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Commentary

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The role of circular RNAs in glucose metabolic reprogramming: impact on cancer progression and therapeutic implications in breast cancer

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Abstract

Breast cancer is one of the most common female malignant tumors, which seriously endangers human health. Glucose metabolic reprogramming in rapidly proliferating cancers drives increased glycolysis to meet energy needs, promoting tumor growth, acidifying the tumor microenvironment, and impairing immune function, which diminishes therapeutic efficacy. Circular RNAs (circRNAs), as key regulators of cellular processes, are increasingly recognized for their involvement in the metabolic reprogramming of cancer. Concurrently, specific circRNAs could be released by tumor cells via exosomes to facilitate intercellular communication, significantly impacting glucose metabolism, cancer progression, and therapy resistance. However, the role of circRNAs in breast cancer and their mechanisms in regulating glucose metabolism remain unclear. Therefore, elucidating these metabolic regulatory pathways could provide valuable insights for developing targeted strategies to exploit metabolic vulnerabilities and improve the prognosis of breast cancer.

Keywords: Breast cancer, glucose metabolic reprogramming, exosome, metastasis, prognosis

INTRODUCTION

Cancer cell metabolism differs significantly from that of normal cells, enabling rapid proliferation and resistance to apoptosis. Typically, cells use various metabolic pathways to generate energy based on the availability of metabolites and biosynthetic needs. In normal conditions, cells primarily rely on glycolysis to convert glucose into pyruvate in the cytosol, which is then further metabolized in the mitochondria through oxidative phosphorylation (OxPhos), the tricarboxylic acid (TCA) cycle, and the electron transport chain (ETC) to produce ATP. Under hypoxic conditions, cells switch to anaerobic glycolysis, converting pyruvate into lactate, which generates ATP at a faster rate but in much smaller amounts (2 ATP molecules *vs.* 36 ATP molecules from mitochondrial oxidation)[1]. Tumor cells often rely on glycolysis for energy production[2], even in the presence of sufficient oxygen-a phenomenon known as aerobic glycolysis or the Warburg effect. This altered metabolic process, a hallmark of cancer, highlights their increased reliance on glycolysis and presents glycolytic pathways as promising targets for cancer therapies.

Circular RNAs (circRNAs) are covalently closed RNA molecules characterized by their stable loop structure, lacking a 5′-cap and 3′-polyadenylated tail. Initially identified as viroids in 1976 and once considered splicing byproducts, circRNAs are now recognized for their diverse roles as microRNA (miRNA) sponges, protein decoys, and protein translators, influencing both physiological and pathological processes[1]. Advances in high-throughput RNA sequencing and bioinformatics have revealed their stability, conserved sequences, and cell- or tissue-specific expression[3]. Recent studies highlight their dual roles as oncogenes or tumor suppressors in various cancers, including breast, endometrial, cervical, lung, liver, esophageal, and colorectal cancers[4-8].

Emerging studies have unveiled circRNAs as crucial regulators in this metabolic change by regulating the expression of key glycolysis-related mediators[9], such as glycolytic enzyme hexokinase 2 (HK2) and glucose transporter 1 (GLUT1), indicating its importance in the regulation of tumor metabolism. A recently published study identified a key mediator of glucose metabolic adaptation, circSIPA1L3, which was enriched in exosomes and had a stimulating effect on breast cancer progression and glycolysis. This finding further broadened our understanding of circRNAs beyond their roles within cells, revealing their enrichment in exosomes and involvement in shaping the metabolic behaviors of surrounding cells[10]. Hence, the present commentary aimed to synthesize recent findings on glucose metabolism regulation and how circRNAs participate in this process of breast cancer, and to explore the possibility of targeting specific regulators to disrupt tumor metabolism as a novel therapeutic strategy.

GLUCOSE METABOLIC REPROGRAMMING IN BREAST CANCER

Despite being less efficient at ATP production, glycolysis is reported to be the primary source of energy and biosynthetic precursors for nucleotides, amino acids, and lipids, which are necessary for the rapid proliferation and survival of breast cancer cells[11]. In addition, enhanced glycolysis could also lead to elevated lactate production, promoting the recruitment and activity of various immune cells. Significantly, the heightened glycolytic potential is often linked to therapeutic resistance, metastatic potential[12], and poor prognosis of breast cancer[13], making this field gaining increased prominence.

