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AGXT2: a promiscuous aminotransferase

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Abstract

Alanine-glyoxylate aminotransferase 2 (AGXT2) is a multifunctional mitochondrial aminotransferase that was first identified in 1978. The physiological importance of AGXT2 was largely overlooked for three decades because AGXT2 is less active in glyoxylate metabolism than AGXT1, the enzyme that is deficient in primary hyperoxaluria type I. Recently, several novel functions of AGXT2 have been "rediscovered" in the setting of modern genomic and metabolomic studies. It is now apparent that AGXT2 has multiple substrates and products and that altered AGXT2 activity may contribute to the pathogenesis of cardiovascular, renal, neurological and hematological diseases. This article reviews the biochemical properties and physiological functions of AGXT2, its unique role at the intersection of key mitochondrial pathways, and its potential as a drug target.

Keywords

alanine; amino acid metabolism; aminotransferase; glyoxylate; methylarginine

AGXT isoforms in glyoxylate metabolism and beyond

There are two known alanine-glyoxylate aminotransferase (AGXT) (see Glossary) isoenzymes in mammals: AGXT1 and AGXT2 [1], both of which catalyze the transfer of an amino group from alanine to glyoxylate (Figure 1A). AGXT1 has been extensively characterized due to its role in the detoxification of glyoxylate and the pathogenesis of primary hyperoxaluria type I [2]. In addition to its alanine-glyoxylate aminotransferase

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activity, AGXT2 possesses several further enzymatic activities that are not shared by AGXT1. Because AGXT2 catalyzes multiple aminotransferase reactions, several alternative names for this enzyme have been proposed. AGXT2 has been referred to as D-3-aminoisobutyrate-pyruvate aminotransferase [3], (R)-3-amino-2-methylpropionate-pyruvate aminotransferase [4] and BAIB-pyruvate aminotransferase [5] due to its ability to utilize D-β-aminoisobutyric acid (BAIB) as an amino group donor (Figure 1B). It has been called dimethylarginine-pyruvate aminotransferase due to its ability to utilize methylarginines such as asymmetric dimethylarginine (ADMA) as amino group donors [6] (Figure 1C), and alanine-*γ, δ*-dioxovaleric acid aminotransferase because it can catalyze the transfer of an amino group from alanine to γ,δ-dioxovaleric acid (DOVA) [7] (Figure 1D). AGXT2 also has been shown to exhibit β-lyase activity towards certain exogenous halogenated alkenes such as S-tetrafluoroethyl-L-cysteine [8] (Figure 2).

AGXT2 was first identified in 1978 [1], and much of what is known about its biochemical properties stems from experiments performed with the purified enzyme over two decades ago. It has been only recently, however, that the multiple enzymatic activities and potential pathophysiological roles of AGXT2 have been “rediscovered” in the setting of modern genomic and metabolomics studies. It is now becoming apparent that some of the multiple substrates and products of AGXT2 may contribute to the pathogenesis of cardiovascular, renal, neurological and hematological diseases. This article reviews current knowledge about the biochemical properties and multiple physiological functions of AGXT2, its unique role at the intersection of several key mitochondrial catabolic and anabolic pathways, and its potential as a therapeutic drug target.

Discovery of AGXT2 and characterization of its alanine-glyoxylate aminotransferase activity

AGXT activity was first detected in rat liver slices in 1955 [9]. In 1978, Noguchi and colleagues identified two distinct AGXT isoenzymes (now known as AGXT1 and AGXT2) that differed in intracellular localization and biochemical activity [1]. The same group confirmed the presence of these two AGXT isoenzymes in several other mammalian species, including humans [10, 11]. AGXT1 is a pyridoxal-phosphate-dependent enzyme that functions as a homodimer with a subunit molecular weight of 40 kDa [10–12]. In mammals, the expression of AGXT1 is restricted to the liver [13, 14]. AGXT1 plays a major role in the clearance of glyoxylate, preventing it from being oxidized to oxalate, a poorly soluble metabolite. Interestingly, the intracellular localization of AGXT1 varies in different mammalian species depending on the major site of glyoxylate production. The principle dietary precursor of glyoxalate in herbivores is glycolate, which is metabolized to glyoxalate in peroxisomes; accordingly, in most herbivores AGXT1 is localized mainly in peroxisomes [15]. By contrast, the major dietary precursor of glyoxalate in carnivores is hydroxyproline, which is converted to glyoxalate in mitochondria, and in most carnivores AGXT1 is localized in mitochondria [15]. In omnivores, the enzyme is often present in both peroxisomes and mitochondria, although in humans AGXT1 is primarily localized in peroxisomes [15]. This variable subcellular localization pattern is determined by species-specific N-terminal mitochondrial and C-terminal peroxisomal targeting sequences.

AGXT2 is a pyridoxal-phosphate-dependent enzyme that functions as a tetramer with a subunit molecular weight of 50–56 kDa [3, 6, 11, 16]. Unlike AGXT1, AGXT2 is localized only in mitochondria in all examined mammalian species [11]. Human AGXT2 is encoded by a nuclear gene located on chromosome 5. After synthesis in the cytoplasm, AGXT2 is transported to mitochondria, where its 41 amino acid N-terminal mitochondrial targeting sequence is cleaved, which leads to formation of the mature form of the enzyme [17]. AGXT2 is primarily expressed in the kidney and liver [18].

