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Review Article

Epigenetics and treatment of systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a disease associated with an impaired autoimmune response; the immune system attacks erroneously own tissues, which leads to inflammation, tissue damage and complement activation. The latter plays a pivotal role in SLE pathology, as complement level is suited as histological marker for disease diagnoses and management. Besides, environmentally factors have been highlighted and their significant contribution for individual genetic predisposition has been pointed out. Here complement factors, their activity and their ability to modify DNA with histone proteins are reviewed; known gene mutations involved in SLE, and new therapeutic approaches suggested for SLE are discussed and summarized, as well.

Keywords

systemic lupus erythematosus (SLE), complement factors, genetic modification, environmental factors, therapy

Introduction

Systemic lupus erythematosus (SLE), is a complex disorder affecting the immune system (Kiriakidou and Ching 2020). It is characterized by a wide range of clinical manifestation, such as renal, dermatological, neurological, and cardiovascular symptoms (Tsokos 2011). The incidence and prevalence varied from 3.2 to 159 per 100.000 and 0.3–8.7 per 100.000 persons (Gergianaki et al. 2017; Fatoye et al. 2022). In the USA the mean of medical costs for patients diagnosed with SLE is approximately 21.000–53.000$ per year (Murimi-Worstell et al. 2021).

The main symptoms of SLE are: Arthritis, associated with painful and swollen joints and morning stiffness; fever; fatigue; rashes; hair loss; changes of skin color in finger and toes; swollen glands and swelling in legs or around the eyes; headaches, dizziness, depression, confusion, or seizures; and/or stomach pain. As SLE in some patients is associated with lupus, inflammation may lead to other problems involving kidneys, heart, or lungs.

Although SLE treatment improved during last decade, the treat-to-target strategy often proposed is as for rheumatoid arthritis (van Vollenhoven et al. 2014). The latter aims to ensure a better quality of life for a long-term period, and to prevent damage to other organs of the individual while taking drugs during SLE treatment, and minimizing co-morbidities and drug toxicity (van Vollenhoven et al. 2014). The aim of this present review is to present the complement pathway and epigenetic factors being involved in SLE, as well as treatment strategies being suggested by different research groups.

An overview of complements

SLE is a complex disease in which complements have been shown to play a pivotal role in its pathogenesis (Sharma et al. 2020; Weinstein et al. 2021). Yet, there are approximately 30 complements reported, which are found in the blood and cell membrane. For activation of complements activation of C3 is most crucial. The complement response is divided into two pathways: the "complement activation" leading to C3 degradation, and the "late complement" pathway finishing with membrane complex formation. Besides the complement activation pathway is divided into three groups: the classical, the lectin and the alternative pathway.

In the alternative pathway C3, hydrolysis occurs in a spontaneous way. The product which is formed is instable C3b; it must bind to pentraxins. C3b together with factor B will bind on cell surface. Other factor such as factor D cleave factor B, leaving "Bb". The complex of C3bBb interacts with enzyme C3 convertase and comes to cleave C3. The complex of C3bBb together with C3 molecule interact with enzyme C5, and help to cleave C5. C5 participates in formation of MAC (membrane attack complex) together with C6, C7, C8, and C9, during the attack of cell membrane to bacteria.

The classical pathway involves C1, C2, C3 and C4 proteins. Protein C1 is a hexamer complex with C1q and C1c and C1s serine proteases. C1 can bind with Fc regions of an antibody. The C1s can cleave C4 and C4b than can bind to antigen-antibody complex at cell surface. It is shown that C1s can cleave C2, and C4bC2a complex is the C3 convertase in the classical pathway. After C3b formation, it can follow the alternative pathway or bind with C3 convertase and form C5 convertase.

The lectin pathway involves only C2, C3, C4 and some homologues of C1 components. The MBL (Mannose Binding Lectin) in blood has higher affinity for a protein called MASP (Mannan Associated Serine Protease). After that, the MBL it is target to mannose on the bacteria surface, and the MASP protein functions as a convertase to bind with complement protein C3 to form C3b (Janeway et al 2001; Bardhan and Kaushik 2023).

