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Review

Krebs cycle dysfunction shapes epigenetic landscape of chromatin: Novel insights into mitochondrial regulation of aging process

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ABSTRACT

Although there is a substantial literature that mitochondria have a crucial role in the aging process, the mechanism has remained elusive. The role of reactive oxygen species, mitochondrial DNA injuries, and a decline in mitochondrial quality control has been proposed. Emerging studies have demonstrated that Krebs cycle intermediates, 2-oxoglutarate (also known as α-ketoglutarate), succinate and fumarate, can regulate the level of DNA and histone methylation. Moreover, citrate, also a Krebs cycle metabolite, can enhance histone acetylation. Genome-wide screening studies have revealed that the aging process is linked to significant epigenetic changes in the chromatin landscape, e.g. global demethylation of DNA and histones and increase in histone acetylation. Interestingly, recent studies have revealed that the demethylases of DNA (TET1-3) and histone lysines (KDM2-7) are members of 2-oxoglutarate-dependent dioxygenases (2-OGDO). The 2-OGDO enzymes are activated by oxygen, iron and the major Krebs cycle intermediate, 2-oxoglutarate, whereas they are inhibited by succinate and fumarate. Considering the endosymbiont origin of mitochondria, it is not surprising that Krebs cycle metabolites can control the gene expression of host cell by modifying the epigenetic landscape of chromatin. It seems that age-related disturbances in mitochondrial metabolism can induce epigenetic reprogramming, which promotes the appearance of senescent phenotype and degenerative diseases.

Contents

Abbreviations: ACLY, ATP-citrate lyase; ATM, ataxia telangiectasia mutated; BCL-2, B-cell leukemia-2; Chk2, checkpoint homolog kinase 2; CiC, citrate carrier; DIC, dicarboxylate carrier; DNMT, DNA methyltransferase; FH, fumarate hydratase; H3K27, histone 3 lysine 27; HAT, histone acetyltransferase; HDAC, histone deacetylases; HIF-1, hypoxia-inducible factor 1; IDH, isocitrate dehydrogenase; INK4 box, INK4B-ARF-INK4A locus; JMJD3, Jumonji domain-containing protein 3; KDM, lysine demethylase; 5-LOX, 5-lipoxygenase; NF-κB, nuclear factor-κB; OGC, 2-oxoglutarate carrier; 2-OGDH, 2-oxoglutarate dehydrogenase; 2-OGDO, 2-oxoglutarate-dependent dioxygenase; PHD, prolyl hydroxylase domain-containing protein; rDNA, ribosomal DNA; ROS, reactive oxygen species; RTG, retrograde regulation protein; SDH, succinate dehydrogenase; SAHF, senescence-associated heterochromatic foci; SIRT, sirtuin; SLC25, solute carrier family 25; TET, ten–eleven translocation hydroxylase.

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1. Introduction

Over a century ago, it was observed that the rate of energy metabolism was linked to the maximum lifespan of species; this subsequently led to the rate-of-living theory [1]. Consequently, Harman [2] proposed that an increased metabolic rate could enhance the production of oxygen free radicals. Since mitochondria are the major source of reactive oxygen species (ROS) in mammalian cells, it was postulated that the ROS-induced damage in mitochondria, in particular to mitochondrial DNA, could be detrimental to energy metabolism and thus provoke a decline in mitochondrial metabolism. There is a substantial literature indicating that the aging process is associated with increased mitochondrial ROS production and oxidative injuries which induce disturbances in the function of Krebs cycle, a decline in the capacity of mitochondrial respiratory chain, and a reduction in the mitochondrial membrane potential [3,4]. However, it seems that the relationship between increased oxidative stress and reduced mitochondrial respiration with aging is simply a correlative one and does not reveal any causal relation. Recent studies have revealed that the cellular responses to ROS production are dose-dependent and oxidative stress can even enhance longevity [5,6].

Lately, more attention has been focused on the mitochondrial quality control and turnover, which declines with aging [7,8]. It is known that many morphological changes appear in mitochondria with aging, i.e. there are simultaneously increases in the number of fragmented, small mitochondria and greater amounts of enlarged, giant mitochondria which contain vacuoles and shortened christae (Fig. 1). These observations indicate that disturbances occur in the regulation of mitochondrial dynamics with aging, e.g. in the control of mitochondrial fission and fusion [7,9]. The decline in autophagic clearance of mitochondria (mitophagy) with aging seems to be a major reason for the accumulation of damaged mitochondria (Fig. 1). Several studies have revealed that the control of mitochondrial dynamics is an important regulatory mechanism in energy metabolism and thus any disturbances can provoke metabolic disorders [9,10]. For instance, the induction of mitochondrial fission reduces mitochondrial respiration and decreases lifespan, whereas the fusion and elongation of mitochondria, as observed in cellular senescence, can increase resistance to apoptosis [9,11,12] (Fig. 1). The appearance of non-functional, senescent cells containing dysfunctional mitochondria increases with aging, enhancing the aging process in tissues [13] (Fig. 1).

