Pyridine Nucleotide Homeostasis in Plant Development and Stress

Ramamurthy Mahalingam* • Niranjani Jambunathan • Anuradha Penaganti

ABSTRACT

The traditional role of pyridine nucleotides (PNs) – NAD(H) and NADP(H), as the key redox couples in the cytoplasm of all living cells is well known. The reversible conversion between oxidized and reduced forms of PNs does not affect the net levels of these molecules. Resynthesis of these metabolites arises due to their participation in signaling reactions. Recent discoveries in animal systems have shown that derivatives of PNs such as ADP-ribose, cyclic ADP-ribose, o-acetyl ADP-ribose, nicotinic acid adenine dinucleotide phosphate are important signaling molecules. Some of these metabolites are reported in plant responses to environmental perturbations. In animal systems it has been shown that derivatives of PNs are involved in at least three important post-translational modifications of proteins – poly(ADP)-ribosylation, mono(ADP) ribosylation and o-acetylation. Role of these modifications in plants is gaining increasing attention. Levels of these PNs in plant cells show considerable changes during various developmental stages indicating these molecules can serve as metabolic read out of cell fate. Recent studies in animal systems show that the redox state of PNs can serve as global metabolic regulators of gene expression. Arabidopsis mutants with altered PN levels show massive changes in gene expression further supporting the animal studies. Our understanding of the role of PNs in plants is only beginning. A systems biology approach will facilitate a thorough understanding of the versatility of these labile redox molecules in plant health and sickness.

Keywords: ADP-ribose, metabolism, post-translational, redox, signaling
Abbreviations: ADP, adenine dinucleotide phosphate; ADPR, adenine dinucleotide phosphate ribose; cADPR, cyclic adenine dinucleotide phosphate ribose; NAADP, nicotinic acid adenine dinucleotide phosphate; o-AADPR, o-acetyl adenine dinucleotide phosphate ribose; PARP, poly(ADP) ribose polymerase; PN, pyridine nucleotide

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INTRODUCTION

Nicotinamide adenine dinucleotide (NAD) and its phosphorylated form, nicotinamide adenine dinucleotide phosphate (NADP), exist as oxidized form (NAD+ or NADP+, respectively) or in reduced form (NADH and NADPH, respectively) (Fig. 1). NAD+, NADP+, NADH and NADPH are together referred to as pyridine nucleotides (PNs). PNs are ubiquitous coenzymes involved in oxidation-reduction reactions in all organisms (Berger et al. 2004). They are central components of the cytoplasmic redox milieu and the reduction versus oxidation states of these metabolites serve as signals for evoking responses to internal developmental changes as well as external environmental perturbations (Dietz 2003).

The concentration of cytosolic NAD in plants is 0.6-0.7 mM, most of which exist in oxidized form, so that free NADH is barely detectable and estimated to be around 1 μM (Heineke et al. 1991; Wigge et al. 1993). On the contrary, the cytosolic NADP (0.2-0.3 mM) is mostly reduced, accounting for NADPH concentrations of 0.15-0.2 mM. The concentrations of NADP(H) is largely regulated by environmental conditions. The reduction state of chloroplast PNs is strongly influenced by light conditions in plants (Heber and Santarius 1965). In sugar beet (Beta vulgaris) and spinach (Spinacea oleracea), 40% of NADPH is in chloroplasts and increases to 60-85% under light conditions (Hunt et al. 2004). In another study with spinach (S. oleracea) leaves, chloroplast NADPH/NADP+ was influenced by CO2 concentrations supplied to the leaves (Dietz and Heber 1983). Chloroplast membrane is impermeable to exogenous PNs indicating that the pool of PNs in this organelle is adjusted internally, maybe by formation of phosphoglycerate during photosynthesis (Hunt et al. 2004). Interestingly, unlike in animals, the plant mitochondria are permeable to PNs (Douce and Neuburger 1989), indicating that cytosolic and mitochondrial NAD+ concentrations are equilibrated. The nuclear membrane is freely permeable to PNs, suggesting that nuclear and cytoplasmic NADH:NAD+ ratios are comparable (Fjeld et al. 2003). This can have a profound
influence on gene regulation in response to alterations in cytosolic redox (discussed later).

