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Genes, Antibodies, and Cytokines in Systemic Lupus Erythematosus: Update of Potential Biomarkers

Lina Zaripova[1], Abai Baigenzhin[2], Alyona Boltanova[3], Talgat Iglikov[4], Maxim Solomadin[5], Diana Makimova[6], Larissa Kozina[3], Elmira Chuvakova[7]

[1]Department of Scientific and Innovation Management, National Scientific Medical Center, Astana, Kazakhstan
[2]Chairman of the Board, National Scientific Medical Center, Astana, Kazakhstan
[3]Central Research Laboratory, National Scientific Medical Center, Astana, Kazakhstan
[4]Genetic laboratory, National Scientific Medical Center, Astana, Kazakhstan
[5]School of Pharmacy, Karaganda Medical University, Karaganda, Kazakhstan
[6]Department of Internal Medicine No. 4, Astana Medical University, Astana, Kazakhstan
[7]Deputy Chairman of the Board in the field of science, National Scientific Medical Center, Astana, Kazakhstan

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Corresponding author:
Lina Zaripova.
E-mail: zaripova_lina@list.ru.
ORCID: 0000-0001-8728-0225.

Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown aetiology, with the broad range of antibodies affecting various organs and tissues, leading to rapid disability and even to lethal outcome. Our objective was to make an analysis of the results of relevant global studies about genetic mutations, spectrum of antibodies and cytokines involved in the pathogenesis of SLE. The search was conducted in PubMed and Google Scholar platforms using keywords “systemic lupus erythematosus”, “genetic mutations”, “autoantibodies”, “cytokine production”, “sequencing”, “NGS" and "exome". Several genes were found to be involved in the pathogenesis of SLE, the majority of which were associated with B- and T-cell abnormal activation. The results of different studies revealed an association of active SLE with the increase in specific circulating autoantibodies. Based on the results of the current review, a preliminary list of autoantibodies, genes and cytokines associated with the development of SLE was prepared. Future directions will include the assessment of association of genes, antibodies and cytokines in SLE patients from the local Kazakh population, and the development of genetic-immunologic panel for the early diagnosis of this disease.

Keywords: systemic lupus erythematosus, genes, antibodies, cytokines.

Background

The urgency of the problem of autoimmune rheumatic diseases is determined by their high prevalence, the severity of the course with rapid disability, unfavourable life prognosis and the difficulty of early diagnosis. Autoimmune diseases represent a global burden on public health with an estimated incidence of 4.5%, disproportionately affecting women (6.4% of women compared to 2.7% of men) [1]. The prevalence of autoimmune diseases steadily rising, the incidence rate is about 3-9% per year according to the report of the British Society of Immunologists [2].

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease with multiple organs impairment, a broad variety of clinical manifestations and life-threatening complications [3]. The mortality in SLE is 3-4 times higher than in general population with the young patients more preferably have SLE as the cause of death [4-6].

Ethnicity plays a vital role in the development of the disease. African Americans are 5-9 times more likely to develop SLE than Americans of European descent; in addition, they usually develop a more severe form of SLE [7]. Māori had worse prognosis in SLE mortality than others in New Zealand [6].

A few studies of SLE in Kazakhstan showed a 62.8% rise in the incidence of this disease from 2012 to 2017 year [8, 9]. Delayed verification of the diagnosis still exists, which highlighted the need of new tools for early diagnosis.

Little is known about the mechanisms underlying the observed differences between ethnic groups. Nevertheless, it is mentioned that differences in human leukocyte antigen (HLA) regions contribute to this fact. Tissue damage often leads to cell death and subsequent presentation of intracellular and nuclear components to adaptive immune cells, their activation and, as a result, to the production of autoantibodies and/or a self-directed lymphocytic response with the production of a large number of cytokines [10]. Finally, the gradual progression of LSE lead to serious damage to organs and tissues often developing even before the autoimmune disease can be diagnosed clinically.

