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# Unraveling the Cancer Metabolism: Fasting Reset, Ketogenic Diet, and Therapeutic Strategies

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**ABSTRACT**

Cancer cells harness a mechanism known as ketolysis to generate energy, a process that involves the enzymes SCOT and ACAT1, instrumental in the creation of a crucial molecule named acetyl-CoA. This molecule plays a vital role in cellular energy production. Interestingly, cancer cells are capable of alternative methods for generating acetyl-CoA, such as the incorporation of external acetate by an enzyme called acetyl-COA synthetase. Although restraining the function of SCOT and ACAT1 may decelerate cancerous growth, inhibiting acetyl-CoA synthetase which feeds the lipogenic pathways could potentially impede the tumor cells' ability to produce necessary new membranes for their survival.

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## Introduction

The human body requires two primary nutrient sources for proper functioning: glucose and ketone bodies. During periods of food scarcity, the body secretes hormones such as glucagon, epinephrine, and cortisol, initiating the breakdown of stored nutrients within various organs. Glucagon aids in releasing energy from stored reserves in the liver and muscles by converting it into accessible glucose, whereas insulin and insulin-like growth factor (IGF) assist in glucose uptake for energy utilization.

Once glucose is available in the body, it undergoes glycolysis, a process that transforms glucose into pyruvate while releasing energy. Subsequently, the process of mitochondrial oxidative metabolism, which is a more efficient energy extractor from glucose, commences. This event occurs in the citric acid Krebs cycle, where an enzyme named pyruvate dehydrogenase changes pyruvate into acetyl-CoA.

The body can also utilize ketone bodies when more energy is required or when glucose supply is inadequate. Hormonal action initiates the breakdown of stored fats that are subsequently converted into acetyl-CoA and, later, into ketone bodies within the liver. These ketone bodies serve as an energy source for tissues that are responsive to anabolic hormones, chiefly insulin and IGF.

We would like to point out that we have made the effort to make our PUBMED article more accessible, for non-biochemists, unlike the article in Reference J. Clin. Med. 2023, 12(4), 1589 https://doi.org/10.3390/jcm12041589 from which this simplified version is taken.

During periods of fasting, the body taps into stored nutrients, ensuring an energy supply to active tissues that require either glucose or ketone bodies.

## The Metabolic Vulnerability of Tumor Cells

### Tumor Metabolism

Substantial findings from Warburg, Eigenbrodt, and Mazurek [1-4] have established that the energy procurement methods in tumor cells differ significantly from those of normal cells. The efficiency of the final step in their sugar-to-energy conversion process is compromised, forcing them to compensate by consuming a greater quantity of sugar. Furthermore, they face an additional complication during the energy creation process within their mitochondria. Rather than converting sugar into energy as normal cells do, tumor cells ferment sugar into lactic acid, which can lead to deleterious effects if allowed to accumulate. Nonetheless, tumor cells have developed a mechanism to export the lactic acid out of the cell, a process that assists in enhancing their energy production.

For tumor cells to proliferate and divide, they need to synthesize certain substances, which is where the citric acid cycle plays a key role [5]. The citric acid cycle also aids in producing the essential fats and membranes required for tumor cell growth. The cycle is triggered when a molecule named citrate is produced within the mitochondria of the cell. The cell then transports citrate out of

the mitochondria and into a different cellular region where it can be used for synthesizing new components [6].

The synthesis of fats and membranes necessitates a compound known as acetyl-CoA, which cells typically derive from sugar or fats. Given the metabolic difficulties tumor cells face regarding both sugar and fat, they resort to a third source, ketones, for generating acetyl-CoA. The liver produces these ketones, which tumor cells then use to create acetyl-CoA [7].

Additionally, tumor cells utilize glutamine to facilitate acetyl-CoA production. Once a sufficient amount of acetyl-CoA is available, tumor cells can synthesize the essential substances required for growth and division.

