Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

The potential regulatory roles of NAD$^+$ and its metabolism in autophagy

Dong-Xia Zhang[a], *Jia-Ping Zhang*[a], *Jiong-Yu Hu*[b], *Yue-Sheng Huang*[a,*]

[a] *Institute of Burn Research, Southwest Hospital, Third Military Medical University, State Key Laboratory of Trauma, Burns and Combined Injury, Chongqing, PR China, 400038*

[b] *Endocrinology Department, Southwest Hospital, State Key Laboratory of Trauma, Burns and Combined Injury, Third Military Medical University, Chongqing, PR China, 400038*

ARTICLE INFO

Article history:
Received 18 June 2015
Accepted 25 November 2015

Keywords:
Autophagy
NAD$^+$
NAD(P)$^+$/NAD(P)H
NAADP/cADPR/ADPR
Ca^{2+}

ABSTRACT

(Macro)autophagy mediates the bulk degradation of defective organelles, long-lived proteins and protein aggregates in lysosomes and plays a critical role in cellular and tissue homeostasis. Defective autophagy processes have been found to contribute to a variety of metabolic diseases. However, the regulatory mechanisms of autophagy are not fully understood. Increasing data indicate that nicotinamide adenine nucleotide (NAD$^+$) homeostasis correlates intimately with autophagy. NAD$^+$ is a ubiquitous coenzyme that functions primarily as an electron carrier of oxidoreductase in multiple redox reactions. Both NAD$^+$ homeostasis and its metabolism are thought to play critical roles in regulating autophagy. In this review, we discuss how the regulation of NAD$^+$ and its metabolism can influence autophagy. We focus on the regulation of NAD$^+$/NADH homeostasis and the effects of NAD$^+$ consumption by poly(ADP-ribose) (PAR) polymerase-1 (PARP-1), NAD$^+$-dependent deacetylation by sirtuins and NAD$^+$ metabolites on autophagy processes and the underlying mechanisms. Future studies should provide more direct evidence for the regulation of autophagy processes by NAD$^+$. A better understanding of the critical roles of NAD$^+$ and its metabolites on autophagy will shed light on the complexity of autophagy regulation, which is essential for the discovery of new therapeutic tools for autophagy-related diseases.

Abbreviations: ADPR, ADP-ribose; AMPK, AMP activated protein kinase; Atg, autophagy; Ca^{2+}, calcium; cADPR, cyclic ADP-ribose; CaM, calmodulin; CaMKK, Ca^{2+}/calmodulin dependent kinase kinase; CICR, Ca^{2+}-induced Ca^{2+} release; CMA, chaperone-mediated autophagy; CoA, coenzyme A; ER, endoplasmic-reticulum; ES, embryonic stem; ETC, electron transport chain; FoxO, Forkhead box O; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; 6GPDH, 6-glyconate phosphate dehydrogenase; G6PDH, glucose-6-phosphate-6-phosphate dehydrogenase; GSH, glutathione; GSSG, glutathione disulfide; IDP, NADP$^+$-dependent isocitrate dehydrogenase; IP3, inositol 1,4,5-trisphosphate; IP3R, inositol 1,4,5-trisphosphate receptor; LC3, microtubule-associated protein 1 light chain 3; LDH, lactate dehydrogenase; Lyso, lysosome; MEFs, mouse embryonic fibroblasts; MEP, NADP$^+$-dependent malic enzyme; Mito, mitochondria; (m)TOR, (mechanistic) target of rapamycin; (m)TORC1, (mechanistic) TOR complex 1; (m)TORC2, (mechanistic) TOR complex 2; MPT, permeability transition; NA, nicotinic acid; NAADP, nicotinic acid adenine dinucleotide phosphate; NAD$^+$, nicotinamide adenine nucleotide; NADK, NAD$^+$ kinases; NADP$^+$, NAD$^+$ phosphate; NAM, nicotinamide; NF-κB, nuclear factor κB; NR, NAM riboside; PAR, Poly(ADP-ribose); PARP-1, Poly(ADP-ribose) (PAR) polymerase-1; PARG, poly(ADP-ribose) glycohydrolase; PASMC, pulmonary arterial smooth muscle cell; PGC-1α, PPARγ coactivator-1α; PTM, post-translational modification; ROS, reactive oxygen species; RyR, Ryanodine receptor; SERCA, sarco/endoplasmic reticulum calcium; SIRT, NAD$^+$-dependent deacetylase sirtuin; SR, Sarcoplasmic reticulum; TSC, Tuberous sclerosis complex; TCA, tricarboxylic acid; TPC, two-pore channel; TRP, transient receptor potential; TRPM, transient receptor potential melastatin; ULK1, unc-51 like autophagy activating kinase 1; VMP1, vacuole membrane protein 1.

* *Corresponding author at:* Institute of Burn Research, State Key Laboratory of Trauma, Burns and Combined Injury, Southwest Hospital, Third Military Medical University, Chongqing, PR China, 400038. Tel./fax: +86 23 6876 6023.

E-mail address: yshuangtmmu@163.com (Y.-S. Huang).

http://dx.doi.org/10.1016/j.metabol.2015.11.010
0026-0495/

1. Introduction

Autophagy was first discovered by Christian de Duve in 1963, who described the phenomenon as an intracellular digestion process of single- or double-membrane vesicles that contained cytoplasm and organelles [1]. Autophagy is classified into the following three types based on the manner in which substrates are delivered to the lysosomal compartment, macroautophagy, microautophagy and chaperone-mediated autophagy (CMA) [2]. These three types of autophagy coexist in almost all mammalian cells. Macroautophagy (hereafter referred to as autophagy) is thought to be the predominant form and is the best studied. In macroautophagy, substrates are sequestered in vesicles that form in the cytosol and then fuse with lysosomes to transfer their contents for degradation [3]. The autophagic process is highly dynamic and is divided into mechanistically distinct steps, including initiation (formation of a phagophore), vesicle elongation, autophagosome maturation and cargo sequestration, autophagosome-lysosome fusion, degradation of autophagosomal contents, and the release of the degradation products for metabolic recycling [4]. The identification of autophagy (Atg)-related genes and the development of microtubule-associated protein 1 light chain 3 (LC3)-based assays, have demonstrated that various signals mediate the regulation of autophagy in mammals.

