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Metabolic aspects of neuronal degeneration: from a NAD+ point of view.

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Abstract

Cellular metabolism maintains the life of cells, allowing energy production required for building cellular constituents and maintaining homeostasis under constantly changing external environments. Neuronal cells maintain their structure and function for the entire life of organisms and the loss of neurons, with limited neurogenesis in adults, directly causes loss of complexity in the neuronal networks. The nervous system organizes the neurons by placing cell bodies containing nuclei of similar types of neurons in discrete regions. Accordingly, axons must travel great distances to connect different types of neurons and peripheral organs. The enormous surface area of neurons makes them high-energy demanding to keep their membrane potential. Distal axon survival is dependent on axonal transport that is another energy demanding process. All of these factors make metabolic stress a potential risk factor for neuronal death and neuronal degeneration often associated with metabolic diseases. This review discusses recent findings on metabolic dysregulations under neuronal degeneration and pathways protecting neurons in these conditions.

Keywords

neurodegeneration; metabolism; axon; nicotinamide adenine dinucleotide; axon degeneration

Introduction

Genetic and epidemiological evidence indicates the role of abnormal metabolism in neurodegenerative diseases. It is known that many neurological disorders are directly caused by mutations in enzymes and transporters of the metabolite, i.e., small molecules essential for cellular metabolism. Growing evidence also suggests the close association of metabolic defects and neuronal degeneration, e.g. type 2 diabetes and Alzheimer's disease. In addition, age dependent decline of cellular metabolism coincides with neurodegenerative diseases including Alzheimer's and Parkinson's disease. Deficits in cellular metabolism result in the failure of energy production, biomolecule synthesis (amino acids, nucleotides, fatty acids,

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lipids), ROS regulation, or proteostasis: ultimately affecting all type of cells in the body. This review will primarily focus on the metabolic consequences in the neuronal cell under neurodegenerative conditions.

1 The link between neuronal degeneration and metabolic defects

The nervous system is a high-energy demanding network of cells that consumes about 15% of the total energy expenditure in the human body. The dysregulation of cellular energy metabolism is the primary risk factor for various neurodegenerative disorders (Camandola and Mattson, 2017; Procaccini et al., 2016). Cellular metabolic regulators collect nutritional information and initiate signals that adapt cellular metabolism for a constantly changing environment. These metabolic regulators including mTOR, PPARγ, and AMPK, are essential for neuronal development and homeostasis. Dysregulated cellular metabolism reflected by alterations of signaling in and out of metabolic regulators are common in neurodegenerative diseases.

1.1 Metabolic dysregulation in neurodegenerative conditions

mTOR signaling: The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that is regulated by the cellular nutrient and growth factor levels (Saxton and Sabatini, 2017; Sengupta et al., 2010). mTOR is the core component of two distinct protein complexes, mTORC1 and mTORC2, which regulate diverse cellular functions including protein synthesis, immune response, cell growth, proliferation, and autophagy. mTORC1 is activated by growth factors and nutrients and inhibited by energetic stresses. FKBP12 suppresses mTORC1 complex formation and downstream kinase cascades upon binding to rapamycin, an FDA-approved antibiotic and immunosuppressant drug. mTORC2 is far less sensitive to rapamycin and activates AKT signaling that in turn promotes cell survival, proliferation and also various metabolic pathways. Growing evidence shows that neurodegenerative disorders including Alzheimer's (AD), Parkinson's (PD), and Huntington's (HD) disease exhibit dysregulated mTOR signaling. Thus, targeting mTOR signaling for neurodegenerative treatment is an emerging topic (Bové et al., 2011; Cai et al., 2015).

Among diverse sets of cellular processes controlled by mTOR, autophagy, a conserved catabolic process that degrades cellular components (Ohsumi, 2014), plays important roles in neurodegeneration (Menzies et al., 2017). Protein misfolding and aggregate formation are a common feature of various age-associated neurodegenerative diseases. Accumulation of misfolded protein is toxic to cells and autophagy dysregulation is implicated in this process. Rapamycin inhibits mTORC1 and stimulates autophagy by increasing autophagosome formation and lysosome-mediated clearance of autophagosomes. It is possible that rapamycin promotes clearance or suppression of misfolded protein aggregates and improves cognitive function. Consistent with this idea, long-term administration of rapamycin in AD model mice PDAPP overexpressing human APP containing V717F (Indiana) mutation or genetic ablation of one copy of mTOR in CNS neurons of AD model mice Tg2576 overexpressing human APP containing the double mutation KM670/671NL (Swedish) mutation showed improved cognitive function, increased autophagy, and reduced Aβ42, a proteolytic cleavage product of APP forming aggregate (Caccamo et al., 2014; Spilman et al., 2010). Rapamycin also depletes the PrP amyloid plaque deposition with increased

autophagy in Gerstmann–Sträussler–Scheinker disease (GSS) model mice (Cortes et al., 2012). In addition, genetic reduction of S6K1, a downstream target of mTOR, leads to the reduced transcription of β-site APP cleaving enzyme 1 (BACE-1) and tau thereby reduces Aβ production and phosphorylated tau in AD mice Tg2576 (Caccamo et al., 2015). Similarly, neuronal mTOR hyperactivation causes various neurological defects depending on the age of the animal (Kassai et al., 2014). Autophagy and BACE1 transcription regulation through mTOR signaling likely play an important role in AD and the mechanism that overactivates mTOR under disease conditions will be a key to understand the pathogenesis of AD.

Parkinson's disease (PD) is characterized by α-synuclein aggregates, mitochondrial damage, and apoptosis in substantia nigra dopaminergic neurons. Mitophagy is an mTOR regulated cellular defense mechanism that induces clearance of damaged mitochondria without releasing proapoptotic factors. In healthy mitochondria, PINK1 shuttled from the cytosol is kept low by mitochondria protease mediated PINK1 c- terminal cleavage, which releases PINK1 from mitochondria. However, mitochondria dysfunction and subsequent membrane potential loss slow PINK1 proteolysis and cause the accumulation of PINK1 on the mitochondria outer membrane. Mitochondria tethered PINK1 phosphorylates PARKIN and stimulates recruitment of PARKIN to mitochondria and activates PARKIN's E3 ligase activity that promotes mitophagy. Mitophagy dysfunction by mutations in PINK1 and PARKIN causes familial PD (Pickrell and Youle, 2015). Rapamycin prevents mitophagy dysfunction and the neurodegenerative phenotype in PD model mice harboring the PARKIN mutation (Siddiqui et al., 2015). In addition, the role of autophagy in the clearance of α-synuclein aggregates is implicated using an *in vitro* cell model (Webb et al., 2003). These results suggest the beneficial effect of restoring the mTOR pathway in the treatment of PD. Stress-induced protein DDIT4 (REDD1 or RTP801) is induced in the postmortem human PD brain as well as cellular or mouse PD models. DDIT4 inhibits AKT pro-survival signaling perhaps through mTORC2 (Malagelada et al., 2008). However, DDIT4 also binds 14–3-3, TSC2 inhibitor, and promotes TSC2 mediated mTORC1 inhibition that is known to protect neurons. Whether the role of DDIT4 is protective or harmful in different stages of PD still needs to be determined.

