Invited Review

Emerging pathophysiological roles of ketone bodies

Hiroaki Tsuruta, Kosuke Yamahara, Mako Yasuda-Yamahara, Shinji Kume

Department of Medicine, Shiga University of Medical Science, Seta, Otsu, Shiga 520-2192, JAPAN

Corresponding authors
Shinji Kume, M.D., Ph.D.
Department of Medicine, Shiga University of Medical Science, Tsukinowa-cho, Seta, Otsu, Shiga 520-2192, Japan.
TEL: +81-775-48-2222
FAX: +81-775-43-3858
E-mail: skume@belle.shiga-med.ac.jp

ABSTRACT

The discovery of insulin approximately a century ago greatly improved the management of diabetes, including many of its life-threatening acute complications like ketoacidosis. This breakthrough saved many lives and extended the healthy lifespan of many patients with diabetes. However, there is still a negative perception of ketone bodies stemming from ketoacidosis. Originally, ketone bodies were thought of as a vital source of energy during fasting and exercise. Furthermore, in recent years, research on calorie restriction and its potential impact on extending healthy lifespans, as well as studies on ketone bodies, have gradually led to a reevaluation of the significance of ketone bodies in promoting longevity. Thus, in this review we discuss the emerging and hidden roles of ketone bodies in various organs, including the heart, kidneys, skeletal muscles, and brain, as well as their potential impact on malignancies and lifespan.

INTRODUCTION

Ketone bodies are distinctive metabolites that play a pivotal role in a range of physiological and pathological states within the body. They are predominantly synthesized in the liver during periods of fasting or caloric restriction and are subsequently utilized as an energy source by various organs—including the heart, brain, kidneys, and muscles (1). They are especially vital as an energy source during the neonatal period (2, 3). Beyond their function as energy substrates, ketone bodies have a wide range of physiological effects, such as participating in signal transduction, making post-translational modifications, modulating the immune system, and exerting antioxidant activities, as well as influencing the sympathetic nervous system (4-11).

Ketone production is upregulated during starvation, fasting, physical activity, and pregnancy, and in individuals consuming a ketogenic diet, which is low in carbohydrates and high in fats (12). This upregulation plays a crucial role in energy homeostasis within the body. However, pathological overproduction of ketone bodies, as seen in diabetic ketoacidosis, can result in severe metabolic acidosis which can potentially progress to organ damage (13). Historically, ketone bodies were often regarded as harmful due to their association with acidosis. Recent studies, however, are revising this perspective, uncovering a myriad of health benefits such as autophagy-mediated organ and renal protection (14-16), seizure prevention (17), and myocardial preservation (18, 19).

This review aims to illuminate the multifaceted role of ketone bodies in the human body, delving into their significance across various organs and diseases, as illustrated by contemporary research. While the impact of ketone bodies may differ depending on the health status of each organ and the context in which they are considered, this review endeavors to provide readers with a comprehensive understanding of the nuanced nature of ketone bodies.

BASIC METABOLISM OF KETONE BODIES

Ketogenesis

Ketone body production predominantly occurs in the liver (Figure.1). While recent research has identified ketogenesis in extrahepatic organs, including the intestines and kidneys, the supply of circulating ketone bodies is predominantly dependent on hepatic function. In the liver-specific HMGCS2-deficient mice model, the fasting-induced increase in plasma ketone body levels is completely abolished (20).

During fasting, circulating free fatty acids generated by adipocytes are transported to

hepatocyte mitochondria via carnitine palmitoyltransferase 1, where they undergo complete mitochondrial β-oxidation to produce acetyl-CoA (Figure. 2). Two molecules of acetyl-CoA are condensed by acetyl-CoA acetyltransferase 1 (ACAT1), which then condenses with acetyl-CoA to synthesize HMG-CoA via the action of 3-Hydroxy-3-Methylglutaryl-CoA Synthase 2 (HMGCS2), which is a key rate-limiting enzyme in ketogenesis. HMG-CoA is cleaved into Acetoacetate (AcAc) and acetyl-CoA by 3-Hydroxymethyl-3-Methylglutaryl-CoA Lyase (HMGCL). Most of the AcAc is reduced to Beta-Hydroxybutyrate (BHB) through the action of BHB dehydrogenase 1(BDH1), in a reaction that is closely balanced between NAD+ and NADH levels. AcAc is partially converted to acetone, which is not metabolically active. The BHB and AcAc that are generated through this process are not directly utilized as energy sources in the liver but are mainly released into the circulation by monocarboxylate transporters 1/2 (MCT1/2) and transported to several tissues. The rate of hepatic ketogenesis is mainly regulated by plasma glucose, insulin, and glucagon levels. Thus, ketone body production increases with several factors, such as exercise, pregnancy, and consumption of a low-carbohydrate, high-fat diet (ketogenic diet), in addition to fasting and calorie restriction. Ketone body production is also enhanced by treatment with SGLT2 inhibitors (21), but the detailed mechanism is still unclear, necessitating further research.

Ketolysis

BHB in the bloodstream is taken up by MCT1/2 and transferred to extrahepatic mitochondria, where it is converted back to acetyl-CoA to produce ATP. BHB first is oxidized via BDH1 to AcAC, which is subsequently activated to AcAc-CoA by succinyl-CoA:3-oxoacid CoA transferase (SCOT), the key enzyme involved in ketolysis. Then, AcAc-CoA undergoes thiolysis by ACAT to generate acetyl-CoA. The CoA used in this process is derived from succinyl-CoA, and the energy produced by AcAc hydrolysis is greater than that consumed by breaking down succinyl-CoA. The majority of the AcAc-CoA enters the TCA cycle as an energy source, while the remainder is utilized for cholesterol biosynthesis. Various factors can interfere with the standard ketone body production pathway, some of which are described below.

Energy metabolism in each organ

BHB produced in the liver is mainly utilized as an energy source in several tissues, such as brain, heart, muscles, and kidneys (22).

1) Brain

The metabolic interaction between neurons and glial cells is essential for maintaining brain functions. Under physiological conditions, glial cells take up blood glucose and then convert it to lactate through glycolysis, which they supply to neurons as a source of energy (23). However, under glucose-deficient starvation conditions, glial cells provide an essential energy source by breaking down fatty acids to produce ketone bodies that neurons use for energy, thus preserving the capacity for memory formation (24, 25). Research in *Drosophila* has shown that, even when glycolysis is inhibited in glial cells, they can survive for weeks by supplying neurons with energy through mitochondrial fatty acid breakdown and ketone body production (26). Furthermore, it was found that, during starvation, glial cells obtain the energy necessary for survival by degrading fatty acids, a process that also produces ketone bodies (26).

2) Heart

The heart is the organ with the highest energy expenditure per day. Under normal conditions, the energy metabolism of the heart depends mainly on fatty acyl-CoA, and glucose consumption in cardiomyocytes is limited (19). Thus, circulating ketone bodies are an important alternative fuel source, especially under pathological conditions such as ischemia, when the heart switches to ketone metabolism (18, 27-30).

3) Muscle

The skeletal muscles adapt to fasting and exercise by utilizing ketone bodies for energy, ensuring their continuing function (31-33). Exercise-trained skeletal muscles have an enhanced ability to take up and oxidize ketone bodies during physical activity (34).

4) Kidney

Renal tubules predominantly utilize lipids, not glucose, as their primary energy source. Furthermore, as with the heart, the kidneys can adapt to using ketone bodies as an alternate energy source; thus, ketone bodies have a vital role in kidney injury (35, 36). We previously showed that tubule energy usage in impaired kidneys shifts towards ketone bodies, and that supplementation with ketone bodies has a renoprotective effect in the context of diabetic kidney disease (DKD) (16).

DISTINCTIVE ROLES OF KETONE BODIES BEYOND SERVING AS AN ENERGY SOURCE

Epigenetic

BHB influences the epigenetic landscape by making unique post-translational modifications to histones and suppressing the activity of class I histone deacetylases (HDACs) (Figure. 3) (37). This process protects against mitochondrial dysfunction, and is therefore particularly relevant to decreasing the inflammatory responses and

promoting antioxidant effects (37). The anti-inflammatory and antioxidant responses induced by HDAC suppression effectively slow the progression of various diseases, such as cancer, muscular atrophy, and Alzheimer's disease (7-9). BHB also regulates chromatin through lysine β-hydroxybutyrylation (Kbhb) of histones; β-hydroxybutyryl addition is mediated by p300 acetyltransferase and reversed by HDAC 1 and 2 (38, 39). It has been reported that Kbhb plays a crucial role as one of the key regulators of metabolic changes in the intestine during fasting (40). Furthermore, Kbhb has been found to be involved in diabetic cardiomyopathy and tumor growth (41, 42). Further research is required to understand the detailed roles of Kbhb in various organs.