In routine analysis, the serum levels of C3, C4 and CH50 generally are measured from peripheral blood; however, urine, pleural fluid, and spinal fluid can also be tested. Lower levels of C3 and C4 cause activation of classical and lectin pathways, whereas lower level of C3 with normal level of C4 are found at the alternative pathway (Lundtoft et al. 2022; Ayano and Horiuchi 2023).

The complement proteins are suited for immunological test, also. For example, in SLE enhanced C1q, C3, and C4 levels are found in the renal glomeruli and skin (Ayano and Horiuchi 2023). There is no gold standard for SLE classification; some systems are based on the variety of immunological abnormalities and distinct organs involved in SLE (Aringer et al. 2019). The decrease of complements C3, C4, and CH50 is defined as a hypocomplementemia (Petri et al. 2012). An association between hypocomplementemia and nephritis, different disorders in hematological system (like anemias in autoimmune and thrombocytopenia), skin rash, and arthritis has been reported (Reynolds et al. 2018; Iwasaki et al. 2022; Jung et al. 2022). Complement deposition which can be checked by immunofluorescence testing is not include in SLE routine pathological classification. However, it is important to emphasize that C1q deposition is typically observed in SLE, while the other complement detectable by fluorescent antibodies are good indicators for different renal diseases (Sethi et al. 2016) (Fig. 1).

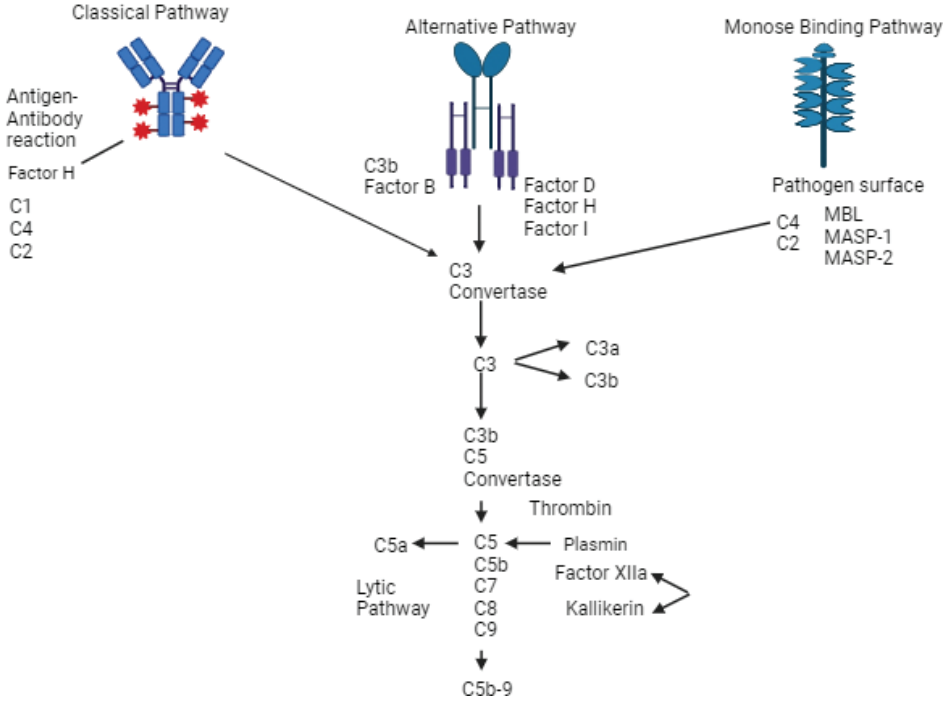

Figure 1. The complement cascade.

Epigenetics and SLE

Epigenetic alterations are reversible, stable and in parts heritable changes of the DNA leading to gene expression changes; DNA-sequence is normally not altered here (Sawalha 2008). The best known example of an epigenetic modification is DNA-methylation, leading to histone modifications, like phosphorylation, acetylation etc. (Hedrich et al. 2017; Álvarez-Errico et al. 2017).