Quantitation of PNs in photosynthetic cells is difficult because tissue NAD(P) concentrations are low and complex enzymatic cycling assays need to be used following the destruction of either oxidized or reduced form in alkali and acid, respectively (Lowry and Passonneau 1972; Matsumara and Miyachi 1980). Further, reliable determination of low concentrations of PNs depends on accelerated quenching of the metabolism due to rapid turnover of PNs in metabolic processes (Dietz 2003). An alternate method for estimating reduced NAD is based on the reaction equilibrium of the 3-phosphoglycerate (3-PGA) reduction, yielding dihydroxyacetone phosphate (DHAP) through the action of 3-PGA kinase, glyceraldehyde-3-phosphate dehydrogenase and triosephosphate isomerase, according to the equation below (Dietz and Heber 1989).

\[
\frac{[3-PGA][NADPH][H^+][ATP]}{[DHAP][NADP^+][ADP][Pi]} = 5.4 \times 10^{-6}
\]

Activation of chloroplast malate dehydrogenase has been used to quantify the reduction state of NADP in this organelle (Hollgrefe et al. 1997). Sophisticated two-photon excitation microscopy has been used to quantitate source and number of subcellular NAD(P)H fluorescence in pancreatic islet cells by comparing with fluorescence from a purified NAD(P)H source (Patterson et al. 2000). Regulation of the C-terminal binding protein in mammalian cells by nuclear NADH levels was demonstrated using this technique (Zhang et al. 2002). Recently, a simple plate reader assay for the rapid analysis of PNs, as well as ascorbate and glutathione redox couples in plant extracts was reported (Queval and Noctor 2007). Development of such sensitive and rapid methods for measuring redox couples will be extremely useful for analyzing the changes in these labile metabolites during plant development and in response to various environmental perturbations.

**SYNTHESIS OF PNs**

Similar to purine and pyrimidine biosynthesis, PNs are synthesized by de novo and salvage pathways (Ashihara et al. 2005) (Fig. 2). In the de novo pathway, L-aspartic acid is oxidized to iminosuccinic acid by L-Asp oxidase enzyme (AO; EC 1.4.3.16). Condensation of iminosuccinate with glyceraldehyde-3-phosphate and cyclization to quinolinic acid is accomplished by quinolinate synthase (QS). Subsequently, phosphoribosyl pyrophosphate (PRPP) and quinolinic acid combine to produce nicotinic acid mononucleotide (NaMN) catalyzed by the enzyme quinolinic acid phosphoribosyl transferase (QPRT). These three enzymes, AO, QS and QPRT are encoded by single genes in the Arabidopsis genome, are localized in the chloroplast, and are indispensable for normal growth (Kato et al. 2006). NaMN is converted to nicotinic acid adenine dinucleotide by nicotinamide mononucleotide adenyltransferase (NaMNAT) and subsequently amidated to NAD by the action of NAD synthetase. The last two enzymes, NaMNAT and NAD synthetase, are encoded by single genes in Arabidopsis genome (Hunt et al. 2004).

In the salvage pathway, nicotinamide generated by the degradation of NAD, by the action of NAD glycohydrolases, NAD-dependent deacetylases, mono-ADP ribosyl transferases and polyADP ribose polymerases, is used for regenerating NAD. Nicotinamidases deamidate nicotinamide to nicotinic acid and transfers it to PRPP (Wang and Pichersky 2007). From this step, the enzymes involved in the NAD biosynthesis are the same as described above for the de novo pathway. Given the overlap between de novo pathway and salvage pathway, we predict that a loss-of-function of NaMNAT or NAD synthetase may be lethal. This needs to be tested using the T-DNA insertional mutants available for these two genes from the Arabidopsis database.

The molecular identification of nicotinamide riboside kinase in mammalian cells and yeast has established a novel route for NAD biosynthesis (Sasak and Saunders 1996; Bieganowski and Brenner 2004). Presence of the nicotinamide riboside in food sources suggests that niacin or vita-
min B3 may not be the only source for de novo synthesis of NAD in plants.