G-protein–coupled receptors

Ketone bodies are also effector molecules of G-protein–coupled receptors (GPR) such as GPR41 and GPR109a. GPR41 is mainly located in the sympathetic ganglia, and ketone bodies directly antagonize GPR41 activity, thereby suppressing the sympathetic nervous system. GPR41 inhibition is thought to contribute to the cardioprotective effects of ketone bodies (11). GPR109a, also known as hydroxycarboxylic acid receptor 2 (HCAR2), regulates metabolism, inflammation, and other physiological processes and is mainly expressed in adipose tissue, immune cells, liver, kidney, and the gastrointestinal tract (43-49). Stimulating GPR109a leads to anti-inflammatory outcomes through the suppression of proinflammatory cytokines from monocytes, macrophages, and adipocytes (43, 50, 51). In addition to anti-inflammatory actions, GPR109a is also involved in the reprogramming of the gut microbiota, and the lack of the GPR109a gene induces severe colitis (51, 52). BHB, but not AcAc, is one of the few known GPR109a ligands and contributes to the antilipolytic and anti-inflammatory effects induced by GPR109a.

THE PATHOPHYSIOLOGICAL ROLES OF KETONE BODIES IN MULTIPLE ORGANS

Heart

Supplementing with exogenous ketone bodies is expected to protect against progressive heart failure induced by metabolic perturbation (Figure. 4). Indeed, various studies have indicated the potential benefits of ketone bodies in protecting against ischemic heart disease (18, 53). Research suggests that there are differences in heart and plasma ketone levels between patients with heart failure with preserved ejection fraction (HFpEF) and patients with heart failure with reduced ejection fraction (54) and that patients with HFpEF and severe diabetes or obesity experience fuel inflexibility (55). Furthermore, it

has been reported that the expression of enzymes associated with ketone body production is altered in damaged heart tissue. Low-flow ischemia has been shown to increase intracardiac ketone body production via HMGCS2, suggesting that accumulated ketone bodies could affect functional recovery (53).

Ketone bodies are also thought to help mediate the cardioprotective effects of SGLT2 inhibitors used to treat heart failure. While SGLT2 inhibitors are primarily used to treat diabetes, their indications have expanded recently to include heart failure (56-58). SGLT2 inhibitor–mediated protection of renal tissue in the context of kidney impairment is related to the production of endogenous ketone bodies (16) (see Kidney section), suggesting that a similar mechanism could be involved in the heart. Empagliflozin has been reported to reduce ischemia-reperfusion injury and myocardial infarction size, and this effect was also produced by administration of BHB alone (56). This suggests that ketone body supply could contribute to the beneficial effects of SGLT2 inhibitors on the heart.

The protective effects of ketone body accumulation on the heart are not entirely explained by their role as an energy source. The EMPA-VISION study reported that empagliflozin treatment was not associated with any changes in cardiac energy metabolism or serum metabolite levels, and concluded that the beneficial effects of SGLT2 inhibitors on heart failure do not depend on improved cardiac energy metabolism (57). Thus, epigenetic regulation by ketone bodies or their protective effects against oxidative stress could be involved. The benefits of ketone bodies for heart diseases are not limited to ischemic injuries; they are also effective in treating diabetic cardiomyopathy. In a mouse model of diabetic cardiomyopathy, a ketone ester diet increased the expression of key enzymes involved in cardiac ketone metabolism—HMGCS2 and SCOT—thereby enhancing resistance to oxidative and redox stress.

Collectively, these studies indicate that ketone bodies benefit damaged heart tissue by providing an alternative energy source or protecting against oxidative stress.

Kidney

Ketone bodies contribute significantly to the kidney protection conferred by SGLT2 inhibitors (59, 60). SGLT2 inhibitor administration has been reported to alleviate renal damage regardless of the presence or absence of proteinuria, and is also thought to protect against chronic kidney disease in non-diabetic individuals. In HMGCS2-deficient mice, SGLT2 inhibitor–induced renal protection is abolished, indicating that endogenous ketone bodies are essential for mediating the renoprotective effects of these drugs (16). The renoprotective effect of ketone bodies is associated with inhibition of

mTORC1, whose activation has been reported to cause renal impairment in DKD (16, 61).

The positive effect of increased endogenous ketone production is not limited to DKD but is also observed in the treatment of polycystic kidney disease (PKD); indeed, a new therapeutic approach involving dietary restriction and fasting-induced ketosis slows PKD progression (62-64). Caloric restriction can also protect against aging-related kidney impairment, an effect that is potentially mediated by ketone bodies (65). Indeed, ketone bodies have been shown to mitigate podocyte aging and damage, with BHB administration reducing diabetic glomerulopathy and albuminuria (66).

A recent study highlighted the role of sodium-coupled monocarboxylate transporter 1 (SMCT1), an enzyme involved in ketone body reabsorption, in slowing the progression of diabetic nephropathy (67). Reduced SMCT1 expression in patients with DKD and in diabetic mouse kidneys correlated with lower serum BHB levels, indicating that SMCT1 is a promising target for DKD treatment.

Neurons

While the ketogenic diet was first developed to treat epilepsy in children (17), recent studies indicate that the utility of ketone bodies is not limited to epilepsy. Ketone bodies are known energy sources in brain cells during fasting, and are involved in memory formation and the ischemic response (68).

The involvement of ketone bodies in memory formation has been reported in humans, with some studies suggesting that intermittent fasting promotes ketone body production, which may prevent Alzheimer’s disease (25). Numerous reports in animal models have also indicated the efficacy of ketone bodies in Alzheimer's disease. This is attributed not only to their role as an energy source but also to their antioxidative effects, prevention of beta-amyloid deposition, and reduction of cerebral blood flow impairment (9, 69, 70). In dementia associated with type 2 diabetes, consuming a ketogenic diet reduces inflammation and the production of reactive oxygen species, leading to restoration of neuronal function (71, 72).

In addition, ketone bodies are associated with recovery after stroke. Stroke patients with high blood BHB levels tend to have a better prognosis after stroke than those with low levels (73). This is thought to be because BHB promotes brain plasticity through a specific signaling pathway, thereby supporting post-stroke recovery.

These studies suggest that ketone bodies play an important role in brain and nerve health and recovery.

Muscle

In addition to their use as an alternative fuel source, ketone bodies also participate in epigenetic mechanisms that are vital for skeletal muscle health and function (74). In particular, enhancing FOXO3A and MT2 activity via HDAC inhibition has been shown to protect against aging-related muscular atrophy. The increase in BHB levels induced by short-term fasting has also been reported to directly promote muscle stem cell (MuSC) quiescence, causing p53 acetylation and activation by inhibiting HDAC (75). P53 activation contributes to MuSC quiescence and survival during fasting. However, ketone bodies do not necessarily have a positive effect on skeletal muscle. Several studies have shown that ketogenic diets that restrict glucose intake do not uniformly benefit muscle functionality and can be linked to muscle fibrosis and atrophy (76, 77). These findings call for a cautious approach in evaluating the role of ketone bodies in muscle physiology.

Intestine

The role of ketone bodies in the small intestine is gradually being elucidated, with preliminary evidence suggesting that they play a role beyond that of an energy source during fasting (78-80). Although ketone body production is primarily hepatic, the rate-limiting enzyme HMGCS2 is also expressed in the small intestine, particularly in crypt cells (Lgr5+ cells) (81). BHB levels in crypt cells are vital for intestinal stem cell self-repair and differentiation, as BHB inhibits class I HDACs and enhances Notch signaling, thereby directing stem cell self-renewal and lineage determination (40). Ketogenic diets enhance stem cell function and regenerative capacity through BHB–mediated Notch signaling, while glucose-centric diets attenuate this effect. BHB produced in the intestine also regulates chromatin regulatory through Kbhb modification of the core histones H3 and H4. During fasting, the promoter and enhancer regions of major genes involved in metabolism show increased levels of H3K9bhb-H3K27ac, driven by BHB. Thus, ketone bodies in the small intestine are involved in the self-repair and differentiation of their own cells and in the regulation of metabolism.

Immune system

Ketone bodies are reported to influence various immune cells such as macrophages, neutrophils, and T cell (82-84). This mechanism involves the inhibition of NLRP3 activity. As described above, the HCAR2 receptor, including GPT109a, is modulated by BHB and related to anti-inflammatory actions. Ketone bodies have also been shown to enhance $CD8^+$ T cell activity (10). During fasting, these cells prefer ketone bodies over

glucose as an energy source, and BHB is a potent bioenergetic substrate for $CD8^+$T cells. Furthermore, ketone bodies not only serve as energy sources but also directly enhance the cytokine production and cytotoxic activity of $CD8^+$T effector cells (10).

Diabetes

In diabetes care, due to the negative impression caused by ketoacidosis, ketone bodies have long been considered harmful. However, recent research has led to a reevaluation of this perception. Because blood glucose is a primary energy source for the brain, severe hypoglycemia during diabetes treatment increases the risk of brain damage. Interestingly, ketone bodies play a crucial role in protecting the brain against severe hypoglycemia, with BHB enhancing brain cell autophagy and thus reducing cell degeneration in the setting of hypoglycemia (85). In this way, ketones can also play a beneficial role in diabetes management.

