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Branched chain amino acid metabolic reprogramming in heart failure☆

Haipeng Sun, Ph.D., Yibin Wang, Ph.D. *

Key Laboratory of Cell Differentiation and Apoptosis of Ministry of Education, Department of Pathophysiology, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China
Departments of Anesthesiology, Physiology and Medicine, David Geffen School of Medicine, University of California, Los Angeles, United States

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ABSTRACT

Metabolic remodeling is a hall-mark of cardiac maturation and pathology. The switch of substrate utilization from glucose to fatty acid is observed during post-natal maturation period in developing heart, but the process is reversed from fatty acids to glucose in the failing hearts across different clinic and experimental models. Majority of the current investigations have been focusing on the regulatory mechanism and functional impact of this metabolic reprogramming involving fatty acids and carbohydrates. Recent progress in metabolomics and transcriptomic analysis, however, revealed another significant remodeled metabolic branch associated with cardiac development and disease, *i.e.* Branched-Chain Amino Acid (BCAA) catabolism. These findings have established BCAA catabolic deficiency as a novel metabolic feature in failing hearts with potentially significant impact on the progression of pathological remodeling and dysfunction. In this review, we will evaluate the current evidence and potential implication of these discoveries in the context of heart diseases and novel therapies. This article is part of a Special Issue entitled: The role of post-translational protein modifications on heart and vascular metabolism edited by Jason R.B. Dyck & Jan F.C. Glatz.

1. Metabolic reprogramming in heart failure

Each day, a normal adult human heart contracts about 100,000 times and delivers more than 2000 gal of blood [1]. This continuing contraction is vital to our survival and dictates the heart as a major organ of energy consumption and a tissue with exquisite sensitivity to nutrient environment. It is, therefore, obvious that metabolic defects can exert major impact on cardiac health and disease process [2,3]. In most current studies, much of the effort on cardiac muscle metabolism is focused on two main classes of bioenergetics substrates, fatty acids and glucose [4,5]. In fetal heart, the primary energy source is glucose, however, the substrate utilization in the heart is switched to fatty acids soon after birth [6]. Interestingly, in diseased heart, the substrate utilization is switched back to glucose [7]. Although it is well established that developmental stage specific metabolic switch is part of the necessary process of cardiomyocyte differentiation and maturation [8,9], the functional significance of metabolic reprogramming from fatty acids to glucose in the diseased heart remains to be controversial. While some studies show preservation of fatty acid utilization is cardioprotective [10,11], others show enhanced glucose utilization is a compensatory process beneficial to stressed myocardium [12,13]. Nevertheless, metabolic reprogramming is well recognized as an integral part of cardiac pathological remodeling, but the main body of current literature and research is very much limited to fatty acid and glucose utilization while relatively limited knowledge is available about other nutrients. Indeed, two recent studies also find a shift in fuel utilization to ketone bodies is associated with heart failure which may potentially serve as a compensatory mechanism in cardiac energy homeostasis [14,15]. The question is are there other nutrient ingredients, such as amino acids, important to the pathogenesis of heart failure?

2. BCAA catabolic regulation

Amino acids are important nutrients for cellular growth and survival. In addition to serving as building blocks for peptides and proteins, amino acids are also significant sources for energy as well as biosynthesis substrates for other cellular structure and signal molecules [16]. Since essential amino acids cannot be generated through *de novo* synthesis process, their supplies largely rely on food intake but can also be modulated by gut microbiota as revealed from several recent studies [17,18]. Thus the intra-tissue homeostasis of essential amino acids is largely maintained by the balance of protein synthesis and degradation, as well as amino acid catabolic activities.

Branched-chain amino acids (BCAA), including leucine, isoleucine and valine, represent the most abundant group of essential amino acids [19]. The steady state levels of BCAA are maintained by their catabolic activities which degrade BCAA through a cascade of catabolic steps into final products of acetyl-CoA and succinyl-CoA and feeding into the

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* Corresponding author at: Room BH569, CHS, 650 Charles E. Young Street, Los Angeles, CA 90095, United States.
E-mail address: yibinwang@mednet.ucla.edu (Y. Wang).