The only de novo mechanism for the formation of NADP is in plants by NAD(H) kinases using NAD(H) and ATP as substrates (Delumeau et al. 2000; Gallais et al. 2001). There are three NAD(H) kinases in the Arabidopsis genome. AtNDK1 can utilize both NAD+ and NADH as substrates and is induced in response to pathogens and oxidative stress (Berrin et al. 2005). AtNDK2 is described as NAD kinase and it also binds calmodulin (Turner et al. 2004). AtNDK3 prefers NAD+ over NADH and is inactivated by thiol-modifying reagents (Turner et al. 2005). The rapid changes in the NAD+/NADP+ in response to wounding and pathogens indicates that there must be specific NADP+ phosphatases (Harding et al. 1997; Moller 2001). NAD+ phosphatase which converts the NADP+ to NAD+ has been reported in the dormant seeds of Avena sativa (Gallais et al. 2001). Thus the kinase/phosphatase ratio can be an important determinant of the nicotinamide nucleotide metabolism (Turner et al. 2005).

**PNs IN PLANT DEVELOPMENT**

In higher plants the organs and tissues of different ages coexist in the same individual and PN levels serve as rate-limiting factors for regulating the metabolism in each part (Yamamoto 1963). In the storage organs such as endosperm and cotyledons, levels of NAD are very high and exist mostly in oxidized form, and NADP levels are very low, and most of it is in reduced form. In hypocotyls levels of NADP are strikingly high. The NADP+/NADPH/ NAD+ NADH ratio is low in storage organs and high in growing parts of a plant. The NADPH/NADP+ ratio in cotyledon, hypocotyls, roots and leaves decreases with increasing age (Yamamoto 1963). In Arabidopsis plants, the NAD+/NADH ratio showed a vast variation in different organs – roots, stem, rosette leaf, cauline leaf, flowers, silique), while the NADP+/NADPH ratio remained fairly constant in these organs (Wang and Pichersky 2007).

Changes in the PN pool levels have been demonstrated to be important signals for rapidly switching the energy metabolism of plants from a vegetative to a reproductive stage (Bonzon et al. 1983). Using plate reader, four redox couples – NAD, NADP, ascorbate and glutathione were analyzed in Arabidopsis plants at five different time points spanning vegetative stage and four different time points during reproductive stage. NAD levels increased during the vegetative stage and plummeted during the flowering stage. However, the levels of NADH remained very stable (~20%) throughout the course of this analysis. NADP levels were least variable both in terms of total contents and redox state (Queval and Noctor 2007). These studies indicate that the NAD and NADP redox couples show very little variation during Arabidopsis growth under controlled conditions. Nonetheless, the sampling frequency (nine time points over a period of 70-75 days) may be masking the subtle modulations in the pyridine nucleotide contents. Also if the sampling were done in the light versus the dark cycle, there may be significant differences in the levels of PNs (Ohhama and Miyachi 1959; Ogren and Krogmann 1965).

**PNs IN PLANT RESPONSES TO STRESSES**

NAD pools in plants are highly plastic and can undergo significant changes in response to the environment (Noctor et al. 2006). Changes in NAD levels can serve as important modulators of metabolic pathways especially during conditions of stress (Dutilleul et al. 2003a, 2003b, 2005) (Fig. 3). In barley leaves infected with the powdery mildew pathogen, Erysiphegraminiv. hordei, 2-fold increase in NAD levels were observed six days after inoculation and this increase was accompanied by an increase in the rate of respiration (Ryrie and Scott 1968). In this study it was reported that the content of NADP+ in the non-chloroplast fraction was around 60% and this redistribution of the PN was responsible for the increase in activity of pentose phosphate pathway and respiration (Ryrie and Scott 1968). Using the French bean suspension-cultured cells treated with elicitors from fungal pathogen Colletotrichum lindemuthianum, a rapid increase in oxygen uptake was accompanied by an increase in hydrogen peroxide levels. This was followed by a rapid decline in the ATP levels and the NADH/NAD+ ratios suggestive of a transient stress in oxidative metabolism and aerobic respiration (Robertson et al. 1995).

