Trends in Cell Biology

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Opinion

Acetate Metabolism in Physiology, Cancer, and Beyond

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Acetate and the related metabolism of acetyl-coenzyme A (acetyl-CoA) confer numerous metabolic functions, including energy production, lipid synthesis, and protein acetylation. Despite its importance as a nutrient for cellular metabolism, its source has been unclear. Recent studies have provided evidence to support the existence of a *de novo* pathway for acetate production derived from pyruvate, the end product of glycolysis. This mechanism of pyruvate-derived acetate generation could have far-reaching implications for the regulation of central carbon metabolism. In this Opinion, we discuss our current understanding of acetate metabolism in the context of cell-autonomous metabolic regulation, cell–cell interactions, and systemic physiology. Applications relevant to health and disease, particularly cancer, are emphasized.

Highlights

Our understanding of the origin of acetate in physiological and disease states is currently evolving and is not limited to exogenous acetate uptake.

The regulation of the production of endogenous pyruvate-derived acetate remains largely unknown.

Pathways of metabolism during periods of nutritional excess and limitation allow metabolic coupling to confer fitness advantages to proximal and systemic cellular partners.

Preferential uptake of acetate by certain tissues is driven not only by the availability of transporters but by environmental pressures such as hypoxia and nutrient scarcity.

Acetyl-CoA's Central Role in Metabolism

Acetyl-CoA is a two-carbon reactive unit that participates in **central carbon metabolism** (see Glossary) [1]. Catabolism or further oxidation of the acetyl moiety in the tricarboxylic acid cycle (TCA) generates ATP. Anabolic metabolism or reductive biosynthesis from acetyl-CoA results in the generation of lipids referred to as ***de novo* lipogenesis**. Possibly due to its central location in metabolism and its usage in both anabolic and catabolic processes, the cellular acetyl-CoA concentration also confers signal transduction functions by mediating protein acetylation [2]. These functions include direct interactions with chromatin that may modify epigenetic status, a concept which has been developed and extensively reviewed elsewhere [3–5].

Acetyl-CoA is generated in the mitochondria from pyruvate by pyruvate dehydrogenase (PDH) and in the cytosol from citrate by ATP-citrate lyase (ACLY). Both processes are coupled to the TCA cycle. In addition, acetyl-CoA is synthesized from acetate by acetyl-CoA synthetase in both the mitochondria (ACSS1) and cytosol (ACSS2) [6,7]. Recent work has also shown that acetate is generated directly from pyruvate both by nonenzymatic chemistry involving hydrogen peroxide metal catalysis and by alternative or neomorphic activities of **ketoacid dehydrogenases** [8,9]. Together these multiple pathways for acetyl-CoA production provide a host of possibilities for biochemical and physiological regulation (Figure 1). This Opinion article aims to bridge current knowledge about central carbon metabolism with recent advances in our understanding of acetate and acetyl-CoA in cellular metabolism, physiology, and disease, most notably cancer.

Sources of Acetate and Acetyl-CoA

Considering the central role of acetyl-CoA in myriad biological processes, the availability of the precursor acetate is of considerable interest. [10]. Saccharolytic fermentation performed by the intestinal microbiota is thought to be the primary source of exogenous acetate through uptake in the colon [11]. Following the ingestion of indigestible carbohydrates, enteric bacteria generate acetate, propionate, and butyrate in a 3:1:1 stoichiometry during fermentation processes [12]. The uptake of these short-chain fatty acids (SCFAs), the greatest in quantity of which is acetate, is, by some very rough estimates, accountable for approximately 10% of total human energy ex-

