



Role of AMP deaminase in diabetic cardiomyopathy

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Abstract

Diabetes mellitus is one of the major causes of ischemic and nonischemic heart failure. While hypertension and coronary artery disease are frequent comorbidities in patients with diabetes, cardiac contractile dysfunction and remodeling occur in diabetic patients even without comorbidities, which is referred to as diabetic cardiomyopathy. Investigations in recent decades have demonstrated that the production of reactive oxygen species (ROS), impaired handling of intracellular Ca^{2+} , and alterations in energy metabolism are involved in the development of diabetic cardiomyopathy. AMP deaminase (AMPD) directly regulates adenine nucleotide metabolism and energy transfer by adenylate kinase and indirectly modulates xanthine oxidoreductase-mediated pathways and AMP-activated protein kinase-mediated signaling. Upregulation of AMPD in diabetic hearts was first reported more than 30 years ago, and subsequent studies showed similar upregulation in the liver and skeletal muscle. Evidence for the roles of AMPD in diabetes-induced fatty liver, sarcopenia, and heart failure has been accumulating. A series of our recent studies showed that AMPD localizes in the mitochondria-associated endoplasmic reticulum membrane as well as the sarcoplasmic reticulum and cytosol and participates in the regulation of mitochondrial Ca^{2+} and suggested that upregulated AMPD contributes to contractile dysfunction in diabetic cardiomyopathy via increased generation of ROS, adenine nucleotide depletion, and impaired mitochondrial respiration. The detrimental effects of AMPD were manifested at times of increased cardiac workload by pressure loading. In this review, we briefly summarize the expression and functions of AMPD in the heart and discuss the roles of AMPD in diabetic cardiomyopathy, mainly focusing on contractile dysfunction caused by this disorder.

Keywords Adenine nucleotides · Diabetic cardiomyopathy · Energy metabolism · Mitochondria-associated membrane · Reactive oxygen species · Xanthine oxidoreductase

Introduction

AMP deaminase (AMPD) plays important roles in energy metabolism, nucleotide pool size regulation, and amino acid metabolism [1–3] (Fig. 1). Deamination of AMP by AMPD,

which lowers AMP level, keeps the adenylate kinase (AK) reaction proceeding in the direction of ATP generation from ADP (i.e., $2\text{ADP} \rightleftharpoons \text{ATP} + \text{AMP}$), while it reduces the adenine nucleotide level. The AK reaction also maintains low ADP level, preserving a high ATP/ADP ratio and thus free energy of ATP hydrolysis ($\Delta G_{\text{ATP}} = \Delta G_{\text{ATP}}^0 + RT \ln([\text{ADP}][\text{Pi}]/[\text{ATP}])$). AMPD competes with cytosolic 5'-nucleotidase for AMP, modulating the level of adenosine, which serves as a substrate of nucleotide synthesis and a ligand of P2 receptors. AMP deamination is an irreversible step in the purine nucleoside cycle (PNC), which supplies citric acid cycle intermediates and regenerates AMP from IMP. These functions of AMPD have been analyzed mostly in skeletal muscle in which AMPD activity is much higher than that in other tissues [4, 5]. AMPD shares its substrate, AMP, with AMP-activated protein kinase (AMPK), and there is an apparent reciprocal relationship between AMPD and AMPK activities [6–14]. AMPD in skeletal muscle has received

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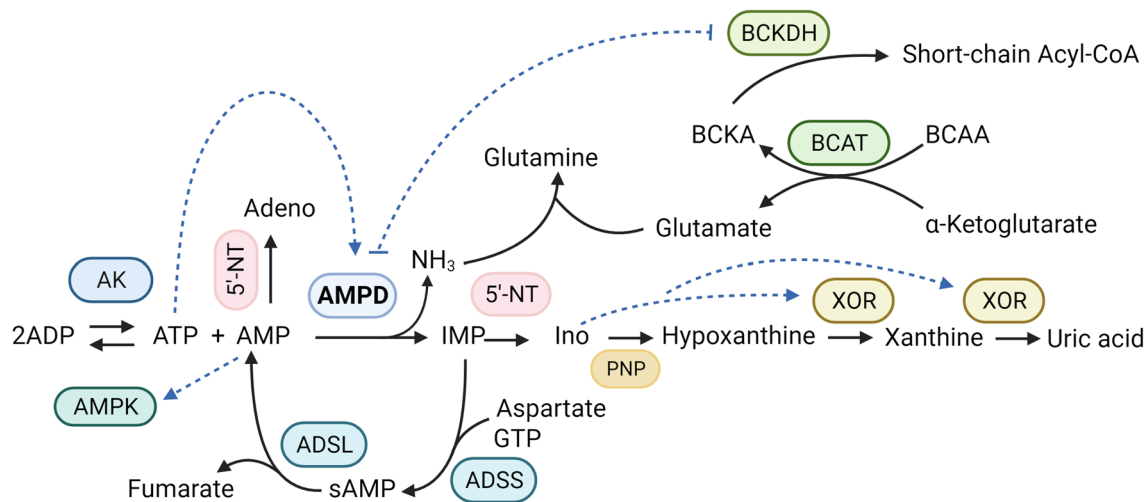


Fig. 1 Overview of the metabolic pathways directly and indirectly regulated by AMP deaminase. Solid lines and dotted lines indicate metabolic pathways and regulatory pathways, respectively. A recent study suggests that there is mutual negative regulation between BCKDH and AMPD3 in cardiomyocytes [38]. AK adenylylate kinase,

AMPD AMP deaminase, AMPK AMP-activated protein kinase, ADSL adenylosuccinate lyase, ADSS adenylosuccinate synthase, BCKDH branched-chain α -keto acid dehydrogenase, 5'-NT 5'-nucleotidase, XOR xanthine oxidoreductase, Adeno adenosine, Ino inosine, sAMP adenylosuccinate. The figure was created with Biorender.com

attention for its roles in exercise endurance [3], myopathy [15], and muscle atrophy [16] and for its manipulation to improve insulin sensitivity via AMPK activation [17–19]. In contrast, the pathophysiological role of AMPD in the heart is poorly understood.

