Published in final edited form as:

J Cell Physiol. 2018 March ; 233(3): 1895–1896. doi:10.1002/jcp.26014.

NAD⁺: A big player in cardiac and skeletal muscle remodeling and aging*

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Abstract

In the past decade, NAD⁺ has gained importance for its beneficial effects as antioxidant and antiaging molecule. A paper in science by Zhang et al (2016) has described that NAD⁺ when replenished, ameliorates muscle dystrophy in mice by improving mitochondrial function. NAD⁺ was also demonstrated by the authors to improve the life span of mice. Cox et al (2002) demonstrated the cardiac effects of NAD⁺ which mitigated chronic heart failure via mitochondrial redox state mechanism. Cox et al (2002) also demonstrated that NAD⁺ is provided in the drinking water, it improves cardiac relaxation in volume overload model of heart failure. Although NAD⁺ has a profound anti-aging and anti-oxidant effects, its effect on humans and use as a dietary supplement needs more exploration.

A recent report in Science by Zhang et al (2016) describes the role of NAD⁺ in aging, however, it does not show the translational aspect of NAD⁺. We have shown that NAD⁺ improves cardiac relaxation, suggesting its potential in translational medicine (Cox et al, 2002). Although NAD⁺ (nicotinamide adenine dinucleotide) has a profound role in redox reactions, it is also an essential substrate for enzymes like sirtuins and PARP (poly-adenosine diphosphate ribose polymerase). Sirtuins act by protein deacetylation while PARPs mediate glycosidic bond cleavage between ADP ribose and nicotinamide (Sauve et al, 2001; Hassa et al, 2006). The nicotinamide generated by these NAD⁺ consuming enzymes is further replenished by salvage pathway in mammalian cells for maintaining the concentration of NAD⁺ above threshold. NAD⁺ concentrations are maintained by two kind of enzymes 1) nicotinamide phospho ribosyltransferases (NAMPT) and 2) NMN (nicotinamide mononucleotide) adenylyltransferases- NMNATs. While NAMPT converts NAD⁺ to NMN, NMNATs convert NMN to NAD⁺ (Figure 1). NMN adenylyltransferases are localized in 1) nucleus- NMNAT1; 2) Golgi- NMNAT2 and 3) mitochondria- NMNAT3. There is a distinct NAD⁺ pool at subcellular levels. Any fluctuation in the NAD⁺ levels can highly affect the structure and function of the enzymes and subcellular organelles.

The functional aspect of NAD⁺ has been earlier described by Cox et al in 2002 in which the authors treated the left ventricle volume overload rat models with NAD⁺ by supplying it in drinking water Cox et al (2002). Apart from decreasing oxidative stress, NAD⁺ treatment

* A part of this study was supported by NIH grant HL-74185

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improved the impaired endothelial dependent cardiac relaxation. This was the first translation study referring to the beneficial effects NAD⁺ in cardiac function. Subsequently the role of NAD⁺ was established as antiaging by regulating the activity of sirtuins and PARPs which are NAD⁺ requiring enzymes. PARP1 plays a critical role in oxidative stress induced cell death and inflammation while loss of sirtuins is associated with the process of aging. In this context Zhang et al (2016) have shown that replenishment of NAD⁺ improved life span in mice by improving mitochondrial and stem cell function. The authors demonstrated that during normal aging adult muscle stem cells in mice are lost. When the mice diet is supplemented with nicotinamide riboside (NR), the effect is ameliorated with improvement in the mitochondrial function in these stem cells Zhang et al (2016) which includes respiration, membrane potential and production of ATP. These mitochondrial improvements did not occur in stem cells lacking SIRT1. In mice model having muscular dystrophy, overexpression of SIRT1 rescued the disease model. Although these studies have referred to the beneficial effects of NAD⁺ they have ignored the important study performed by Cox et al (2002) where NAD⁺ proved beneficial to the cardiac muscle cells by improving endothelial dependent cardiac relaxation (Figure 2). Although the resurgence of NAD⁺ in mouse diet has proved to be beneficial the translation in humans and its use as a dietary supplement is still far away.

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Figure 1. NAMPT converts NAD⁺ to NMN, NMNATs convert NMN to NAD⁺

Figure 2. Effects of NAD⁺ on muscle dystrophy