The mTOR inhibitor, rapamycin or its analogue CCI-779, improves behavior tasks and reduces aggregate formation in fly or mouse Huntington's disease (HD) models (Ravikumar et al., 2004). Huntingtin (Htt) interacts with Rheb, a small GTPase protein that stimulates mTORC1 activity and induces mTOR signaling (Pryor et al., 2014). The activation of mTORC1 by the deletion of one copy of TSC1, a negative regulator of mTORC1, accelerates the onset of motor deficits and premature death (Pryor et al., 2014). Another study showed that the activation of mTORC1 by the expression of constitutively active Rheb alleviates striatal atrophy as well as other metabolic defects in HD disease model mice (J. H. Lee et al., 2015). Interestingly, the striatal autophagy signal is increased in the case of Rheb activation and Htt aggregates are reduced after Rheb mediated mTORC1 activation in the striatum. These results show activation of mTOR signaling has a biphasic effect on HD pathophysiology. Although further studies are required, it is clear that cellular metabolism modulates HD pathophysiology through mTOR signaling.

Diabetes is known as a potential risk factor for Alzheimer's disease, with abnormalities in insulin signaling reported in AD brains from human patients and model mice (Frölich et al., 1998; Orr et al., 2014). Brain insulin signal dysregulation (hyper phosphorylation of IRS1 and downstream kinases PI3K and AKT) and Aβ burden in AD model mice Tg2576 expressing mutant APP (Swedish) are suppressed by the removal of one copy of mTOR (Caccamo et al., 2018). The administration of a high sucrose diet to AD model mice 3xTg expressing mutant APP (KM670/671NL), Tau (P301L), and PSEN1 (M146V) exaggerates the dysregulation of brain insulin signaling and accumulation of Aβ and phosphorylated Tau. Interestingly, the sucrose-mediated effects are mTOR dependent and administration of rapamycin blocks the effects of sucrose (Orr et al., 2014). In contrast, brain hypometabolism due to low glucose levels is common in Alzheimer's disease patients. Accordingly, the selective expression of glucose transporter GLUT1 in neurons rescued the life span, behavior, and pathology of Aβ42 expressing AD Drosophila by increasing unfolded protein response (Niccoli et al., 2016). Metformin that stimulates glucose transport mimic the GLUT1-mediated rescue effects. These results indicate that high glucose stimulates or suppresses AD pathology depending on the context. It seems that the balance between glucose stimulation and mTOR activity is important or the effect of glucose may differ in different models and disease stages. Further studies are required to fully evaluate the role of glucose homeostasis in AD brains.

PPARγ signaling: Peroxisome proliferator-activated receptor (PPAR) is a ligand activated nuclear hormone receptor. PPAR regulates cellular metabolic processes including inflammation signaling, mitochondria function, and lipid metabolism, which are pathways often dysregulated in neurodegeneration. PPAR is activated by a diverse set of fatty acids and forms heterodimers with the retinoid X receptors (RXRs), which then bind to PPAR response elements (PPRE) to modulate gene expression (Desvergne et al., n.d.). There are three subtypes of PPAR, α, β/δ, and γ, and all subtypes are expressed in the brain (Warden et al., 2016). PPARγ regulates various pathways that are linked to insulin sensitivity, blood glucose, lipid metabolism, antioxidants, and inflammation. Interestingly, PPARγ depletion from CNS neurons attenuates high-fat, diet-induced weight gain by reducing food intake and increasing energy expenditure (Lu et al., 2011), suggesting that PPARγ is one of the key molecules connecting the nervous system to systemic metabolism.

The involvement of PPAR signaling in neuronal degeneration is indicated by experiments showing beneficial effects of PPARγ activation in neurodegenerative models (Corona and Duchen, 2016). Conditional depletion of PPARγ in neurons results in increased brain damage and oxidative stress after middle cerebral artery occlusion (Zhao et al., 2009). Cultured PPARγ KO neurons are more susceptible to oxidative glucose deprivation compared with wild type and pharmacological activation of PPARγ suppresses neuronal death. PPARγ activation induces the expression of antioxidant genes including catalase, SOD1, and GST, suggesting PPARγ-mediated neuronal protection is, at least partially, dependent on the enhancement of antioxidant pathways (Zhao et al., 2009). PPARγ agonists are also neuroprotective in traumatic brain injury model (Qi et al., 2010).

In addition, PPARγ agonist genistein promotes Aβ clearance through increased expression of APOE in AD model mice APPswe/PS1dE9 (or AβPP/PS1) expressing mutant APP

(KM670/671NL) and pathogenic PSEN1 lacking exon 9 (Bonet-Costa et al., 2016). PPARγ activity is also regulated by the recruitment of cofactors including PGC1α. Ectopic expression of PGC1α suppresses the expression of BACE1, reduces Aβ production, and improves spatial and recognition memory in AD model mice expressing pathogenic APP (Katsouri et al., 2016). PGC1α expression is shown to decrease in the AD patient brain, suggesting the role of PGC1α in AD pathogenesis (Katsouri et al., 2011)

AMPK signaling: AMP-activated protein kinase (AMPK) is an energy-sensing enzyme that is activated by reduced energy availability reflected by an increase of AMP:ATP ratio (Burkewitz et al., 2014). Activated AMPK suppresses ATP consumption and increases ATP generation via fatty acid oxidation. AMPK is a heterotrimer consisting of a catalytic α subunit and a regulatory β and γ subunit. AMPK is activated by the phosphorylation of the α subunit Thr172 by upstream kinases LKB1, CaMKKβ, and Tak1. AMPK kinase activity is allosterically activated, to a much lesser extent than Thr172 phosphorylation, by the binding of AMP to the γ subunit. However, this AMP binding facilitates the LKB1 mediated α subunit Thr172 phosphorylation. AMPK regulates numerous metabolic pathways including mTOR, which is inhibited by the phosphorylation of TSC2 and raptor (Gwinn et al., 2008; Inoki et al., 2003). AMPK is a potential therapeutic target for diseases involving metabolic dysregulation.

The AMPK pathway is dysregulated under neurodegenerative conditions including Parkinson's, Huntington's, and Alzheimer's disease. Extracellular Aβ oligomer formation and intracellular accumulation of hyperphosphorylated tau are two prominent features of Alzheimer's and other related dementia. Aβ42 oligomers induce AMPK activation (pT172 AMPK) depending on the CAMKK2 in cultured hippocampal neurons. This CAMKK2-AMPK signaling induces tau phosphorylation (S262), causing synaptic toxicity in AD model mice (APP/SWE, IND) (Mairet-Coello et al., 2013). Deletion of AMPKα2, the most abundant AMPK catalytic subunit, reduces the phosphorylation of endogenous tau in wild type mice and induces significant reduction of insoluble and MC1 positive tau (a form of pathological tau found in an early phase of AD) in AD model mice expressing Tau P301S (Domise et al., 2016). These results suggest the important role of AMPK mediated tau phosphorylation in AD pathogenesis.