Diabetes mellitus is characterized by dysfunctional insulin-mediated signaling and an altered profile of energy substrates to cells, which modulates mechanistic target of rapamycin complex (mTORC) signaling, leading to adaptation and/or maladaptation in energy production. As the shortage of ATP is sensed in cells through the elevation of AMP levels [20], it is conceivable that AMPD-mediated pathways are modified in diabetes. In fact, significantly increased levels of AMPD activity in the hearts of diabetic animal models were

first reported more than 30 years ago [21], and the diabetes-induced change in AMPD activity in the heart and other organs was confirmed by animal models of type 1 and type 2 diabetes [9, 22–24] but not in a model of short-term diabetes [25] (Table 1). Unfortunately, the pathophysiological roles of AMPD upregulation in diabetes and insulin resistance have not been explored until recently [7, 9, 13, 24, 26, 27], while significant progress has been made in our knowledge regarding the mechanisms of diabetes-induced heart failure, fatty liver, and sarcopenia [28–35]. However, the results of a series of studies from this laboratory [23, 36–39] support the notion that AMPD upregulation plays an important role in diabetic cardiomyopathy as it does in diabetes-induced sarcopenia and fatty liver [7, 9, 13, 24, 26]. In this article,

Table 1 Alterations in AMPD in animal models of diabetes and insulin resistance

Animal model	Organ	Change in AMPD	References
BB/Wistar rats	Heart	Increased activity	Jenkins et al. [21]
STZ-induced diabetic rats	Heart	Increased activity	Jenkins et al. [21]
STZ-induced diabetic rats	Heart, Kidney, and Liver	No significant change in activity	Pawelczyk et al. [25]
STZ-induced diabetic rats	Heart	Increased activity	Podgorska et al. [22]
High-fat diet-fed mice	Heart	Increased activity	Rybakowska et al. [82]
OLETF rats	Heart	Increased activity	Kouzu et al. [23]
OLETF rats	Heart	Increased activity and protein expression	Tatekoshi et al. [36]
Sucrose-fed rats	Liver	Increased activity	Lanaspa et al. [7]
STZ-induced diabetic mice	Liver	Increased activity without a change in protein level	Cicerchi et al. [9]
Fructose-fed rats	Liver	Increased activity	Castro et al. [24]
CKD mice with insulin resistance	Skeletal muscle	Increased activity and protein expression	Andres-Hernando et al. [27]

STZ streptozotocin, OLETF Otsuka Long-Evans Tokushima Fatty, CKD chronic kidney disease

we briefly review the functions and regulations of AMPD and its contribution to diabetic cardiomyopathy. We mainly focused on the roles of AMPD in diastolic dysfunction at an early stage of diabetic cardiomyopathy since mechanisms in the early stage possibly trigger those that lead to subsequent systolic dysfunction and adverse cardiac remodeling.

Expression and function of AMPD in the heart

AMPD expression and activity regulation in the heart

There are three main isoforms of AMPD in human and rat tissues: isoform A (rat) or M (human) in skeletal muscle, isoform B (rat) or L (human) in the liver, and isoform C (rat) or E (human) in erythrocytes and the heart. While AMPD A/M isoform expression is primarily restricted to skeletal muscle, the B/L isoform and C/E isoform are expressed in many tissues. AMPD1, AMPD2, and AMPD3 genes encode AMPD A/M, AMPD B/L, and AMPD C/E, respectively, [40–42]. The AMPD isoforms have native tetrameric structures [41, 43, 44] and their assembly is thought to be driven by the relative abundance of polypeptides with no apparent preference for similar subunits [44]. Human AMPDs contain conserved C-terminal domains, where catalytic residues reside, and divergent N-terminal domains. The N-terminal domains of AMPD modulate binding capacities to actomyosin and cytoplasmic membranes, regulating intracellular distribution [45, 46] and catalytic activity [44, 47].

Western blot analysis for AMPD proteins shows full-length forms and N-terminal truncated forms [44, 48–51]. The N-terminal regions of AMPD proteins are very sensitive to proteolysis, and truncation of the N-terminal region is observed during purification and storage of the peptide at 4 °C. The apparent Km values of N-terminal truncated forms of human AMPD1 and AMPD3 in absence of ATP were lower than those of the full-length forms [44], and truncated AMPD3 exhibited altered sensitivity to phosphoinositide compared with its full-length form [47]. Recently, Ronca and Raggi [52] discussed the physiological importance of AMPD1 truncation by a calpain-like protease and effects of the truncation on AMPD-troponin T interaction in skeletal muscle cells in a review article. However, whether such mechanisms apply to cardiomyocytes in vivo remains to be investigated.

In rodent hearts, hypoxia-inducible factor 1 (HIF-1) [53] and miR301b [36] were shown to regulate the transcription and translation of the AMPD3 gene, respectively. Foxo1/3/4 and HDAC3 in skeletal muscle [54, 55] and cyclin-dependent kinase-7 (CDK7)-mediated assembly of a super-enhancer in renal tubular cells [56] were also reported to be involved

in regulation of AMPD3 expression, although their functions in the heart have not been confirmed. In addition, mutual regulation between AMPD3 and branched-chain α -keto acid dehydrogenase (BCKDH) in cardiomyocytes was revealed in a recent study [38] (Fig. 1); in rat neonatal cardiomyocytes, siRNA knockdown of BCKDH-E1 α increased AMPD3 expression levels and activity, and conversely, knockdown of AMPD3 expression increased BCKDH activity without increasing BCKDH protein. Although the mechanism of mutual regulation remains to be further investigated, there is a possibility that suppression of BCKDH activity by upregulated AMPD contributes to impaired metabolism of branched-chain amino acids (BCAAs) in diabetic hearts as discussed in the section entitled *AMPD and BCAA metabolism*.

Studies using rats, rabbits, and piglets showed that cardiac AMPD is activated by ATP, ADP, adenosine, Ca²⁺, and NADH, while it is inhibited by GTP, inorganic phosphates, phosphoinositide and palmitoyl-CoA [57–60]. The regulation of cardiac AMPD by ATP (Fig. 1) is distinct from that of skeletal muscle AMPD, which is inhibited by ATP [52]. Protein kinase C (PKC) phosphorylates AMPD, which reduces the Km value of AMPD without affecting Vmax, and this posttranslational modification does not affect the allosteric response of AMPD to ATP and ADP [59, 61, 62]. In contrast, protein kinase A (PKA) does not appear to regulate AMPD activity in either the heart or skeletal muscle [62, 63]. Interaction with Ca²⁺-calmodulin has been shown to activate AMPD3 in erythrocytes [64], but the role of this interaction in the heart remains unknown.

