 DOI: https://doi.org/10.5114/ceji.2018.77875

Systemic lupus erythematosus and glycation process

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Abstract

Systemic lupus erythematosus (SLE) is a disease of unclear causes, which leads to major immunological disorders. It is characterized by an abnormal immune system activity resulting in the production of autoantibodies. In patients, antibodies targeting normal nuclear components, double-stranded DNA (dsDNA), and phospholipids (cardiolipin) can be detected. The inflammatory process occurs in various tissues and organs, damaging their functions and structure. Disease's course includes stages of acute symptoms and remissions, and there is no known cure. Pathogenesis and biochemical pathways accompanying systemic lupus erythematosus are widely studied, as existing medication can only bring temporary relief to patients. The recent findings suggest that occurrence of SLE depends on interactions between genetic background of the disease and environmental risk factors such as exposure to tobacco smoke, chemical factors, and hormonal therapy. In the addition, chronic inflammation accompanying SLE disturbs oxidative/antioxidative balance. These processes are linked to intensified advanced glycation end products (AGEs) formation, thus level of AGEs themselves and their receptors (RAGE, sRAGE) are gaining researches attention.

Key words: *systemic lupus erythematosus (SLE), sRAGE, advanced glycation, advanced glycation end products, smoking, AGEs.*

(Centr Eur J Immunol 2020; 45 (1): 93-98)

Epidemiology

The prevalence of lupus varies worldwide, with a noticeable increasing tendency. It might be caused by recognition of new, mild forms of SLE and more accurate diagnostic methods. This tendency is fortunately accompanied by an improvement in survival of affected patients. What draws attention, is the high prevalence of SLE in Italy, Spain, Martinique, and among Afro-Caribbean population of United Kingdom. It is supposed that west Africa women are affected by higher genetic risk of developing SLE [1].

Usually, the disease appears between the ages of 16 to 55-years-old (2/3 of cases) [2], but there is also juvenile or childhood SLE (cSLE) distinguished. A 20% of SLE cases starts before the age of 19, which is often linked to a poor prognosis [3].

Characteristic features of systemic lupus erythematosus

Differential diagnosis of SLE is difficult, with multiple similar disorders that have to be excluded to administer a proper treatment. Therefore, the American College of Rheumatology developed diagnosis criteria, and a diagnosis is confirmed if at least four of them are fulfilled. These criteria can be briefly characterized as follow:

- malar rash,
- discord rash,
- photosensitivity,
- oral or nasopharyngeal ulcerations,
- nonerosive arthritis involving at least 2 joints,
- pleuritis or pericarditis,
- renal disorders manifesting as persistent proteinuria or cellular casts in urine,
- neurologic disorders such as seizures or psychosis,
- hematologic disorders: hemolytic anemia or thrombocytopenia or leucopenia (≥ 2 occasions) or lymphopenia (≥ 2 occasions),
- immunologic disorders: anti-DNA, anti-Sm, or antiphospholipid antibodies presence [4].

These above mentioned symptoms, followed by fatigue, depression, weight loss, and hair loss, are undoubtedly uncomfortable or even life-threatening for patients. Their quality of life is lowered and the disease affects their social life [1, 2].

The activity of disease and damage it causes is measured by the British Isles Lupus Assessment Group

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Submitted: 24.01.2018; Accepted: 23.02.2019

(BILAG) index and systemic lupus erythematosus disease activity index (SLEDAI) [5, 6].

SLE is undeniably associated with serious renal disorders and is a source of lupus nephritis development. The disease can also affect central nervous system. The autoantibodies can bind to murine and human N-methyl-D-aspartate receptors, leading to neurons apoptosis. The damage causes a wide range of symptoms. Unfortunately, methods of monitoring lupus in central nervous system are insufficient [1].