Furthermore, with the advent of SGLT2 inhibitors, the significance of ketone bodies is undergoing further reassessment. SGLT2 inhibitors increase blood ketone body levels, protecting organs like the heart and kidneys. Recent studies have elucidated the mechanism by which SGLT2 inhibitors induce ketone body production. Subjects with type 2 diabetes taking SGLT2 inhibitors who are injected with glucose show an increase in ketone body levels, lower serum insulin, and higher glucagon levels. However, pancreatic clamp conditions abolish these changes, while endogenous glucose levels continue to rise, suggesting that enhanced ketone body production by SGLT2 inhibitors is derived from the change in circulating insulin and glucagon levels. BHB in itself also improves insulin resistance through HCAR2 activation, with BHB inhibiting PPARγSer273 phosphorylation (86). Clinical trials also have documented improvements in glucose tolerance following the administration of ketone bodies (87). Furthermore, enzyme activities involved in ketone body oxidation are also implicated in glucose metabolism. Overexpression of ACAT2 in the liver suppresses glucose and ketone metabolism (88), and SCOT activity within muscles is also involved in the pathology of obesity-related diabetes (89).

Vascular system

In cardiovascular endothelial cells, ketone bodies are oxidized as an energy source, and this process has been shown to promote cell proliferation, migration, and sprouting of new blood vessels (90). The ketogenic diet transiently promotes the proliferation of vascular endothelial cells in the mouse heart, which may help protect the heart by preventing vascular scarcity (90).

BHB is also related to autophagy, whose activation is expected to preserve the vascular system (91-94). The previous report has shown that BHB is an autophagy-sensitive metabolite from the liver that can cause vasodilation via potassium channels, not via GPR109a (95). Of interest, a high-salt diet, which causes vascular damage and hypertension, is reported to suppress both BHB biosynthesis and liver autophagy, and BHB prevents the endothelial dysfunction induced by high-salt diet (95). These results indicate that the supplementation of ketone bodies may be a useful approach to treating hypertension.

Collectively, ketone bodies might have positive effects on the vascular system. Further studies are needed to clarify the role of ketone bodies in the vascular system.

Cancer

The impact of ketone bodies on cancer is highly complex. The role of ketone bodies in tumor reduction encompasses both their function as an energy source and their non-energy-related aspects. Furthermore, the role of ketone bodies in tumors varies greatly depending on tumor type, treatment modality, and how plasma ketone levels are increased.

1) Energy Metabolism in Tumor Cells

Tumor cells generally prefer anaerobic metabolism, primarily relying on the glycolytic pathway to derive energy from glucose (Warburg effect) and not typically utilizing ketone bodies as an energy source (96, 97). Indeed, many tumor cells do not express SCOT, the enzyme that mediates ketolysis. Thus, under conditions of calorie restriction or consumption of a low-carbohydrate diet, tumor cells would starve, which could potentially lead to tumor reduction (98). In fact, consumption of a ketogenic diet has been shown to be effective in the treatment of glioma, given that brain cells can utilize ketone bodies as an energy source (99). However, some tumor cells, such as hepatocellular carcinoma cells, exhibit upregulated SCOT expression during fasting (100). The production of ketone bodies by tumor cells themselves also presents a problem; for instance, HMGCS2 expression in colorectal cancer has been reported as a poor prognostic factor.

2) Ketone Bodies as Immunological Agents in Tumor Suppression

Ketogenic diet and treatment with BHB have been shown to delay tumor growth in mice in a T-cell–dependent manner (101). This effect has also been observed in melanomas and renal cell cancers that did not respond to anti-PD-1/anti-CTLA4

inhibitors (101). Immunological changes induced by variations in carbohydrate intake and ketone body production may be one cause, as these factors can alter the gut microbiota. Indeed, in colorectal cancer, ketone bodies have been shown to inhibit tumor growth via HCAR2. BHB activates HCAR2, which induces expression of the transcriptional regulator HOPX, which inhibits cell proliferation (102).

3) The Negative Aspects of Ketone Bodies as an Energy Source for Tumor Growth

Some reports indicate that ketone bodies may serve as an energy source that supports tumor growth and metastasis. Studies have shown that ketone body metabolism can be activated in pancreatic ductal adenocarcinoma, with BHB functioning as an energy source to promote tumor growth and progression (103). In other studies, exogenous administration of BHB has been shown to promote colorectal cancer proliferation and metastasis (104). Interestingly, metabolomic analysis of serum from patients with colorectal cancer showed increased levels of BHB, suggesting its role as a marker. Additionally, increased ACAT1 expression in human colorectal cancer cells has been linked to their increased proliferation(104). These findings indicate that exogenous administration of BHB does not have uniformly anti-tumor effects; rather, the effect varies depending on the type and state of the tumor, the presence or absence of chemotherapy, and more. Furthermore, anti-tumor effects do not necessarily correlate with extended lifespan; studies of mice fed a ketogenic diet show that, while tumor growth is delayed, cachexia onset is accelerated, shortening survival (105). These results highlight the need to evaluate the overall impact of the therapeutic use of ketone bodies, not solely the effect on tumors.

ROLE OF KETONE BODIES IN LONGEVITY

The contribution of ketone bodies to multiple organs, as described above, is closely associated with survival rates in some disease conditions. For instance, ketone bodies have been reported to extend lifespan by promoting recovery from myocardial and cerebral infarctions (53, 73), and by preventing malignant tumors (101). Furthermore, the improvement of insulin resistance (86), the prevention of kidney diseases (16), and the improvement of muscle function (74) may be indirectly related to longevity and healthy lifespan.

Furthermore, recent studies suggest that ketone bodies impact lifespan even in normal aging process, with intriguing findings suggesting that endogenous ketone body production promotes longevity. We previously reported that mice lacking HMGCS2 have a shortened lifespan, and that this can be prevented by regular intake of the ketone

body precursor 1,3-butanediol (106). Of note, early consumption of 1,3-butanediol increased mortality in non-elderly mice, while it extended the lifespan in elderly mice. Furthermore, treatment with ketone bodies increased the lifespan in a mouse model of atherosclerosis (106). These findings indicate that the impact of ketone supplementation on lifespan varies with the method of administration and health status. It has been reported that ketogenesis is not only essential for aging models but also critically important for the longevity of neonates. In neonates, ketogenesis preserves the mitochondria's ability to produce energy, preventing the over-acetylation of proteins within the mitochondria (107). Similarly, an isocaloric moderately high-fat diet (IHF) significantly extended the lifespan of mice. Consumption of the IHF decreases palmitic acid levels, which reduces oxidative stress and inflammation (108). These results suggest that ketone production and consumption of a high-fat diet have a complex impact on lifespan. It has been reported that administering a ketogenic diet to 12-month-old mice leads to improvements in muscle strength and endurance, tumor suppression, and enhanced survival rates. This suggests that ketone bodies are important not only for survival but also for extending the healthy lifespan (109). Further investigation of the relationships among ketone bodies, fatty acid metabolism, and lifespan may provide new insights into aging and promoting a healthy lifespan.

CONCLUSION

Despite a long-standing negative perception of ketone bodies that is rooted in their association with the life-threatening effects of ketoacidosis in patients with diabetes, a more positive picture of ketone body function is beginning to emerge in the field of anti-aging research, primarily centered around calorie restriction. Recent advances in ketone body research suggest that maintaining adequate ketone levels may promote tissue repair and organ protection. Hopefully, continuing research into ketone bodies will uncover their hidden potential to promote cell and tissue survival under starvation conditions. Ketone body research has the potential to extend healthy lifespans in an aging society.

ACKNOWLEDGEMENTS

This study was supported by the JSPS [21H03353 and 22H03128], and JST [Moonshot R&D; Grant Number JPMJMS2023]. We thank Emily Crow, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

REFERENCE

1. **Cahill GF**. Fuel metabolism in starvation. *Annu Rev Nutr* 26: 1-22, 2006.
2. **Ward Platt M, and Deshpande S**. Metabolic adaptation at birth. *Semin Fetal Neonatal Med* 10: 341-350, 2005.
3. **Hegardt FG**. Mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase: a control enzyme in ketogenesis. *Biochem J* 338 (Pt 3): 569-582, 1999.
4. **Bough KJ, Wetherington J, Hassel B, Pare JF, Gawryluk JW, Greene JG, Shaw R, Smith Y, Geiger JD, and Dingledine RJ**. Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. *Ann Neurol* 60: 223-235, 2006.
5. **Gambardella J, Jankauskas SS, Kansakar U, Varzideh F, Avvisato R, Prevete N, Sidoli S, Mone P, Wang X, Lombardi A, and Santulli G**. Ketone Bodies Rescue Mitochondrial Dysfunction Via Epigenetic Remodeling. *JACC Basic Transl Sci* 8: 1123-1137, 2023.
6. **Ji L, He Q, Liu Y, Deng Y, Xie M, Luo K, Cai X, Zuo Y, Wu W, Li Q, Zhou R, and Li T**. Ketone Body. *Oxid Med Cell Longev* 2022: 2513837, 2022.
7. **Jain SK, and McVie R**. Hyperketonemia can increase lipid peroxidation and lower glutathione levels in human erythrocytes in vitro and in type 1 diabetic patients. *Diabetes* 48: 1850-1855, 1999.
8. **Jain SK, Kannan K, Lim G, McVie R, and Bocchini JA**. Hyperketonemia increases tumor necrosis factor-alpha secretion in cultured U937 monocytes and Type 1 diabetic patients and is apparently mediated by oxidative stress and cAMP deficiency. *Diabetes* 51: 2287-2293, 2002.
9. **McPherson PA, and McEneny J**. The biochemistry of ketogenesis and its role in weight management, neurological disease and oxidative stress. *J Physiol Biochem* 68: 141-151, 2012.
10. **Luda KM, Longo J, Kitchen-Goosen SM, Duimstra LR, Ma EH, Watson MJ, Oswald BM, Fu Z, Madaj Z, Kupai A, Dickson BM, DeCamp LM, Dahabieh MS, Compton SE, Teis R, Kaymak I, Lau KH, Kelly DP, Puchalska P, Williams KS, Krawczyk CM, Lévesque D, Boisvert FM, Sheldon RD, Rothbart SB, Crawford PA, and Jones RG**. Ketolysis drives CD8. *Immunity* 56: 2021-2035.e2028, 2023.
11. **Kimura I, Inoue D, Maeda T, Hara T, Ichimura A, Miyauchi S, Kobayashi M, Hirasawa A, and Tsujimoto G**. Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). *Proc Natl Acad Sci U S A* 108: 8030-8035, 2011.
12. **Puchalska P, and Crawford PA**. Multi-dimensional Roles of Ketone Bodies in Fuel Metabolism, Signaling, and Therapeutics. *Cell Metab* 25: 262-284, 2017.
13. **Misra S, and Oliver NS**. Diabetic ketoacidosis in adults. *BMJ* 351: h5660, 2015.
14. **Takagi A, Kume S, Kondo M, Nakazawa J, Chin-Kanasaki M, Araki H, Araki S, Koya D, Haneda M, Chano T, Matsusaka T, Nagao K, Adachi Y, Chan L, Maegawa H, and Uzu T**.