Intracellular localization of AMPD in the heart

While AMPD has been thought to be present mostly in the cytosol, its localization in the sarcoplasmic reticulum (SR) as a member of the “cardiac SR-glycogenolytic complex” was proposed by Entman et al. [65–69] almost five decades ago. In addition, it was found that AMPD interacts with sarcomeric proteins, such as myosin, leading to a change in the level of soluble AMPD depending on the status of muscle contraction [42]. We recently postulated that AMPD may localize in mitochondria in addition to the SR and cytosol because AMPD is functionally linked with AK (Fig. 1), which plays a crucial role in high-energy phosphotransfer from ATP generation sites to ATP utilization sites as does the creatine kinase (CK) system. Although the majority of AKs are localized in the cytosol, their different isoforms have been found to be localized in mitochondria, nuclei, and plasma membranes [20]. In our study, AMPD3 signals were detected in cytosolic fractions, fractions of mitochondria-associated endoplasmic reticulum membrane (MAM), and fractions of endoplasmic reticulum (ER)/outer mitochondrial membrane and were barely in mitochondrial fractions

derived from rat hearts [39]. AMPD3 proteins in the ER/SR and MAM appear to be involved in the regulation of BCAA metabolism and mitochondria-ER/SR contact formation, respectively, as discussed below (sections entitled *AMPD and BCAA metabolism* and *AMPD and increased mitochondria-ER/SR contacts in diabetic cardiomyopathy*). There were marked differences between the intracellular compartments in the proportions of signals corresponding to 90-kDa full-length AMPD3 and a signal of an approximately 78-kDa protein. In our previous studies [36–39], we interpreted the 78-kDa protein as a truncated form of AMPD3. However, the interpretation recently turned out to be wrong because our recent Western blot analysis using the same anti-AMPD3 antibody (Proteintech 23997-1-AP) and AMPD3-knockout mouse samples confirmed that the signal of the 90-kDa protein is specific to AMPD3 but that of the 78-kDa protein is not (Kouzu et al. 2023 unpublished observation). Nevertheless, Western blotting showed that full-length AMPD3 localizes not only in the cytosol but also in the SR and MAM in the rat heart. Immunogold labeling with electron microscopy revealed that AMPD1 was localized in myofibrils and the SR and nuclei in skeletal muscle [70, 71], but a similar analysis for cardiomyocytes has not been reported.

Role of the PNC in the heart

AMPD is one of the three enzymes that constitute the PNC (Fig. 1). AMPD catalyzes the conversion of AMP to IMP, which reacts with aspartate and GTP, generating adenylosuccinate by adenylosuccinate synthase (ADSS). The formed adenylosuccinate generates fumarate and AMP by adenylosuccinate lyase, completing the cycle. Since fumarate is not readily transported via the mitochondrial inner membrane, it is converted to malate before being taken up into the mitochondrial matrix. In skeletal muscle, elevation of workload stress increases the rate of the PNC, which is indicated by increased levels of citric acid cycle intermediates, decreased levels of aspartate, and increased ammonia release [72, 73].

In contrast to skeletal muscle, increased workload in isolated perfused rat hearts did not induce metabolite changes that reflect an increase in PNC-mediated metabolism [74]. In rat hearts in situ, an increase in ventricular afterload tended to elevate adenylosuccinate levels, but aspartate levels were also elevated, arguing against the possibility of an increased rate of the PNC [23]. The difference between skeletal muscle and cardiac muscle in response to increased workload might be attributable to lower ADSS levels and AMPD activity in cardiac muscle than in skeletal muscle [4, 5, 75, 76]. However, the PNC in the heart might play a protective role against ischemic injury. A recent study by Wu et al. [53] showed that treatment with hadacidin, an inhibitor of ADSS, significantly augmented both ATP and ADP depletion and AMP accumulation during ischemia in mouse

hearts, suggesting that the PNC contributes to the preservation of energy charge in the ischemic myocardium.

AMPD and BCAA metabolism

Recent studies [3, 13, 38] have revealed that the PNC is not the only connection between AMPD and amino acid metabolism. Miller et al. [13] comprehensively examined the impact of AMPD3 overexpression on the metabolome and transcriptome of C2C12 cells. They found that BCAAs, glycolysis, and ceramide metabolic pathways were among the most highly enriched by overexpressed AMPD3 as were purine metabolism pathways. Overexpression of AMPD3 increased the intracellular levels of BCAAs, branched-chain α -keto acids (BCKAs), pyruvate, and α -ketoglutarate and increased the release of BCKAs and alanine into the culture medium. An increase in glutamine release into the culture media was not detectable possibly due to pre-existing glutamine in the culture medium. BCKDH activity was not directly determined in the study by Miller et al. [13], but the increase in intracellular BCKA levels was much larger than the increase in BCAA levels (i.e., 2–3-fold vs. 1.1–1.2-fold) in AMPD3-overexpressing C2C12 cells, and the levels of BCKAs in the culture media were also higher. Moreover, ATP was reduced with no change in ADP/ATP and AMP/ATP ratios. These findings might reflect reduced metabolic flux from BCKAs to short-chain acyl-CoA species by BCKDH in AMPD3-overexpressing cells.