NADPH is important reducing energy equivalent required for several antioxidant defense systems. In Arabidopsis, cytosolic NADPH is generated by AtNADK3, a NADH kinase (Chai et al. 2006). Loss-of-function of NADK3 renders the plants more sensitive to oxidative stress, further supporting the role of PNs especially NADPH for strengthening defense responses. Maintenance of high NADPH levels has been suggested to be an important factor in preventing injury in cold-hardened pea plants, hardened wheat plants subjected to drought stress and during cold acclimation in winter rape plants (Kuraishi et al. 1995; Maciejewska and Kacperska 1987; Zagdanska 1989). In transgenic rice plants over-expressing a NADPH-DC toxin reductase, synthesis of PNs were increased, which in turn led to enhanced tolerance to cell death by hydrogen peroxide the cytosolic Glycerol-3-phosphate dehydrogenase leads to...
Fig. 3 Interconnections between reactive oxygen species, calcium and pyridine nucleotides. CaM, calmodulin, O$_2^-$, superoxide; H$_2$O$_2$, hydrogen peroxide. Oxidative signaling includes changes in gene expression, enzyme activity, second messengers.

Fig. 4 Structures of pyridine nucleotide derived metabolites.
and bacterial pathogens (Hayashi et al. 2005). Mutations in increased NADH/NAD⁺ ratios in the mutant plants leading to increased ROS levels and sensitivity to salt stress (Shen et al. 2006). The Arabidopsis nuxia hydrolase Atmu7 hydrolyzes NADH and ADP-ribose in vitro (Ogawa et al. 2005; Olejnik and Kraszewska 2005) Mutation in Atmu7 leads to increased ROS, NADH and increased resistance to virulent bacterial pathogens (Jambunathan and Mahalingam 2002). The ADP-ribose polymerase (PARP) enzymes induced by stress is a major consumer of NAD since this enzyme transfers ADP-ribose units from NAD to target proteins, releasing nicotinamide and forming long ADP-ribose chains with concomitant depletion of ATP (Amor et al. 1998; Graziani et al. 2005). cADPR (Sanchez et al. 2005). NAADP mediated calcium release has been shown in the microosomal vesicles of red beets (Beta vulgaris) and cauliflower (Brassica oleracea) (Navazio et al. 2000). This nonvacular pathway for calcium release distinct from the intronosol phosphates and cADPR gated pathways, provides an important facet of the calcium signaling in plants which is regulated by these distinct second messengers. In vitro, NAADP synthesis required high levels of nicotinic acid (30 mM) and low pH (4.5–5) (Lee 2000), both of which are not physiologically relevant. This suggests that alternative routes for their biosynthesis may exist in plants and animals and needs to be determined.

**PNs AND SIGNAL TRANSDUCTION**

The reversible conversion of NAD(P) between oxidized and reduced forms does not impact the overall consumption of PNs in a cell. Hence the synthesis of these metabolites does not arise due to its well-known role as redox carriers, but from their participation in cellular signaling reactions (Pollak et al. 2007). The increasing attention given to NAD in recent years stems from their ability to serve as precursors of several important second messenger molecules. This includes ADP-ribose (ADPR), cyclic ADP-ribose (cADPR), and o-acetyl ADP ribose (o-AADPR), all of which are derived from NAD⁺. Nicotinic acid adenine dinucleotide phosphate (NAADP), is the only NADP derived second messenger (Fig. 4).

