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Mini-review

Mitochondrial dysfunctions in cancer: Genetic defects and oncogenic signaling impinging on TCA cycle activity

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ABSTRACT

The tricarboxylic acid (TCA) cycle is a central route for oxidative metabolism. Besides being responsible for the production of NADH and $FADH_2$, which fuel the mitochondrial electron transport chain to generate ATP, the TCA cycle is also a robust source of metabolic intermediates required for anabolic reactions. This is particularly important for highly proliferating cells, like tumour cells, which require a continuous supply of precursors for the synthesis of lipids, proteins and nucleic acids. A number of mutations among the TCA cycle enzymes have been discovered and their association with some tumour types has been established. In this review we summarise the current knowledge regarding alterations of the TCA cycle in tumours, with particular attention to the three germline mutations of the enzymes succinate dehydrogenase, fumarate hydratase and isocitrate dehydrogenase, which are involved in the pathogenesis of tumours, and to the aberrant regulation of TCA cycle components that are under the control of oncogenes and tumour suppressors.

1. Introduction

Although mitochondria are often presented as power plants producing ATP by means of the oxidative phosphorylation (OXPHOS), this limited view does not reflect the importance of these organelles for cellular viability. Indeed, ATP production is only one of the innumerable functions in which mitochondria are involved. For instance, they are responsible for the activation of programmed mechanisms of cell death through the release of pro-apoptotic molecules (e.g. cytochrome *c* and apoptosis-inducing factor) [1]. Mitochondria are also the organelles where the enzymes involved in the tricarboxylic acid (TCA) cycle reside. The TCA cycle is pivotal for the entire cellular metabolism. Besides providing NADH and $FADH_2$ required for the function of the electron transport chain (ETC), many TCA cycle intermediates can be converted and channeled towards anabolic pathways producing lipids, nucleic acids and proteins [2]. In the light of the essential role of mitochondria, it is not surprising that defects in mitochondria components have been found to be involved in the most diverse human diseases, ranging from neurodegeneration and cardiovascular diseases to obesity and cancer [3–5]. In this review, we aim at summarising the current knowledge concerning the relationship linking defects and aberrant regulation of TCA cycle components to tumour formation and progression.

2. Overview on the TCA cycle

In its most simplistic conception (Fig. 1), the TCA cycle (also known as Kreb's cycle or citric acid cycle) is a cyclic metabolic pathway consisting in the oxidation of acetyl-CoA, deriving from glycolysis through pyruvate dehydrogenase and from lipid β-oxidation, to CO_2, with the concomitant production of NADH and $FADH_2$, which feed the ETC, and GTP/ATP. Namely, the net production is 3 NADH, 1 $FADH_2$ and 1 GTP/ATP for each molecule of acetyl-CoA consumed. The TCA cycle begins with the condensation of the acetyl moiety of acetyl-CoA with oxaloacetate by citrate synthase to form citrate. Citrate is reversibly isomerised to isocitrate by mitochondrial aconitase (ACO2) and then decarboxylated to α-ketoglutarate (α-KG) by mitochondrial isocitrate dehydrogenase (IDH). In this reaction, one molecule of CO_2 is released and one molecule of NAD^+ is reduced to NADH. In the next step, α-KG is further decarboxylated to succinyl-CoA by α-KG dehydrogenase (α-KGDH) complex, with the release of a second molecule of CO_2 and the production of a further molecule of NADH. The second part of the TCA cycle consists of a set of reactions aimed at oxidising

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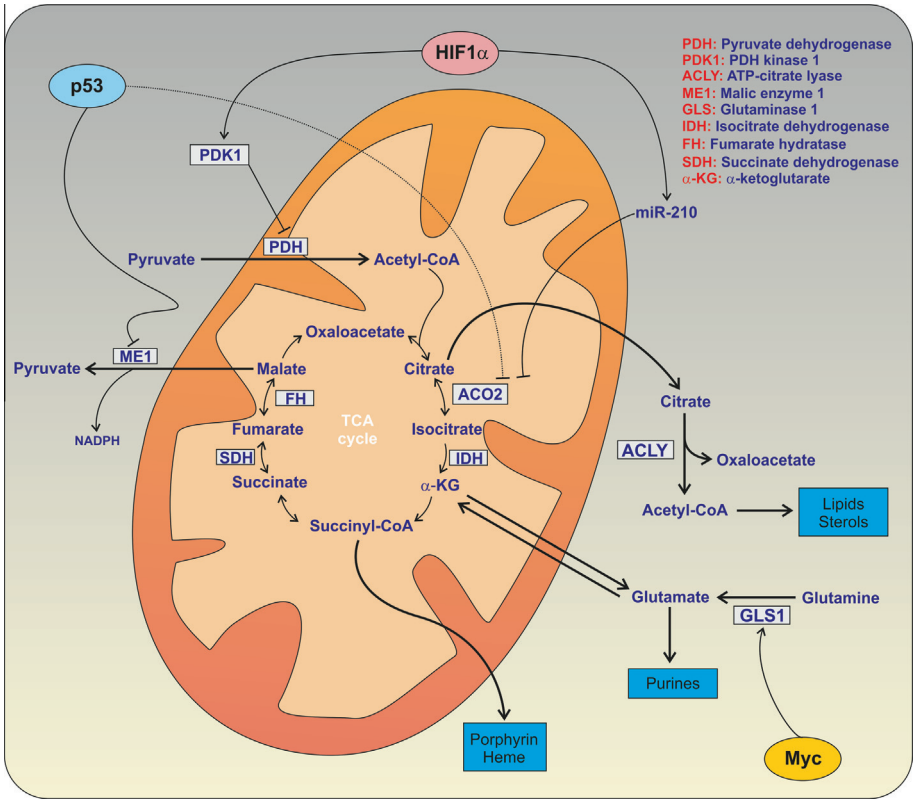

