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## **Therapeutic challenge of minicircle vector encoding Klotho in animal model**

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**Objectives:** Klotho treatment is a promising approach against kidney injury, but its clinical application is still undetermined. We developed a novel strategy to allow self-production of Klotho protein, using minicircle technology, and evaluated its feasibility in therapeutic Klotho delivery.

**Methods:** We engineered minicircle vectors to carry cassette sequences of Klotho and verified the self-production of Klotho protein from in HEK293T cells. We evaluated the location and persistence of delivered minicircle in vivo, and the duration of Klotho protein production from minicircles by serial measurement of Klotho protein in blood. We subsequently evaluated the therapeutic potential of Klotho-encoding minicircles in experimental model of renal injury.

**Results:** We confirmed the production of Klotho from minicircle by its significant availability in cells transfected with the minicircle, as well as in its conditioned medium, compared to that in cells transfected with parent vector. Minicircles were delivered in vivo by hydrodynamic injection via tail vein. After a single injection of minicircles, red fluorescence protein was detected until 30 days in liver, and Klotho protein was maintained until 10 days in the blood, suggesting the production of Klotho protein from minicircles via protein synthesis machinery in liver. Therapeutic effect of minicircle was confirmed by functional and histological improvement seen in mouse model of acute ischemia-reperfusion injury and unilateral ureteral obstruction.

**Conclusions:** Together, these findings implied that self-generated Klotho protein, using minicircle technology, is functionally active and relevant as a therapeutic approach in renal injury.