Neurochemistry International 109 (2017) 193–201

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/nci

Mitochondrial NUDIX hydrolases: A metabolic link between NAD catabolism, GTP and mitochondrial dynamics

Aaron Long [a], Nina Klimova [a, b, c], Tibor Kristian [a, b, *]

[a] Veterans Affairs Maryland Health Center System, 10 North Greene Street, Baltimore, MD 21201, United States
[b] Department of Anesthesiology and the Center for Shock, Trauma, and Anesthesiology Research (S.T.A.R.), United States
[c] Program in Neuroscience, University of Maryland School of Medicine, Baltimore, MD 21201, United States

ARTICLE INFO

Article history:
Received 31 January 2017
Received in revised form
28 February 2017
Accepted 9 March 2017
Available online 14 March 2017

Keywords:
NAD^+
PARP1
NUDIX
AMP
GTP
Mitochondrial dynamics

ABSTRACT

NAD^+ catabolism and mitochondrial dynamics are important parts of normal mitochondrial function and are both reported to be disrupted in aging, neurodegenerative diseases, and acute brain injury. While both processes have been extensively studied there has been little reported on how the mechanisms of these two processes are linked. This review focuses on how downstream NAD^+ catabolism via NUDIX hydrolases affects mitochondrial dynamics under pathologic conditions. Additionally, several potential targets in mitochondrial dysfunction and fragmentation are discussed, including the roles of mitochondrial poly(ADP-ribose) polymerase 1(mtPARP1), AMPK, AMP, and intra-mitochondrial GTP metabolism. Mitochondrial and cytosolic NUDIX hydrolases (NUDT9α and NUDT9β) can affect mitochondrial and cellular AMP levels by hydrolyzing ADP- ribose (ADPr) and subsequently altering the levels of GTP and ATP. Poly (ADP-ribose) polymerase 1 (PARP1) is activated after DNA damage, which depletes NAD^+ pools and results in the PARylation of nuclear and mitochondrial proteins. In the mitochondria, ADP-ribosyl hydrolase-3 (ARH3) hydrolyzes PAR to ADPr, while NUDT9α metabolizes ADPr to AMP. Elevated AMP levels have been reported to reduce mitochondrial ATP production by inhibiting the adenine nucleotide translocase (ANT), allosterically activating AMPK by altering the cellular AMP: ATP ratio, and by depleting mitochondrial GTP pools by being phosphorylated by adenylate kinase 3 (AK3), which uses GTP as a phosphate donor. Recently, activated AMPK was reported to phosphorylate mitochondria fission factor (MFF), which increases Drp1 localization to the mitochondria and promotes

Abbreviations: ADPr, ADP- ribose; ADPrP, ADPr-phosphate; AIF, apoptosis inducing factor; AK3, adenylate kinase 3; AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; ANT, adenine nucleotide translocase; ARH3, ADP-ribosyl hydrolase-3; ARTD1, ADP-ribosyltransferase diphtheria toxin-like one; ARTs, ADP-ribosyl transferases; cADPr, cyclic ADP-ribose; CaMKKβ, calmodulin-dependent protein kinase kinase-β; CD38 / CD157, ADP-ribosyl cyclases or cyclic ADP-ribose synthases; Drp1, Dynamin-related protein 1; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; HDACs, histone deacetylases; HK1, hexokinase 1; IM, inner membrane; IMS, intermembrane space; LKB1, liver kinase B1; macroD, Macro domain; MARylation, mono-ADP-ribosylation; MFF, mitochondria fission factor; MFN, mitofusin; mtPARP1, intramitochondrial localized PARP1; Nam, nicotinamide; NAADP, nicotinamide acid ADP; NDPK, nucleoside diphosphate kinase; NMN, nicotinamide mononucleotide; NMNATs, NMN adenyl transferases; NR, nicotinamide riboside; NUDIX, nucleoside diphosphate linked to another moiety *x*; OAADPr, O-acetyl-ADP-ribose; OM, outer membrane; OPA1, optic atrophy protein; PARG, poly(ADP-ribose) glycohydrolase; PARP1, Poly(ADP-ribose) polymerase 1; PARylation, poly-ADP-ribosylation; Polγ, DNA polymerase gamma; ROS, reactive oxygen species; SCS, succinyl-CoA synthetase (ligase); TCA, tricarboxylic acid cycle; TRPM2, Transient receptor potential melastatin 2.