Calorie restriction (CR) promotes lifespan by slowing the progression of age-associated diseases including neurodegeneration (Bayliss et al., 2016; Gräff et al., 2013). Genetic and pharmacological evidence supports the strong connection between CR and AMPK activation (Cantó and Auwerx, 2011). While a high-fat/cholesterol diet regimen upregulates BASE1 expression, CR reduces BACE1 transcription via the activation of the AMPK-SIRT1-PGC-1 pathway (R. Wang et al., 2013). Similarly, the cognitive deficits and neuroinflammation associated with altered APP processing are observed in wild type mice after eight weeks of a high fat/high cholesterol diet regimen that inactivates AMPK (Thirumangalakudi et al., 2008).

Overactivation of AMPK is reported in the HD patient brain and HD model mice. AMPK activation by AICAR facilitates Htt aggregate formation and neuronal death by nuclear translocation of AMPKα1 (Ju et al., 2011). Mechanistically, AMPKα1 is activated and

translocated into the striatal neuron nucleus in HD model mice and suppresses Bcl2 expression, thereby promoting neuronal cell death.

Overactivation of AMPK is also observed in Lewy body disease (Jiang et al., 2013). Increased lactate, likely due to the mitochondrial dysfunction that is a hallmark of PD, is known to activate AMPK and may contribute to the initial AMPK activation process (Ross et al., 2010). Activated AMPK then phosphorylates α-synuclein S129 and induces PIKE-L, a small GTPase that negatively regulates AMPK to bind to α-synuclein. This leads to the sequestration of PIKE-L into α-synuclein containing Lewy bodies, hinders PIKE-L from AMPK inhibition, and further activates AMPK with a feed forward loop manner (Kang et al., 2017). Overactivation of AMPK results in FOXO3a translocation into the nucleus and increases the expression of proapoptotic Bim and cleaved caspase3 in the hypoxia-ischemia rat brain damage model (D. Li et al., 2017).

1.2 NAD^+ metabolism and neurodegeneration—Nicotinamide adenine dinucleotide (NAD^+), its reduced form NADH, and its phosphorylated forms are central regulators of cell metabolism by serving as cofactors for glycolysis, oxidative phosphorylation, TCA cycle, redox reactions, and protein modifications including acetylation and ADP-ribosylation. Mammalian NAD+ synthesis pathways consist of multiple enzymes and substrates (Fig.1). Vitamin B3 (nicotinamide (Nam) or nicotinic acid (NA)) is the primary precursor of NAD^+ synthesis in mammalian cells. Nam is converted to nicotinamide mononucleotide (NMN) by NAMPT and NA is converted to nicotinic acid mononucleotide (NaMN) by NaPRT, respectively. There are three mammalian enzymes, NMNAT1, 2, and 3, that convert NMN to NAD^+ or NaMN to nicotinic acid adenine dinucleotide (NaAD). NMNAT1, 2, and 3 localize to the nucleus, Golgi/cytosol, and mitochondria, respectively, suggesting discrete regulation of NAD^+ metabolism in different cellular compartments (Berger et al., 2005; Gilley and Coleman, 2010; Ryu, 2018). NAD^+ synthase produces NAD^+ from NaAD. Nrk1 and 2 provide an alternative route to synthesize NMN from nicotinamide riboside (NR). NaMN is also produced from tryptophan (Trp) via a de novo NAD^+ synthesis pathway consisting of multiple enzymes. The availability and usage of NAD^+ precursors including tryptophan (Trp), Nam, NA, NMN, NaMN, and NR vary depending on the type of cells. While the interconversion between NAD^+ and NADH is a major reaction in the redox pathway, NAD^+ is consumed by different classes of enzymes including deacetylase, ADP ribosylase, and NAD^+ glycohydrorase. The half-life of NAD^+ estimated by using isotope labelled NAD^+ precursors is about one hour in Hela derivative cells, 15 minutes to 15 hours in various moue tissues, and seven hours in cultured neurons, indicating the active nature of NAD^+ consuming enzymes (Ijichi et al., 1966; Liu et al., n.d.; Rechsteiner et al., 1976; Sasaki et al., 2016).

NAD^+ metabolism is impaired in various neurological disorders including Alzheimer's, Parkinson's, and retinal degeneration diseases (Cantó et al., 2015; Fang et al., 2017; J. B. Lin et al., 2016; Verdin, 2015) and neuronal injury accelerates NAD^+ consumption (see detail in section 2.2). CD38 is a constitutively active NAD^+ glycohydrolase that mainly produces ADPR and Nam but also has the capability to produce cADPR and NaADP (Graeff et al., 2009; W. K. Lin et al., 2017). Mice deficient in CD38 show elevated NAD^+ in various tissues including the brain and show social behavior deficits (Jin et al., 2007; Young et al.,

2006). Recent studies show that the depletion of CD38 reduces the number of Aβ plaque and both soluble and insoluble forms of Aβ in AD model mice APP.PS expressing mutant APP (KM670/671NL) and pathogenic PSEN1 lacking exon 9 (Blacher et al., 2015). In these mice, α-, β-, and γ-secretase activity is significantly reduced without altering their expression levels. Increased NAD^+, a CD38 inhibitor, or a cADPR antagonist reduced Aβ production in cultured neurons from APP, suggesting that CD38 enzymatic activity and the product cADPR likely modulate APP processing. CD38 also modulates the recruitment of microglia and macrophage in the hippocampus of APP/PS mice. Consistent with the reduced Aβ burden and microglia/macrophage accumulation, APP.PS:CD38−/− mice showed significant improvement in special learning memory and cortical synaptophysin levels compared with APP.PS mice.

The tryptophan catabolic route and the kynurenine pathway produces the NAD^+ precursor, quinolinic acid, by using multiple enzymes (Fig.1). Some of the kynurenine pathway metabolites have neuromodulation activities. Quinolinic acid (QA) is a NMDA agonist and kynurenic acid (KYNA) is an antagonist for excitatory amino acid receptors including NMDA, AMPA, kainic acid, and glutamate receptors. Metabolites in the kynurenine pathways are altered in AD, PD, and HD patient brains. KYNA in the serum and red blood cells are decreased in AD patients (Hartai et al., 2007). The reduction in KNA and KYNA and the increase in 3-hydroxy kynurenine (3HKYN) are observed in various regions of the PD brain (Ogawa et al., 1992). QA and 3HKYN are increased in the HD brain (Guidetti et al., 2004). The inhibition of two kynurenine pathway enzymes, TDO, a rate-limiter of QA synthesis, and KMO, ameliorates neurodegenerative phenotypes including neuronal death, motor function, and life span in *Drosophila* AD (Aβ42), PD(α-Syn), and HD (Htt93Q) models (Breda et al., 2016; Campesan et al., 2011). Although the underlying mechanism is not clear, pharmacological inhibition of TDO also provides robust neuroprotection in *Drosophila* neurodegeneration models (Campesan et al., 2011).