**An Essential Observation Illustrates the Ketolytic Dependency of Tumor Cells**

A critical finding underscores the significant reliance of tumor cells on a process known as ketolysis, resulting in the production of a molecule termed acetyl-CoA. This procedure is initiated by an enzyme named ACAT1, which forms stable clusters within tumor cells. Notably, ACAT1 possesses the ability to suppress another crucial enzyme, PDH (which is responsible for glycolytic entry and glucose utilization), further reinforcing the ketolytic dependency of tumor cells [8]. Another molecule, BHB, influences tumor cells by inhibiting an enzyme known as HDAC, which oversees gene expression. BHB's inhibition of HDAC leads to the activation of genes typically expressed only during fetal development, offering potential therapeutic benefits for certain conditions [9].

BHB enters cells via specific transporters and is subsequently converted into acetoacetate. This molecule then feeds into the ketolysis pathway, culminating in the production of acetyl-CoA [10]. Interestingly, BHB also counteracts lactate release, which benefits tumor cells. However, suppression of ACAT1 can reduce the production of acetyl-CoA, potentially retarding the growth of tumor cells [9].

The inhibition of MCT transporters may also be an efficient strategy to curb tumor cell growth. With MCT transporter inhibition, lactic acid accumulation may occur, potentially disrupting the NAD+ supply and tumor glycolysis. Additionally, limiting BHB influx may deprive tumor cells of acetyl-CoA and lead to the reactivation of HDAC, prompting cellular differentiation and potential apoptosis.

To thwart tumor cells from producing new membranes necessary for growth and division, fatty acid synthesis can be inhibited using lipoic acid and hydroxycitrate. We have previously conducted investigations using these compounds to achieve this objective; detailed information is available in references [11,12]. Tumor cells also have the capacity to absorb external acetate, a process that can be hindered by allicin or orotic acid [13,14].

In the realm of marine biology, a compound known as butenolide was discovered to delay the progression of barnacles from larvae to adults by suppressing ACAT1, resulting in a larger availability of BHB for HDAC inhibition [15, 16]. In the plant kingdom, HDAC inhibitors are discharged into the soil to restrict the growth of rival plants [17].

In totality, ketolysis plays a critical role in tumor cell proliferation and presents a potential therapeutic target. The inhibition of ACAT1, MCT transporters, and HDAC may curb tumor cell growth, potentially inducing differentiation and apoptosis.

Another noteworthy observation concerns the role of butenolides in the germination of dormant seeds following forest fires. Smoke-derived butenolides (karrikins, striglol) [18] signal the seed to initiate germination: "if there was fire—there is air". It is postulated that karrikins mimic plant hormones such as auxin and gibberellin.

Inhibition of ACAT1 by butenolides might negate acetylation blocking PDH [8], reactivating oxidative metabolism.

The potential inhibition of ACAT1 by vitamin C, a butenolide, may warrant exploration, considering some of its favorable effects in cancer treatment.

**What about Ketone Diets?**

Specific types of tumors can proliferate in the presence of a substance known as BHB, a product generated during a ketogenic diet. However, there are circumstances where BHB, sourced from fasting, can be beneficial, a benefit not necessarily derived from a high-fat ketogenic diet [19]. This is because certain fatty acids, abundant in high-fat diets, can activate a pathway leading to the synthesis of new lipids essential for cellular growth, an effect not observed during fasting. Conversely, unsaturated fatty acids such as DHA have the capacity to inhibit this pathway, thus impeding cell growth.

If the pathway enabling the tumor to utilize BHB is suppressed, the tumor is deprived of the vital nutrients required for its survival, and reducing BHB levels can also attenuate inflammation. BHB can interact with a receptor named HCA2 to decrease inflammation, potentially explaining the varying outcomes observed when researching the effects of BHB on tumors [21, 22]. Agonists of HCA2, like niacin, stimulate the release of prostaglandin PGD2 from cells infiltrating the tumor. Niacin (Vitamin B3) and PGD2 provoke a skin flush reaction [20].

Studies focusing on breast cancer cells demonstrate that ketones and lactate can fuel tumor growth and metastasis, while alternate research indicates that ketones can reduce tumor cell viability and extend survival [23,24]. Transporters responsible for the movement of lactate and BHB into and out of cells can also influence tumor growth, as modulating lactate concentration can inhibit tumor progression. Furthermore, tumor cells can form a symbiotic relationship with cancer-associated fibroblasts, mutually promoting growth and survival. Inhibiting lactate transport can disrupt this advantageous interaction utilized by tumor cells [25,26].