* Corresponding author. Department of Anesthesiology, School of Medicine, University of Maryland Baltimore, 685 W, Baltimore Street, MSTF 534, Baltimore, MD 21201, United States.
E-mail address: tkristian@anes.umm.edu (T. Kristian).

http://dx.doi.org/10.1016/j.neuint.2017.03.009
0197-0186/Published by Elsevier Ltd.

mitochondrial fission. Moreover, the increased AK3 activity could deplete mitochondrial GTP pools and possibly inhibit normal activity of GTP-dependent fusion enzymes, thus altering mitochondrial dynamics.

Published by Elsevier Ltd.

1. Introduction

Mitochondrial impairment is commonly recognized as an underlying factor in neurological disease and has been suggested to play a significant role in cell death processes (Beal, 2005; Kristian and Fiskum, 2004; Owens et al., 2013; Perez-Pinzon et al., 2012; Sullivan et al., 2005). The significance of mitochondrial involvement in cell death is well established and while several underlining mechanisms were proposed (Balog et al., 2016; Marino et al., 2014; Rimessi et al., 2016; Tann et al., 2011) this area of research is still not completely understood and the possible interplay between the individual mechanisms have not been studied. Additionally, it is unclear how significantly the pathophysiology of mitochondria contribute to mechanisms of cell death (Brunyanszki et al., 2016) and what role does mitochondrial dynamics and disruption in normal NAD^+ anabolism/catabolism play in the process (Fouquerel and Sobol, 2014; Owens et al., 2015; Verdin, 2015). Answering these questions on the role and mechanisms of mitochondrial dysfunction is important in improving treatment for normal aging, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), acute brain injury such as traumatic brain injury (TBI), and ischemia-reperfusion (Bai et al., 2015; Golpich et al., 2017; Menzies et al., 2015). This review will focus on mitochondrial dysfunction related to the interplay between NAD^+ catabolism, NUDIX hydrolases, GTP, and mitochondrial dynamics.

2. Pathology of NAD^+ catabolism and downstream metabolic products

NAD^+ is an important cofactor involved in multiple metabolic reactions that have a central role in cellular metabolism and energy production (Belenky et al., 2007; Frederick et al., 2016; Mouchiroud et al., 2013). Normally, NAD^+ levels decline with age (Camacho-Pereira et al., 2016; Massudi et al., 2012; Verdin, 2015; Zhu et al., 2015) and NAD^+ pools have been shown to decrease during neurodegenerative diseases and after ischemia-reperfusion or TBI (Kauppinen and Swanson, 2007; Martire et al., 2015; Park et al., 2016; Verdin, 2015; Zhou et al., 2015). This decline could be the result of the increased activity of several enzymes that use NAD^+ as their substrate; these include: sirtuins, ADP-ribosyl transferases (ARTs), and the cyclic ADP-ribose synthases/ADP-ribosyl cyclases (CD38 and CD157) (Belenky et al., 2007; Feijs et al., 2013; Jesko et al., 2016; Malavasi et al., 2008; Mayo et al., 2008). These NAD^+ dependent enzymes hydrolyze NAD^+ to ADP-ribose (ADPr) or an ADPr variation (e.g. cyclic ADPr), and nicotinamide (Nam). The resulting Nam can function in a negative feedback fashion by inhibiting the activity of NAD^+ dependent enzymes (Avalos et al., 2005; Long et al., 2016; Suzuki et al., 2010), however levels of Nam are usually too low to inhibit sirtuins activity under physiological conditions (Liu et al., 2013). Nam is also the precursor for nicotinamide mononucleotide (NMN), the immediate precursor to NAD^+ via the salvage pathway (Imai and Guarente, 2014). The conversion of NMN to NAD^+ is ATP dependent and catalyzed by the NMN adenyl transferases (NMNATs): NMNAT1 (nucleus), NMNAT2 (Golgi apparatus/endosomes), and NMNAT3 (mitochondria) (Berger et al., 2005; Mayer et al., 2010). Additionally, commonly in acidic environments, NAD^+ levels can also be depleted by NAD^+ kinase, by phosphorylating NAD^+ to $NADP^+$ (Zhang et al., 2016a).

