We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Introductory Chapter: Systemic Lupus Erythematosus - Different Predisposing Factors

Wahid Ali Khan

Additional information is available at the end of the chapter

1. Introduction

Systemic lupus erythematosus (SLE) is a complex, multisystem autoimmune disease characterized by impaired immune tolerance resulting in the production of pathogenic autoantibodies and immune complexes [1]. Prevalence of SLE ranges between 20 and 150/100,000 and its incidence ranges between 1 and 10/100,000 [2]. American College of Rheumatology revised their criteria for the classification of SLE [3]. Their incidence is moat common in some ethnic group such as Asians, Australian Aborigines, African Americans, and Hispanics. Incidence rate has been raised in recent years that may probably due to better detection techniques for the disease. In the past few decades, the prognosis for SLE patients has been improved, and it was found that about 90% of the cases have 10-year survival rate [4]. This might be due to the fact that a combination of diagnosis of earlier disease and of milder disease and partially due to the development of various serological test used for SLE and combined used of steroids and various immunosuppressive drugs and availability of the techniques such as renal dialysis and transplantation [5]. Although, the exact cause of SLE remains elusive, but there is a consensus that it might be due to the combination various factors such as immunological, genetic and environmental. All these factors may somehow responsible for the chronic course of the disease. It is found that autoreactive T cells hold responsible for the activation of B cells that might be stimulated to produce antibodies by high levels of cytokines (pro-inflammatory) such as interleukin 10, interleukin 6, tumor necrosis factor-α and interferon γ in different SLE patients [6]. In addition, production of antibody might be elevated further by B and T cells through interaction via co-stimulatory molecules that inhibit apoptosis. Autoantibodies produce from these cells are very likely responsible for the pathogenic effect on tissues in different SLE patients [7]. In addition, impaired production of IL-10 and IL-12 causing B cell

INTECH
open science | open minds

activation and inhibition in the normal function of T cells [8]. Interleukin 12 responsible for the down-regulation of interleukin 10 and lower level somehow correlate with elevated activity and nephritis [9]. More recently, it has been assumed that the stimulus of autoantibodies production is the inability to depose apoptotic cells from the body [10].

2. Different factors predisposing to SLE

SLE is an autoimmune disease which involves multisystem disorder whose etiology is unknown but supposes to be multifactorial in origin. Different epidemiological data showed that there are many factors that might trigger SLE. These include gender, age, racial, hormonal, genetic, and environmental factors.

2.1. Hormonal factors

The incidence and prevalence of SLE varies considerably worldwide [11]. In addition, gender discrepancies are also observed in SLE burden, with a higher number of cases was found in women as compared to men. It has been observed that this disease has been affected to about 80–90% women of all the reported cases [12]. Prevalence of SLE is far more in women in comparison to men [13]. In addition, if we compare female to male ratio during childhood, it was found to about 12:1 [14]. These data showed that hormone plays an important role in etiology of SLE [15]. Hormones such as estrogen have both anti-inflammatory and pro-inflammatory properties depending upon different influencing factors [16]. There are various studies that can explain the role of estrogen and its metabolites in SLE [15, 17]. The 2-hydroxyestrogens was found to be 10 times lower in patients with SLE than the control subjects, and the ratio of 16-hydroxyestrone/2-hydroxyestrogen was found to be 20 times higher in these SLE patients [18]. Previous studies also showed that SLE patients have increased the concentration of serum 16-hydroxyestrone. α-Hydroxylation of estrogen was found to increased in SLE patients, producing more estrogen metabolites that were reported to elevate B cell differentiation and activation of T cells [19]. Another important mechanism through which estrogen plays a role in SLE etiopathogenesis is the involvement of quinone-semiquinone redox cycling of estrogen to produce free radicals that can damage DNA. This would probably alter its antigenicity leading to the induction and increased level of SLE autoantibodies that somehow cross-reacting with native DNA [20].

Estrogens are known to have higher immune reactivity in females and are also contribute to triggering autoimmune diseases including SLE [14]. Various conditions (physiological, therapeutic, and pathological) such as menstrual cycle, inflammatory cytokines, chronic stress, treatment with a corticosteroid, oral contraceptives, and steroid hormone replacement might cause variation in serum estrogen concentration and this variation in concentration contribute to SLE in different groups of the population [21].