Recent studies show that the administration of NAD^+ precursors that promote NAD^+ synthesis modulate the progression of neurodegenerative diseases. For example, systemic administration of nicotinamide riboside (NR) significantly improves cognitive function in AD model mice Tg2576 expressing mutant APP (KM670/671NL) (B. Gong et al., 2013). NR treatment increases the NAD^+ level in cerebral cortex and the expression of PGC1α whose expression is known to be reduced in AD patient brains (Katsouri et al., 2011). Ectopic expression of PGC1α suppressed the expression of β-site APP cleaving enzyme 1 (BACE1), the main enzyme involved in Aβ generation, and reduced Aβ deposition which then improved spatial and recognition memory in AD model mice APP23 expressing APP (KM670/671NL) (Katsouri et al., 2016). Accordingly, NR administration reduces BACE1 expression levels in a PGC1α dependent manner. Mechanistically, PGC1α promotes BACE1 degradation through ubiquitin proteasomal systems and improves Aβ pathology and cognitive function (B. Gong et al., 2013). NR also increases PGC1α associated energy metabolism genes including citrate synthase, aconitase, and pyruvate dehydrogenase kinase, and this may partially contribute to the improvement of cognitive function in AD mice (B. Gong et al., 2013). Genotoxic stresses also have a significant impact on AD disease progression. Introducing the heterozygosity of polymerase β, the primary base-excision repair enzyme, into 3xTgAD mice exacerbates AD disease phenotypes. NR administration

significantly reduces Tau phosphorylation in 3xTgAD/Polβ mice brain without altering Aβ production or plaque formation, also suggesting the beneficial effect of NR towards Tau burden (Hou et al., 2018). The protection of mice from noise-induced hearing loss by systemic NR mediated SIRT3 activation suggests the beneficial effect of NR for acute neuronal injury as well (Brown et al., 2014).

Administration of nicotinamide mononucleotide (NMN), an alternative NAD^+ precursor found in various tissues, also suppressed cognitive impairment in Alzheimer's disease model mice APPswe/PS1dE9 (or AβPP/PS1) expressing mutant APP (KM670/671NL) and pathogenic PSEN1 lacking exon 9 (Yao et al., 2017). The elevations of p-JNK and Aβ in the hippocampus and cerebral cortex of AD mice are markedly reduced with NMN administration. NMN increases non-pathogenic α-secretase cleavage of APP and inhibits the APP Thr668 phosphorylation that promotes the β-secretase cleavage of APP and Aβ accumulation in AD mice. NMN administrated mice also attenuated inflammation and synaptic loss in AD brain (Yao et al., 2017). NMN improved mitochondrial bioenergetics and dynamics in the same AD mouse brain expressing mutant APP (KM670/671NL) and pathogenic PSEN1 lacking exon 9 (Long et al., 2015). Using a rat AD model generated by an intracerebroventricular Aβ oligomer infusion, NMN showed sustained improvement in cognitive function (X. Wang et al., 2016). NMN attenuated neuronal cell death and inhibition of LTP, and restored levels in NAD^+ and ATP in the Aβ oligomer-treated hippocampal slices.

NMNAT2 is dominantly expressed in neuronal tissues and is an essential NAD^+ biosynthesis enzyme for the peripheral nervous systems homeostasis (Hicks et al., 2012). NMNAT2 is also important for brain function, as higher NMNAT2 mRNA levels are associated with better cognitive performance and lower AD pathology in an aged human brain (Ali et al., 2016). NMNAT2 expression is positively regulated by the binding of phosphorylated cAMP-response element binding protein (pCREB) to CRE sites in the NMNAT2 promoter. The expression of pCREB and recruitment of pCREB to CRE are both suppressed and NMNAT2 is down regulated in the hippocampus and cortex of AD mice Tg4510 expressing pathogenic human Tau (P301L) (Ljungberg et al., 2012). Overexpression of NMNAT2 or NMNAT1 but not NMNAT3 significantly reduces AD related phenotypes in Tg4510. The NMNAT2:HSP90 complex reduced hyperphosphorylated Tau in the Tg4510 hippocampus while total Tau levels remained unchanged (Ali et al., 2016). The overexpression of NMNAT2 also reduced hyperphosphorylated Tau by restoring the activity of PP2A, the most active Tau phosphatase whose activity is reduced in the human AD brain and the AD mouse brain (Cheng et al., 2013; C. X. Gong et al., 1995).

NMNAT1 overexpression preserved cortical neuron functional connectivity and decreased the accumulation of detergent-insoluble tau in the cerebral cortex of AD model mice expressing pathogenic Tau (P301S) (Musiek et al., 2016). Although the detailed mechanism is still obscure, NMNAT improved AD related neuropathology by reducing the accumulation of hyperphospohrylated or detergent insoluble Tau.

DLK (MAP3K12) is a MAPKKK that promotes various injury-stimulated pathways in axon degeneration, neuronal apoptosis, or axonal regeneration (Miller et al., 2009; Pozniak et al.,

2013; Shin et al., 2012; Yang et al., 2015). Genetic or pharmacological inhibition of DLK improved neuronal survival, synaptic integrity and cognitive functions in neurodegenerative models including Alzheimer's disease and amyotrophic lateral sclerosis (ALS) (Le Pichon et al., 2017). Interestingly, DLK signaling promotes NMNAT2 turnover, a critical determinant of axonal homeostasis. The inhibition of DLK and downstream kinases, MKK4/7 and JNK, elevate the NMNAT2 level (Walker et al., 2017a). These results suggest the inhibition of DLK likely increases the neuronal NMNAT2 that may facilitate axonal stability and reduce accumulation of hyperphosphorylated Tau in AD brain.