Different breast cancer subtypes seem to exhibit distinct metabolic phenotypes[14], which might be the synergistic effect between intrinsic factors[15], such as p53 mutation and MYC amplification, and extrinsic factors, such as hypoxia and oxidative stress. ER^+ breast cancers show a reverse Warburg phenotype[16], where the glycolytic end products used by cancer cells are supplied by neighboring cancer-associated fibroblasts. For $HER2^+$ breast cancer, the glycolytic phenotype was more pronounced than mitochondrial oxidative phosphorylation[17], which might be attributed to the kinase activity of HER2 to active signaling

pathways involved in glucose uptake and glycolytic process. In addition, triple-negative breast cancer (TNBC) exhibits a predominant Warburg-type metabolic phenotype with significantly reduced mitochondrial respiration and elevated expression of various glycolytic genes[10,18].

The glycolytic phenotype is also observed in breast cancer stem cells (BCSC), with elevated activity of various glycolytic enzymes[10,19]. Several studies reported the shift between glycolysis and oxidative phosphorylation in BCSCs based on the availability of nutrients and oxygen[20], which allows CSCs to adapt to various microenvironmental conditions, making them more resilient to therapeutic interventions and contributing to tumor recurrence.

Recent studies also shed light on how metabolic reprogramming of tumor cells affects the TME. Elevated lactate accumulation produced by cancer cells acidified the extracellular environment, promoting the recruitment of immunosuppressive cells and influencing their activity[10,21]. In addition, metabolic byproducts of cancer cells can affect the composition and function of the extracellular matrix (ECM), constructing a more permissive environment for tumor invasion and spread.

Notably, the propensity to adopt specific metabolic phenotypes is also seen in tumor-associated stromal cells[11]. The antitumor subtype (M1) macrophages tend to undergo glycolysis, while the pro-tumor subtype (M2) macrophages have a higher oxidative phosphorylation level[22]. Moreover, the high glucose uptake capacity in M2-like TMAs led to O-GlcNAcylation and secretion of protease cathepsin B into the TME, promoting chemoresistance and metastasis[23]. Tregs are oxidative and less affected by lactate[24], while effector T cells have upregulated glycolysis and are easily inhibited by high lactate levels[25]. In addition, lactate accumulation attenuates IFNα production by dendritic cells and induces the formation of Treg cells[26]. This lactate-induced immunosuppression reduces the efficacy of immune checkpoint inhibitors (ICIs) in cancers like TNBC with high glycolysis.

CRUCIAL METABOLIC REGULATORS IN GLUCOSE METABOLISM

Various studies have highlighted the importance of specific enzymes and transporters in glucose metabolism[27], revealing their contribution to the aggressive nature of breast cancer. The crucial metabolic regulators in glucose metabolism are shown in Figure 1.

HK, the first rate-limiting enzyme in glycolysis, catalyzes the conversion of glucose to glucose-6-phosphate. Among the four isoforms of HK, HK2 is frequently overexpressed in breast cancer cells, leading to enhanced glycolysis, tumor progression, and drug resistance[28], and is associated with poor clinical outcomes of breast cancer patients[29]. Recent studies demonstrated that HK2 also has non-metabolic functions, which could act as a protein kinase to phosphorylate Ikβ-α, leading to Ikβ-α degradation and NF-κB activation to enhance PD-L1 transcription[30].

As the second rate-limiting enzyme in glycolysis, phosphofructokinase-1 (PFK-1) catalyzes the conversion of fructose-6-phosphate to fructose-1,6-bisphosphate. In breast cancer, phosphofructokinase platelet-type (PFKP) is the major isoform that contributes to the aggressive features and poor survival of breast cancer[31]. Mechanistically, the expression of PFKP could be transcriptionally activated by KLF4[32] or restrained by BRCA1/ZBRK1 axis[33], while the ubiquitination level of PFKP was bidirectionally regulated by TRIM25[34] and USP5[35].

