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Review

Unsuspected task for an old team: Succinate, fumarate and other Krebs cycle acids in metabolic remodeling

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ABSTRACT

Seventy years from the formalization of the Krebs cycle as the central metabolic turntable sustaining the cell respiratory process, key functions of several of its intermediates, especially succinate and fumarate, have been recently uncovered. The presumably immutable organization of the cycle has been challenged by a number of observations, and the variable subcellular location of a number of its constitutive protein components is now well recognized, although yet unexplained. Nonetheless, the most striking observations have been made in the recent period while investigating human diseases, especially a set of specific cancers, revealing the crucial role of Krebs cycle intermediates as factors affecting genes methylation and thus cell remodeling. We review here the recent advances and persisting incognita about the role of Krebs cycle acids in diverse aspects of cellular life and human pathology.

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1. Krebs cycle(s)

As depicted by Hans Adolf Krebs before the Second World War, the mitochondrial catabolism of organic acids is structured around a one-piece cycle, the so-called tricarboxylic acid cycle, also known as the Krebs cycle [1]. However, this proposal should be reexamined to take into account the kinetic split that isolates two segments in the cycle *in vivo* (Fig. 1) [2]. The occurrence of a shortcut resulting from the transamination reaction catalyzed by the aspartate aminotransferase actually allows the two independent segments to function at different rates. This entanglement links amino and organic acid catabolism and confers a key function to the glutamate/aspartate couple in controlling the overall kinetic of Krebs cycle acids (KCA) conversion. An additional level of complexity results from the subcellular distribution of Krebs cycle protein components. While all Krebs cycle enzymes are found in the mitochondrial matrix, a subset of these enzymes are also found, variably according to tissues, in the cytosol with yet unknown functions in most cases [3]. The subcellular compartmentation of the enzymes is combined with a discriminating permeability of the mitochondrial inner membrane towards each KCA [4]. In response to adverse conditions, part of the Krebs cycle enzymes may also functionally associate with additional enzymes. Thus, the α-ketoglutarate dehydrogenase using the NAD^+ generated by the mitochondrial diaphorases may provide succinyl CoA to the succinyl CoA ligase, allowing for an ATP generation in the case of respiratory chain complex I blockade [5]. Hence, it is probably wise to consider that the organization and function of the Krebs cycle is not unique and static but is modulated to fit the fluctuating metabolic demand of each cell type.

To ensure this flexibility, a set of genes encoding the components of the cycle is available in the human genome. Both concerted and individual regulations have been reported to modulate the expression of these genes, making use of the full panoply of regulatory processes, including control by miRNAs with indirect (e.g., miR-378 through PGC-1β) [6] or direct (e.g., miR-183 on IDH2) [7] actions on the members of the Krebs cycle [8].

Flux through the Krebs cycle is determined by both enzyme activities and substrate concentrations. Except under peculiar conditions,

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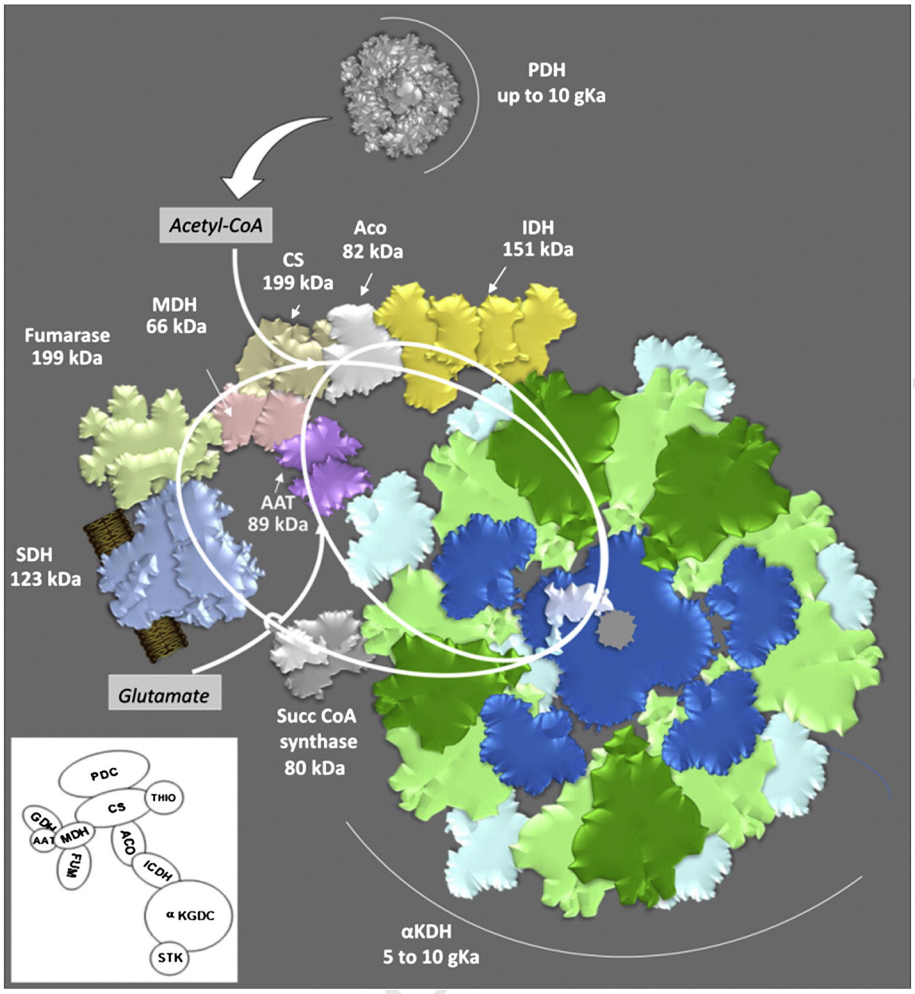

