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Review Article

Molecular Biochemistry of Nutrient Metabolism How Cells Process Carbohydrates, Lipids, and Proteins

Sidra Riaz[1], Mah Noor Fatima[2]*, Asha Khalid[3], Zarmina Taj[4], Muhammad Wasim[5], Rabbia Manzoor[6], Nimra Razzaq[7], Iqra Hafeez[8], Amina Bibi[2]

[1]Scientific Adviser, Ministry of Science and Technology, Islamabad Pakistan
[2]National Institute of Food Science and Technology, University of Agriculture, Faisalabad, Punjab Pakistan
[3]School of Biological Sciences, University of Portsmouth, UK
[4]Department of Food Nutrition and Home Sciences, University of Agriculture, Faisalabad, Pakistan
[5]Department of Human Nutrition and Dietetics, Arid Agricultural University of Rawalpindi, Pakistan
[6]School of Biochemistry and Biotechnology University of the Punjab, Pakistan
[7]Faculty of Pharmacy & Pharmaceutical Sciences, Ziauddin University, Karachi, Sindh Pakistan
[8]Department of Biological and Environmental Sciences, Emerson University Multan, Pakistan

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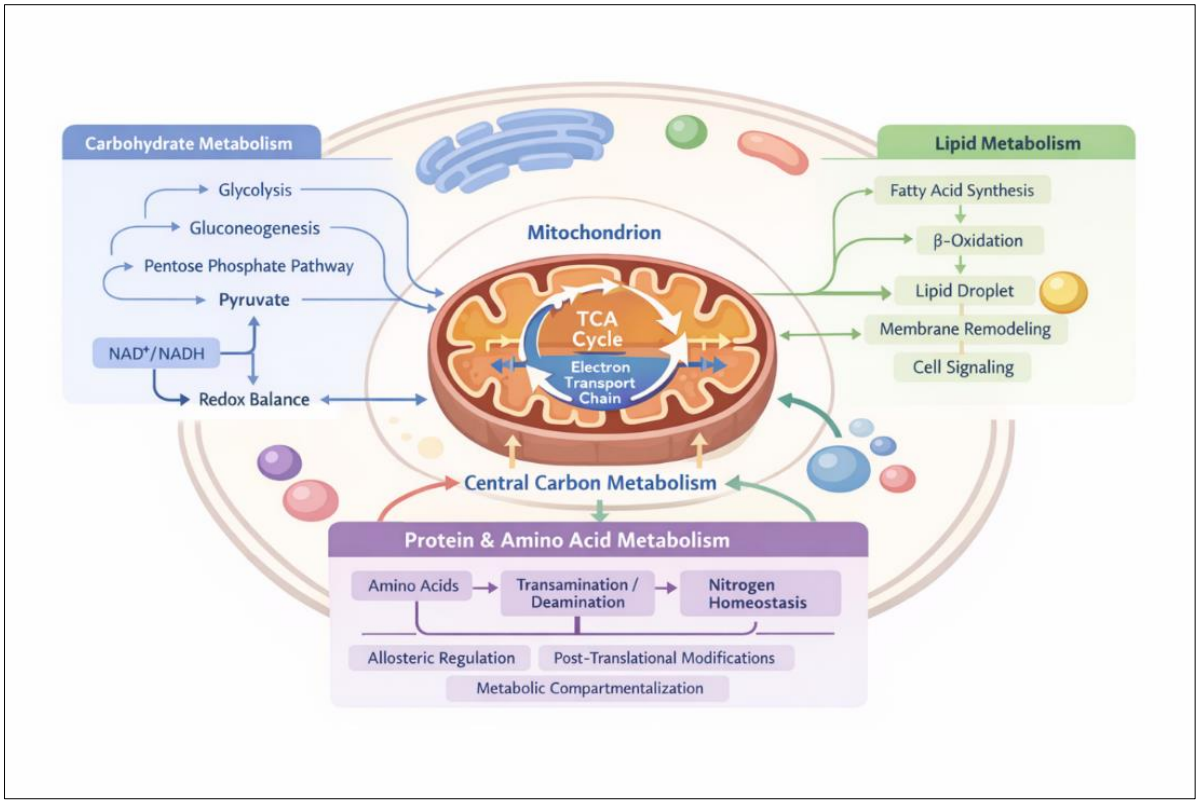
***Corresponding author:** Mah Noor Fatima
National Institute of Food Science and Technology, University of Agriculture, Faisalabad, Punjab Pakistan

