

BIOMARKERS IN SYSTEMIC LUPUS ERYTHEMATODES

V. Reshkova, S. Monov

Rheumatology Clinic, Multiprofile University Hospital for Active Treatment, "Sv. Ivan Rilski"
Medical University – Sofia

Abstract. A biomarker is defined as a genetic, biological, biochemical or molecular event, whose alterations correlate with the pathogenesis and/or manifestations of a disease and can be evaluated qualitatively and/or quantitatively in laboratories. Biomarkers are used for diagnosis, assessment of activity and better understanding of the pathogenesis of systemic lupus erythematoses (SLE). Biomarkers in SLE are conditionally subdivided into markers of genetic susceptibility, markers of diagnosis and markers of disease activity. Recent genetic studies of SLE have focused on correlating SLE (susceptibility, disease spectrum and severity) with polymorphisms of hypothetical candidate genes. These include genes coding for mannose-binding lectin (MBL), cytokines (IL-6, IL-10, IL-21, TNF- α and osteopontin), chemokines (MCP-1), cytokine receptors/antagonists (type II TNF- α receptor and IL-1 receptor antagonist), Fc γ receptors (Fc γ RIIa, Fc γ RIIb, Fc γ RIIIa, and Fc γ RIIIb), IFN α , programmed death protein-1 (PD-1; also known as PDCD-1) and other cell surface receptors (cytotoxic T lymphocyte antigen-4 (CTLA-4) involved in the pathogenesis of SLE. Biomarkers for diagnostic are anti-dsDNA, erythrocyte-bound C4d/Erythrocyte-CR1 and platelet-bound C4d. Markers of disease activity are complement components, cytokines, soluble cytokine receptors IL-2R, TNFR, IL-1Ra, soluble molecules expressed on the cell surface – BLyS (BAFF), CD27, CD154, endothelial dysfunction markers – sICAM, sVCAM, thrombomodulin, circulating endothelial cells, acute-phase proteins – CRP, ferritin. Genetic testing for biomarkers in SLE patients is currently being introduced in the Rheumatology Clinic to "Sv. Ivan Rilski" Multiprofile University Hospital for Active Treatment, Sofia, Bulgaria. Its performance is expected to help solve multiple unmet needs in SLE patients – precise diagnosis, identification and prediction of the timing of disease flares, clinical assessment and adequate treatment approach.

Key words: biomarker, SLE

INTRODUCTION

Systemic lupus erythematoses (SLE) is a chronic, autoimmune, multisystem connective tissue disorder. SLE is most prevalent in females, with a female:male ratio of approximately 9:1 and highest incidence between 20 and 40 years of age [1].

A biomarker is defined as a genetic, biological, biochemical or molecular event, whose alterations correlate with the genetic predisposition, pathogenesis and/or manifestations of a disease and can be evaluated qualitatively and/or quantitatively in laboratories [2, 3].

Genetic susceptibility, diagnosis, disease activity assessment and understanding of the pathogenesis of SLE are likely to require a composite panel of biomarkers that span the gamut of laboratory and clinical features of SLE.

Biomarkers are biological molecules found in blood, urine or tissues in the body. Their detection at specific levels along with other symptoms may be informative regarding the onset, progression and prognosis of SLE. Biomarkers are successfully used

for diagnosis prediction and monitoring of treatment. They also play a critical role in scientific studies and clinical practice [2].

Clinical manifestations of SLE are likely the consequence of a multifaceted, patient-unique autoimmune process, which evolves over the course of disease and is characterized by production of auto-antibodies, immune complex/complement-mediated tissue injury, and vasculopathy [3]. Based on these etiopathogenic features of SLE, SLE biomarkers are categorized in different classes.

BIOMARKERS FOR SLE SUSCEPTIBILITY/ GENETIC FACTORS

Pathogenesis and clinical evolution

Genetic factors, either protective or provocative, clearly play a major role in determining whether an individual will develop SLE. The genetic susceptibility is undoubtedly influenced by environmental factors, although these triggers remain poorly identified. Recent searches for "lupus genes," primarily through candidate gene-association studies and

single nucleotide polymorphism (SNP) association scans, have clearly demonstrated that SLE is a disease with complex genetic inheritance and no single causative gene. The regulation of the thresholds of autoreactivity and disease onset probably involves multiple genes (Table 1).