Tau hyperacetylation is implicated in neurodegeneration and cognitive decline in the AD brain. Depletion of SIRT1 exacerbates premature mortality, synapse loss, and behavioral deficits in AD model mice (tauP301S) with increased acetylation at Lys174 of Tau in post synaptic density enriched brain lysate (Min et al., 2018). Ectopic expression of SIRT1 in the hippocampus reduces the acetylated Tau and attenuates the spread of Tau pathology. SIRT3 is markedly decreased in the AD brain and consequently acetylated P53 at Lys 320 is increased. Mitochondrial P53 negatively regulates the expression of ND2 and ND4, subunits of respiratory chain complex1, by occupying the P53 binding element in the mitochondrial DNA. SIRT3 overexpression restores ND2 and ND4 expression and mitochondrial oxygen consumption in cultured cortical neurons (J. Lee et al., 2018). SIRT3 overexpressing mice are also resistant to noise-induced hearing loss (Brown et al., 2014). SIRT6 expression is reduced in AD patients and (a) neuron specific SIRT6 deletion in mice brains resulted in DNA damage, neuronal cell death, and hyperphosphorylation of Tau due to increased GSK3α/β, a major Tau phosphorylating enzyme (Kaluski et al., 2017). Inhibition of SIRT2 is neuroprotective for the *Drosophila* HD model and reduces polyglutamine toxicity in cultured striatal neurons through downregulation of sterol biosynthesis genes (Luthi-Carter et al., 2010; Outeiro et al., 2007). In another study, SIRT2 overexpression is protective and pharmacological inhibition of SIRT2 is harmful for SHSY5Y cells treated with rotenone or diquat, suggesting a context dependent role of SIRT2 for neuronal homeostasis (Singh et al., 2017). A deficiency of SIRT5, mitochondria matrix sirutuin, increases kainic acid induced seizures, hippocampal neuronal degeneration, and mortality rates (F. Li and Liu, 2016). Similarly, SIRT4 deficient mice show a worsened seizure phenotype after kainic acid treatment without altering the mortality rate or percent of animals that responded. However, these defects are mainly due to the reduction of astrocyte glutamate transporter expression (Shih et al., 2014). These results indicate the important roles of sirtuins in neuronal homeostasis and studies to investigate the function of sirtuins in different types of cells and different types of diseases will provide further insight into the roles of these important NAD^+ dependent enzymes.

While hyperactivation of MAP kinase signaling is detrimental to the nervous system, hypoactivity of MAP kinase signaling also causes neuronal dysfunction. JNK is constitutively phosphorylated and plays important roles in the maintenance of the adult nervous system. Deletion of neuron specific isoform JNK3 caused dysregulation of circadian rhythm behavior (Yoshitane et al., 2012). Depletion in the neuron of MKK7, an upstream kinase of JNK, resulted in age-dependent hypoactivity, dysregulated circadian behavior, and motor neuron axon degeneration with increased APP in the nervous system (Yamasaki et al., 2017). Recent studies suggest a link between neurodegeneration and the mechanism causing

disruptions of the circadian clock (Musiek and Holtzman, 2016; Panda, 2016). One of the important functions of the circadian clock is to synchronize the body's metabolism and adjust it to the rhythmic behavior of day and night cycles. The circadian clock is also known to regulate NAD^+ metabolism through the NAD^+ rate limiting enzyme NAMPT and NAD^+ dependent deacetylase SIRT1 (Nakahata et al., 2009), suggesting the role of NAD^+ metabolism in neurodegeneration induced by the dysregulation of the circadian clock.

2. Axonal homeostasis and neuronal degeneration

Degeneration of nervous systems is initiated by vascular change, neuroinflammation, glial dysfunction, or neurons themselves, and results in the loss of neuronal connections due to the death of the neuron and/or axon degeneration. The estimated cumulative length of axons is 149,000 to 176,000 km, about four times the Earth's circumference, in human brain white matter at the age of 20 (Marner et al., 2003). This enormous stretch of the axon is generated during development and maintained throughout life. Since axons are highly vulnerable and poorly regenerated, the total length of axons in the white matter is reduced by 10% each decade after 20 years old with a much smaller decline in gray matter, resulting in the reduced complexity of the neuronal network in the aged brain (Marner et al., 2003). Axonal loss is also observed in various neurological disorders including Alzheimer's, Parkinson's, ALS, and genetic or acquired sensory neuropathies. While the axon is the highly important component of neuronal degeneration, the mechanism of axonal degeneration during aging and age-associated neuronal degeneration is not fully understood.

2.1 Axonal degeneration—

The axon is an essential component of nervous system, establishing a complex network of neurons and target cells. The distal part of the axon is far from the cell body and axonal transport supplies the majority of components required for its homeostasis (Maday et al., 2014). ATP necessary for fast axonal transport is supplied by the glycolytic enzymes carried on its own cargo (Zala et al., 2013). Axons also have the capability to translate proteins locally to respond to acute environmental changes using mRNAs transported through the axon (Cioni et al., 2018). Defects in axonal transport or the physical disruption of an axon cuts its lifeline and causes degeneration of the axon distal to the affected site.

Axonal loss is at least partially secondary from the loss of neuronal soma (dying forward). However, growing evidence shows additional mechanisms of axon dismantling during development, aging, and neuronal degeneration (Luo and O'Leary, 2005). A dying back axon degeneration, observed in developmental nervous systems or neurodegenerative conditions, and Wallerian degeneration extensively studied using a traumatic axonal injury model, are two different types of axon degeneration that also share some features (Yaron and Schuldiner, 2016). Understanding the molecular mechanisms underlying these different types of axonal degeneration is an emerging topic.

Axonal degeneration is observed in various neurodegenerative conditions including Alzheimer's, Parkinson's, and Huntington's disease. A subset of disease shows a relatively early phase of axon degeneration, suggesting its role in the pathogenesis of these diseases. Axonal dystrophy within the regions occupied by senile plaques, extracellular deposits of

amyloid β, are observed in both early and late stages of brains from Alzheimer's patients (Benes et al., 1991). Long-term *in vivo* imaging of axonal segments near Aβ plaques in the Alzheimer's disease model mice APPswe/PS1dE9 revealed the dynamic nature of axonal dystrophies (Blazquez-Llorca et al., 2017). The lifetime of dystrophic structure is about 80 days. Dystrophic structures disappear followed by axonal degeneration; the loss of whole axons or one side of axon in the microscopic field. That the volume of dystrophic structure increases and decreases during its life suggests the existence of a balancing mechanism of disease progression and protection.

Mice expressing human LRRK2(R1441G) BAC transgene, a model of the most common form of familial Parkinson's disease, showed a reduction in the number of TH-positive dendrites and the appearance of dystrophic neurites without SN dopamine neuron loss (Y. Li et al., 2009). A later study identified that the signs of axonopathy were preceding the abnormality in the TH-positive dendrites (Tagliaferro et al., 2015). Additional evidence also supports the early axonal phenotypes in Parkinson's disease (Decressac et al., 2012; Kordower et al., 2013; Nuber et al., 2013). In Huntington's disease model mice ($Hdh^{Q140/Q140}$), axonal swelling dramatically increases before the loss of cell bodies, dendritesa, and synapses (Marangoni et al., 2014).

Many studies suggest the presymptomatic appearance of axon terminal defects in ALS model mice (Dadon-Nachum et al., 2010). Three-dimensional live imaging of nerves using stimulated raman scattering microscopy revealed significant axonal degeneration in the peripheral nerves preceding the physiological motor dysfunctions in *SOD1* mutant ALS model mice (Tian et al., 2016). However, the study of familial ALS associated with TDP-43 containing inclusions suggests the corticofugal spreading of disease in which anterograde axonal transport of pathogenic molecules spreads the disease, suggesting that disease onset is before axonal degeneration (Braak et al., 2013). The studies that test the efficacy of axonal protection on SOD1 mutant ALS models are not successful (Fischer et al., 2005; Velde et al., 2004). Further studies are required to elucidate the roles of axon degeneration in the pathogenesis of ALS.