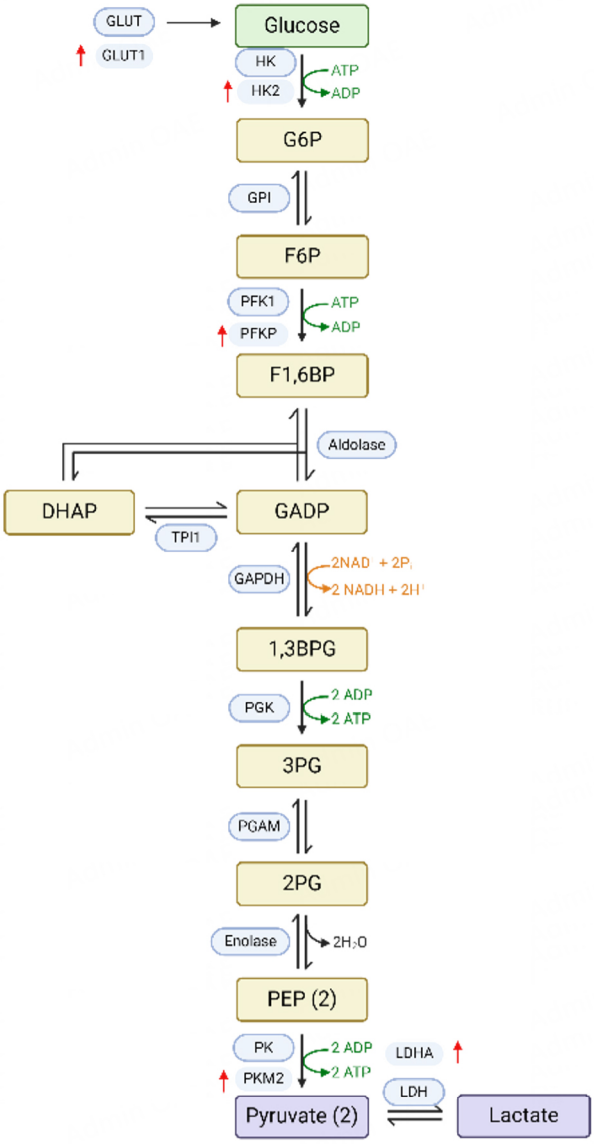

Figure 1. Crucial metabolic regulators in glucose metabolism. The red arrows indicate upregulated regulators in breast cancer.

Pyruvate kinase (PK) is the final rate-limiting enzyme in glycolysis, diverting pyruvate away from oxidative phosphorylation to support anabolic processes. PKM2 is the major isoform that is abnormally highly expressed in cancers, and is associated with the development, progression, and drug resistance of breast cancer[36]. Apart from its enzymic activity, PKM2 also acts as a transcriptional coactivator or protein kinase to regulate the expression of glycolytic and proliferative genes[37,38], further contributing to metabolic switch and cancer progression.

The final enzyme in the glycolytic pathway is lactate dehydrogenase (LDH), catalyzing the conversion between pyruvate and lactate. Significantly, the elevation of LDH in serum and its link to poor prognosis was observed in breast cancer[39]. LDHA isoform is frequently overexpressed in breast cancer[40-42], which has a crucial role in tumor metastasis, stem-like traits, and drug resistance. Moreover, as the predominant contributor to lactate production, LDHA shows multifaceted roles through altering pH within cells or

TME[43,44], such as mediating breast cancer cell motility, angiogenesis, extracellular matrix degradation, and hampering immune response. Recently, a novel post-translational modification called lactylation was identified, which produced covalently modified proteins by lactate and influenced the expression or function of target genes[45], further broadening our understanding of the end-product of the glycolytic pathway.

The GLUT family proteins are transmembrane proteins, which are responsible for glucose uptake into cells[46], further affecting cell growth and treatment sensitivity. The expression and activity of GLUT1 isoform are often upregulated in breast cancer, and are associated with aggressive phenotypes and poor prognosis[47]. The GLUT1 expression in breast cancer cells could be transcriptionally induced by several factors[48,49], such as c-Jun and YAP1-TEAD1, while AKT could stabilize its plasma membrane localization[50].

