FEATURED NEW INVESTIGATOR

Assessment of the translational value of mouse lupus models using clinically relevant biomarkers

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Lupus is an autoimmune disease with a poorly understood etiology that manifests with a diverse pathology. This heterogeneity has been a challenge to clinical drug development efforts. A related difficulty is the uncertain translational power of animal models used for evaluating potential drug targets and candidate therapeutics, because it is unlikely that any 1 preclinical model will recapitulate the spectrum of human disease. Therefore, multiple models, along with an understanding of the immune mechanisms that drive them, are necessary if we are to use them to identify valid drug targets and evaluate candidate therapies successfully. To this end, we have characterized several different mouse lupus models and report their differences with respect to biomarkers and symptoms that are representative of the human disease. We compared the pristane-induced mouse lupus disease model using 3 different strains (DBA/1, SJL, BALB/c), and the spontaneous NZB x NZW F_1(NZB/W) mouse model. We show that the models differ significantly in their autoantibody profiles, disease manifestations such as nephritis and arthritis, and expression of type I interferon-regulated genes. Similar to the NZB/W model, pristane-induced disease in SJL mice manifests with nephritis and proteinuria, whereas the pristane-treated DBA/1 mice develop arthritis and an interferon-driven gene signature that closely resembles that in human patients. The elucidation of each model's strengths and the identification of translatable biomarkers yields insight for basic lupus research and drug development, and should assist in the proper selection of models for evaluating candidate targets and therapeutic strategies. (Translational Research 2014;163:515–532)

Abbreviations: BUN = blood urea nitrogen; cDNA = complementary DNA; ELISA = enzyme-linked immunosorbent assay; FC = fold-change; IFN = interferon; Ig = immunoglobulin; MPO = myeloperoxidase; NZB/W = NZB x NZW F_1; PBMC = peripheral blood mononuclear cell; PBS = phosphate-buffered saline; RiboP = ribosomal phosphoprotein P; qPCR = quantitative polymerase chain reaction; SLE = systemic lupus erythematosus; TLDA = Taqman low-density array; TMPD (pristane) = 2,6,10,14-tetramethylpentadecane; UACR = urinary albumin-to-creatinine ratio

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AT A GLANCE COMMENTARY

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Background

Systemic lupus erythematosus remains an incompletely addressed medical need of very heterogeneous presentation. As the genetics and pathology of the disease are elucidated, appropriate methods to translate from murine preclinical models to testing in appropriate patient subpopulations are needed.

Translational Significance

Using 4 different mouse lupus models, we examined clinically relevant symptoms and markers of disease, including proteinuria, arthritis, autoantibodies, and interferon gene signature, and found they differed significantly among models. The results should assist in choosing the correct model to validate targets, establish preclinical proof of concept for different disease populations, and to identify biomarkers for clinical use.

Lupus is an autoimmune disease that can affect numerous organ systems with varying severity, including the skin, musculoskeletal system, kidneys, and central nervous system. The disease can reduce quality of life significantly and is fatal in some cases. Lupus is not only variable in symptomatology but also in its disease pathogenesis and etiology.[1] The etiology of the disease is poorly understood, but is likely a result of a complex interplay between environmental and genetic factors.[2] Disease pathogenesis involves the generation of autoantibodies and their subsequent deposition in end organs. Although a wide variety of different autoantibody reactivities has been found in patients with lupus, and they have served as biomarkers, correlating them with disease subsets or mechanisms has been complicated. Exploring the causal link of autoantibody specificity and disease severity and outcome remains an active area of research.[3,4] Given the significant heterogeneity in human lupus etiology, pathology, and symptomatology, it is unlikely that a single animal model will recapitulate all the different patient subsets. Therefore, a variety of animal models may be needed to represent more fully the lupus patient population to enable accurate evaluation of candidate lupus drugs. Understanding the diverse models also facilitates preclinical analysis of potential biomarker and pharmacodynamic readouts in preparation for the clinic.

A variety of mouse lupus models have been described,[5] including those with a genetic susceptibility to spontaneous disease development (ie, NZB/W, BXSB-*Yaa*, and MRL/*lpr*) and those in which disease is chemically induced (ie, pristane). In the NZB/W model, lupus-like disease develops spontaneously as a result of a combination of at least 3 genetic loci affecting immune activation, apoptosis, and end organ susceptibility to damage.[6] A newer, less commonly used model is the pristane-induced model, which involves intraperitoneal injection of the hydrocarbon 2,6,10,14-tetramethylpentadecane (TMPD, also commonly known as pristane) to trigger lupus-like disease development.[7] The pristane model can be performed in a variety of mouse strains, and interesting variations in the lupus disease characteristics and severity have been documented across different strains.[8]

There are few available efficacious lupus treatments, and unmet need remains high. A critical step in the development of new treatments is the evaluation of candidate drugs and targets in animal lupus models. The NZB/W and MRL/*lpr* models have served as the primary preclinical drug evaluation models,[5,9] whereas the pristane model has not been used routinely for this purpose. The selection of an appropriate mouse model for evaluating a candidate lupus drug is crucial given the time-intensive nature of these lengthy studies and the resource investment associated with running lengthy lupus clinical trials. Having mouse lupus models that are characterized with regard to etiology, pathogenesis, and translatable readouts for disease symptoms and drug impact would help immensely in determining how these models relate to the human lupus condition and would allow selection of appropriate models for target evaluation, drug evaluation, and biomarker discovery studies.

To address this issue, we characterized the pathogenesis and disease manifestations of several different mouse lupus models and explored clinically relevant biomarkers that increase their translational value. Specifically, we compared the NZB/W lupus model and the pristane model performed in the DBA/1, BALB/c, and SJL mouse strains. Our findings indicate that the models differ in the timing for disease development, pathogenesis of the disease, and the end organ manifestations. Furthermore, we have used advanced biomarker methods such as autoantibody profiling, bioluminescent imaging, and quantitative polymerase chain reaction (qPCR) analysis of interferon (IFN)-driven gene expression that may elucidate further the translatability of the models. This report increases the understanding and translational value of mouse lupus models described in this study and should aid in model selection for the