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TCA cycle for respiration [20]. However, recent reports have indicated that BCAA catabolic derivatives also contribute to signaling (by 3-HIB) in skeletal muscle vasculature [21] or to contribute directly to branched-chain fatty acids synthesis in adipocyte [22,23]. BCAA catabolic enzymes are largely located in the mitochondrial matrix, except for the cytosolic branched-chain amino acid transaminase 1 (BCAT1). Among the enzymatic cascade for BCAA degradation, the branched-chain alpha-keto acid dehydrogenase (BCKD) is the rate-limiting step shared by all three amino acids [24]. It is remarkable that BCKD complex shares extensive similarity in terms of subunit structure and necessary coenzymes with two other complexes, pyruvate dehydrogenase complex (PDC) and alpha-ketoglutarate dehydrogenase complex (OGDC), which are also key regulatory steps for glucose metabolism and citric acid cycle, respectively. Like PDC or OGDC, BCKD is also the molecular target of BCAA catabolic regulation, involving substrate induced allosteric activation, nutrient dependent phosphorylation and transcriptional regulation [20].

3. BCAA catabolic defects and diseases

Genetic defects at different catabolic steps of BCAA lead to a spectrum of inborn metabolic disorders, including Maple Syrup Urine Disease (MSUD) which is caused by BCKD deficiency. MSUD is a relatively common amino acid metabolic disorder, second only to phenylketonuria in frequency among newborns in the United States. The classic form of MSUD (complete loss of BCKD activity) causes early lethality in newborns due to brain damage [25]. In recent years, BCAA catabolic defects and abnormal BCAA or BCAA metabolites in plasma or tissues have also been associated with other major human diseases, including Huntington's diseases, pancreatic cancer, cardiovascular diseases, diabetes and obesity [26–32]. Therefore, BCAA catabolic activity and disorder have a broad impact on human health and diseases. Also like metabolic regulation of fatty acid and glucose, inter-organ interaction of BCAA catabolism may also be very important to global homeostasis. BCKD are present in all tissues but their regulatory genes, including the negative and positive regulators BCKDK and PP2Cm are enriched in specific tissues and highly regulated by nutrients and stress signals [33,34]. It is reported that obesity associated inhibition of hepatic BCKD activity can contribute to BCAA accumulation in skeletal muscle and insulin resistance [35].

4. BCAA catabolic defects in failing hearts

In an early study by Peterson et al., total free amino acid concentrations were measured and found to be increased in the human failing right ventricles [36]. Using metabolomic method, Kato et al. investigated intra-tissue metabolic changes in Dahl Salt-Sensitive rat hearts and observed significant changes of several amino acids including elevated valine, isoleucine, and leucine levels associated with high-salt induced hypertension [37]. Using multi-systems approaches, two recent reports also demonstrated that abnormal amino acid metabolism, including BCAA, were associated with pathological remodeling in response to pressure overload and myocardial infarction [38,39]. In a relatively small cohort of PREDIMED study, higher concentrations of baseline BCAAs were linked to increased risk of cardiovascular diseases [40]. Beyond these association studies, Sun et al. revealed that BCAA catabolism was the most significantly altered metabolic pathway in pressure-overload induced mouse failing hearts based on transcriptome analysis, involving global reduction of a significant number of genes from BCAA catabolic pathway [41]. In the same study, marked accumulation of branched-chain alpha-keto acids (BCKAs) was detected in the stressed heart tissues. Sun et al. also demonstrated similar transcriptional and metabolic changes in human dilated cardiomyopathy hearts, indicating BCAA catabolic deficiency across different species [41]. It is interesting to note that proteins involved in the rate-limiting step of BCAA degradation, including BCKD E1alpha, E1beta, and E2 subunits, are coordinately downregulated in the diseased hearts. In addition, *Ppm1k*, the gene coding for the BCKD phosphatase (PP2Cm, a key positive activator to BCKD) is suppressed in cardiomyopathy hearts while *Bckdk*, the gene for BCKD kinase (an inhibitor for BCKD) is not affected. Similar to Sun's report, a more recent study by Wang et al. observed dynamic changes of BCKD activity following myocardial infarction [42]. In this report, a transient induction of BCAA catabolic activity was observed within one-week post-MI but significantly depressed beyond the one-week time point, coinciding with a progressive loss of BCKD phosphatase, PP2Cm. Therefore, pathological remodeling in heart is marked by a coordinated transcriptional change in BCAA catabolic pathway across different disease models and species. The elevated levels of intra-tissue BCAA or BCKA resulted from the loss of BCAA catabolic flux, together with the suppressed BCAA catabolic gene expression, should serve as potentially useful metabolic biomarkers for cardiomyopathy.