Initial genetic studies focused on genes that are historically considered to be key components of immune responses, such as major histocompatibility complex (MHC) genes. Specific alleles of MHC (called human leukocyte antigen (HLA) in humans) have been found to be associated with SLE in ethnic groups. Recent studies have identified several susceptible loci that harbor many candidate genes with known immune-related functions.

Table 1. Biomarkers for SLE susceptibility

Biomarkers for SLE susceptibility	Complement (C1q, C2, C4) deficiency
	FcyRIIa, FcyRIIb, FcyRIIIa polymorphism
	Low copy number of FcyRIIb gene
	CTLA-4 polymorphism
	MBL polymorphism
	MHC alleles (DRB1, A1, B8)
	IL-10, IL-6, TNF α polymorphism
	TNFR, IL-1Ra polymorphism
	PD-1 polymorphism
	IRF5 polymorphism
	PTPN22 polymorphism
	STAT4 polymorphism

Complement deficiency

The genes that most warrant being referred to as “lupus genes” are those encoding the components of the classical complement pathway. Complete deficiency of one of the early components, C1q, C1r, C1s, C4, or C2, is a strong, albeit rare, risk factor for developing SLE and/or lupus-like diseases.

Much more common is the partial deficiency of these complement genes, often reflected by varying low levels of circulating complement protein (e.g., C4) [4, 5]. Partial C4 deficiency, particularly C4A deficiency, occurs in 30-40% of patients with SLE and has been associated with lupus susceptibility [4, 5].

FcyRIIa, FcyRIIb, FcyRIIIa polymorphism

Fanciulli, Atiman et al. have recently investigated the CNV (copy number variation) of the FcyRIIb gene in patients from the United Kingdom (501 SLE patients with or without nephritis; 90 Wegener's granulomatosis (WG); 76 microscopic polyangiitis (MPA); compared with 862 healthy controls) and

France (77 WG versus 181 healthy controls).⁶ They reported that low CNV of the FcyRIIb gene (< 2 copies) was significantly associated with increased susceptibility to SLE ($p = 0.001$), MPA ($p = 0.013$) or WG ($p = 0.015$) [6].

Furthermore, the frequency of complete deficiency of FcyRIIb (zero copy) was significantly increased in patients with these autoimmune diseases (2%; 21 patients with SLE, one with WG, and one with MPA) as compared to healthy controls (0.1%). This finding suggests that complete FcyRIIb deficiency renders an individual at considerably increased risk for autoimmune diseases, particularly SLE.

Protein tyrosine phosphatase N22 (PTPN22)

PTPN22 regulates the T-cell receptor (TCR) signaling in memory and is strongly associated with SLE in Caucasian patients. PTPN22 C1858T polymorphism was found to be a risk factor for SLE, especially in North American patients with European ancestry and in patients with SLE and concurrent autoimmune thyroid disease. Studies have demonstrated significant associations of the PTPN22 C1858T polymorphism with other autoimmune diseases including rheumatoid arthritis (RA), type 1 diabetes mellitus (DM), and dermatomyositis (DM) [6].

INTERFERON REGULATORY FACTOR 5 (IRF5)

During the recent years it has been universally acknowledged that some SLE patients are characterized by increased expression of type I IFN α -regulated genes. A large number of human genes (up to 10%) are controlled by type I IFN. There is substantial overlap between genes regulated by type I IFN and type 2 IFN and they are deemed to contribute to gene expression regulation in SLE patients [7].

Gene expression profiling of peripheral blood mononuclear cells in SLE patients has revealed a striking pattern of increased expression of IFN-inducible genes (subsequently termed “IFN signature”) in a subset of SLE patients. Furthermore, it was determined that this IFN gene expression „signature“ serves as a predictive marker for more severe disease, such as cerebritis, nephritis, and hematological involvement in those patients. It can also provide insights into some unsolved questions in SLE patients in Bulgaria such as whether changes in the IFN signature genes expression correlate with clinical outcomes:

- disease flares
- new organ involvement and
- response to treatment in SLE patients? [7].

