Review

NMNATs, evolutionarily conserved neuronal maintenance factors

Yousuf O. Ali[1,2,3], David Li-Kroeger[2,4], Hugo J. Bellen[2,3,4,5], R. Grace Zhai[6], and Hui-Chen Lu[1,2,3,5]

[1] The Cain Foundation Laboratories, Texas Children's Hospital, Houston, TX 77030, USA
[2] Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, Houston, TX 77030, USA
[3] Department of Pediatrics, Baylor College of Medicine, Houston, TX 77030, USA
[4] Department of Molecular and Human Genetics, and Howard Hughes Medical Institute (HHMI), Baylor College of Medicine, Houston, TX 77030, USA
[5] Program in Developmental Biology and Department of Neuroscience, Baylor College of Medicine, Houston, TX 77030, USA
[6] Department of Molecular and Cellular Pharmacology, Miller School of Medicine, University of Miami, Miami, FL 33136, USA

Proper brain function requires neuronal homeostasis over a range of environmental challenges. Neuronal activity, injury, and aging stress the nervous system, and lead to neuronal dysfunction and degeneration. Nevertheless, most organisms maintain healthy neurons throughout life, implying the existence of active maintenance mechanisms. Recent studies have revealed a key neuronal maintenance and protective function for nicotinamide mononucleotide adenylyl transferases (NMNATs). We review evidence that NMNATs protect neurons through multiple mechanisms in different contexts, and highlight functions that either require or are independent of NMNAT catalytic activity. We then summarize data supporting a role for NMNATs in neuronal maintenance and raise intriguing questions on how NMNATs preserve neuronal integrity and facilitate proper neural function throughout life.

NMNATs maintain neuronal health

The vast majority of neurons are born during embryogenesis. Maintaining the long-term health of neurons throughout the life of an organism therefore represents a major challenge. Loss of neuronal function from inability to maintain homeostasis during accumulating stress is highlighted by neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease (reviewed in [1]). Hence, neurons require a continuous maintenance plan that enables them to endure the demands of varying workloads and to blunt damage from oxidative stress, injury, toxic compounds, and genetic stress. Here we define a neuronal maintenance factor as a protein or molecule whose deficiency enhances age- and/or activity-dependent degeneration in mature neurons.

Corresponding authors: Ali, Y.O. (yoali@bcm.edu); Lu, H.-C. (hclu@bcm.edu).
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A neuronal maintenance function has been attributed to NMNAT proteins, first characterized as essential enzymes catalyzing NAD synthesis. *Drosophila* has a single NMNAT gene, whereas mice and humans have three, NMNAT1–3, whose products differ in their kinetic properties [2]. *Drosophila* NMNAT (*d*NMNAT) is widely distributed within cells [3], whereas mammalian NMNAT1–3 proteins have distinct subcellular localizations [4]: NMNAT1 is localized to the nucleus, NMNAT2 is present in the Golgi, and NMNAT3 is present in mitochondria (Figure 1). Complete loss-of-function of *dNmnat* causes very severe post-development photoreceptor neurodegeneration in *Drosophila* (Box 1) [3]. *Nmnat1* loss-of-function mutant mice are embryonic lethal, whereas *Nmnat1* heterozygous mice develop normally without detectable neurodegeneration or axonal pathology [5]. *Nmnat2* knockout mice die at birth with a reduction in the number of peripheral nervous system (PNS) neurons and axons [6]. By contrast, NMNAT overexpression provides varying degrees of neuroprotection against a wide range of stressors and toxic insults (reviewed in [7] and Table 1).

In this review we summarize our current knowledge of NMNAT biology, focusing on neuronal maintenance, and review evidence for and against a requirement for NMNATs enzymatic activity in mediating specific neuroprotective effects. We also discuss the protective effects of NMNAT in key models of neurodegeneration and consider the implications for NMNAT as a neuroprotective agent in human diseases.