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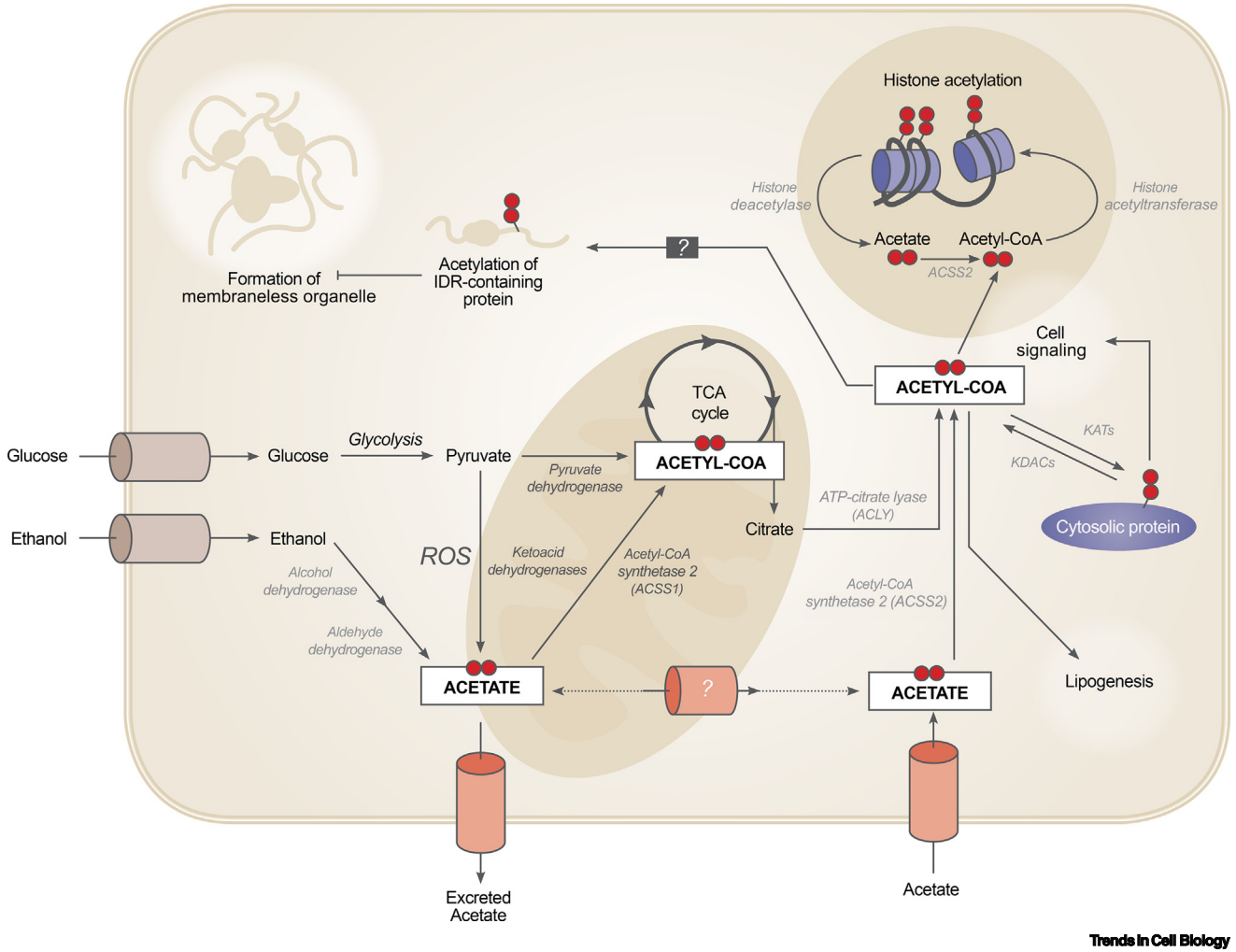

Figure 1. Summary of Uptake Pathways and Potential Cellular Fates for Acetate in Mammalian Cells. Acetate and the related acetyl-CoA metabolism are important for cellular homeostasis and functions through a number of different pathways throughout the cell, including in the mitochondria, the cytosol, and the nucleus. ROS, reactive oxygen species; IDR, intrinsically disordered regions; KAT, lysine acetyltransferase; KDAC, lysine deacetylase; TCA, tricarboxylic acid cycle.