Initially, a Swedish research group screened single nucleotide polymorphisms (SNPs) in 13 genes from the IFN α pathway in 679 Northern European (Swedish, Finnish, and Icelandic) patients with SLE, 798 unaffected family members, and 438 healthy controls [8, 9]. They discovered that several SNPs in the tyrosine kinase 2 (TYK2) and IRF5 genes displayed strong linkage and association with SLE. This team and others have subsequently confirmed that a common IRF5 haplotype, which is characterized by a SNP (rs2004640) that leads to increased expression of IRF5, is an important genetic risk factor for SLE in different ethnic groups [8, 9]. Additional IRF5 SNPs/haplotypes have recently been identified and shown to be either risk or protective genetic factors for SLE [9, 10].

Signal transduction and activator of transcription 4 (STAT4)

Another immune function-related gene is the signal transduction and activator of transcription 4 (STAT4) gene. The STAT 4 gene encodes a transcription factor involved in the signaling pathways of several cytokines, including IL-12, IL-23, and type 1 IFN (such as IFN α). An international team of investigators has identified by screening a haplotype marked by SNP rs7574865 within the third intron of the STAT4 gene [10]. The haplotype marked by rs7574865 in the STAT4 gene was found to be significantly associated with increased risk for both SLE (OR = 1.55) and RA (OR = 1.32) and other autoimmune diseases including IBD and type 1 DM [10].

Other biomarkers for SLE susceptibility that may provide useful information are:

- cytokines (e.g. IL-6, IL-10, IL-15),
- soluble cytokine receptors (SIL-2 receptor),
- thrombomodulin.

In conclusion, the field of SLE genetics holds great promise. Practical and universal genetic biomarkers for SLE susceptibility still await further search and validation. With the unprecedented advance in the complex genetics of SLE worldwide, there is now more than ever a need for accurate phenotyping/subsetting of SLE patients according to patient-unique conditions such as ethnic origins, clinical manifestations, and living environment. This approach is likely to help elucidate the specific roles of individual lupus genes that have been identified in some but not other studies involving widely heterogeneous study cohorts [11].

BIOMARKERS FOR LUPUS DIAGNOSIS

More sensitive and specific biomarkers for lupus diagnosis would also improve efficiency and accuracy of clinical trials (Table 2).

Table 2. Biomarkers for SLE diagnosis

Biomarkers for SLE diagnosis	Anti-dsDNA
	Erythrocyte-bound C4d/Erythrocyte CR1
	Platelet-bound C4d

Once clinical symptoms have developed, prompt diagnosis and proper management of SLE remain great challenges to physicians. Laboratory tests or biomarkers that facilitate early and accurate diagnosis of SLE are essential (Figure 1).

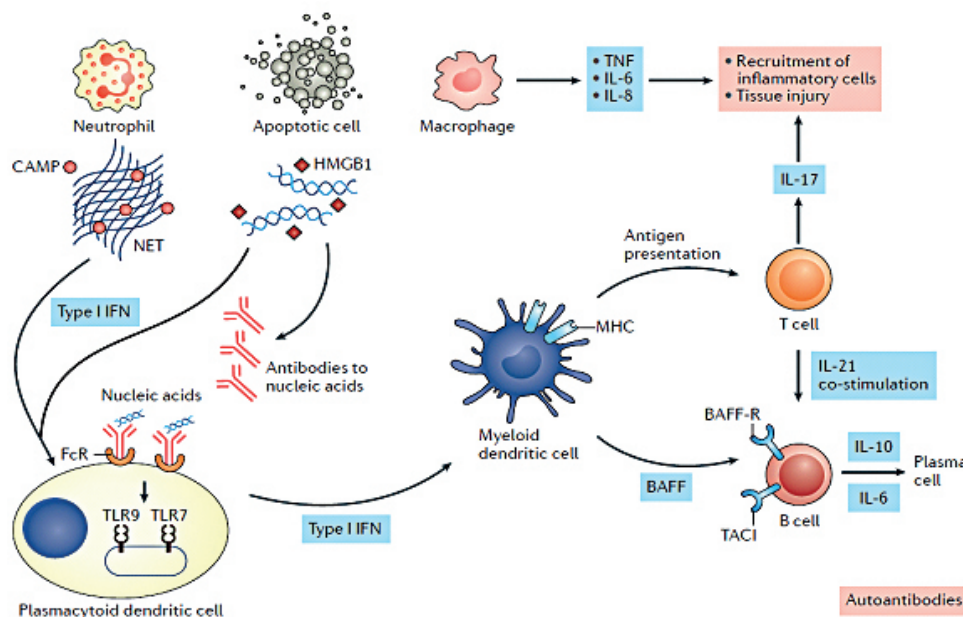


Fig. 1. Immunological pathogenesis of SLE – a way to biomarkers for disease assessment