Fig. 1. A schematized view of the Krebs cycle(s) emphasizing the respective size of cycle(s) components and their arrangement as metabolons. Large white circles indicate different metabolic fluxes observed through Krebs cycle segments. The acetylCoA and the glutamate inputs are also indicated in white. The active, polymeric forms of enzymes are depicted with the corresponding molecular weights predicted from the human amino acid sequences (human mitochondrial protein database; http://bioinfo.nist.gov/hmpd/) after presequence cleavage. Protein structures and other data are derived from the RCSB PDB-101 (protein data base; http://www.rcsb.org/pdb/). Inset: The metabolon build from the Krebs cycle components as proposed by P. Srere in 1987 [67]. Abbreviations: AAT, aspartate aminotransferase (EC 2.6.1.1); Aco, aconitase (EC 4.2.1.3); CS, citrate synthase (EC 2.3.3.1); Fum, fumarate hydratase (EC 4.2.1.2); GDH, glutamate dehydrogenase (EC 1.4.1.2); IDH, isocitrate dehydrogenase (EC 1.1.1.41); αKDH (αKGDC), α-ketoglutarate dehydrogenase multienzyme complex (multiple copies of EC 1.2.4.2, EC 2.3.1.61 and EC 1.8.1.4); MDH, malate dehydrogenase (EC 1.1.1.37); PDH (PDC), pyruvate dehydrogenase multienzyme complex (multiple copies of EC 1.2.4.1, EC 2.3.1.12 and EC 1.8.1.4); Succ CoA synthase (STK), succinyl CoA synthase (EC 6.2.1.5); SDH, succinate dehydrogenase (EC 1.3.5.1).

including skeletal muscle under intensive exercise, the capacity of the Krebs cycle enzymes exceeds the need as does the respiratory chain, allowing to face variable feeding of substrates and variable cell energetic demand [9,10].

The handling of the KCA within the mitochondria is not independent of the cytosolic fate of these acids. The active malate–aspartate shuttle is widely admitted to act as a transfer mechanism for reduced equivalents from mitochondrial matrix NADH to cytosolic NAD^+ [11]. However, taking into account the newly described roles of KCA in the cytosol, their proper distribution in the cytosol ensured by this shuttle is presumably of crucial importance as well. There is actually, outside of mitochondria, a plethora of targets for KCA, possibly acting as primary substrates, signal molecules or actors of post-translational modifications (PTMs).

2. Krebs cycle acids and post-translational modifications

PTMs include the acetyl-CoA-dependent acetylation of either the N-terminus or at protein lysine residues [12–14]. Proteins can be also modified by succinylation whereby a succinyl group (–CO-CH2-CH2-CO–), presumably from succinyl-CoA, is added to a lysine residue (Fig. 2, bottom right) [15]. Both acetylation and succinylation of lysine residue modify the charge (from 1 to −1) with more steric hindrance in the case of succinylation. Because of this, succinylation is expected to more readily affect protein properties. In term of cellular targets, lysine modification, including acetylation and succinylation, possibly regulates numerous eukaryotic proteins involved in metabolism, cell cycle, aging, growth, angiogenesis and cancer [14], making PMTs identification an active field in proteomics research [16]. In particular, SOD1 protein is subjected to succinylation, and this appears as a critical factor for growth of lung tumor cells, an effect counterbalanced by SIRT5-dependent de-succinylation of the enzyme [17]. However, low levels of lysine succinylation are observed in eukaryotic cells and many possibly crucial sites remain unidentified. [15]. Mitochondrial matrix proteins can also be modified *via* a widely spread non-enzymatic acylation, dependent on the pH of the mitochondrial matrix and the actual concentration of acyl-CoA inside the mitochondria [18]. The presence of three matrix-located sirtuins (SIRT 3-5) with NAD^+-dependent deacetylase activity further suggests an essential role of mitochondrial protein acetylation in metabolism regulation [19,20].

The PTMs of histones are known to have a general impact on gene expression and DNA repair. Succinylation is one among these PTMs, with thirteen lysine succinylation sites described in HeLa cells so far, thus linking Krebs cycle metabolites to histone biology [21]. Cysteine is another residue that can undergo PTMs by a Michael addition

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