COMMENTARY


Qingjun Pan1, Yanse Chen1, Shujun Wang1, Yong-Zhi Xu1,* and Hua-Feng Liu1,*

1Key Laboratory of Prevention and Management of Chronic Kidney Disease of Zhanjiang City, Institute of Nephrology, Affiliated Hospital of Guangdong Medical University, 57th South Renmin Road, Zhanjiang 524001, Guangdong, China

Mitochondria, autonomous double-membrane organelles, execute numerous key intracellular processes in the cell including oxidative phosphorylation, amino acid biogenesis, fatty acid catabolism, calcium homeostasis and apoptosis [1-4]. Consequently, mitochondria play a critical role in maintaining normal cellular physiology, and mitochondrial defects are associated with some diseases, including autoimmune diseases [5]. Recently, the association between abnormal mitochondria and Systemic Lupus Erythematosus (SLE) pathogenesis has gained increasing interest [6], an autoimmune disorder associated with inflammation and abnormal autoantibody production [7, 8]. Multi-system damage that adversely affects human health, and traditional treatment methods primarily rely on steroids and immunosuppressors, thus rendering SLE a somewhat refractory disease with a high recurrence rate after remission [9]; therefore, novel pathogenic mechanisms prompting the use of therapeutic targets are urgently required.

Yang et al. recently described the potential and emerging pathogenetic mechanisms in SLE, which depend on mitochondria and, more specifically, on the roles that mitochondria play either as autoantigens or potential evidence of SLE. They reviewed studies on the abnormal structure and function of mitochondria in SLE and therapies targeting mitochondria in several databases. Thus, they tested the hypothesis that mitochondrial chaos may involve factors and risk elements of SLE. Interestingly, mitochondria serving as antigen resources may be implicated in the following aspects: (i) retention of mitochondrial DNA-oxidized residues; (ii) modification of mtDNA by the hydroxyl radical; (iii) formation of Neutrophil Extracellular traps (NETs) containing mtDNA structures rooted from oxidative damaged T and B cells. Furthermore, they investigated that mitochondrial dysfunction underlies the pathogenesis of SLE, including mitochondrial somatic mutations, expression of specific genes and mtDNA haplogroups, mitochondrial dynamics, aberrant energy metabolism, augmented mitochondrial ROS production, and inflammation [10].

Furthermore, maintenance of homeostasis in mitochondrial biogenesis by reducing NO production, reversing the effects of NO, activating mTOR, and altering Ca2+ signaling in T cells of patients may serve as novel treatment strategies for SLE. Conversely, Yang et al. speculated that aberrant mitochondria-induced apoptosis protects against SLE pathogenesis, while necrosis may increase the vulnerability to SLE and damage target tissues [10]. Probably, the molecule underlying mitochondrial dysfunction, potentially contributing to easy diagnosis and therapeutic targets, has self-contradictory and cross-interactive effects.

SLE is a prototypic autoimmune disease that can potentially affect multiple organs. A major contributor to morbidity and mortality among SLE patients is kidney involvement, manifesting as Lupus Nephritis (LN) [11]. Recently, we observed that accelerated senescence in glomerular cells potentially contributes to glomerular injury in LN, and dexamethasone treatment can attenuate elevated glomerular expression of Senescence-associated β-galactosidase (SA-β-Gal) [12]. LN
has been proposed to be mitigated through some novel drug targeting pathways including abatacept, anti-CD80/CD86 therapy; BIIB-023, a tumor necrosis factor-like weak inducer of apoptosis (TWEAK)-specific mAb; sirukumab, an IL-6-specific mAb; and the immunomodulator laquinimod sodium [11]. However, these upcoming biological agents primarily target patients with high disease activity, while most other patients still remain in dire conditions. Yang et al. reported the progressive association between mitochondria and LN [12]. As an active organ, kidneys need a mass of energy consumption, which is primarily derived from mitochondria. On reviewing several databases, the authors found some studies suggesting that mtDNA, anti-mtDNA autoantibodies and aberrant T cell activation mediated by endothelial Nitric Oxide Synthase (eNOS) contributed to the pathogenesis of prototypical LN.

Actually, the mitochondrial pathological aspects of LN might be extended to the pathogenesis of more similar immune-mediated renal diseases with yet unknown underlying mechanisms. For instance, a recent study reported that a Nod-like Receptor Pyrin domain-containing-3 (NLRP3) localizes to the tubular epithelium in the human kidney and decreases in abundance in progressive IgA nephropathy [13], an immune-mediated primary glomerulonephritis. NLRP3 inflammasomes are reportedly activated by mitochondrial reactive oxygen species in albumin-induced tubulo-interstitial inflammation [14], and resveratrol suppresses NLRP3 inflammasome activation by preserving mitochondrial integrity and augmenting autophagy [15]. In addition, Tsai et al. reported that IgA immune complexes activate NLRP3 inflammasomes in macrophages, thus disrupting mitochondrial integrity and inducing mitochondrial ROS, and knockout of NLRP3 or a kidney-targeting delivery of shRNA of NLRP3 improves renal function and renal injury in a mouse IgAN model [16]. Moreover, serum albumin, a major intravascular antioxidant, which significantly attenuated intracellular reactive oxygen species and mitochondrial injury induced by hydrogen peroxide in mouse mesangial cells and in human kidney cells, was downregulated in IgAN patients with end-stage renal disease [17]. Interestingly, two case reports have indicated the possibility of mitochondrial dysfunction contributing to IgA pathogenesis [18, 19].

Understanding the mechanisms underlying mitochondrial defects will accelerate the identification of therapeutic targets in several diseases [20]. Thus far, few studies have explored the potential association between mitochondria and IgA; however, emerging evidence from the aforementioned studies may broaden this possibility. Unfortunately, the association between mitochondria and purpuric nephritis, another immune-mediated glomerulonephritis secondary to Henoch-Schönlein purpura [21], has not been reported. Perhaps, an unconventional study methodology and a more extensive analysis of the pathogenesis of immune-mediated nephropathy would be beneficial.

In conclusion, Yang et al. depicted the potential mechanisms underlying mitochondrial dysfunction in autoimmunity, including mitochondrial DNA damage, mitochondrial dynamics, abnormal mitochondrial biogenesis and energy metabolism, mitophagy, elevated oxidative stress, inflammatory reactions, apoptosis, and NETosis, which may also be implicated in other autoimmune diseases, in addition to SLE.

REFERENCES


The Role of Mitochondria in Systemic Lupus Erythematosus


Yong-Zhi Xu* and Hua-Feng Liu*

Key Laboratory of Prevention and Management of Chronic Kidney Disease of Zhanjiang City, Institute of Nephrology, Affiliated Hospital of Guangdong Medical University, 57th South Renmin Road, Zhanjiang 524001, Guangdong, China; Tel/Fax: 86-759-2387583; E-mails: lxyzhi@126.com (Y.X.); hf-liu@263.net (H.L.)

Current Medicinal Chemistry, 2021, Vol. 28, No. 10 2079