2.2. Genetic factors

The difference (polymorphism) in various types of genes may also enhance the risk for the development of SLE, and in most of the cases, different genetic factors are thought to contribute

to the pathogenesis of this disease. In most of the cases, SLE is caused by a mutation in multiple genes and rarely seen by a mutation in the single gene. Multiple genes, that are causing SLE, are linked to the function of the immune system and difference in this most likely effect proper controls and targeting of the immune system. Genetic factors along with environmental factors play an important role in the determination of SLE susceptibility [22]. It is suggested that genetic factors play an important role not only in disease susceptibility but also in the development of SLE phenotype [22]. The genes that can increase SLE susceptibility are the genes included in the interferon pathway, also containing IRF5, IF1H1, and STAT4 [23]. The biggest genetic risk for SLE is confirmed by deficiencies of complement pathway proteins such as C1q, B and C4A, and C2. Mutation in TREX1 gene causing the accumulation of DNA that encodes for 3'repair endonuclease activity. The defect in these genes is although rare but susceptibility in most patients arises from a combination of normal variation in different genes. High-density SNP screening of the major histocompatibility complex in SLE showed strong evidence for independent susceptibility regions including HLADR2, HLADR3, and HLA-DRB1 [24]. There are other types of genes that can regulate the immune system, are also implicated in SLE. These genes include those that can influence the function or survival of T and B lymphocytes (BANK-1, PTPN22, OX4OL, BLK, LYN, PD-1) or those involved in the clearance of immune complex including FcγRIIa, ITGAM, and complement proteins. The class II alleles HLA-DR2 and HLA-DR3 were found to be the most prominent genetic risk factors for SLE in some group (Caucasian group) and these alleles showed twofold to threefold increased the risk for this disease [25]. There are two alleles namely HLA-DQ and –DR, which interestingly showed a close association with SLE autoantibodies [26]. The signal transducer and activator of transcription (STAT4) genes were first identified in rheumatoid arthritis and later on, it shows strong association with SLE [27]. Careful analyses of this gene revealed that there is a strong association of this gene not only with SLE nephritis but also with double-stranded DNA, autoantibodies and younger age of onset [28]. The difference in the promoter of certain genes (pentraxin C-reactive protein, CRP) has been linked with SLE or SLE nephritis in some ethnic group [29]. CRP is an important candidate for SLE susceptibility. This protein is found to be an effective innate immune modulator that brings out the clearance of cell debris and apoptotic bodies and we know that any defect in the clearance of apoptotic waste is belief to be an important process that mainly responsible for the promotion and development of autoantibodies in SLE patients [29]. From all these studies, it is observed that genetic factors play an important role in SLE pathogenesis. These evidence suggest that these factors play a role not only in disease susceptibility but also in the development of disease phenotype.

2.3. Environmental factors

Although hormonal and genetic factors predispose towards SLE but the initiation of the disease may trigger from various environmental and exogenous factors. Different environmental toxicants and agents, such as alcohol, smoking, various chemical, ultraviolet light, various infectious agents, hormone, and therapeutic agents, have been involving in inducing SLE. All these environmental agents along with other types of factors have been associated with the occurrence of SLE [30]. Infectious agents may disturb immune regulation and stimulate various immune response through molecular mimicry; food influence the production of inflammatory mediators; drug or toxin alter cellular responsiveness and antigenicity of self-antigen;

