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Minireview

Mitochondria and L-lactate metabolism

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Abstract **Although mitochondria have been the object of intensive study over many decades, some aspects of their metabolism remain to be fully elucidated, including the L-lactate metabolism.**

We review here the novel insights arisen from investigations on L-lactate metabolism in mammalian, plant and yeast mitochondria. The presence of L-lactate dehydrogenases inside mitochondria, where L-lactate enters in a carrier-mediated fashion, suggests that mitochondria play an important role in L-lactate metabolism. Functional studies have demonstrated the occurrence of several L-lactate carriers. Moreover, immunological investigations have proven the existence of monocarboxylate translocator isoforms in mitochondria.

Keywords: L-Lactate; Metabolism; Mitochondria; Mitochondrial transport; Dehydrogenase

1. Mitochondrial metabolism of L-lactate in mammals

A fundamental change in the overall view of the role of L-lactate (L-LAC) in metabolism occurred when it was shown that O_2 limitation is not a requirement for net formation, and that L-LAC is an important intermediary in glucose metabolism, a mobile fuel for aerobic metabolism, perhaps a mediator of redox state among various compartments both within and between cells [1]. Moreover, very recently, L-LAC was proposed to work as a signal in gene expression [2].

Recently, L-LAC metabolism has been the subject of several reviews [1,3–5 and refs. therein] and consequently we will limit the scope of this review to the role of mitochondria in L-LAC metabolism. Indeed, even though mitochondrial L-LAC metabolism was originally reported as early as 1959 [6], whether and how mitochondria participate to L-LAC metabolism has mostly been investigated only in the last two decades (Table 1). Contrarily, evidence of the existence of mitochondrial L-LAC carriers, as functionally investigated, was shown only in 2002 [7]. Our present position, based on our own work and that of others reviewed here is that the evidence for mitochondrial metabolism of L-LAC, due to the existence of both L-LAC carrier-mediated transport processes and of the mitochondrial L-lactate dehydrogenase (mL-LDH) is now compelling.

1.1. Spermatozoa

The first evidence in favour of the presence of a putative mL-LDH was from Clausen who found that about 40% of total activity in sperm cells was present in a particulate fraction showing high succinate dehydrogenase activity [8].

The existence of the mL-LDH which can reduce pyridine nucleotide in the mitochondrial matrix was demonstrated in hypotonically treated rabbit epididymal spermatozoa by means of oxygen uptake and fluorimetric studies [9]. It was also shown that the mL-LDH functions actively in these cells. In sperm cells the cytosolic L-lactate dehydrogenase (cL-LDH) and mL-LDH appear to be the same isoenzyme unique to those cells: L-LDH-X. The dual localization of the enzyme enables mammalian spermatozoa to exchange cytosolic and mitochondrial reducing equivalents by means of a L-LAC/pyruvate (PYR) shuttle, as suggested by Blanco et al. [10] and reconstituted later [11].

1.2. Liver

Since liver possesses the enzymatic machinery for gluconeogenesis (GNG) and since L-LAC is a major substrate for GNG, liver play a major role in L-LAC metabolism. Indeed, metabolism of L-LAC has traditionally been considered solely as a function of the cL-LDH in spite of the fact that the L-LAC oxidation by mitochondria and the existence of an mL-LDH in the inner compartments of isolated rat liver mitochondria (RLM) has been widely reported [12–15]. In a recent detailed investigation de Bari et al. [16] showed that externally added L-LAC can be oxidized in the matrix by an mL-LDH, with reduction of intramitochondrial $NAD(P)^+$ and generation of a mitochondrial electrochemical proton gradient. Mitochondrial L-LAC transport was investigated and the rate of L-LAC metabolism in vitro was found to be limited by the rate of L-LAC transport into the mitochondria. Three separate L-LAC translocators, distinct from those which translocate