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penditure after absorption from the colonic lumen [13,14]. The largest proportion of acetate is absorbed in the proximal colon and the absorptive capacity of the colonic epithelium decreases throughout the tract, with the lowest uptake occurring in the rectum [15]. Acetogenic bacteria like *Blautia hydrogenotrophica* are thought to be responsible for a smaller contribution of acetate, processing formate to acetyl-CoA, H_2, and CO_2 via the **Wood–Ljungdhal pathway** [16].

Independent of the bacterial metabolism of dietary fiber, other dietary sources of acetate are prevalent in particular foods such as cheese and processed meats [17]. While ingested foods contribute directly to circulating acetate, their contribution is likely to be small. Intriguingly, alcohol consumption and hepatic metabolism of ethanol may be a considerable source, since one serving of alcohol contributes to approximately 100 calories of acetate, with kinetics likely to be considerably faster than the digestion of other macronutrients. Following NAD^+-dependent catabolism to acetaldehyde in the liver, aldehyde dehydrogenases catalyze the conversion to acetate [18]. Thus, while baseline plasma concentrations of acetate in humans ranges between 50 μM and 200 μM [19–21], alcohol ingestion can induce sustained increases of plasma acetate to concentrations greater than 0.5 mM [22]. These increases in plasma acetate are more marked during chronic alcohol consumption, possibly due to an enhanced oxidative capacity to metabolize ethanol. Fluorodeoxyglucose (FDG)-positron emission tomography (PET)-based imaging of patients following acute intoxication has demonstrated increased uptake and utilization of [^{11}C] acetate as well, with greater uptake noted in chronic alcoholics [22].

Since acetyl-CoA is the focus of central carbon metabolism, the ability to generate acetyl-CoA from endogenous sources could be useful for maintaining metabolic fitness, especially during times of limited nutrient availability. The **metabolic flux** through ACLY, which is responsible for cleaving citrate exported from the mitochondria to acetyl-CoA and oxaloacetate, is a key factor in this regulation [5]. Acetate can also be generated endogenously by the deacetylation of proteins such as histones [23]. In turn, acetate can generate acetyl-CoA via flux through ACSS2, which may be regulated in response to cellular stresses like hypoxia or serum starvation [24–26].

While under nutritionally replete conditions acetyl-CoA is largely derived from glucose, hypoxia and other nutritional challenges lead to acetate utilization as a major metabolic source, an adaptation that has been well studied particularly in the context of the tumor microenvironment [4,24,25,27]. Protein deacetylation and acetyl-CoA hydrolase activity also produce acetate but these contributions to the overall pool are likely to be small. New evidence supports a pathway of *de novo* acetate production from pyruvate. This pathway was observed to be especially pronounced during periods of **overflow metabolism**, when the metabolic supply outpaces the demand, which results in the accumulation and excretion of intermediate products [28]. Hyperactive metabolism such as what occurs during the **Warburg effect** in tumors leads to increased glucose uptake, incomplete metabolism, and the release of metabolic intermediates, like acetate, into the extracellular space [29]. Thus, a model for metabolism in the tumor would include a symbiotic relationship between proximal cells, with well-vascularized portions of the neoplasm providing metabolic intermediates as a resource for neighboring nutrient-limited cells (Figure 2). Several studies have provided evidence supporting the existence of this phenomenon for other downstream products of glucose metabolism such as lactate and alanine [30–33]. This pyruvate-derived acetate overflow pathway is proposed to occur via two mechanisms in parallel: (i) via the oxidative decarboxylation of pyruvate, facilitated by reactive oxygen species (ROS); and (ii) via incomplete oxidation by ketoacid dehydrogenases (kDHs) in a thiamine- and glutathione-dependent manner. Given the number of inputs to these reactions and the relations to mitochondrial function, this *de novo* acetate generation is likely to be an adaptive mechanism, with interesting potential implications for pathophysiology linked to altered redox metabolism and other aspects of mitochondrial function that we will further discuss.

