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EDITORIAL COMMENT

From Fuel to Code

How Ketones Drive Coronary Revascularization

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RETHINKING KETONE BODIES IN CARDIAC DISEASE

Ketone bodies (KBs) have historically been associated with diabetic ketoacidosis and metabolic dysregulation. However, a growing body of evidence suggests that KBs, particularly β-hydroxybutyrate (BHB), are not merely alternative energy substrates but also play crucial roles in cardiovascular homeostasis. When glucose and fatty acid oxidation are compromised—such as in heart failure or ischemic heart disease—ketones step in to provide an efficient fuel source that helps sustain myocardial function.[1,2] Accordingly, ketone treatment has been shown to improve cardiovascular hemodynamics and alleviate myocardial remodeling across the heart failure spectrum.[3-5]

Yet, a growing body of research challenges the notion that the cardiovascular benefits of ketones solely arise from their metabolic effects. Instead, KBs exert diverse nonmetabolic effects, including modulating inflammation, altering cell signaling pathways and, critically, remodeling the epigenetic landscape. Along these lines, in this issue of *JACC: Basic to Translational Science,* Li et al[6] provide compelling evidence that BHB promotes coronary microvascular growth following myocardial infarction (MI) through an epigenetic mechanism rather than its oxidative capacity. Their study highlights the novel epigenetic pathways histone lysine β-hydroxybutyrylation (Kbhb) as a key modification that regulates angiogenic gene expression[7] and raises crucial questions regarding the therapeutic potential of BHB in vascular remodeling (**Figure 1**).

REVISITING KETONES IN THE CONTEXT OF MI

The link between ketones and endothelial adaptation has been highlighted by previous findings showing elevated ketone oxidation in proliferating endothelial cells, as well as the ability of ketone bodies to promote angiogenesis in ischemic tissues.[8] Building on this, Li et al[6] first established a correlation between high circulating BHB levels and enhanced collateral vessel formation in MI patients. They then validated these findings in a mouse model of MI, in which chronic BHB administration reduced infarct size, mitigated adverse cardiac remodeling, and promoted coronary microvascular growth. Complementary in vitro experiments in cultured endothelial cells (ECs) demonstrated that BHB enhances proliferation, migration, and tube formation under both normoxic and hypoxic conditions, reinforcing the concept that increased ketone availability facilitates angiogenesis. Notably, when β-hydroxybutyrate dehydrogenase 1, the rate-limiting enzyme in BHB oxidation, was knocked down, the proangiogenic effects of BHB persisted. This observation indicated that the angiogenic response was not dependent on BHB oxidation as an energy substrate but rather involved an alternative, nonmetabolic mechanism. The authors moved toward testing the hypothesis that epigenetic regulation may underlie the observed effects. To investigate this, a multiomics approach was employed, integrating Cleavage Under Targets and Tagmentation, single-cell RNA sequencing, and Assay for Transposase-Accessible Chromatin (ATAC-seq).

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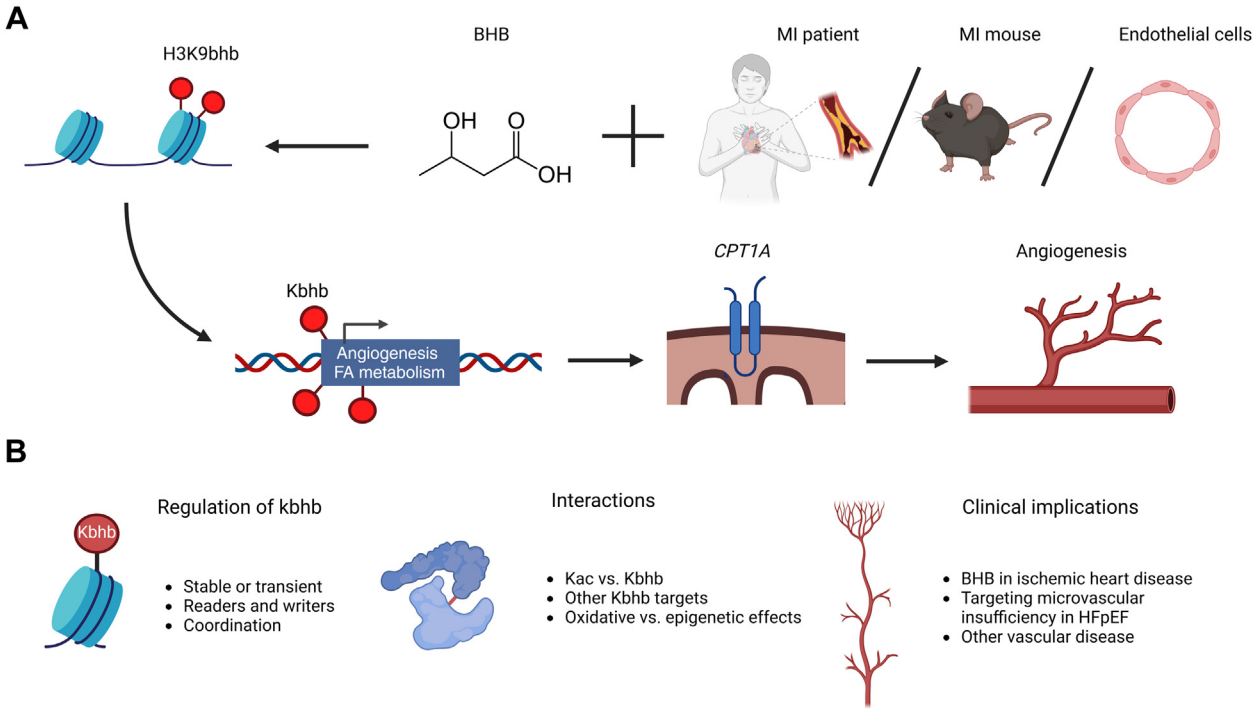
FIGURE 1 **Overview of Study Results and Unresolved Questions**