The pathogenesis of SLE is compound; it is caused by the interaction of genetic and environmental factors leading to loss of immune tolerance and the occurrence of an autoimmune response. An analysis of the results of relevant global studies about genetic mutations, spectrum of antibodies and cytokines in patients with SLE due to identify commonalities, differences and gaps in existing knowledge could improve understanding of etiopathogenesis of this disease. This observation confirms the need for immunological and genetic studies aimed at improving the diagnosis of autoimmune diseases in the early stages, before irreversible damage of organs and tissues occurs. The importance of understanding the fundamental mechanisms of pathogenesis stimulated the search for new diagnostic methods.

The modern approach for the treatment of SLE is based on timely diagnosis, which determines the possibility of initiating treatment at an early stage of the disease ("window of therapeutic opportunities"). There is a therapeutic window in the pre-SLE phase, in which pathological processes can be stopped more quickly and effectively and the development of the disease prevented. Modern diagnostic technologies make it possible to detect autoimmune disease at an early stage in most patients, however, in some cases, the clinical picture, laboratory and instrumental methods do not provide complete data for the diagnosis. This requires the earliest and most complete diagnosis, which includes not only immunological tests, but also genetic analysis.

Objective

The aim of the study is to assess the antibodies, cytokines and genetic mutations involved in the pathogenesis of SLE by a systematic review and to develop a panel of genetic and immunological markers for early diagnosis of autoimmune diseases.

Methods

Possible genetic mutations, autoantibodies and cytokines produced during autoimmune aggression in the SLE were selected based on a systematic review of the available data from biomedical literature platforms, as well as comparison with available genetic panels of world manufacturers.

The literature search was made on the PubMed and Google Scholar platforms. A combination of keywords was used, including "systemic lupus erythematosus (SLE)", "genetic mutations", "autoantibodies", "cytokine production", "sequencing", "NGS" and "exome". Full-text publications in English devoted to these topics were included in the review. Retrieved articles were screened for relevance and included if they provided insight into the prevalence of genetic mutations, autoantibodies, or cytokine profiles from the research with targeted autoimmune disease. Exclusion criteria involved literature reviews, abstracts and other forms of small publications. Priority was given to peer-reviewed studies, systematic reviews and meta-analyses. In addition, Ion AmpliSeq™ Designer gene repository was used to allocate disease related genes. A schematic search strategy is shown in the Figure 1.

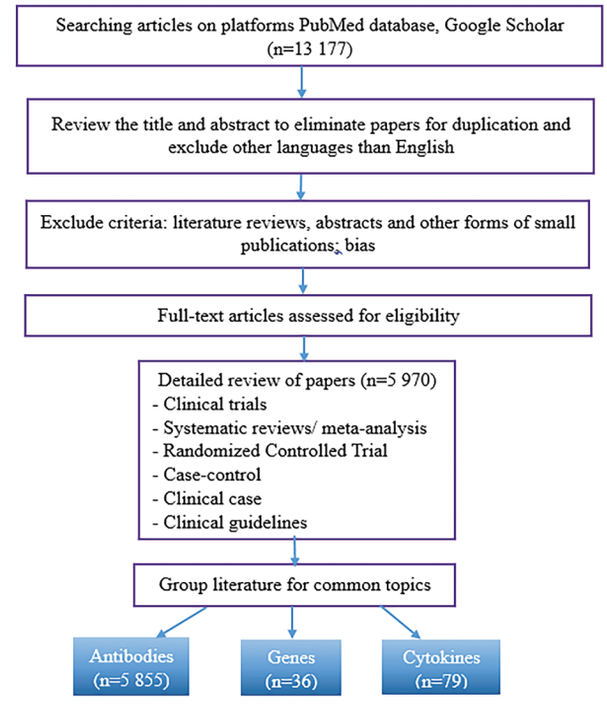

Figure 1 - Search strategy (n – number of articles).

Results

For the period from 1990-2023, the amount of 13 177 publications were found on the topic presented above, of which only 5 970 publications met the criteria of human research or systematic reviews and were included in this analysis.