In search of biomarkers with better specificity and sensitivity for SLE diagnosis, Manzi et al. have suggested abnormal levels of erythrocyte-bound complement activation product C4d (E-C4d) and complement receptor 1 (E-CR1) as candidates [12]. These investigators showed that patients with SLE had significantly higher E-C4d and lower E-CR1 levels than did patients with other diseases or healthy controls. The E-C4d/E-CR1 test was shown to be 81% sensitive and 91% specific for SLE versus healthy controls. These data suggest that simultaneous determination of E-C4d and E-CR1 by flow cytometry may have significant impact on the accuracy and timing of SLE diagnosis [12].

BIOMARKERS FOR SLE ACTIVITY

Traditionally, determination of autoantibodies such as antinuclear antibodies (ANA), anti-extractable nuclear antigen antibodies (e.g., anti-Ro/SSA, anti-La/SSB, anti-snRNP, and anti-Sm), and anti-double stranded DNA (anti-dsDNA) is used in diagnosing and monitoring SLE [11].

Table 3. Biomarkers for SLE activity

Biomarkers for SLE activity	Anti-dsDNA
	Serum complement – C3, C4, C3a, C5a, C3d, C4d, Ba, Bb, sC5b-9
	Serum cytokines levels – IL-6, IL-10, IL-12, IL-15, IL-18, IFN α , IFN γ , TNF α
	Soluble cytokine receptors IL-2R, TNFR, IL-1Ra
	Soluble cell surface molecules – BLyS (BAFF), CD27, CD154
	Endothelial activation markers – sICAM, sVCAM, thrombomodulin, circulating endothelial cells
	Acute phase proteins – CRP, ferritin
	Anti-nucleosome, anti-C1q antibodies
	CD27 plasma cells
	Erythrocyte /Reticulocyte-bound C4d

Currently, disease activity in SLE is often assessed using composite disease activity indices, such as SLE Disease Activity Index (SLEDAI), Systemic Lupus Activity Measure (SLAM), European Consensus Lupus Activity Measure (ECLAM), and British Isles Lupus Assessment Group Index (BILAG), which comprise a variety of clinical and laboratory parameters (Table 3) [11]. These instruments require appropriate training to interpret and complete accurately, making universal application more challenging. Consequently, the value of conventional tests measuring serum complement and autoantibodies as markers of SLE disease activity is being revisited.

IFN- α and IFN-inducible gene profiles

During the recent years it has been universally acknowledged that some SLE patients are characterized by increased expression of type I IFN-regulated genes. A large number of human genes (up to 10%) are controlled by type I IFN. There is substantial overlap between genes regulated by type I IFN and type 2 IFN and they are deemed to contribute to gene expression regulation in SLE patients [13].

An investigation method with 5000-fold increase of sensitivity, used in 2017, has found significantly elevated serum levels of circulating IFN- α in SLE patients. Gene expression profiling of peripheral blood mononuclear cells in SLE patients has revealed a pattern of increased expression of IFN-inducible genes (subsequently termed “IFN signature”). IFN gene expression „signature“ is a predictive marker for more severe disease, such as neurolupus, nephritis, and hematological involvement in those patients. IFN signature (increased expression levels of type IFN-inducible genes) is detected in 70% of adult patients and in 90% of children with SLE. The regulatory effect of IFN is manifested from initiation of immune response to organ involvement in SLE (Figure 2).

A Canadian research group recently investigated the expression levels of selected IFN α -inducible genes, serological variables, and clinical disease activity (as measured by SLEDAI) in 94 SLE patients over a period of 3-12 months. Expression levels of IFN α -inducible genes were found to be significantly elevated and associated with high SLEDAI scores, active lupus nephritis, decreased C3 levels, and positive anti-dsDNA and anti-RNA-binding protein autoantibodies [13].