DNA methylation appears by adding of a methyl-group to 5' cytosine in CpG dinucleotide. The enzymes being responsible for the maintenance of DNA methylation belong to DNA methyltransferase (DNMT) family. There are two classes of DNMTs: a) DNMT1 is responsible for re-methylation during the cell division; and b) the de novo DNMTs (DNMT3a and DNMT3b) (Hedrich and Tsokos 2011; Hedrich et al. 2014; Hedrich et al. 2017).

In the SLE patients $CD4^+$T cells have decreased DNA methylation in the promoter of *CD40LG*, the *CD40LG* genes, which are coding for B cells costimulatory of CD40L (Iezzi et al. 2009). Hypomethylation of genes *MIR886* and *TRIM69*, and hypermethylation of *RNF39* gene were found in SLE patients (Renauer et al. 2015). Change of 5mC to 5-hydroxymethylcytosine (5-hmC), is a very important epigenetic alternation during embryonic development (Pastor et al. 2013). Interestingly, in SLE patients the 5-hmC level is increased at promoter region (Zhao et al. 2016).

DNA hypomethylation of $CD4^+$T cells derived from SLE patients is associated with decreased expression level of *GADD45A* (growth arrest and DNA damage-induced 45) gene (Barreto et al. 2007). The autoreactivity of the $CD4^+$T cells in SLE patients is inhibited by hypermethylation of CD11a and CD70 promoter regions. The hyperexpression of the *GADD45A* gene can cause demethylation of CD11a in SLE CD4+T cells (Li et al. 2010).

Histone modifications are very important for creating a specific epigenetic code (Farivar and Shaabanpour Aghamaleki 2018). Even though the importance of histone acetylation is unresolved in SLE pathology, hypoacetylation of H3 and H4 histones in the $CD4^+$T cells is reported (Zhang et al. 2010) and in overexpression of TNF-α in SLE patients (Sullivan et al. 2007).Trimethylation of the H3K4 plays pivotal role in the regulation of transcription in SLE patients (Zhang et al. 2016).

Regulatory factor X-box 1 (RFX1) can interact with histone deacetylase 1 (HDAC1); RFX1 down-regulation contributes to histone H3 hyperacetylation of the CD11a and CD70 promoters in $CD4^+$T cells of SLE patients. This leads to CD11a and CD70 overexpression, thereby triggering autoimmune responses. Besides, RFX1 recruits SUV39H1 to the promoter regions of the CD11a and CD70 genes in $CD4^+$T cells, thereby regulating local H3K9 tri-methylation levels. These findings suggest a central role of RFX1 down-regulation in the epigenetic de-repression of auto-immune related genes in SLE (Zhao et al. 2010a). Also, HPK1 (hematopoietic progenitor kinase 1) triggers trimethylation of histone H3 lysine K27 (H3K27me3), which increases the level of the $CD4^+$T cells in SLE patients (Long et al. 2009). Histone silencing can also be achieved by downregulation of expression in IL-2, which is mediated by cAMP (Rauen et al. 2011).

Gene association with SLE

According to OMIM different genes provide to in the SLE pathogenesis:

