Molecular and Cellular Endocrinology 455 (2017) 62–74

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

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

NAD and the aging process: Role in life, death and everything in between

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ARTICLE INFO

Article history:
Received 30 April 2016
Received in revised form
22 September 2016
Accepted 3 November 2016
Available online 5 November 2016

Keywords:
CD38
PARP
SIRTUINS
NAD^+
Mitochondrial function
Aging

ABSTRACT

Life as we know it cannot exist without the nucleotide nicotinamide adenine dinucleotide (NAD). From the simplest organism, such as bacteria, to the most complex multicellular organisms, NAD is a key cellular component. NAD is extremely abundant in most living cells and has traditionally been described to be a cofactor in electron transfer during oxidation-reduction reactions. In addition to participating in these reactions, NAD has also been shown to play a key role in cell signaling, regulating several pathways from intracellular calcium transients to the epigenetic status of chromatin. Thus, NAD is a molecule that provides an important link between signaling and metabolism, and serves as a key molecule in cellular metabolic sensoring pathways. Importantly, it has now been clearly demonstrated that cellular NAD levels decline during chronological aging. This decline appears to play a crucial role in the development of metabolic dysfunction and age-related diseases. In this review we will discuss the molecular mechanisms responsible for the decrease in NAD levels during aging. Since other reviews on this subject have been recently published, we will concentrate on presenting a critical appraisal of the current status of the literature and will highlight some controversial topics in the field. In particular, we will discuss the potential role of the NADase CD38 as a driver of age-related NAD decline.

1. Introduction

NAD was discovered over a hundred years ago (Harden and Young, 1906), and now that it has achieved its status as a supercentenarian molecule, its role in the biological process of aging is being recognized (Braidy et al., 2011; Gomes et al., 2013; Lin et al., 2000; Massudi et al., 2012; Scheibye-Knudsen et al., 2014; Zhu et al., 2015). It has been shown that NAD levels decline during chronological aging, and that this decline is both a consequence of the aging process and also a contributor to the development of age-related cellular dysfunction (Braidy et al., 2011; Gomes et al., 2013; Massudi et al., 2012; Scheibye-Knudsen et al., 2014; Verdin, 2015; Zhu et al., 2015). It is possible that a vicious cycle exists in which molecular mechanisms involved in the aging process, such as oxidative stress, DNA damage, senescence, and inflammation, lead to tissue NAD decline which subsequently exacerbates the processes that caused its decline in the first place (Fig. 1). To potentially intervene in this vicious cycle it is crucial that we understand the mechanisms that lead to cellular NAD decrease during aging and, in particular, whether the decrease is mediated primarily by changes in its degradation, synthesis, or both. Furthermore, it is critical to understand how oxidative stress, DNA damage, inflammation, and senescence impact cellular NAD metabolism during the aging process. In the current review we will present a critical analysis of this subject, and will provide new mechanistic hypotheses to explain the age-related NAD decline.

2. The discovery of NAD and its role in oxidation-reduction reactions

The study of NAD began around 1906 when Sir Arthur Harden and William John Young first identified a heat-stable low molecular weight fraction implicated in sugar fermentation in yeast (Harden and Young, 1906). These investigators observed that this fraction could support fermentation, and therefore postulated it to be a cofactor in this process (Harden and Young, 1906). Almost thirty years later, Hans von Euler-Chelpin identified this low molecular weight factor as being composed of two mononucleotides,

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http://dx.doi.org/10.1016/j.mce.2016.11.003
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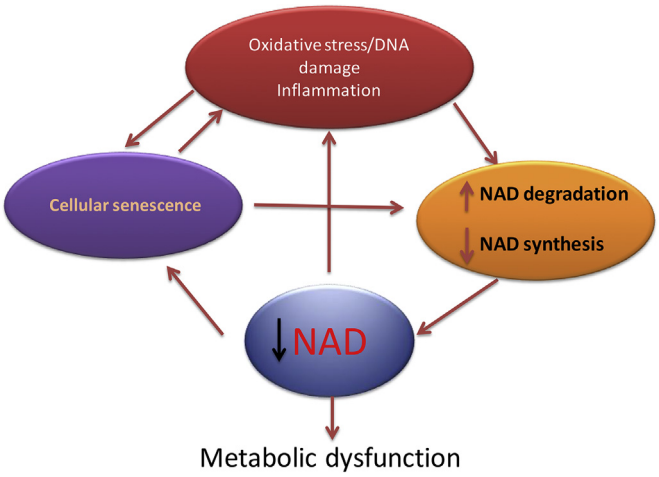

Fig. 1. A vicious cycle that amplifies tissue NAD decline, cellular senescence and damage during aging. We propose that a vicious cycle exists in which molecular mechanisms involved in the aging process, such as oxidative stress, DNA damage, senescence, and inflammation, lead to tissue NAD decline which subsequently exacerbates the processes that caused its decline in the first place.

