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The roles of NADPH and isocitrate dehydrogenase in cochlear mitochondrial antioxidant defense and aging

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Abstract

Hearing loss is the third most prevalent chronic health condition affecting older adults. Age-related hearing loss affects one in three adults over 65 years of age and is caused by both extrinsic and intrinsic factors, including genetics, aging, and exposure to noise and toxins. All cells possess antioxidant defense systems that play an important role in protecting cells against these factors. Reduced nicotinamide adenine dinucleotide phosphate (NADPH) serves as a co-factor for antioxidant enzymes such as glutathione reductase and thioredoxin reductase and is produced by glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, isocitrate dehydrogenase 1 (IDH1) or malic enzyme 1 in the cytosol, while in the mitochondria, NADPH is generated from mitochondrial transhydrogenase, glutamate dehydrogenase, malic enzyme 3 or IDH2. There are three isoforms of IDH: cytosolic IDH1, and mitochondrial IDH2 and IDH3. Of these, IDH2 is thought to be the major supplier of NADPH to the mitochondrial antioxidant defense system. The $NADP^+$/NADPH and NAD^+/NADH couples are essential for maintaining a large array of biological processes, including cellular redox state, and energy metabolism, mitochondrial function. A growing body of evidence indicates that mitochondrial dysfunction contributes to age-related structural or functional changes of cochlear sensory hair cells and neurons, leading to hearing impairments. In this review, we describe the current understanding of the roles of NADPH and IDHs in cochlear mitochondrial antioxidant defense and aging.

Keywords

inner ear; cochlea; mitochondrial dysfunction; oxidative stress; isocitrate dehydrogenase; antioxidant defense

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1. Introduction

1.1. Mitochondria and ROS

Mitochondrial DNA (mtDNA) mutations have been hypothesized to contribute to aging and age-related disorders because of their critical role in energy metabolism (Balaban et al., 2005; Finkel and Holbrook, 2000; Kujoth et al., 2007; Someya and Prolla, 2010; Wallace, 2005). Most of the chemical energy needed to drive biochemical reactions is produced by the mitochondria. However, it is estimated that during this process ~90% of intracellular unstable reactive oxygen species (ROS) are generated as a by-product (Balaban et al., 2005; Finkel and Holbrook, 2000; Wallace, 2005). Both superoxide and the hydroxyl radical are extremely unstable ROS (Beckman and Ames, 1998; Finkel and Holbrook, 2000). Hydrogen peroxide is freely diffusible and long-lived. Of the sites along the electron transport chain, Complex I (NADH dehydrogenase), Complex II (succinate dehydrogenase), and Complex III (ubiquinone-cytochrome c reductase) are thought to generate superoxide. Under normal metabolic environments, Complex III is thought to be the major site of superoxide production.

1.2. Mitochondrial antioxidant defense system

It is thought that the mitochondrial antioxidant defense systems do not keep pace with the age-related increase in mitochondrial ROS production, and that during aging, the balance between the mitochondrial antioxidant defense and ROS production shifts progressively toward a more pro-oxidant state (Rebrin and Sohal, 2008). To protect the mitochondria from the damaging effects of ROS imbalance, the antioxidant defense systems interact to convert ROS into less toxic forms (Balaban et al., 2005; Finkel and Holbrook, 2000; Halliwell and Gutteridge, 2007; Mari et al., 2009). For example, mitochondrial superoxide dismutase 2 (SOD2) converts superoxide into hydrogen peroxide. The mitochondrial glutathione and thioredoxin antioxidant defense systems then decompose hydrogen peroxide into water (Fig. 1). Within the glutathione antioxidant system, GSR (glutathione reductase) depends on NADPH to reduce oxidized glutathione (GSSG) to reduced glutathione (GSH). In the thioredoxin system, TXNRD2 (thioredoxin reductase 2) depends on NADPH to reduce oxidized thioredoxin 2 (TXN2) to reduced TXN2. In the mitochondria, NADPH is generated from mitochondrial transhydrogenase (NNT), glutamate dehydrogenase (GLUD1), malic enzyme 3 (ME3) or isocitrate dehydrogenase 2 (IDH2) (Dang and Su, 2017; Reitman and Yan. 2010; Plaitakis et al., 2017; Arkblad et al., 2002; Francisco et al., 2022) (Fig. 2). Thus, NADPH plays an important role in both glutathione and thioredoxin antioxidant defense systems, and the $NADP^+$/NADPH couple is essential for maintaining a large array of biological processes, including cellular redox state, and energy metabolism, mitochondrial function (Xiao et al., 2017). In this review, we describe the current understanding of the roles of NADPH and IDH in cochlear mitochondrial antioxidant defense and aging in laboratory animals and humans.