Traumatic brain injury (TBI) is a leading cause of death and disability and 130 patients die every day in the United States from injuries that include TBI. TBI causes post-injury pathologies affecting memory, sensation, and emotion, and raises the risk for neurological disorders such as Alzheimer's and Parkinson's disease (Blennow et al., 2016; Prins et al., 2013). While the mechanism behind these brain pathologies is not well understood, it is known that TBI induces severe metabolic burden characterized by reduced cerebral blood flow, impairment of glucose uptake, and NAD^+ reduction. These metabolic defects likely cause post-TBI energetic crisis followed by various TBI related pathologies. TBI is also known to induce axonal degeneration that continues years after injury in humans (Johnson et al., 2013). In the model mice brain, severe axonal degeneration is observed at 48 hours post TBI, and the depletion of SARM1 or induction of the *Wlds* transgene (see details in section 2.2) completely abolished the axon degeneration (Henninger et al., 2016; Yin et al., 2016). TBI induced metabolic dysfunctions in the brain, the reduction of total choline and n-acethylaspartate, are also attenuated in the absence of SARM1 (Henninger et al., 2016). Importantly, blocking axon degeneration attenuates post TBI symptoms including cognitive,

motor, and visual deficits in these mice, suggesting the primary roles of axonal degeneration in post TBI pathologies.

It is clear that axon degeneration is an important component of neurodegenerative diseases, especially in its early phases. Axon degeneration may serve as an early disease marker and also may be a therapeutic target of neurodegenerative diseases. To evaluate the therapeutic potential of axonal protection and to develop treatments, further studies on the signal that initiate axon degeneration in different neurodegenerative diseases are warranted.

2.2 Axonal degeneration and NAD^+ metabolism—Prior to current histopathological evidences of axon degeneration in neurodegenerative diseases, Augustus Waller first described the importance of axon degeneration by analyzing the destruction of frog hypoglossal nerves upon axotomy. The seminal finding of the mouse harboring mutant gene, Wallerian degeneration slow (*Wlds*), whose transected nerves remain intact more than 14 days, later led to the novel concept that axon degeneration is an active regulated process. *Wlds* is composed of the N-terminal portion of Ufd2a and full length NMNAT1. Many excellent reviews on the topics of axon degeneration are published elsewhere (Adalbert and Coleman, 2013; Coleman and Freeman, 2010; Conforti et al., 2014; Geden and Deshmukh, 2016; Gerdts et al., 2016; Neukomm and Freeman, 2014; Salvadores et al., 2017; J. Wang and He, 2009). In these series of studies, many molecules and pathways are identified in the axon degeneration signaling cascade and the NAD^+ biosynthesis pathway is one of the most important pathways modulating axon homeostasis (Fig.2). The major findings of axon degeneration signaling related to NAD^+ metabolisms are: 1) NMNAT and its NAD^+ synthesis activity are necessary and sufficient components of axonal protection by Wlds (Araki et al., 2004); 2) NMNAT2 is a labile axon maintenance factor and its degradation results in axon degeneration (Gilley and Coleman, 2010; Hicks et al., 2012); 3) SARM1 is a primary axon executor, degrading NAD^+ with intrinsic and stimulus dependent NADase activity by the TIR domain (Essuman et al., 2017; Gerdts et al., 2016; Osterloh et al., 2012). These studies placed NAD^+ metabolism as a central regulator of the axon degeneration signaling pathway.

Remarkably, increasing axonal NMNAT and blocking the NMNAT2-SARM1 pathway that promotes axon degeneration after axotomy also attenuates axon degeneration in a diverse set of neurodegenerative disease models *in vivo* including TBI (Henninger et al., 2016; Yin et al., 2016; Ziogas and Koliatsos, 2018), Glaucoma (Williams et al., 2017; Zhu et al., 2013), peripheral neuropathy (Geisler et al., 2016; Turkiew et al., 2017; M. S. Wang et al., 2002), CMT (Meyer zu Horste et al., 2011; Samsam et al., 2003), motor neuron degeneration (Ferri et al., 2003), Ischemic injury (Verghese et al., 2011), gracile axonal dystrophy (Mi et al., 2005), and so on (Conforti et al., 2014). These results suggest that the manipulation of NAD^+ biosynthesis is a potential therapeutic target.

Axonal injury induces rapid NAD^+ decline preceding the loss of ATP and morphological degeneration (Gerdts et al., 2016; J. Wang et al., 2005). NAD^+ is consumed by a variety of enzymes including CD38, Sirtuins, PARPs, and ART, and inhibition of these NAD^+ consumers may delay axon degeneration. However, depletion of CD38 and PARP1, two major NAD^+ consuming enzymes, did not alter axon degeneration profiles both *in vitro* and

in vivo (Sasaki et al., 2009). Similarly, forced NAD^+ depletion induced rapid axon degeneration, suggesting NAD^+ depletion is sufficient to induce axon degeneration. We found that SARM1 is responsible for injury induced NAD^+ depletion, however, the actual enzyme that degrades NAD^+ was not identified (Gerdts et al., 2015). Much to our surprise, our recent efforts to identify the molecules responsible for injury induced NAD^+ degradation revealed that the Toll/interleukin-1 receptor (TIR) domain of SARM1 is a NADase domain (Essuman et al., 2017). Interestingly, exogenous expression of NMNAT1 is able to block injury induced SARM1 NADase activity through an unknown mechanism (Sasaki et al., 2016). The next question is how NAD^+ depletion leads to axonal degeneration. Since ATP decline is followed by NAD^+ degradation, one can speculate that the failure of ATP dependent processes including axonal transport, ion homeostasis, and cytoskeletal organization directly leads to axon destruction. However, a recent report indicates the existence of additional axon degeneration signaling mediated by a *Drosophila* protein called axunded (axed) downstream of multiple axon injury insults (Neukomm et al., 2017). Axed, BTB (*b*ric-à-brac, *t*ramtrack, *b*road complex) and a BACK (*B*TB *a*nd *C*-terminal *K*elch) containing protein, is required for a broad range of axonal degenerations after injury, SARM activation, axonal NMNAT depletion, and a combination of SARM activation and NMNAT depletion (Neukomm et al., 2017). Further studies are required to understand axon degeneration signals downstream of SARM and axed.

