. 24, no. 2, pp. 303–308, 1997.

[10] B. K. Pelton, W. Hylton, and A. M. Denman, "Activation of IL-6 production by UV irradiation of blood mononuclear cells from patients with systemic lupus erythematosus," *Clinical and Experimental Immunology*, vol. 89, no. 2, pp. 251–254, 1992.

[11] J. K. Lacki, P. Leszczynski, J. Kelemen, W. Müller, and S. H. Mackiewicz, "Cytokine concentration in serum of lupus erythematosus patients: the effect on acute phase response," *Journal of Medicine*, vol. 28, no. 1-2, pp. 99–107, 1997.

[12] J. F. Viallard, J. L. Pellegrin, V. Ranchin, et al., "Th1 (IL-2, interferon-gamma (IFN-γ)) and Th2 (IL-10, IL-4) cytokine production by peripheral blood mononuclear cells (PBMC) from patients with systemic lupus erythematosus (SLE)," *Clinical and Experimental Immunology*, vol. 115, no. 1, pp. 189–195, 1999.

[13] A. M. Beebe, D. J. Cua, and R. de Waal Malefyt, "The role of interleukin-10 in autoimmune disease: systemic lupus erythematosus (SLE) and multiple sclerosis (MS)," *Cytokine and Growth Factor Reviews*, vol. 13, no. 4-5, pp. 403–412, 2002.

[14] K. Ohtsuka, J. D. Gray, M. M. Stimmler, and D. A. Horwitz, "The relationship between defects in lymphocyte production of transforming growth factor-beta in systemic lupus erythematosus and disease activity or severity," *Lupus*, vol. 8, no. 2, pp. 90–94, 1999.

[15] D. A. Horwitz, J. D. Gray, K. Ohtsuka, M. Hirokawa, and T. Takahashi, "The immunoregulatory effects of NK cells: the role of TGF-β and implications for autoimmunity," *Immunology Today*, vol. 18, no. 11, pp. 538–542, 1997.

[16] G. G. Illei, Y. Shirota, C. H. Yarboro, et al., "Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study," *Arthritis and Rheumatism*, vol. 62, no. 2, pp. 542–552, 2010.

[17] W. B. van den Berg, P. L. van Lent, L. A. B. Joosten, S. Abdollahi-Roodsaz, and M. I. Koenders, "Amplifying elements of arthritis and joint destruction," *Annals of the Rheumatic Diseases*, vol. 66, supplement 3, pp. iii45–iii48, 2007.

[18] E. M. Moran, R. Mullan, J. McCormick, et al., "Human rheumatoid arthritis tissue production of IL-17A drives matrix and cartilage degradation: synergy with tumour necrosis factor-α, Oncostatin M and response to biologic therapies," *Arthritis Research & Therapy*, vol. 11, no. 4, article R113, 2009.

[19] F. Cheng, Z. Guo, H. Xu, D. Yan, and Q. Li, "Decreased plasma IL22 levels, but not increased IL17 and IL23 levels, correlate with disease activity in patients with systemic lupus erythematosus," *Annals of the Rheumatic Diseases*, vol. 68, no. 4, pp. 604–606, 2009.

[20] C. K. Wong, C. Y. Ho, F. W. S. Ko, et al., "Proinflammatory cytokines (IL-17, IL-6, IL-18 and IL-12) and Th cytokines (IFN-γ, IL-4, IL-10 and IL-13) in patients with allergic

asthma," *Clinical and Experimental Immunology*, vol. 125, no. 2, pp. 177–183, 2001.

[21] J. J. Hooks, H. M. Moutsopoulos, and A. L. Notkins, "Circulating interferon in human autoimmune diseases," *Texas Reports on Biology and Medicine*, vol. 41, pp. 164–168, 1981.

[22] S. R. Ytterberg and T. J. Schnitzer, "Serum interferon levels in patients with systemic lupus erythematosus," *Arthritis and Rheumatism*, vol. 25, no. 4, pp. 401–406, 1982.

[23] T. Kim, Y. Kanayama, N. Negoro, M. Okamura, T. Takeda, and T. Inoue, "Serum levels of interferons in patients with systemic lupus erythematosus," *Clinical and Experimental Immunology*, vol. 70, no. 3, pp. 562–569, 1987.

[24] E. Robak, P. Smolewski, A. Wozniacka, A. Sysa-Jedrzejowska, H. Stepień, and T. Robak, "Relationship between peripheral blood dendritic cells and cytokines involved in the pathogenesis of systemic lupus erythematosus," *European Cytokine Network*, vol. 15, no. 3, pp. 222–230, 2004.

[25] A. A. Bengtsson, G. Sturfelt, L. Truedsson, et al., "Activation of type I interferon system in systemic lupus erythematosus correlates with disease activity but not with antiretroviral antibodies," *Lupus*, vol. 9, no. 9, pp. 664–671, 2000.