The results of different studies revealed an association of active disease with increase in specific circulating autoantibodies and cytokines in SLE patients. The amount of 5 855 studies discovered the broad range of SLE autoantibodies. Autoantibody against cell nuclei (antinuclear antibodies, ANA) and other intranuclear antibodies production including double stranded DNA (dsDNA) were suggested as a hallmark of SLE [11]. The following antibodies were mentioned in the majority of the research: anti dsDNA first, then SS-A 60 kDA, SS-A 52 kDA, AFA, anti-Smith, anti U1RNP, anti Cq1 and La. The criteria for SLE recommended by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) included dsDNA and Sm nucleoprotein as relatively specific for SLE [12]. However, other antibodies assist to investigate the diagnosis of SLE as well. Some of them represented the link with special syndromes or symptoms. Thus, anti-SSA/Ro60 and anti-Ro52 were found to be positively associated with photosensitivity and xerophtalmia/xerostomia [13]. Additionally, hypocomplementemia was associated with anti-SSA/Ro60, while anti-Ro52 and anti-RNP antibodies were found to be correlated with Raynaud's syndrome [13, 14]. Anti-Sm antibodies were detectable in 5-30% of SLE patients (preferably in those who have the activity of renal involvement) and were included in the serological criteria for diagnosing of SLE [14]. Anti-C1q is known to be important in the inflammatory processes of SLE, but mainly associated with the hypocomplementemia and renal involvement [15, 16].

There is evidence of the association of different interleukins, both inflammatory and immunoregulatory, with SLE development. The excessive cytokine production was found in 79 studies reflecting both innate and adaptive immune system activation. Thus, over the past decade the type I interferon (IFN) was shown to play a vital role in SLE by promoting feedback loops, disturbing immune tolerance and enhance

disease activity. Analysis of the 79 research articles revealed cytokines commonly implicated in lupus, including IFN (IFN-α, IFN-β), TNF-α and IL-1β [17]. It was also showed an increase of cytokines IL-21, IL-17, IL-21, BlyS, IL-18, IL-2, IL-5 and IL-6 cytokines in serum obtained from patients with SLE [18]. Certain cytokines and autoantibodies contribute to more severe course of the disease. Thus, recent studies have shown that high levels of IL-5, IL-6, IL-4, IFN-γ were registered three years before clinical manifestation of SLE or even appearance of SLE-associated autoantibodies [19, 20].

Autoimmune diseases such as SLE, rheumatoid arthritis, and systemic sclerosis present complex pathogeneses with significant genetic predispositions. Current genetic screenings are insufficient in capturing the broad spectrum of genetic variations associated with these conditions. Several studies indicated the involvement of the following genes in the pathogenesis of SLE: BANK1, CD4, C4B, IRAK4, ORF2p, P2RX7, TREX1, BCR, LAG3, P40, PTPN22, TAM, TLR7, BLK, CR2, CXCL10, IL-1β, LTK, P450, RASGRP1, TLR5, CTLA4, FCGR2B, IL-18, MIF, PDCD1, RTK, TNFSF4, CCL19, C4A, NCF2, TNFAIP3, IFIT1, MX1, LY6E, ISG15, CXCL13, STAT1, STAT2, STAT3, PDGF, HAS2, SLC5A11 [21-23] (table 1). The majority of these genes were associated with B- and T-cell function and signaling pathways.

Currently the interferon-related immune pathway was detailly studied and showed the importance in the pathogenesis of SLE. IFIT1(interferon-induced with tetratricopeptide repeats 1) was the first gene described as a candidate gene for SLE. An overexpression of IFIT1 was confirmed in SLE patients included children SLE [24, 25]. IFIT1 interact with Rho/Rac guanine nucleotide exchange factor and activate Rho proteins which might be a potential target for novel tools in SLE therapy [24].

