Inhibition of PARP-1 Attenuates Rat Renal Ischemia Reperfusion Injury

Christina Bracken1, Effie Tozzo1, Katelyn Pulito1, Jeff Stanwix1, Robert W Shine1, Mahati Krishna2, Nan Ji1, Dominique Stickens1
1Mitobridge, Inc. Cambridge, MA 02138; 2Syngene International, Bangalore, India

Background

Acute renal ischemia reperfusion injury (IRI) generates superoxide and other reactive species that activate PARP-1 to repair ROS-mediated DNA strand breaks. However, PARP-1 activation depletes the cells from NAD+ and ATP, and promotes pro-inflammatory signaling, exacerbating kidney injury. We hypothesized that PARP-1 inhibition would decrease/revert NAD+ depletion and reduce ischemia-reperfusion-induced acute kidney injury (IR-AKI), offering a potential therapeutic treatment for AKI.

Methods

In vitro: We evaluated the ability of Cmpd A, a novel and selective PARP1 inhibitor, to boost NAD+ and mitochondrial respiration and control cisplatin challenged human renal proximal tubule epithelial cells (PTCs). In vivo: Sprague-Dawley rats underwent a 50 minute bilateral IR and were administered Cmpd A (or vehicle), twice daily at 0.1, 0.3, 1, 5 or 10 mg/kg beginning 4 hours post reperfusion. Cmpd A activity was assessed by measuring renal PAR levels, NAD+ and mitochondrial respiration in control and cisplatin challenged human PTCs.

Cmpd A Blocks NAD+ Catabolism In Vivo

Cmpd A is dose-proportionally increased in rat plasma 30 mins post-dose. Similar results (not shown here) were obtained in kidney tissue (E). PARP levels measured in the kidney cortex from Cmpd A treated rats are inversely correlated to exposure (F).

PARP-1 Inhibition Attenuates IR-AKI in vivo

PARP-1 inhibitor, Cmpd A reduces PAR levels (A), and boosts NAD+ (B) in human PTCs translating to increased basal and maximal respiration (C). hTERT iPSCs are treated with Cmpd A for 24 hours then analyzed from total NAD+ and PAR by ELISA, and oxygen consumption using Seahorse. Importantly, in HK2 cells challenged with a sub-lethal dose of cisplatin, which reduces NAD+, Cmpd A is able to fully rescue the CDOD-mediated NAD+ loss (D).

At 24 hours, after just two IV doses, Cmpd A dose-dependently reduces plasma biomarkers of acute kidney injury (G), translating to a restoration of renal function (H). As injury resolves at 48 hours, Cmpd A sustains reduction of AKI biomarkers and maintains renal function.

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