Redox Biology 11 (2017) 297–311

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

The mitochondria-targeted antioxidant MitoQ ameliorated tubular injury mediated by mitophagy in diabetic kidney disease via Nrf2/PINK1

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ARTICLE INFO

Keywords:
Mitoq
Diabetic kidney disease
Mitophagy
Tubular

ABSTRACT

Mitochondria play a crucial role in tubular injury in diabetic kidney disease (DKD). MitoQ is a mitochondria-targeted antioxidant that exerts protective effects in diabetic mice, but the mechanism underlying these effects is not clear. We demonstrated that mitochondrial abnormalities, such as defective mitophagy, mitochondrial reactive oxygen species (ROS) overexpression and mitochondrial fragmentation, occurred in the tubular cells of db/db mice, accompanied by reduced PINK and Parkin expression and increased apoptosis. These changes were partially reversed following an intraperitoneal injection of mitoQ. High glucose (HG) also induces deficient mitophagy, mitochondrial dysfunction and apoptosis in HK-2 cells, changes that were reversed by mitoQ. Moreover, mitoQ restored the expression, activity and translocation of HG-induced NF-E2-related factor 2 (Nrf2) and inhibited the expression of Kelch-like ECH-associated protein (Keap1), as well as the interaction between Nrf2 and Keap1. The reduced PINK and Parkin expression noted in HK-2 cells subjected to HG exposure was partially restored by mitoQ. This effect was abolished by Nrf2 siRNA and augmented by Keap1 siRNA. Transfection with Nrf2 siRNA or PINK siRNA in HK-2 cells exposed to HG conditions partially blocked the effects of mitoQ on mitophagy and tubular damage. These results suggest that mitoQ exerts beneficial effects on tubular injury in DKD via mitophagy and that mitochondrial quality control is mediated by Nrf2/PINK.

1. Introduction

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease. [1] Tubular injury plays a critical role in DKD progression, which correlates with renal functional deterioration, a primary change associated with the disease. [2] The pathogenesis of DKD is not clear, but mitochondrial abnormalities largely contribute to its development. [3–5].

Mitochondria are dynamic organelles that undergo frequent fission and fusion events modulated by profission proteins (Drp1 and Fis1) and profusion proteins (Mfn1/2 and OPA1), which maintain mitochondrial turnover and cellular network balance. [3] Dysfunctional mitochondria exhibit fragmentation and membrane depolarization, generate massive amounts of reactive oxygen species (ROS) and release apoptogenic proteins (e.g., caspase-3) in response to stressors, such as diabetic nephropathy, which eventually activate the mitochondrial cell death pathway. Renal proximal tubular cells contain an enrichment of mitochondria and rely on oxidative phosphorylation. Therefore, tubules are vulnerable to mitochondrial impairment. [4] Accumulating data indicate that excessive mitochondrial oxidative stress and aberrant dynamics are the primary factors responsible for tubule damage in DKD. [3,6–9] However, the mechanism underlying this process is not fully understood.

Selective macroautophagic (mitophagic) targeting of damaged or dysfunctional mitochondria via PTEN-induced putative kinase 1(PINK)/Parkin-dependent and independent (e.g., BNIP3 and FUNDC1) pathways has been emphasized in recent years. [10,11] These pathways play an essential role in maintaining mitochondrial turnover and quality control. [10,12] Zhan M et al. recently observed decreased tubular cell mitophagy in high-glucose (HG) ambient and

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http://dx.doi.org/10.1016/j.redox.2016.12.022
Received 5 November 2016; Received in revised form 9 December 2016; Accepted 19 December 2016
Available online 21 December 2016
2213-2317/

