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UCP1 regulates cardiolipin metabolism and mediates mitochondrial homeostasis maintenance of ANXA1 in diabetic nephropathy

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Objectives : Diabetic nephropathy (DN) is accounted for a large proportion of chronic kidney disease (CKD) and is the leading cause of end-stage renal disease (ESRD) nowadays. The complex pathogenesis of DN has hindered the development of a single effective medicine, so it is of great significance to seek new therapeutic targets. Uncoupling of mitochondrial respiration by chemical uncouplers has proven effective in ameliorating obesity, insulin resistance, and hyperglycemia, which were risk factors for DN. Recently, we found that ANXA1 could improve mitochondrial function to mitigate DN progression. However, the underlying mechanism is not fully clear yet.
Methods : We used kidney samples from patients in our hospital. ANXA1-KO mice with local renal overexpression of UCP1 were constructed, UCP1-KO mice were constructed for STZ/HFD modeling, and db/db mice were treated with CL316243. UCP1-KO mice with renal overexpression of CRLS1 were constructed. Mice with PTECs-specific deletion of ANXA1 were constructed. Cell lines with UCP1/ANXA1/GATA3 knockdown and UCP1/ANXA1/GATA3 overexpression were constructed, and cell reversal tests were performed using Ac2-26, CL316243 and siRNA targeting the above genes.
Results : Here, we identified 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.
Conclusions : Thus, our data unraveled specific mechanism by which UCP1 mediated mitochondrial homeostasis maintenance via the ANXA1-GATA3-UCP1-ARX-CRLS1 signaling pathway. This work established a novel principle to harness the power of uncouplers for the treatment of DN.

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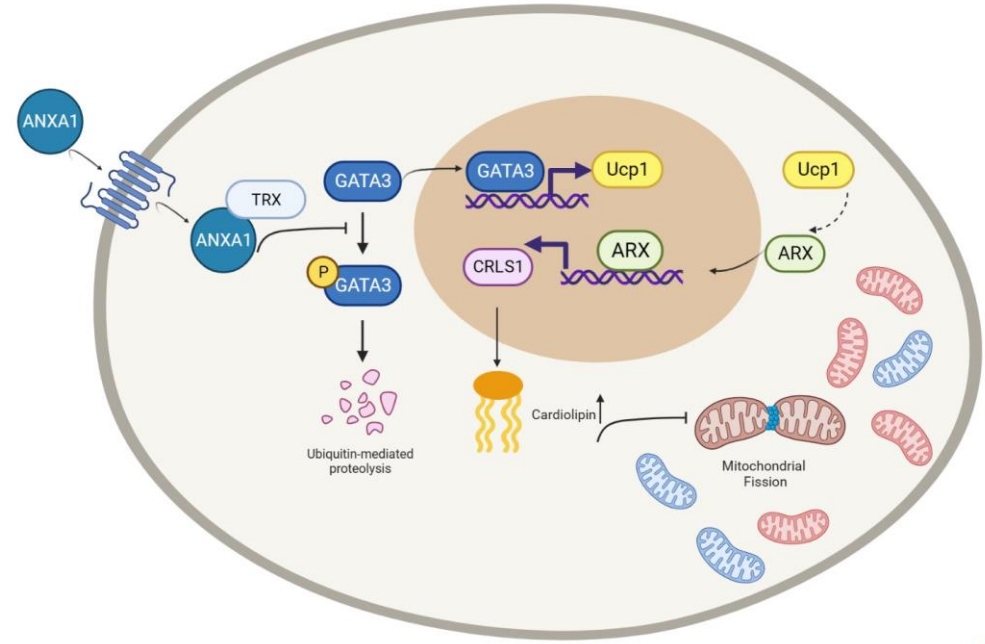
ANXA1
TRX
ANXA1
GATA3
P
GATA3
GATA3
Ucp1
CRLS1
ARX
Ucp1
ARX
Ubiquitin-mediated proteolysis
Cardiolipin
Mitochondrial Fission