While the role of BCAAs as energy substrates in the heart is small, their roles in the maintenance of normal function and morphology of the heart were indicated by the findings that inactivation of BCKDH worsened heart failure [77, 78] and that cardiomyocyte-selective deletion of BCKDH-E1 α induced deterioration of cardiac function and adverse ventricular remodeling [79]. Cardiac BCKDH was found to localize not only in mitochondria but also in the ER where the E1 α and E2 subunits of BCKDH physically interact with AMPD3 [38] (Fig. 2). As mentioned in the section titled *AMPD expression and regulation in the heart*, there is mutual negative regulation between BCKDH and AMPD3 functions (Fig. 1), and BCKDH activity was shown to be increased when AMPD3 expression was suppressed in cardiomyocytes in vitro. The physiological function of AMPD-mediated regulation of BCKDH is unclear. However, there is a possibility that, under the condition of sufficient ATP supply, AMPD activity, which is positively regulated by ATP, suppresses BCAA catabolism via BCKDH inhibition to spare BCAAs for protein synthesis. Interestingly, the suppression of BCKDH activity modifies the expression of enzymes relevant to fatty acid oxidation as well as AMPD expression in cardiomyocytes in vitro [38]. The relationship between BCKDH and AMPD3 may play a significant role in metabolic changes in diabetic hearts. In

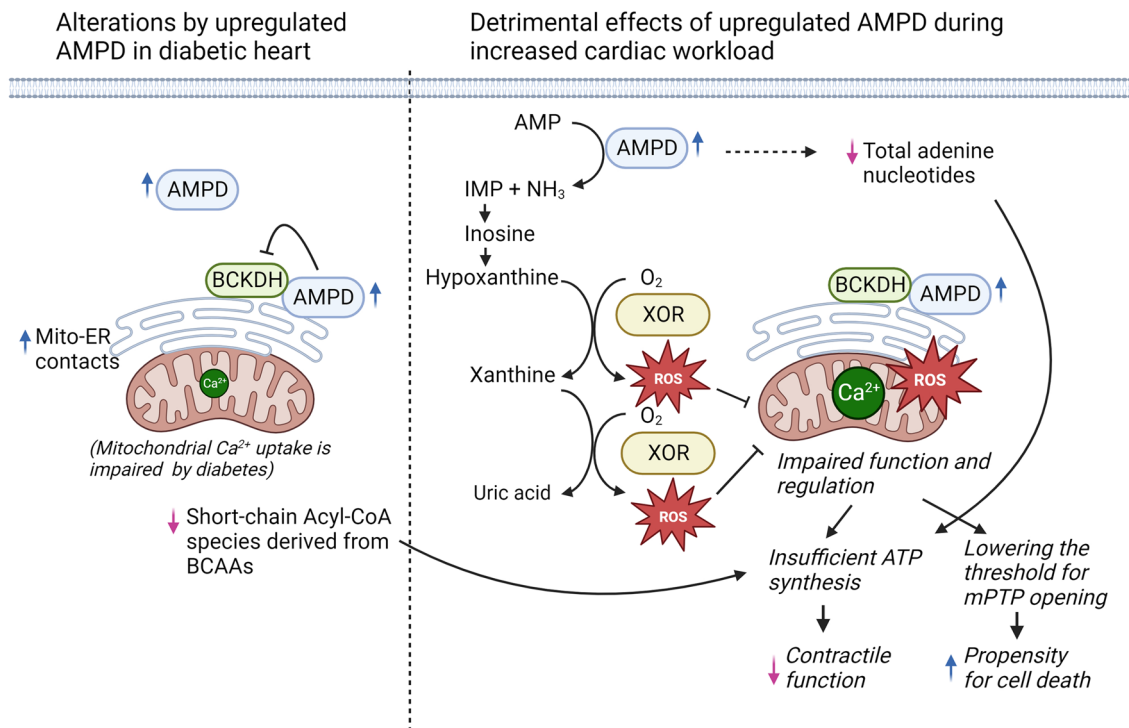


Fig. 2 Current working hypothesis for the pathophysiological roles of upregulated AMPD in diabetic hearts. Upregulation of AMPD in diabetic hearts is possibly an adaptive response that supports AK-mediated high-energy phosphotransfer, compensates for impaired Ca²⁺ uptake in mitochondria by remodeling mitochondria-ER/SR contacts, and prevents excessive BCAA use for ATP synthesis. In the normal heart, the role of BCAAs as energy substrates in the heart is small, but their role might be larger during increased ATP demand

in diabetic hearts, in which glucose oxidation is suppressed. When an increased cardiac workload raises the rate of ATP hydrolysis to a higher level, adverse actions of AMPD upregulation are exerted by enhancement of IMP generation and Ca²⁺ influx into mitochondria. AMPD AMP deaminase, IMP inosine monophosphate, Mito-ER contacts mitochondria-endoplasmic reticulum contacts, mPTP mitochondrial permeability transition pore, ROS reactive oxygen species, XOR xanthine oxidoreductase. The figure was created with Biorender.com

fact, reduced BCKDH expression in hearts of Otsuka Long-Evans Tokushima Fatty (OLETF) rats (a model of type 2 diabetes) was associated with upregulated AMPD3 activity and the accumulation of BCAAs and lipid droplets in cardiomyocytes [38, 80].

In contrast to the observations in C2C12 cells and OLETF rat hearts [13, 38], AMPD3 upregulation induced by HDAC3 deletion in skeletal muscle was associated with upregulation of enzymes participating in BCAA metabolism and increased oxidation of amino acids and fatty acids [3]. The reason for the different impacts of upregulated AMPD3 on amino acid and fatty acid oxidation between the studies [3, 13, 38] is unclear, but the PNC may function differently depending on the cell type and HDAC3 deletion may affect other targets besides AMPD3.

AMPK-mediated signaling pathways and AMPD

AMP functions as a primary sensor of the balance of energy supply/consumption in cells. Dzeja and Terzic [20] proposed an “adenylate kinase metabolic monitoring system” in which the change in the intracellular ADP level is

amplified by AK to a larger change in AMP, leading to the activation of AMP-mediated processes that normalize the ADP/ATP balance. When ATP generation does not meet its demand, increased AMP activates AMPK by three mechanisms: promotion of Thr172 phosphorylation, inhibition of Thr172 dephosphorylation, and allosteric activation [81]. Activated AMPK promotes the catabolism of energy substrates (glucose uptake and glycolysis, fatty acid uptake and oxidation), except for lipolysis, and inhibits anabolic processes (gluconeogenesis, synthesis of glycogen, fatty acids, triglycerides, phospholipids, sterols, and proteins), enabling ATP synthesis to match ATP demand. In addition to AMP, LKB1- and CaMKK β -mediated phosphorylation at Thr172 and Akt-mediated phosphorylation at Ser485 modulate AMPK activity.