It is well-known that abnormal stimulation of innate immunity in SLE happens through Toll-like receptors. The toll-like receptor-7 (TLR-7) genetic variations (rs179019 and rs179010) are associated with an elevated risk of developing SLE according to meta-analysis of 15,472 SLE cases and 16,721 healthy controls [26]. Resent research reported mutations in TREX1 in SLE patients (especially SLE with neurological manifestations) that contribute to the accumulation of nucleic acid [27].

Human complement component 4 (C4) play the critical role in the processing of immune complexes in the pathogenesis of SLE. SLE patients are characterised by genetic deficiency for both C4A and C4B with low gene copy-number and decreased serum protein levels [28, 29]. The deletion of the C4A gene detected in different HLA haplotypes and might be suggested as a common genetic marker associated with SLE susceptibility [29]. Moreover, it was shown that low C4 gene copy number (GCN) in SLE were associated with the higher disease damage by Systemic Lupus International Collaborating Clinics – Damage Index (SLICC-DI) and serositis, while low C4B GCN was found in patients with arthritis [30]. The sodium-dependent glucose cotransporter (SLC5A11) was associated with low C4, anti-Sm, clinical serositis. It interacts with immune-related gene and might induce apoptosis through the TNF-alpha and PDCD1 pathway [31].

Proteomic quantification and genes sequencing of active SLE and inactive SLE were performed to determine biomarkers of active SLE [32]. Li et al. (2022) identified IFIT3, MX1, TOMM40, STAT1, STAT2, and OAS3 combination as biomarker for SLE diagnosis, while PHACTR2, GOT2, L-selectin, CMC4, MAP2K1, CMPK2, ECPAS, SRA1, and STAT2 were significantly increased in active SLE and may be uses for activity monitoring [32].

The genes HCY, HDL, GTF21, RIPK1, TYK2.34 were found to allocate SLE from Ion AmpliSeq™ Designer gene repository and double checked in GeneCards®: The Human Gene Database.

According to the data obtained, a comprehensive gene Next-Generation Sequencing panel was developed to identify germline mutations implicated in SLE, leveraging extensive PubMed and Google Scholar data and robust in-silico analyses. The finalized gene panel exhibited high diversity, covering key research areas in skin and connective tissue diseases, musculoskeletal disorders, and immune system pathologies. Preliminary in-silico assessments demonstrate a coverage of >99% and gene uniformity of >90% in wet-lab conditions, indicating a high potential to detect known and novel pathogenic variants.

Discussion

Autoimmune diseases are characterized by unregulated activation of immune cells, production of a broad range of autoantibodies and cytokines, which impair various organs and tissues. Nowadays, worldwide, chronic and steadily progressive autoimmune diseases affect approximately 5-10% of the population, while recently there has been an increase in the incidence, which promote a pronounced disability of able-bodied population [68, 69]. Early diagnosis of autoimmune diseases is extremely important, since timely therapy prevents the development of structural lesions and reduces the risk of disability of patients.

An increase in chronic and steadily progressing autoimmune diseases contributes to the growth of disability of the young, able-bodied population. SLE deserves great attention as the heterogeneous autoimmune disease with the life-threatening complications [3]. Over the past decade, the scope of therapeutic approaches has increased, however, there is still no cure for this disease.

The pathophysiology of autoimmune diseases is related to genetic mutations that cause the disease, or to a combination of genetic predisposition and epigenetic modifications resulting from environmental contact [70].

Autoimmune diseases such as SLE, rheumatoid arthritis, and systemic sclerosis present complex pathogeneses with significant genetic predispositions. Current genetic screenings are insufficient in capturing the broad spectrum of genetic variations associated with these conditions. The concordance rates of SLE consisted in 14.3–40% for monozygotic twins [71, 72]. These observations led to hypotheses that disease-causing mutations of a single gene in rare autoimmune diseases may result in the development of the disease, but do not predict outcomes [70].