The only “head-to-head” comparison of the relative aminotransferase activity of AGXT1 and AGXT2, using alanine as the amino donor and glyoxylate as the amino acceptor, was performed by Noguchi and colleagues [10]. These authors reported that the Km value for glyoxylate was 14–fold higher with AGXT2 than with AGXT1 in rats (1.0 vs. 0.07 mM) and 4-fold higher with AGXT2 than with AGXT1 in mice (0.72 vs. 0.2 mM). These findings suggest that, at least in rodents, AGXT1 is more efficient than AGXT2 in catalyzing the alanine-glyoxylate aminotransferase reaction. This observation also is consistent with the known importance of AGXT1 in glyoxylate detoxification. Santana and colleagues estimated the Km of recombinant human AGXT1 for glyoxylate as 0.36 mM [19], while the Km of human AGXT2 towards glyoxylate still needs to be determined.

The strongest evidence that AGXT1 rather than AGXT2 is responsible for the bulk of glyoxalate metabolism in humans comes from the observation that patients with inborn AGXT1 deficiency have impaired detoxification of glyoxalate in the liver, which leads to increased oxidation of glyoxylate to oxalate, deposition of insoluble calcium oxalate crystals in the kidney and urinary tract, and subsequent renal failure [20]. Consistent with the human data, Salido and colleagues demonstrated increased urine oxalate levels and predisposition to urolithiasis in AGXT1-deficient mice [21]. Impairment of glyoxalate metabolism in the setting of AGXT1 deficiency occurs despite presumably intact AGXT2 expression and activity, which suggests that the metabolism of glyoxylate by AGXT2 cannot compensate for the absence of AGXT1. The remainder of this review will therefore focus on the alternative catalytic activities of AGXT2.

Metabolism of D-β-aminoisobutyric acid (BAIB)

In 1951, Crumpler and colleagues demonstrated that human urine contains D-β-aminoisobutyric acid (BAIB) [22], a metabolite that was subsequently shown to be a product of thymine catabolism (Figure 3) [23]. In 1953, an autosomal recessive metabolic trait leading to increased BAIB levels in urine (hyper-β-aminoisobutyric aciduria) was described [24]. The prevalence of this trait was shown to be less than 10% in the European population [24] but higher than 30% in Asian populations [25]. Kakimoto and colleagues reported in 1969 that patients with hyper-β-aminoisobutyric aciduria had impaired activity of an enzyme responsible for BAIB metabolism, which they called D-β-aminoisobutyrate-pyruvate aminotransferase [5]. Twenty-four years later, Kontani and coauthors demonstrated the identity of this enzyme with AGXT2 [3]. Deamination of BAIB by AGXT2 leads to formation of methylmalonate semialdehyde (Figure 1B), which is subsequently converted to proprionyl CoA (Figure 3). Both glyoxylate and pyruvate can serve as amino acceptors in the BAIB deamination reaction [6]. Using glyoxylate as the amino acceptor at pH 7.3, the

apparent Km of rat AGXT2 towards BAIB is 18 times lower than the Km for alanine (0.12 mM vs. 2.2 mM), which suggests that BAIB might be a preferred substrate for AGXT2 under physiological conditions [3]. On the other hand, Ogawa and colleagues showed that, at pH 10.0 and with glyoxylate as the amino acceptor, the relative activity of rat AGXT2 was 60-fold higher with alanine than with BAIB [6], raising the intriguing possibility that substrate specificity of AGXT2 may be strongly pH-dependent. Recent data suggest that the pH inside mitochondria varies from 7.5 to 8.2 [26]. There are some conditions that influence the mitochondrial pH, such as glucose stimulation [27] and uptake of cations [28]. Mitochondrial pH also plays a role in the generation of reactive oxygen species [29]. However, it remains unanswered whether physiological changes in pH in the matrix of mitochondria are sufficient to influence the substrate specificity of AGXT2.

Recent genomic studies have generated a resurgence of interest in the pathophysiology of BAIB and its metabolism by AGXT2. Suhre and colleagues showed in 2011 that hyper-β-aminoisobutyric aciduria is associated with a single nucleotide polymorphism (rs37369) that causes a valine to isoleucine substitution (Val140Ile) in human AGXT2 [30]. Nicholson and colleagues independently reported that hyper-β-aminoisobutyric aciduria is associated with two polymorphisms in *AGXT2*, rs37369 and rs37370, and suggested that the *AGXT2* locus may have undergone recent positive selection in the European population [31]. In agreement with these findings, an association between the *AGXT2* rs37370 polymorphism and plasma BAIB levels was detected in a genome-wide association study performed with samples from the Framingham Heart Study [32]. In another recent study, the AGXT2 polymorphisms rs37369 and rs16899974 (Val496Leu) were found to be associated with increased BAIB levels in plasma and urine in healthy Caucasian volunteers [33]. Despite the fact that plasma levels of BAIB in healthy individuals (2.3 ± 1.9 μM) [34] are considerably lower than the estimated Km for BAIB of the rat AGXT2 enzyme, the clear association between AGXT2 polymorphisms and BAIB levels strongly suggests that AGXT2 plays a physiological role in regulating BAIB levels in humans *in vivo*.