adenosine monophosphate (AMP) and nicotinamide mononucleotide (NMN) (von Euler-Chelpin, 1930). Next, Otto Warburg isolated NAD and described its role in electron transfer in biological systems (Warburg and Christian, 1936). Since Warburg's discovery, the electron-transferring properties of NAD have been widely recognized (Ziegler and Niere, 2004). The role of NAD in oxidation-reduction (oxidoreduction) reactions is due to the fact that its redox potential is at an intermediary value between biological donors and acceptors of electrons. NAD and its phosphorylated analogue NAD(P) are involved in both catabolic and anabolic reactions, serving as acceptors or donors of electrons. Some key cellular metabolic pathways where NAD(P)(H) plays a crucial role include, transfer of electrons during aerobic and anaerobic glycolysis, mitochondrial oxidative phosphorylation, biosynthetic lipid pathways, metabolism of several pharmacological and biological compounds, and cellular protection against oxidative stress (Ziegler and Niere, 2004). In these electron transfer reactions there is an interconversion between oxidized and reduced forms of NAD (NAD^+, NADH), and these reactions are easily reversible. Therefore, the oxidoreduction reactions do not contribute directly to changes in total NAD levels in cells. This is not to say that electron transfer reactions do not modify the availability of NAD to other processes. In particular, the metabolic status of the organism can change the ratio between NAD^+ and NADH (known as the NAD^+/NADH ratio). Since NAD^+ is the actual substrate of several NAD-dependent enzymes involved in protein modification and signal transduction, it is plausible that changes in NAD^+/NADH ratios in cells could have a key role in the regulation of several cellular functions (Lin et al., 2004; Cantó et al., 2009).

3. Since the 1960s it has been recognized that NAD is a substrate for covalent protein modifications and cell signaling

Interestingly, several years after the discovery of the role of NAD in electron transfer in biological systems, it was recognized that NAD is also involved in non-oxidoreduction pathways in cells (Chambon et al., 1963). These "novel" roles of NAD include protein modification by ADP-ribosylation, generation of cellular second messengers, and modulation of the acetylation status of histones and other proteins (Chambon et al., 1963; Chini et al., 1995; Clapper et al., 1987; Imai and Guarente, 2010; Lee, 2012). In these reactions the oxidized form of NAD (NAD^+) serves as a substrate for a wide range of enzymes, such as poly-ADP-ribose polymerases (PARPs), CD38, and SIRTUINS that are involved in signal transduction and cell signaling. For example, NAD^+ is used as a substrate for the generation of calcium-regulating second messengers, such as cyclic-ADP-ribose (cADPR) and likely nicotinic acid adenine dinucleotide phosphate (NAADP) (Chini et al., 1995; Chini and Dousa, 1995; Lee, 2012). These signaling pathways have been shown to be very important in many physiological conditions, like egg fertilization, and pathological conditions such as cellular dysfunction induced by toxins and infectious agents (Chini, 2009; Wei et al., 2014). Due to the key role of NAD in multiple biological functions, it is crucial to characterize the mechanisms that control its metabolism. In recent years, we have learned much about the cellular mechanisms of NAD synthesis and degradation, and also about several of the *in vivo* NAD metabolites (Garten et al., 2015; Cantó et al., 2015).

4. NAD is highly abundant in cells and can be converted into several molecules of biological significance

As discussed above, the molecular structure of NAD consists of two nucleotides: an adenine base and nicotinamide, which are joined by a phosphate group (Fig. 2). The β diastereomer is the one that supports cellular biochemical reactions. Reported NAD concentrations in cells vary between studies and methodologies, but are generally in the range of 0.2–0.3 mM, making this a very abundant molecule in cells. The fact that NAD is a key molecular coin in energy metabolism and is abundant in cells raises the inevitable analogy with ATP (the main energy coin of living

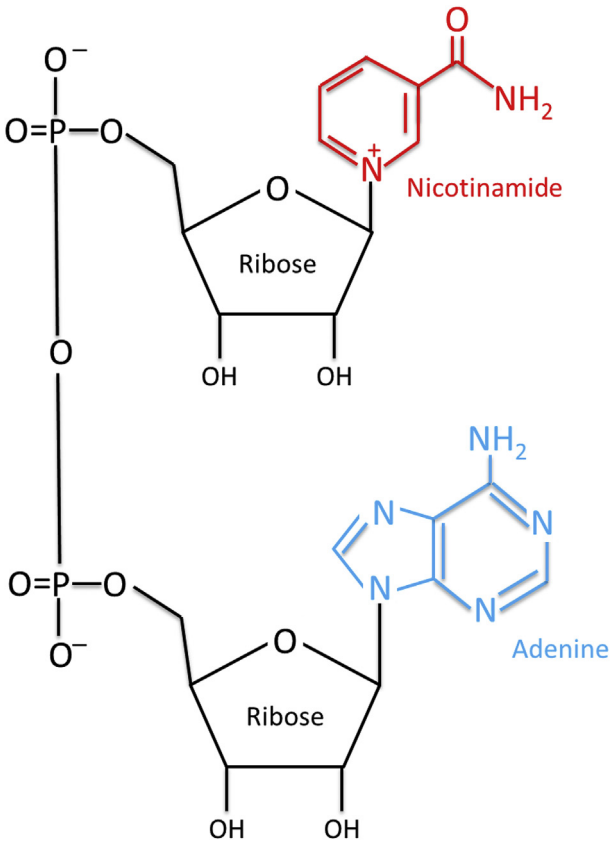

Fig. 2. The structure of NAD+. The molecular structure of NAD, including the two riboses, the adenine and the nicotinamide base.