Targeting pyruvate dehydrogenase complex to improve Barth syndrome cardiac function
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Q&A

Q: Is decreased NAD/NADH is an expected result due to the stress of accumulated NADH on dysfunctional ETC? As a result, DCA may not be beneficial in the long run?
A: Yes, NAD/NADH or at least NADH and FADH levels would be expected to decrease when the ETC becomes muted at I, II, and ? II, IV. However, unbiased metabolomics do not clearly support the decrease in NADH in our monocyte cell models (references 2 and 3). We previously reported that NAD increases by de novo synthesis in the low energy anti-oxidative state of disease tolerance in monocytes (reference 4) to support physiological resolution. We in monocytes (references 2 and 3 below) find evidence for maintaining NADH by anaplerosis from branched chain amino acids, oxaloacetate and glutamate, as also reported by you in the JBC 2019 publication that I listed on a presentation slide.

In reference 1 below, we show our clinical study and septic mice that with one does a DCA at 25 mg per kilogram, homeostasis is re-captured and if this is true as a stand, DCA presumably. would not be necessary as chronic treatment of the sepsis acute problem. We hope to find out in an NIH clinical trial in human sepsis. BTHS treatment using DCA would be entirely different.
If BARTH foundation shows interest, we will apply in 2021 to test DCA in mice cardiolipin genetic KO deficiency model, with and without sepsis stress with and without DCA. Maybe you would like to collaborate.

study introduces the new concept of PDC targeting as a potential for treating human sepsis by broadly promoting immunometabolic and bioenergy homeostasis.


3. Xuewei Zhu, David Long, Manal Zabalawi, Brian Ingram, Barbara Yoza, Petr Stacpoole, and Charles McCall. “Stimulating pyruvate dehydrogenase complex (PDC) reduces itaconate levels and promotes TCA cycle anabolic bioenergetics in inflamed monocytes” J. Leukocyte Biology (in press). This in vitro study in human monocytes supports that PDC controls TCA cycle bioenergetics by balancing itaconate levels, reducing oxidative stress, and rejuvenating anabolism ATP generation.

4. Jingpu Zhang 1, Jie Tao 1, Yun Ling 2, Feng Li 3, Xuewei Zhu 4, Li Xu 1, Mei Wang 3, Shuye Zhang 1, Charles E McCall 4, Tie Fu Liu 1 Switch of NAD Salvage to de novo Biosynthesis Sustains SIRT1-RelB-Dependent Inflammatory Tolerance PMID: 31681271 PMCID: PMC6797595 DOI: 10.3389/fimmu.2019.02358

Q: How does DCA act to enhance the trans-sulfuration cycle?
A: We found evidence for increased transsulfuration in human THP1 human monocyte cell models of severe acute inflammation, which mimics in many ways sepsis in humans and mice, as the adaptive or tolerance state emerges. The data were not quantitative, but suggested by decreased methionine, increased cysteine, taurine and GSH/GSSG, temporally aligned as activation is being replaced by deactivation or tolerance. The results are shown in reference 2 below. Unpublished stable carbon one labeling of serine support an increases in transsulfuration in activating state monocytes.

In contrast, Dichloroacetate (DCA) as a promoter of the PDC/PDK/PDP homeostat seemed to decrease the need for transsulfuration in the sepsis cell model, presumably by rebalancing redox. We are studying redox balance in mice and human sepsis using tissue and metabalomics probes. The effects of DCA on redox in the sepsis simulating monocyte model are reported in reference 3 below. In an unpublished study under review of isolated hepatocytes and plasma of septic mice, DCA reversed oxidant stress in alignment with rebalancing GSG/GSSG and signs of lipid oxidant stress.

Reference 1 is DCA PKK/PDC targeting to increase survival in septic mice.

This in vivo/ex vivo preclinical study introduces the new concept of PDC targeting as a potential for treating human sepsis by broadly promoting immunometabolic and bioenergy homeostasis.


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