Abstract



Graphical Abstract

Nutrient metabolism is a basic biochemical paradigm to which cells draw energy and produce biosynthetic precursors, as well as maintain homeostasis. At the molecular scale, the integrative processing of carbohydrates, lipids, and proteins are regulated by highly regulated enzymatic systems that dynamically react to cellular energy requirements, nutrient levels and physiological conditions. This review presents the existing knowledge of the molecular biochemistry in nutrient

metabolism, with the focus being on the integrated character of metabolic pathways, as opposed to the reactions occurring in isolation. The process of carbohydrate metabolism is a fast and flexible energy source by glycolysis, gluconeogenesis, and pentose phosphate pathway which connects the production of ATP and the maintenance of redox homeostasis with anabolic needs. The long-term energy storage and structural components in lipid metabolism are based on fatty acid production, 2-oxidation as well as complex lipid remodeling and they are the centre of focus in the membrane dynamics as well as signaling processes. Protein metabolism provides functional macromolecules as well as metabolic intermediates, which the catabolism of amino acids connects to the relationships of central carbon metabolism and nitrogen homeostasis. In addition to the classics of pathway descriptions, this review identifies the regulatory processes that provide the flexibility of their metabolic reactions, such as allosteric enzyme regulation, post-translational changes, and intracellular compartmentalization. The interaction between carbohydrate, lipid and protein metabolism allows the cells to quickly adjust to changes in nutrient levels without compromising the metabolic effectiveness. These molecular processes are critical in explaining the biochemical basis of growth and development and disease because metabolic dysregulation causes many pathological conditions. The article offers a conceptual framework of future studies aimed at optimizing metabolism, therapeutic intervention, and system-level metabolic engineering by offering a single and sequential description of how nutrient metabolism works on the molecular level.

Keywords: Nutrient metabolism, Molecular biochemistry, Cellular energy regulation, Metabolic integration, Carbohydrate-lipid-protein crosstalk, Metabolic homeostasis

INTRODUCTION

Survival of living cells depends on well-coordinated biochemical mechanisms that help them to obtain energy, produce structural elements and control signaling mechanisms (Green *et al.,* 2014). Nutrient metabolism is the biochemical point of contact between the nutrient availability in the environment and the functional requirement in the cell. The carbohydrate, lipid, and protein metabolism on the molecular level is not an amalgamation of several independent processes but a network that is moving and interrelated and maintains the cell growth, adaptation, and homeostasis (DeBerardinis *et al.,* 2012). The mechanism of cellular processing of these macronutrients helps give a critical insight into normal physiology and the molecular pathogenesis of disease. Carbohydrates are the quickest and most adaptable energy source for the majority of cells. There is constricted control in glucose metabolism, such that it maximizes the rapid production of ATP and at the same time, it provides intermediates to be used in biosynthesis (Vander Heiden *et al.,* 2009). Simultaneously, alternative pathways like glycolysis and the pentose phosphate pathway rival each other to enable the cells to regulate the production of energy versus the synthesis of reducing equivalents and nucleotide precursors. The regulation of cellular glucose is a dynamic process that is controlled by enzymatic control points to respond to metabolic demand and energy status (Lunt *et al.,* 2011). Carbohydrate metabolism helps in supplying short term energy requirements as well as long term cellular maintenance through these mechanisms.

Lipids have a dual purpose in the metabolism of cells, as they serve as reserves of dense energy, and as structural components (Van Meer *et al.,* 2008). The amount of energy stored by fatty acids per unit mass is much higher than that stored by carbohydrates and lipid metabolism is therefore important when there is a long period of energy requirements. Other than energy storage, lipids play a key role in membrane architecture, intracellular compartmentalization and signal transduction (Harayama *et al.,* 2018). The production of fatty acids, oxidation and lipid remodelling are spatially and temporally regulated in accordance to the needs of the cell. The changes between using carbohydrates and lipids by the cells can show metabolic flexibility, a trait of a well-coordinated metabolic system (Smith *et al.,* 2018). Proteins are the main functional molecules in the cell, which are used as enzymes, transporters, structural components, and regulatory components. Protein metabolism is necessary not just in energy generation, but also cellular identity and flexibility (Klaips *et al.,* 2018). The dietary intake or protein turnover sources of the amino acids are involved in the biosynthesis and energy metabolism especially during nutrient deficiency. The balance of nitrogen and interchange of amino acids are energetically maintained to avoid the presence of toxic byproducts and maintain metabolic efficiency (Kurmi *et al.,* 2020). Molecularly, the regulation of nutrient metabolism is created by a complex of stimulatory networks that combine enzyme activity, substrate concentration, and intracellular signals. Metabolic sensors detect energy status and nutrient concentrations and signal pathway flux to either energy production or biosynthesis, where it is needed (Saxton *et al.,* 2017). Mitochondria are considered to be a metabolic hotspot, balancing the oxidative metabolism and synthesizing the contributions of the carbohydrate pathway, lipid pathway, and protein pathway. This incorporation enables the cells to respond quickly to the change of environment, stress and developmental signals (Purvis *et al.,* 2013). The macronutrient pathway interdependence emphasizes the idea of metabolic crosstalk in which intermediates in one pathway can regulate and affect the efficiency of other pathways. As an example, lipid synthesis can be stimulated by an excess of carbohydrate, whereas amino acid catabolism can restore the essential metabolic intermediates (Bender *et al.,* 2012). This type of flexibility guarantees metabolic resilience but at the same time, makes the system susceptible to dysregulation. The nutrient metabolic imbalances are becoming more associated with metabolic diseases, cardiovascular pathology,