**Metabolic Features of Ketolytic-Dependent Tumors**

**The Keto Diet: Is It Appropriate?**

In a pioneering study, a researcher named Brünings conducted a study [27] with cancer patients who were administered a low-carbohydrate diet in combination with insulin injections, aimed at curtailing the glucose supply to tumors. Initially, this strategy resulted in tumor shrinkage, but subsequently, the tumors reemerged when the patients were switched to a high-fat diet. Current understanding suggests that insulin stimulates the release of a substance known as somatostatin, which suppresses glucagon and ketone production, potentially contributing to inhibition of the growth of ketone-dependent tumors. However, it was not common knowledge back then. So it is quite plausible that the rebound growth of the tumors was due to the inability of insulin to sustain sufficient somatostatin levels to keep the tumors in control

which was likely the causal factor for the initial tumor reduction [28]. Over time, the decrease in somatostatin ceases to hinder glucagon, which then elevates ketone production, supplying fuel to the tumor [29].

In prior studies involving animal models of cancer, researchers discovered that octreotide, a substance analogous to somatostatin, reduces tumor volumes [12]. It is posited that tumor cells respond to both the growth-promoting hormone insulin and the catabolic hormone glucagon, resulting in a hybrid metabolic state. The root of the issue is speculated to lie within the endocrine pancreas, where the release of GABA by beta cells fails to deactivate alpha cells, which are responsible for glucagon release, and delta cells, which secrete somatostatin. This dysfunction sends a conflicting anabolic/catabolic signal, which new stem cells with both receptors respond to, while mature cells become insensitive to insulin. Consequently, this sets up a hybrid metabolic state in tumor cells, while differentiated tissues produce glucose and ketone bodies to fuel the ketolysis-dependent tumor cell division.

**Why Is Pyruvate Kinase Phosphorylated?**

When the body demands more glucose, the hormone glucagon springs into action. Glucagon instructs the body to manufacture fresh glucose from raw components via a process known as neoglucogenesis. In the course of neoglucogenesis, glucagon delivers a signal to halt glucose degradation and to initiate the production of new glucose molecules. This is accomplished by stimulating a protein named protein kinase A (PKA), which in turn inhibits an enzyme known as pyruvate kinase (PK) that typically facilitates glucose breakdown. Instead, alternative molecules like amino acids are utilized for glucose creation. This is significant as glucose is essential to fuel the body's cells with energy.

**How Do We Switch Back to Glycolysis?**

When our muscles are engaged in activity, or when insulin is present in our system, it leads to an elevation in the levels of calcium within our cells. This induces a process that stimulates enzymes instrumental in glucose breakdown for energy, while concurrently suppressing the production of new glucose.

Furthermore, the increased calcium levels also increase the quantity of glucose transporters present on the cell membrane, enabling a higher intake of glucose into the cell for energy utilization.

When the shift back to glucose for energy provision occurs, the body also ceases fatty acid production. This is a result of the activation of a molecule named AMP kinase, which obstructs enzymes that facilitate the formation of fatty acids. Instead, fatty acids are metabolically broken down into a molecule named acetyl-CoA, which can be used as an energy source.

The concentration of a molecule known as DAG also impacts the choice of acetyl-CoA source that our body employs for energy. When DAG levels are elevated, our body utilizes fatty acids for energy, shutting down the acetyl-CoA supply from glucose breakdown. When DAG levels are diminished, both glucose and fatty acids can supply acetyl-CoA for energy production.

**Role of AMP Deaminase**

A high intake of saturated fatty acids through a diet rich in fats triggers the stimulation of the body's AMP deaminase. This activity leads to a reduction in AMP levels, which in turn deactivates AMP kinase, a molecule typically involved in inhibiting fatty acid synthesis. Consequently, the body begins to generate more fatty acids, while the production of acetyl-CoA from the breakdown of fatty acids is halted. If DAG (a molecule instrumental in fatty acid metabolism) levels fall, the pathway blocking the glycolytic supply of acetyl-CoA is deactivated, permitting glucose to be harnessed for energy generation. In contrast, if DAG levels rise, the glycolytic supply of acetyl-CoA and the fatty acid supply are both switched off. In such scenarios, the body must rely on ketone bodies for energy production, a condition observed in tumor cells.