Functional diversity of NMNAT

The neuroprotective role of NMNAT first emerged with the characterization of a spontaneous chromosomal rearrangement in Wallerian degeneration slow (Wld^S) mice ([8], reviewed in [7,9]). These mice carry a dominant mutation that delays Wallerian degeneration of injured axons. The mutation results in a chimeric gene of the E4 ubiquitination factor Ube4b and the entire coding region of mouse NMNAT1, associated with a gene triplication [10,11]. The neuroprotective effects of this mutant protein have stimulated considerable efforts to uncover possible mechanisms. Hence, NMNAT1 has been studied in numerous contexts to

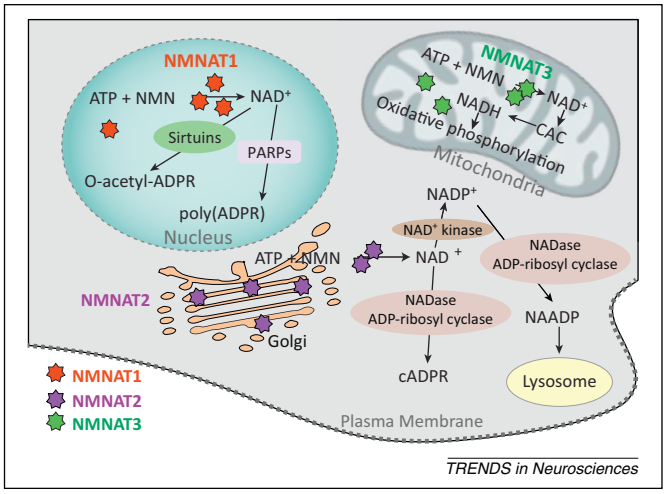

Figure 1. Mammalian NMNATs have distinct subcellular localizations. NMNAT1 is a nuclear protein with a predicted nuclear localization signal (NLS) between Glu^{107} and Lys^{146} [87]. NMNAT2 is localized to the Golgi apparatus via palmitoylation of Cys^{164} and Cys^{165} [4,87]. In the mouse brain, NMNAT2 is enriched in numerous membrane compartments, including synaptic terminals and synaptic vesicles [4,22]. NMNAT3 is predominantly localized in mitochondria and its first 25 residues encode a mitochondrial targeting sequence [50]. NAD^+, the enzymatic product of NMNATs, is an essential cofactor for many metabolic processes, transcriptional regulation, and several protein modification reactions. The NAD signaling pathway generates precursors of several intracellular calcium mobilizing agents including cADPR and NAADP. Abbreviations: ADPR, ADP-ribose; CAC, citric acid cycle; cADPR, cyclic ADP-ribose; NAADP, nicotinic acid adenine dinucleotide phosphate; NADase, bifunctional NAD glycohydrolase/ADP-ribosylcyclase; NMNAT, nicotinamide mononucleotide adenylyl transferase; PARP, poly-ADP-ribose polymerase.

understand if the protection provided by Wld^S and the other NMNAT isoforms is widespread and can be attributed to the enzymatic function of this protein or to some novel, enzyme-independent function [3,4,11–29].

NMNATs: essential housekeeping enzymes

NMNATs were initially characterized as enzymes catalyzing the reversible condensation of ATP with nicotinic acid mononucleotide (NaMN) or nicotinamide mononucleotide (NMN) to produce nicotinic acid adenine dinucleotide (NaAD) or nicotinamide adenine dinucleotide (NAD) [30–32]. NAD is an essential cofactor in many cellular processes including transcriptional regulation and oxidative reactions [18]. NMNAT enzymatic activity enables an appropriate flux of NAD in cells by salvaging byproducts of NAD-consuming chemical reactions to maintain NAD at levels necessary for internal homeostasis. Furthermore, the distinct subcellular distribution of mammalian NMNATs (Figure 1) allows local production of NAD, which presumably optimizes site-specific NAD-requiring metabolism.