2. Roles of NADPH and IDH in Antioxidant Defense

2.1. NADPH and antioxidant defense

NADPH is the phosphorylated form of NADH and is formed through de novo synthesis from NAD^+ by NAD^+ kinases or from $NADP^+$ by NADPH producing enzymes (Pollack et al., 2007; Ying, 2008; Xiao et al., 2017). NADPH provides reductive equivalents for a variety of cellular reactions including the biosynthesis of fatty acids, cholesterol, neurotransmitters and nucleotides, and in the cytochrome P450 system that functions in the metabolism of toxic compounds (Berg et al., 2002). NADPH also plays critical roles for both the cytosolic and mitochondrial glutathione and thioredoxin antioxidant defense systems (Fig. 1) (Ying, 2008). Under normal physiological conditions, the NADP pool largely remains in its reduced state in order to be readily available for its use by antioxidant defense systems (Pollack et al., 2007). In the cytosol, NADPH is produced by isocitrate dehydrogenase 1 (IDH1), malic enzyme 1 (ME1), glucose-6-phosphate dehydrogenase (G6PD), and 6-phosphogluconate dehydrogenase (6PGD). In the mitochondria, NADPH is produced by IDH2, ME3, GLUD1 and NNT (Fig. 2).

2.2. IDH and mitochondrial antioxidant defense

In the cytosol, ME1 catalyzes the reversible oxidative decarboxylation of malate to pyruvate and $NADP^+$ to NADPH for fatty acid biosynthesis (Ying, 2008). G6PD is the first and rate limiting enzyme of the pentose phosphate pathway and catalyzes the conversion of glucose-6-phosphate to 6-phosphogluconate and $NADP^+$ to NADPH. G6PD is thought to be the major supplier of NADPH for the cytosolic antioxidant defense system and is regulated by the cytosolic NADPH/$NADP^+$ ratio in response to the production of ROS (Nkhoma et al., 2009). 6PGD catalyzes the conversion of 6-phosphogluconate to ribulose 5-phosphate and $NADP^+$ to NADPH in the pentose phosphate pathway.

In the mitochondria, ME3 catalyzes the decarboxylation of malate to pyruvate and converts $NADP^+$ to NADPH. GLUD1 catalyzes the reversible metabolism of glutamate to α-KG and ammonia and $NADP^+$ to NADPH (Plaitakis et al., 2017). Mitochondrial NNT is an inner mitochondrial membrane (IMM) protein that functions as a proton pump and catalyzes the hydride transfer between NADH and $NADP^+$, using the energy from the proton translocation to produce NADPH (Arkblad et al., 2002; Francisco et al., 2022). The C57BL/6J mouse strain has a null mutation of the *Nnt* gene that influences diet-induced obesity (Nicholson et al., 2010;), but his mutation is not present in the C57BL/6NJ substrain (Kane et al., 2017). Johnson and co-workers have shown previously that C57BL/6 and C57BL/6NJ mice have identical hearing loss onset times and rates of progression, indicating that *Nnt* deficiency does not accelerates age-related hearing loss (Kane et al., 2017). Cytosolic IDH1 and mitochondrial IDH2 and IDH3 are the three isoforms of isocitrate dehydrogenase (IDH). Although all three isoenzymes catalyze the conversation of isocitrate to α-ketoglutarate (α-KG), IDH1 and IDH2 convert $NADP^+$ to NADPH while IDH3 converts NAD^+ to NADH (Fig. 3) (Dang and Su, 2017; Reitman and Yan. 2010). IDH1 is involved in lipid metabolism, glucose sensing, and cytosolic antioxidant defense (Reitman and Yan 2010).

Of these mitochondrial NADPH-producing enzymes, IDH2 is thought to be a major source of NADPH for mitochondrial GSR and TXNRD2 (Dang and Su, 2017; Reitman and Yan. 2010; Jo et al., 2001). In agreement with this view, overexpression of *Idh2* increases resistance to oxidative stress (Jo et al., 2001) in mouse NIH3T3 fibroblast cells. In rat hearts, *Idh2* deficiency results in early onset of cardiac hypertrophy and increased levels of oxidative stress (Benderdour et al., 2004). In human IMR-90 fibroblasts, *IDH2* knockdown increases levels of ROS, decreases NADPH/total NADP ratio, and GSH levels in the mitochondria (Kil et al., 2006), while overexpression of *Idh2* increases resistance to oxidative stress due to increased NADPH levels in human HEK293 kidney cells (Someya et al., 2010). Collectively, these reports show a crucial role of IDH2 as the major source of NADPH for the mitochondrial antioxidant system in both rodents and humans.