Mammalian autophagy is essential for hepatic and renal ketogenesis during starvation. *Sci Rep* 6: 18944, 2016.

15. **Takagi A, Kume S, Maegawa H, and Uzu T**. Emerging role of mammalian autophagy in ketogenesis to overcome starvation. *Autophagy* 12: 709-710, 2016.
16. **Tomita I, Kume S, Sugahara S, Osawa N, Yamahara K, Yasuda-Yamahara M, Takeda N, Chin-Kanasaki M, Kaneko T, Mayoux E, Mark M, Yanagita M, Ogita H, Araki SI, and Maegawa H**. SGLT2 Inhibition Mediates Protection from Diabetic Kidney Disease by Promoting Ketone Body-Induced mTORC1 Inhibition. *Cell Metab* 32: 404-419.e406, 2020.
17. **Huttenlocher PR**. Ketonemia and seizures: metabolic and anticonvulsant effects of two ketogenic diets in childhood epilepsy. *Pediatr Res* 10: 536-540, 1976.
18. **Abbasi J**. Ketone Body Supplementation-A Potential New Approach for Heart Disease. *JAMA* 2021.
19. **Matsuura TR, Puchalska P, Crawford PA, and Kelly DP**. Ketones and the Heart: Metabolic Principles and Therapeutic Implications. *Circ Res* 132: 882-898, 2023.
20. **Venable AH, Lee LE, Feola K, Santoyo J, Broomfield T, and Huen SC**. Fasting-induced HMGCS2 expression in the kidney does not contribute to circulating ketones. *Am J Physiol Renal Physiol* 322: F460-F467, 2022.
21. **Musso G, Saba F, Cassader M, and Gambino R**. Diabetic ketoacidosis with SGLT2 inhibitors. *BMJ* 371: m4147, 2020.
22. **Fukao T, Song XQ, Mitchell GA, Yamaguchi S, Sukegawa K, Orii T, and Kondo N**. Enzymes of ketone body utilization in human tissues: protein and messenger RNA levels of succinyl-coenzyme A (CoA):3-ketoacid CoA transferase and mitochondrial and cytosolic acetoacetyl-CoA thiolases. *Pediatr Res* 42: 498-502, 1997.
23. **Pellerin L, and Magistretti PJ**. Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. *Proc Natl Acad Sci U S A* 91: 10625-10629, 1994.
24. **Silva B, Mantha OL, Schor J, Pascual A, Plaçais PY, Pavlowsky A, and Preat T**. Glia fuel neurons with locally synthesized ketone bodies to sustain memory under starvation. *Nat Metab* 4: 213-224, 2022.
25. **Walsh JJ, Caldwell HG, Neudorf H, Ainslie PN, and Little JP**. Short-term ketone monoester supplementation improves cerebral blood flow and cognition in obesity: A randomized cross-over trial. *J Physiol* 599: 4763-4778, 2021.
26. **McMullen E, Hertenstein H, Strassburger K, Deharde L, Brankatschk M, and Schirmeier S**. Glycolytically impaired Drosophila glial cells fuel neural metabolism via β-oxidation. *Nat Commun* 14: 2996, 2023.
27. **Aubert G, Martin OJ, Horton JL, Lai L, Vega RB, Leone TC, Koves T, Gardell SJ, Krüger M, Hoppel CL, Lewandowski ED, Crawford PA, Muoio DM, and Kelly DP**. The Failing Heart Relies

on Ketone Bodies as a Fuel. *Circulation* 133: 698-705, 2016.

28. **Doenst T, Nguyen TD, and Abel ED**. Cardiac metabolism in heart failure: implications beyond ATP production. *Circ Res* 113: 709-724, 2013.
29. **Uchihashi M, Hoshino A, Okawa Y, Ariyoshi M, Kaimoto S, Tateishi S, Ono K, Yamanaka R, Hato D, Fushimura Y, Honda S, Fukai K, Higuchi Y, Ogata T, Iwai-Kanai E, and Matoba S**. Cardiac-Specific Bdh1 Overexpression Ameliorates Oxidative Stress and Cardiac Remodeling in Pressure Overload-Induced Heart Failure. *Circ Heart Fail* 10: 2017.
30. **Shemesh E, Chevli PA, Islam T, German CA, Otvos J, Yeboah J, Rodriguez F, deFilippi C, Lima JAC, Blaha M, Pandey A, Vaduganathan M, and Shapiro MD**. Circulating ketone bodies and cardiovascular outcomes: the MESA study. *Eur Heart J* 44: 1636-1646, 2023.
31. **Katz A, Sahlin K, and Broberg S**. Regulation of glucose utilization in human skeletal muscle during moderate dynamic exercise. *Am J Physiol* 260: E411-415, 1991.
32. **Féry F, and Balasse EO**. Response of ketone body metabolism to exercise during transition from postabsorptive to fasted state. *Am J Physiol* 250: E495-501, 1986.
33. **Féry F, and Balasse EO**. Effect of exercise on the disposal of infused ketone bodies in humans. *J Clin Endocrinol Metab* 67: 245-250, 1988.
34. **Winder WW, Baldwin KM, and Holloszy JO**. Exercise-induced increase in the capacity of rat skeletal muscle to oxidize ketones. *Can J Physiol Pharmacol* 53: 86-91, 1975.
35. **Palmer BF, and Clegg DJ**. Starvation Ketosis and the Kidney. *Am J Nephrol* 52: 467-478, 2021.
36. **Sapir DG, and Owen OE**. Renal conservation of ketone bodies during starvation. *Metabolism* 24: 23-33, 1975.
37. **Shimazu T, Hirschey MD, Newman J, He W, Shirakawa K, Le Moan N, Grueter CA, Lim H, Saunders LR, Stevens RD, Newgard CB, Farese RV, de Cabo R, Ulrich S, Akassoglou K, and Verdin E**. Suppression of oxidative stress by β-hydroxybutyrate, an endogenous histone deacetylase inhibitor. *Science* 339: 211-214, 2013.
38. **Xie Z, Zhang D, Chung D, Tang Z, Huang H, Dai L, Qi S, Li J, Colak G, Chen Y, Xia C, Peng C, Ruan H, Kirkey M, Wang D, Jensen LM, Kwon OK, Lee S, Pletcher SD, Tan M, Lombard DB, White KP, Zhao H, Roeder RG, Yang X, and Zhao Y**. Metabolic Regulation of Gene Expression by Histone Lysine β-Hydroxybutyrylation. *Mol Cell* 62: 194-206, 2016.
39. **Sabari BR, Zhang D, Allis CD, and Zhao Y**. Metabolic regulation of gene expression through histone acylations. *Nat Rev Mol Cell Biol* 18: 90-101, 2017.
40. **Terranova CJ, Stemler KM, Barrodia P, Jeter-Jones SL, Ge Z, de la Cruz Bonilla M, Raman A, Cheng CW, Allton KL, Arslan E, Yilmaz Ö, Barton MC, Rai K, and Piwnica-Worms H**. Reprogramming of H3K9bhb at regulatory elements is a key feature of fasting in the small intestine. *Cell Rep* 37: 110044, 2021.
41. **Luo W, He M, Luo Q, and Li Y**. Proteome-wide analysis of lysine β-hydroxybutyrylation in the

myocardium of diabetic rat model with cardiomyopathy. *Front Cardiovasc Med* 9: 1066822, 2022.