neurodegeneration and malignancy, which highlights the clinical significance of molecular metabolic regulation (Hanahan *et al.,* 2022).

The development of molecular biochemistry has demonstrated that nutrient metabolism goes beyond energy generation and it has an impact on gene expression, epigenetics, and cellular signaling (Souza *et al.,* 2025). The metabolites are signaling molecules that regulate transcriptional programs and cellular fate choices. This broadened perspective of metabolism focuses on the fact that it is a regulatory system, but not a strictly biochemical process. It, therefore, follows that to design specific therapy and nutrition interventions, it is necessary to comprehend the metabolism of nutrients on a molecular scale (Souza *et al.,* 2025). The review is a synthesis of the existing body of knowledge on the molecular biochemistry of carbohydrate, lipid, and protein metabolism, with an emphasis on how these metabolites interact to form a system in cellular systems. Through the study of cellular coordination of these pathways, the review seeks to offer a broad outline of metabolic regulation on health and disease (Peng-Winkler *et al.,* 2026). The main aim of this review is to describe the molecular processes that control cell-metabolism of carbohydrates, lipids, and proteins with a special focus on the mechanisms through which these processes are performed at the biochemical level to facilitate energy production and biosynthetic needs. Besides that, the review also aims to show the integrative behavior of metabolic networks by considering the regulatory coordination and crosstalk of macronutrient pathways that facilitate metabolic flexibility and cellular adaptation. Lastly, this paper aims to highlight the importance of nutrient metabolism in cellular homeostasis and to highlight its applicability in the prevention of metabolic dysfunction in disease and physiological imbalance.

2. Metabolite-Driven Allostery and Phase Separation in Nutrient Processing

2.1 Metabolites as Structural and Organizational Cues

Traditional views of metabolism have presented the isolated catalytic activities of enzymes as dependent on substrate concentration and following Michaelis-Menten kinetics (Liebermeister *et al.,* 2014). Although this framework has proved to be invaluable, it does not, in any way, reflect the higher-order regulatory logic that exists within the crowded and heterogeneous intracellular setting. New paradigms are emerging that metabolites play a role in reactants or products as well as structural cues that control the conformation and supramolecular assembly and spatial organization of enzymes. Metabolites, in this case, drive nutrient availability-dependent dynamical reorganization of metabolic networks in response to nutrient availability. This broader perspective identifies metabolism as an adaptive and spatially structured system whereby biochemical flux is highly coupled to cell structure so that a rapid and reversible tuning of the metabolic states is possible that cannot be described by classical kinetics (Yang *et al.,* 2026).

2.2 Allosteric Regulation of Phosphofructokinase-1 (PFK-1) and Acetyl-CoA Carboxylase (ACC) by Glycolytic and Lipid Intermediates

Allosteric regulation is a sensitive process whereby direct metabolic remodelling of enzyme activity and metabolic flux occurs directly in response to metabolites (Wei *et al.,* 2021). An example of the response of glycolytic intermediates to stabilize specific conformational states of an enzyme involves phosphofructokinase-1 (PFK-1), a major glycolytic control point, which responds to glycolytic intermediates as feedback signals to stabilize glycolytic pathways. Likewise, the rate-limiting enzyme of fatty acid biosynthesis, acetyl-CoA carboxylase (ACC) is sensitive to lipid-derived metabolites which regulate its oligomerization and catalytic competence. In both the cases the metabolite binding is more than merely the inhibition or activation but it triggers structural reorganization that affects enzyme assembly, maintenance, and sensitivity. By guaranteeing metabolic coherence through the coordination of the metabolism of carbohydrates and lipids with cellular energy conditions and biosynthetic needs, these allosteric effects are metabolite-driven (Chaneton *et al.,* 2012).