**A Metabolic Hypothesis for How Cancer Forms?**

Numerous factors can induce cell death, which consequently triggers the growth of new cells to repair damaged tissue. However, persistent issues with the endocrine pancreas (a key regulator of our metabolic processes) can influence the growth and development patterns of stem cells. This interference leads to alterations in their metabolism, making them reliant on ketone bodies for energy. Concurrently, other cells in the body become insensitive to insulin and start producing ketones to fuel these growing cells. This shift in metabolism can have epigenetic implications, hindering the normal differentiation process of new cells and potentially leading to the formation of a tumor.

**How to Undo the Metabolic Advantage of Tumors**

Various metabolic peculiarities inherent to cancer cells, such as modifications in signaling pathways and metabolic reprogramming, have been subjected to scientific discussion, with a view to leveraging these characteristics for cancer therapy [30]. Despite their particular metabolic transformations, a commonality among tumors is their ability to procure nutrients and consequently augment their biomass. The metabolites linked to this process can elicit epigenetic changes in the tumor cells and their microenvironment [31]. Investigations have brought to light alterations in the energy generation process of cancer cells, including their dependency on mitochondria and oxidative metabolism, which are key to the growth of cancer.

Cancer cell energy utilization, known as the Warburg effect, has also been studied by researchers. They found that mitochondria and oxidative metabolism are important for cancer growth, and can adapt to different conditions. By understanding these processes, scientists can develop treatments that target specific metabolic pathways in cancer cells to slow or stop tumor growth [32].

**A Possible Reset of the Metabolic Rewiring Mechanism in Cancer**

Glucose is a preferred source of energy for tumor cells. However, they face a stumbling block in the form of two enzymes, PK M2 and PDH, that obstruct the conversion of glucose into energy. This is akin to the body's metabolic switch from glucose production to glucose consumption. If you fast for a certain period, your body may rectify these enzymes and restart using glucose for energy. Nevertheless, during fasting, the body also creates ketones, which tumor cells can utilize as fuel. There are strategies to counteract this, for instance, consuming supplements like green tea and epigallocatechin during fasting can limit the excess ketones reaching the tumor cells, yet permit beneficial signals to pass [33,34]. Further, supplements such as DHA and EPA can restrict the conversion of ketones into fat. Often, after extended fasting, the body may recover these enzyme functions and return to using glucose for energy.

**Cutting the Ketone Influx**

Figure 1 illustrates the blockage of both glycolytic and fatty acid inputs for mitochondrial acetyl-CoA as indicated by PK and PDH impediments at the glycolytic gateway. Concurrently, a single

obstruction by malonyl-CoA curtails the fatty acid input for acetyl-CoA, as the tumor must generate its fatty acids to establish new membranes. Consequently, the ketolysis of BHB emerges as a significant acetyl-CoA supplier, furthering, for instance, the growth of breast tumors. Adipocytes generate BHB, which is absorbed by tumor cells via MCT 2 transporters [35,36].