[26] M. C. Dall'era, P. M. Cardarelli, B. T. Preston, A. Witte, and J. C. Davis Jr., "Type I interferon correlates with serological and clinical manifestations of SLE," *Annals of the Rheumatic Diseases*, vol. 64, no. 12, pp. 1692–1697, 2005.

[27] J. Wenzel, S. Zahn, T. Bieber, and T. Tüting, "Type I interferon-associated cytotoxic inflammation in cutaneous lupus erythematosus," *Archives of Dermatological Research*, vol. 301, no. 1, pp. 83–86, 2009.

[28] L. Rönnblom and G. V. Alm, "The natural interferon-α producing cells in systemic lupus erythematosus," *Human Immunology*, vol. 63, no. 12, pp. 1181–1193, 2002.

[29] S. Blomberg, M. L. Eloranta, B. Cederblad, K. Nordlind, G. V. Alm, and L. Rönnblom, "Presence of cutaneous interferon-α producing cells in patients with systemic lupus erythematosus," *Lupus*, vol. 10, no. 7, pp. 484–490, 2001.

[30] L. Farkas, K. Beiske, F. Lund-Johansen, P. Brandtzaeg, and F. L. Jahnsen, "Plasmacytoid dendritic cells (natural interferon-α/β-producing cells) accumulate in cutaneous lupus erythematosus lesions," *American Journal of Pathology*, vol. 159, no. 1, pp. 237–243, 2001.

[31] B. Cederblad, S. Blomberg, H. Vallin, A. Perers, G. V. Alm, and L. Rönnblom, "Patients with systemic lupus erythematosus have reduced numbers of circulating natural interferon-α-producing cells," *Journal of Autoimmunity*, vol. 11, no. 5, pp. 465–470, 1998.

[32] M. Tucci, S. Ciavarella, S. Strippoli, F. Dammacco, and F. Silvestris, "Oversecretion of cytokines and chemokines in lupus nephritis is regulated by intraparenchymal dendritic cells: a review," *Annals of the New York Academy of Sciences*, vol. 1173, pp. 449–457, 2009.

[33] P. Blanco, A. K. Palucka, M. Gill, V. Pascual, and J. Banchereau, "Induction of dendritic cell differentiation by IFN-α in systemic lupus erythematosus," *Science*, vol. 294, no. 5546, pp. 1540–1543, 2001.

[34] L. Rönnblom and G. V. Alm, "A pivotal role for the natural interferon α-producing cells (plasmacytoid dendritic cells) in the pathogenesis of lupus," *Journal of Experimental Medicine*, vol. 194, no. 12, pp. F59–F63, 2001.

[35] H. M. Lee, T. Mima, H. Sugino, et al., "Interactions among type I and type II interferon, tumor necrosis factor, and β-estradiol in the regulation of immune response-related gene expressions in systemic lupus erythematosus," *Arthritis Research & Therapy*, vol. 11, no. 1, article R1, 2009.

[36] L. Bennett, A. K. Palucka, E. Arce, et al., "Interferon and granulopoiesis signatures in systemic lupus erythematosus blood," *Journal of Experimental Medicine*, vol. 197, no. 6, pp. 711–723, 2003.

[37] E. C. Baechler, F. M. Batliwalla, G. Karypis, et al., "Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 5, pp. 2610–2615, 2003.

[38] G. M. Han, S. L. Chen, N. Shen, S. Ye, C. D. Bao, and Y. Y. Gu, "Analysis of gene expression profiles in human systemic lupus erythematosus using oligonucleotide microarray," *Genes and Immunity*, vol. 4, no. 3, pp. 177–186, 2003.

[39] T. Ishii, H. Onda, A. Tanigawa, et al., "Isolation and expression profiling of genes upregulated in the peripheral blood cells of systemic lupus erythematosus patients," *DNA Research*, vol. 12, no. 6, pp. 429–439, 2005.

[40] X. Feng, H. Wu, J. M. Grossman, et al., "Association of increased interferon-inducible gene expression with disease activity and lupus nephritis in patients with systemic lupus erythematosus," *Arthritis and Rheumatism*, vol. 54, no. 9, pp. 2951–2962, 2006.

[41] J. Alcocer-Varela, D. Aleman-Hoey, and D. Alarcon-Segovia, "Interleukin-1 and interleukin-6 activities are increased in the cerebrospinal fluid of patients with CNS lupus erythematosus and correlate with local late T-cell activation markers," *Lupus*, vol. 1, no. 2, pp. 111–117, 1992.

[42] K. Baraczka, K. Nékám, T. Pozsonyi, I. Szüts, and G. Ormos, "Investigation of cytokine (tumor necrosis factor-alpha, interleukin-6, interleukin-10) concentrations in the cerebrospinal fluid of female patients with multiple sclerosis and systemic lupus erythematosus," *European Journal of Neurology*, vol. 11, no. 1, pp. 37–42, 2004.

[43] R. Herrera-Esparza, O. Barbosa-Cisneros, R. Villalobos-Hurtado, and E. Avalos-Díaz, "Renal expression of IL-6 and TNFα genes in lupus nephritis," *Lupus*, vol. 7, no. 3, pp. 154–158, 1998.