3. Mitochondrial dysfunction and hearing loss

3.1. Mitochondrial DNA mutations and hearing loss

A large number of genetic syndromes associated with hearing loss are due to defects in mitochondria (Chinnery et al., 2000; Fischel-Ghodsian, 2003; Kokotas et al., 2007; Someya and Prolla, 2010), suggesting that cochlear cells, including hair cells, spiral ganglion neurons, and stria vascularis cells, are exquisitely sensitive to energy metabolism disturbances. In support of this idea, increases of deletions, point mutations, or both in mtDNA were observed in human archival temporal bone samples from patients with age-related hearing loss (ARHL) (Bai et al., 1997). The 4977-bp mtDNA deletion was more frequently found in the archival temporal bones from patients with ARHL compared to those with normal hearing. Moreover, in archival temporal bones from patients with ARHL, specific point mutations in the mitochondrial *COX2* (mitochondrially encoded cytochrome c oxidase II) gene were more frequently found compared to those with normal hearing (Fischel-Ghodsian et al., 1997). Additionally, our group (Kim, M.J. et al., 2019) has shown that mtDNA deletions accumulate with age in the inner ears of CBA/CaJ mice, a well-established model of ARHL.

The most common genetic defect observed in individuals with mitochondrial diseases are point mutations or deletions (Krishnan, 2008) and over 100 different mtDNA deletions have been identified in individuals with mitochondrial diseases (MITOMAP, 2019). Previous literature has documented that a common symptom in individuals with inherited mtDNA mutations is hearing loss (Chinnery et al., 2000; Fischel-Ghodsian, 2003; Kokotas et al., 2007; Xing et al., 2007): Kearns-Sayre syndrome (KSS), a sporadic mitochondrial disorder caused by a 4977-bp deletion, includes progressive sensorineural hearing loss (Chinnery et al., 2000; Fischel-Ghodsian, 2003; Kokotas et al., 2007; Taylor and Turnbull, 2005). Additionally, numerous studies report mtDNA deletions in aged postmitotic tissues such as brain and in neurodegenerative diseases, including Parkinson's disease (Bender et al., 2006; Chen et al., 2011; Copeland and Longley, 2014; Kauppila et al., 2017; Kraytsberg et al., 2006; Krishnan et al., 2008; Schon et al., 2012; Schon and Przedborski, 2011; Taylor and Turnbull, 2005). Individuals with KSS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), and myoclonic epilepsy with ragged red fibers (MERRF) may have hearing loss as a clinical feature of the genetic disorder (Chinnery,

2000). Neurogenic weakness, ataxia, and retinitis pigmentosa (NARP), diabetes insipidus, diabetes mellitus, optic atrophy, Wolfram syndrome, and Pearson syndrome are all caused by a large spectrum of mtDNA mutations and hearing loss is not always but is frequently a symptom in individuals with these disorders (Kokotas et al., 2007).

The only active DNA polymerase in the mitochondria is mitochondrial DNA polymerase gamma (POLG). Previous reports demonstrated that in mice carrying a mutator allele of mitochondrial *Polg*, accumulation of mtDNA mutations led to reduced lifespan, osteoporosis, and early onset of hearing loss (Kujoth et al., 2007; Someya et al., 2008; Someya and Prolla, 2010), providing direct evidence for mtDNA mutations in the development of hearing loss. Compared to age-matched control mice, young mitochondrial mutator mice exhibited a 500-fold increase in mtDNA point mutations in brain and heart tissues (Vermulst et al., 2008) and a 238-fold increase in mtDNA point mutation frequencies in the inner ears (Kim, M.J. et al., 2019). Additionally, middle-aged mtDNA mutator mice displayed significant cochlear spiral ganglion neuron loss and early-onset AHL (Kim, M.J. et al., 2019; Kujoth et al., 2005; Niu et al., 2007; Someya et al., 2008). In humans, several mutations in *POLG* have been identified as a cause of Alper's syndrome and deafness (Mancuso et al., 2004; Kujoth et al., 2007; Someya and Prolla, 2010). Together, these studies strongly suggest that mtDNA mutations and subsequent mitochondrial dysfunction contribute to the development of hearing loss.