Coordinated down-regulation of expression for key genes associated with BCAA catabolic pathway indicates a shared transcriptional or post-transcriptional regulatory circuit. Indeed, in the report by Sun et al., a transcription factor KLF-15 is identified to be the responsible upstream regulator for the down-regulation of BCAA catabolic genes [41]. KLF-15 is a master transcription regulator for nutrient mobilization in response to starvation and circadian regulation, and many of its targets genes are also involved in glucose and fatty acid metabolic regulation [43–49]. KLF15 expression is known to be diminished in pathologically stressed myocardium. Therefore, it is very likely that loss of BCAA catabolic activity is a significant part of an orchestrated metabolic remodeling in the diseased heart controlled by a conserved transcriptional regulatory network involving key transcription factors, such as KLF-15 (Fig. 1). However, our current knowledge in BCAA catabolic regulation remains very limited, and the underlying molecular mechanisms for BCAA regulation at transcriptional and post-transcriptional levels in response to nutrient environment and stress stimulation are yet to be established.

In summary, elevated BCAA and defects in BCAA catabolic activities are emerging metabolic and molecular features associated with heart failure. However, much of our current knowledge is based on correlative observations in animal models of heart diseases. Fundamental questions remain to be addressed including the underlying transcriptional pathway and possible interactions with other metabolic processes, such as fatty acid and glucose utilization in the context of heart diseases. In addition to the intrinsic catabolic defects in cardiomyocytes, abnormal cardiac BCAA/BCKA may also be contributed by BCAA catabolic defects in other tissues such as liver or fat in the setting of obesity or other global metabolic disorders [32]. Although not yet directly demonstrated, it is highly plausible that a systemic induction of BCAA/BCKA could serve as a potential metabolic link between metabolic disorders and elevated risks of heart diseases [40].

5. Functional impact of BCAA catabolic defects in heart

Like the role of BCAA catabolic abnormality in other human diseases, it is a critical question to ask if turning-off BCAA catabolic flux in stressed heart is a compensatory event to protect heart against pathological stress or a detrimental event to promote pathological remodeling [50]. Cardiomyocyte hypertrophy is a common response to both physiological and pathological stress, yet there are qualitative differences between the two scenarios, involving drastically different molecular changes, intracellular signaling and functional outcome [51]. Branched amino acids are not a major contributing component of cardiac bioenergetics sources [52], however, it is reasonable to speculate that turning-off BCAA catabolic flux can be a compensatory step to preserve free amino acids in order to provide building blocks for protein synthesis required for cellular growth during cardiac hypertrophy. Based on this logic, BCAA catabolic reprogramming may function as a compensatory process to maintain cardiac output or wall stress by increasing muscle mass and wall thickness. However, so far no studies have shown BCAA catabolic change is associated with or necessary for

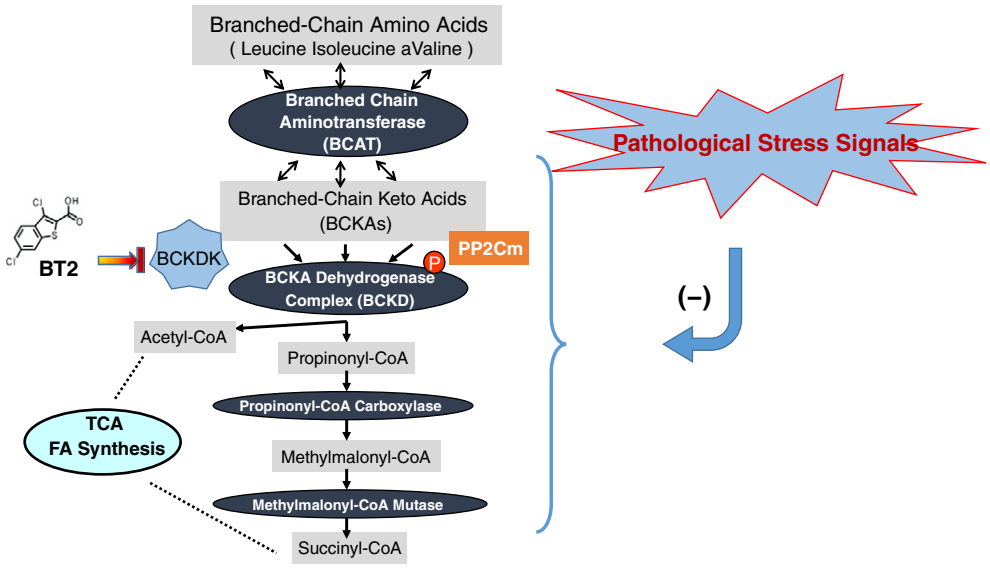

Fig. 1. Illustration of branched-chain amino acid (BCAA) catabolic pathway and dysregulation in stressed heart. Branched amino acids are degraded by a cascade of enzyme complexes (indicated in oval shapes) into their final products of acetyl-CoA and succinyl-CoA, through a number of metabolic intermediate products (in shaded rectangular boxes). Pathological stressors affect many of the enzyme complexes and regulators, including BCKD and PP2Cm. BCKDK, BCKD kinase; PP2Cm, BCKD phosphatase; PDP, PDH phosphatase; PDK, PDH kinase; BCAA, branch-chain amino acids; BCKA, branched-chain alpha-keto acids; and BT2, BCKDK specific inhibitor.

physiological hypertrophy in the heart induced by exercise or during late pregnancy. On the contrary, BCAA catabolic defect appears to be a common signature in diseased hearts induced by pathological stress.