[44] S. H. Lee, S. H. Park, J. K. Min, et al., "Decreased tumour necrosis factor-beta production in TNFB*2 homozygote: an important predisposing factor of lupus nephritis in Koreans," *Lupus*, vol. 6, no. 7, pp. 603–609, 1997.

[45] M. Aringer, G. Steiner, W. B. Graninger, E. Höfler, C.W. Steiner, and J. S. Smolen, "Effects of short-term infliximab therapy on autoantibodies in systemic lupus erythematosus," *Arthritis and Rheumatism*, vol. 56, no. 1, pp. 274–279, 2007.

[46] A. K. Palucka, J. P. Blanck, L. Bennett, V. Pascual, and J. Banchereau, "Cross-regulation of TNF and IFN-α in autoimmune diseases," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 9, pp. 3372–3377, 2005.

[47] K. Miyake, H. Nakashima, M. Akahoshi, et al., "Genetically determined interferon-γ production influences the histological phenotype of lupus nephritis," *Rheumatology*, vol. 41, no. 5, pp. 518–524, 2002.

[48] K. Kim, S. K. Cho, A. Sestak, B. Namjou, C. Kang, and S. C. Bae, "Interferon-gamma gene polymorphisms associated with susceptibility to systemic lupus erythematosus," *Annals of the Rheumatic Diseases*. In press.

[49] M. Funauchi, H. Sugishima, M. Minoda, and A. Horiuchi, "Serum level of interferon-gamma in autoimmune diseases," *The Tohoku Journal of Experimental Medicine*, vol. 164, no. 4, pp. 259–267, 1991.

[50] W. S. Uhm, K. Na, G. W. Song, et al., "Cytokine balance in kidney tissue from lupus nephritis patients," *Rheumatology*, vol. 42, no. 8, pp. 935–938, 2003.

[51] M. Harigai, M. Kawamoto, M. Hara, T. Kubota, N. Kamatani, and N. Miyasaka, "Excessive production of IFN-gamma in patients with systemic lupus erythematosus and its contribution to induction of B lymphocyte stimulator/B cell-activating factor/TNF ligand superfamily-13B," *Journal of Immunology*, vol. 181, no. 3, pp. 2211–2219, 2008.

[52] C. Haas, B. Ryffel, and M. Le Hir, "IFN-γ receptor deletion prevents autoantibody production and glomerulonephritis in lupus-prone (NZB $\times$ NZW)F_1 mice," *Journal of Immunology*, vol. 160, no. 8, pp. 3713–3718, 1998.

[53] T. Karonitsch, E. Feierl, C. W. Steiner, et al., "Activation of the interferon-γ signaling pathway in systemic lupus erythematosus peripheral blood mononuclear cells," *Arthritis and Rheumatism*, vol. 60, no. 5, pp. 1463–1471, 2009.

[54] A. T. Masi and R. A. Kaslow, "Sex effects in systemic lupus erythematosus: a clue to pathogenesis," *Arthritis and Rheumatism*, vol. 21, no. 4, pp. 480–484, 1978.

[55] R. G. Lahita, H. L. Bradlow, J. Fishman, and H. G. Kunkel, "Abnormal estrogen and androgen metabolism in the human with systemic lupus erythematosus," *American Journal of Kidney Diseases*, vol. 2, no. 1, supplement 1, pp. 206–211, 1982.

[56] M. R. Gubbels Bupp, T. N. Jørgensen, and B. L. Kotzin, "Identification of candidate genes that influence sex hormone-dependent disease phenotypes in mouse lupus," *Genes and Immunity*, vol. 9, no. 1, pp. 47–56, 2008.

[57] C. R. Meier, M. C. J. M. Sturkenboom, A. S. Cohen, and H. Jick, "Postmenopausal estrogen replacement therapy and the risk of developing systemic lupus erythematosus or discoid lupus," *The Journal of Rheumatology*, vol. 25, no. 8, pp. 1515–1519, 1998.

[58] R. G. Lahita, "Emerging concepts for sexual predilection in the disease systemic lupus erythematosus," *Annals of the New York Academy of Sciences*, vol. 876, pp. 64–70, 1999.

[59] A. Doria, L. Iaccarino, P. Sarzi-Puttini, et al., "Estrogens in pregnancy and systemic lupus erythematosus," *Annals of the New York Academy of Sciences*, vol. 1069, pp. 247–256, 2006.

[60] A. Doria, M. Cutolo, A. Ghirardello, et al., "Steroid hormones and disease activity during pregnancy in systemic lupus erythematosus," *Arthritis Care and Research*, vol. 47, no. 2, pp. 202–209, 2002.

[61] A. Doria, A. Ghirardello, L. Iaccarino, et al., "Pregnancy, cytokines, and disease activity in systemic lupus erythematosus," *Arthritis and Rheumatism*, vol. 51, no. 6, pp. 989–995, 2004.