3.2. Mitochondrial antioxidant enzymes and hearing loss

Previous reports suggest that mitochondrial antioxidants play an important role in protection of hearing. Catalase (CAT) is one of the most energy-efficient antioxidant enzymes found in cells (Halliwell and Gutteridge, 2007). It converts H_2O_2 into water and oxygen: each catalase molecule can decompose millions of H_2O_2 molecules every second, indicating the importance of this antioxidant enzyme in protecting the cells against ROS. Catalase is primarily localized in the peroxisomes although catalase expression is also observed in the cytosol and mitochondria. Schriner and co-workers (Schriner et al., 2005) have shown that mice overexpressing human mitochondrial catalase (MCAT) had extended median and maximum lifespans, while median lifespan was slightly extended in mice overexpressing peroxisome catalase (PCAT). Overexpression of catalase in nuclei did not show a significant extension of median nor maximum life span. Importantly, in centenarians, CAT activity was found to be significantly higher in red blood cells (Klapcinska et al., 2000). Our group (Someya et al., 2009) has shown previously that young MCAT mice display normal hearing compared to age-matched WT mice; however, middle-aged MCAT mice display significantly lower ABR thresholds at low, middle and high frequencies than those of middle-aged WT mice. Furthermore, middle-age MCAT mice exhibited reduced oxidative DNA damage and loss of spiral ganglion neurons and hair cells in the cochlea. In agreement with these results, middle-age C57BL/6 mice displayed increased oxidative nuclear DNA damage (Someya et al., 2009), while middle-age CBA/J mice displayed increased oxidative protein damage in the cochlea (Jiang et al., 2007). Collectively, these studies suggest that enhancing CAT activity in cochlear mitochondria may protect cochlear hair cells and slow the development of ARHL.

Coenzyme Q_{10} is an essential component of the mitochondrial electron transport chain and acts as a mitochondrial antioxidant (Sohal and Forster, 2007). Guastini and colleagues (Guastini et al., 2011) have shown that patients with ARHL had significantly improved pure tone audiometric thresholds at 1000, 2000, 4000, and 8000 Hz when treated with coenzyme Q_{10} . In mice, supplementation with coenzyme Q_{10} delayed the onset of age-related hearing loss at high frequencies in mice (Someya et al., 2009).

Glutathione peroxidase 1 (GPX1) plays an important role in mitochondrial antioxidant defense by decomposing H_2O_2 into water (Halliwell and Gutteridge, 2007; Mari et al., 2009). Ohlemiller and colleagues found that *Gpx1*$^{-/-}$ mice exhibited significantly greater ABR threshold shift compared to WT mice after noise exposure (Ohlemiller et al., 2000). Nose-exposed *Gpx1*$^{-/-}$ mice also had greater loss of sensory hair cells compared to WT mice. In agreement with these results, C57BL/6 mice exhibited elevated cochlear ROS levels following acute noise exposure (Ohlemiller et al., 1999), while increased hair cell loss was found in the cochlea of mice lacking *Sod1* when compared to WT mice (McFadden et al., 1999). Therefore, a decline in GPX1 activity in the mitochondria may lead to increased levels of ROS, which in turn result in mitochondrial dysfunction, leading to cochlear cell loss and associated hearing loss.

GSH acts as the major small molecule antioxidant in cells and the glutathione antioxidant system is one of the major antioxidant defense systems in the mitochondria (Anderson, 1998; Halliwell and Gutteridge, 2007; Mari et al., 2009). Alpha-lipoic acid and N-acetylcysteine are thiol compounds that have been shown to reduce mitochondrial ROS production (Banaclocha, 2001; Hart, et al., 2004; Palaniappan and Dai, 2007). In rats, supplementation with alpha-lipoic acid slowed the development of ARHL (Seidman et al., 2000). Guinea pigs treated with GSH displayed increased hair cell survival and decreased noise-induced temporary threshold shifts (Ohinata et al., 2000), while treatment with N-acetyl cysteine reduced loss of cochlear outer hair cells and reduced levels of noise-induced hearing loss (NIHL) (Wu et al., 2010). In mice, supplementation with alpha-lipoic acid or N-acetylcysteine delayed the onset of ARHL at the high frequency (Someya et al., 2009; Ahn et al., 2008). In humans, treatment with N-acetyl cysteine significantly reduced noise-induced temporary threshold shift in male workers with glutathione transferase mu1 (GSTM1) and glutathione transferase theta 1 (GSST1) polymorphisms (Lin et al., 2010). Taken together, these reports support the idea that mitochondrial antioxidants may protect cochlear cells and slow the progression of ARHL.

