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Overview of Signal Processing by the Immune System in Systemic Lupus Erythematosus

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Systemic lupus erythematosus SLE is considered a chronic inflammatory disease, with periods of waxing and waning, where the disease pathogenesis is attributed to circulating antinuclear autoantibodies (1;2) and the dysfunction of T and B lymphocytes (3-5) and dendritic cells (6; 7). Although the pathogenesis is believed to lie in the dysregulation of the immune system, the involvement of various organ systems often leads to secondary morbidities resulting from renal failure, hypertension, and atherosclerosis (8). The cause of SLE is incompletely understood and current therapies have limited efficacy. A rational approach for therapeutic design requires a detailed understanding of disease pathogenesis. Independent lines of evidence have implicated environmental factors and genetic determinants of the host in the causation of the disease (9). Concordance rates for SLE are approximately 25% in monozygotic twins (10). Alternatively, the discordance rate may be as high as 70% among monozygotic twins (11), suggesting a significant role for exogenous agents (12;13). Genome-wide association studies have identified numerous chromosomal loci that may harbor lupus susceptibility genes (14), however, the functional significance of these lupus-associated polymorphisms is presently unknown. Therefore, further characterization of the molecular and cellular basis of signaling abnormalities within the immune system that lead to autoreactivity and inflammation and their relationship to regulation of gene expression remain critical for understanding of disease pathogenesis (15).

In the first paper of the special issue of Autoimmunity Reviews dedicated to the signaling abnormalities in lupus, Stanford Peng provides an authoritative review of T and B cell dysfunction and their genetic bases. Fernandez et al demonstrate that mitochondrial dysfunction characterized by elevated transmembrane potential and increased mitochondrial mass causes accumulation of Ca^{2+} in mitochondria and enhanced Ca^{2+} fluxing upon T cells activation as well as predisposition to death by necrosis; the latter of which is pro-inflammatory stimulating B cells and dendritic cells by releasing oxidized DNA and high mobility group B1 protein. Rapamycin treatment that inactivates the mammalian target of rapamycin (mTOR), a protein of the outer mitochondrial membrane sensing changes in the transmembrane potential normalizes Ca^{2+} fluxing in SLE patients. Next, Jose Crispín and George Tsokos focus on the regulation of IL-2 expression of T cells which they view as a fundamental defect of T cell dysfunction. They discuss the newly discovered role of chromatin re-organization through acetylation of histones and the influence of Foxp3 in “non-regulatory” T cells. Gabriela

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Gorelik and Bruce Richardson make the case that T-cell hyperactivity is causing by a general hypomethylation of DNA due to impaired ERK and PKC δ signaling. Alessandra Pernis shows that deficiency of IRF4 allows inappropriate activation of a subsets of Rho GTPases, defective ERK signaling and persistence of self-reactive CD4 T cells leading to autoimmunity. Pulieva et al. show that failure of CD8 cytotoxic T lymphocytes may allow persistence of CD4 T cell-driven polyclonal B cell activation resulting in clinical lupus. Kim et al. emphasize the role of the innate immune system in SLE. Nucleic acid-containing immune complexes activate the innate response by engaging specific Toll-like receptors (TLRs) and promote the generation of autoantibodies. Importantly, nucleic acids become more immunogenic in SLE due to hypomethylation and increased oxidization. As reviewed by Jenks and Sanz, B-cell depletion by anti-CD20 antibody (rituximab) has emerged as an effective treatment modality for a subset of patients with rheumatoid arthritis and lupus and studies of rituximab-treated patients allow a unique opportunity to assess the role of B-cells in dysfunction of other cell types, such as T cells and dendritic cells. Liu and Mohan emphasize the importance of B-cell activation with a focus on activation of the Akt/mTOR pathway. Thus, activation of the redox-sensitive mTOR pathway may play a central regulatory role of metabolic control of gene expression in both T and B cells in SLE. There is significant overlap among the altered signaling pathways and further mechanistic studies will be needed to establish their molecular order and relative significance as a therapeutic targets in SLE.

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