Furthermore, SLE manifests in cardiovascular system due to intensified atherosclerosis. A higher prevalence of cardiovascular disease is observed among lupus patients [1, 7]. De Leeuw *et al.* discovered a positive correlation between skin accumulation of advanced glycation products and intima-media thickness (its value is an indicator of atherosclerosis). Glycation process is therefore probably linked to acceleration of changes occurring in SLE patients' blood vessels [8]. Therefore, SLE can be described as a risk factor in cardiovascular disorders. Additionally, SLE patients are at higher risk of non-Hodgkin lymphoma development [1].

Risk factors

Recent findings suggest that occurrence of SLE depends on interactions between environmental risk factors and genetic background of the disease. Epigenetic modifications of genes are likely to be involved [9].

Systemic lupus erythematosus is 6-10 times more common among females than males, usually affecting women during childbearing age [2, 9]. This phenomenon is believed to be associated with female sex hormones activity and X chromosome (even the inactive one) [1, 9]. The change in levels of dehydroepiandrosterone, estradiol, prolactin, and testosterone was discovered in women with SLE [9]. It was observed that hormone replacement therapy (HRT) and the use of oral contraceptive hormones influenced higher risk of SLE. However, studies results have been ambiguous regarding the connection of exogenous estrogen usage with the presence of SLE and symptoms relapses (flares) [1, 9]. A link between early menarche, early (or surgical) menopause, endometriosis, and increased risk of SLE also suggests important role of estrogen in pathogenesis [9, 10]. Drugs intake may cause drug-induced lupus erythematosus (DILE). There are over one hundred drugs known to induce lupus such as hydralazine and D penicillamine [1, 2, 10].

Other chemical factors that induce SLE are mercury, silica, organic solvents, particulate matter air pollution, petroleum, phthalates, and pesticides, which pose a risk for agricultural workers and farmlands inhabitants [1, 9, 10]. Antinuclear antibodies might be developed after exposure to asbestos [9]. Organochlorines and trichloroethylene are responsible for intensified presence of disease symptoms in subjects who already suffer from SLE [9].

Widely recognized environmental factor that triggers SLE symptoms is ultraviolet (UV) radiation. Usually, skin manifestation of lupus appears within 24 hours after the exposure [1, 2, 10]. It is recommended for SLE patients to supplement vitamin D and avoid direct sunlight [10].

Another factor that is linked to SLE is the Epstein-Barr virus (EBV). While majority of human population is infected but will not develop lupus, the amount of infected B cells is higher in SLE patients compared to controls [1]. Vaccination effect on SLE presence is also discussed, and while there are case reports suggesting such a link, epidemiological studies have not confirmed it [9].

As diet can influence oxidative status, methyl group intake, and inflammation in organisms, foods and drinks consumed are investigated as additional SLE factors. Black tee consumption might increase the risk of SLE, while in patients with already diagnosed SLE, low intake of omega-3 accompanied by high intake of carbohydrate can trigger disease activity [9].

Freemer *et al.* demonstrated a relation between smoking status and presence of SLE diagnostic marker, dsDNA autoantibodies. Patients who never smoked and former smokers are less likely to be dsDNA seropositive than current smokers [9, 11]. The clear relation between oxidative stress and systemic lupus erythematosus signalizes how important smoking is as the risk factor of the disease. Tobacco use increases the oxidative stress in the organism and damages DNA, which can be observed through rise in DNA ROS (reactive oxygen species) damage marker level, 8-hydroxydeoxyguanosine. The modified DNA can initiate an immunologic response [11].

On the contrary, moderate alcohol intake is accompanied by lowered risk of SLE presence. The protective influence of alcoholic drinks might be caused by their content of substances that counteract inflammation. Most positive effects are achieved with wine consumption, which is known for resveratrol content [9].

Genetic background

Several genes may be important in SLE development and pathogenesis. This include overexpression of multiple unique isoforms of common interferon regulatory factor 5 (IRF5) and the type I interferon pathway. Another genetic factor is a single nucleotide polymorphism (SNP) discovered in the programmed cell death 1 gene (PDCD1). This small inheritable change in nucleotides is associated with SLE in patients [1].