B-lymphocyte stimulator (BLyS)

B lymphocyte stimulator (also known as BAFF, TALI-1, THANK, or TNFSF13B) is expressed as a transmembrane protein on monocytes, macrophages, and monocyte-derived dendritic cells. A soluble form of BLyS, cleaved from the cell surface by a furin protease, is biologically active and critical for B cell growth and survival. The relationship between BLyS overexpression and SLE has been demonstrated convincingly in humans – approximately 30% of SLE patients had significantly elevated circulating levels of BLyS. Elevated BLyS levels appeared to correlate with increased total IgG and autoantibody (particularly anti-dsDNA) levels, and disease activity (as measured by SLEDAI). Since BLyS is not known to have direct or immediate proinflammatory activities, changes in serum BLyS levels

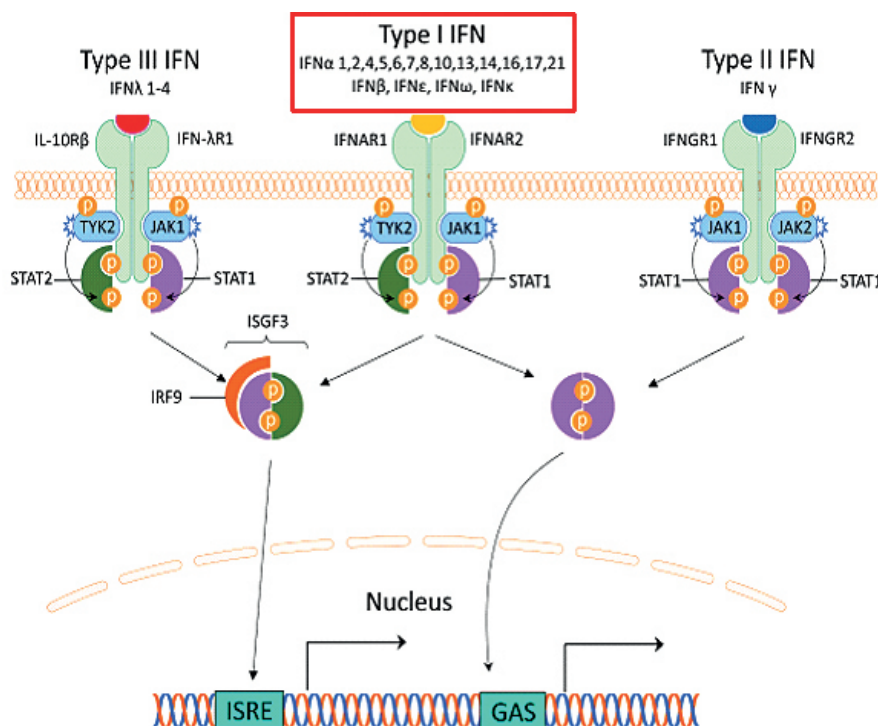


Fig. 2. Mode of action of type I IFN

are unlikely to trigger acute inflammatory reactions and disease manifestations. It is possible that an increase in disease activity may lag behind increases in circulating BLYS levels due to indirect or “delayed” effects of BLYS in the systemic immune-inflammatory reactions of SLE. Multivariate analyses showed that a greater increase in the SELENA-SLEDAI score in the current visit was significantly associated with higher BLYS levels at the previous visit (p

$= 0.0042$). Similarly, a greater increase in the BLYS level from the previous visit was associated with a greater SELENA-SLEDAI score in the subsequent follow-up visit ($p = 0.0007$). These results suggest a “delayed” causative relationship between circulating BLYS levels and SLE disease activity [5, 14]. B lymphocyte stimulator has played a key role in the development of Belimumab, a drug for treatment of SLE (Figure 3).

