Acetate transport into mitochondria does not require a carnitine shuttle mechanism

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Dear Editor,

A recent metabolic imaging study by Koellish and colleagues has demonstrated the potential for the use of hyperpolarized ^{13}C magnetic resonance to follow the fate of acetate in rat hearts (1). However, the work includes an unfortunate basic misrepresentation of the cellular metabolic fate of acetate as outlined in the Introduction section and Figure 1 of the paper (1). The authors state that, as acetate is capable of being activated in the cytosol by cytosolic acetyl-CoA synthetase, the only way that acetyl-CoA can be generated inside the mitochondrial matrix is through a shuttle mechanism resembling the carnitine-based one dedicated to the transfer of activated *long-chain* fatty acids. The latter is a key mechanism for enabling the β-oxidation of long-chain fatty acids, whereby two mitochondrial inner membrane carnitine *palmitoyl*transferases (CPT1 and CPT2) and a carnitine acylcarnitine translocase (CACT) mediate the transfer of the long-chain fatty acid moiety into the mitochondrial matrix (2). CPT1 enzymes (CPT1A, CPT1B and CPT1C) are encoded by three separate genes, which are differentially expressed in tissues (2). CPT1A is abundant in the liver but is also found in other tissues, whereas CPT1B is primarily present in cardiac and skeletal muscle and brown adipose tissue. CPT1C is expressed in neurons, but shows elevated expression in some cancer cell types (3). In the older literature these carnitine long-chain *acyl*transferases were referred to as CAT (carnitine acyltransferase) enzymes, and this is what seems to have resulted in the misunderstanding that has now arisen in the paper by Koellisch et al who use the acronym CAT for carnitine *acetyl*transferase.

Carnitine *acetyl*transferase (abbreviated as CrAT or CAT) is present in both the mitochondrial matrix and peroxisomes, and are both transcribed from a single gene (4). However, acetate transport into mitochondria is not considered to require a carnitine shuttle mechanism, as acetate is easily permeable through the mitochondrial inner membrane and can be directly activated by a specific intra-mitochondria acetyl-CoA synthetase (5).

Given the very different cellular metabolic fates of the acetate and long-chain acyl moieties, it imperative not to confuse CAT/CrAT with CPTs as this can lead to a very basic metabolic understanding. As this is not the first instance of studies in which it has been assumed that acetate requires CPT1 (which they refer to as CAT) for metabolism in the mitochondria, we consider it necessary to draw attention to this inappropriate use of terminology as it is leading to a potentially serious misunderstanding of the underlying biochemical processes involved in acetate and long-chain fatty acid mitochondrial metabolism.

References

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