Among the various modulation signals, Unc-51-like autophagy activating kinase 1 (ULK1) is considered to be not only an essential component of autophagy initiation but also an important kinase involved in the regulation of autophagic activity [5]. (Mechanistic) target of rapamycin ((m)TOR) is an atypical serine/threonine protein kinase that forms two distinct signaling complexes: (mechanistic) target of rapamycin complex 1 (mTORC1) and (mechanistic) target of rapamycin complex 2 (mTORC2). mTORC1 plays a central role in the inhibition of autophagy initiation by inhibiting ULK1 activity or destabilizing ULK1 [6]. AMP-activated protein kinase (AMPK) is a cellular energy sensor and signal transducer that is regulated by a wide array of metabolic stresses. AMPK inhibits mTORC1 activity and upregulates autophagy by phosphorylating tuberous sclerosis complex (TSC) 2, an upstream negative regulator of mTORC1, or Raptor, a component of mTORC1 [7]. Additionally, AMPK can directly stimulate autophagy through the phosphorylation and activation of ULK1 [8]. AMPK is highly activated and mTORC1 activity is inhibited in response to various stimuli (i.e., nutrient starvation, oxidative stress, hormonal stimuli and accumulation of unfolded proteins), thereby promoting autophagosome formation [9]. Defects in the autophagic process have been found to contribute to a variety of diseases, including cancer, neurodegenerative diseases, infectious diseases, ischemic diseases, and metabolic diseases; such defects can also influence cellular development and senescence [10]. As the complexity of the autophagy process in mammals has become apparent, increasing data have indicated that nicotinamide adenine nucleotide (NAD^+) homeostasis plays an important role in modulating autophagy.

NAD^+ is a ubiquitous cellular coenzyme that was first discovered by Arthur Harden [11]. In mammals, intracellular NAD^+ is compartmentalized into different cellular pools involving the cytosol, mitochondria, nucleus, endoplasmic reticulum (ER) and Golgi complex. The variety of specialized functions of NAD^+ is thought to be regulated by its fine subcellular localization [12]. In the cytosol and mitochondria, NAD^+ primarily functions as an electron acceptor by shuttling between its oxidized form (NAD^+) and reduced form (NADH) accompanying the production of ATP. There are two classes of NAD^+ consumers in the nucleus: poly-ADP-ribose polymerases (PARPs) and sirtuins. By consuming NAD^+, PARPs facilitate DNA repair and genomic integrity, whereas sirtuins regulate multiple transcriptional activities and control various cellular processes, including proliferation, differentiation and circadian rhythms [13]. Moreover, NAD^+ can be converted into its phosphorylated form (NAD+ phosphate (NADP+)), and both NAD^+ and $NADP^+$ can be metabolized into calcium-mobilizing second messengers (cyclic ADP-ribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP), respectively) by ADP-ribosyl cyclases (e.g., CD38) [14]. The metabolic homeostasis of NAD^+ involves its biosynthesis and consumption. NAD^+ is not consumed in redox reactions. However, NAD^+ can be consumed as a substrate in ADP-ribose transfer reactions that require the continuous biosynthesis of NAD^+[15]. In mammals, the synthesis of NAD^+ has been reported to occur through two major pathways: a de novo pathway (from tryptophan) and a salvage pathway (from the vitamin niacin, consisting of nicotinic acid (NA), nicotinamide (NAM), and NAM riboside (NR)) [16]. The consumption of NAD^+ is primarily mediated by three classes of proteins: PARPs, sirtuins and NAD glycohydrolases (e.g., CD38). Recent studies suggested that NAD^+ and its metabolism play potential regulatory roles in autophagy. In multiple myeloma, NAD^+ depletion caused by nicotinamide phosphoribosyltransferase inhibition by FK866 led to autophagy or autophagic cell death [17]. In brain ischemia, NAD^+ administration blocked post-ischemic autophagy and reduced ischemic brain damage [18]. These studies indicated that NAD^+ metabolism played critical roles in autophagy. In this review, we will summarize our understanding of the roles of NAD^+ and its metabolism in the control of autophagy, with an emphasis on how NAD^+ homeostasis and its metabolites affect the autophagy processes. Finally, we will discuss the potential underlying mechanisms.

2. NAD^+ Metabolism and Energetics

In mammalian cells, energy deficits (i.e., a decrease in the ATP level or reduction in the AMP/ATP ratio) can rapidly activate AMPK and induce autophagy [19]. NAD^+ is a potential regulator of ATP generation. In the cytosol, the NAD^+/NADH redox pair participates in ATP generation through glycolysis [20]. In the mitochondria, the NAD^+/NADH redox pair can affect ATP generation by modulating multiple metabolic processes. First, NAD^+/NADH may affect ATP generation by modulating acetyl CoA generation. NAD^+/NADH are cofactors of pyruvate dehydrogenase in pyruvate oxidation and of 3-OH acyl-CoA dehydrogenase in fatty acid β-oxidation, both of which are important enzymes for acetyl CoA generation [21]. Second, the NAD^+/NADH ratio regulates ATP generation by affecting the TCA cycle flux. Many dehydrogenase activities in the TCA cycle,