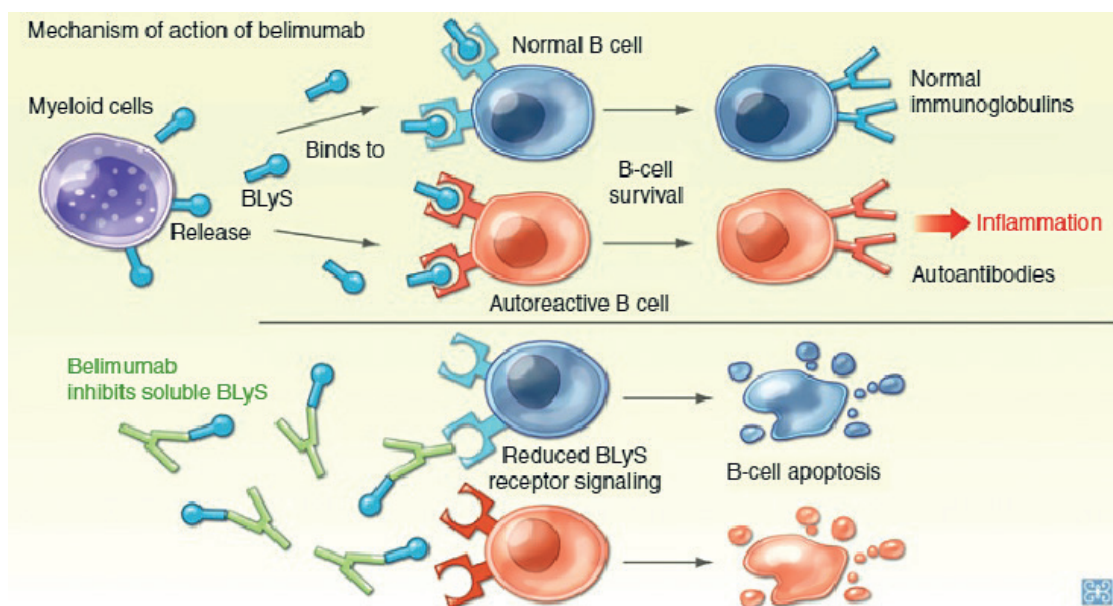


Fig. 3. B lymphocyte stimulator and mode of action of Belimumab

CD27 High plasma cells

B cells play a central role in the pathogenesis of SLE, reflected by an alteration of peripheral B cell homeostasis. The frequency and absolute number of CD19+CD20-CD27 high plasma cells increase dramatically in patients with active disease. What is the role of autoantibody-producing plasma cells in the pathogenesis of SLE?

Jacobi and colleagues conducted a study to investigate whether B cell abnormalities, as reflected by altered homeostasis and phenotypes of peripheral blood B cells may correlate with SLE disease activity. These investigators reported that the number and frequency of CD27 high plasma cells were significantly correlated with disease activity scored by SLEDAI, ECLAM and the titer of anti-dsDNA antibodies. These results suggest that alteration of the B cell subpopulation (namely the increase in CD27high plasma cells) may be a valuable biomarker for monitoring SLE activity [5].

Other soluble biomarkers

In recent years, a number of humoral factors, including cytokines (IL-6, IL-10, IL-16, and IL-18), soluble cytokine receptors (sIL-2 receptor), soluble adhesion molecules (sICAM and sVCAM), acute phase proteins (CRP and ferritin), autoantibodies (anti-nucleosome and anti-CRP), and soluble thrombomodulin, have been investigated for their associations with the activity and severity of SLE [15].

Interleukin 10 (IL-10)

Interleukin 10 (IL-10), the major inducer of type II IFN, has been proposed as a biomarker of disease activity. Among IL-1 family cytokines and receptors, the soluble form of ST2/IL-1 receptor 4 (IL-1R4) has been recently proposed as new biomarker in SLE. The soluble form of the receptor prevents the interaction of IL-33. Soluble IL (sIL)-1R4 levels are increased in active SLE patients, and highly correlated with disease activity index and with anti-dsDNA and anti-C1q antibody levels. When the diagnostic value of sIL-1R4 is directly assessed by means of multivariate analysis, sIL-1R4 contributes to a similar extent as anti-dsDNA and IL-18BP to the identification of patients with active nephritis, and is the most relevant variable in discriminating active from inactive patients [5, 15].

Other important players in the inflammation of affected organs are cell adhesion molecules, which are expressed on vascular endothelium and interact with leucocyte integrins, allowing their extravasation into inflamed tissues.

In lupus nephritis, vascular cell adhesion molecule 1 (VCAM-1) expression is upregulated in glomerular epithelial cells, mesangium, proximal tubular cells; activated leucocyte CAM (ALCAM) is also hyperexpressed on macrophages and glomerular endothelia. Other adhesion molecules that are emerging as biomarkers in lupus nephritis are E-selectin and ICAM that is also detectable in urine by a sensitive and specific rapid assay [5].