- As mentioned before, the complementary system plays pivotal role in the pathogenesis of monogenic SLE. Defects which are possible to occur in the complementary cascade (made by 30 proteins) are thought to be stimulate autoimmunity (Lintner et al. 2016). The primary binding signal of SLE in the MHC region are localized in HLA-DRB1 (MHC class II region) or long-range HLA gene haplotypes linked to HLA-DRB1. It is difficult to identify the exact genetic variant being responsible to cause SLE, because there are disequilibria about allelic heterogeneity in populations (Lessard et al. 2015; Sun et al. 2016; Bang et al. 2016);
- Deoxyribose deficiency based on genes *DNaseI*, *DNase1L3*, *DNaseII*, and *TREX1* are connected with monogenic SLE (Bruschi et al. 2020), and can be early diagnosed by presence of antibodies ANA and anti-dsDNA and hypocomplementemia (Al-Mayouf et al. 2011; Rodero et al. 2017). Two Turkish families with *DNase1L3* mutations had hypocomplementemia urticalitis vasculitis (VUS) (Özçakar et al. 2013); VUS and SLE share many clinical symptoms. Accordingly, a heterozygous mutation in *DNase1L3* (c.G764A) was evidenced in an SLE case (Lee et al. 2022). A homozygous frameshift alteration (c.289_290delAC/ p.Thr97Ilefs*2) for *DNase1L3* was also reported (Batu et al. 2018). The single nucleotide polymorphism (SNP) in *DNaseI* in exon 8, p.Gln244Arg is associated with autoantibodies which engrave SLE (Shin et al. 2004). *DNaseI* mutations SLE patients are found at the position p.Gly127Arg and p.Pro154Ala (Almlöf et al. 2019); *TREX1* (*DNaseIII*) is encoding a 3'-5' DNA endonuclease that inhabits the cytosol and acts on single and double strand DNA. Its main function is to cleave mismatches and to modified DNA at 3' end (Stetson et al. 2008). *TREX1* gene mutations cause defective exonuclease activity (Ellyard et al. 2014). Some gene mutations such as p.Asp200Asn and p.Asp18Asn are described as dominant in autoimmune diseases (Lehtinen et al. 2008). Lee et al (2022) has reported a corresponding pThr224Met and a homozygous c.292_293 ins A; p.Cys99Met fs mutation (Lee et al. 2022);
- Loss of function in *SAM* (sterile alpha motif) gene results in increase of the deoxyribonuclease triphosphate level by inhibiting the degradation of the DNA precursors (Costa-Reis and Sullivan 2017; Alperin et

al. 2018). The pathogenic variants are found in the SLE patients, similar in symptoms to *TREX1* mutation carriers (Ravenscroft et al. 2011). Also, in a pediatric SLE patient, at heterozygote mutation in *SAMHD1* (c.1423G>A) was described (Hong et al. 2022);

- A heterozygous missense mutations in *IFIH1* gene was found in a 16 year old girl with mutation p.Arg779His (Van Eyck et al. 2015). Other mutations were in position p.Ala946Thr (Robinson et al. 2011) and p.Arg77Trp (Gitlin et al. 2006);
- In a Greece SLE-family a heterozygous mutations in *TMEM173* gene at p.Gly166Glu was reported (König et al. 2017);
- The *ACP5* gene plays a pivotal role for preventing, monitoring and treating different types of tumors, as well as development of therapeutic strategy for human genetic diseases (Ren et al. 2018). Homozygote missense mutations in pediatric SLE patients (c.1152G>T and c.420G>A) were found (Hong et al. 2022);
- *SLC7A7* (solute carrier family 7 member 7) may be associated with monogenic SLE; however, only 2 cases of concomitant hereditary coproporphyria (HCP) and SLE are available; heterozygous variants in *SLC7A7* c.250G >A (p. V84I) in exon 3 and c.625+1G >A (splicing) in intron 4 are known (Liu et al. 2022);
- Heterozygous mutations in the *TLR7* gene (Xp22) may cause SLE (Brown et al. 2022);
- Mutations in genes affecting the cascade pathway were reported as:

  - homozygous non-sense alterations (c.622C>T/p.Gln208Ter) and (c.79C>T/p.Gln27Ter) or homozygous missense alternation (c.100G>A/p.Gly34Arg) for *C1QA* (Batu et al. 2018);
  - homozygous missense alteration (c.1945G>C/p.Ala649Pro) for *C1S* (Batu et al. 2018); heterozygous mutation in *C1S* (c.G1241A; p.R414H) (Lee et al. 2022);
  - heterozygous mutation in *C2* (c.C1558T; p.R520C) (Lee et al. 2022);
  - heterozygous mutation in *DNase1* (c.G370A; p.E124K) (Lee et al. 2022);
  - heterozygous mutation in the *CFHR4* gene (c.T103C) (Lee et al. 2022) in SLE and deletions in *CFHR4* were present in atypical hemolytic uremic syndrome (aHUS), a form of TMA (thrombotic microangiopathy) (Lee et al. 2022) (Table 1).

Table 1. Some important gene mutation found in SLE diagnostic patients.