Glossary

Central carbon metabolism: the routes of carbon metabolism involving the uptake of carbohydrates, amino acids, and lipids. It involves oxidation to make ATP (catabolism) and reduction to undergo biosynthesis (anabolism).
***De novo* lipogenesis:** the endogenous synthesis of fatty acids from the two-carbon unit acetyl-CoA derived from several sources including glucose, amino acids, and acetate.
Ketoacid dehydrogenases: family of enzyme complexes catalyzing the oxidative decarboxylation of alpha-ketoacids, aided by coenzymes and cofactors. An example is the PDH complex, which generates acetyl-CoA from pyruvate.
Liquid–liquid phase separation (LLPS): the process by which components of the cytosol, typically disordered proteins and nucleic acids, interact noncovalently and precipitate into liquid droplet-like structures. This event can allow the concentration of cellular materials into the liquid droplet and has been proposed to play a role in the regulation of biochemical reactions.
Metabolic flux: the rate of flow of metabolites through a metabolic pathway; a measure of how active a metabolic pathway is in response to a stimulus.
Overflow metabolism: condition where cells take in excessive amounts of nutrients and inefficiently catabolize them, leading to the production of metabolic intermediates that are released into extracellular space.
Redox balance: a type of cellular homeostasis involving maintaining a balance between the generation and removal of ROS to help regulate several cellular processes while preventing irreversible damage to cellular components.
Warburg effect: one type of overflow metabolism, typically a feature of hyperproliferative cells, where cells rely on the increased uptake of glucose and generation of lactate to fuel their metabolic demands despite the presence of oxygen, instead of the more energy-efficient oxidative phosphorylation.
Wood–Ljungdhal pathway: process of acetyl-CoA generation, which involves the reduction of CO_2 to a methyl group that reacts with CO and CoA through condensation.