Despite the impressive amount of data that have validated novel biomarkers, as summarized in Table 1, experimental work is ongoing in the attempt to discover new biomarkers tools for the diagnosis, staging and management of SLE patients.

The planned introduction of genetic testing for markers of susceptibility and disease activity in SLE patients at the Clinic of Rheumatology to the "Sv. Ivan Rilski" Multiprofile University Hospital for Active Treatment in Sofia is expected to enable prediction and monitoring of the clinical and immunological disease activity, the choice of most appropriate therapy and prediction of the timing of disease flares. Evidence-based testing for SLE biomarkers shall ensure better diagnostic accuracy, prediction of disease risk and proper clinical staging of SLE.

The following arguments are important in this setting:

First, SLE is commonly misdiagnosed, even by experienced rheumatologists. The diagnosis requires interpretation of complex criteria developed by the American College of Rheumatology, as no single test is sufficiently sensitive and specific to be diagnostic.

Second, the course of SLE in a given patient is characterized by unpredictable flares and remissions. Again, there is no laboratory test with reliable capacity to identify or predict the beginning or end of a disease flare.

Third, lack of biomarkers has impeded efforts to evaluate new SLE therapeutics in clinical trials.

Given that SLE is a heterogeneous, complex, multisystem disease, a new drug may have subtle but beneficial effects in perhaps only a subset of patients. Currently, it is difficult, if not impossible, to measure such a clinical response.

SLE is undoubtedly one of the most fitting case studies for systems biology. The greatest challenge in identifying and developing specific biomarkers for SLE is its complex etiopathogenesis and clinical heterogeneity. Moreover, owing to the multifactorial nature of SLE, no unique biomarker is likely to emerge. The rapid progress we are witnessing in

this field will most likely lead to a validated “Lupus Biomarker Panel” that will include assays for individual molecules as well as for “molecular biosignatures”.

The attempt to discover useful biomarkers for SLE has traditionally been conducted based on hypothesis-driven approaches, i.e., to investigate a single or a small number of factors (e.g., genes, autoantibodies, and cytokines) that are thought to be important in the underlying pathophysiologic mechanisms. Advances in high throughput technology during the past decade have opened new avenues to study the complex dynamic disease process in SLE and discover efficient biomarkers for SLE. In this new research arena, several experimental approaches are likely to be the most productive “mines” for lupus biomarkers. Discovery and development of biomarkers can be achieved through two distinct, yet, complementary, approaches. In one approach, attempts to identify potential biomarkers are made based on established cellular and molecular mechanisms of SLE. In the other approach, the “survey” or “scan” search of potential biomarkers is driven by novel, high-throughput technology (e.g., genomics and proteomics) [15].

No studies of biomarkers for genetic susceptibility and correlation with SLE development and prognosis have been performed in Bulgaria. Our intention is to conduct a study for determining the relationship between the presence of biomarkers for genetic susceptibility to SLE – Interleukin-1 – Receptor Antagonist Human, Human IL-6, Human IL-10, Human IL-15, Human sIL-2R, Thrombomodulin (CD141) Human, Anti-C1-q and the course of clinical evolution of the disease by comparing biomarker values with those in a control group of healthy individuals.

There are also no studies in Bulgaria on biomarkers for the activity, evolution and prognosis of SLE. The Clinic of Rheumatology plans to conduct a study for biomarkers of SLE clinical activity – Human IFN-gamma, Human IFN-alpha, Human sICAM-1, Human sVCAM-1, Human sIL-2R, TNF-R. The aim of the study is to determine a connection between biomarkers and the clinical course of the disease through comparison of biomarker values with a control group of healthy individuals. The expected results will be highly valuable for prevention of severe organ impairment and reduction of disability and mortality in SLE patients in Bulgaria.

CONCLUSIONS

1. Measurement of autoantibodies and complement are currently assays of choice in daily clinical practice. The results of autoantibody/complement tests are likely most informative if interpreted in a “personalized” manner, in the context of the long-term disease course in a given patient.

2. Discovery and development of biomarkers can be achieved through two distinct, yet, complementary, approaches. In one approach, attempts to identify potential biomarkers are made based on established cellular and molecular mechanisms of SLE. In the other approach, the “survey” or “scan” search of potential biomarkers is driven by novel, high-throughput technology (e.g., genomics and proteomics).