42. **Liu K, Li F, Sun Q, Lin N, Han H, You K, Tian F, Mao Z, Li T, Tong T, Geng M, Zhao Y, Gu W, and Zhao W**. p53 β-hydroxybutyrylation attenuates p53 activity. *Cell Death Dis* 10: 243, 2019.
43. **Feingold KR, Moser A, Shigenaga JK, and Grunfeld C**. Inflammation stimulates niacin receptor (GPR109A/HCA2) expression in adipose tissue and macrophages. *J Lipid Res* 55: 2501-2508, 2014.
44. **Lee AK, Kim DH, Bang E, Choi YJ, and Chung HY**. β-Hydroxybutyrate Suppresses Lipid Accumulation in Aged Liver through GPR109A-mediated Signaling. *Aging Dis* 11: 777-790, 2020.
45. **Benyó Z, Gille A, Kero J, Csiky M, Suchánková MC, Nüsing RM, Moers A, Pfeffer K, and Offermanns S**. GPR109A (PUMA-G/HM74A) mediates nicotinic acid-induced flushing. *J Clin Invest* 115: 3634-3640, 2005.
46. **Jadeja RN, Jones MA, Fromal O, Powell FL, Khurana S, Singh N, and Martin PM**. Loss of GPR109A/HCAR2 induces aging-associated hepatic steatosis. *Aging (Albany NY)* 11: 386-400, 2019.
47. **Singh N, Gurav A, Sivaprakasam S, Brady E, Padia R, Shi H, Thangaraju M, Prasad PD, Manicassamy S, Munn DH, Lee JR, Offermanns S, and Ganapathy V**. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. *Immunity* 40: 128-139, 2014.
48. **Sivaprakasam S, Prasad PD, and Singh N**. Benefits of short-chain fatty acids and their receptors in inflammation and carcinogenesis. *Pharmacol Ther* 164: 144-151, 2016.
49. **Li YJ, Chen X, Kwan TK, Loh YW, Singer J, Liu Y, Ma J, Tan J, Macia L, Mackay CR, Chadban SJ, and Wu H**. Dietary Fiber Protects against Diabetic Nephropathy through Short-Chain Fatty Acid-Mediated Activation of G Protein-Coupled Receptors GPR43 and GPR109A. *J Am Soc Nephrol* 31: 1267-1281, 2020.
50. **Zandi-Nejad K, Takakura A, Jurewicz M, Chandraker AK, Offermanns S, Mount D, and Abdi R**. The role of HCA2 (GPR109A) in regulating macrophage function. *FASEB J* 27: 4366-4374, 2013.
51. **Thangaraju M, Cresci GA, Liu K, Ananth S, Gnanaprakasam JP, Browning DD, Mellinger JD, Smith SB, Digby GJ, Lambert NA, Prasad PD, and Ganapathy V**. GPR109A is a G-protein-coupled receptor for the bacterial fermentation product butyrate and functions as a tumor suppressor in colon. *Cancer Res* 69: 2826-2832, 2009.
52. **Macia L, Tan J, Vieira AT, Leach K, Stanley D, Luong S, Maruya M, Ian McKenzie C, Hijikata A, Wong C, Binge L, Thorburn AN, Chevalier N, Ang C, Marino E, Robert R, Offermanns S, Teixeira MM, Moore RJ, Flavell RA, Fagarasan S, and Mackay CR**. Metabolite-sensing receptors GPR43 and GPR109A facilitate dietary fibre-induced gut homeostasis through regulation of the inflammasome. *Nat Commun* 6: 6734, 2015.
53. **Lindsay RT, Dieckmann S, Krzyzanska D, Manetta-Jones D, West JA, Castro C, Griffin JL, and Murray AJ**. β-hydroxybutyrate accumulates in the rat heart during low-flow ischaemia with implications for functional recovery. *Elife* 10: 2021.

54. **Hahn VS, Petucci C, Kim MS, Bedi KC, Wang H, Mishra S, Koleini N, Yoo EJ, Margulies KB, Arany Z, Kelly DP, Kass DA, and Sharma K**. Myocardial Metabolomics of Human Heart Failure With Preserved Ejection Fraction. *Circulation* 147: 1147-1161, 2023.
55. **Thai PN, Miller CV, King MT, Schaefer S, Veech RL, Chiamvimonvat N, Bers DM, and Dedkova EN**. Ketone Ester D-β-Hydroxybutyrate-(R)-1,3 Butanediol Prevents Decline in Cardiac Function in Type 2 Diabetic Mice. *J Am Heart Assoc* 10: e020729, 2021.
56. **Santos-Gallego CG, Requena-Ibáñez JA, Picatoste B, Fardman B, Ishikawa K, Mazurek R, Pieper M, Sartori S, Rodriguez-Capitán J, Fuster V, and Badimon JJ**. Cardioprotective Effect of Empagliflozin and Circulating Ketone Bodies During Acute Myocardial Infarction. *Circ Cardiovasc Imaging* 16: e015298, 2023.
57. **Hundertmark MJ, Adler A, Antoniades C, Coleman R, Griffin JL, Holman RR, Lamlum H, Lee J, Massey D, Miller JJJJ, Milton JE, Monga S, Mózes FE, Nazeer A, Raman B, Rider O, Rodgers CT, Valkovič L, Wicks E, Mahmod M, and Neubauer S**. Assessment of Cardiac Energy Metabolism, Function, and Physiology in Patients With Heart Failure Taking Empagliflozin: The Randomized, Controlled EMPA-VISION Trial. *Circulation* 147: 1654-1669, 2023.
58. **Pietschner R, Kolwelter J, Bosch A, Striepe K, Jung S, Kannenkeril D, Ott C, Schiffer M, Achenbach S, and Schmieder RE**. Effect of empagliflozin on ketone bodies in patients with stable chronic heart failure. *Cardiovasc Diabetol* 20: 219, 2021.
59. **Vallon V, and Verma S**. Effects of SGLT2 Inhibitors on Kidney and Cardiovascular Function. *Annu Rev Physiol* 83: 503-528, 2021.
60. **Kim MN, Moon JH, and Cho YM**. Sodium-glucose cotransporter-2 inhibition reduces cellular senescence in the diabetic kidney by promoting ketone body-induced NRF2 activation. *Diabetes Obes Metab* 23: 2561-2571, 2021.
61. **Huber TB, Walz G, and Kuehn EW**. mTOR and rapamycin in the kidney: signaling and therapeutic implications beyond immunosuppression. *Kidney Int* 79: 502-511, 2011.
62. **Oehm S, Steinke K, Schmidt J, Arjune S, Todorova P, Heinrich Lindemann C, Wöstmann F, Meyer F, Siedek F, Weimbs T, Müller RU, and Grundmann F**. RESET-PKD: a pilot trial on short-term ketogenic interventions in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant* 38: 1623-1635, 2023.
63. **Torres JA, Kruger SL, Broderick C, Amarlkhagva T, Agrawal S, Dodam JR, Mrug M, Lyons LA, and Weimbs T**. Ketosis Ameliorates Renal Cyst Growth in Polycystic Kidney Disease. *Cell Metab* 30: 1007-1023.e1005, 2019.
64. **Knol MGE, Bais T, Geertsema P, Connelly MA, Bakker SJL, Gansevoort RT, van Gastel MDA, Drenth JPH, Peters DJM, Salih M, de Fijter JW, Nijenhuis T, Hoorn EJ, and Meijer E**. Higher beta-hydroxybutyrate ketone levels associated with a slower kidney function decline in ADPKD. *Nephrol Dial Transplant* 2023.

65. **Kume S, Uzu T, Horiike K, Chin-Kanasaki M, Isshiki K, Araki S, Sugimoto T, Haneda M, Kashiwagi A, and Koya D**. Calorie restriction enhances cell adaptation to hypoxia through Sirt1-dependent mitochondrial autophagy in mouse aged kidney. *J Clin Invest* 120: 1043-1055, 2010.
66. **Fang Y, Chen B, Gong AY, Malhotra DK, Gupta R, Dworkin LD, and Gong R**. The ketone body β-hydroxybutyrate mitigates the senescence response of glomerular podocytes to diabetic insults. *Kidney Int* 100: 1037-1053, 2021.
67. **Guo Z, Zhong F, Hou M, Xie J, Zhang AZ, Li X, Li Y, Chang B, and Yang J**. Key enzyme in charge of ketone reabsorption of renal tubular SMCT1 may be a new target in diabetic kidney disease. *Nephrol Dial Transplant* 2023.
68. **Broom GM, Shaw IC, and Rucklidge JJ**. The ketogenic diet as a potential treatment and prevention strategy for Alzheimer's disease. *Nutrition* 60: 118-121, 2019.
69. **Pinto A, Bonucci A, Maggi E, Corsi M, and Businaro R**. Anti-Oxidant and Anti-Inflammatory Activity of Ketogenic Diet: New Perspectives for Neuroprotection in Alzheimer's Disease. *Antioxidants (Basel)* 7: 2018.
70. **Fernando WM, Martins IJ, Goozee KG, Brennan CS, Jayasena V, and Martins RN**. The role of dietary coconut for the prevention and treatment of Alzheimer's disease: potential mechanisms of action. *Br J Nutr* 114: 1-14, 2015.
71. **Lennerz BS, Koutnik AP, Azova S, Wolfsdorf JI, and Ludwig DS**. Carbohydrate restriction for diabetes: rediscovering centuries-old wisdom. *J Clin Invest* 131: 2021.
72. **Bai L, Zhou Y, Zhang J, and Ma J**. The Role of a Ketogenic Diet in the Treatment of Dementia in Type 2 Diabetes Mellitus. *Nutrients* 15: 2023.
73. **Lin YH, Yang D, Ni HY, Xu XM, Wu F, Lin L, Chen J, Sun YY, Huang ZQ, Li SY, Jiang PL, Wu HY, Chang L, Hu B, Luo CX, Wu J, and Zhu DY**. Ketone bodies promote stroke recovery via GAT-1-dependent cortical network remodeling. *Cell Rep* 42: 112294, 2023.
74. **Yakupova EI, Bocharnikov AD, and Plotnikov EY**. Effects of Ketogenic Diet on Muscle Metabolism in Health and Disease. *Nutrients* 14: 2022.
75. **Benjamin DI, Both P, Benjamin JS, Nutter CW, Tan JH, Kang J, Machado LA, Klein JDD, de Morree A, Kim S, Liu L, Dulay H, Feraboli L, Louie SM, Nomura DK, and Rando TA**. Fasting induces a highly resilient deep quiescent state in muscle stem cells via ketone body signaling. *Cell Metab* 34: 902-918.e906, 2022.
76. **Nakao R, Abe T, Yamamoto S, and Oishi K**. Ketogenic diet induces skeletal muscle atrophy via reducing muscle protein synthesis and possibly activating proteolysis in mice. *Sci Rep* 9: 19652, 2019.
77. **Li Y, Yang Z, Wang Y, Fan M, Nie C, Xue L, Wang L, and Qian H**. Low-Carbohydrate Diet Modulates Glucose-Lipid Utilization in Skeletal Muscle of Diabetic Mice. *Nutrients* 15: 2023.
78. **Ang QY, Alexander M, Newman JC, Tian Y, Cai J, Upadhyay V, Turnbaugh JA, Verdin E, Hall KD, Leibel RL, Ravussin E, Rosenbaum M, Patterson AD, and Turnbaugh PJ**. Ketogenic Diets

