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Introduction: The first Merinoff Symposium, ‘Systemic Lupus: Bringing Science to the Patient’

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Systemic Lupus Erythematosus (SLE), a chronic, inflammatory autoimmune disease affects 1 in 500 women, 90% being women in the age range of 14–45 years. During SLE the immune system produces autoantibodies that attack skin, kidneys, heart, lung, brain and other cells. Intermittent periods of illness (flares) can be followed by long periods of disease remission. SLE is difficult to diagnose and treat in part because of the significant uncertainties about pathogenesis, and the role of genetic and environmental triggers. The existing treatment options for SLE are steroids, anti-malarials, nonsteroidal anti-inflammatory drugs and cytotoxic agents. Current treatment has broad immunosuppressive effects but there is an unmet, urgent need to develop more specific targeted treatment regimens to help in the management of this disease.

The Merinoff Symposia is a new entity sponsored by the Feinstein Institute to host scientific meetings focused on important topics in clinical and translational science. The objective is to create dialogue between clinicians and basic science investigators. The major gaps in understanding the nature of SLE and optimal therapeutic approaches indicate the need to provide a venue to assimilate new ideas and key information with the goal of providing an integrated approach to future patient care. Recently, the Feinstein Institute for Medical Research and the Merinoff Foundation cosponsored the first Merinoff Symposium in conjunction with Journal of Internal Medicine. The Symposium entitled ‘Systemic Lupus: Bringing Science to the Patient’ was held from September 24–27, 2008 in New York. This was a unique platform for discussions of current advances in basic and translational research for this debilitating disease. The environment included clinical investigators, laboratory researchers and trainees, who interacted and talked about basic science models and clinical trials for SLE and the application of this knowledge to patient care. Here we highlight several of the topics discussed at this symposium, as detailed in the following and six reviews [1–6]. These reviews focus on autoimmunity, autoantigens [1], B cell activation [2], T-effector cells [3], autoantibodies in pregnancy [4], cholinergic control of inflammation [5] and genes and genome-wide association studies for SLE [6].

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Conflict of interest

No conflict of interest was declared.

A major challenge to the study of human autoimmune diseases is the heterogeneous and complex nature of multiple potentially interacting parameters encompassing genetic and environmental influences. Rosen and Casciola-Rosen [1] review autoantigens in systemic autoimmunity and discuss the process of antigen selection. The authors propose a model in which neo-antigens are not ubiquitously present but are formed as a result of dynamic interactions that occur between immune effector pathways and specific target tissues. It is these neo-antigens that, in context, then provoke autoreactive immune responses. Rosen *et al.*, propose that in autoimmunity 'the patterns of autoantibodies produced arise from an integrated, amplified output of unique target tissue, specific stimulated gene expression pathways, and distinct combination of immune effector forces' [1].

B cells are known to play an important role in autoimmune diseases as effectors producing autoantibodies. This focuses attention on B cells and how they are involved in the pathophysiology of autoimmune disease. Rothstein and Guo [2] discuss the novel concept of receptor re-programming and provide evidence that IL-4 alters the nature of B cell receptor (BCR) signal transduction as a result of receptor crosstalk. A key outcome of this change is B cell production and secretion of osteopontin, an autoimmunity associated cytokine that is also a polyclonal B cell activator. This work illustrates a new mechanism for autoimmunity in which B cells secrete activating cytokines when BCR signaling is altered by specific environmental influences.

T cells are a key component of the immune system and altered regulation of T cell responses have been implicated in autoimmune diseases such as SLE and Rheumatoid Arthritis (RA). A great deal of interest has been generated in the recently discovered Th17 subset of cells that is involved in multiple autoimmune diseases. Pernis [3] discusses recent reports that focus on the mechanisms and pathways involved in generating Th17 cells and the role of Th17 cells in SLE and RA. Th17 cells make cytokines including IL-17 and IL-21 that regulate the mucosal antimicrobial peptides and inflammatory responses. Alterations in the production of these cytokines contribute to the pathogenesis of SLE and RA.

Buyon *et al.* [4] present an integrated clinical and research approach for the management of autoimmune associated congenital heart block (CHB), a manifestation of the neonatal lupus syndromes. CHB arises as a result of passively acquired autoimmunity due to antibodies that cross the placental barrier and that react with components of the SSA/Ro–SSB/La ribonucleoprotein complex. Eighty-five percent of fetuses identified with CHB are from mothers with antibodies to SSA/Ro–SSB/La. This is associated with increased morbidity and mortality to the fetus and neonate. A registry for neonatal lupus established in 1994 provides the authors with a key source of information that permits the translation of clinical information to understanding the underlying science. The authors discuss their working model of the pathogenesis, current evaluation strategies, and preventive methods for CHB.

Controlled cytokine production occupies a crucial role in maintaining homeostasis within the immune system, because unregulated cytokine production mediates inflammation, damage to target organs, and even death. Inflammation is integral to the pathogenesis of autoimmune diseases, and elevated cytokine levels have been implicated in tissue damage in SLE and RA. Rosas-Ballina and Tracey review the cholinergic control of inflammation [5]

and discuss the concept that inflammation is regulated by neural mechanisms. The 'cholinergic anti-inflammatory pathway' is comprised of the vagus nerve, the neurotransmitter acetylcholine, and the $\alpha 7$ subunit of the nicotinic acetylcholine receptor which regulates innate immunity. The authors review the status of this field, and discuss potential therapeutic applications based on vagus nerve stimulation and pharmacological activation of this pathway in treating inflammation and autoimmunity.

A recent flurry of genome-wide association studies (GWAS) have led to reports of several novel SLE risk genes. Graham *et al.*, review the GWAS data for SLE in a meta-analysis that summarizes 17 validated risk variants for SLE, including four newly confirmed variants [6]. The confirmed SLE risk variants offer an early glimpse into the major pathways dysregulated in human SLE and include neutrophil function, B cell development and signalling as well as toll-like receptors 7 and 9.

The sessions included discussions on the induction of autoreactivity with a focus on (i) triggers and innate immunity; (ii) adaptive immunity and animal models; two sessions on human disease: (iii) tissue responses and (iv) adaptive immunity; and (v) a final session on genes and gene expression. Thirty-eight exciting presentations were discussed in these sessions and included talks on TLR7, natural antibody regulation of innate immunity, induction of interferon pathway activation, tolerance checkpoints and potential triggers for Lupus, particularly the role of EBV. Additionally, findings of impaired phagocytic capacity of apoptotic cells and increased extracellular DNA and RNA in SLE patients were presented by Dr Herrmann. He also noted that impaired clearance of apoptotic cells provides autoimmunogens for autoimmunization, provides autoantigens for immune complex formation, provokes inflammation by release of endogenous danger molecules and is neither necessary nor sufficient to induce autoimmune diseases. The effects of oestrogen on lupus, novel signalling pathways, abnormalities in cerebrospinal fluid in patients with neuropsychiatric lupus, mediators and mechanisms of pregnancy complications in SLE, gene expression profiling, BAFF blockade in SLE, clinical trials in SLE, disturbances of memory B cells, the evolution and pathogenesis of human anti-DNA antibodies were also discussed at length.

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