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Abbreviations: cL-LDH, cytosolic L-lactate dehydrogenase; COX, cytochrome *c* oxidase; GNG, gluconeogenesis; L-LAC, L-lactate; mL-LDH, mitochondrial L-lactate dehydrogenase; MCT, monocarboxylate transporter; MCT1, monocarboxylate transporter isoform 1; MCT2, monocarboxylate transporter isoform 2; MPC, mitochondrial pyruvate carrier; OAA, oxaloacetate; PYR, pyruvate; RHM, rat heart mitochondria; RLM, rat liver mitochondria

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Table 1
The history of the L-lactate-mitochondria affair

Authors	Year	Source	Experimental approach	Main conclusions	Refs
Sacktor	1959	RBM	Oxygen uptake by polarography	RBM can oxidize L-LAC	[6]
Clausen	1969	Human sperm cells and rat tests	L-LDH and SDH spectrophotometric assay	L-LDH X isoenzyme is associated with SDH	[8]
Baba and Sharma	1971	RHM and RSMM	Histochemical and EM techniques	L-LDH is associated with the inner membrane and located in the mitochondrial matrix	[24]
Skilleter and Kun	1972	RLM	RLM fractionation with digitonin	NAD^+-dependent L-LDH is found in the intermembrane space fraction	[12]
Blanco et al.	1976	Mouse testes	L-LDH spectrophotometric assay	L-LDH X is located in the heavy fraction of mitochondria	[10]
Storey and Kayne	1977	HTRES	Oxygen uptake by polarography and fluorimetric measurements	Existence of an L- LDH in the mitochondrial matrix	[9]
Kline et al.	1986	RLM	Oxygen uptake by polarography	L-LDH is located in mitochondria	[13]
Brandt et al.	1987	RHM, RLM, RKM and RLYM	RLM fractionation with digitonin and treatment with subtilisin	L-LDH is located in the inner mitochondrial compartments	[14]
Szczesna-Kaczmarek	1990	RSMM	Oxygen uptake by polarography	L-LAC is oxidized by RSMM in a manner sensitive to oxamate and respiratory chain inhibitors	[32]
Popinigis et al.	1991	HSMM	Oxygen uptake by polarography	No evidence of m-L-LDH or L-LAC oxidation by mitochondria	[39]
Laughlin et al.	1993	Dog heart	Isotopic measurements	L-LAC metabolism takes place in mitochondria	[25]
Gallina et al.	1994	Mouse, rat and rabbit STM	Spectrophotometric assay	In vitro reconstruction of L-LAC/PYR shuttle	[11]
Izumi et al.	1997	Rat hippocampal slices	Histological measurements	L-LAC is an adequate energy substrate for sustaining brain function	[48]
Brooks et al.	1999	RLM, RHM and RSMM	Polarographic measurements and electrophoretic analysis	An intramitochondrial L-LDH pool facilitates L-LAC oxidation	[15]
Nakae et al.	1999	Muscle fibers of mdx gastrocnemius	Confocal microscopy and immunofluorescence analysis	L-LDH colocalizes with SDH	[35]
Dubouchaud et al.	2000	HSM	Immunoblotting analysis	Human mitochondrial preparations contain L-LDH	[36]
McClelland and Brooks	2002	RHG, RSRG, RSWG	Immunoblotting analysis	Rat mitochondrial preparations contain L-LDH	[37]
Valenti et al.	2002	RHM	Spectrophotometric assay	In vitro reconstruction of L-LAC/PYR shuttle	[7]
de Bari et al.	2004	RLM	Oxygen uptake by polarography, fluorimetric measurements of $\Delta\psi$ generation and L-LAC uptake by RLM, potentiometric measurements of H^+ uptake	L-LAC is taken up by RLM in a carrier-mediated manner and oxidized inside RLM, providing OAA outside RLM with partial GNG reconstituted	[16]
Sahlin et al.	2002	RSMM	Oxygen uptake by polarography and electrophoretic measurements	No evidence of an intracellular L-LAC shuttle	[40]
Rasmussen et al.	2002	HSM and MSM	Oxygen uptake by polarography and electrophoretic measurements	L-LDH is not a mitochondrial enzyme	[41]
Ponsot et al.	2005	HSF, MSF	In situ study of mitochondrial oxygen uptake	No sign of direct mitochondrial L-LAC oxidation	[42]