Polymorphisms of C-reactive protein (CRP) also drive researchers attention. SLE, while being an autoimmune disease, does not lead to an increased level of CRP. There are two haplotypes of CRP, 2 and 4, which lower the ex-

pression of CRP. What is more, CRP 4 haplotype is linked to SLE's typical feature: autoantibodies production [1].

Pathogenesis

SLE is a disease characterized by multifactorial etiology, where environmental stimuli might influence epigenetic changes or induce SLE because of existing genetic susceptibility. Multiple defects (e.g. in T cells signaling pathways) were described in immunological system of patients [1].

Autoantibodies (e.g. anti-DNA, anti-La, antinuclear, antiphospholipid, anti-RNP, anti-Ro, anti-Sm) appear years before the development of the disease is recognizable. However, anti-DNA, anti-Sm, and anti-RNP may appear shortly before the diagnosis [1]. The key element of pathogenesis is immune complexes (IC) formation. They are deposited in skin and kidneys, damaging their functions [12].

What causes the development of autoantibodies is still under study. A defect of apoptotic cells clearance may cause intracellular compounds being left to be collected by macrophages. These internal cell elements might be recognized as autoantigens and later presented to T and B cells. This triggers an immune response against own tissues [1]. Another cause of autoaggession might be a molecular mimicry, where endogenous and exogenous antigens similarity triggers immunological response [9, 13]. When such a mimicry occurs, epitopes can amplify and diversify through process described as "epitope spreading" to form a wide range of autoantibodies [13].

Widely recognized implication of chronic inflammation is the state of increased oxidative stress and distorted oxidative/antioxidative balance [14].

Advanced glycation products

Both in living organisms and foodstuffs, a spontaneous glycation of proteins occurs. Reaction of reducing sugars and amino acids is called the Maillard reaction, and causes formation of various Maillard reaction products (MRPs). In vivo sugars can similarly react with proteins, with lipids, and nucleic acids, to produce advanced glycation end products (AGEs). These compounds are more abundant in inflamed tissues, and inflammatory process is associated with oxidative stress. Reference data show a link between oxidative stress, AGEs formation, and autoimmune diseases such as SLE [7].

Advanced glycation end products examined in patients included pentosidine, carboxymethyllysine (CML), and its homologue carboxyethyllysine (CEL), which are presented in Table 1 [7, 15]. AGEs are markers of glycation occurrence in organisms. They can affect tissues both structurally (e.g. through cross-linking with proteins they damage extracellular matrix) and functionally (e.g. due to interactions with receptors) [7].

Accumulation of AGEs in skin of SLE patients was confirmed [7, 8]. There is also a positive correlation between AGEs accumulation and duration of the disease, but skin autofluorescence does not correlate with antiphospholipid autoantibodies presence [8]. The increased presence of AGEs in blood of patients is still discussed. Nienhuis *et al.* indicated that there were no significant differences between SLE patients and controls in blood plasma levels of two specific AGEs such as CML and CEL. AGEs levels did not correlate with CRP levels. Authors suggested that advanced glycation end products were mostly accumulated in tissues rather than in plasma proteins [7]. This point of view is supported by study conducted by Vytášek *et al.* Authors observed no significant difference between healthy controls and SLE patients' blood levels of CEL and antigen binding to mononuclear antibody 103-E3 (unknown product of protein and ribose reaction) [16]. Also, pentosidine level was not increased in blood of SLE patients examined as a group by Rodríguez-García *et al.* Noteworthy, some patients showed remarkably high pentosidine levels and in all subjects, fructosamine serum level was increased [16]. However, data proving an increase in AGEs of blood plasma were obtained by Der-Yuan Chen *et al.* Authors evaluated levels of CML and pentosidine,

