Mitochondrial cristae thinning upon higher substrate load in Hep-G2 cells

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Cristae morphology reflects the energetic demands of the cell. Reminiscent of Hackenbrock findings of orthodox *vs*. condensed cristae conformation, hypoxia is leading to cristae widening, clustering of mitofilin/Mic60 due to its ~20% decrease, and to decrease in ATP-synthase dimers [1]. In glycolytic HepG2 cells hypoxia also induces partly dormant oxidative phosphorylation with concomitant respiration decrease [2]. Searching for the reversal of cristae widening, using transmission electron microscopy, assaying intracristal space (ICS) volume decreases by 3D superresolution Biplane FPALM microscopy with Eos–conjugated ICS–located lactamase-β and Mic60 distribution by 3D dSTORM immunocytochemistry, we have found that cristae thinning at faster metabolism proceeds in glycolytic HepG2 cells previously adapted to hypoxia upon a sudden addition of membrane–permeant Krebs cycle substrate dimethyl-2-oxoglutarate. Thus, dimethyl-2-oxoglutarate instantly increases the previously hypoxia-downregulated respiration of glycolytic HepG2 cells and the yet unknown regulations shrunk the ICS, resulting in cristae thinning. This is reflected by the ICS volume decrease in majority of segments along the entire length of mitochondrial reticular network. The instant dimethyl-2-oxoglutarate addition to both normoxic and hypoxic cells increased by 20% and up to about twice, respectively, the MitoSOX-monitored superoxide formation released to the matrix. In conclusion, we described exemplar situations when cristae are literary breathing by thickening/thinning at decreasing/increasing substrate load.

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References:

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[2] L. Plecitá-Hlavatá, J. Ježek, P. Ježek, Aglycemia keeps mitochondrial oxidative phosphorylation under hypoxic conditions in HepG2 cells. J Bioenerg Biomembr 47(2015) 467-76.