Alter the Gut Microbiome Resulting in Decreased Intestinal Th17 Cells. *Cell* 181: 1263-1275.e1216, 2020.

79. **Huang C, Wang J, Liu H, Huang R, Yan X, Song M, Tan G, and Zhi F**. Ketone body β-hydroxybutyrate ameliorates colitis by promoting M2 macrophage polarization through the STAT6-dependent signaling pathway. *BMC Medicine* 20: 2022.
80. **Wang Q, Zhou Y, Rychahou P, Fan TW-M, Lane AN, Weiss HL, and Evers BM**. Ketogenesis contributes to intestinal cell differentiation. *Cell Death & Differentiation* 24: 458-468, 2017.
81. **Cheng CW, Biton M, Haber AL, Gunduz N, Eng G, Gaynor LT, Tripathi S, Calibasi-Kocal G, Rickelt S, Butty VL, Moreno-Serrano M, Iqbal AM, Bauer-Rowe KE, Imada S, Ulutas MS, Mylonas C, Whary MT, Levine SS, Basbinar Y, Hynes RO, Mino-Kenudson M, Deshpande V, Boyer LA, Fox JG, Terranova C, Rai K, Piwnica-Worms H, Mihaylova MM, Regev A, and Yilmaz Ö**. Ketone Body Signaling Mediates Intestinal Stem Cell Homeostasis and Adaptation to Diet. *Cell* 178: 1115-1131.e1115, 2019.
82. **Puchalska P, Martin SE, Huang X, Lengfeld JE, Daniel B, Graham MJ, Han X, Nagy L, Patti GJ, and Crawford PA**. Hepatocyte-Macrophage Acetoacetate Shuttle Protects against Tissue Fibrosis. *Cell Metab* 29: 383-398.e387, 2019.
83. **Goldberg EL, Asher JL, Molony RD, Shaw AC, Zeiss CJ, Wang C, Morozova-Roche LA, Herzog RI, Iwasaki A, and Dixit VD**. β-Hydroxybutyrate Deactivates Neutrophil NLRP3 Inflammasome to Relieve Gout Flares. *Cell Rep* 18: 2077-2087, 2017.
84. **Youm YH, Nguyen KY, Grant RW, Goldberg EL, Bodogai M, Kim D, D'Agostino D, Planavsky N, Lupfer C, Kanneganti TD, Kang S, Horvath TL, Fahmy TM, Crawford PA, Biragyn A, Alnemri E, and Dixit VD**. The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. *Nat Med* 21: 263-269, 2015.
85. **Torres-Esquivel C, Montiel T, Flores-Méndez M, and Massieu L**. Effect of β-Hydroxybutyrate on Autophagy Dynamics During Severe Hypoglycemia and the Hypoglycemic Coma. *Front Cell Neurosci* 14: 547215, 2020.
86. **Zhang Y, Li Z, Liu X, Chen X, Zhang S, Chen Y, Chen J, Wu F, and Chen GQ**. 3-Hydroxybutyrate ameliorates insulin resistance by inhibiting PPARγ Ser273 phosphorylation in type 2 diabetic mice. *Signal Transduct Target Ther* 8: 190, 2023.
87. **Nakagata T, Tamura Y, Kaga H, Sato M, Yamasaki N, Someya Y, Kadowaki S, Sugimoto D, Satoh H, Kawamori R, and Watada H**. Ingestion of an exogenous ketone monoester improves the glycemic response during oral glucose tolerance test in individuals with impaired glucose tolerance: A cross-over randomized trial. *J Diabetes Investig* 12: 756-762, 2021.
88. **Ma Z, Huang Z, Zhang C, Liu X, Zhang J, Shu H, Ma Y, Liu Z, Feng Y, Chen X, Kuang S, Zhang Y, and Jia Z**. Hepatic Acat2 overexpression promotes systemic cholesterol metabolism and adipose lipid metabolism in mice. *Diabetologia* 66: 390-405, 2023.

89. **Al Batran R, Gopal K, Capozzi ME, Chahade JJ, Saleme B, Tabatabaei-Dakhili SA, Greenwell AA, Niu J, Almutairi M, Byrne NJ, Masson G, Kim R, Eaton F, Mulvihill EE, Garneau L, Masters AR, Desta Z, Velázquez-Martínez CA, Aguer C, Crawford PA, Sutendra G, Campbell JE, Dyck JRB, and Ussher JR**. Pimozide Alleviates Hyperglycemia in Diet-Induced Obesity by Inhibiting Skeletal Muscle Ketone Oxidation. *Cell Metab* 31: 909-919.e908, 2020.
90. **Weis EM, Puchalska P, Nelson AB, Taylor J, Moll I, Hasan SS, Dewenter M, Hagenmüller M, Fleming T, Poschet G, Hotz-Wagenblatt A, Backs J, Crawford PA, and Fischer A**. Ketone body oxidation increases cardiac endothelial cell proliferation. *EMBO Mol Med* 14: e14753, 2022.
91. **Nussenzweig SC, Verma S, and Finkel T**. The role of autophagy in vascular biology. *Circ Res* 116: 480-488, 2015.
92. **Abdellatif M, Sedej S, Carmona-Gutierrez D, Madeo F, and Kroemer G**. Autophagy in Cardiovascular Aging. *Circ Res* 123: 803-824, 2018.
93. **Hughes WE, Beyer AM, and Gutterman DD**. Vascular autophagy in health and disease. *Basic Res Cardiol* 115: 41, 2020.
94. **Abdellatif M, Ljubojevic-Holzer S, Madeo F, and Sedej S**. Autophagy in cardiovascular health and disease. *Prog Mol Biol Transl Sci* 172: 87-106, 2020.
95. **McCarthy CG, Chakraborty S, Singh G, Yeoh BS, Schreckenberger ZJ, Singh A, Mell B, Bearss NR, Yang T, Cheng X, Vijay-Kumar M, Wenceslau CF, and Joe B**. Ketone body β-hydroxybutyrate is an autophagy-dependent vasodilator. *JCI Insight* 6: 2021.
96. **Vander Heiden MG, Cantley LC, and Thompson CB**. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 324: 1029-1033, 2009.
97. **Elisia I, and Krystal G**. The Pros and Cons of Low Carbohydrate and Ketogenic Diets in the Prevention and Treatment of Cancer. *Front Nutr* 8: 634845, 2021.
98. **Woolf EC, Syed N, and Scheck AC**. Tumor Metabolism, the Ketogenic Diet and β-Hydroxybutyrate: Novel Approaches to Adjuvant Brain Tumor Therapy. *Front Mol Neurosci* 9: 122, 2016.
99. **Woolf EC, and Scheck AC**. The ketogenic diet for the treatment of malignant glioma. *J Lipid Res* 56: 5-10, 2015.
100. **Huang D, Li T, Wang L, Zhang L, Yan R, Li K, Xing S, Wu G, Hu L, Jia W, Lin SC, Dang CV, Song L, Gao P, and Zhang H**. Hepatocellular carcinoma redirects to ketolysis for progression under nutrition deprivation stress. *Cell Res* 26: 1112-1130, 2016.
101. **Ferrere G, Tidjani Alou M, Liu P, Goubet AG, Fidelle M, Kepp O, Durand S, Iebba V, Fluckiger A, Daillère R, Thelemaque C, Grajeda-Iglesias C, Alves Costa Silva C, Aprahamian F, Lefevre D, Zhao L, Ryffel B, Colomba E, Arnedos M, Drubay D, Rauber C, Raoult D, Asnicar F, Spector T, Segata N, Derosa L, Kroemer G, and Zitvogel L**. Ketogenic diet and ketone bodies enhance the anticancer effects of PD-1 blockade. *JCI Insight* 6: 2021.
102. **Zhao H, Jin H, Xian J, Zhang Z, Shi J, and Bai X**. Effect of Ketogenic Diets on Body

Composition and Metabolic Parameters of Cancer Patients: A Systematic Review and Meta-Analysis. *Nutrients* 14: 4192, 2022.