The early lethality associated with loss of either *Nmnat1* and *Nmnat2* in mice [5,6] suggests that there is little functional redundancy among NMNAT1–3 proteins. In mammals, for example, the nuclear-localized NMNAT1 interacts at gene regulatory elements with both poly ADP ribose polymerase-1 (PARP1) and Sirtuin-1 (Sirt1) to regulate expression of target genes, including *ATXN10* and *NAT1* [33–35]. PARP1 uses NAD as a substrate to modify proteins [36–38], whereas Sirtuin uses NAD to deacetylate target proteins and to control gene expression [39–43]. The interaction of NMNAT1 with Sirt1 or PARP1 at specific

Box 1. NMNAT maintains healthy neurons, independently of their development, in *Drosophila melanogaster*

In the *Drosophila* embryo, loss of *Nmnat* does not affect neuronal development, although global loss of function is lethal. During the larval stage, *d*NMNAT is required for maintaining proper dendrite arborization and axonal integrity in type IV da neurons. Wild type da neurons ($Nmnat^{+/+}$) have extensive arborizations of dendrites, whereas heterozygous *Nmnat* mutants ($Nmnat^{+/-}$, middle) exhibit reduced arborization (Figure I). Homozygous *Nmnat* mutant ($Nmnat^{-/-}$) da neurons suffer from progressive fragmentation of axons (arrow). During pupation, a mosaic eye containing $Nmnat^{-/-}$ neurons develops similarly to the normal eye throughout 80% of pupal development. $Nmnat^{-/-}$ photoreceptors rapidly degenerate, showing fragmentation of rhabdomeres (red broken box), the rod-like component of a photoreceptor cell, and loss of active zones (green broken box). Additionally, $Nmnat^{-/-}$ sensory neurons (dpr^+ neurons) show progressive deterioration of axons.

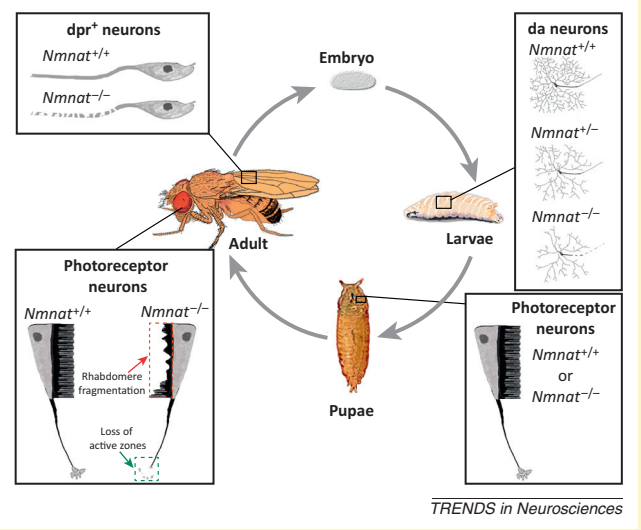

Figure I. Effects of *Nmnat* gene loss-of-function in *Drosophila*. Abbreviations: da, dendritic arborization sensory neurons; *dpr*, defective proboscis extension response.

DNA regulatory elements likely establishes a local pool of NAD important for activating Sirt1 and for providing the NAD for PARP1 catalytic activity necessary for regulation of target genes by these enzymes. Recent studies found that the axonal localization of catalytically active NMNAT1 or NMNAT2 is crucial in preventing axonal degeneration [44,45]. These findings suggest that the specific subcellular localizations of NMNATs allow them to provide NAD in precise cellular domains to activate specific signaling cascades.

NMNAT: a novel chaperone

Molecular chaperones are defined as proteins that assist in multi-protein complex assembly, protein folding, and protein refolding after damage [46]. Enzyme-independent functions of NMNATs were first explored after the surprising observation that an enzymatically inactive form of *d*NMNAT protected photoreceptors from degeneration in *Drosophila* [28]. Subsequent studies provided additional support that NMNATs can act as chaperones [13,28,47,48].

The following are typical chaperone activities that have been associated with NMNATs.

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