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# Impaired mitochondrial energy metabolism in Alzheimer's disease: Impact on pathogenesis via disturbed epigenetic regulation of chromatin landscape

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ABSTRACT

The amyloid cascade hypothesis for the pathogenesis of Alzheimer's disease (AD) was proposed over twenty years ago. However, the mechanisms of neurodegeneration and synaptic loss have remained elusive delaying the effective drug discovery. Recent studies have revealed that amyloid-β peptides as well as phosphorylated and fragmented tau proteins accumulate within mitochondria. This process triggers mitochondrial fission (fragmentation) and disturbs Krebs cycle function e.g. by inhibiting the activity of 2-oxoglutarate dehydrogenase. Oxidative stress, hypoxia and calcium imbalance also disrupt the function of Krebs cycle in AD brains. Recent studies on epigenetic regulation have revealed that Krebs cycle intermediates control DNA and histone methylation as well as histone acetylation and thus they have fundamental roles in gene expression. DNA demethylases (TET1-3) and histone lysine demethylases (KDM2-7) are included in the family of 2-oxoglutarate-dependent oxygenases (2-OGDO). Interestingly, 2-oxoglutarate is the obligatory substrate of 2-OGDO enzymes, whereas succinate and fumarate are the inhibitors of these enzymes. Moreover, citrate can stimulate histone acetylation via acetyl-CoA production. Epigenetic studies have revealed that AD is associated with changes in DNA methylation and histone acetylation patterns. However, the epigenetic results of different studies are inconsistent but one possibility is that they represent both coordinated adaptive responses and uncontrolled stochastic changes, which provoke pathogenesis in affected neurons. Here, we will review the changes observed in mitochondrial dynamics and Krebs cycle function associated with AD, and then clarify the mechanisms through which mitochondrial metabolites can control the epigenetic landscape of chromatin and induce pathological changes in AD.



**Contents**



*Abbreviations:* ACL, ATP-citrate lyase; AD, Alzheimer's disease; APP, amyloid-β precursor protein; BACE, β-site APP-cleaving enzyme; C/EBP, CCAAT-enhancer binding protein; DNMT, DNA methyltransferase; Drp, dynamin-related protein; ER, endoplasmic reticulum; FH, fumarate hydratase; GABA, γ-aminobutyric acid; HAT, histone acetyltransferase; HDAC, histone deacetylase; HIF, hypoxia-inducible factor; KDM, histone lysine demethylase; LSD, lysine-specific demethylase; Mfn, mitofusin; 2-OGDH, 2-oxoglutarate dehydrogenase; 2-OGDO, 2-oxoglutarate-dependent oxygenase; OXPHOS, oxidative phosphorylation; PHD, prolyl 4-hydroxylase; ROS, reactive oxygen species; SDH, succinate dehydrogenase; SIRT, silent information regulator; TET, Ten-Eleven Translocation.

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## 1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder involving a gradual decline in cognitive capacities, eventually leading to dementia. The deposition of amyloid-β-containing extracellular plaques and the intracellular accumulation of hyperphosphorylated tau-protein into neurofibrillary tangles are the two histopathological hallmarks of AD (Selkoe, 2001). Despite extensive research, the pathogenesis of AD is still not well understood and there are only symptomatic treatments for AD. In 1991, Hardy and Allsop formulated the amyloid cascade hypothesis, postulating that the processing of amyloid-β precursor protein (APP) into toxic amyloid-β peptides would play a key role in the pathogenesis of AD leading to the deposition of neuritic plaques. This hypothesis has represented the main principle in the field of AD research. In 2004, Swerdlow and Khan presented the mitochondrial cascade hypothesis which placed greater emphasis on the crucial role of mitochondrial dysfunction in late-onset AD. They underlined the role of oxidative stress and the decline in the efficiency of oxidative phosphorylation as a mechanism involved on the route to amyloid-β-induced pathology in AD. Recently, they noted that mitochondrial dysfunction appeared to be an upstream regulator of amyloid cascade, e.g. affecting APP processing (Swerdlow et al., 2014). Interestingly, there is mounting evidence that amyloid-β can accumulate within intracellular compartments, especially in the mitochondria, and affect mitochondrial dynamics and disturb mitochondrial energy metabolism (LaFerla et al., 2007; Reddy, 2009; Chen and Yan, 2010; Pagani and Eckert, 2011; DuBoff et al., 2013).