2.3 Carbohydrate-Rich Granules and Lipid Droplet–Associated Enzyme Hubs

Metabolic enzymes are increasingly recognized to localize within biomolecular condensates, membrane-less compartments formed through reversible phase separation (Kliegman *et al.,* 2025). Carbohydrate-rich granules serve as organizational centers where glycolytic enzymes transiently concentrate, enhancing local substrate channeling and flux efficiency under nutrient-rich conditions. In parallel, lipid droplets have emerged as active metabolic platforms rather than passive storage depots, hosting enzyme hubs involved in lipid synthesis, remodeling, and signaling. The recruitment of enzymes to these condensates is often driven by metabolite abundance, which alters protein-protein and protein–metabolite interactions. Such spatial clustering enables rapid metabolic reprogramming while minimizing diffusion constraints and protecting reactive intermediates from nonspecific cellular interactions (Sweetlove *et al.,* 2018).

2.4 Amino Acid Sensing via mTORC1 Recruitment to Lysosomal Surfaces through Rag GTPase–Metabolite Interactions

Amino acid availability exerts profound control over cellular growth through spatial regulation of signaling complexes. Central to this process is the recruitment of the mechanistic target of rapamycin complex 1 (mTORC1) to lysosomal membranes, a step governed by Rag GTPases that directly respond to intracellular amino acid levels (Kim *et al.,* 2019). Rather

than functioning solely as switches, Rag GTPases integrate metabolite-derived signals to orchestrate the precise localization of mTORC1 within the cell. This spatial coupling ensures that anabolic signaling is activated only when nutrient sufficiency is sensed in the appropriate subcellular context. The lysosomal surface thus emerges as a metabolic signaling nexus where amino acid–dependent molecular interactions translate nutrient cues into coordinated metabolic and biosynthetic responses (Sung *et al.,* 2023).

2.5 Nutrient-Dependent Liquid–Liquid Phase Separation as a Spatial Regulatory Layer in Metabolic Compartmentalization

Based on these observations, we postulate the existence of an extra level of control, nutrient-dependent-liquid-liquid phase separation, in metabolic regulation (O'Flynn *et al.,* 2021). According to this model, it is active changes in metabolites that promote the formation and dissolution of condensates of enzymes, allowing the spatial compartmentalization of the cell without any membrane-bound organelles. This phase behavior enables cells to quickly switch metabolic routes to changing nutrient landscapes, trading efficiency, flexibility, and robustness. This assumption puts metabolites as organizers of the intracellular architecture, which can rearrange the topology of metabolism by using physicochemical principles. Phase separation is an essential property of metabolism that can be used to provide a consistent picture of enzyme kinetics, signaling, and spatial biology that is included in a single nutrient processing model (McSwiggen *et al.,* 2019).

3. Circadian Control of Substrate Utilization at the Molecular Level

Circadian rhythms provide the cellular metabolism with a top-down temporal organization, which allows the organisms to predict and respond to predictable environmental variations, which include feeding-fasting programs and light-dark transitions (Panda *et al.,* 2016). Instead of passively taking in nutrients as they become available, metabolic systems are programmed to swing over the course of the 24-hour/ day to optimize the use of substrates, energy efficiency and metabolic hardiness. This temporal organization occurs at the molecular level, and this is done by an endogenous circadian clock that orchestrates transcriptional regulation, post-translational enzyme modification, and intracellular signaling pathways in metabolic tissues. This system, when maintained, keeps nutrient influx and metabolic capacity very accurately matched with each other; and when disturbed, it causes metabolic inflexibility, ectopic accumulation of substrates, and raises the risk of disease (Petersen *et al.,* 2018).