The physiological and pathophysiological roles of BAIB and the potential consequences of its accumulation are still poorly understood. In a cross-sectional analysis of Framingham Heart Study data, elevated plasma levels of BAIB were associated with decreased levels of serum triglycerides [32]. Moreover, in a zebrafish model, knockdown of *agxt2* gene expression resulted in alterations in tissue levels of triglycerides and cholesterol esters [32]. The role of BAIB in producing this phenotype is uncertain, however, since levels of BAIB were unexpectedly decreased, rather than increased, in the *agxt2* knockdown morphants [32]. Interestingly, Spitsyn and Afanas'eva reported an increased frequency of hyper-β-aminoisobutyric aciduria in patients with coronary atherosclerosis in two selected populations [35]. Clearly, more work is needed to determine whether BAIB directly affects lipid homeostasis or serves as a biometabolomic marker of AGXT2 deficiency and increased cardiovascular risk. Interestingly, a recent metabolomic study identified BAIB as small molecule "myokine" that is secreted from myocytes and induces a brown adipose-like phenotype in both adipocytes and human pluripotent stem cells and improves glucose homeostasis in mice [36]. The authors suggest that BAIB may contribute to exercise-induced protection from metabolic diseases [36].

Metabolism of methylarginines

The endogenous guanidine-methylated analogues of L-arginine, N^G–monomethyl–L–arginine (NMMA), asymmetric N^G, N^G–dimethyl–L–arginine (ADMA) and symmetric N^G, N'^G–dimethyl–L–arginine (SDMA), have received considerable attention as novel cardiovascular risk factors [37–39]. Both NMMA and ADMA have been postulated to produce adverse cardiovascular effects via inhibition of nitric oxide synthase (NOS). ADMA is considered to be a more physiologically relevant NOS inhibitor than NMMA due to its higher concentration in plasma. Elevated blood levels of ADMA are associated with increased cardiovascular morbidity and mortality, and ADMA has been proposed to be an independent cardiovascular risk factor [39–41]. Elevation of ADMA levels in animal models or human subjects leads to endothelial dysfunction, decreased renal blood flow, increased renovascular resistance, renal sodium retention, and elevated systemic blood pressure [42].

Elevation of SDMA also has been found to be associated with some cardiovascular and renal pathologies [42]. Unlike NMMA and ADMA, however, SDMA does not directly inhibit NOS, and the exact mechanisms of the potential adverse biological effects of SDMA are not entirely understood. SDMA has been proposed to compete with L-arginine for the common transporter and thus indirectly decrease intracellular L-arginine concentration and NO production [43]. A recent report has suggested that SDMA can modify high-density lipoprotein (HDL) particles to become activators of toll-like receptor-2, triggering an innate immune pathway leading to vascular oxidative stress and endothelial dysfunction [44]. SDMA has also been proposed to stimulate production of reactive oxygen species in monocytes by augmenting calcium entry inside the cells via store-operated Ca2+-channels [45]. Further work is needed to confirm this finding and clarify the relative importance of SDMA vs. NMMA and ADMA in cardiovascular pathophysiology.

The primary pathway of methylarginine catabolism is thought to occur via a hydrolysis reaction catalyzed by dimethylarginine dimethylaminohydrolase (DDAH), which can hydrolyze both ADMA and NMMA, but not SDMA. It has been recognized since at least 1990, however, that methylarginines also can undergo transamination reactions catalyzed by AGXT2 [6]. AGXT2 has broad substrate specificity for methylarginines; it can utilize not only ADMA or NMMA, but also SDMA, as a substrate [6, 46, 47]. The product of ADMA deamination catalyzed by AGXT2 is α-keto-δ-(NG, NG-dimethylguanidino)valeric acid (DMGV) (Figures 1C and 4). The AGXT2-mediated pathway of ADMA metabolism received relatively little attention until our group cloned the human *AGXT2* gene in 2010 [17]. We found that overexpression of human AGXT2 in mice led to decreases in plasma and tissue levels of ADMA [17]. Recent experiments with stable isotope-labeled ADMA have demonstrated endogenous AGXT2 activity towards ADMA, detected by conversion of ADMA to DMGV in the liver and kidney of mice [48]. In agreement with these findings, Caplin and colleagues showed that AGXT2-deficient mice have increased plasma concentrations of both ADMA and SDMA, suggesting that endogenous AGXT2 contributes to the regulation of plasma levels of methylarginines [46]. Elevation of plasma ADMA and SDMA also occurs after systemic infusion of BAIB in mice, presumably due to competitive inhibition of AGXT2's activity toward methylarginines [47]. Finally, ADMA and SDMA levels were found to inversely correlate with AGXT2 expression in allografts of renal

transplant recipients [46], which suggests that AGXT2 also regulates methylarginine metabolism in humans. Caplin and coworkers also provided experimental evidence that AGXT2 isolated from murine kidney mitochondria can metabolize ADMA at physiological concentrations [46]. Another recent study found the AGXT2 polymorphism rs37369 to be associated with increased SDMA levels in the plasma and urine of healthy human volunteers [33].