The next question is how SARM1 NADase activity is regulated. Upon axonal injury, NMNAT2 in the distal axons sharply declined due to its short half-life and lack of supplies from the cell bodies (Gilley and Coleman, 2010). One possibility is that the loss of NMNAT2 in the axon leads to the activation of SARM1 NADase activity. NMN, the precursor of NAD^+, increases after axotomy due to the loss of its consuming enzyme NMNAT2 in the axon and it is suggested that the elevation of NMN promotes axon degeneration (Di Stefano et al., 2015). The expression of NMNAT in the axon rescues the NMN increase by compelling NMNAT2 loss. Similarly, exogenous expression of *E. coli* NMN deamidase, which reduces cellular NMN level by converting NMN to NaMN, provides strong axonal protection that is equivalent to NMNAT1 expression (Di Stefano et al., 2015). Similar to the injury-induced axon degeneration, depletion of NMNAT2 in mice caused reduced axon stability leading to insufficient innervation of phrenic nerves on the diaphragm muscle after birth (Hicks et al., 2012). Importantly, both SARM1 KO and NMN deamidase transgenic mice rescue NMNAT2 KO lethality and axonal phenotypes (Gilley et al., 2017; Hicks et al., 2012). This strong genetic evidence supports the idea that NMN accumulation is a trigger of axon degeneration dependent on SARM1 (Di Stefano et al., 2015). However, high NMN in the axon after NAMPT expression or exogenous application of NR to NRK1 expressing neurons did not cause axon degeneration (Sasaki et al., 2016). This suggests the presence of alternative mechanisms other than a simple NMN increase as a trigger of SARM1 activation.

Recent reports showed a positive correlation of NMNAT2 mRNA expression with the global cognition score in an aged cohort (Ali et al., 2016). Reduced NAD^+ and NMNAT2 expression are also observed in the spinal cord of motor neuron disease model mice (Röderer et al., 2018), suggesting the importance of NMNAT2 in neuronal homeostasis. The NMNAT2 level in the distal tip of axons is predicted to be extremely low when considering

the length of peripheral axons (1 meter), speed of axonal transport (0.04 meters/day), and the short half-life of NMNAT2 (24 hours). It is important to understand the mechanism of distal axon homeostasis under low NMNAT2 levels and axon degeneration signaling upon NMNAT2 loss.

The prodegenerative role of MAP kinase signaling cascade is first shown using MAPKKK DLK deficient mice and identified JNK as a downstream target of DLK (Miller et al., 2009). Later MKK4/7 was identified as primary MAPKKs linking DLK (MAPKKK) and JNK(MAPK) in axonal ATP depletion that lead to axonal degeneration after traumatic injury (Yang et al., 2015). It is important to determine the role of DLK-MKK4/7- JNK signaling in the SARM1 dependent axon degeneration cascade. While the role of MKK4/7 is found downstream of SARM1 using direct activation of SARM1 by TIR dimerization (Yang et al., 2015), MKK4/7 inhibition did not block the NAD^+ loss induced by TIR dimerization (Walker et al., 2017b). It seems that MKK4/7 is upstream of SARM1 judging by the NAD^+ degradation that is a direct readout of SARM1 activation. Strong genetic evidence supports that NMNAT2 loss induced axonal degeneration is SARM1 dependent. It is shown that MKK4/7 or JNK is required for the first turnover of NMNAT2 in the axon and inhibition of this signaling increases the axonal NMNAT2 (Walker et al., 2017b). Thus, the DLK-MKK-JNK pathway likely promotes the turnover of axon survival factor after injury, leading to SARM1 activation.

AKT phosphorylate MKK4 Ser78 antagonizes the prodegenerative Ser257/Thr261 phosphorylation of MKK4 that stimulates JNK phosphorylation and axonal degeneration after traumatic injury (Yang et al., 2015). However, the AKT mediated survival signal is diminished with unknown mechanisms and axonal degeneration proceeds in normal cells. Independent studies showed that the overexpression of AKT significantly delays axon degeneration, supporting the roles of AKT for axonal survival (Wakatsuki et al., 2011). While former studies showed the inhibition of MKK and ATP depletion as downstream, the latter showed that the inhibition of GSK3β and microtubule reorganization by AKT is responsible for axonal protection. Consistently, GSK3α/β promotes Tau hyper phosphorylation and neuronal degeneration, and suppression of GSK3β provides axonal protection (Gerdts et al., 2011; Kaluski et al., 2017). Further studies on the mechanism that links MAP kinase signaling and neuronal metabolism after injury will be required.

3. Conclusions

Growing evidence indicates important roles of cellular metabolism in pathogenesis and progression of neurodegeneration. Studies of signaling pathways related to cardinal metabolic regulators including mTOR, PPARγ, and AMPK provide valuable information on cellular metabolic statuses in different stages of the disease. Analysis of metabolites and pathways in synthesis and consumption of NAD^+, the central metabolic regulator, also convey cellular energetic status and activity of various NAD^+ dependent enzymes that is crucial for neuronal homeostasis. Mechanisms that activate or inhibit these metabolic nodes in the course of neurodegeneration are not fully understood and will be important in future studies.

Metabolic genes are often universal across many types of cells. It should be noted that metabolic changes in non-neuronal cells including glial, immune, and vasculature cells must be taken into account to evaluate metabolic effects for pathogenesis and progression of neuronal degeneration. Inhibition of a metabolic enzyme may exert biphasic consequences in different types of cells.

While many pathways and molecules altered in neurodegeneration are identified, the cause of neuronal degeneration is uncertain. Axonal degeneration is often seen in early phase neurodegeneration and, regardless of cause or consequence, the signaling that leads to axon degeneration will provide valuable information on the pathogenesis of neurodegenerative diseases. Recent studies show the central role of NAD^+ metabolism for the trigger of axon degeneration, suggesting this universal metabolic regulator may serve as an important check point for neuronal homeostasis.

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Highlights

- Dysregulations of cellular metabolism play important roles in neurodegeneration.
- Axonal degeneration is a crucial component of neurodegeneration.
- NAD+ metabolism governs axonal degeneration.