ADPR is a toxic metabolite that can lead to glycation and glycoxidation of long-lived intracellular proteins such as histones (Cervantes-Lauren et al. 1996). ADPR can be generated from NAD by several different metabolic pathways. The DNA breakage induced ADPR polymers synthesized by PARPs are rapidly turned over by polyADP-ribose glycohydrolases (PARGs), that can lead to ADPR accumulation. In the Arabidopsis genome, there are three genes that are annotated as PARPs and three genes as PARGs. Rapid induction of parp1 and parp2 during DNA breaks induced by ionizing radiation or oxidative stress has been reported (Douce-Chabeaud et al. 2001). In soybean (Glycine max) cells expressing the antisense of parp2 mRNA, ADPR due to hydrogen peroxide was inhibited (Amor et al. 1998). However, direct evidence for changes in ADP-ribose metabolite levels in response to stresses in plants have not been reported yet. In animal systems the removal of ADPR moiety from proteins by protein mono-ADP-ribosyltransferases has been reported to be another source for ADPR. However, such mono-ADP-ribosyltransferase activity has not been observed in plants yet.

cADPR plays a vital role in the modulation of calcium release from internal cellular stores (Lee and Aarhus 1991; Lee 1994; Lee et al. 1995). cADPR is synthesized from NAD by ADP-ribose cyclase enzyme (Lee 1994) while cyclic-ADP ribose hydrolases catalyze the breakdown of cyclic ADP ribosyl monomers leading to ADP ribose accumulation. The plant hormone ABA induces the activity of ADP-ribose cyclase within 15 minutes after treatment and nearly 28% of ABA-responsive genes are similarly regulated by cADPR (Sanchez et al. 2004). These studies established that cADPR is an important component of ABA signaling pathway (Wu et al. 1997; Sanchez et al. 2004). Further, the fact that more than 400 cADPR responsive genes act independent of the ABA pathway suggests that this signaling molecule may be playing an important role in other unknown signaling pathways.

o-AADPR is formed during the deacetylation reaction carried out by a group of proteins called as sirtuins that play a role in suppression of recombination, and ageing (Tanner et al. 2000; Denu 2003; Blander and Guarente 2004). o-AADPR has calcium mobilizing properties via activation of TRPM2 channel (Liu et al. 2005). In the Arabidopsis genome there are two potential homologues of sirtuins, however, these genes have not been characterized yet (Hunt et al. 2004) and no studies of o-AADPR in plants has been reported yet.

NAADP has been characterized as the most potent calcium-mobilizing messenger (Yamasaki et al. 2005). NAADP mediated calcium release has been shown in the microsomal vesicles of red beets (Beta vulgaris) and cauliflower (Brassica oleracea) (Navazio et al. 2000). This nonvacular pathway for calcium release distinct from the intronosol phosphates and cADPR gated pathways, provides an important facet of the complex calcium signaling in animals that is regulated by these distinct second messengers. In vitro, NAADP synthesis required high levels of nicotinic acid (30 mM) and low pH (4.5–5) (Lee 2000), both of which are not physiologically relevant. This suggests that alternative routes for their biosynthesis may exist in plants and animals and needs to be determined.

**PNs AND PROTEIN MODIFICATIONS**

Three important protein modifications are brought about by the second messenger molecules derived from PNs – poly (ADP-ribosyl)ation, mono(ADP-ribosyl)ation and protein deacetylation (Fig. 5).

Poly(ADP-ribosyl)ation is catalyzed by PARPs (Jacobson and Jacobson 1999; Burkle 2001). Using NAD as substrates, these enzymes form branched polymers of ADP-ribose that are then attached to glutamate residues of acceptor proteins. Based on studies in animal systems, PARPs are involved in a gamut of cellular processes such as DNA repair, cell cycle regulation, apoptosis and maintenance of chromosome length (Burkle 2001; Virag and Szabó 2002; Chiarugi and Moskowitz 2003). Based on studies in various plant species, PARPs are important for induction of defense mechanisms (Berglund et al. 1996) and in response to different stresses (Amor et al. 1998; Douce-Chabeaud et al. 2001). Using PARP inhibitors and antisense approach it was shown that Brassica plants with reduced PARP activity have higher energy levels and are more resistant to abiotic stresses like high light, drought and heat (De Block et al. 2005). Though these studies demonstrated a role for PARPs in stress signaling and DNA repair, the targets of poly ADP-ribosylation are not known yet.