A reciprocal relationship between AMPD and AMPK activity has been shown in some but not all studies in which AMPD was overexpressed or genetically deleted. In hepatic and renal cell lines in vitro, activation of AMPD suppressed AMPK activity [6–14]. Upregulation of AMPD2 in the liver in diabetic mice was associated with decreased AMPK phosphorylation and increased gluconeogenesis via the

upregulated expression of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase, while the suppression of AMPK was mediated by increased uric acid levels [9]. AMPD3 overexpression for 48 h reduced AMPK-Thr172 phosphorylation and the mitochondrial oxygen consumption rate in skeletal muscle [13]. In a study by Davis et al. [12], ATP and ADP levels were reduced by AMPD3 overexpression for 48 h in C2C12 cells, but the AMP/ATP ratio and Thr172-phospho-AMPK level were unchanged. Both the contraction of skeletal muscle during tetanic contraction and its relaxation were impaired in AMPD1-deficient mice when the levels of AMP, AMP/ATP ratio, and phosphorylation of Thr172-AMPK were elevated [14]. Pharmacological inhibition of AMPD or knockout of AMPD1 increased tissue AMP and p-Thr172-AMPK levels during the stimulated contraction of skeletal muscles, although such impacts of AMPD suppression were not detected under resting conditions [10]. Taken together, these findings suggest that AMPD can participate in AMPK regulation by modulating the AMP/ATP ratio, although an increase in AMPD activity alone is not always sufficient to reduce the AMP/ATP ratio to a low enough level to inhibit AMPK. In other words, AMPD activity appears to elevate the threshold for activation of AMPK in response to mechanisms that increase ATP consumption and modify the AMP/ATP ratio.

Unfortunately, few data on AMPD–AMPK relationships in the heart have been reported. In studies by Rybakowska et al. [82, 83], changes in AMPD activity induced by a high-fat diet were not correlated with AMPK activity. In our study, there was no difference in Thr172-phospho-AMPK levels between control and OLETF rat hearts under baseline conditions despite two-fold higher AMPD levels in OLETF rat hearts. However, activation of AMPK/ULK1/mTORC signaling induced by ischemic heart failure was observed in control rats but not in OLETF rats [84]. The lack of AMPK activation in OLETF rats was associated with impaired autophagy in the myocardium and increased mortality due to heart failure. AMPK functions are downregulated in diabetic hearts [29] and whether the upregulated AMPD activity is involved in the suppression of the stress-induced activation of AMPK in diabetic hearts remains to be further investigated.

AMPD and SR/ER functions

ATP for Ca^{2+} uptake in the SR is supplied by glycolysis and two phosphotransfer systems, the CK system and the AK system. Several lines of evidence support the important contribution of glycolysis in the proximity of the SR to SR function. Mark Entman's group [65–69] found that the SR is physically associated with glycogen and a series of enzymes involved in glycogenolysis (i.e., phosphorylase b kinase, phosphorylase b/a, debranching enzyme, adenylate

cyclase, PKA), and they proposed that the “SR-glycogenolytic complex” regulates glycogenolysis in the SR. In a study by Xu et al. [85], the entire chain of glycolytic enzymes was associated with SR vesicles from both cardiac and skeletal muscles. The inhibition of glycolysis by iodoacetate, an inhibitor of GAPDH, suppressed Ca^{2+} uptake by SR vesicles, and the uptake was restored by phosphoenolpyruvate (PEP). The addition of a soluble hexokinase ATP trap eliminated Ca^{2+} uptake by ADP and PEP but had little effect on Ca^{2+} uptake induced by endogenous ATP, suggesting that glycolysis-derived ATP was preferentially used by the SR. Glycogen has been shown to be a preferential source for glucose oxidation in the working heart [86, 87]. Unfortunately, the role of AMPD in glycogenolysis or glycolysis in the heart has not been specifically investigated. However, it is possible that AMPD in the SR-glycogenolytic complex finely tunes phosphorylase b activity. AMP is a much more potent physiological activator of phosphorylase b than IMP [88] and thus IMP generation from AMP by AMPD could decrease phosphorylase b activation, potentially suppressing glycogenolysis in the SR.

AK isoforms localize in the cytosol, mitochondria, and/or nucleus, and AK1 is the major cytosolic AK isoform in humans [89]. The specific role of the AK system in SR function has not been characterized. However, circumstantial evidence suggests that AMPD in the SR/ER supports the adaptive increase in AK-mediated energy transfer to the SR in the heart under stress. The contribution of AK to high-energy phosphotransfer reactions is much smaller than that of CK (~10% vs. 89%) in healthy hearts [90]. However, in a dog model of pacing-induced heart failure, phosphotransfer via AK increased by 134%, contributing 21% to the total ATP turnover, while the contribution of CK was reduced from 89 to 40% [90]. In two murine models of heart failure (i.e., heart failure induced by transaortic constriction and that induced by myocardial infarction), CK activity was reduced, while AK activity remained unchanged [91]. As AMPD is important for the AK reaction to proceed in the direction of ATP formation, the role of AMPD would become larger when myocardial stress increases AK-mediated phosphotransfer reaction in ATP-consuming sites, including the SR.

Role of AMPD in diabetic cardiomyopathy

Diastolic dysfunction in diabetic cardiomyopathy

Diabetic cardiomyopathy progresses from an early stage with diastolic dysfunction alone to later stages with diastolic/systolic dysfunction, hypertrophy and loss of cardiomyocytes, reduced capillary density, and interstitial fibrosis [28, 29, 92]. The natural history of diabetic cardiomyopathy is explained by the sequential activation

of multiple cardiac pathological mechanisms (increased generation of reactive oxygen species [ROS], impaired Ca^{2+} handling, altered Ca^{2+} sensitivity of myofilaments, mitochondrial dysfunction, remodeling of cytoskeletons and extracellular matrix, and impaired microcirculation) and extracardiac mechanisms (activation of neurohumoral systems, diabetic autonomic neuropathy, increased stiffness of peripheral arteries, and dysregulation of circulating blood volume due to nephropathy) [28–32]. Of these, increased generation of ROS, impaired Ca^{2+} handling in cardiomyocytes, and changes in myofilaments and their regulatory proteins [28, 31, 93–95] have been proposed to cause impaired diastolic function with preserved systolic function, a hallmark of the early stage of diabetic cardiomyopathy.