Thus, the current experimental evidence strongly suggests that endogenous AGXT2 regulates systemic levels of ADMA and other methylarginines *in vivo*. These results, however, stand in puzzling contrast with the observation that the estimated Km of purified rat AGXT2 towards ADMA is in the range of 10 mM [6], which is about four orders of magnitude higher than plasma ADMA concentrations in rodents or humans [49–51]. One potential explanation for this paradox is that intracellular ADMA concentrations might be higher than plasma levels [52], although it is likely that the intracellular concentrations are still considerably lower than the estimated Km. Another potential explanation might be that the kinetic properties of ADMA transamination by AGXT2 *in situ* within the mitochondrial milieu might differ from those of the purified enzyme, for example due to the presence of as yet unidentified cofactors.

The kidney appears to be the major site of metabolism of ADMA by AXGT2. In a landmark experiment, Ogawa et al. injected radiolabeled ADMA into rats, and found that most of the radioactivity recovered in the urine within 12 hours was in the form of either ADMA, DMGV, or the DMGV-metabolite α-keto-δ-(NG, NG-dimethylguanidyno)butyric acid (DMGB) [53]. This observation suggests that there may be two mechanisms for renal clearance of ADMA: a direct mechanism wherein ADMA is excreted into the urine unchanged, and an indirect mechanism in which ADMA is first metabolized by AGXT2 and then excreted into the urine as DMGV or DMGB. Interestingly, kidney extracts had 8-fold higher levels of radiolabeled ADMA than DMGV and DMGB, whereas the ratio of radioactive ADMA to DMGV and DMGB in urine was approximately 1:1 [53], which suggests that clearance of ADMA through the AGXT2-mediated mechanism is much more efficient than the direct excretion of ADMA. A possible role of AGXT2 in renal ADMA metabolism and clearance is further supported by the observation that AGXT2 is specifically localized to the epithelium of Henle’s loop [18].

The discovery that endogenous AGXT2 can regulate systemic levels of methylarginines suggests a mechanism by which AGXT2 may protect from cardiovascular diseases. This hypothesis is consistent with the finding that upregulation of AGXT2 can protect from ADMA-mediated impairment of NO production in cultured endothelial cells [17], and with the observed phenotype of endothelial dysfunction and hypertension in AGXT2 knockout mice [46]. It is also consistent with the results of a study demonstrating an association between the *AGXT2* gene locus with plasma levels of SDMA and heart rate variability in young adults [54].

Metabolism of γ, δ-dioxovalerate (DOVA)

The formation of δ-aminolevulinic acid (ALA) is the first committed step in the porphyrin biosynthetic pathway leading to the synthesis of heme. ALA is synthesized from glycine and succinyl Co-A by the mitochondrial enzyme ALA synthase [55, 56] (Figure 5). An alternative pathway for the synthesis of ALA was proposed in the early 1980s to be catalyzed by a transamination reaction between alanine and γ, δ-dioxovalerate (DOVA), yielding pyruvate and δ-aminolevulinic acid (Figures 1D and 5). This alternative reaction was first described by the group of Varticovski, who isolated a pyridoxal-phosphate-dependent DOVA transaminase from bovine liver mitochondria [7]. Using radiolabelled DOVA, Morton and colleagues showed that DOVA transaminase-mediated formation of ALA can occur in liver cells [57] and whole animals [58]. Okuno and colleagues demonstrated the biosynthesis of ALA by DOVA transamination in the liver of rats, rabbits and humans, which further supported the potential *in vivo* importance of this alternative pathway for ALA synthesis [59]. DOVA transaminase was reported to be identical to AGXT2 by Noguchi and colleagues [60], although this conclusion was questioned by another group [61]. Thus, there is still considerable uncertainty about the role of AGXT2 in catalyzing DOVA transamination. Perhaps the time is now right to re-explore this neglected metabolic activity of AGXT2 and determine the potential impact of AGXT2 on porphyrin and heme biosynthesis.

Other aminotransferase activities of AGXT2

AGXT2 clearly has broad aminotransferase substrate specificity, allowing it to utilize many different amino donors and acceptors in different combinations. In addition to the substrates described above, AGXT2 also can utilize amino donors such as β-alanine (a product of uracil catabolism), L-ornithine (a metabolite of the urea cycle), α-aminobutyric acid (a precursor of ophthalmic acid) and several other endogenous amino compounds. Furthermore, *ex vivo* experiments have suggested that AGXT2 may exhibit aminotransferase activity towards exogenous substrates such as α-fluoro-β-alanine (a metabolite of 5-fluorouracil) and β-chloro-L-alanine [62]. Pyruvate and glyoxylate are the most common AGXT2 amino acceptors in these reactions, but several other ketone compounds, including DOVA and oxaloacetate, also can serve as amino acceptors. The potential pathophysiological significance of these reactions remains to be defined.