(A) Higher concentrations of the ketone body beta hydroxybutyrate (BHB) were associated with angiogenesis in patients and mice with myocardial infarction (MI) as well as in endothelial cell (EC) cultures. This was linked to increased β-hydroxybutyrylation (Kbhb) of lysine 9 on histone H3 (H3K9bhb) and increased expression of genes implicated in angiogenesis and fatty acid (FA) metabolism. Of these, carnitine palmitoyltransferase 1A (CPT1A) was identified as a key target of H3K9bhb and a critical regulator of the observed microvascular growth. (B) A summary of intriguing questions that remain related to the regulation of Kbhb, the interplay between H3K9bhb targets, and the potential clinical implications. HFpEF = heart failure with preserved ejection fraction; Kac = lysine acetylation.

Although global histone acetylation was unaltered following BHB exposure, a substantial increase in histone Kbhb was observed in cultured ECs. Among the histone sites susceptible to Kbhb, lysine 9 on histone H3 (H3K9bhb) exhibited the most pronounced enrichment. Mapping of these epigenetic marks onto transcriptomic data from hypoxic ECs revealed that H3K9bhb was preferentially localized to the promoter regions of genes involved in starvation responses and angiogenesis, leading to their transcriptional up-regulation. The Assay for Transposase-Accessible Chromatin further confirmed that these genes exhibited increased chromatin accessibility, underscoring the role of BHB in chromatin remodeling to prime proangiogenic genes for enhanced transcriptional activity. To refine the functional relevance of these findings, single-cell RNA sequencing data from infarcted mouse hearts were integrated with multiomics data from cultured ECs. This analysis identified a subset of genes highly enriched in endothelial angiogenic pathways, including well-established regulators such as vascular endothelial growth factor, as well as a distinct cluster associated with fatty acid metabolism. Among these, carnitine palmitoyltransferase 1A (CPT1A) emerged as a key epigenetic target, because BHB-induced H3K9bhb at the CPT1A promoter correlated with increased gene and protein expression both in vitro and in vivo. Finally, the proangiogenic effects of BHB were lost after small interfering RNA–mediated knockdown of CPT1A, validating the role of this protein in BHB-mediated angiogenesis. Together, these findings suggest that BHB exerts a regulatory role in endothelial adaptation through epigenetic modifications, rather than solely serving as an alternative fuel.

KBHB AS A NOVEL EPIGENETIC MODIFIER OR A METABOLIC READOUT?

Li et al[6] provide strong evidence that BHB induces histone β-hydroxybutyrylation in a site-specific manner, with H3K9bhb emerging as the dominant

mark, raising key questions regarding its broader specificity, functional impact, and longevity. It is well-established that BHB inhibits class I histone deacetylases, increasing histone acetylation (Kac) and broadly promoting transcription. However, β-hydroxybutyrylation represents a distinct mechanism, involving the covalent attachment of BHB to lysine residues.[7]

Unlike Kac, which is highly dynamic and reversible, Kbhb appears to be more stable, raising the possibility that it serves as a longer-term epigenetic signal. Additionally, although Kbhb appears to be preferentially enriched at genes involved in angiogenesis and fatty acid metabolism, the observation that histone acetylation remained largely unchanged suggests a distinct regulatory mechanism. This dual mechanism—broad histone deacetylase inhibition and targeted β-hydroxybutyrylation—underscores a broader concept in metabolic epigenetics, where intermediate metabolites act as both fuel sources and epigenetic regulators, especially under physiological or pathological stress.[9] Yet, key questions remain: does Kbhb function independently of Kac, or do these modifications interact in a coordinated fashion to fine-tune gene expression? Another critical question is whether Kbhb uniquely primes genes for prolonged activation or merely reflects metabolic flux.