4. Mitochondrial IDH and hearing loss

A growing body of evidence suggests that mitochondrial IDH2 plays an important role in protection against oxidative stress as well as hearing loss. A previous study has shown that homozygous mutations in *Idh2* resulted in a 41% increase in heart size, extensive damage to the heart, and cardiac dysfunction (Ku et al., 2015). This was associated with a 55% decrease in ATP production and mitochondrial dysfunction in the heart. In young mouse kidney, loss of *Idh2* resulted in decreased NADPH levels, increased oxidative damage markers, and greater kidney damage after ischemia-reperfusion compared to wild-type mice (Han et al., 2017). Calorie restriction (CR) is known to extend lifespan and delays a

variety of age-related diseases in multiple species (Weindruch and Walford, 1988; Sohal and Weindruch, 1996; Someya et al., 2007; Colman et al., 2009). In mice, CR increased mitochondrial NADPH levels and IDH2 activities in the brain, liver, and inner ear tissues (Someya et al., 2010). In contrast, *Idh2* KO mice on a high fat diet exhibited increased weight gain and decreased mitochondrial function and increased accumulation of ROS in brown adipose tissue (Lee et al., 2020). A recent study (Kim, Y.R. et al., 2019) found profound hearing loss in 10-month-old C57BL/6N; $Idh2^{-/-}$ mice with hair cell and spiral ganglion neuron degeneration. The authors also demonstrated that supplementation of MitoQ an analog of ubiquinone, protected cochlear explants from H_2O_2. In rats, brain tissue homogenates 120 hours after severe traumatic brain injury had significantly decreased gene expressions of the tricarboxylic acid cycle genes, including *Idh2, Idh3, Odh* (α-ketoglutarate dehydrogenase), *Scs* (succinyl-CoA synthetase), *Sdh* (succinate dehydrogenase), *Me2* and *Me3* (Lazzarino et al, 2019). Our group has recently shown that loss of *Idh2* resulted in decreased NADPH redox state and mitochondrial TXNRD2 activity in inner ears of young *Idh2* KO mice (White et al., 2018). Loss of *Idh2* also increased oxidative DNA damage, apoptotic cell death, and profound loss of spiral ganglion neurons and hair cells in the cochlea, and accelerated age-related hearing loss in mice on the CBA/CaJ background. Furthermore, in HEI-OC1 mouse auditory cells, knockdown of *Idh2*, resulted in a decline in cell viability and mitochondria oxygen consumption. Collectively, these results along with the previous reports suggest the importance of IDH2 function in the supply of NADPH for the mitochondrial antioxidant defense system and a crucial role of IHD2 in the protection of cochlear hair cells and neurons under normal physiological conditions as well as during aging.

5. Conclusion

The National Institute on Aging and Deafness and Other Communication Disorders (NIDCD) estimates that 50% of Americans over 75 years of age and 33% of Americans between the ages of 65 and 74 have hearing loss (Oyler, 2012). The WHO estimates that by 2050 more than 700 million persons will have some form of disabling hearing loss (WHO, 2021). It is estimated that if left unaddressed, the impact of hearing loss will cost $980 billion. Because it is projected that nearly 72.1 million people will be over 65 years of age by 2030, the number of older adults with ARHL is expected to rise dramatically and hence, AHL is expected to become a major health care problem. Currently, cochlear implants and hearing aids are the only treatments for ARHL.

ARHL is defined as the loss of hearing that gradually occur in the elderly (Gates and Mills, 2005) that is primarily caused by aging and or the accumulation of extrinsic and intrinsic damage (Liu and Yan, 2007). It is characterized by impaired temporal resolution, central auditory processing deficits, and difficulty understanding speech in noise (Yamasoba et al., 2013). ARHL is typically associated with the progressive loss of sensory hair cells, synaptic loss, spiral ganglion neurons, and or cells of the stria vascularis (Yamasoba et al., 2007). However, the precise molecular mechanisms underlying ARHL still remain unclear since ARHL is thought to be a multifactorial condition resulting from the interaction of numerous causes including aging, exposure to noise and ototoxic chemicals, genetics, epigenetic variables, comorbidities, and lifestyle (Yamasoba et al., 2013).

A growing body of evidence supports a central role for mitochondrial dysfunction in progressive hearing impairments (Biousse and Newman, 2001; Chinnery et al., 2000; Fischel-Ghodsian, 2003; Gorman and Taylor, 2011; Hudson and Chinnery, 2006; Kenney et al., 2010; Kokotas et al., 2007; Kujoth et al., 2007; McKechnie et al., 1985; Someya and Prolla, 2010). Because mitochondrial NADPH acts as a substrate for mitochondrial antioxidant enzymes, mitochondrial IDH2 is the major supplier of NADPH for the mitochondrial antioxidant defenses, and the NADP+/NADPH couple is essential for maintaining a large array of biological processes, including cellular redox state mitochondrial function (Xiao et al., 2017), a decline in mitochondrial NADPH production and IDH2 activity likely contributes to the development of age-related disease, including ARHL. In agreement with this idea, Szu and co-workers have shown that decreased levels of IDH1 and IHD2 were observed in old mouse brain (Guo et al., 2020). In summary, this report reviewed what has been learned about the roles of mitochondrial NADPH and IDH2 in mitochondrial function, mitochondrial dysfunction, and hearing loss. These findings have significantly advanced the field of cochlear mitochondrial function and dysfunction.