103. **Gouirand V, Gicquel T, Lien EC, Jaune-Pons E, Da Costa Q, Finetti P, Metay E, Duluc C, Mayers JR, Audebert S, Camoin L, Borge L, Rubis M, Leca J, Nigri J, Bertucci F, Dusetti N, Iovanna JL, Tomasini R, Bidaut G, Guillaumond F, Vander Heiden MG, and Vasseur S**. Ketogenic HMG-CoA lyase and its product β-hydroxybutyrate promote pancreatic cancer progression. *EMBO J* 41: e110466, 2022.
104. **Mao T, Qin F, Zhang M, Li J, and Lai M**. Elevated serum β-hydroxybutyrate, a circulating ketone metabolite, accelerates colorectal cancer proliferation and metastasis via ACAT1. *Oncogene* 42: 1889-1899, 2023.
105. **Ferrer M, Mourikis N, Davidson EE, Kleeman SO, Zaccaria M, Habel J, Rubino R, Gao Q, Flint TR, Young L, Connell CM, Lukey MJ, Goncalves MD, White EP, Venkitaraman AR, and Janowitz T**. Ketogenic diet promotes tumor ferroptosis but induces relative corticosterone deficiency that accelerates cachexia. *Cell Metab* 35: 1147-1162.e1147, 2023.
106. **Tomita I, Tsuruta H, Yasuda-Yamahara M, Yamahara K, Kuwagata S, Tanaka-Sasaki Y, Chin-Kanasaki M, Fujita Y, Nishi E, Katagiri H, Maegawa H, and Kume S**. Ketone bodies: A double-edged sword for mammalian life span. *Aging Cell* 22: e13833, 2023.
107. **Arima Y, Nakagawa Y, Takeo T, Ishida T, Yamada T, Hino S, Nakao M, Hanada S, Umemoto T, Suda T, Sakuma T, Yamamoto T, Watanabe T, Nagaoka K, Tanaka Y, Kawamura YK, Tonami K, Kurihara H, Sato Y, Yamagata K, Nakamura T, Araki S, Yamamoto E, Izumiya Y, Sakamoto K, Kaikita K, Matsushita K, Nishiyama K, Nakagata N, and Tsujita K**. Murine neonatal ketogenesis preserves mitochondrial energetics by preventing protein hyperacetylation. *Nat Metab* 3: 196-210, 2021.
108. **Shi D, Han T, Chu X, Lu H, Yang X, Zi T, Zhao Y, Wang X, Liu Z, Ruan J, Liu X, Ning H, Wang M, Tian Z, Wei W, Sun Y, Li Y, Guo R, Wang Y, Ling F, Guan Y, Shen D, Niu Y, and Sun C**. An isocaloric moderately high-fat diet extends lifespan in male rats and Drosophila. *Cell Metab* 33: 581-597.e589, 2021.
109. **Roberts MN, Wallace MA, Tomilov AA, Zhou Z, Marcotte GR, Tran D, Perez G, Gutierrez-Casado E, Koike S, Knotts TA, Imai DM, Griffey SM, Kim K, Hagopian K, McMackin MZ, Haj FG, Baar K, Cortopassi GA, Ramsey JJ, and Lopez-Dominguez JA**. A Ketogenic Diet Extends Longevity and Healthspan in Adult Mice. *Cell Metab* 26: 539-546.e535, 2017.

Figure.1

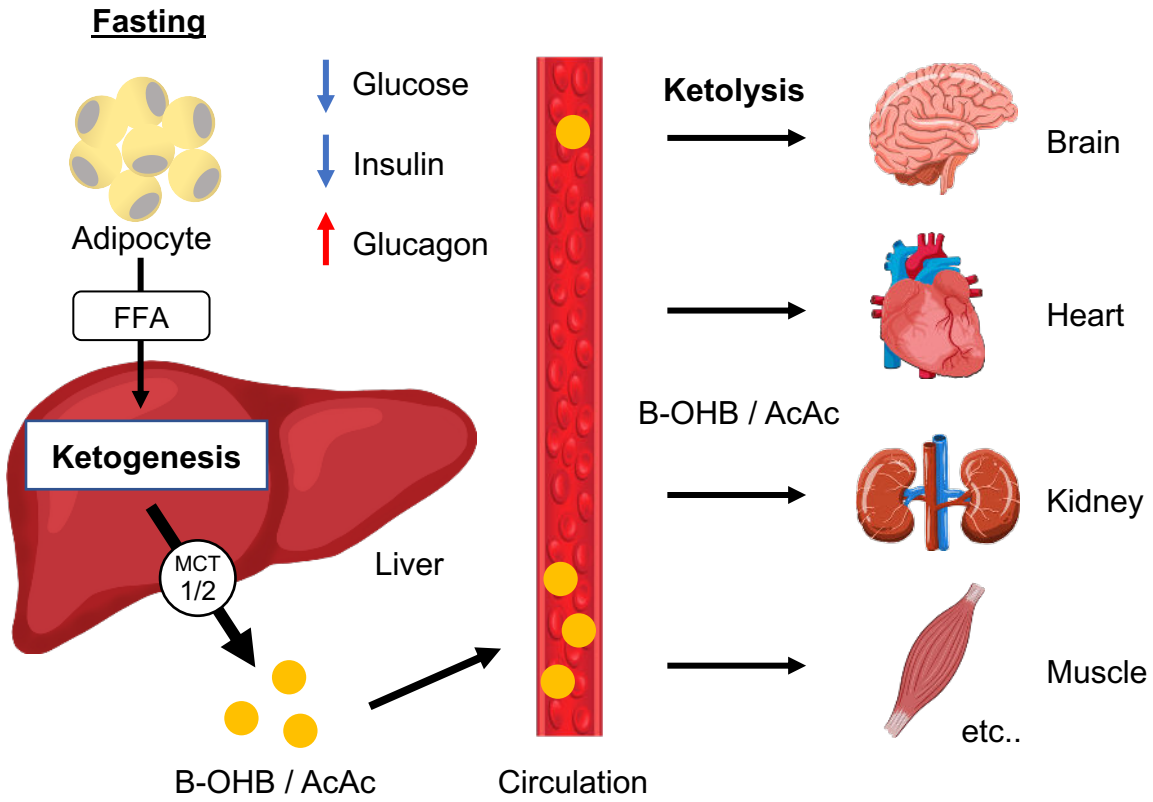

Figure.1 Ketone Body Production and Utilization During Fasting
During fasting, FFA released from adipocytes undergo ketogenesis in the liver, producing B-OHB/AcAc. B-OHB/AcAc are transported into circulation via MCT1/2 and utilized through ketolysis as an energy source in various organs including the brain, heart, kidneys, and muscles. AcAc: acetoacetate, B-OHB: beta-Hydroxybutyrate, FFA: free fatty acids.

