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From old concerns to new advances and personalized medicine in lupus: The end of the tunnel is approaching

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A B S T R A C T

The significant decrease in mortality rates worldwide, the increased proportion of patients achieving a durable remission, and the recent approval of a new drug after several decades are encouraging advances in the tangled history of systemic lupus erythematosus (SLE). However, when data are observed more closely, the research findings on disease pathogenesis and targeted treatments have been quite misleading, as illustrated by the central role of B cells but the missed endpoints in rituximab clinical trials which are burdened by the wide variability of SLE manifestations or the ethnic determinants of disease severity. Other biologic therapies, on the other hand, inhibit B cell stimulating factor BAFF but are proving to be short of revolutionary, not yet overcoming high-dose long-term glucocorticoids still largely used without an agreement on what clinical targets are to be sought in the proposed treat-to-target approach. The large amount of data from genome-wide association studies, the detailed reports on T cell epigenetics, or the numerous established and novel animal models have also proven insufficient to change our understanding of the human disease. Nonetheless, we have now tools for a better and earlier SLE diagnosis, thanks to reliable biomarkers, improved care of kidney involvement, better pregnancy outcomes, while the neuropsychiatric manifestations remain challenging. These advances are well mirrored by some proposed synthetic drugs, such as tacrolimus, or biologics, including IFNα inhibitors and other drugs capable to modulate the immune system. Ultimately, we may foresee that genetic and epigenetic data, along with the variable clinical manifestations represent the bases for SLE to become an ideal candidate for the introduction of truly personalized medicine.

1. Introduction

Systemic lupus erythematosus (SLE) is a complex disease, and its care has dramatically changed in the last 50 years, resulting in significantly longer survival rates with lower disease incidence and higher prevalence [1]. Indeed, mortality has dramatically dropped with earlier diagnosis and new treatments but the scenario is not as shiny as it seems [2]. SLE still has a highly variable course and unpredictable prognosis depending mainly on the type and severity of organ involvement, particularly nephritis and neuropsychiatric involvement [3,4], despite new proposed biomarkers [5]. The advent of new targeted therapies, particularly monoclonal antibodies, opened a new avenue in SLE treatment but have been ultimately less convincing than initially hoped to treat organ involvement, with lupus nephritis being the most severe manifestation where the promise of biologics remains unfulfilled [6–10]. Conversely, we can assert that in 2016 we have reliable biomarkers for SLE diagnosis and monitoring, allowing an earlier recognition and management of organ involvement and subsequent complications [11–14]. SLE is known to have heterogeneous clinical manifestations, potentially affecting every organ with relevant outcomes, but phenotypes are currently included in clinimetric evaluations with limited homogeneity in study cohorts [15–19]. In this view, neuropsychiatric signs and symptoms represent the most challenging features of the disease [20], and despite large efforts the delayed suspicion and recognition remain common. Neuropsychiatric SLE (NPSLE) is a common manifestation of the disease, which may affect both the central and peripheral nervous system, with diffuse or focal abnormalities. Moreover, inflammatory and vascular accidents may develop. There is a lack of specific NPSLE biomarkers, making the diagnosis and monitoring a challenge [5,12]. Albeit the large amount of technology we can use, several cases remain not diagnosed, leading to severe impairment of the quality of life and inability, also due to the lack of standardized therapies and adequate definitions of NPSLE [21]. Lastly, as SLE mainly affects women of childbearing age [22], pregnancy is a major issue in the disease management and most women have successful pregnancies, as measures can be taken to reduce the risks of adverse maternal or fetal outcomes [22], also with biologics [23].

The present article is intended to briefly highlight the disappointments and false hopes in SLE research and care, while in this issue of Journal of Autoimmunity the latest research issues on SLE are discussed in detail, with special regards to pathogenesis, biomarkers and treatment options (see Table 1).