β-lyase activity

Halogenated alkenes (e.g. trichloroethylene, tetrachloroethylene and tetrafluoroethylene) are common in both industrial and commercial use. They have nephrotoxic effects in rodents and are associated with kidney and liver tumors in experimental animals and humans [63]. One mechanism of the toxicity of halogenated alkenes is the formation of corresponding S-conjugates, which are subsequently metabolized by cysteine S-conjugate β-lyases into pyruvate, ammonium, and reactive sulfur-containing fragments (Figure 2) [64]. Some of the resulting sulfur containing fragments are reactive molecular species that can thioacylate macromolecules, especially at ε-amino groups of protein lysine residues [65]. Several S-conjugate β-lyases have been identified in mitochondria. Their presence makes

mitochondrial proteins common targets of halogenated alkenes [66]. Recently Cooper and colleagues demonstrated that AGXT2 isolated from rat kidney mitochondria possess β-lyase activity towards two halogenated alkene S-conjugates (S-(1,1,2,2-tetrafluoroethyl)-L-cysteine and S-(benzothiazolyl)-L-cysteine) [8]. This observation suggests that AGXT2 may promote the toxicity of halogenated alkenes and that AGXT2 polymorphisms associated with decreased β-lyase activity may be protective. Further studies are necessary to further define the exogenous and endogenous substrates for the β-lyase activity of AGXT2.

Concluding remarks

It has been recognized for three decades that AGXT2 is a promiscuous aminotransferase capable of utilizing a wide array of endogenous and exogenous substrates. In recent years, there has been a resurgence of interest in the multiple roles of AGXT2 in amino group metabolism due to findings from molecular, genomic, and metabolomic studies. The picture that is emerging is one in which AGXT2 plays a complex role in mitochondrial function that may extend well beyond amino acid metabolism.

Several experimental approaches are now available to investigate the physiological and pathophysiological roles of AGXT2. *AGXT2* gene polymorphisms have been found in relatively high allele frequency in many populations, providing the ability to assess pathophysiological and metabolomics phenotypes via genome-wide association studies [30–32, 54, 67, 68]. More work is needed to better define the functional consequences of these polymorphisms on the enzymatic activities of AGXT2 and their associated clinical phenotypes. A mouse model of AGXT2 deficiency has been developed [46]. AGXT2-deficient mice develop vascular dysfunction and hypertension, which has been hypothesized to be caused by elevated levels of endogenous methylargininines such as ADMA [46]. It is possible, however, that the accumulation of other AGXT2 substrates such as BAIB also contributes to the vascular phenotype of these mice. It remains to be determined whether the observed association between hyper-β-aminoisobutyric aciduria and coronary heart disease prevalence [35] is related to elevated concentrations of BAIB, other AGXT2 substrates such as methylarginines, or another mechanism. There is also a need to better define the potential pathophysiological effects of AGXT2's activity toward its other substrates, including SDMA, DOVA, β-alanine, L-ornithine, and α-aminobutyric acid. Though AGXT2 does not appear to play a substantive role in the detoxification of glyoxylate, it remains possible that its alanine-glyoxylate aminotransferase activity may serve another function within mitochondria.

Because it is a multifunctional enzyme, AGXT2 may be an attractive potential therapeutic drug target because it offers the potential for the development of compounds that selectively inhibit a subset of its activities. Several small molecule inhibitors of AGXT2 have already been described [3, 4, 7, 10, 69, 70], some of which are endogenous molecules and others are analogs of drugs or toxins. Further studies are needed to better characterize the known inhibitors and develop new lead compounds that selectively inhibit a subset of the specific metabolic pathways regulated by AGXT2 without inhibiting its other enzymatic activities. Selective AGXT2 inhibitors would also be very useful research tools. Likewise, the development of approaches to increase or upregulate AGXT2 activity would not only

facilitate research but also could potentially lead to new therapies for the prevention and treatment of cardiovascular and metabolic diseases.