Mono(ADP) ribosylation refers to the enzymatic transfer of ADPR from NAD⁺ to acceptor proteins (Corda and Di Girolamo 2003). These are catalyzed by cellular ADP-ribosyltransferases. ADP-ribosylation usually leads to protein inactivation, providing a mechanism for inhibiting protein functions in both physiological and stress conditions. The identification of ADP-ribosylhydrolases that reverse the reaction by hydrolyzing the protein-ADP-ribose linkage substrates that reversibly react with cell death proteins has not been demonstrated yet.

Protein deacetylation is carried out by sirtuin proteins that catalyze the NAD-dependent deacetylation reaction that requires the acetylated lysine found in the N-terminus of histones. For every acetyl group removed from a lysine molecule, one molecule of NAD is hydrolyzed to form a molecule of nicotinamide (Tanny and Moazed 2001). As described earlier the acetyl group is transferred to ADP-ribose to give rise to a new signaling molecule called O-
AADPR. There are two potential Arabidopsis homologues of Sir2 and both lack nuclear localization signals suggesting its substrate may be non-histone cytosolic or mitochondrial proteins (Hunt et al. 2004). Yeast Sir2 is regulated by plant polyphenols (Howitz et al. 2003). Since plants produce a variety of polyphenols, especially in response to stresses, it has been speculated that these compounds can act as sir2 regulators in plants (Hunt et al. 2004).

**PNs AND GENE REGULATION**

In animal systems, NAD salvage pathway plays an important role in transcriptional silencing at the telomere and rDNA loci (Smith and Boeke 1997; Anderson et al. 2002; Sandmeier et al. 2002). Sir2p activity is required for this silencing, which requires NAD (Lin and Guarente 2003). Since salvage pathway proteins are localized to the nucleus it has been suggested that NAD can be readily utilized by Sir2p. Functional characterization of the Sir2 proteins in plants will aid in determining if such global transcriptional silencing at the telomeres and rDNA loci can be regulated by PNs.

NAD redox status plays an important role in regulating the transcription factors involved in circadian control in animals (Rutter et al. 2001). In Arabidopsis, mutation at the tej loci affects clock-controlled genes and alters the timing of photoperiod dependent transition from vegetative to flowering stage (Panda et al. 2002). TEJ encodes a poly (ADP-ribose) glycohydrolase protein suggesting that post-translational poly(ADP-ribosylation) of an oscillator component contribute to setting the period of a central oscillator in Arabidopsis (Panda et al. 2002). As indicated earlier identification of the target proteins for poly (ADP-ribosylation) will enable a clear understanding of the role of PNs, in the establishment of period length in plants.

The carboxyl-terminal binding protein (CtBP) a strong co-repressor that binds to transcriptional repressors is regulated by PNs, especially the levels of nuclear NADH (Zhang et al. 2002). Mutation in two different Arabidopsis genes – cytosolic glyceraldehyde–3-phosphate dehydrogenase and nudix hydrolase 7 that alter the NADH levels in the plants have been described recently (Jambunathan and Mahalingam 2006; Shen et al. 2006). A T-DNA insertion line in the promoter region of the Arabidopsis nudix hydrolase 7 (NUDT7) gene does not cause any phenotypic abnormalities in the mutant plant (Jambunathan and Mahalingam 2006). NUDT7 is a NADH and ADP-ribose pyrophosphatase (Ogawa et al. 2005; Jambunathan and Mahalingam 2006). In the nudt7 knock-down lines the levels of NADH were higher than in the wild-type plants (Jambunathan and Ma-
PNs are the most versatile redox molecules essential for energy transduction in a cell. Studies in animal system and yeast have led to the identification of PN derivative molecules that play vital regulatory roles, indispensable for normal growth of a cell and in responses to perturbations in the environment. The signaling role of PNs in plant development and stress signaling is gaining increasing attention. The finding that the PN levels are highly plastic in a plant cell and potentially can act as a read out of cell fate under scores the importance of these molecules. Our current understanding of the role of PNs in a cell can only be described as the tip of the iceberg. A combination of forward and reverse genetic approaches in conjunction with metabolite profiling is necessary to dissect the complex cellular redox network coordinated by PNs and its derivatives.

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