Fig. 1. Oncogenes and tumour suppressors tune the TCA cycle. TCA cycle alterations induced by oncogenes and tumour suppressors are shown. The tumour suppressor p53 represses ACO2 expression and the TCA cycle-related enzyme ME1. HIF1-α upregulates PDK1 expression and indirectly downregulates ACO2. Myc upregulation replenishes TCA cycle by increasing GLS expression.

succinyl-CoA to restore oxaloacetate. Succinyl-CoA is transformed to succinate by succinate-CoA ligase (SUCL), also known as succinate-CoA synthetase. SUCL is a dimeric protein consisting of one α subunit (SUCL1) and one of β subunits, that can be either the ADP-forming (SUCLA2) or the GDP-forming (SUCLG2); the nucleotide, ATP or GTP, generated in the reaction, depends on the type of the β subunit present. Succinate is then oxidised to fumarate by succinate dehydrogenase (SDH), which also represents the complex II of the ETC. In this step, a molecule of $FADH_2$ is produced. Then fumarate is hydrated to malate by fumarate hydratase (FH) and finally malate is oxidised by malate dehydrogenase to restore oxaloacetate.

Besides being a central pathway for energetic metabolism, the TCA cycle provides metabolic intermediates for biosynthetic reactions (cataplerosis) leading to the *de novo* synthesis of proteins, lipids and nucleic acids. This property is particularly exploited by fast-proliferating cells, such as tumour cells, which require a continuous production of biomass to sustain their accelerated growth rate. Citrate can be exported to the cytosol where it is cleaved by ATP-citrate lyase (ACLY) to acetyl-CoA and oxaloacetate. While acetyl-CoA is essential to sustain the *de novo* fatty acid synthesis, oxaloacetate can be converted to malate and then to pyruvate, with the concomitant production of NAD^+ and NADPH, two essential cofactors for glycolysis and for the antioxidant defense, respectively [6]. α-KG and oxaloacetate can be converted into their related aminoacids, glutamate and aspartate, by glutamate dehydrogenase and aspartate aminotransferase, and these amino acids can act as precursors for the synthesis of other amino acids and for the *de novo* synthesis of purines. Finally, succinyl-CoA is an intermediate in porphyrin and heme synthesis [7], whose increase is a hallmark of some tumour types, such as human breast carcinoma and non-small-cell lung cancer [8,9]. Although many cancer cells rely primarily on glycolysis, rather than on OXPHOS to produce ATP [10–12], on the basis of what is mentioned above the TCA cycle must be preserved to avoid the depletion of its intermediates. In particular, different reactions (anaplerosis) which refill and maintain the TCA cycle are induced to comply with this condition. Two of the most important anaplerotic reactions are the ATP-dependent carboxylation of pyruvate to oxaloacetate by pyruvate carboxylase, and the conversion of glutamate, mainly deriving from the deamination of glutamine by glutaminase 1, to α-KG by glutamate dehydrogenase [2,13].

3. Genetic defects in the TCA cycle are linked to cancer occurrence

Genetic defects have been found to affect TCA cycle components and to be responsible for the onset of a number of diseases, mainly the neurodegenerative ones. Fumarate hydratase autosomic recessive mutations cause severe and early encephalopathy [14]. Patients with an inherited deficiency of α-KGDH present a progressive, severe encephalopathy with axial hypotonia and psychotic behaviour [15], while mutations in the gene encoding for SUCLA2, have been found in patients affected by encephalomyopathy and mitochondrial DNA (mtDNA) depletion [16]. Despite the strong connection between TCA cycle alterations and pathological conditions, the connection between tumourigenesis and cancer progression remained elusive for long time. Indeed, only recently the development of some tumour types has been linked to dominant mutations of genes encoding for three TCA cycle enzymes, IDH, SDH and FH, paving the way for investigations about metabolic enzymes-mediated oncogenesis [17–19].

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