To gain insight into the role of AMPD in the mechanisms of diastolic dysfunction, we selected a model of type 2 diabetes, OLETF rat, for a series of studies [23, 36–39]. Although OLETF rats have not been frequently used for studies on diabetes in the literature, this model has several useful features. OLETF rats have a deficit in the cholecystokinin-1 (CCK1) receptor gene, causing the absence of the CCK1 receptor in the brain and gastrointestinal tract [96]. This genetic abnormality causes hyperphagia, obesity, and type 2 diabetes [97–99], and the time course of diabetes and its cardiovascular complications have been well characterized [99–105]. OLETF rats at ages of 29–35 weeks have features suitable for analysis of diastolic dysfunction due to impaired cardiomyocyte relaxation. At these ages, OLETF rats have hyperinsulinemic diabetes, and ventricular pressure–volume relationship analyses show diastolic dysfunction with preserved systolic function; *tau* (the left ventricular diastolic pressure time constant) and left ventricular end-diastolic pressure (LVEDP) were only modestly increased at baseline [23, 37, 106]. Ventricular pressure loading induces a larger upward shift in the end-diastolic pressure–volume relationship (EDPVR) in OLETF rats than in their nondiabetic control (Long-Evans Tokushima rats, LETO rats), although indices of systolic function were unchanged by the increased loading. Importantly, there was no difference in pressure–volume relationships between OLETF and LETO rats when cardiac arrest was executed with a cardioplegic solution *in vitro* [23], indicating that diastolic dysfunction shown *in vivo* is due to the impaired relaxation of the myocardium but not due to the increased stiffness of the myocardium. In this model of diabetes, both AMPD activity and protein levels were increased by approximately two-fold, while PKC- α activation and inorganic phosphate level reduction were not detected, suggesting that the change in the AMPD activity is mainly due to its increased protein level [23, 36–39].

Increased AMPD activity in diabetic hearts

Although an increase in cardiac AMPD activity has been observed in different models of diabetes (Table 1), its mechanism is poorly understood. In the OLETF heart, in which the AMPD3 protein level was elevated without a change in its mRNA level, increased translation of the AMPD3 gene by repression of miR301b was suggested to be involved [36]. In addition, the downregulation of BCKDH in diabetes might contribute to the upregulation of AMPD. The expression of most enzymes needed for BCAA metabolism, including BCKDH, is suppressed in diabetic hearts, adipose tissues, and the liver [107–109]. The reduction of BCKDH-E1 α expression by siRNA increased AMPD3 mRNA and protein level by more than five-fold in rat cardiomyocytes *in vitro*, although the underlying mechanism remains unclear [38].

AMPD and dysregulation of intracellular Ca^{2+} in diabetic cardiomyopathy

Impaired Ca^{2+} handling in cardiomyocytes, which causes delay in cytosolic Ca^{2+} transient, has been observed in different models of early diabetes [28, 29, 31, 93, 106]. Its proposed mechanisms include downregulated protein expression and/or reduced activity of SERCA2a. In the alterations in SERCA2a protein and activity levels, a reduction in SERCA2a mRNA expression, enhanced SERCA2a degradation by elevated ER stress, and modification of SERCA2a by advanced glycation end products (AGEs), O-GlcNAcylation, and ROS have been suggested to be involved. Upregulated AMPD is unlikely to be involved in the change in the protein level of SERCA2a as overexpression of AMPD3 did not alter levels of SERCA2a, GRP78, or GRP94 in HEK293 cells [39]. However, AMPD activity potentially affects SR Ca^{2+} uptake during increased cardiac workload by reducing intracellular ATP levels via three mechanisms: depletion of adenine nucleotides, enhanced suppression of BCKDH activity, and inhibition of ATP synthesis in mitochondria [23, 37–39].

Upregulated AMPD promoted metabolic flux from AMP to the IMP/inosine/hypoxanthine/xanthine pathway and potentially reduced ATP generation by suppressing glycolysis and BCAA oxidation and inhibiting mitochondrial respiration [23, 37–39]. Upregulation of AMPD3 expression was found to reduce BCKDH activity, limiting the supply of BCAA-derived short-chain acyl-CoA species to the tricarboxylic cycle in cardiomyocytes [38], and to suppress mitochondrial state-3 respiration by inhibiting complex I in HEK293 cells [39]. Increased generation of ROS during pressure loading in OLETF rats was closely associated with mitochondrial dysfunction (as discussed in the following section) [37]. Collectively, these findings support the notion

that upregulated AMPD expression is causally related to both increased AMP depletion and insufficient ATP synthesis in OLETF rat hearts [23, 37, 38]. In contrast to diastolic function, systolic function was preserved during pressure loading despite the reduced tissue ATP level, which can be explained by the higher energy demand of SERCA2a (52 kJ/mol) than that of actomyosin ATPase (45–50 kJ/mol) [110].

Ca²⁺ regulation in mitochondria is also impaired by diabetes. Mitochondrial Ca²⁺ uptake is reduced in cardiomyocytes subjected to high concentrations of glucose and in animal models of type 1 and type 2 diabetes [111–116]. Several mechanisms have been proposed for the reduction in mitochondrial Ca²⁺ levels by diabetes: lowered peak of cytosolic Ca²⁺ transient [117–119], which is induced by reduced Ca²⁺ stores in the SR and/or impaired SR functions, reduced Ca²⁺ transfer from the ER/SR to mitochondria [115], impaired function of the mitochondrial Ca²⁺ uniporter (MCU) complex (MCUC) [113, 114, 120], and increased Ca²⁺ efflux via mitochondrial Na²⁺–Ca²⁺ exchange [116]. Mitochondrial matrix Ca²⁺ activates the pyruvate dehydrogenase complex (PDC) by an allosteric mechanism and by its dephosphorylation via activation of PDC phosphatases. In addition, Ca²⁺ stimulates the regeneration of NADPH, which provides electrons for the production of reduced glutathione from oxidized glutathione. Thus, a reduction in mitochondrial matrix Ca²⁺ uptake in diabetic hearts is associated with suppressed glucose oxidation, reciprocally upregulated fatty acid oxidation, and increased generation of ROS in mitochondria [27, 112].

