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ANXA1 Plays A Nephroprotective Role By Maintaining Mitochondrial Homeostasis Via Upregulating Uncoupling Protein 1 In Diabetic Nephropathy

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Abstract : Uncoupling of mitochondrial respiration by chemical uncouplers has proven effective in ameliorating obesity, insulin resistance, and hyperglycemia, which were risk factors for diabetic nephropathy (DN). Recently, it was found that annexin A1(ANXA1) could improve mitochondrial function to mitigate DN progression. However, the underlying mechanism is not fully clear yet. Here, it was identified that uncoupling protein 1 (UCP1), an inner membrane protein of mitochondria, as a key to mitochondrial homeostasis improved by ANXA1. Specifically, ANXA1 attenuated mitochondrial dysfunction via appropriately upregulating UCP1 by stabilizing its transcription factor GATA binding protein 3 (GATA3) through combining with thioredoxin. Moreover, specific overexpression of UCP1 in renal cortex rescued renal injuries in diabetic Anxa1-KO mice. UCP1 deletion aggravated renal injuries in HFD/STZ-induced diabetic mice. Mechanistically, UCP1 reduced mitochondrial fission through the aristaless-related homeobox (ARX)/cardiolipin synthase 1 (CRLS1) pathway. Therapeutically, CL316243, a UCP1 agonist, could attenuate established DN in db/db mice. This work established a novel principle to harness the power of uncouplers for the treatment of DN.

Keywords : diabetic nephropathy, uncoupling protein 1, mitochondrial homeostasis, cardiolipin metabolism
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