Sequencing of the first human genome took place in 2003 [2]. Since then, advances in sequencing technologies allowed to reduce costs and enabled the generation of massive volumes of high-quality human sequence data used to create considerable catalogues of both population and disease-causing variations. The presence of such databases means that we can investigate all types of genetic variations of many diseases [2]. Genetic research identified different loci associated with autoimmune diseases. Several studies have proven the contribution of rare and suspected variants of pathogenic genes to the development of autoimmune diseases, for example, SLE. It was discovered that the missense variant rs35677470 of deoxyribonuclease I-like 3 (DNASE1L3) gene was associated with the development of SLE [73]. Mutations in C1QA, C1QC, C2, DNASE1L3 and IKZF1 were considered as congenital immune disorders and accounted for 7% of cases of SLE with onset in childhood, studied by a

Table 1 The genes included in the pathogenesis of SLE: currently available research data.

N	Gene abbreviation	Gene name	Summary (role, mechanism of working, findings)	Reference
Significant genes associated with susceptibility to the development of SLE				
1.	BANK1	B-cell scaffold protein with ankyrin repeats 1	Polymorphisms in BANK1 is associated with susceptibility to SLE Promote Lyn-mediated tyrosine phosphorylation of inositol 1,4,5-trisphosphate receptors	[33]
2.	BCR	Breakpoint cluster region	Patients with SLE showed increased BCR clonotypes in comparison with healthy people.	[34]
3.	BLK	BLK proto-oncogene, Src family tyrosine kinase	The risk variant rs922483 in the BLK gene is strongly associated with regulation of BLK mRNA and protein expression in B cells	[35]
4.	CR2	Complement component 3d receptor 2	CR2 connects with Complement component C3 and transit signals through CD19, so decrease the activation threshold of B-cells.	[36]
5.	CTLA4	Cytotoxic T-lymphocyte associated protein 4	CTLA-4 participates in regulation of signals by T-cells receptors	[37]
6.	CXCL10	C-X-C motif chemokine ligand 10	CXCL10 increases migration of proinflammatory cells through the activation of ERK	[38]
7.	IL1B	Interleukin 1 beta	Proinflammatory cytokine, play a key role in inflammatory and immune reactions	[39]
8.	ISG15	ISG15 ubiquitin-like modifier	SLE patients with lymphocytopenia have high ISG15 expression	[40]
9.	LTK	Leukocyte receptor tyrosine kinase	SLE is associated with LTK	[41]
10.	NCF2	Neutrophil cytosolic factor 2	NCF2 is a subunit of the NADPH enzyme that produces superoxide in the phagosomes of neutrophils and other phagocytic leukocytes	[42]
11.	PDCD1	Programmed cell death 1	An inhibitory receptor on antigen-activated T cells Plays a key role in the maintenance of immune self-tolerance	[43]
12.	PTPN22	Protein tyrosine phosphatase, non-receptor type 22	Participates in regulating CBL function in the T-cell receptor signaling pathway Mutations in PTPN22may be associated with SLE and rheumatoid arthritis	[44]
13.	RASGRP1	RAS guanyl releasing protein 1	Activates the Erk/MAP kinase cascade Regulates the development and differentiation of T- and B-cells Altered expression of various isoforms of this protein cause susceptibility to SLE	[45]
14.	SLC5A11	Solute carrier family 5 member 11	Induces apoptosis via the TNF-alpha, PDCD1 pathway associated with low C4, anti-Sm, clinical serositis	[31, 46]
15.	STAT1	Signal transducer and activator of transcription 1	SLE T- and B-cells characterised by the increased levels of STAT1 transcript enhance STAT1 signaling responses to IFN·	[32, 47]
16.	STAT2	Signal transducer and activator of transcription 2	In response to cytokines and cell growth elements, STATs phosphorylate receptors associated with kinases Than release homo- or heterodimers that translocate into the cell, where they act as transcriptional activators In response to interferon (IFN), this protein forms a complex with STAT1 and the IFN regulatory factor p48 protein group (ISGF3G), mediating innate antiviral activity	[32]
17.	STAT3	Signal transducer and activator of transcription 3	STAT3 plays a key role in the differentiation of Th17, T follicular helper and B-cells STAT3 inhibition may represent a possible future therapeutic target in SLE	[47]
18.	TLR5	Toll like receptor 5	This gene encodes a member of the toll-like receptor (TLR) family Play a key role in pathogen recognition and activation of innate immune responses Recognizes specific pathogen-associated molecular patterns that are expressed on infectious agents Activation of this receptor mobilizes the nuclear factor NF-kappa B, which activates a variety of target genes associated with inflammation	[48]
19.	TNFAIP3	Tumor necrosis factor alpha induced protein 3	The encoded protein: inhibit NF-kappa B activation and TNF-mediated apoptosis involved in cytokine-mediated immune responses	[49]