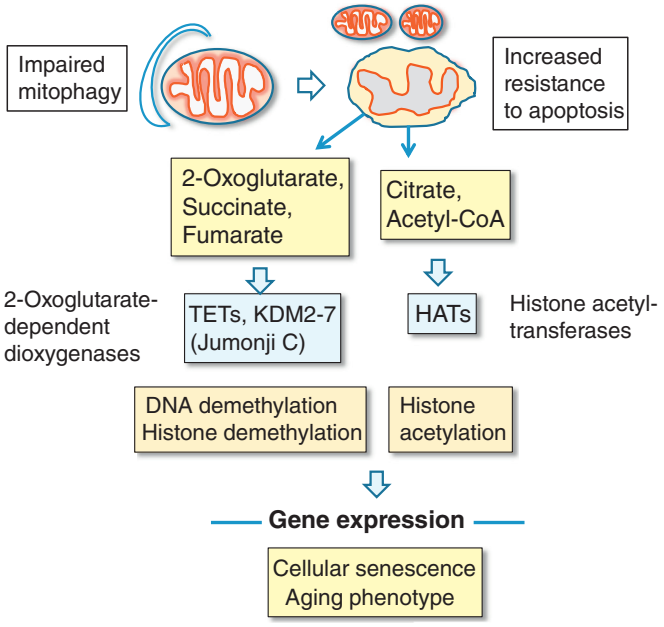

Fig. 1. Dysfunctions in the Krebs cycle promote the aging process by shaping the epigenetic landscape of chromatin. Age-related decline in mitochondrial quality control and turnover impairs the function of the Krebs cycle. The accumulation of crucial metabolic intermediates, e.g. 2-oxoglutarate, succinate and fumarate, regulates the activities of DNA demethylases (TET1-3) and histone demethylases (KDM2-7), which trigger changes in the epigenetic landscape of chromatin and thus affect gene expression. Citrate, also a Krebs cycle metabolite, stimulates the production of acetyl-CoA in the cytosol, which activates histone acetyltransferases (HATs) and subsequently, stimulates histone acetylation. This epigenetic genome reprogramming driven by the impaired Krebs cycle function with aging can promote the appearance of senescent phenotype.

Mitochondria are crucial players in energy metabolism and disruptions in their function can trigger stress signaling via the mitochondria-to-nucleus pathway, which induces changes in nuclear gene expression. This signaling is also called the mitochondrial retrograde pathway [6,9,14]. Currently, the signaling mechanisms are mostly unknown in mammalian cells although roles for Ca^{2+}, ROS, ADP/ATP, and NAD^{+} have been proposed [9,14]. In yeast, the retrograde signaling protein, RTG2, and transcription factors RTG1 and RTG3 regulate the transcription of several metabolic and stress-related genes [15]. Recently, Schroeder et al. [6] described another retrograde pathway of yeast, where chronic ROS production in mitochondria inactivated histone demethylase Rph1p by activating the yeast homologs of mammalian DNA damage response kinases, ATM and Chk2. This epigenetic pathway was specifically targeted to the maintenance of subtelomeric heterochromatin. The trimethylation of H3K36 enhanced the binding of Sir3p to the subtelomeric region, which stabilized the region and extended the chronological lifespan of yeasts. In mammalian cells, it is known that NAD^{+} activates histone deacetylation via the Sirtuins of class III deacetylases, in particular through SIRT1 and SIRT6 [16]. Surprisingly, emerging studies have revealed that three Krebs cycle intermediates, 2-oxoglutarate (also known as α-ketoglutarate), succinate and fumarate, can regulate the level of DNA and histone methylation, since these intermediates control the activities of the demethylases including in the family of 2-oxoglutarate-dependent dioxygenases [17–19]. Moreover, citrate, also a Krebs cycle metabolite, can stimulate histone acetylation [20]. Bearing in mind the endosymbiont origin of mitochondria, it is not surprising that the metabolites of Krebs cycle can control the gene expression of the host cell via retrograde epigenetic regulation. These observations provide a novel insight into the mitochondrial hypothesis of aging, since there is significant evidence indicating that changes in both energy metabolism and the epigenetic landscape of chromatin are involved in the regulation of the aging process.

2. Krebs cycle intermediates control 2-oxoglutarate-dependent dioxygenases

The methylation of both DNA and histones has a fundamental role in the epigenetic control of gene expression [21]. The methyltransferases and demethylases are the key enzymes in this process, for both DNA and histones. Interestingly, the major enzymes carrying out the demethylation/hydroxylation reactions of DNA and histones are included in a large family of 2-oxoglutarate-dependent dioxygenases (2-OGDO) [19,22,23]. Ten–eleven translocation hydroxylases (TET1-3) are involved in DNA demethylation and accordingly, the Jumonji C domain containing lysine demethylases (KDM2-7) are the major histone demethylases (Sections 2.1 and 2.2) (Fig. 1). In addition, prolyl 4-hydroxylases (PHD1-3) regulating the function of hypoxia-inducible factor (HIF-1) as well as prolyl-3 and prolyl-4 hydroxylases (P3H, P4H) controlling collagen synthesis are the members of 2-OGDO family. The Krebs cycle intermediate, 2-oxoglutarate, and O_2 are obligatory co-substrates for the function of 2-OGDO enzymes [19,22,23]. Moreover, 2-OGDO enzymes require the presence of Fe(II) as a cofactor in their catalytic activity. Ascorbate (vitamin C) induces the reduction of the oxidized Fe(IV) to Fe(II) and restores the activity of 2-OGDO enzymes. All 2-OGDO enzymes contain an eight-fold β-sheet core domain, also called the jelly-roll fold, which has two binding sites (e.g. KDM4) for 2-oxoglutarate [19,22,23]. The binding domains are highly specific for 2-oxoglutarate molecule, and thus many similar compounds act as inhibitors of 2-OGDO enzymes. For instance, succinate and fumarate, also Krebs cycle intermediates, are potent inhibitors of 2-OGDO enzymes