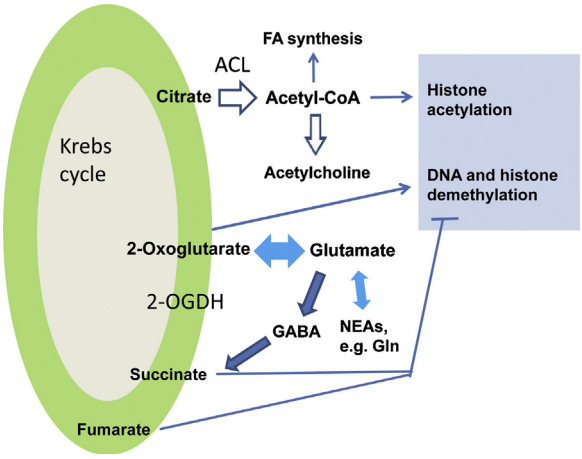


**Fig. 1.** An overview of the connections between the major Krebs cycle metabolites to neurotransmitter synthesis and the epigenetic regulation of chromatin landscape. The citrate/acetyl-CoA pathway controls acetylcholine and fatty acid synthesis as well as histone acetylation. 2-Oxoglutarate regulates glutamate synthesis and triggers the GABA shunt. Moreover, 2-oxoglutarate activates DNA and histone demethylases, whereas succinate and fumarate inhibit these enzymes and increase DNA and histone methylation. The reactions between 2-oxoglutarate, glutamate and non-essential amino acids can be reversible. ACL, ATP-citrate lyase; FA, fatty acid; NEA, non-essential amino acid; 2-OGDH, 2-oxoglutarate dehydrogenase.

There are emerging studies demonstrating that mitochondrial energy metabolism regulates the epigenetic landscape of chromatin via the intermediates of the Krebs cycle, i.e. 2-oxoglutarate, citrate, succinate and fumarate (Kaelin and McKnight, 2013; Benit et al., 2014; Salminen et al., 2014a,b) (Fig. 1). The key enzymes removing the methyl groups from DNA and histones are members of a family of 2-oxoglutarate-dependent oxygenases (2-OGDO), i.e. Ten-Eleven Translocation 1-3 (TET1-3) which undertake DNA demethylation whereas the Jumonji C domain containing histone lysine demethylases 2-7 (KDM2-7) are the main demethylating enzymes of histones (Section 4.2). 2-Oxoglutarate is a mandatory compound for the activation of 2-OGDO enzymes, whereas two other Krebs cycle intermediates, succinate and fumarate, correspondingly are potent inhibitors of these enzymes. This indicates that Krebs cycle intermediates are involved in retrograde epigenetic signaling from the mitochondria to the nucleus. This may reflect the endosymbiont origin of eukaryotic cells, when aerobic bacteria invaded anaerobic archael prokaryotic cells and later they were transformed to mitochondria (Gray et al., 1999; Davidov and Jurkevitch, 2009). There is mounting evidence that in AD there are changes appearing in the epigenetic landscape of chromatin, which could affect the pathogenesis, particularly induce disturbances in late-onset AD (Section 5). Given that amyloid-β can impair the mitochondrial energy metabolism, it seems that Krebs cycle intermediates can disturb not only neurotransmitter synthesis (Section 3.3) but also induce the stochastic disruption of gene expression and thus trigger neuronal degeneration (Fig. 2). We will review how changes in mitochondrial dynamics and energy metabolism can be linked to the neuronal disturbances encountered in AD and subsequently examine the emerging evidence that energy metabolism can shape the epigenetic landscape of chromatin and thus influence gene expression. Finally, we will discuss the potential role of epigenetic disturbances induced by impaired energy metabolism in the pathogenesis of AD.

## 2. Mitochondrial changes in AD

### 2.1. Changes in mitochondrial dynamics

Mitochondria are dynamic cellular organelles; their morphology is regulated by several large GTPases (Palmer et al., 2011; Chan, 2012; Otera et al., 2013; Dhingra and Kirshenbaum, 2014). Mitofusin 1 and 2 (Mfn1 and Mfn2) along with Optical atrophy 1 (Opa1) control the fusion (elongation) of mitochondria, whereas