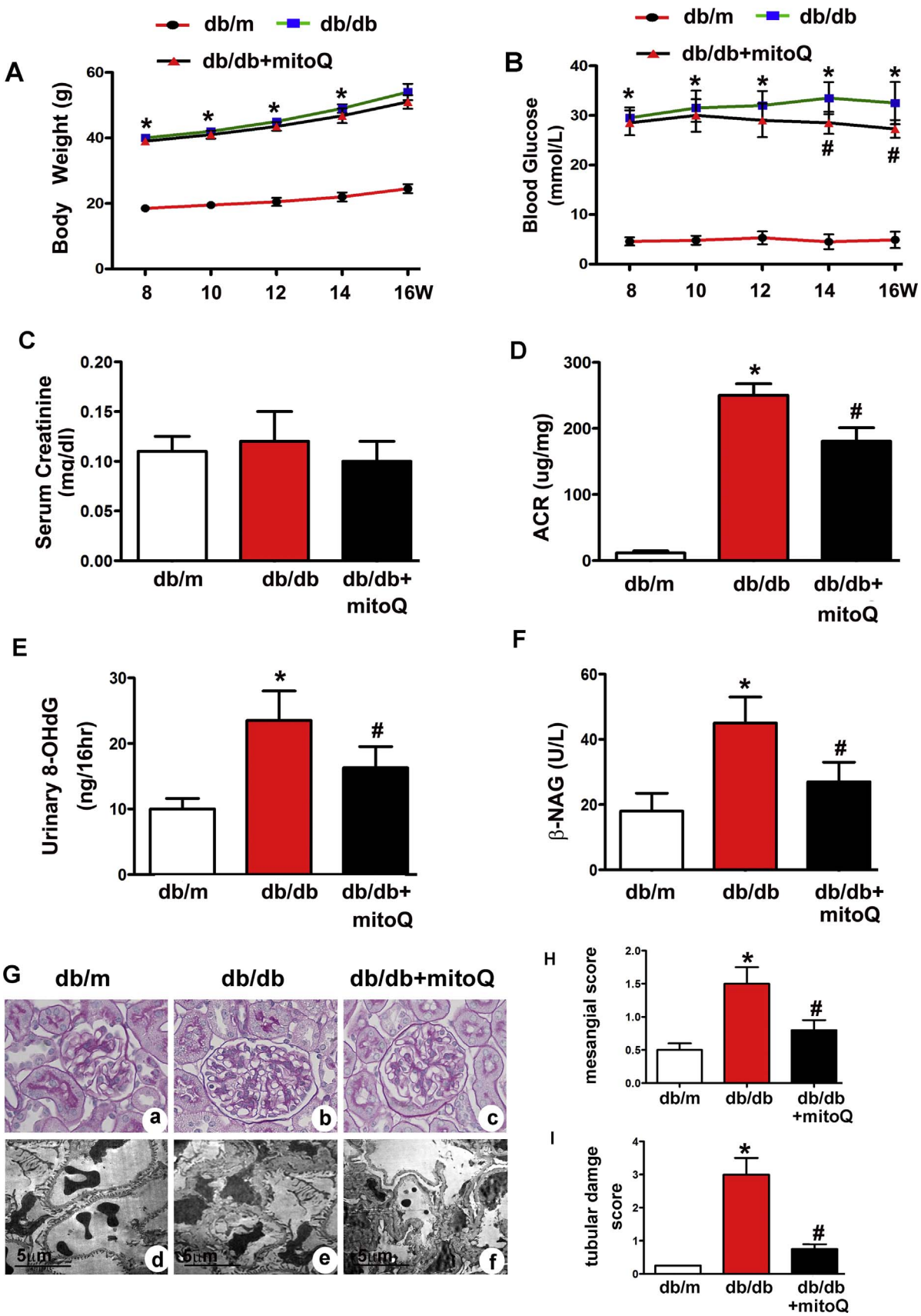

Fig. 1. Effect of mitoQ on renal functional and morphological characteristics in db/db mice. A: Body weight changes in db/m, db/db and db/db mice receiving mitoQ treatment for 8–16 weeks. B: Blood glucose concentrations in each group. C: Serum creatinine levels. D: Urinary ACRs. E and F: Urinary excretion of 8-OHdG and urine β-NAG levels. G: PAS staining (top panels) and EM (bottom panels) showing notable deformations in the tubules and glomeruli of db/db mice compared to those of db/m mice (Gb vs. Ga and Ge vs. Gd). These changes were dramatically ameliorated by mitoQ administration (Gc vs. Gb and Gf vs. Ge). H and I: Quantitative analysis of mesangial scores and tubular damage in each group. Values are the mean ± SE, *P < 0.05 vs. db/m; #P < 0.05 vs. db/db mice. n=6.