Table 1. Available data on levels of various AGEs (advanced glycation products) in SLE (systemic lupus erythematosus) patients compared to controls: total AGEs level, pentosidine, CML (carboxymethyllysine), CEL (carboxyethyllysine), unknown product of protein and ribose reaction

Examined compounds	Results (compared to control)	Examined material	Reference
AGEs	Increased in SLE patients	Skin (autofluorescence)	7, 8
	Increased in SLE patients with active disease Positive correlation with disease activity	Blood plasma	15
Pentosidine	No difference	Blood serum	17
CML	No difference	Blood plasma	7
CEL	No difference	Blood plasma	7
	No difference	Blood serum	16
Protein and ribose reaction product	No difference	Blood serum	16

and noted a positive correlation between SLEDAI score and AGEs concentration [15].

Receptor for advanced glycation end products

Receptor for AGEs comes in transmembrane (RAGE) and circulating (soluble – sRAGE; endogenous secretory – esRAGE) forms. It is a glycoprotein that belongs to immunoglobulin super family and it binds with multiple ligands, including advanced glycation end products, high mobility group protein B1 (HMGB-1), β-amyloid, amphoterin, and S100/calgranulin family members [7, 12, 18].

If the HMGB-1 is not bound by sRAGE, an interaction between RAGE and HMGB-1 occurs easier, which results in pro-inflammatory response [12].

SLE activity correlates with S100A8/A9 level in serum. S100A8/A9 belongs to previously mentioned S100 proteins family that exhibits various functions and may be excreted by cells during inflammation. The level of S100A12 does not differ between SLE patients and healthy subjects. However, levels of S100A8/A9 and S100A12 correlate with cardiovascular risk in SLE patients [12, 19, 20].

The ligands seems to be mostly related to inflammation, hyperglycation, and cell stress processes; the expression of receptor itself is directly related to inflammation [21]. S100A12 induces lymphocytes proliferation and cytokine release through binding with RAGE and it causes the immune response to amplify. S100/calgranulin and RAGE levels are increased in inflammation areas in laboratory animals. The inflammation symptoms can be attenuated by administration of sRAGE or antibodies against S100/calgranulin and RAGE [18].

It was also observed that RAGE receptor can bind non-specifically with nucleic acids and compounds with sugar-phosphate backbones lacking nucleotide bases through electrostatic attraction. It plays a key role in self-tolerance to extracellular DNA and RNA. It promotes intracellular uptake and allows TLR9 (Toll-like receptor 9; nucleic acid immune receptor) to interact with nucleic acids. Membrane RAGE deficiency prevents the immune response to DNA. RAGE is expressed by endothelial and vascular smooth muscle cells, macrophages, neutrophils, and T cells. Notably, RAGE is highly expressed in lung epithelia, so the role of tobacco smoke exposure and silica exposure seems to be even more clear and important in SLE development [21]. sRAGE can also bind to the RAGE, blocking its functions [12].

Binding AGEs to RAGE leads to enhanced expression of molecules involved in inflammation, adhesion, and RAGE itself. Also, the expression of RAGE is enhanced by TNF-α (tumor necrosis factor α). The soluble form is believed to be a decoy receptor that prevents interactions between transmembrane form and AGEs. sRAGE seems to have a protective effects on organisms, with low levels of the receptor increasing the risk of all-cause death. It remains unknown if SLE patients have autoantibodies against RAGE and sRAGE, but the sRAGE functions are insufficient in these subjects [7]. A decreased amount of

Table 2. Available data on levels of sRAGE in SLE patients compared to healthy controls