As demonstrated in most reports, a major consequence of BCAA catabolic defect is the accumulation of intra-tissue BCAA and their catabolic intermediate products. It is well established that leucine is a potent signal molecule which functions through mTOR pathway to regulate cellular growth and metabolism [53,54]. Indeed, leucine is a potent promoter for mTOR activity and protein synthesis, and is used as a food supplement to prevent muscle wasting [55]. Leucine deprivation is a classic stressor for cellular autophagy triggered by mTOR inhibition [54]. mTOR is highly implicated in cardiac hypertrophy, although a direct role for BCAA such as leucine in cardiac pathological hypertrophy or dysfunction has not yet been demonstrated [53]. However, the recent report by Wang et al. indeed showed direct treatment of BCAA further aggravated pathological remodeling and dysfunction following myocardial infarction in an mTOR dependent fashion [42]. Important insights have been revealed from more recent studies in human or animal models with genetic defects in BCAA catabolic pathway [56]. In human MSUD where BCKD activity is diminished, the pathological impact on neurons is attributed to the elevated plasma BCKA levels since BCKA can directly induce the production of reactive oxygen species (ROS) [57,58]. Likewise, Sun et al. investigated a mouse model of PP2Cm deficiency where impaired BCKD activity led to elevated BCKA levels in heart tissue [59]. The PP2Cm deficient mice showed earlier onset of contractile dysfunction during normal ageing process and exacerbated heart failure upon pressure-overload, yet cardiac hypertrophy as measured from heart weight and ventricular mass was not affected [41]. Similar to what was reported in the brain, Sun et al. detected significantly elevated ROS in the PP2Cm deficient cardiac tissues. Indeed, direct treatment of BCKA to isolated cardiac mitochondria *in vitro* resulted in a dose-dependent induction of superoxide production and inhibition of mitochondrial respiration, suggesting a direct impact of BCKA on cardiomyocyte redox regulation and mitochondrial function [41]. It is important to note that the levels of BCKA used to demonstrate the direct effect on ROS induction *in vitro* are comparable to the elevated BCKA levels observed in the PP2Cm deficient hearts and the human cardiomyopathy hearts. These lines of evidence support a working model that BCAA catabolic defects in the pathologically stressed heart cause significant accumulation of BCAA and BCKA, which in turn might contribute to the pathogenesis of heart failure by mTOR activation and ROS production and mitochondrial dysfunction (Fig. 2).

Although BCAA/BCKA accumulations appear to be a pathogenic factor to both neurological pathology and heart failure, the underlying mechanism remains elusive. Many key questions need to be addressed. What are the molecular targets of BCAA induced mTOR activity and BCKA induction in mitochondria or cells which lead to ROS induction and respiration inhibition? Are accumulated BCAA/BCKA the only metabolites responsible for the cytotoxic effect or other metabolites downstream of BCKA degradation? Are ROS production and oxidative

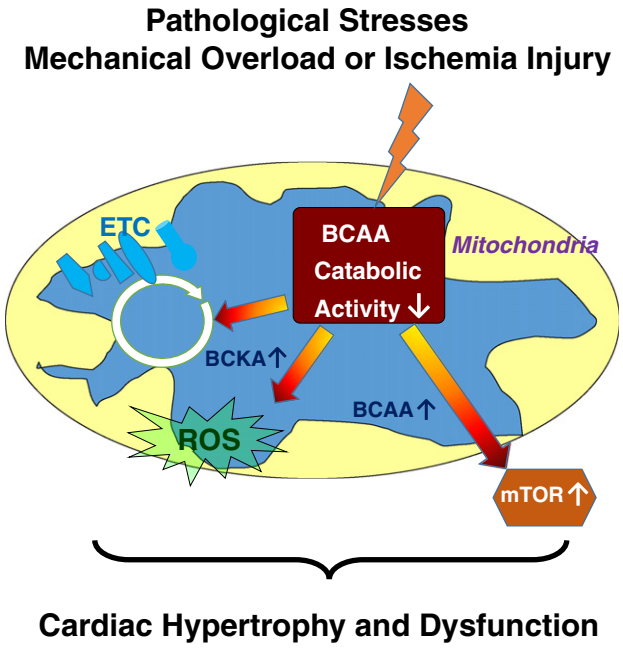

Fig. 2. Functional impact and potential mechanism in BCAA/BCKA induced pathological remodeling and dysfunction in the heart. This is a working model depicting how BCAA catabolic defects can lead to downstream accumulation of BCKAs, mTOR activation and ROS induction. Each has been implicated in the pathogenesis of cardiac hypertrophy and dysfunction. ROS, reactive oxygen species; and ETC, electron-transfer chain.