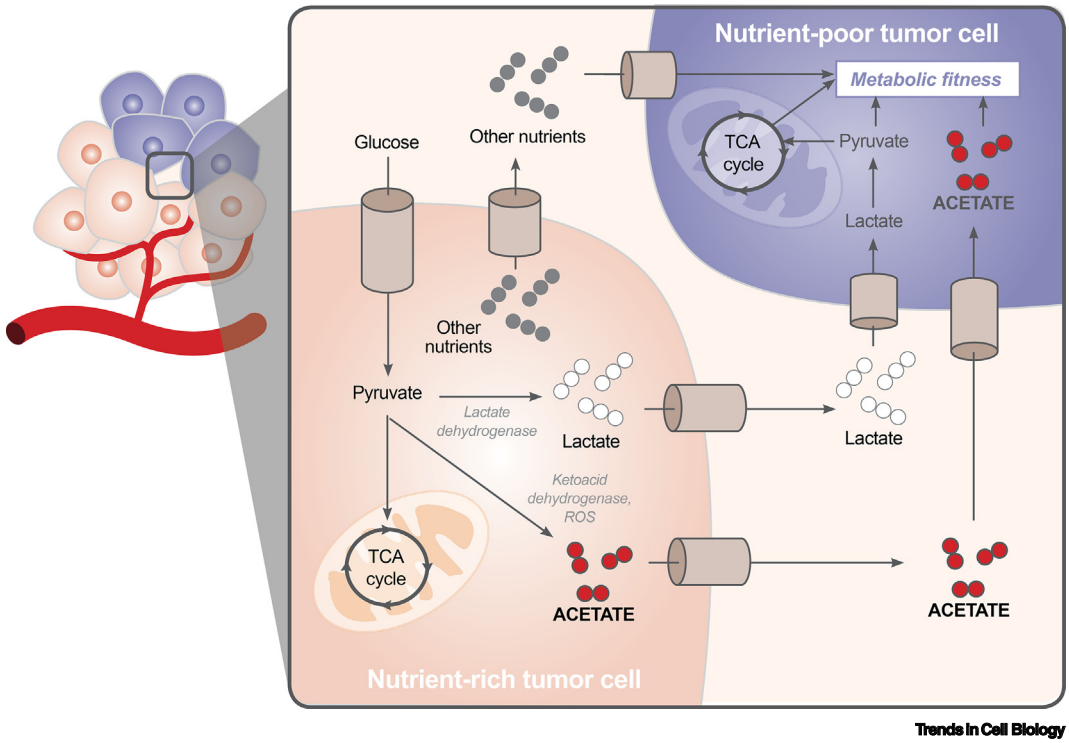

Figure 2. Cell–Cell Interactions in the Tumor Microenvironment Confer Survival Advantages for Nutrient-Poor Cells. Metabolites generated during overflow metabolism can be released from nutrient-rich tumor cells into the extracellular space, where they can be taken up by nutrient-poor tumor cells. This metabolic coupling allows the proliferation of tumor cells in poorly vascularized environments.

Regulation and Function of Acetate and Acetyl-CoA Metabolism Pathways

Cell Autonomous

Acetate plays a critical role in maintaining intracellular pools of acetyl-CoA, and dysregulation of acetate metabolism has been linked to several human diseases [17,34,35]. While the precise mechanisms of extracellular uptake remain largely uncharacterized, certain monocarboxylate transporters (MCTs) have been implicated in the active transport of acetate coupled to the cotransport of sodium, proton, or bicarbonate molecules; however, the function and regulation of these transporters are still debated [17]. In light of the existence of pyruvate-derived, *de novo* acetate production, numerous scenarios exist in which this pathway is coupled to mitochondrial functions and other aspects of acetyl-CoA metabolism. For example, the reaction is catalyzed by ROS and thus defects in mitochondrial TCA and corresponding electron transport chain activity that increase ROS will lead to upregulation of *de novo* acetate metabolism. In some instances, this could be a compensatory pathway to maintain acetyl-CoA pools. Other interactions with mitochondrial metabolism are likely to be present in some situations. During limitation of PDH activity, acetate would be produced that could maintain acetyl-CoA in both the mitochondria and the cytosol. In each of these cases, acetyl-CoA may be used to maintain or possibly enhance lipogenesis, which is shown to require acetate through ACSS2 [36]. This could lead to intriguing possibilities in, for example, liver or adipose tissue, where *de novo* lipogenesis could be enhanced by these adaptive pathways. Thus, these connections imply interesting, albeit highly speculative, molecular links. For example, oxidative stress and lowered mitochondrial activity by promoting acetate-dependent lipogenesis could

contribute to obesity. Also, the effects of oxidative stress-inducing exercise on reducing adiposity could be limited by this compensatory mechanism.

This *de novo* pathway allows regulation through its coupling to other sources of acetate. When environmental acetate is limited, *de novo* acetate can compensate and vice versa. Additionally, excess acetate can be stored on histones for possible later use [23]. This *de novo* pathway provides additional regulatory networks to couple to ACLY activity. When citrate is limited, pyruvate can compensate. Finally, considering that ROS contributes to pyruvate-derived acetate production, this pathway may also serve as a sink for endogenous or exogenous sources of ROS. The depletion of ROS as a result might function to minimize oxidative stress under nutrient-limiting conditions. Additionally, the conversion of acetate and the resulting overflow metabolism results in the net cytosolic generation of NADH in contrast to the reduction of pyruvate to lactate, which is redox neutral. These excess electrons may be of relevance in numerous contexts, such as during increased ATP demands when they can be shuttled into the mitochondria. Thus, the function of acetate in maintaining the intracellular **redox balance** through NADPH and NADH could also be crucial for some aspects of metabolic fitness [37].