20.	TLR-7	Toll like receptor 7	Enhanced TLR7 signaling leads to aberrant survival of B- cell receptor (BCR)-activated B-cells and cell-intrinsic accumulation of CD11c+ aged B cells Increases follicular and extrafollicular helper T-cells	[26, 50]
21.	TREX1	Three prime repair exonuclease 1	TREX1 deficiency result in: the accumulation of cytosolic DNA as well as activation of the cGAS-STING-IFN signaling pathway tissue inflammation and autoimmune diseases	[27, 51]
22.	C4B	Complement C4B null allele	Deficiency of the complement C4B null allele leads to the inflammatory, infectious or chronic autoimmune conditions included SLE	[28]
23.	C4A	*C4* complement components	Associates with the presence of SSA/SSB autoantibodies The copy number of *C4* correlates with C4 level in plasma	[29, 52]
24.	LAG3	Lymphocyte activation gene 3	High LAG3 expression associated with T cell dysfunction Decrease of LAG3 cause impaired immune tolerance and may lead to autoimmune conditions	[53]
25.	TAM	Tyro3, Axl, and Mer receptor tyrosine kinases	Participates in the apoptotic cell clearance and immune responses TAM deficiency leads to SLE	[54]
26.	RTK	TAM receptor tyrosine kinase	Recognises apoptotic cells Circulating TAM receptors have an immunoregulatory function May be a biomarker for SLE prognosis	[54]
27.	IFIT1	Interferon-induced with tetratricopeptide repeats 1	Highly expressed in SLE in children IFIT1 interact with Rho/Rac guanine nucleotide exchange factor May activate Rho proteins	[25]
Genes increased during active disease				
1.	CD4	CD4 molecule	Activation of CD4 (+) T-cells is a key factor for SSc and SLE Realise proinflammatory cytokines	[55]
2.	CXCL13	C-X-C motif chemokine ligand 13	CXCL13 attracts C-X-C chemokine receptor type 5 (CXCR5)-expressing B cells and T follicular helper cells to the follicle	[56]
3.	IL18	Interleukin 18	Proinflammatory cytokine; play a key role in immune reactions and activation of Th1 cells	[57]
4.	IRAK4	Interleukin 1 receptor associated kinase 4	Key regulator of native immune response	[58]
5.	MIF	Macrophage migration inhibitory factor (glycosylation-inhibiting factor)	MIF works as a mediator of innate immunity by promoting host inflammatory responses through the induction of proinflammatory cytokines	[59]
6.	MX1	MX dynamin like GTPase 1	Patients with SLE and anti Smith (Sm), RNP, Ro/SSA или La/SSB have higher level of MX1	[60]
7.	PDGFB	Platelet derived growth factor subunit B	Participats in the stimulation of pronounced hyperplasia of fibroblast-like cells	[61]
8.	P2RX7	Purinergic receptor P2X 7	Receptor P2X7 induce release of proinflammatory molecules (IL1β, proteases)	[62]
9.	STAT2	Signal transducer and activator of transcription 2	In response to cytokines and cell growth elements, STATs phosphorylate receptors associated with kinases and then release homo- or heterodimers that translocate into the cell cell, where they act as transcriptional activators. In response to interferon (IFN), this protein forms a complex with STAT1 and the IFN regulatory factor p48 protein group (ISGF3G), mediating innate antiviral activity.	[32]
10.	C4A	*C4* Complement components	There is an association between low C4A gene copy number and SLE severity.	[30]
11.	LY6E	Lymphocyte antigen 6 complex, locus E	Increased level of LY6E was found in SLE patients with low C4 levels Active SLE patients were characterised by elevated LY6E in comparison with patients in remission. LY6E expression levels correlated with SLEDAI-2K scores.	[63, 64]
12.	P40	Protein subunit of interleukins 12	SLE antibodies reactive with p40 Higher in SLE patients with flare	[65]
13.	CCL19	Chemokine (C-C motif) ligand 19, MIP-3B	The level of CCL19 in serum is higher in patients with active SLE Potential marker for disease activity in SLE	[66]
14.	HAS2	Hyaluronan synthase 2	Plays a key role in fibrosis The level of HAS2 increases in the active phase of lupus nephritis	[67]