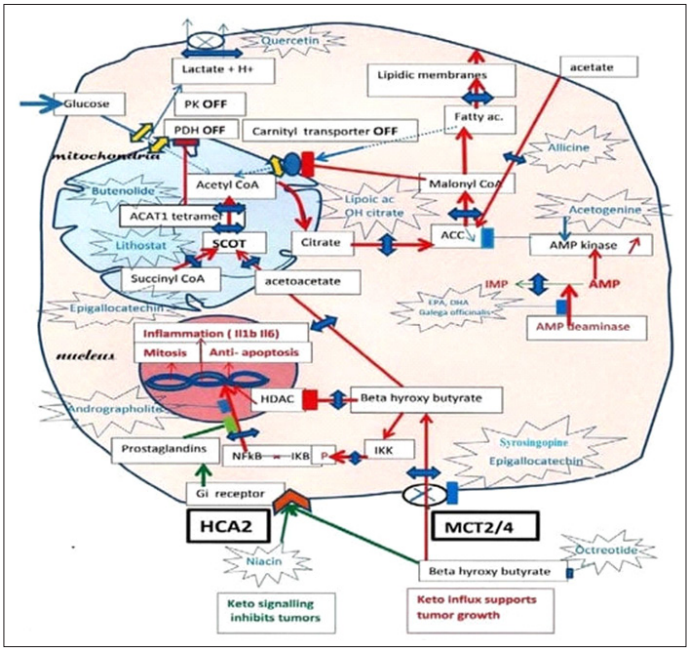


Figure 1 offers insight into the nutrient consumption pattern of cancer cells and how this knowledge could be utilized to inhibit tumor growth. Healthy cells conventionally utilize glucose for energy. In contrast, cancerous cells resort to a distinct mechanism called ketolysis, relying on ketone bodies instead of glucose as their primary energy source. This preference stems from the elevated presence of ketone bodies in the bloodstream of cancer patients, which tumors capitalize on as an energy resource to thrive and endure.

The researchers determined that cancer cells employ a specific enzyme known as SCOT-ACAT1 to assimilate ketone bodies and utilize them for energy. Furthermore, they discovered that ketone bodies induce other effects on cancer cells, including the promotion of inflammation and the suppression of mature gene expression, both crucial for modulating cell growth and inhibiting cancer.

To curb cancer progression, the researchers suggest the inhibition of the SCOT-ACAT1 enzyme, consequently obstructing the assimilation of ketone bodies by cancer cells. They propose the utilization of compounds such as Syrosingopine from Rauwolfia [36], Quercetin, or Epigallocatechin [33,34] to obstruct the absorption of ketone bodies. Moreover, they recommend employing other substances like hydroxamic acid HDAC derivatives to deactivate the SCOT enzyme, thereby depriving the tumor of its energy source. Through the inhibition of the SCOT-ACAT1 pathway and the blockage of ketone body absorption, cancer cells can be starved, and the inflammation and suppression of mature genes caused by ketone bodies can be halted. Additionally, niacin or other HCA2 receptor agonists found in natural substances like Andrographis Paniculata [37] may also be employed to suppress inflammation and hinder cancer growth.

**Cutting the SCOT-ACAT1 Ketolytic Steps**

Our strategy is to obstruct the ketolytic pathway, primarily focusing on the SCOT-regulated step that provides acetyl-CoA to lipogenesis. We applied this approach in an animal cancer model [38]. ACAT1 tetramers cooperate with SCOT to acquire the ketolytic nutrient, therefore we suggest the deployment of inhibitors for both enzymes. A common SCOT inhibitor is acetohydroxamic acid, developed by Pickart and Jencks [39].

The Siderophores iron chelator family molecules contain numerous other hydroxamic acid derivatives that could be evaluated on SCOT. Exploring ACAT1 inhibitors, such as Butenolides, vitamin C, Arecoline, and trimetazidine (Vastarel) is also of interest.

**Possible Compounds for Inhibiting SCOT**

Lithostat acetohydroxamic acid is a standard SCOT inhibitor, typically used for bladder stones. Pimozide [40, 41], a psychiatric medication, has also demonstrated potential in cancer risk reduction. Researchers have identified Mitoketoscine as a potential SCOT inhibitor and are collaborating with pharmaceutical firms to ascertain the safest and most effective variant for animal cancer models [42].

Additional potential SCOT inhibitors have been found in treatments for other diseases. Drugs that inhibit HDAC, such as Vorinostat (SAHA), Quisinostat, and Trichostatin [43], exhibit anticancer properties and could be tested for their impact on SCOT. Certain bacteria counteract acid by generating urease, which can be blocked by compounds like acetohydroxamic acid. Hydroxamate derivatives present in iron-binding siderophores also demonstrate potential as SCOT inhibitors and possess anticancer properties [44,45].

Recent studies have examined Lithostat and Lithothamnion, a compound from red algae, revealing their anticancer effects [46, 38]. Other potential siderophores for exploration as SCOT inhibitors include Ferrioxamines, siderophores [47] from marine bacteria, and soluble seawater marine siderophores. Iron chelators like desferroxamine (desferal) exhibit anti-neuroblastoma effects [48], thus they would be valuable for future leukemia treatments. Scientists are keen on testing Soluble seawater marine siderophores (Ferrioxamines) and other siderophores, such as phytoplankton siderophore from Rhodomonas Ovalis or siderophore from the marine bacterium Alteromonas luteoviolacea (alterobactine) [49], to evaluate their performance in the SCOT assay developed by Williamson [50,51].