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2. Genetics and epigenetics

Similar to all rheumatic diseases, SLE derives from environmental factors acting on a permissive genetic background to lead to immune system dysregulation [24–26]. First, nearly 30 years of attempts to identify candidate genes through isolated candidate gene hypothesis-driven studies have not been successful except for the confirmed associations with polymorphisms of the human leukocyte antigen (HLA) loci, Fc gamma receptor, PTPN22, STAT4 and two interferon type-I related genes, IRF5 and TYK2 [27]. Genome-wide association studies (GWAS) have overcome the limitations of single candidate approaches and identified more than 60 risk loci robustly associated with the disease, regardless of geographical areas and ethnicities [28], as more than half of the loci are present in European and Chinese patients [29]. More recently, Latin Americans have also been included in GWAS confirming several loci and including a new one, thus enriching the potential loci implied in SLE pathogenesis, thus suggesting that it might have different specificities in different ethnicities [30]. However, despite the numerous identified polymorphisms, genetic factors remain quite disappointing and fell short of any clinical application or significance. Indeed, the majority of GWAS associations fall into non-coding regions, suggesting a possible regulatory effect of the variants in disease pathogenesis but the functional influence of most variants is unknown; furthermore, most of the genes identified by GWAS are also associated with other autoimmune diseases, particularly rheumatoid arthritis (RA) [27,31]. Cumulatively, genetics is insufficient to determine autoimmune disease onset, as elegantly shown by the largely incomplete concordance in monozygotic twins [32] and epigenetic modifications may constitute the missing link and provide the information on genetic interactions with environment, to ultimately explain part of the missing heritability [33]. In SLE, epigenetic dysregulation is expected to play a role, as evidence suggested alterations in DNA methylation, histone modification, noncoding RNA expression, and X chromosome inactivation patterns. Only DNA hypomethylation and X chromosome genes escaping inactivation may represent SLE hallmarks [31], particularly for organ involvement [34], and especially with lupus nephritis [35,36]. Nonetheless, genetics and epigenetics are considered as the two major disappointments in our understanding of SLE etiology with clinical applications currently remaining wishful thinking.

3. Animal models

Human studies take a great advantage from animal models of diseases, but SLE models may be now less informative as once we believed. The New Zealand Black (NZB), New Zealand White (NZW), (NZB × NZW)F1 hybrid, and NZM2410 (a recombinant inbred strain derived from an (NZB × NZW)F2 intercross) are the most widely studied murine models of SLE, as well as the first to be described with a scientific longevity well beyond any other disease model. NZB/W F1 hybrids develop severe lupus-like phenotypes comparable to that of lupus patients, including lymphadenopathy, splenomegaly, elevated serum antinuclear (ANA), and anti-double stranded DNA (dsDNA) IgG autoantibodies [37], immune complex-mediated glomerulonephritis that becomes apparent at 5–6 months of age, resulting in kidney failure and death at 10–12 months of age [38,39]. Despite being the first and most studied animal model also in recent works [40], it has been suggested that this model might not be as informative as it was believed as mice spontaneously develop the disease, and there is no agreement on the loci leading to the renal manifestations.

Further research on the genetic predisposition based on NZM2410 will allow the identification of new loci, but their role remains largely unknown. Moreover, therapeutic studies on mouse model lead to inevitable delusions, as for example glomerulonephritis in NZM is irreversible [41], while other human clinical manifestations are difficult to reproduce in models, especially for the neuropsychiatric, dermatological and articular phenotypes [42]. Newer mouse models are promising and may prove closer to the complexity of human SLE [43,44], however none encompasses the systemic definition of the disease, and while genetic studies can be suited to the NZM model, therapeutic approaches are unfit [38].

4. Biologic therapies

Similar to the oncology field, biologics have dramatically changed the natural course of rheumatic diseases, particularly rheumatoid arthritis and spondyloarthritis [45], reducing the burden of disease, ameliorating the disease-related quality of life and preventing the development of comorbidities, mainly atherosclerosis-related manifestations, and reduce the need for long-term and high-dose corticosteroids. Given this success story, much hope was relied of B cell depleting therapies for SLE with rituximab ultimately failing randomized controlled trials [46–49], as almost all studies using other B cell depleting strategies [50], while new strategies are approaching but are not fully satisfactory [15,51]. Most recently, one new drug was approved for SLE after decades and belimumab, an anti-BAFF antibody, is currently used worldwide in the clinical armamentarium [15], with a growing experience [52]. SLE is an heterogeneous disease with many clinical and laboratory features, which are difficult to take all into account when designing a trial, along with the need to enroll an homogeneous population [53], also for organ specific manifestations, i.e. nephritis being more common in some ethnic groups or with specific biomarkers [54]. Moreover, outcome definition is a difficult task in SLE trials, with some being too strict or requiring a long observation period (such as the time to renal failure and need for substitutive therapy) while others may not reflect a benefit for patients. Finally, severe patients who have already received cyclophosphamide or other treatments are usually excluded from randomized clinical trials [55]. An International agreement on the inclusion criteria and outcome definition will be critical in SLE to allow the possibility to develop new drugs. In the meantime, cornerstone therapies as corticosteroids, hydroxychloroquine should be provided to SLE patients, while immunomodulators, as

Table 1
The good and the bad news regarding SLE in 2016.

Hopes	Disappointments
• Successful pregnancies are a reality in SLE women, also with kidney involvement; • An early diagnosis is possible, especially thanks to new biomarkers in association with known autoantibodies; • Renal biopsy is a critical exam to obtain in SLE, a new tool for guiding the physician is available; • Immunomodulators remain the SLE cornerstone therapy	• Severe forms of SLE do not always respond to new treatments; • Neuropsychiatric manifestations are common, but still underdiagnosed; • Animal models are not as reliable as once thought • Genetics and epigenetics provided conflicting results with limited clinical use