A different opinion on the reported role of Poldip2 and ACSM1 in a mammalian lipoic acid salvage pathway controlling HIF-1 activation.

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Paredes et al recently described Poldip2 as a novel regulator of mitochondrial lipoylation through stabilisation of ACSM1 (1). We have several concerns with their proposed model based on the following reasons.

Prior mammalian and yeast biochemical studies are not consistent with a significant physiological role for lipoate scavenging in eukaryotes (2, 3). Genetic depletion or germline mutations in de novo lipoic acid synthesis enzymes (LIAS, LIPT1 and LIPT2) result in loss of mitochondrial lipoylation, respiration, and developmental defects in mammals, which are not reversed with exogenous lipoic acid (2, 4). While LIPT1 has an established role in this de novo synthesis pathway, there is no evidence that LIPT1 is a scavenging enzyme, as implied by Paredes et al. The suggestion that all lipoate-dependent enzymes are octanoylated by LIPT2 and support LIAS-mediated lipoate synthesis is not, to our knowledge, supported by experimental studies.

ACSM1 is a promiscuous enzyme reported to activate the native (D) and unnatural (L) stereoisomers of lipoate in vitro (5). This lack of enantiomeric specificity makes it unlikely that ACSM1-catalysed lipoate activation is physiological. Furthermore, as ACSM1 uses GTP (5), rather than ATP, it is unclear how ACSM1 would form the lipoyl-AMP intermediate proposed in the model by Paredes et al. The authors also provide no explanation as to the source of the scavenged lipoate.

The identification that impaired lipoylation of the 2-oxoglutarate (2-OG) dehydrogenase complex (OGDHc) leads to stabilisation of HIF-1α, replicates earlier work by

Burr et al (6), whereby 2-OG accumulation promotes the formation of L-2-hydroxyglutarate (L-2-HG) and inhibition of the prolyl hydroxylases (PHDs) is observed. This activation of HIFs following 2-OG and L-2-HG accumulation has been reproducibly observed in hypoxia and under acidotic conditions (7, 8). The mechanism proposed by Paredes et al is inconsistent with these prior observations. Loss of OGDHc activity leads to an increase in 2-OG levels (6, 9), rather than the decrease suggested by Paredes et al. Indeed, unbiased metabolomic flux studies show LIAS or OGDH deficiency increase cellular 2-OG in both cancer cells and primary dermal fibroblasts (6). Moreover, this increase in 2-OG is also observed in humans with germline mutations in lipoic acid synthesis (2). Paredes et al use an indirect method to measure 2-OG levels and provide no explanation as to why 2-OG levels are reduced in their model. More detailed measurements of the metabolic consequences of Poldip2 loss are required before concluding that HIF stabilisation is due to decreased 2-OG.

Finally, ACSM1 has previously been shown to be depleted in conditions of HIF stabilisation such as VHL depletion (10), so it is equally plausible that the loss of ACSM1 in hypoxia simply represents its suppression as part of its canonical role in fatty acid beta oxidation.

References

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