The roles of cytosolic and intramitochondrial Ca^{2+} and the mitochondrial Ca^{2+}-uniporter (MCU) in the stimulation of mammalian oxidative phosphorylation

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Szibor *et al.* (1) concluded that mitochondrial pyruvate oxidation is regulated primarily by cytosolic Ca^{2+} ($[Ca^{2+}]_{cyt}$) activation of the malate-aspartate shuttle, rather than by mitochondrial Ca^{2+} ($[Ca^{2+}]_{mit}$) activation of intramitochondrial dehydrogenases. Pyruvate dehydrogenase (PDH) activity largely reflects the ratio of active nonphosphorylated PDH to inactive phosphorylated PDH (PDHP) (2), but Szibor *et al.* (1) did not measure PDH/PDHP ratios. Moreover, their studies used unphysiological conditions with isolated mitochondria (saturating ADP); with synaptosomes, thymocytes, and fibroblasts (uncoupler and high pyruvate); and with perfused hearts (high pyruvate). These conditions likely suppress ATP-linked PDH kinase activity (inhibited by ADP and pyruvate), resulting in very high PDH/PDHP ratios. This severely limits any potential activation of PDH by the $[Ca^{2+}]_{mit}$-stimulated PDHP phosphatase, inevitably delivering the results obtained. Under more physiological conditions, where PDH/PDHP ratios are lower, many studies have shown that $[Ca^{2+}]_{mit}$ is a key activator of pyruvate oxidation (3–5).

We suggest that stimulation of the malate-aspartate shuttle by $[Ca^{2+}]_{cyt}$ (increasing mitochondrial oxidation of cytoplasmic NADH) complements regulation of intramitochondrial dehydrogenases by $[Ca^{2+}]_{mit}$ (2). The latter may be regarded as an evolutionary refinement of "intrinsic" mechanisms (also present in lower organisms) increasing ATP production without lowering ATP/ADP ratios (2). Indeed, blockade of the mitochondrial Ca^{2+} uniporter (MCU) using ruthenium red decreases ATP/ADP ratios in stimulated hearts (6), consistent with reduced exercise tolerance in MCU-null mice (7), even though core intrinsic mechanisms are retained. Furthermore, mitochondrial Ca^{2+} influx is not completely suppressed by MCU deletion (7).

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Conflict of interest—The authors declare that they have no conflicts of interest with the contents of this article.

References

1. Szibor, M., Gizatullina, Z., Gainutdinov, T., Endres, T., Debska-Vielhaber, G., Kunz, M., Karavasili, N., Hallmann, K., Schreiber, F., Bamberger, A., Schwarzer, M., Doenst, T., Heinze, H. J., Lessmann, V., Vielhaber, S., *et al.* (2020) Cytosolic, but not matrix, calcium is essential for adjustment of mitochondrial pyruvate supply. *J. Biol. Chem.* **295,** 4383–4397 CrossRef Medline
2. McCormack, J. G., Halestrap, A. P., and Denton, R. M. (1990) Role of calcium ions in regulation of mammalian intramitochondrial metabolism. *Physiol. Rev.* **70,** 391–425 CrossRef Medline
3. McCormack, J. G., Edgell, N. J., and Denton, R. M. (1982) Studies on the interactions of Ca^{2+} and pyruvate in the regulation of rat heart pyruvate dehydrogenase activity: effects of starvation and diabetes. *Biochem. J.* **202,** 419–427 CrossRef Medline
4. Hansford, R. G., and Castro, F. (1985) Role of Ca2+ in pyruvate dehydrogenase interconversion in brain mitochondria and synaptosomes. *Biochem. J.* **227,** 129–136 CrossRef Medline
5. Griffiths, E. J., and Rutter, G. A. (2009) Mitochondrial calcium as a key regulator of mitochondrial ATP production in mammalian cells. *Biochim. Biophys. Acta* **1787,** 1324–1333 CrossRef Medline
6. Unitt, J. F., McCormack, J. G., Reid, D., MacLachlan, L. K., and England, P. J. (1989) Direct evidence for a role of intramitochondrial Ca^{2+} in the regulation of oxidative phosphorylation in the stimulated rat heart studies using ^{31}P n.m.r. and ruthenium red. *Biochem. J.* **262,** 293–301 CrossRef Medline
7. Pan, X., Liu, J., Nguyen, T., Liu, C., Sun, J., Teng, Y., Fergusson, M. M., Rovira, I. I., Allen, M., Springer, D. A., Aponte, A. M., Gucek, M., Balaban, R. S., Murphy, E., and Finkel, T. (2013) The physiological role of mitochondrial calcium revealed by mice lacking the mitochondrial calcium uniporter. *Nat. Cell Biol.* **15,** 1464–1472 CrossRef Medline