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Interplay between mitochondrial metabolism and oxidative stress in ischemic stroke: An epigenetic connection

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ABSTRACT

The advent of epigenetics brought in a tectonic shift in the understanding of molecular basis of complex diseases like ischemic stroke (IS). Substantial scientific inquiry into the epigenetic basis of neurodegenerative diseases has bolstered the idea that altered carbon flux into central carbon metabolism and disturbed redox states govern the attendant transcriptional profiles through stochastic epigenetic changes. In view of an increasing understanding of the link between mitochondrial energy metabolism, oxidative stress and epigenetics in IS, the hitherto underappreciated 'neuroenergetics' is gaining sustained attention. Defined metabolic transitions during IS are necessarily a function of transiently altered abundance of critical metabolic substrates of Krebs cycle and other pathways viz., acetyl-CoA, citrate, 2-oxo-glutarate, succinate, fumarate, S-adenosyl methionine, β-hydroxybutyrate and co-factors (NAD^+, FAD, ATP, vitamin C) in neuronal mitochondria. These changes impinge on the cellular transcriptome by regulating the activity of several chromatin modifying enzymes that bring about epigenomic transition through alteration in DNA methylation and histone post translational modifications. This triggers downstream signaling cascades that circumstantially evoke adaptive and cell death responses during IS. Indeed, they also prevail on the functionality of neuronal network, brain plasticity and neurogenesis during post stroke recovery. Understanding the epigenetic underpinnings of IS that explicitly alter the brain transcriptomes could open new vistas of therapeutic opportunity. In the current review, we present an update on various aspects linking mitochondrial energy metabolism, oxidative stress and epigenetic modifications in the pathological setting of IS.

Contents

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1. Introduction

Ischemic stroke (IS) is a complex debilitating disorder with a late onset phenotype and an increasing prevalence in global population that is experiencing extended life expectancy, changing life style and environment (Mozaffarian et al., 2015). Despite considerable improvement in acute stroke management, it is still dubbed as a chronic 'intractable malady' due to the narrow window of therapeutic opportunity, that makes it less amenable to treatment by mechanical recanalization or reperfusion strategies and other therapeutic modalities (Moskowitz et al., 2010). IS outcome in the form of moderate to severe neurological deficits and mortality results from cerebral ischemia/reperfusion (CI/R). CI is associated with a pronounced reduction in glucose and oxygen (O_2) supply to cerebral tissue due to major arterial occlusion. It is well understood that brain glucose metabolism and blood flow serve as bona fide indices of neuronal synaptic activity. Hence, a disruption in these activities explicitly correlates with an impaired synaptic transmission as observed in the hypo-perfused and electrically silent ischemic penumbra (Hertz, 2008; Hofmeijer and van Putten, 2012). It is indeed well appreciated that neuronal activity is tightly coupled with mitochondrial function (Kann and Kovács, 2007). Mitochondria constitute the hub of metabolic networks, owing to their central role in generation of ATP and reducing power (NADH, $FADH_2$), anaplerosis, Ca^{2+} homeostasis and free radical detoxification. In line with this, a series of metabolic disruptions occur during CI/R in the highly dynamic mitochondrial compartment of neurons following oxygen and glucose deprivation (OGD) and glutamate induced excitotoxicity (Nicholls et al., 2007). These induce discernible changes in the levels of endogenous metabolites and energy intermediates of core pathways of intermediary metabolism (Villa et al., 2013). As mitochondria are quantifiable sources of reactive oxygen species (ROS), alteration in metabolic fluxes aggravates existing oxidative and nitrosative stress that begets bioenergetic failure. Alongside, antioxidant defense goes awry due to an overwhelming production of ROS and reactive nitrogen species (RNS). Collectively, these perturbations impinge on cellular transcriptome and elicit an adaptive cellular phenotype following CI/R (Sims and Muyderman, 2010).

In this context, it would be appropriate to state that the canonical epigenetic modifications viz., DNA methylation and post translational modifications (PTMs) of histones together with epigenetic effectors catalogued under epigenetic 'readers', 'writers' and 'erasers' act as connecting links between mitochondrial energetics and transcriptional regulation (Minocherhomji et al., 2012; Shaughnessy et al., 2014). Impairment of mitochondrial oxidative metabolism limits the availability of endogenous metabolites and impedes ROS signaling which impact the epigenetic landscape (Cyr and Domann, 2011; Martínez-Reyes et al., 2016). More precisely in cerebral milieu, modified epigenetic marks as a function of synaptic activity transduce changes in redox metabolism to the transcriptome (Cyr and Domann, 2011; Guo et al., 2011a, 2011b). These in turn synergize with altered signaling pathways to generate a coherent phenotype as IS (Qureshi and Mehler, 2010; Hwang et al., 2013; Schweizer et al., 2013). These marks in general aid in spatial resolution of neuronal gene expression that accords plasticity to synaptic connections with an innate temporal diversity (Guzman-Karlsson et al., 2014). As the concerted role essayed by RO/NS and intermediary metabolism in modulating epigenetic events gets clearer, they can conceivably fit into the hierarchy of 'epigenator-epigenetic initiator-epigenetic maintainer' proposed by Berger (2007).

In the current review we present an overview of the connection between energy metabolism, oxidative stress and epigenetic modifications in CI/R setting. In this regard, a fundamental and also pertinent question that is posed and addressed in the review through available knowledge is how the transient alteration in the levels of energy substrates, activity of intermediary metabolism enzymes and RO/NS induce epigenetic changes that determine temporal and spatial expression of specific gene suites modulating neuronal survival/death in ischemic brain. Further, based on these energy mandates, a brief account of endogenous metabolites that can intervene with pathological modules of CI/R injury and alleviate the attendant damage will be presented.

2. Mitochondrial metabolism and neuroepigenetics-general considerations

The cellular availability of molecular oxygen (O_2) and high energy catalytic intermediates from the core pathways of intermediary metabolism such as NAD^+, FAD, S-adenosyl methionine (SAM), ATP, acetyl Co-A and crucial metabolites like pyruvate, 2-oxo-glutarate (2-OG), succinate, fumarate and β-hydroxy butyrate (BHB) forge a link between redox metabolism and epigenetic modifications (Shaughnessy et al., 2014; Katada et al., 2012; Lu and Thompson, 2012; Gut and Verdin, 2013). This is predicated on the fact that normoxia and optimum levels of redox intermediates and endogenous metabolites under homeostatic conditions facilitate fine tuning of gene expression through changes in chromatin dynamics (Minocherhomji et al., 2012; Salminen et al., 2014; Benit et al., 2014). This renders neurons amenable to plasticity (axonal and dendritic) through refinement of synapses, dendritic arborization, enhanced synaptic strength and transmission that preserve neural connectivity (Felling and Song, 2015). Conversely, subtle changes in their levels induced by altered metabolic and energetic status as in CI/R evoke mitohormetic or compensatory adaptive transcriptional responses by directly affecting the activity of chromatin modifying enzymes (Shaughnessy et al., 2014). These in turn impinge on chromatin architecture through appropriate epigenetic marks that induce durable changes in the coordinate expression of bioenergetic genes in a 'cis' or 'trans' manner. At this point, the temporality of these epigenetic marks becomes the decisive factor for disease evolution, as persistence of these responses renders them maladaptive, thereby precipitating bio-energetic failure and neuronal death.