Another speculative role for acetate metabolism is in the compartmentalization of biochemical reactions through protein acetylation by forming membrane-less organelles through **liquid–liquid phase separation (LLPS)**. These are domains of proteins and nucleic acids that interact through noncovalent interactions and exhibit properties of liquid droplets in that they are flexible, reversible, and in dynamic equilibrium with the surrounding cytoplasm or nucleoplasm. Their formation is dictated by the physical properties (e.g., concentration, valency) of their component macromolecules, making them tightly controlled cellular events. Various intracellular functions for LLPS include the formation of stress granules, Cajal bodies, and nucleoli and, potentially, transcriptional regulation through superenhancers [38,39]. Acetylation has been shown to allow or inhibit the formation of phase-separated domains in different cellular contexts by neutralizing positively charged lysines, enabling or disabling noncovalent crosslinking of component molecules. It has been shown to inhibit LLPS-dependent maturation of stress granules – implicated in the activation of the stress response [40] – and to inhibit LLPS-dependent nucleation of the amyloid protein Tau, although its role in related pathophysiologies remains controversial [41,42]. The spatiotemporal control of these events by acetate and acetyl-CoA metabolism remains poorly understood and points to new, unexplored roles for the metabolic regulation of cellular physiology [43].

Notably, these mechanisms are likely to have specific effects in different contexts in tissues. For example, in neuronal development ACSS2-dependent histone acetylation has been shown to activate neuronal genes and is implicated in memory consolidation. In a hippocampal-ACSS2-knockout mouse model, altered histone acetylation was shown to inhibit the assimilation of long-term spatial memory [44]. In the context of immunity, acetate has also been shown to be transiently released into the circulation in response to systemic bacterial infection, as an adaptive host resistance mechanism. Acetate can be taken up by $CD8^+$ memory T cells, where it upregulates glycolysis and subsequently enhances immune function [45]. Cells infected by human cytomegalovirus (HCMV) have also been shown to upregulate pyruvate-derived acetate production and generate cytosolic acetyl-CoA through ACSS2 to support lipogenesis, a process which is critical for successful viral infection [9].

Non-Cell Autonomous and/or Cell–Cell Interactions

Symbiosis of neighboring cells during periods of metabolic stress is responsible for ensuring metabolic fitness. Metabolite generation and shuttling between proximal cells has been largely

studied in the context of tumors, where hypoxic, nutrient-poor, and well-vascularized areas are relatively delineated. Nutritionally replete areas of the tumor exhibit aberrant metabolism, with rapid glucose uptake outpacing the oxidative capacity of the cell in a metabolic rewiring known as the Warburg effect. Overflow metabolism from these cells leads to the production of metabolic intermediates, like acetate and lactate, and previous work has suggested that these metabolites can be taken up from the tumor microenvironment by cells with limited nutrient availability [31]. These nutrient-limited cells are dependent on these alternative nutrient sources from the intratumoral space and thus adapt to preferentially metabolize them [46]. Recent studies have also underscored the importance of acetate utilization in tumor cell interactions [25,47,48]. Nutrient-limited tumor cells have been shown to capture acetate as a carbon source to support catabolic and anabolic demands [6,49]. In this context, the intracellular mechanisms of generating and shuttling acetate between cells suggests metabolic vulnerabilities that can be targeted by pharmacological therapies.

While cancers provide an intriguing model for studying metabolic substrate shuttling, metabolic symbiosis between proximal cells exists in healthy tissues as well and the function of acetate in these cooperative pathways has not been fully elucidated. Some of these pathways, including lactate shuttling, have been observed in the brain [50–52]. While the preferential uptake of acetate by astrocytes remains controversial [53], the upregulation of particular acetate importers in glial cells has supported the notion of acetate uptake as a marker for astrocytic metabolism. Isotope tracing and *in vivo* imaging has shown that the combination of acetate with an anaplerotic substrate facilitates the conversion of α-ketoglutarate into glutamate and glutamine, which can then be shuttled to neurons [54]. This metabolic coupling between astrocytes and neurons potentially confers an advantage for neurons during periods of glucose deprivation such as during hypoglycemia or chronic alcoholic consumption [55].