Observations	Material examined	Reference
Increased level of sRAGE in SLE patients compared to healthy controls Positive correlation with anti-dsDNA antibodies' level	Blood serum	7
Increased level of sRAGE in SLE patients compared to healthy controls	Blood plasma	22
Decreased level of sRAGE in SLE patients compared to healthy controls	Blood serum Synovial fluid	3
Decreased level of sRAGE in SLE patients compared to healthy controls Higher level of sRAGE in SLE patients who undergone long-term treatment compared to patients treated shorter than a month No difference of sRAGE level between treated and untreated SLE patients Increased level of sRAGE in SLE patients with serositis and cutaneous manifestation of the disease	Blood plasma	12
Decreased level of sRAGE in SLE patients compared to healthy controls Higher level of sRAGE in SLE patients who undergone long-term treatment compared to patients treated shorter than a month No difference of sRAGE level between treated and untreated SLE patients Increased level of sRAGE in SLE patients with rash and serositis	Blood plasma	20
Decreased level of sRAGE in SLE patients compared to healthy controls No correlation between sRAGE level and disease activity	Blood plasma	24
Decreased level of sRAGE in SLE patients compared to healthy controls Negative correlation between sRAGE level and SLEDAI score	Blood plasma	15
Decreased level of sRAGE in SLE patients with active disease compared to healthy controls	Blood plasma	23

sRAGE was detected in Sjogren's syndrome, showing a possible link between SLE and visual disturbance [12].

Contradictory data about the level of sRAGE in SLE patients are summarized in Table 2. Nienhuis *et al.* reported that the concentration of sRAGE is increased in lupus patients serum [7]. Also, Nashaat Abou-Raya *et al.* discovered higher concentration of sRAGE in blood plasma of lupus patients. In their study, sRAGE levels positively correlated with SLEDAI score [22].

On the other hand, more references describe decrease of sRAGE level in SLE patients' blood plasma compared to healthy controls [12, 15, 20]. Similar findings apply to cSLE patients [3]. Yu *et al.* noted a decrease in plasma sRAGE level in patients with active SLE and at the same time, an increased level of full-length form of RAGE receptor present on monocytes' surface [23]. It is believed that enlarged amount of receptor's ligands in patients' blood leads to intensified consumption of sRAGE. Of note, treated and untreated SLE patients have similar levels of sRAGE, and subjects who received long-term medication have a higher concentration of the soluble receptor than subjects who undergo short-term treatment (< 1 month). What is more, short administration of medication causes a significant fall in the level of sRAGE, compared to the control and long-term treated subjects. Authors of both studies suggest the receptor has a different role in initial and progressed stage of the disease [12, 20]. A study focused on patients displaying antiphospholipid antibodies (APA) or antiphospholipid antibody syndrome (APS) involved SLE patients. Both groups, SLE+APA and SLE+APS patients showed a decrease of sRAGE level in blood plasma compared to healthy controls. What is more, subjects diagnosed with APS, but without lupus, had the level of sRAGE no different from control [24].

The level of the soluble receptor displays a relation with some blood parameters including leucocytes and lymphocytes amounts, neutrophils and monocytes amounts, and C4 complement component [3, 12, 20]. This fact suggest the soluble receptor is associated with inflammation and leucocytes recruitment [12]. However, the level of the soluble receptor may not correlate with autoantibodies presence [20].

RAGE and sRAGE have ability to interact with themselves and multiple ligands. Also, their ligands can interact with one another [21]. Receptors and ligands are directly related to immunological response, infection, and protein glycation. These processes increase oxidative stress in organism. Oxidation and RAGE actions with additional sRAGE deficiency can cause formation of neoepitopes, which induce formation of auto-antibodies.

Conclusions

Although diagnostic criteria of systematic lupus erythematosus are defined and many factors of the pathophysiology of SLE have been recognized, there are still no definite premises for the proper causes of this disease. Some of advanced glycation end products correlated with the progression of this disease, that is why further researches are necessary to determine their role in the pathogenesis of SLE.

Acknowledgments

The work was supported by the KNW-1-038/K/7/0 project of the Medical University of Silesia in Katowice.

The authors declare no conflict of interest.

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