Glossary

ADMA (asymmetric dimethylarginine)	N^G, N^G dimethyl L arginine, a product of catabolism of proteins methylated on arginine residues; an endogenous inhibitor of nitric oxide synthesis;a biomarker of cardiovascular, neural and renal diseases
ALA (δ-aminolevulinic acid)	a precursor in the porphyrin biosynthetic pathway leading to the synthesis of heme
Alanine-glyoxylate aminotransferase 1 (AGXT1)	an aminotransferase that transfers an amino group from alanine to glyoxylate; deficiency of AGXT1 causes primary hyperoxaluria type I
Alanine-glyoxylate aminotransferase 2 (AGXT2)	a multifunctional aminotransferase that is localized in mitochondria
Aminotransferase (or transaminase)	an enzyme that catalyzes the transfer of an amino group between an amino acid and an α-keto acid
BAIB (D-β-aminoisobutyric acid)	a product of thymine catabolism and one of multiple substrates for AGXT2l
Dimethylarginine dimethylaminohydrolase (DDAH)	An enzyme that hydrolyzes methylarginines such as ADMA and NMMA
DMGB (α-keto-δ-(N^G,N^G-dimethylguanidyno)butyric acid)	a metabolite of DMGV
DMGV (α-keto-δ-(N^G,N^G-dimethylguanidino) valeric acid)	a product of ADMA metabolism by AGXT2
DOVA (γ, δ-dioxovaleric acid)	an alternative substrate for the synthesis of ALA via DOVA transamination
High density lipoprotein (HDL)	an atheroprotective lipoprotein
Hyper-β-aminoisobutyric aciduria	an autosomal recessive metabolic trait that causes increased BAIB levels in urine
NMMA (N^G monomethyl L arginine)	an endogenous guanidine-methylated analogue of L-arginine that can inhibit nitric oxide synthase
Nitric oxide synthase (NOS)	an enzyme that catalyzes the production of nitric oxide from L-arginine; can be inhibited by ADMA and NMMA
Primary hyperoxaluria type I	an autosomal recessive disorder caused by deficiency of AGXT1. Absence of AGXT1 leads

	to excessive conversion of glyoxylate to oxalate, a poorly soluble metabolite that accumulates in the kidney and other organs
SDMA (symmetric dimethylarginine)	N^G, N'^G dimethyl L arginine, an endogenous guanidine-methylated analogue of L-arginine; a cardiovascular risk factor but, unlike ADMA and NMMA, does not inhibit nitric oxide synthase

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Highlights

- AGXT2 is a mitochondrial aminotransferase that has diverse functions in cellular physiology
- Several substrates and products of AGXT2 are biomarkers of cardiovascular and metabolic diseases
- AGXT2 may be an attractive therapeutic drug target for cardiovascular disease

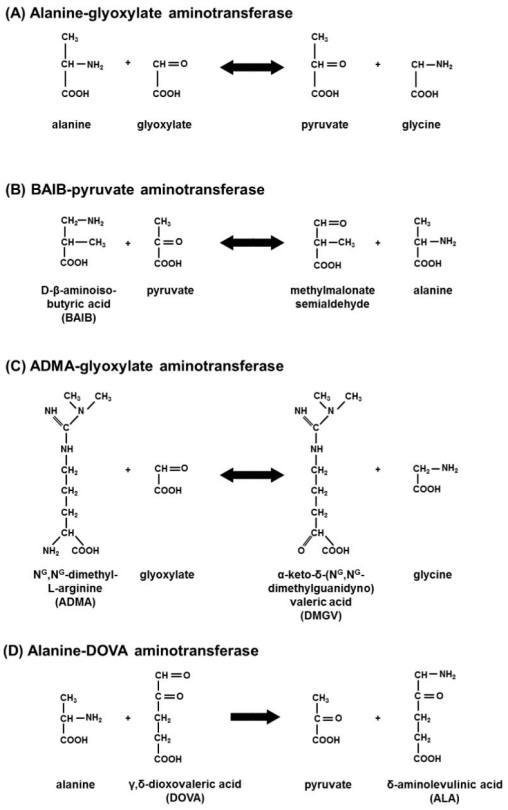

Figure 1.

Some of the aminotransferase activities of AGXT2. In addition to its alanine-glyoxylate aminotransferase activity (A), AGXT2 catalyzes several additional aminotransferase reactions, including BAIB-pyruvate aminotransferase activity (B), ADMA-glyoxylate aminotransferase activity (C), and alanine-DOVA aminotransferase (DOVA transaminase) activity.

