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Insights into the pathophysiology of MCAD deficiency

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Propositions

1. Upon fasting and acute cold exposure, the reduction in blood glucose in medium-chain acyl-CoA dehydrogenase (MCAD) knockout mice is not caused by increased peripheral demand, but rather by an impairment in the glucose supply by the liver (This thesis).
2. Given the potential role of coenzyme A (CoA) availability in the pathogenic mechanisms of MCAD deficiency, the remodeling of CoA metabolism may serve as a compensatory adaptation; working towards both increasing the CoA availability and relieving the accumulation of potentially toxic C8-acyl-CoA (This thesis).
3. While increasing the CoA pool may seem a reasonable therapeutical strategy for MCADD, the associated excessive generation of medium-chain acyl-CoA esters should be taken into account when considering its therapeutic supplementation (This thesis).
4. Different metabolic pathways share metabolites and, therefore, accumulation or depletion of metabolites has a broad impact. Thus, when studying an inherited metabolic disorder, one should “zoom-out” from single reactions or isolated pathways, and approach them in a broader network (This thesis).
5. Mimicking the complexity of living organisms *in vitro* remains a central challenge in the field and, therefore, an educated choice of the experimental model system and conditions is critical to obtain relevant research outcomes.
6. The development, optimization, and characterization of patient-derived *in vitro* and *in silico* models set the groundwork for personalized studies in the near future.
7. Models are generated as representations of real-life phenomena. As approximations, they have limitations. The acceptance of the uncertainty of a specific model depends on both its scientific base and one’s background and views (Hans Bouwmeester, adapted).
8. In times in which science is compartmentalized in increasingly specific sub-fields, working in interdisciplinary teams allows us to approach a scientific question from different and complementary angles. Such an approach enhances the impact of the work and, perhaps, brings us closer to a better understanding of complex real-life phenomena.
9. When failure is not an option, we can forget about creativity, learning, and innovation (Brené Brown).
10. The reward of the young scientist is the emotional thrill of being the first person in the history of the world to see something or to understand something. Nothing can compare with that experience (Cecilia Payne-Gaposchkin).
11. Incredible change happens in your life when you decide to take control of what you do have power over instead of craving control over what you don't (Steve Maraboli).