Data Availability

No data was used for the research described in the article.

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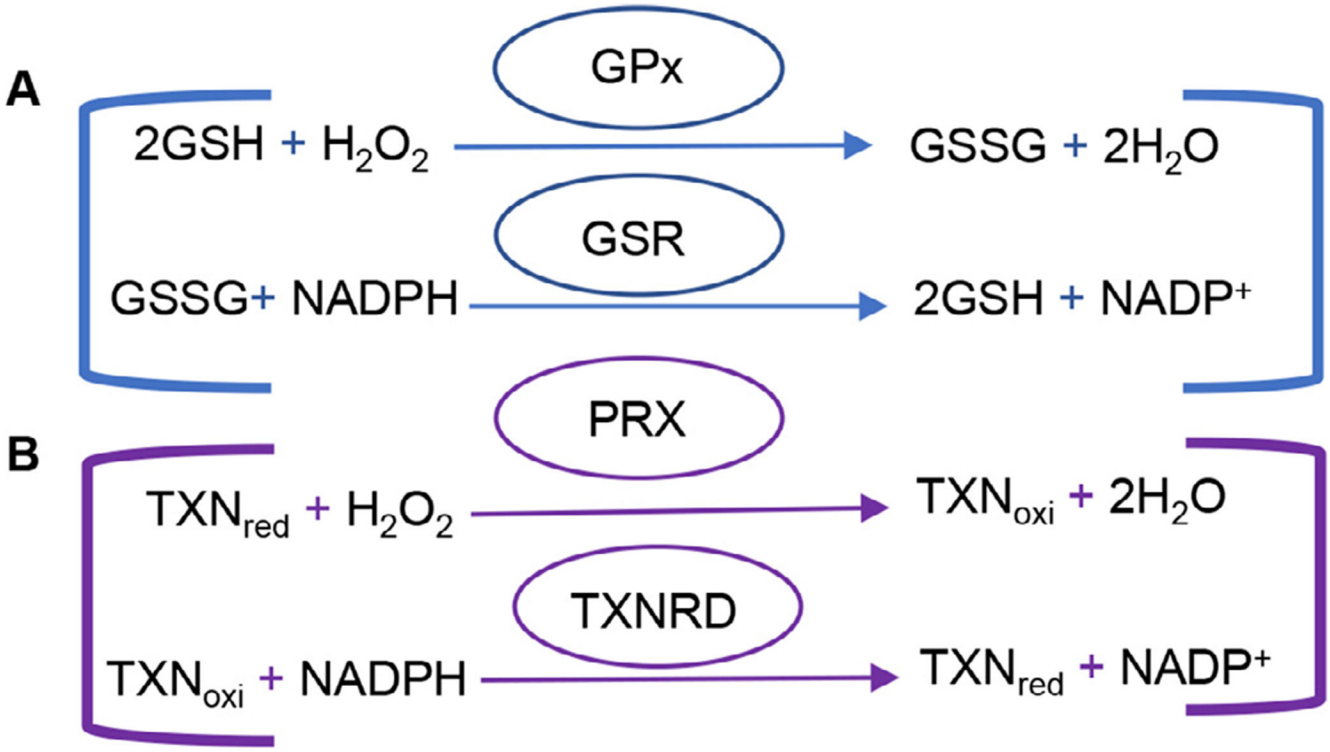

Fig 1.

Glutathione and thioredoxin antioxidant defense systems. (A) Reduced glutathione functions in quenching radicals, maintaining thiol groups, serving as a co-enzyme for glutathione peroxidase and maintaining cellular redox homeostasis. GPx reduces H_2O_2 to H_2O while oxidizing GSH to GSSG. GSR then uses NADPH as a co-factor to form -SH groups in proteins that interact with the reduction of GSSG to GSH. (B) Thioredoxin reduces H_2O_2 and protein disulfide, in protein repair and DNA synthesis, regulating transcription factors and apoptosis, and in immunomodulation. PRX reduces H_2O_2 to H_2O while oxidizing reduced thiore-doxin. NADPH-dependent TXNRD then catalyzes the reduction of oxidized thioredoxin. GPx=glutathione peroxidase, GSH = reduced glutathione, GSSG = oxidized glutathione, GSR = glutathione reductase, NADP = reduced nicotinamide adenine dinucleotide phosphate, PRX = peroxiredoxin, TXNRD = thioredoxin reductase

