Advance in immune pathogenesis of systemic lupus erythematosus: Gaps in the disease paradigm

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System lupus erythematous (SLE) is a systemic multi-organ autoimmune disease characterized by widespread loss of immune tolerance to nuclear self-antigens. The pathogenesis of SLE are multi-step process require induction, maintenance and progression of the disease that may take long time leading to tissue injury. Both genetic and environmental factors are well documented contribute to the genesis of profound abnormalities in innate and adaptive immunity and progression of lupus

The dysregulation of immune responses includes defects in central and peripheral tolerance, apoptosis defects with increased antigenic load, excess T cell help with abnormal signaling, B cell hyperactivity and autoantibody production, cytokine imbalance ultimately lead to immune complex formation and complement activation causing immunologically mediated tissue injury and disease onset. SLE patients have shown increased numbers of CD3+CD4–CD8– T cells and interleukin 17 producing T cells along with regulatory T cells decreasing. Follicular helper T cells (Tfh) drive B cells differentiation in germinal center (GC) play an important role in promoting pathogenic autoantibody production. Abnormal generation of Tfh cells in the GCs or peripherals blood could lead to autoimmunity. Regarding T cell signaling, SLE patients demonstrated decreased levels of CD3ζ and abnormal association of *FcRγ* with the CD3–TCR complex results in the ’rewiring’ of the TCR intracellular signaling through *Syk* rather than ZAP-70. Subsequently, an imbalance of increasing intracellular calcium result in transcription factor activation

The disruptions in innate immunity are critical to the initiation and perpetuation of the disease. Pathogen recognition is possibly one of the most important initiators of autoimmunity. Neutrophils are not only the key players in the recognition and elimination of pathogens but also sense self-nucleic acids and products of sterile tissue damage. Neutrophils can undergo a specialized form of cell death termed NETosis (neutrophil cell death via neutrophil extracellular trap) that immobilize and kill invading microbes extracellularly which increased in SLE derived neutrophils. These dysfunctions might contribute to vascular complications, lupus nephritis and cutaneous lupus erythematosus. Toll-like receptors (TLRs) localized on the cell surface or in endosomes have played a critical role in innate immunity responses against different pathogens. Internalized nucleic

acids immune complexes act as endogenous ligands that activate intracellular TLRs, which subsequently initiate a cascade of signaling pathways leading to the increased production of type I interferons (IFNs) in plasmacytoid dendritic cells (pDCs). Type I IFNs have the causative roles of increased apoptosis, NETosis, innate immune signaling, and viral infection-induced autoimmunity.

The present SLE management largely depends on empiric immunosuppressive therapies with substantial toxicities and possibly inadequate control of the disease. The development of targeted therapies and elucidation the markers of tissue damage that specifically address disease pathogenesis individually may provide new advances to improve the SLE treatment