Mitochondria, the major organelle for ATP production in aerobic conditions, play a critical role in various cellular functions, including metabolism. The alteration of mitochondrial morphology involving fusion and fission, referred to as mitochondrial dynamics, was regulated by several genes[51]. Modulating mitochondrial dynamics can disrupt the balance between glycolysis and oxidative phosphorylation, thereby impacting tumor growth and drug resistance[52].

circRNAS AND THEIR IMPACT ON GLUCOSE METABOLIC REPROGRAMMING

Recently, circRNAs have emerged as significant players in cancer biology, particularly in the realm of glucose metabolic reprogramming[9], which could modulate the expression and function of regulators involved in glucose uptake and processing.

Several circRNAs that participate in glucose metabolism in breast cancer cells have been identified. For example, circ-PDCD11[53] and circ-CSNK1G1[54] were upregulated in breast cancer tissues, and enhanced LDHA expression by sponging miR-432-5p or miR-28-5p, accelerating glycolysis and cancer progression. Circ-0069094 reprogrammed glucose metabolism to glycolysis in breast cancer cells via regulating miR-591/HK2 axis[55], repressing apoptosis and facilitating malignancy. Circ_0001955 interacts with miR-1299 to upregulate GLUT1 expression[56], promoting glucose consumption, lactate, and ATP production in breast cancer. These findings emphasized that circRNAs can sequester miRNAs that would otherwise suppress genes involved in metabolic processes, thereby enhancing glycolysis and supporting tumor growth.

CircRNAs can also influence glucose metabolism by regulating transcription factors (TFs)[57], subsequently influencing the expression of glycolytic enzymes and glucose transporters. Hypoxia-inducible factor 1-alpha (HIF-1α) is a well-known TF associated with glycolysis, facilitating the expression of glycolysis-related genes[58], such as GLUT, HK, PKM, and MCT4. Recent studies have identified specific circRNAs that modulate HIF-1α expression, such as circRNF20[5] and circZFR[59]. In turn, the upregulation of HIF-1α under hypoxic conditions could elevate the expression of circDENND4C[60,61], further enhancing glycolysis and metastasis of breast cancer. Another key TF involved in glycolysis is c-Myc, which could also collaborate with HIF-1 to upregulate the expression of glycolysis-related enzymes[62]. Several circRNAs were found to interact with c-Myc to prevent ubiquitination-mediated degradation or promote its nuclear translocation, such as circXPO6[63] and circ-Amotl1[64], further upregulating the expression of its targets. Additionally, the modulation of circRNAs on multiple signaling pathways or factors that participate in the regulation of glucose metabolism[65-67], such as the AMPK pathway, the mTOR pathway, and HMGA2, could also alter the metabolic state of cancer cells, thereby influencing the tumor biology. Together, these findings highlight the extremely complex mechanism of circRNAs in the regulation of metabolic pathways.

Recent studies illustrated that circRNAs could be capsulated by exosomes, small extracellular vesicles facilitating intercellular communication, to influence various biological processes, including metabolic reprogramming of surrounding or distant cells[68], further facilitating immune escape and tumor progression. Using bioinformatics and qRT-PCR assay, Lu *et al.* identified an upregulated circRNA, circ_0001142, in breast cancer tissues and cells, which promoted glycolysis, growth, and metastasis of breast cancer[69]. Additionally, circ_0001142 could be secreted by cancer cells, transferred to macrophages via exosomes, and further regulate its polarization processes through miR-361-3p/PIK3CB pathway. This study elucidated the mechanisms behind exosomal circRNA transfer between cancer cells and their microenvironment, contributing to immunosuppressive microenvironment and tumor progression. Another study focused on the roles of exosomes from BCSCs, which detailed how exosomal circRNAs can modulate signaling pathways in recipient cells[70]. Based on circRNA array analysis, the researchers found elevated circCARM1 expression in BCSC exosomes, which was the pivotal circRNA mediating BCSC exosomes-regulated glycolysis by sponging miR-1252-5p to regulate PFKFB2 expression. The exosomal transfer facilitates the spread of oncogenic signals from BCSCs and contributes to tumor growth and metastasis, proposing the potential of targeting exosomal circRNAs to enhance cancer treatment efficacy. Recently, a study examined glucose metabolism-related circRNAs using RNA-seq analysis[10]. A specific circRNA, circSIPA1L3, was found to enhance the glycolytic and metastatic abilities of breast cancer cells, and elevated circSIPA1L3 was associated with unfavorable prognosis of breast cancer patients. Mechanistically, circSIPA1L3 could modulate the expression of SLC16A1 and RAB11A via either enhancing their interaction with IGF2BP3 or sponging miR-665, leading to effective lactate export and glucose intake. Furthermore, exosomal circSIPA1L3 contributed to cancer progression by reprogramming the metabolic state of recipient cells, highlighting its potential as a diagnostic biomarker and therapeutic target for breast cancer. These findings underscore the carcinogenic role of exosomal circRNAs by mediating glucose metabolism, providing insights into how exosomal circRNAs contribute to the aggressive nature of breast cancer, which may be promising diagnostic and prognostic biomarkers and potential therapeutic targets. The roles of circRNAs in breast cancer are summarized in Table 1.