and different chemical and physical agents like ultraviolet light, alcohol, etc. induce inflammation, causes cellular apoptosis, and also damage tissue and DNA. Various types of drugs like procainamide and hydralazine (aromatic amines or hydrazines) induce lupus-like symptoms in those individuals who are ingested or in contact with these agents [31, 32]. In addition, more use of hair dyes, which consists of aromatic amines, have been associated with the development of SLE [33]. Sunlight exposure is one of the main environmental factors associated with the induction and exacerbation of SLE. Exposure of ultraviolet light is found to be an important factor that may trigger SLE in many patients. This exposure of skin with ultraviolet light alter the position and structure of DNA as well as Ro and nRNP antigen and somehow increase its immunogenicity [34]. Several dietary factors along with various infectious agents are involved in the pathogenesis of SLE. There are the reports that showed that ingestion of alfalfa sprouts that consists of L-canavanine, might involved in the development of lupus-like syndrome [35]. The use of environmental estrogen had been increasing over the years and they are present in the human body from the consumption of meat and milk product from lives stock that is given synthetic estrogen [36]. Moreover, these estrogens have also been used by postmenopausal women and for contraceptive purposes. Hormone replace therapy as well as oral contraceptives has been shown to be a risk factor in the development of SLE [37]. The environmental estrogen with another endocrine hormone may act as an important agent to trigger autoimmunity in susceptible individuals. The development of SLE may depend on several factors such as genetic background, dose, sex, age, a period of exposure, and status of the immune system at the time of contact of these environmental agents.

Author details

Wahid Ali Khan

Address all correspondence to: wahidalikhan@rediffmail.com

Department of Clinical Biochemistry, College of Medicine, King Khalid University, Abha, Kingdom of Saudi Arabia

References

[1] Oon S, Wilson NJ, Wicks I. Targeted therapeutics in SLE: Emerging strategies to modulate the interferon pathway. Clinical and Translational Immunology. 2016;**5**:e79

[2] Squatrito D, Emmi D, Silvestri E, et al. Pathogenesis and potential therapeutic targets in systemic lupus erythematosus from bench to bedside. Autoimmune Highlights. 2014;**5**:33–45

[3] Hochberg MC. Updating the American College of rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis & Rheumatology. 1997;**40**:1725

[4] Peschken CA, Esdaile JM. Systemic lupus erythematosus in North Americans Indians: A population base study. The Journal of Rheumatology. 2000;**27**:1884–1891

[5] Goldblatt F, Isenberg DA. New therapies for systemic lupus erythematosus. Clinical & Experimental Immunology. 2005;**140**:205–212

[6] Davas EM, Tsirogianni A, Kappou I, et al. Serum IL-6, TNFα, p55 srTNFα, p75 srTNFα, sr II-2α levels and disease activity in systemic lupus erythematosus. Clinical Rheumatology. 1999;**18**:17–22

[7] Hagelberg S, Lee Y, Bergman I, et al. Long term follow up of childhood lupus nephritis. The Journal of Rheumatology. 2002;**29**:2635–2642

[8] Emilie D, Mariette X. Interleukin 10: A new therapeutic target in systemic lupus erythematosus? Joint Bone Spine. 2001;**68**:1–5

[9] Min DJ, Cho ML, Cho CS, et al. Decreased production of interleukin-12 and interferon-gamma is associated with renal involvement is systemic lupus erythematosus. Scandinavian Journal of Rheumatology. 2001;**30**:159–163

[10] Taylor PR, Carugati A, Fadok VA, et al. A hierarchical role for classical pathway complement proteins in the clearance of apoptotic cell in vivo. The Journal of Experimental Medicine. 2000;**192**:359–366

[11] Danchenko N, Satia JA, Anthony MS, Epidemiology of systemic lupus erythematosus: A comparison of worldwide disease burden. Lupus. 2006;**15**:308–318

[12] Siegel M, Lee SL. The epidemiology of systemic lupus erythematosus. Seminars in Arthritis and Rheumatism. 1973;**3**:1–54

[13] Jacobson DL, Gange SJ, Rose NR, Graham NMH. Epidemiology an estimated population burden of selected autoimmune disease in the United States. Clinical Immunology and Immunopathology. 1997;**84**:223–243

[14] Ramsey-Goldman R, Manzi S. Systemic lupus erythematosus. Women and Health. Academic Press. 2000:704

[15] Khan WA, Habib S, Khan WA, et al. Enhanced binding of circulating SLE autoantibodies to catecholestrogen-copper-modified DNA. Molecular and Cellular Biochemistry. 2008;**315**:143–150

[16] Straub RH. The complex role estrogen in inflammation. Endocrine Reviews. 2007;**28**: 521–574

[17] Cohen-Solal JF, Jeganathan V, Grimaldi CM, et al. Sex hormone and SLE: Influencing the fate of autoreactive B cells. Current Topics in Microbiology and Immunology. 2006;**305**:67–88