Gene	Position/Codon	Reference
ACP5	c.1152G>T c.420G>A	(Hong et al. 2022)
C1QA	c.622C>T/p.Gln208Ter	(Batu et al. 2018)
C1QC	c.79C>T/p.Gln27Ter	(Batu et al. 2018)
C1QC	c.100G>A/p.Gly34Arg	(Batu et al. 2018)
C1S	c.1945G>c/p.Ala649Pro	(Batu et al. 2018)
C1S	c.G1241A;p.R414H; c.C1558T;p.R520C	(Lee et al. 2022)
CFHR4	c.T103C	(Lee et al. 2022)
DNase1L3	c.289_290delAC/p.Thr97Ilefs*2	(Batu et al. 2018)
DNase1L3	c.G764A	(Lee et al. 2022)
DNase1	c.G370A;p.E124K	(Lee et al. 2022)
DNase1	p.Gln244Arg	(Shin et al. 2004)
DNase1	p.Gly127Arg; p.Pro154Ala	(Almlöf et al. 2019)
IFIH1	p.Arg77Trp	(Gitlin et al. 2006)
SAMHD1	c.1423G>A	(Hong et al. 2022)
SLC7A7	c.250G>A(p.V84I) c.625+1G>A	(Liu et al. 2022)
TMEM173	p.Gly166Glu	(König et al. 2017)
TREX1	p.Asp200Asn; pAsp18Asn	(Lehtinen et al. 2008)
TREX1	c.292_293 ins A; p.Cys99Met	(Lee et al. 2022)

Therapy for SLE

In recent times, the SLE treatment has moved forward by using of hydroxychloroquine (HCQ), glucocorticoid steroids, and immunosuppressive drugs. HCQ is an antimalarial compound with the ability to reduce antigen loading in lysosomes and to inhibit interferon activation (Dima et al. 2022). In SLE patients the HCQ was well tolerated, improved life expectancy (Shinjo et al. 2010), decreased thrombosis risk (Petri et al. 2021), and had positive effects on skin disease (Shipman et al. 2020). Using the HCQ early it has been shown to serve as a reverse inflammatory cytokine in the SLE patients (Lambers et al. 2021). Other compounds used for SLE treatment are glucocorticoids, with prednisone at amount 5–10 mg, for mild SLE cases, in the serve cases the amount must be higher up to 0.5–1 mg/kg prednisone (Illei et al. 2001).

Recent therapy for SLE

Belimumab (BEL) is a human immunoglobulin monoclonal antibody having the ability to inhibit binding of soluble B-lymphocyte stimulator to B cells and decrease the B cell survival. BEL was approved by FDA and EMA for treatment of SLE patients. It is available as i.v. infusion or subcutaneous injection. In phase III BEL used additional to standard therapy was very effective and reduced incidence and severity of flares (Blair and Duggan 2018; Lazar and Kahlenberg 2023). There was no indication adverse side effects in SLE patients (Singh et al. 2021), and even. Recently, the efficacy of renal response was good (Furie et al. 2020).

Rituximab (RTX) is a chimeric mono-antibody targeting in B-cell the CD20. The treatment of SLE including lupus nephritis patients gave good result (Leandro et al. 2005; Lu et al. 2009; Beckwith and Lightstone 2014).

Anifrolumab is a human mono-antibody targeting interferon receptor type I. Intravenous application of anifrolumab at 30mg showed 16% better achieving composite endpoints of disease activity response and oral corticosteroid reduction (Tanaka and Tummala 2021).

Voclosporin (VSC) was approved by the FDA for treatment of lupus nephritis to inhibit calcineurine. VSC is

given in combination with immunosuppressive agents (Rovin et al. 2019).

Trichostatin A (TSA) inhibits HDAC (histone deacetylase). It is able to suppress INFα production (Zhao et al. 2010b).

Suberoylanilide hydroxamic acid (SAHA) is also a HDAC inhibitor and can improve renal symptoms and proteinuria. It is used in serve lupus glomerulonephritis, downregulates NO (nitric oxide), and induces NO synthase, IL-6 and TNF-α (Zhao et al. 2010b).

Givinostat (ITF2357), another HDAC inhibitor, is applied as anti-inflammatory, anti-angiogenic, and anti-neoplastic substance. It downregulates autoantibody production and inhibits Th17 differentiation (Glauben et al. 2014).