IMPLICATIONS FOR CANCER RESEARCH AND THERAPY

The integration of recent findings on glucose metabolic reprogramming and exosomal circRNAs highlights several important implications for cancer diagnosis and therapy.

Understanding the metabolic flexibility and mitochondrial dynamics of cancer cells offers novel targets for therapeutic intervention[52,71]. By designing molecules that specifically target metabolic pathways or mitochondrial function, researchers could potentially modulate glucose metabolism in cancer cells. For example, the small molecule inhibitors targeting key enzymes[29,36,72,73], such as HK2(C-02: novel HK2 degraders), PKM2 (imidazopyridine-based thiazole derivative 7d: PKM2 inhibitors), GLUT1 (BAY-876: Small molecule inhibitor targeting GLUT1), and LDHA (quinoline 3-sulfonamides: LDHA inhibitors), are being investigated as novel means to disrupt the enhanced glycolysis and lactate production observed in cancer cells, which might be leveraged to treat breast cancer. Another promising strategy involves the use of glucose analogs, such as 2-deoxy-D-glucose (2-DG), which can interfere with glycolysis by mimicking glucose and inhibiting key glycolytic enzymes. Clinical trials are underway to evaluate the efficacy of these agents in combination with other treatments to improve therapeutic outcomes[74]. Clinical and preclinical targets of glucose metabolism are listed in Table 2.

Recent advances in the field have also underscored the potential for using metabolic biomarkers to aid cancer diagnosis and prognosis prediction. Elevated levels of glycolytic intermediates or lactate in blood or tumor tissue can serve as indicators of metabolic dysregulation and tumor activity[78]. In addition, imaging

Table 1. Roles of circRNAs in breast cancer

CircRNAs	Changes	Effects	Mechanisms
circ-PDCD11 and circ-CSNK1G1	Upregulation	Accelerated cancer progression	Enhanced LDHA expression by sponging miR-432-5p or miR-28-5p
circ-0069094	Upregulation	Repressed apoptosis and facilitated malignancy	Reprogrammed glucose metabolism to glycolysis via regulating miR-591/HK2 axis
circ_0001955	Upregulation	Promoted malignant development of breast cancer	Promoted glucose consumption, lactate, and ATP production by interacting with miR-1299
circDENND4C	Upregulation	Enhancing the metastasis of breast cancer	Upregulation of HIF-1α elevated the expression of circDENND4C, which enhanced glycolysis of breast cancer
circ_0001142	Upregulation	Promoted the growth and metastasis of breast cancer	Promoted glycolysis of breast cancer
circSIPA1L3	Upregulation	Enhanced the glycolytic and metastatic abilities of breast cancer cells	Modulate the expression of SLC16A1 and RAB11A via either enhancing their interaction with IGF2BP3 or sponging miR-665, leading to effective lactate export and glucose intake