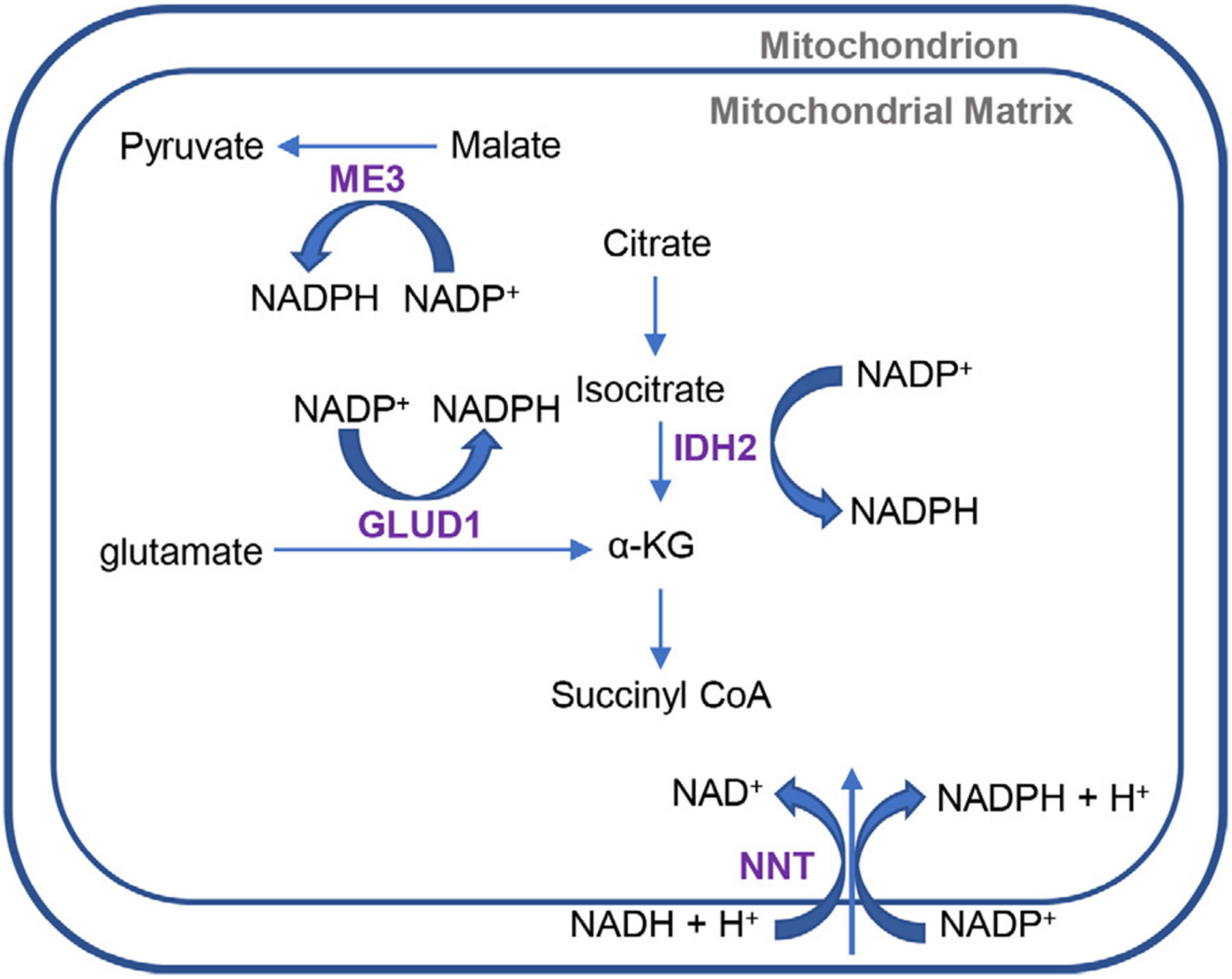

Fig 2.