Figure.2

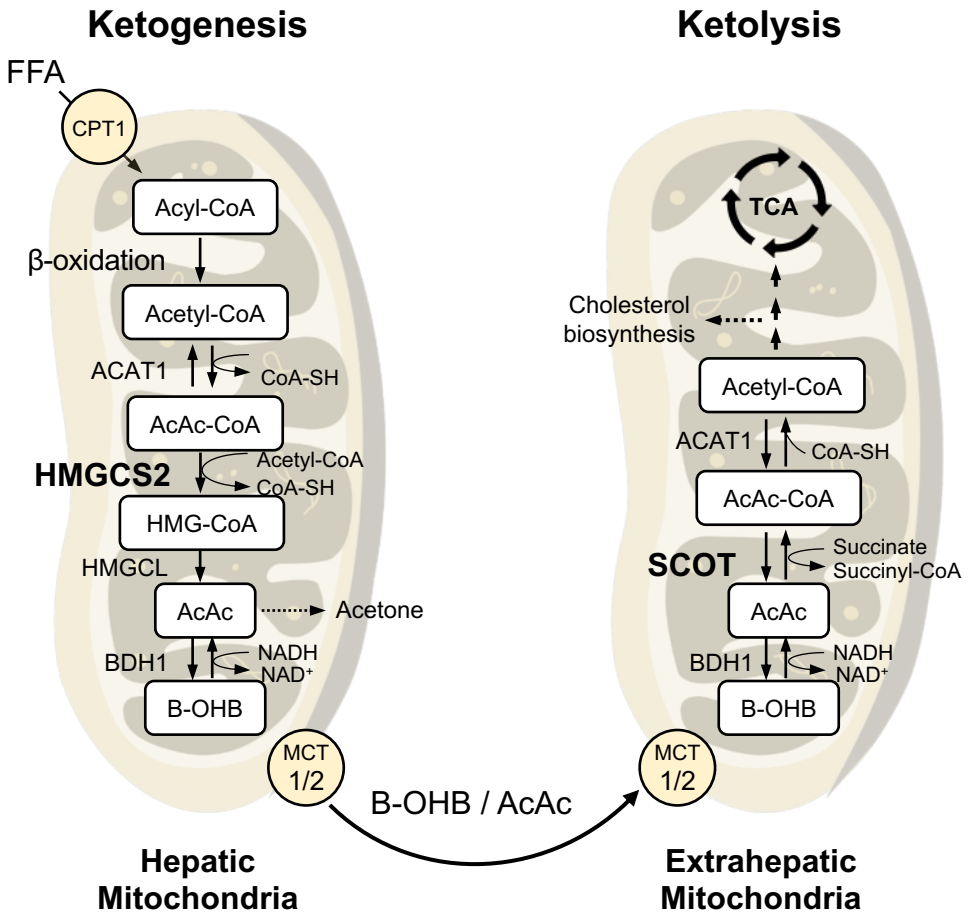

Figure.2 Metabolic Pathway of Ketogenesis and Ketolysis
During fasting, FFA from adipocytes are taken to liver mitochondria by carnitine palmitoyltransferase 1. Here, β-oxidation produces acetyl-CoA, which, through acetyl-CoA acetyltransferase 1 and HMGCS2, forms HMG-CoA. HMG-CoA is split into AcAc and acetyl-CoA by HMGCL, and AcAc is largely reduced to B-OHB by BDH1, which also regulates NAD+/NADH. The liver releases B-OHB and AcAc into circulation via MCT1/2. Circulating B-OHB and AcAc are used by extrahepatic mitochondria for energy. It's transported from blood by MCT1/2 to the mitochondria, converted to acetyl-CoA, and enters the TCA cycle. B-OHB is oxidized to AcAc, then transformed to AcAc-CoA by SCOT, and finally to acetyl-CoA, fueling ATP.
AcAc: acetoacetate, ACAT1: acetyl-CoA acetyltransferase 1, BDH1: B-OHB dehydrogenase, B-OHB: beta-Hydroxybutyrate, FFA: free fatty acids, HMGCL: 3-Hydroxymethyl-3-Methylglutaryl-CoA Lyase, HMGCS2: 3-hydroxy-3-methylglutaryl-CoA synthase 2, SCOT: succinyl-CoA:3-oxoacid CoA transferase.

Figure.3

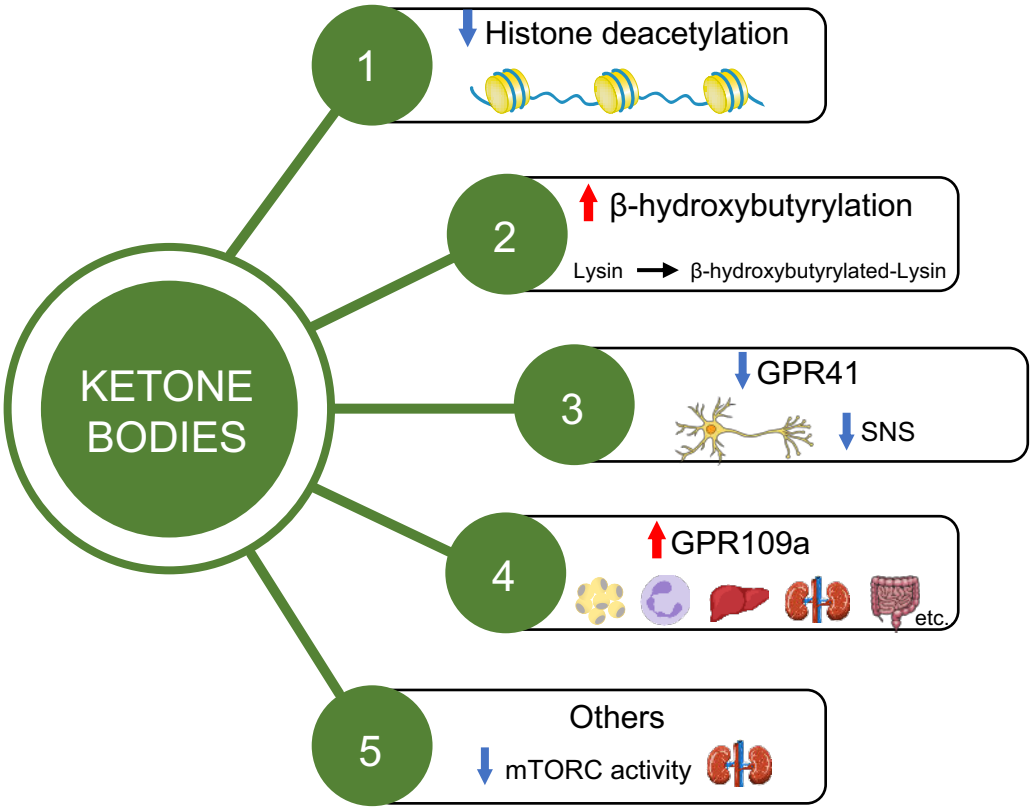

Figure.3 Physiological Roles of Ketone Bodies Beyond Alternative Energy Source
Apart from serving as an energy substrate, ketone bodies are involved in epigenetic responses, regulation of GPR activities, and modulation of various signaling pathways. GPR: G-protein–coupled receptors, mTORC: mammalian target of rapamycin complex. SNS: sympathetic nervous system.

Figure.4

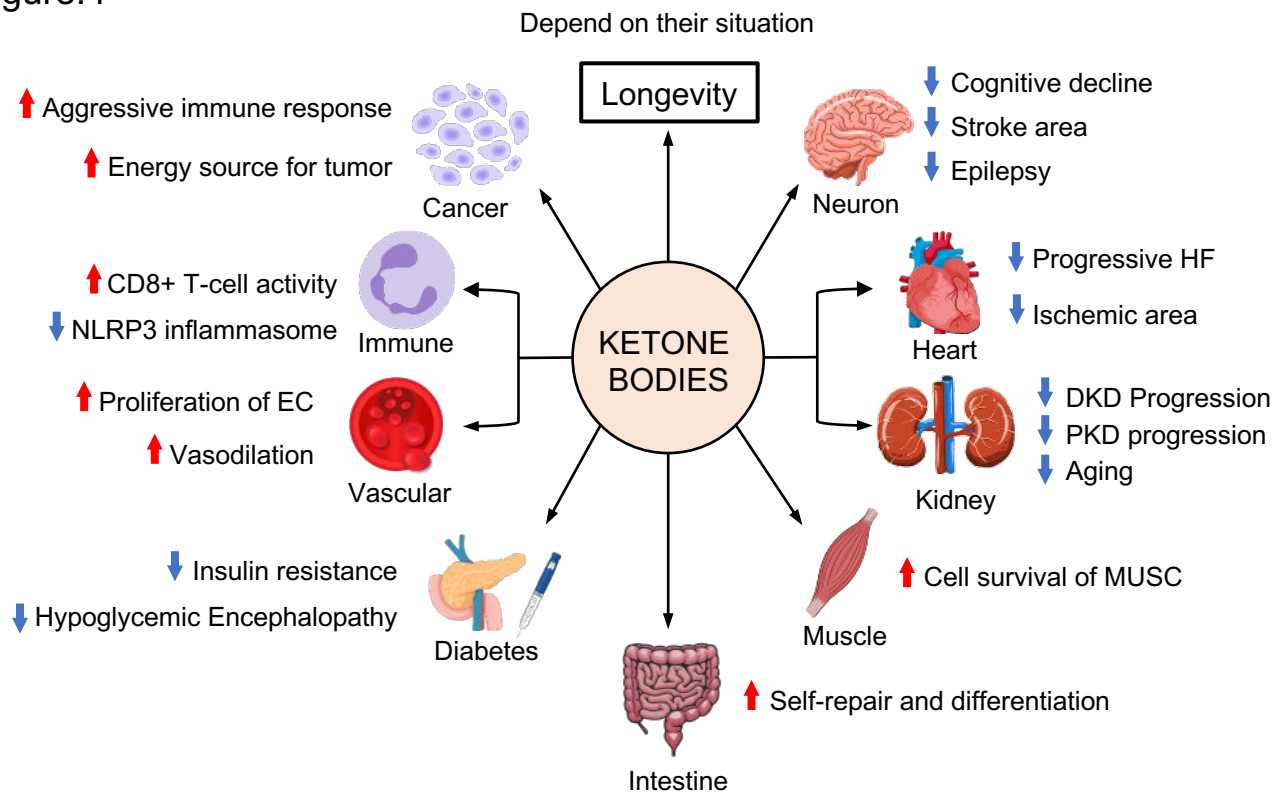

Figure 4 Diverse Functions of Ketone Bodies Across Different Organs
Pleiotropic effects of ketone bodies have been observed in multiple organs. DKD: diabetic kidney disease, EC: endothelial cell, MUSC: muscle stem cell, NLRP3: NLR Family Pyrin Domain Containing 3, PKD: polycystic kidney disease.