ACUTE KIDNEY INJURY

Targeting NAD$^+$ synthesis to boost mitochondrial function and protect the kidney

NAD$^+$ is an essential co-substrate for a variety of regulatory proteins, including the sirtuin family of NAD$^+$-dependent deacylases, which have key roles in the regulation of redox status and energy metabolism. Several studies have demonstrated beneficial effects of NAD$^+$ and sirtuin activity on mitochondrial homeostasis, organ metabolism and lifespan across different species, and supplementation with the NAD$^+$ precursor, niacinamide, has previously been shown to protect against acute kidney injury (AKI). Now, researchers show that inhibition of α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD), an enzyme that limits production of the NAD$^+$ precursor quinolinic acid, increases NAD$^+$ levels in a tissue-specific manner and provides protection in models of AKI and non-alcoholic fatty liver disease (NAFLD). "Inhibiting the activity of ACMSD is a highly innovative way to boost NAD$^+$ levels in a tissue-specific fashion," say researchers Roberto Pellicciari and Johan Auwerx. "The fact that ACMSD is expressed only in kidney and liver provides a huge opportunity as it allows specific targeting of these tissues without causing side effects in other tissues, in contrast to other enzymes involved in NAD$^+$ synthesis and salvage, which are expressed in a wide number of tissues."

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To assess the potential of targeting ACMSD to increase NAD$^+$ activity the researchers first characterized the function of ACMSD in *Caenorhabditis elegans*. "We used a cross-species approach, as we believe that essential regulatory pathways are conserved across evolution," explains Auwerx. "Hence, what works in the worm should also work in mammals such as the mouse; this approach also increases our chances of translating our findings towards clinical trials in humans." Using RNA-mediated interference (RNAi), the researchers demonstrated that reducing transcript levels of the *ACMSD* orthologue *acds-1* induced an increase in NAD$^+$ and mitochondrial content and stimulated a stress response, known as the unfolded protein response (UPR), in mitochondria. RNAi-induced inhibition of *acds-1* also extended the lifespan of *C. elegans* — an effect that was dependent on the function of the mitochondrial UPR and the mitochondrial oxidative stress response.

In humans, ACMSD is present mainly in liver and kidney. To assess the effect of ACMSD inhibition in mammals, the researchers first confirmed in cultures of mouse primary hepatocytes that using a short hairpin RNA to reduce levels of *Acmsd* could induce expression of NAD$^+$, enhance mitochondrial function and increase levels of mitochondrial UPR transcripts, in line with findings from *C. elegans*. They then developed two selective ACMSD inhibitors and showed that pharmacological inhibition of ACMSD dose-dependently increased NAD$^+$ levels and enhanced mitochondrial function in primary mouse hepatocytes and in a human kidney cell line. In addition, ACMSD inhibition protected hepatocytes from fatty acid-induced apoptosis and protected human HK-2 kidney cells from cisplatin-induced apoptosis. "Our finding that both genetic and pharmacological inhibition of ACMSD resulted in the same phenotypic changes indicated that the pharmacological inhibitors were indeed hitting the same target as our genetic studies," notes Pellicciari.

Finally, the researchers assessed the efficacy of their ACMSD inhibitors in models of disease. In mice with diet-induced NAFLD, supplementation with the ACMSD inhibitor attenuated hepatic steatosis and improved the liver toxicity profile. In two mouse models of AKI (cisplatin-induced AKI and ischaemia–reperfusion injury), administration of the ACMSD inhibitor protected against structural and functional kidney damage, associated with preservation of NAD$^+$ levels and indices of mitochondrial function. "By affecting cellular NAD$^+$ levels, we show that ACMSD is an important gatekeeper of sirtuin activity and as such has a major impact on mitochondrial biogenesis and function," says Auwerx. "We expect to exploit the NAD$^+$ boosting activity of ACMSD inhibitors in the clinic to treat kidney and liver diseases that represent large unmet medical needs and are often linked with abnormal mitochondrial function."

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