Mitochondrial production of NADPH. IDH2, ME3, NNT, and GLUD1 are all mitochondrial enzymes that produce NADPH. GLUD1 catalyzes the oxidative deamination of glutamate to alpha-ketoglutarate and ammonia and convert $NADP^+$ to NADPH. NNT is an inner mitochondrial membrane protein that functions as a proton pump and couples hydride transfer between NADH and $NADP^+$ to proton translocation across the inner mitochondrial membrane. ME3 is localized to the mitochondria and catalyzes the decarboxylation of malate to pyruvate and convert $NADP^+$ to NADPH. IDH2 catalyzes the decarboxylation of isocitrate to α-KG and converts $NADP^+$ to NADPH. IDH2 = isocitrate dehydrogenase 2, ME3 = malic enzyme 3, NNT = nicotinamide nucleotide transhydrogenase, GLUD1 = glutamate dehydrogenase, α-KG = α-ketoglutarate, $NADP^+$ = oxidized nicotinamide adenine dinucleotide phosphate, NADPH = reduced nicotinamide adenine dinucleotide phosphate

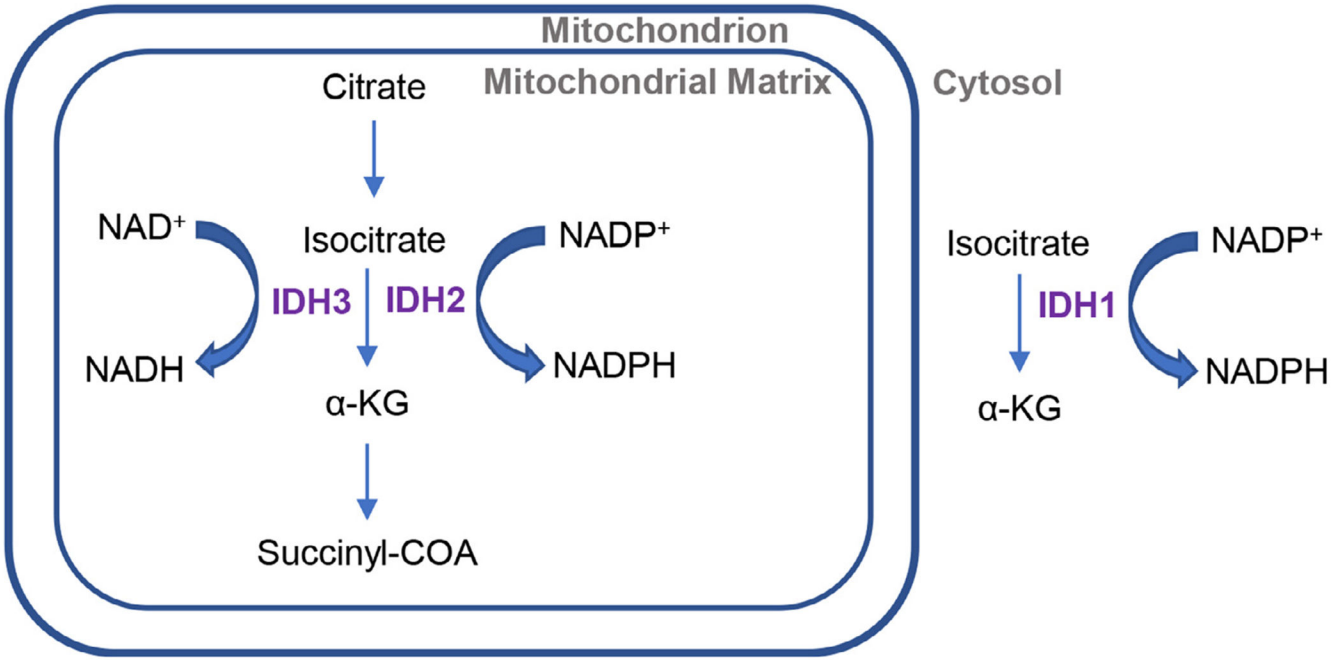

Fig 3.

IDH isoforms. The isocitrate dehydrogenases (IDH1, IDH2 and IDH3) catalyze the oxidative decarboxylation of isocitrate to α-KG. IDH3 is localized to the mitochondria and serves as an intermediate within the Tricarboxylic Acid (TCA) cycle. IDH3 converts NAD^+ to NADH, while IDH2 convert NADP+ to NADPH in the mitochondrion. IDH1 is localized to the cytosol convert $NADP^+$ to NADPH. IDH1 = cytosolic isocitrate dehydrogenase 1, IDH2 = mitochondrial isocitrate dehydrogenase 2, IDH3 = mitochondrial isocitrate dehydrogenase 3, NAD^+ = oxidized nicotinamide adenine dinucleotide, NADH = reduced nicotinamide adenine dinucleotide, $NADP^+$ = oxidized nicotinamide adenine dinucleotide phosphate, NADPH = reduced nicotinamide adenine dinucleotide phosphate