Systemic Physiology

In addition to cell–cell transport of acetate within tissues, the systemic physiology associated with the release and utilization of acetate in different tissues throughout an organism is also of relevance. Since acetyl-CoA is the focus of central carbon metabolism, the ability to produce and consume acetate is likely to be a critical adaptive response at the systemic level (Figure 3). During periods of nutritional stress, acetyl-CoA thioesterase (ACOT12), an acetyl-CoA hydrolase found in the liver, is activated and generates free acetate from acetyl-CoA [56]. This free acetate subsequently enters the circulation, where it can be taken up by peripheral tissues [57–59]. There is ongoing speculation about a more extensive role for acetate as a signaling molecule, including as a ligand for G protein-coupled receptors [17]. Nevertheless, molecular specificity for acetate as a ligand would be hard to establish given its low chemical complexity and modest concentration dynamics in plasma under most conditions. So, its physiological role as a nutrient source and metabolite is more plausible.

The impact of acetyl-CoA and acetate on autonomic nervous system activation and related systemic physiology has been an emerging area of interest. The gut microbiota and host interact extensively through immune, humoral, endocrine, and neural pathways and this brain–gut–microbiota axis has been recently highlighted as a key factor for insulin resistance and metabolic syndrome [60]. Evidence to support the role of microbial metabolites as a modulating influence on brain function and behavior suggests that microbial acetate production may exert extensive autonomic effects. In mice and rats with increased circulating acetate due to either altered gut microbiota or intraarterial infusion of exogenous acetate, parasympathetic nervous system activation was noted, associated with increased pancreatic β-cell activity, glucose-stimulated insulin secretion (GSIS), hyperphagia, and obesity [34]. These effects were abrogated by vagotomy to prevent efferent parasympathetic communication, thus precluding direct effects of acetate on

Figure 3. Mechanisms of Systemic Metabolic Crosstalk via Acetate. Acetate can be released into the systemic circulation and taken up by various tissues in diverse contexts during health and disease. Here we illustrate the processing and release of acetate with particular emphasis on its role in neuron–astrocyte interactions, hepatic compensation during nutrient stress, the immune response, and gut microbiome commensalism.

pancreatic β-cell activity as the key driver. Brain–gut–microbiota interactions through acetate were concluded to be the initial point of control.

Concluding Remarks

Overall, we have discussed emerging roles for acetate metabolism in health and disease. These concepts include at the cellular level the recent quantitative biochemical elucidation of a *de novo* acetate-generating pathway that occurs through direct conversion of pyruvate to acetate. The cellular contexts and possible regulatory mechanisms are largely unexplored and thus these ideas are largely speculative. More work is undoubtedly needed (see Outstanding Questions). Similarly, the role of acetate in mediating cell–cell interactions and the extent to which acetate functions in mediating crosstalk in the tumor microenvironment as well as in other situations are largely unknown.

Finally, at the systemic level, while it is currently appreciated that interorgan metabolic communication occurs via acetate metabolism, whether this crosstalk may have a role in mediating tumorigenesis and cancer outcomes is unknown. A speculative role for acetate metabolism in supporting tumor growth through gut microbiota and liver interactions is intriguing and warrants further investigation. Furthermore, as acetate uptake is involved in immunity, whether this crosstalk may be involved in the response to pathogenic challenges or the mediation of tumor immunity is mostly unexplored. Nevertheless, it is our hope that some of the speculations in this Opinion may serve as a framework for further investigation of the role of acetate in health and disease.

Outstanding Questions

How does *de novo* acetate production impact our understanding of the conditions of acetate limitation/addiction?

How does overflow metabolism of acetate and other metabolites contribute to intercellular metabolism?

Does diet or host metabolism play a role in acetate metabolism in tumors or acetate-dependent tissues?

Does acetate and acetyl-coA metabolism have a role in mediating the assembly of membraneless organelles through phase separation?

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