AMPD and increased mitochondria-ER/SR contacts in diabetic cardiomyopathy

Recently, we found that AMPD3 protein expression is increased not only in the cytosol but also in MAMs in OLETF rat hearts compared with that in nondiabetic control, LETO rat hearts [39]. Assessment of the extent of mitochondria-ER/SR contacts by electron microscopy showed that areas of mitochondria-ER/SR contact are significantly increased in OLETF rat cardiomyocytes. The causal relationship between the upregulated AMPD expression and the increase in mitochondria-ER/SR contacts is supported by the observations that the overexpression of AMPD3 increased mitochondria-ER/SR contacts in HEK293 cells and that this structural change was inhibited by knockdown of GRP78, a protein that tethers mitochondria to the ER/SR [39]. However, it is not clear whether AMPD3 proteins localized in the MAM primarily mediate the remodeling of mitochondria-ER/SR contacts.

As expected from the change in mitochondria-ER/SR contacts, the increase in mitochondrial Ca²⁺ levels in response to pressure loading was larger in OLETF rat hearts than in LETO rat hearts, while there was no difference in the

levels at baseline [39]. These findings support the notion that AMPD modulates Ca²⁺ regulation in mitochondria by remodeling mitochondria-ER/SR contacts. It is possible to speculate that increased mitochondria-SR/ER contacts by AMPD upregulation is an adaptive mechanism to compensate for impaired Ca²⁺ uptake in mitochondria in diabetes, although it increases the risk of mitochondrial Ca²⁺ overload during increased cardiac workload and during pathological elevation of cytosolic Ca²⁺ levels.

AMPD and generation of ROS in diabetic cardiomyopathy

The role of ROS in the pathogenesis of diabetic cardiomyopathy has been extensively studied, and it has been proposed that excessive generation of ROS occurs before the development of diastolic dysfunction [31, 121]. In cardiomyocytes, there are multiple ROS-generating mechanisms and antioxidant defense mechanisms, both of which are reported to be modified in diabetes mellitus or hyperglycemia. ROS generated by NADPH oxidase (NOX) [122–125], mitochondria [126–130], uncoupled nitric oxide synthase [131–133], and/or xanthine oxidoreductase (XOR) [37, 134–136] are involved in diabetic cardiomyopathy, depending on the type or stage of diabetes mellitus models. Reported alterations in the ROS-mediated injury defense system in diabetic hearts include upregulation of superoxide dismutase (SOD) and catalase expression, which appears to be adaptive [137–142], and downregulation of peroxiredoxins [143, 144], SIRT3 [145, 146], NF-E2-related factor 2 (NRF2) [147, 148], and nicotinamide phosphoribosyltransferase (NAMPT) [149] expression, which augments ROS-induced injury. However, alterations in the antioxidant defense systems are also different between models of diabetes and their roles in pathogenesis of diabetic cardiomyopathy remain to be further investigated.

Our recent studies showed that increased AMPD activity in diabetes contributes to ROS-mediated injury via augmentation of ROS generation by XOR [37]. Hypoxanthine and xanthine are metabolites downstream of AMP deamination by AMPD, and it is therefore expected that upregulated AMPD increases XOR-derived ROS when the ATP turnover rate is increased, for example, by increased cardiac workload. In fact, while baseline levels of tissue hypoxanthine, xanthine and uric acid were similar in OLETF rats and their nondiabetic control, LETO rats, ventricular pressure loading increased tissue xanthine and uric acid to higher levels in OLETF rats [37]. In addition to its substrates, the activity of XOR was found to be increased by 20–30% during pressure loading via a mechanism mediated by accumulated inosine, while there was no activation of XOR by CKD5-mediated XOR-Thr222 phosphorylation [150] or increased intracellular iron levels [151, 152]. The causal role of XOR-derived

ROS in diastolic dysfunction in OLETF rats was confirmed by the findings that a specific XOR inhibitor, topiroxostat, suppressed the elevation of tissue biomarkers of ROS (levels of 4-HNE and carbonylated proteins) and improved diastolic function during pressure loading [37].

An XOR-independent mechanism might also be involved in the generation of ROS by upregulated AMPD (Fig. 2). Inhibition of XOR in the OLETF rat myocardium to a level lower than that in the nondiabetic control did not completely restore state-3 respiration of mitochondria [37]. On the other hand, state-3 respiration on pyruvate/malate, but not that on succinate, in mitochondria was inhibited in AMPD3-overexpressing cells, indicating complex I inhibition by AMPD upregulation [39]. Inhibition of complex I induces generation of ROS [153, 154], and mitochondrial Ca^{2+} stimulates the production of ROS and greatly enhances the detrimental effect of ROS on the mitochondrial respirasome [155]. Thus, there is the possibility that increased mitochondrial ROS generation by enhanced mitochondrial Ca^{2+} influx via remodeled MAMs partly contributes to the excessive generation of ROS in AMPD3-upregulated hearts.

AMPD and increased vulnerability of cardiomyocytes to cell death

Cardiomyocyte death is one of the mechanisms underlying the irreversible progression of chronic heart failure [156, 157]. At late stages of diabetic cardiomyopathy, multiple mechanisms, including ischemia caused by insufficient microcirculation and inflammatory cytokines, have been proposed to trigger the programmed and unprogrammed cell death of cardiomyocytes [28, 31, 158]. Excessive generation of ROS and impaired Ca^{2+} handling, two important mechanisms of contractile dysfunction in diabetic cardiomyopathy, increase the propensity for mitochondrial permeability transition pore (mPTP) opening. mPTPs are nonselective channels in the inner mitochondrial membrane and open either in reversible low conductance mode or in irreversible high conductance mode, mediating redox signals or cell death, respectively [159–161]. The threshold for irreversible mPTP opening is regulated by multiple factors including the interaction of signal molecules, intracellular pH and Ca^{2+} , and ATP levels in the matrix. Toxic levels of ROS and/or mitochondrial Ca^{2+} overload trigger irreversible opening of mPTPs, leading to necrotic cell death. As diabetes induces excessive production of ROS and dysregulation of intracellular Ca^{2+} homeostasis in cardiomyocytes, it is conceivable that the opening of mPTPs underlies progressive cardiomyocyte death in diabetic cardiomyopathy. This hypothesis is difficult to directly test because of technical difficulty in quantifying dead cardiomyocytes present at very small numbers in the heart. However, an increase in myocardial susceptibility to infarction after ischemia/reperfusion and a

lowered threshold for mPTP opening in diabetic hearts have been reported in many, but not all, animal models of diabetes [114, 162–165].