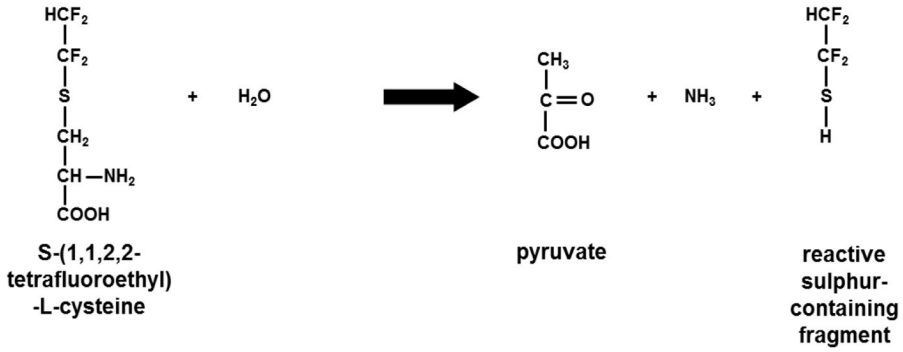

Figure 2. β-lyase activity of AGXT2

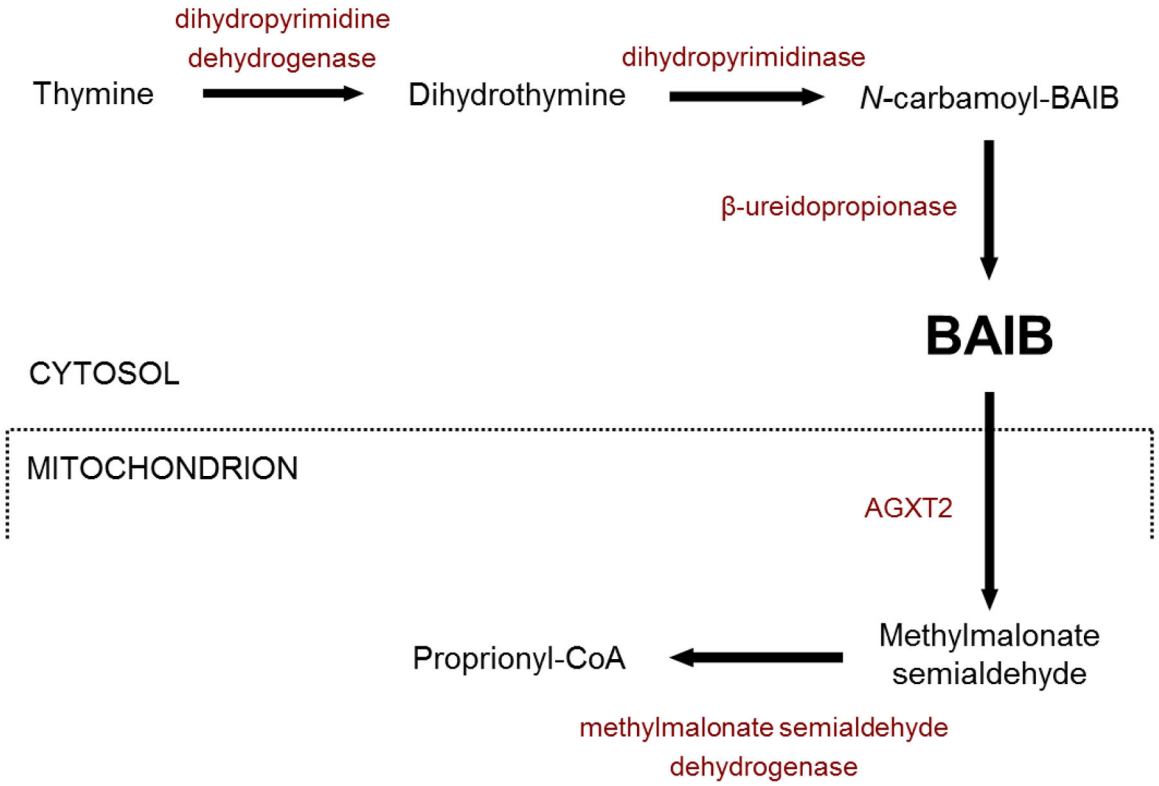

Figure 3.

Role of AGXT2 in thymine metabolism. D-β-aminoisobutyric acid (BAIB) is a product of thymine catabolism, which is subsequently converted to methylmalonate semialdehyde by AGXT2 and then to proprionyl-CoA by methylmalonate semialdehyde dehydrogenase.