Vitamin D supplementation is helpful in SLE-patients as vitamin insufficiency and deficiencies are wide spread here. lack of vitamin D is correlated with higher level of fatigue, and increased risk of thrombosis (Lazar and Kahlenberg 2023). Intense dose of 7.5 mg as an initial dose followed by 1.25 mg/months is recommended to increase in serum vitamin D level (Andreoli et al. 2015).

Vitamin E supplementation in SLE is rarely reported. Decreased vitamin E levels are documented in SLE patients (0.64+/-0.09 mg/dl) compared with normal control (0.80+/-0.21 mg/dl) (Comstock et al. 1997). Oral administration of vitamin E (150–300 mg/day) has been shown to be advantageous in SLE patients (Maeshima et al. 2007). Other studies reported that vitamin E supplementation decreases oxidative stress, secretion of inflammatory cytokine, and expression of MHC (major histocompatibility complex) class 2 (Hsieh and Lin 2005).

Vitamin A supplementation is suggested to be used as 5–10 mg/kg orally, as it reduced dermal thickness in this SLE mouse model (Ikeda et al. 2005). It plays a pivotal role for the immune system, and in the function of many genes (Liao et al. 2015). Daily administration of vitamin A at 100,000 U enhanced antibody-dependent cellular cytotoxicity, natural killer cell and IL-2 activities in patients with SLE (Vien et al. 1988).

Vitamin B supplementation seems to be indicated as several studies have reported low levels of vitamin B in SLE patients. Vitamin B2 (riboflavin) deficiency was present in 88% of SLE patients (Molad et al. 1990; Minami et al. 2011; Islam et al. 2020). Intake of vitamin B6 (pyridoxine) (1.7 mg/day) reduced the risk of active SLE (Minami et al. 2011).

Vitamin C supplementation (109.99 mg/day) was significantly inversely associated with a risk of developing active SLE (Minami et al. 2003) (Table 2).

Table 2. The drugs and vitamin compound used in the clinical practice of SLE patients.

Drugs	Dosage	References
Anifrolumab	300 mg every 4 weeks for 48 weeks	(Morand et al. 2020)
Azathioprine	5 mg/kg day orally	(Trindade et al. 2021)
Belimumab	10 mg/kg every 4 weeks, IV	(Trindade et al. 2021)
Methotrexate	15-20 mg/m^2 orally or subcutaneous	(Trindade et al. 2021)
Rituximab	750 mg/m^2 or 375 mg/m^2 with interval of 7 days, IV	(Trindade et al. 2021)
Vitamin D	7.5 mg	(Andreoli et al. 2015)
Vitamin E	150-300 mg/day	(Maeshima et al. 2007)
Vitamin A	5-10 mg/kg g	(Ikeda et al. 2005)
Vitamin B6	1.7 mg/kg	(Minami et al. 2011)
Voclosporin	Voclosporin 23.7 mg BID for 7 days + 2 g/day MMF	(Van Gelder et al. 2022)

Conclusion

SLE is a typical multigenic disorder, which may be the result of multiple genetic alterations and environmental factors, including epigenomic dysregulation. To understand SLE etiology better further intense studies specifically of complement system and genes involved in SLE-development are necessary. In addition, epigenetics and clinical subtypes SLE like neuropsychiatric systemic lupus erythematosus (NPSLE), atypical hemolytic uremic syndrome (aHUS), or active lupus nephritis need to be considered, it must be clarified, as the latter may be caused in parts be identical genes, if they are indeed different diseases or only variants of a disease (group).

Due to multiple causative genes SLE diagnostics must be implemented based on of genome-wide association studies (GWAS). It has to be seen if GWAS studies can be responsibly replaced at a certain point by panel diagnostics.

Concerning therapies, it is unlikely that gene therapy will be more than just helpful in exceptional cases (Nelson et al. 2015). Development of drugs with positive influence on patients' symptoms seem to be most promising for now. Effective strategies to harmonize personalized therapy and social environment may have for longer times the hugest impact on quality life for SLE patients.

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