Table 2. Clinical and preclinical targeting glucose metabolism

Drugs	Targets	Cancer type	Stage	Therapeutic effect
2-DG	HK	Thyroid cancer with brain metastasis	Case	The size of metastatic tumors decreased significantly
2-DG	HK	malignant cerebral gliomas	Phase I/II	Improved survival rate
BAY-876/ WZB117	GLUT1	TNBC	Preclinical	Inhibited the growth of cancer cells
Ivosidenib or enasidenib	Mutant isocitrate dehydrogenase (mIDH)	Acute myeloid leukemia	Phase I	Well tolerated, mIDH clearance was high[75]
HMGB2-shRNA	LDH	Breast cancer	Preclinical	Decreased the growth and glycolysis of breast cancer cells[76]
Galloflavin	LDH	Breast cancer	Preclinical	Inhibited the proliferation of tumor cells and increased the apoptosis of tumor cells[77]

techniques such as positron emission tomography (PET) using the glucose analog fluorodeoxyglucose (FDG) can provide valuable information about glucose uptake and metabolism in tumors[79].

Due to the stability and abundance of circRNAs in various biological fluids[80], exosomal circRNAs hold promise as biomarkers for cancer diagnosis, monitoring disease progression, response to therapy, and prognosis. Additionally, personalized therapies targeting specific circRNAs or their interactions with target miRNAs or RNA-binding proteins[10,68,81] could disrupt the oncogenic signaling pathways they mediate, providing a novel approach to prevent or treat advanced diseases. Therefore, exosomal circRNAs offer novel insights into how tumors can modulate their environment and interact with surrounding tissues, opening up potential avenues for innovative diagnostic and therapeutic approaches.

CHALLENGES AND FUTURE DIRECTIONS

Despite these promising findings, several challenges remain in the field of circRNA-mediated glucose metabolism in cancer.

One major challenge is developing selective inhibitors that target cancer cells without affecting normal tissue. Metabolic pathways are often shared between cancer and normal cells, making it difficult for current therapeutic drugs to achieve specificity. In addition, the dynamic nature of metabolism and its interactions with other cellular processes complicate the development of effective therapies. Future research is needed to address these challenges by developing more precise targeting strategies and combining metabolic inhibitors

with other therapeutic modalities.

Another challenge is to identify specific circRNAs involved in metabolic processes and elucidate their exact functional roles and regulatory mechanisms in different cancer types. Current studies mainly focused on the miRNA sponge effect of circRNAs in the glycolysis of breast cancer. Delving into other mechanisms, such as protein-binding and protein-coding ability, to deeply understand how circRNAs integrate with other components of the glucose metabolic network will provide novel insights into their potential as therapeutic targets and biomarkers. Due to its unique covalently closed structure, circRNA allows open reading frames (ORFs) to span across splice sites and even extend beyond the RNA's length. This enables circRNAs to produce proteins longer than 100 amino acids[82]. For example, peptides encoded by circFAM53B exhibit a strong binding affinity for both HLA-I and HLA-II molecules, triggering antitumor immune responses[83]. Moreover, a novel 113-amino acid protein encoded by circ-CUX1 promotes lipid metabolic reprogramming, enhances mitochondrial activity, and boosts the proliferation, invasion, and metastasis of neuroblastoma cells, highlighting its significant role in regulating metabolism[84]. Exploring peptides encoded by circRNAs is a promising avenue for future research. Additionally, translating these findings into clinical practice requires further validation and the development of circRNA-based targeted delivery systems. The implementation of clinical genetic testing and RNA testing will help improve the diagnosis and treatment of cancer[85].

Notably, the metabolic shift in cancer cells is not merely a consequence of the cells themselves. Metabolic reprogramming of cells in the TME could, in turn, influence the metabolism of cancer cells, forming a complex metabolic crosstalk. However, more efforts are needed to elucidate the underlying mechanism and complicated regulatory network.

CONCLUSION

Recent literature underscored that circRNAs represent a crucial regulatory layer of cancer metabolism. Their ability to influence metabolic pathways and facilitate intercellular communication through exosomes advanced our understanding of how glucose metabolic reprogramming supports cancer development and progression. Continued research and innovation in this field will undoubtedly hold promise for improving the diagnosis, treatment, and management of cancers.

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Authors' contributions

Concept and design of the study, article writing, editing, and review: Liang Y, Yang Q

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Not applicable.

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Conflicts of interest

Yang Q is an Editorial Board member of the journal *Cancer Metastasis and Treatment*. Yang Q was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, and decision making. Liang Y declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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