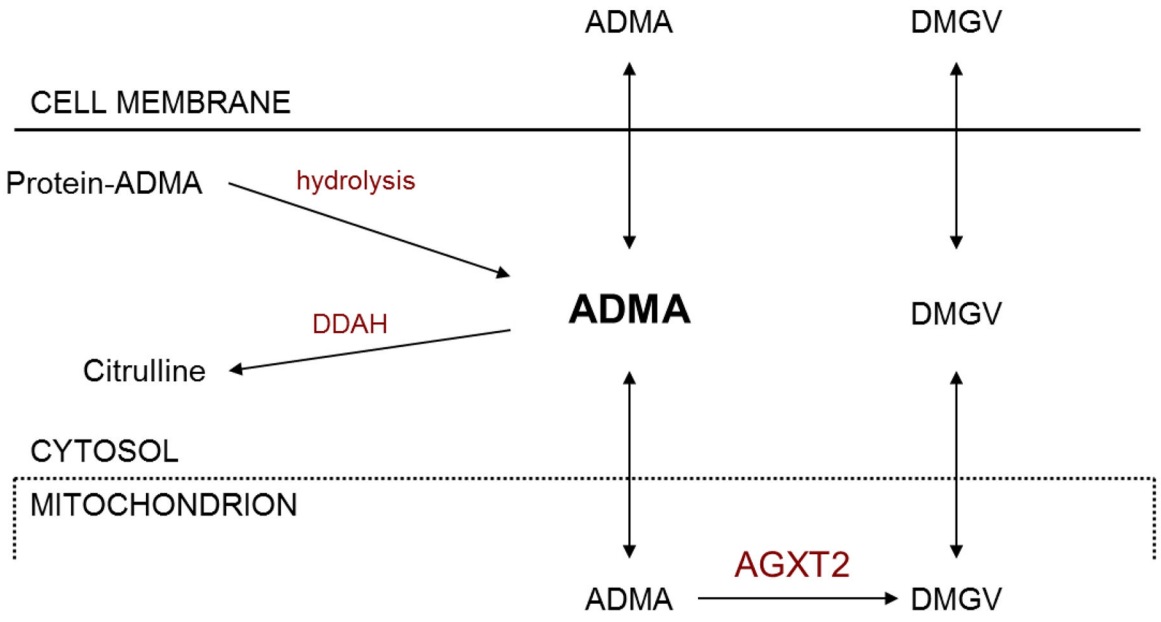

Figure 4. Role of AGXT2 in ADMA metabolism

Asymmetric N^G, N^G–dimethyl–L–arginine (ADMA), derived from hydrolysis of proteins containing methylarginine, can be converted either to citrulline by dimethylarginine dimethylaminohydrolase (DDAH) in the cytoplasm or to α-keto-δ-(NG, NG-dimethylguanidino) valeric acid (DMGV) by AGXT2 in the mitochondrion.

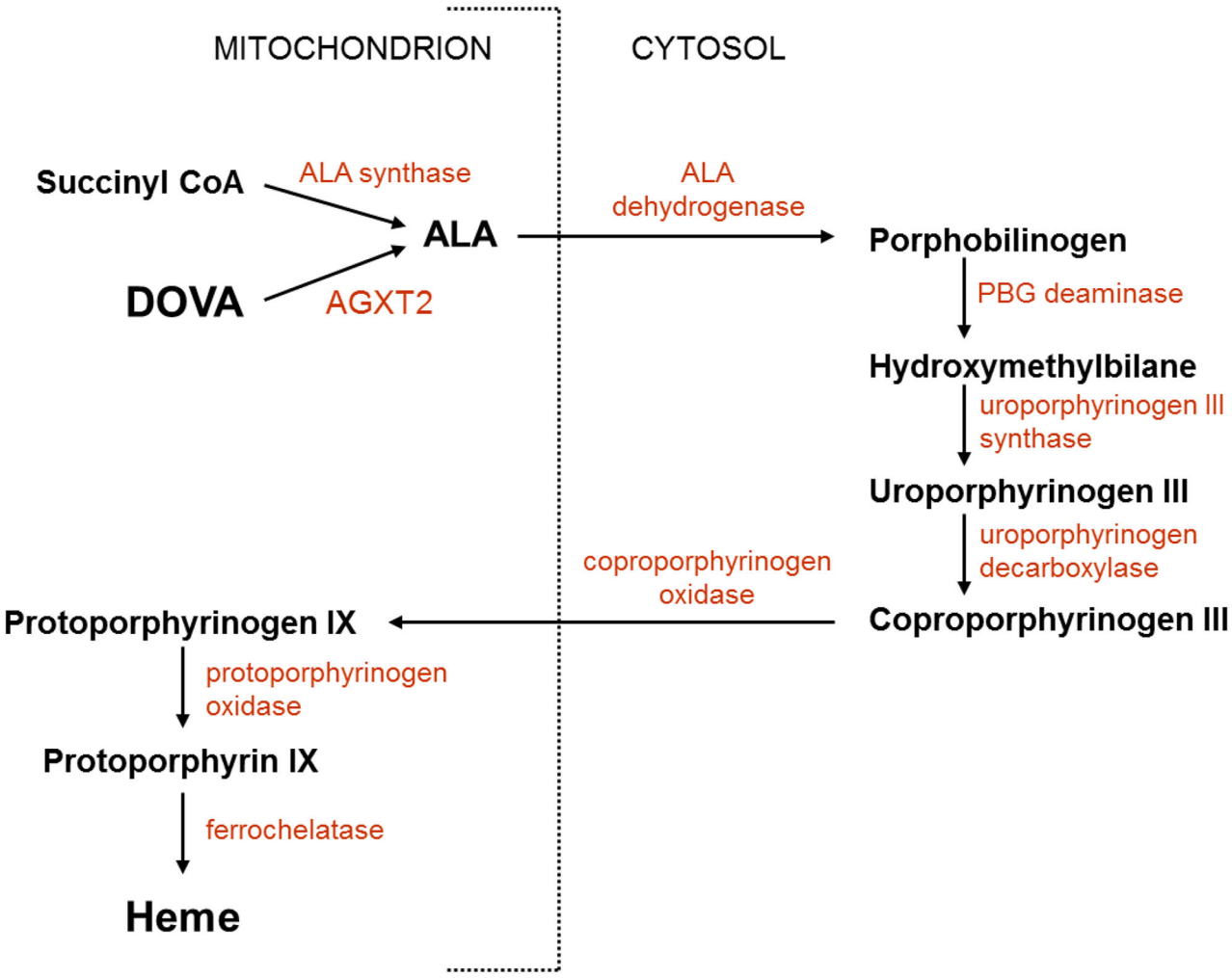

Figure 5.

Potential role of AGXT2 in heme synthesis. The heme precursor molecule δ-aminolevulinic acid (ALA) is produced from succinyl-CoA in the mitochondrion by the enzyme ALA synthase. An alternative source of ALA in the mitochondrion has been proposed to be mediated by the DOVA transaminase activity of AGXT2.