As upregulated AMPD promotes generation of ROS and elevates mitochondrial Ca^{2+} levels during increased cardiac workload (as discussed above), it is expected that the level of AMPD expression correlates with the propensity for mPTP opening. In fact, the Ca^{2+} retention capacity (CRC) of isolated mitochondria (i.e., mitochondria with some extent of ER/SR contacts in crude mitochondrial fractions) was reduced by AMPD3 overexpression in H9c2 cardiomyoblasts and HEK293 cells, while the levels of mPTP regulatory proteins, cyclophilin D, GSK-3 β , and Ser9-phospho-GSK-3 β , in the mitochondrial fractions were unchanged [39]. Furthermore, ROS-induced mPTP opening, which was determined by the loss of mitochondrial membrane potential, was augmented by the overexpression of AMPD3 and conversely suppressed by the knockdown of AMPD3 expression in H9c2 cardiomyoblasts [39]. Consistent with these findings in cell lines in vitro, the CRC of mitochondria isolated from OLETF rat hearts was significantly lower than that of mitochondria from nondiabetic control hearts, although the change in CRC is likely partially due to a reduced level of Ser9-GSK-3 β phosphorylation in mitochondria [162]. Future studies using a specific inhibitor of AMPD [18] or deletion of AMPD genes are necessary to elucidate the relative importance of AMPD among other regulatory factors in mPTP regulation. Nevertheless, it is important to note that detrimental effects exerted by upregulated AMPD on adenine nucleotides [23], tissue biomarkers of ROS [37], and mitochondrial Ca^{2+} levels [39] were undetectable under the baseline condition but were detected after an increase in cardiac workload. Thus, the impact of AMPD upregulation on the propensity for mPTP-mediated cell death is likely to depend on factors modulating cardiac work.

AMPD in human heart diseases

Mutations in AMPD2, which is predominantly expressed in the heart, brain, and liver, were found to cause pontocerebellar hypoplasia without gross abnormalities in the heart [166, 167]. In contrast, the C34T (Glu12Stop) mutation in exon 2 of human AMPD1 was found to be associated with lower cardiac AMPD activity in heart failure patients; cardiac AMPD activity in patients with CT or TT genotypes was approximately 50% lower than that in patients with the wild-type CC genotype [168, 169]. Possible explanations for the lower cardiac AMPD activity include the heteromeric composition of cardiac AMPD and/or a change in the expression pattern induced by heart failure since the expression of AMPD1 and AMPD3 transcripts can be detected in human hearts [170]. Whether the CT or TT genotype is resistant to diabetic cardiomyopathy is an interesting question that, if

answered, can provide insight into the role of AMPD in the human diabetic heart.

Although the concept of diabetic cardiomyopathy in the human heart has not been established as that in animal models, diabetes is clearly a major risk factor of both heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. In light of complex mechanisms that have been shown in animal models of diabetic cardiomyopathy and human diabetic hearts [28–32], multiple approaches to different targets are currently employed in prevention and management of heart failure in diabetic patients [171, 172]. Whether a therapy targeting AMPD significantly protects hearts from diabetic cardiomyopathy remains to be further investigated.

Summary and conclusion

Multiple AMPD genes are expressed in the heart, while AMPD3 and AMPD2 are predominantly expressed in the rat heart and human heart, respectively. In the rat heart, AMPD3 was found to localize in the cytosol, SR/ER, and MAM, while its presence in mitochondria appears to be very low or negligible. The localization of AMPD overlaps with that of AK, which is consistent with the functional relationship between AMPD and AK. Circumstantial evidence suggests that AMPD negatively regulates BCAA-BCKA catabolism by suppressing BCKDH activity in the ER and AMPK signaling pathways when not only AMP levels but also AMP/ATP ratios are increased in cardiomyocytes. The physiological significance of the two AMPD functions is unclear. However, because ATP is an activator of AMPD, it is possible that the suppression of BCKDH and AMPK by activated AMPD, leading to reduced catabolism of energy substrates, is a feedback mechanism for fine-tuning the rate of ATP synthesis while sparing BCAAs for protein synthesis.

Upregulation of AMPD activity in myocardial tissue has been observed in different models of type 1 and type 2 diabetes. However, its pathophysiological role has been characterized only in one model of type 2 diabetes, OLETF rats. In this model, AMPD protein levels were increased in the cytosol, ER, and MAM but not in mitochondria. AMPD upregulation was associated with enlarged areas of mitochondria-ER/SR contact, which might be a compensatory response to the reduction in mitochondrial Ca^{2+} uptake in diabetic hearts. Diastolic dysfunction induced by ventricular pressure loading in OLETF rats was correlated with depletion of ATP and adenine nucleotides, increased generation of ROS, and augmented elevation of mitochondrial Ca^{2+} levels. Most of the detrimental effects of AMPD upregulation are attributable to increased XOR-derived ROS production as a result of increased flux from AMP to uric acid and depletion of adenine nucleotides, although enhanced mitochondrial

Ca^{2+} influx via remodeled MAMs is possibly an additional mechanism (Fig. 2). Increased generation of ROS and modulation of mitochondrial Ca^{2+} handling by AMPD upregulation increase the propensity for necrotic cell death by lowering the threshold for mPTP opening (Fig. 2). As a major limitation, the proposed roles of upregulated AMPD in diabetic cardiomyopathy are based on findings in cultured cells with manipulated AMPD expression and metabolomic analyses in OLETF rat hearts. The findings need to be further confirmed by the use of specific inhibitors of AMPD and AMPD knockout mice, which would provide insight into a role of AMPD as a therapeutic target in the diabetic heart. However, cardiac-specific knockout of a single AMPD gene may provide results that are difficult to interpret, as did the effect of AMPD1 knockout on the contractile function of skeletal muscle [10, 14, 173], because of the compensatory function of co-expressed AMPD genes. Nevertheless, it is important to note that significant roles of AMPD in a rat model of diabetic cardiomyopathy were undetectable at the baseline condition and manifested in conditions of increased cardiac work. Thus, levels of physical activity and cardiac workload would need to be taken into account to characterize the roles of AMPD in human heart diseases in future investigations.

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