3. NAD^+/NADH

Other then being a substrate, NAD^+ plays a key role in cellular bioenergetic metabolism by reversibly being reduced to NADH and ultimately contributing to ATP generation via the glycolytic pathway and in the mitochondria through oxidative phosphorylation (Srivastava, 2016). The reduction of NAD^+ is most apparent in the mitochondria, with liver mitochondrial NAD^+/NADH ratios being tightly controlled around 7 to 8, while cytoplasmic ratios being much higher, ranging from 60 to 700 in most cells (Stein and Imai, 2012). Techniques to get more accurate measurements are relatively new but suggest that NAD^+ pools and NAD^+/NADH ratios can vary based on cell type (Cambronne et al., 2016; Christensen et al., 2014). The reduction of NAD^+ to NADH is essential for the glyceraldehyde 3-phosphate (GAPDH) step of glycolysis and multiple steps in the tricarboxylic acid cycle (TCA) (Akram, 2014; Sirover, 1999). NADH generated in the mitochondria will be oxidized to NAD^+ and donate electrons to complex I of the electron transport chain (Sazanov, 2015).

4. ARTs/PARP1/mtPARP1

There are 22 known human genes that encode proteins with an ADP-ribosyltransferase (ART) catalytic domain. These proteins transfer ADPr from NAD^+ onto targeted amino acid residues of proteins. To generate the ADPr chains, ART's release Nam from NAD^+, and then form an $\alpha(1-2)$O-glycosidic bond between two ADPr molecules. This post-translational modification is named either mono- or poly-ADP-ribosylation (MARylation or PARylation), depending if the ART's are transferring a single ADPr or are generating a chain (Gibson and Kraus, 2012; Hottiger et al., 2010). In vitro, these chains of APD-ribose can be around 200 residues, with the length and branching being dependent on the concentration of available NAD^+ (Alvarez-Gonzalez and Jacobson, 1987; Alvarez-Gonzalez and Mendoza-Alvarez, 1995). This process of PARylation is reversible and is constantly being regulated by poly (ADP-ribose) glycohydrolase (PARG) and the mainly mitochondrial, ADP-ribosyl hydrolase-3 (ARH3) (Di Meglio et al., 2003; Mashimo et al., 2013; Niere et al., 2012). PARG and ARH3 associated degradation of PAR can result in releasing intact PAR chains (endoglycohydrolase) or by releasing free ADR-ribose (exoglycohydrolase) (Gibson and Kraus, 2012).

Poly (ADP-ribose) polymerase 1 (PARP1), also known as ADP-ribosyltransferase diphtheria toxin-like one (ARTD1), is responsible for the majority of PARylation and is involved in the repair of moderate single stranded DNA damage. Historically, PARP1 has been reported to be exclusively nuclear, although there is growing evidence for PARP1 associated mitochondrial functions. Several studies report PARP1 can modulate mitochondria from the nucleus through: PAR translocation from the nucleus to the mitochondria, depletion of cellular NAD^+ pools, and epigenetic regulating of nuclear genes that are involved in mitochondrial DNA transcription