Identifying a non-toxic inhibitor proficient in specifically targeting SCOT remains challenging. Certain compounds associated with iron metabolism, like melatonin and another substance named febrifugine, derived from a plant utilized in Chinese medicine, and its derivative Halofuginone, exhibit potential as SCOT inhibitors [52]. Notably, the liver only carries out ketogenesis and not the SCOT-driven specific step, which may be associated with the liver's function in iron recycling and metabolism. During infections, our immune system battles bacterial siderophores to retain iron.

**Compounds Affecting ACAT1**

Compounds that affect ACAT1, an enzyme crucial for energy extraction from ketones by cancer cells, could also impact SCOT, another enzyme involved in the same process. Substances like Butenolide, Vitamin C, and particular plant compounds like Karrikins and strigol are known to inhibit ACAT1. Arecoline,

originating from Areca catechu, can also hinder ACAT1, though it may also lead to oral cancer. Additional ACAT1 inhibitors such as Vastarel could be examined alongside SCOT inhibitors to investigate their combined effects on cancer cells. Interesting compounds called acetogenins from anones, possessing a furan ring, might inhibit not only ACAT1 but also another enzyme aiding cancer cells in fat synthesis. Fungal siderophores from Phellinus linteus or Phellinus baumii [53,54] might impact both SCOT and ACAT1. Moreover, inoscavin, which also has a furan ring, is likely to affect ACAT1.

**Compounds Acting downstream of SCOT-ACAT1**

Earlier research discovered that Lipoic acid and Hydroxycitrate from Garcinia can limit body fat production by inhibiting the formation of citrate, an essential component for fat synthesis. The use of allicine or orotic acid can enhance this effect. An alternate strategy to reduce fat production involves employing DHA to hinder AMP deaminase, thereby blocking the initial step of fat synthesis. This effect can be amplified by utilizing statins or Bergamotin [55] to reduce cholesterol production. An intriguing report suggests that tumors can utilize glutamine to generate citrate and synthesize fat [56], a process governed by a protein named IDH2. Long-term activation of the oncogene K-ras can escalate IDH2 activity, encouraging fat production in tumors. Different tumors exhibit varied metabolic adaptations, and this review did not cover all these variations [57].

**Conclusions**

Tumor cells face a challenge in utilizing an energy source known as glycolysis due to certain alterations in a protein in the cell. This compels them to depend heavily on glucose and lactic acid production. For growth and division, tumor cells require fatty acids, but this process hinders them from utilizing acetyl-CoA, an essential component for energy production. Consequently, tumor cells lean on ketones for energy generation. However, this also aids tumor growth, creating a dilemma in discerning whether ketones are beneficial or detrimental in cancer research.

Researchers speculate that a specific enzyme known as SCOT serves as a crucial target for cancer treatment. They aim to tackle each phase of the ketolytic process to gradually starve the tumor without damaging other tissues. By targeting the downstream pathway of SCOT-ACAT1 with compounds like Lipoic acid, Hydroxycitrate, Allicine, Docosahexanoic acid, and Bergamotin, researchers can diminish the lipogenic supply. Upstream of SCOT-ACAT1, researchers intend to inhibit the ketone transporters MCT2-4 using compounds like epigallocatechin, syrosingopine, while curtailing ketogenesis with octreotide. For SCOT, researchers are exploring the optimal hydroxamic acid derivative to employ as a treatment, without causing harm to other tissues.

Additionally, researchers aim to limit the ketone supply to the SCOT ketolytic pathway to conserve the signaling action over the HCA2 receptors, vital for tumor growth. They recommend testing these compounds on animal models to look out for possible toxic interactions and advise against a high-fat keto diet.

Researchers posit that using a combination of low toxicity compounds to target each phase of the ketolytic supply to ketone-dependent tumor cells will gradually impede their metabolic advantage and immortality. This will render them noticeable to the immune system and guide them towards an apoptotic demise.

**Author Contributions**

Following discussions with G.T. and E.B. on fasting, cancer and on the "Keto paradox", they convinced M.I. that it was necessary to explain the ketone dependency of tumors, and to write this review. All authors have read and agreed to the published version of the manuscript.

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**Conflicts of Interest**

The authors declare no conflict of interest.

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