[18] Weidler C, Harle P, Schedel J, et al. Patients with rheumatoid arthritis and systemic lupus erythematosus have increased renal excretion of mitogenic estrogen in relation to andogenous antiestrogen. The Journal of Rheumatology. 2004;**31**:489–494

[19] Lahita RG. The connective tissue diseases and the overall influence of gender. International journal of fertility and menopausal studies. 1996;**41**:156–160

[20] Khan WA, Moinuddin, Khan MWA, Chabbra HS. Catecholestrogen: Possible role in systemic lupus erythematosus. Rheumatology. 2009;**48**:1345–1351

[21] Cutolo M, Sulli A, Capellino S, et al. Sex hormone influence on the immune system: Basic and clinical agents in autoimmunity. Lupus. 2004;**13**:635–638

[22] Ceciarelli F, Perricone C, Borgiani P, et al. Genetic factors in systemic lupus erythematosus: Contribution in disease phenotypes. Journal of Immunology Research. 2015;**745647**: 1–11

[23] Hagberg N, Ronnblom S. Sytemic lupus erythematosus – A disease with a dysregulated type I interferon system. Scandinavian Journal of Immunology. 2015;**82**:199–207

[24] Barcellos LF, May SL, Ramsay PP, et al. High-density SNP screening of the major histocompatibily complex in systemic lupus erythematosus demonstrate strong evidence for independent susceptibility genes. PLoS Genetics. 2009;**5**:e1000696

[25] Tsao BP, Wu H. The genetics of human lupus. In: Wallace DJ, Hahn BH, editors. Dubois Lupus Erythematosus. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. pp. 54–81

[26] Fernando MM, Stevens CR, Sabeti PC, et al. Identification of two independent risk factors for lupus within the MHC in United Kingdom families. PLoS Genetics. 2007;**3**:e192

[27] Remmers EF, Plenge RM, Lee AT, et al. STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. The New England Journal of Medicine. 2007;**357**:977–986

[28] Taylor KE, Remmers EF, Lee AT, et al. Specificity of the STAT4 genetic association for severe disease manifestation of systemic lupus erythematosus. PLOS Genetics. 2008;**4**:e1000084

[29] Edberg JC, Wu J, Langefeld CD, et al. Genetic variation in the CRP promoters: Association with systemic lupus erythematosus. Human Molecular Genetics. 2008;**17**:1147–1155

[30] Mak A, Tay SH. Environmental factors, toxicants and systemic lupus erythematosus. International Journal of Molecular Sciences. 2014;**15**:16043–16056

[31] Adoms LE, Mongey AB. Role genetic factors in drug-related autoimmunity. Lupus. 1994;**3**:443–447

[32] Reidenberg MM, Drayer DE, Lorenzo B, et al. Acetylation phenotypes and environmental chemical exposure of people with idiopathic systemic lupus erythematosus. Arthritis & Rheumatology. 1993;**36**:971–973

[33] Freui-Titulaer LW, Kelley DB, Grow AG, et al. Connective tissues decrease in southern Georgia: A case–control study of etiology factors. American Journal of Epidemiology. 1989;**130**:404–409

[34] Furukawa F, Kashihara-Sawami M, Lyons MB, et al. Binding of antibodies to the extractable nuclear antigens SS-A/Ro and SSB/La is induce on the surface of human keratinocytes by ultraviolet lights (UVL): Implications for the pathogenesis of photosensitive cutaneous lupus. Journal of Investigative Dermatology. 1990;**94**:77–85

[35] Prete PE. The mechanism of action of L-canavanine in inducing autoimmune phenomena. Arthritis & Rheumatology. 1985;**28**:1198–1200

[36] Ahmed SA, Hissong BD, Verthelyi D, et al. Gender and risk of autoimmune disease: Possible role of estrogenic compound. Environmental Health Perspectives. 1999;**107**: 681–686

[37] Sanchez-Guerrero J, Liaug MH, Karlson EW, et al. Postmenopausal estrogen therapy and the risk for developing systemic lupus erythematosus. Annals of Internal Medicine. 1995;**122**:430–433