phosphorylation the only mitochondrial processes affected by BCKA or other metabolites? More recently, Jang et al. report that a BCAA metabolite functions as a signal to regulate vascular fatty acid uptake with a significant role in lipid accumulation and insulin desensitization in skeletal muscle [21]. This observation may be potentially relevant to heart diseases if the same mechanism also plays a role in cardiac metabolic reprogramming from fatty acid to glucose utilization, especially in the context of metabolic disorders. In short, the molecular mechanisms of the functional impact of BCAA catabolic defects in the context of cardiac pathology are not well understood and should be further investigated.

6. BCAA targeted therapy: dietary *vs.* pharmacological intervention

These recent findings suggest that the impaired BCAA catabolic gene expression and the accumulated BCAA metabolites are newly recognized molecular and metabolic hallmarks of cardiomyopathy. In addition to the obvious diagnostic values, a critical question is whether this insight can be translated into a potential therapy. BCAA dietary supplement is already widely used for various health issues. Although several reports have indicated certain beneficial impact of BCAA enriched dietary supplement in clinic or pre-clinical studies related to heart failure [60–63] [64], it remains inconclusive regarding the underlying mechanisms. If the pathogenic culprit of BCAA catabolic defect is the accumulated BCKA in cardiac tissue, enhancing BCAA catabolic flux could be a potential therapeutic strategy. Indeed, BCAA catabolic activity is highly regulated in response to nutrient environment, and their gene expressions are sensitive to fasting or feeding conditions [33,65]. We could speculate that dietary supplement of BCAA may lead to enhanced BCAA catabolic flux and counter-act with stress-induced loss of BCAA catabolism and accumulation of BCKA in diseased heart. Indeed, BCAA treatment exacerbated pathological remodeling and dysfunction in the post-MI hearts as shown by Wang et al.[42]. Therefore, increasing consumption of amino acids may exacerbate cardiac tissue accumulation of BCKA or other yet-to-be-identified pathogenic metabolites. Therefore, BCAA supplement as a therapeutic approach for heart failure should be carefully evaluated with consideration of the status of the BCAA catabolic activities under specific pathological conditions.

More recently, efforts from Chuang's laboratory lead to the development of a potent and specific BCKD kinase inhibitor, BT2 compound, based on structural insights of the BCKD kinase [66,67]. This compound has demonstrated significant efficacy to block BCKD kinase activity *in vivo*, leading to an enhanced BCKD activity and reduced BCAA/BCKA accumulation. Most significantly, in the report by Sun et al., BT2 treatment administered along with the onset of pressure-overload has a significant ameliorative effect on the progression of heart failure [41]. Consistent with this report, Wang et al. also demonstrated that BT2 treatment following myocardial infarction significantly ameliorated pathological remodeling and dysfunction following the injury [42]. With the caveat that systematic treatment of BT2 may affect other tissues, the data is a very promising first demonstration that enhancing BCAA catabolic flux can have a significant protective effect against heart failure. Nevertheless, the therapeutic potential targeting BCAA catabolism must be better demonstrated in other heart failure models. Moreover, the efficacy of its therapeutic potential should be investigated in more clinically relevant experimental settings, e.g. administration of BT2 is implemented only after heart failure is already initiated or established.

7. Summary

BCAA catabolism is a highly conserved metabolic pathway with increasing recognition for its importance for cellular growth and normal physiology. In addition to its established contribution to inherited metabolic disorders in human, recent progresses have led to the discovery of BCAA catabolic defects as an integral part of metabolic reprogramming in many common diseases, including cardiomyopathy. Abnormal BCAA and their downstream metabolites are not only potential biomarkers for heart failure, but also function as contributing factors in the pathogenesis of the disease. Novel therapeutic approach targeted to correct the loss of BCAA catabolic activity may prove to be efficacious to blunt the onset and progression of heart failure. As so much remain unknown about BCAA catabolic dysregulation and the underlying mechanism of the consequent pathological effects, our quest has just begun to uncover the full impact of BCAA catabolism in human diseases, and to translate such insights into novel diagnosis and therapies.

Transparency Document

The Transparency document associated with this article can be found, in online version.

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