LINKING FATTY ACID UPTAKE TO ANGIOGENESIS

The authors identify CPT1A as a transcriptional target of BHB-induced H3K9bhb. Although CPT1A is best known for its role in fatty acid oxidation, emerging evidence suggests it may also regulate endothelial function beyond metabolism. At first glance, the link between fatty acids—which typically require substantial oxygen for their metabolism—and microvascular growth under hypoxia can seem counterintuitive. Although ECs do not rely on fatty acids for energy under these conditions, they still require them for essential precursors in nucleoside triphosphate synthesis.[10]

It should be noted that small interfering RNA-mediated knockdown of β-hydroxybutyrate dehydrogenase 1 and CPT1A led to a partial reduction in protein expression, raising the question of whether a complete knockout would allow for a more conclusive distinction between the oxidative and epigenetic roles of ketones. In addition, CPT1A was selected from a large group of genes involved in angiogenesis and metabolism, indicating that proangiogenic effects of BHB may be more far-reaching than the mere import of fatty acids via CPT1A. Last, ketone treatment in the mouse model resulted in smaller infarct size, reduced interstitial fibrosis, and improved cardiac function. These systemic advantages likely also affected microvascular density, indicating that microvascular growth is not the only factor involved in the observed differences in microvascular density.

BEYOND ISCHEMIA: CAN KBHB FUNCTION IN OTHER CARDIOVASCULAR CONDITIONS?

An intriguing aspect of this study is whether Kbhb-mediated transcriptional regulation extends beyond hypoxic endothelial cells. Li et al[6] focus on ischemia-driven angiogenesis, but vascular rarefaction is also prominent in metabolic heart failure—particularly HFpEF—where microvascular dysfunction occurs in a normoxic, inflammatory, and insulin-resistant environment. If Kbhb acts as a fundamental angiogenic signal, it could be leveraged to counteract endothelial dysfunction in HFpEF. BHB-induced CPT1A expression enhances endothelial proliferation and migration, suggesting a similar mechanism might help restore capillary density in HFpEF. Additionally, ketones reduce oxidative stress and inflammation in the vasculature; yet, how Kbhb influences endothelial senescence, permeability, or immune interactions remains unclear. If it can selectively regulate angiogenic genes, perhaps it also impacts vascular integrity and inflammatory responses. Furthermore, examining its interplay with other metabolic processes could illuminate how Kbhb might benefit various cardiovascular conditions beyond ischemic events.

CAN KBHB BE TARGETED FOR MYOCARDIAL REVASCULARIZATION?

Because ketones influence epigenetic remodeling, targeting Kbhb to enhance revascularization is an appealing prospect. Yet, specificity remains a challenge. Exogenous ketone supplementation can elevate circulating BHB levels, but systemic ketosis may also produce off-target effects. Because Kbhb marks genes linked to fatty acid metabolism, higher BHB levels might trigger untoward metabolic shifts in cardiomyocytes or other cells. Still, short-term BHB treatment improved hemodynamics in heart failure with a reduced and preserved ejection fraction, suggesting minimal adverse consequences.[4,5]

A more refined strategy could involve targeting enzymes responsible for Kbhb deposition and removal. Although histone acetyltransferases and deacetylases for Kac are well-characterized, the

machinery governing Kbhb remains partly partially unknown. The identification of specific writers and erasers of β-hydroxybutyrylation in a disease-/tissue-dependent context could open new therapeutic avenues for revascularization with fewer off-target effects.

CONCLUSIONS

This elegant study illuminates an underexplored role of ketones in cardiac pathophysiology, promoting coronary revascularization via BHB-mediated H3K9β-hydroxybutyrylation and CPT1A up-regulation. By integrating advanced multiomics approaches, the authors show that BHB-driven epigenetic regulation underpins proangiogenic responses, revealing a novel function for the fatty acid transporter CPT1A in microvascular growth under hypoxia. This work expands our understanding of ketone-induced epigenetic changes, indicating that ketones serve not merely as alternative substrates but also as active regulators of vascular fate.

However, as with any emerging concept, enthusiasm must be paired with rigorous mechanistic validation. The journey of Kbhb in cardiovascular health is still unfolding, and future research should explore its interactions with other metabolic and signaling networks to refine our understanding of ketone-mediated cardioprotection. These insights underscore the importance of moving beyond a purely "fuel-centric" view of ketones, toward a more integrated perspective that leverages their epigenetic potential in combating heart disease.

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