genetic analysis of British and French cohorts [74]. However, according to the growing number of known autoimmune conditions, the interindividual variability of phenotypes and outcomes, pathophysiology of SLE is not fully understood [75].

Now studies show that there are a relatively large number of risk loci associated with the development of SLE, but specific genes responsible for the development of pathogenetic mechanisms have not been found. According to the modern concept of understanding autoimmune diseases, SLE might be determined as a disease without single monogenic cause, but with genetic predisposition, which can be realised under the influence of environmental factors that determine the manifestation of the disease [10, 76]. Recently it was identified more than hundred gene loci associated with the development of SLE [77]. The gene loci associated with susceptibility to SLE may also contribute to the development of other autoimmune diseases [77]. And the same tendency may be seen in the other direction, having a family history of autoimmune disease increases the risk of SLE [78].

The study of genetic mutations in SLE can shed light on certain aspects of the aetiology of autoimmune diseases, and their connection with the activity of pathological process with the production of autoantibodies and cytokines.

Identification of gene mutations occurring in SLE and their associations with the severity of the disease, the production of autoantibodies and cytokines is necessary, given the importance of understanding the development of the disease at the genetic level. The modern strategy of therapy is based on early diagnosis, which determines the possibility of initiating treatment at a very early stage of the disease ("window of therapeutic possibilities") with appointment of active therapy. However, this requires the earliest and most complete diagnosis, which includes not only immunological tests, but also genetic analysis. Autoimmune diseases are variable in their clinical manifestations, organ and tissue injury, laboratory analysis, response to therapeutically agents; all of these differences might be associated with genetic variability [79]. The strategy of searching for pathogenic genetic mutations and their associations with the production of autoantibodies and cytokine secretion is crucial for the development of successful personalised programs for patients with severe autoimmune diseases such as SLE [2].

The applicability of the research results for development of healthcare consists in the improvement of the diagnostic tool for early diagnosis and initiation of therapy. The applicability of the results for science consists in the expanding the range of knowledge about genetic mutations and associations with the production of antibodies, cytokines and the severity of the disease. Due to include these cytokines analysis and genes sequencing into routine practice firstly it would be necessarily to assess them in SLE patients of Kazakh origin. Currently we collected material more over 100 patients and started the investigation. After that the list of autoantibodies, genes and cytokines will be propose for implementation to the Healthcare of Kazakhstan.

Conclusion

Based on the results of the current review, a preliminary list of autoantibodies, genes and cytokines associated with the development of SLE was prepared. The immunological-genetic panel made according to this review offers a targeted approach to uncover the genetic basis of SLE, facilitating the early diagnosis, personalized treatment and a deeper understanding of the molecular mechanisms underlying this autoimmune disease.

This is the first attempt of genetic examination of SLE patients in Kazakhstan during which we hope to investigate new panel.

Prospects for further research

Future directions will include the investigation of the unique genetic and immunological patterns on autoimmune diseases in the local Kazakh population. Ongoing work will validate gene panel in a clinical setting and assess its utility in patient stratification, prognostic evaluations, and as a tool for unveiling the genetic landscape of autoimmune diseases.

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