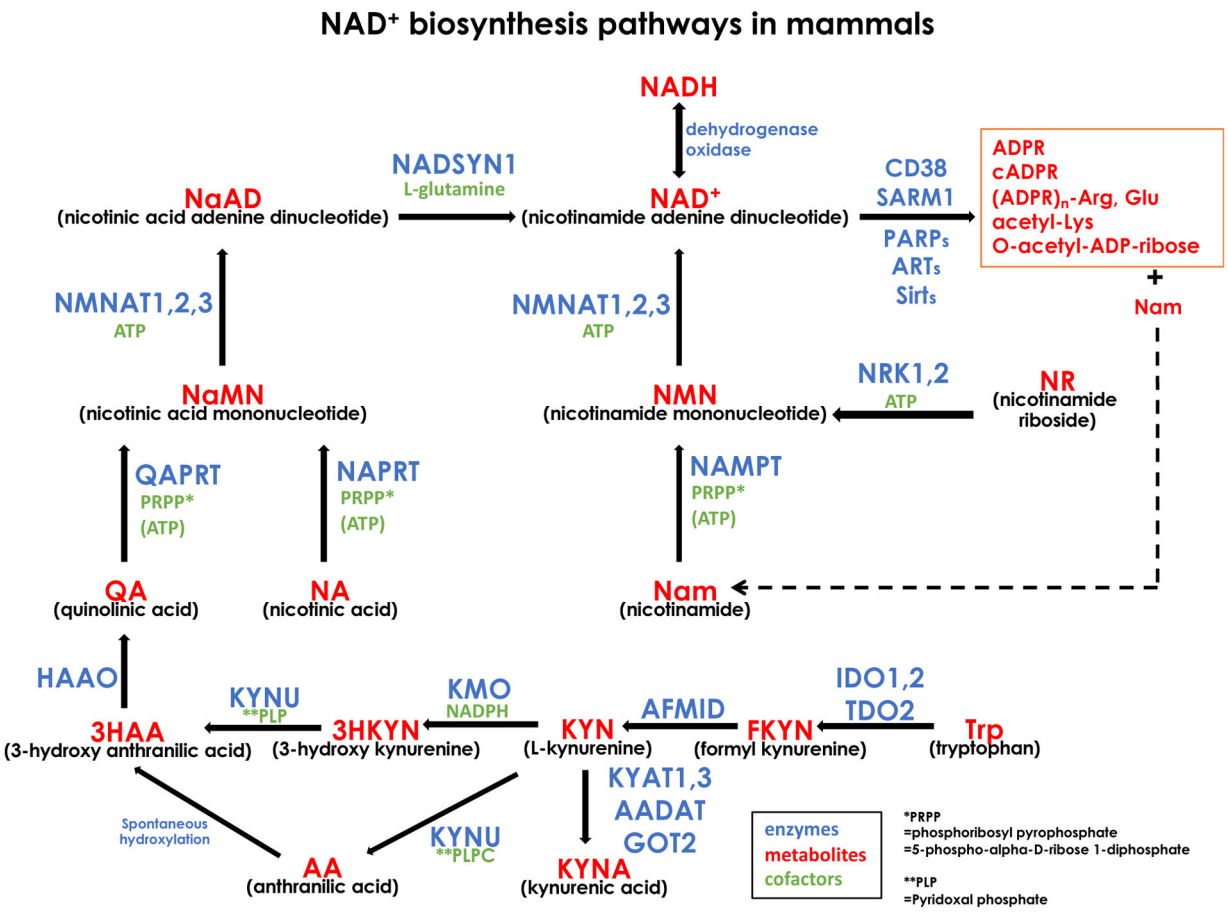

Figure1. NAD$^+$ biosynthesis pathways.

A summary of mammalian NAD$^+$ synthesis and catabolism. Official gene symbols of each enzyme, metabolites and their common abbreviated names, and cofactors necessary for enzymes are summarized.

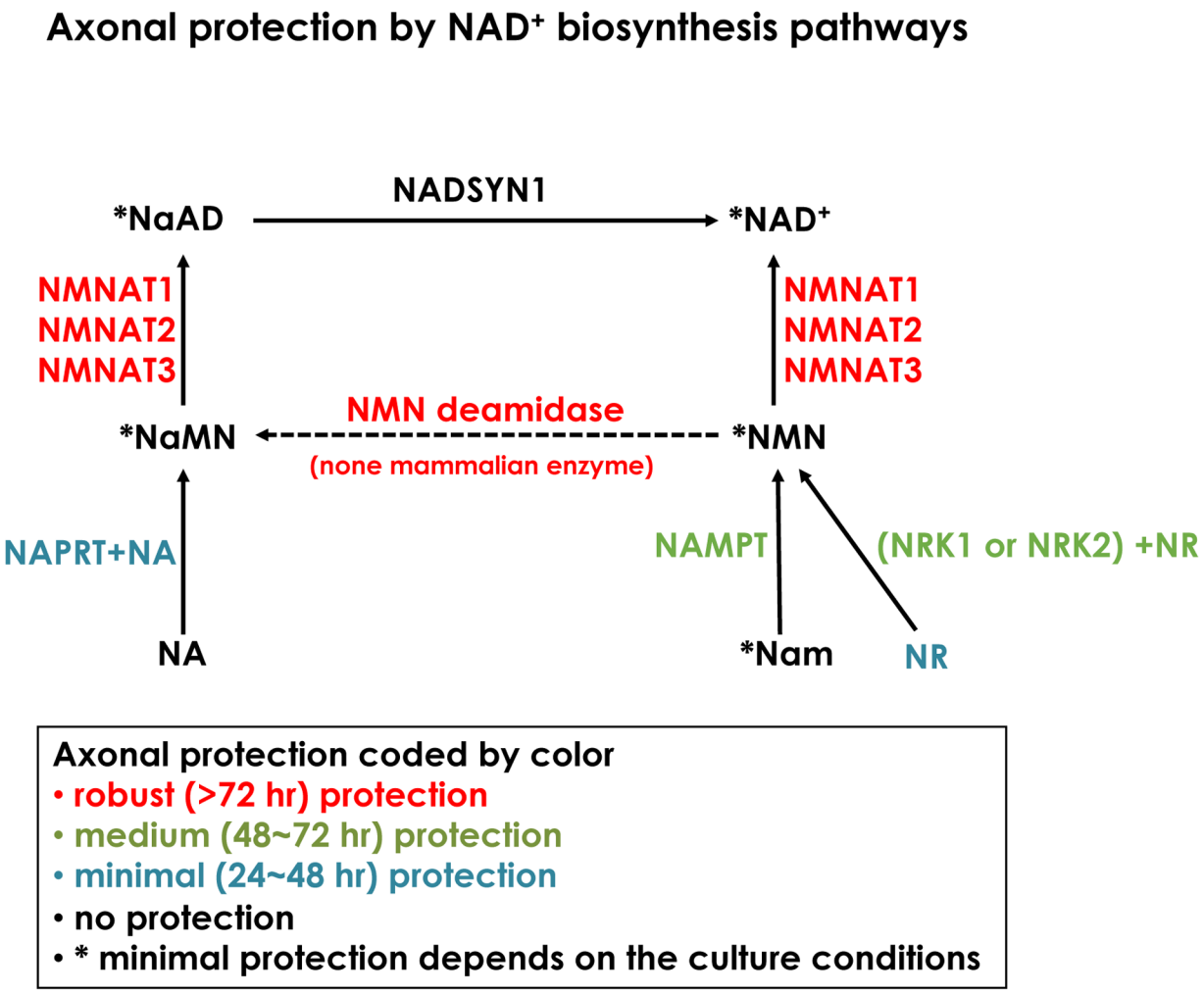

Figure2. Axonal protection mediated by NAD$^+$ biosynthesis pathways.

A summary of the effect of NAD$^+$ biosynthesis pathways on injury induced axon degeneration using cultured DRG neurons. Official gene symbols of each enzyme, metabolites and their combinations are shown with the duration of axonal protection that is represented by colors indicated in the figure. Data is summarized from previous publications (Araki et al., 2004; Sasaki et al., 2016; 2006; J. Wang et al., 2005).