3. Large-scale multicenter and longitudinal studies are essential for successful validation of promising biomarkers.

4. SLE patients should not be considered equal due to individual heterogeneity in clinical manifestations, disease progression rate, and perhaps pathogenic mechanisms.

5. Validation of each biomarker in specific subgroups of SLE patients (selected based on scientific rationale such as the biological basis of the biomarker and relevance to particular clinical manifestations) may yield more useful insight than validation performed using the population of all SLE patients.

6. Validated biomarkers might identify potential therapeutic targets and provide direction for drug development.

7. Physicians and patients should be educated and encouraged to actively participate in exploratory or validating studies of potential biomarkers.

Библиография / References

1. Aringer M, Costenbader K, Daikh D et al. European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis* 2019; 78:1151-9.
2. FDA-NIH Biomarker Working Group. BEST (Biomarkers, Endpoints, and Other Tools) Resource. Silver Spring, MD: Food and Drug Administration (US); Bethesda, MD: National Institutes of Health (US). <http://www.ncbi.nlm.nih.gov/books/NBK326791/> (22 September 2017, date last accessed).
3. Califf RM. Biomarker definitions and their applications. *Exp Biol Med* (Maywood) 2018; 243: 213-21.
4. Scott D, Botto M. The paradoxical roles of C1q and C3 in autoimmunity. *Immunobiology* 2016; 221: 719-25.
5. Leffler J, Bengtsson AA, Blom AM. The complement system in systemic lupus erythematosus: an update. *Ann Rheum Dis* 2014; 73: 1601-6.
6. Capecchi R, Puxeddu I, Pratesi F, Migliorini P. New biomarkers in SLE: from bench to bedside. *Rheumatology* December

- 2020; 59 (Suppl 5), v12-v18. <https://doi.org/10.1093/rheumatology/keaa484>.
7. Batliwalla FM et al. Interferon-regulated chemokines as biomarkers of systemic lupus erythematosus disease activity: a validation study. *Arthritis Rheum* 2009; 60: 3098-107.
 8. Wiedeman A. Type I IFN system in the development and manifestations of SLE. *Curr Opin Rheumatol* 2012; 24: 499-505.
 9. Elkon KB, Wiedeman A. Type I IFN system in the development and manifestations of SLE. *Curr Opin Rheumatol* 2012; 24: 499-505.
 10. Rönnblom L, Leonard D. Interferon pathway in SLE: one key to unlocking the mystery of the disease. *Lupus Sci Med* 2019; 6.
 11. Catalina MD, Owen KA, Labonte AC, Grammer AC, Lipsky PE. The pathogenesis of systemic lupus erythematosus: harnessing big data to understand the molecular basis of lupus. *J Autoimmun* 2020; 110.
 12. Margery-Muir AA, Wetherall JD, Castley AS et al. Establishment of gene copy number-specific normal ranges for serum C4 and its utility for interpretation in patients with chronically low serum C4 concentrations. *Arthritis Rheumatol* 2014; 66: 2512-2011.
 13. Bauer JW, Petri M, Batliwalla FM et al. Interferon-regulated chemokines as biomarkers of systemic lupus erythematosus disease activity: a validation study. *Arthritis Rheum* 2009; 60: 3098-3107
 14. Naradikian MS, Perate AR, Cancro MP. BAFF receptors and ligands create independent homeostatic niches for B cell subsets. *Curr Opin Immunol* 2015; 34: 126-129
 15. Italiani P, Manca ML, Angelotti F et al. IL-1 family cytokines and soluble receptors in systemic lupus erythematosus. *Arthritis Res Ther* 2018; 20-27.

Постъпил за печат: 7.11.2022 г.

Submitted: 7.11.2022

✉ *Адрес за кореспонденция:*

Д-р Валентина Решкова, дм, дн
Клиника по ревматология
УМБАЛ "Св. Иван Рилски"
Медицински университет – София
tel.: 0878622443
e-mail: v_reshkova@abv.bg

✉ *Correspondence address:*

Valentina Reshkova, MD, PhD, DSc
Rheumatology Clinic
UMHAT "Sv. Ivan Rilski"
Medical University – Sofia
tel.: 0878622443
e-mail: v_reshkova@abv.bg