3.1 Core Clock Proteins as Transcriptional Regulators of Metabolic Enzymes

The molecular circadian clock is powered by transcriptional-translational feedback loops that are interlocked, whereby the core clock proteins directly control genes that are involved in the Macronutrient metabolism. The BMAL1/ CLOCK heterodimer is a central transcriptional activator that rhythmically activates the expression of enzymes, which regulate glycolysis, lipid synthesis, fatty acid oxidation, and amino acid turnover (Reinke *et al.,* 2016). This rhythmic transcription sets up reliable day-to-day fluctuations in metabolic capacity such that the enzyme machinery is present before nutrient ingestion as opposed to reacting to nutrient ingestion. In response to this activation, other nuclear receptors like REV-ERB 2 also operate by repressing transcription as a metric to control metabolic timing. REV-ERBalpha imposes temporal compartmentalization of anabolic and catabolic processes through suppression of genes that affect mitochondrial oxidative capacity, lipid biosynthesis and glucose metabolism during an inappropriate circadian stage (Bugge *et al.,* 2012). All these counteracting transcriptional forces produce strong metabolic oscillations that coordinate the metabolism of cellular energy with physiological needs in the entire body.

3.2 Diurnal Oscillation of Glycolytic Flux via Rhythmic Regulation of Glycolytic Enzymes

Glycolysis is one of the main points of entry of energy in carbohydrates and it is highly circadian-modulated. The expression and activity of major regulatory enzymes, such as hexokinase and pyruvate kinase isoforms exhibits these time-of-day oscillations and provide oscillations in the glycolytic throughput (Zlacká *et al.,* 2021). This rhythmic regulation controls the rate of glucose phosphorylation, pyruvate synthesis and carbon distribution between oxidative and biosynthetic metabolic routes. The active or feeding phases are characterized by increased glycolytic capacity that facilitates rapid burning of glucose and generation of energy. On the other hand, in fasting or rest periods, glucose is conserved by inhibition of a glycolytic flux and unwarranted substrate cycling is restricted. This temporal regulation of glycolysis is essential to the maintenance of glucose homeostasis and the avoidance of the presence of competition between the oxidation of carbohydrates and other forms of energy like fatty acids.

3.3 Circadian Gating of Lipolysis and β-Oxidation Through Clock–Nuclear Receptor Interactions

The circadian regulation is closely connected to lipid metabolism involving clock protein-lipid-sensing nuclear receptor interactions. PER2 has a key role in the limitation of fatty acid oxidation through suppression of transcriptional regulations controlled by PPAR3, a lipid catabolic master regulator. This repression defines circadian windows where lipolysis and mitochondrial 2-oxidation are either stimulated or suppressed (Gooley *et al.,* 2016). The circadian clock avoids the overuse of fatty

acids by temporarily separating lipid oxidation episodes with intervals of nutrient richness, during which glucose and diet lipids are easily accessible. Rather, lipid oxidation becomes selectively stimulated during long periods of fasting or rest, which facilitates generation of energy at the expense of maintaining metabolic plasticity. Any interruption with this mechanism of gating causes improper lipid oxidation, defective switching of substrates, and lipid intermediates that are linked to insulin resistance.

3.4 Time-of-Day–Dependent Amino Acid Catabolism and Nitrogen Handling

Circadian modulation of protein and amino acid metabolism is another part of the oscillations that are mostly coordinated by the oscillations of the autophagy and nitrogen disposal pathways. There is high time variation in autophagic activity and peaks are found during periods of limited nutrient supply. It involves the release of intracellular amino acids which could be diverted to either gluconeogenesis, oxidative metabolism or biosynthetic reactions according to systemic energy requirements (Torres *et al.,* 2023). At the same time, the activity of urea cycle enzymes varies during the circadian cycle which provides adequate detoxification of ammonia produced during the metabolism of amino acids. This coordinated control prevents nitrogen excess and synchronizes protein breakdown and metabolic requirements to support the idea that amino acids are not just structural elements, but also temporally controlled metabolic intermediates.

3.5 Chrononutrition and Metabolic Disease: Consequences of Temporal Misalignment

The fact that circadian clocks are closely linked to the use of substrates makes it clear why nutrient timing is such an important determinant of metabolic health. Nutrient processing is energy efficient and optimal when food intake is in accordance with the endogenous metabolic rhythms. Conversely, the consumption of food at biologically inappropriate times disturbs the clock-regulated metabolic programs, causing poor glucose tolerance, impaired lipid metabolism, and poor amino acid metabolism. A persistent circadian disruption, e.g. abnormal eating patterns, night feeding, shift work, etc., overturns natural metabolic timing signals and facilitates insulin resistance, ectopic lipid deposition and low-grade inflammation (Catalano *et al.,* 2022). These dysadaptive responses point at chrononutrition as an interface defining the relationship between behavior and molecular metabolism. The ability to match dietary habits with inherent circadian rhythms proves to be one of the strongest approaches to maintaining metabolic flexibility and avoidance of metabolic illness.

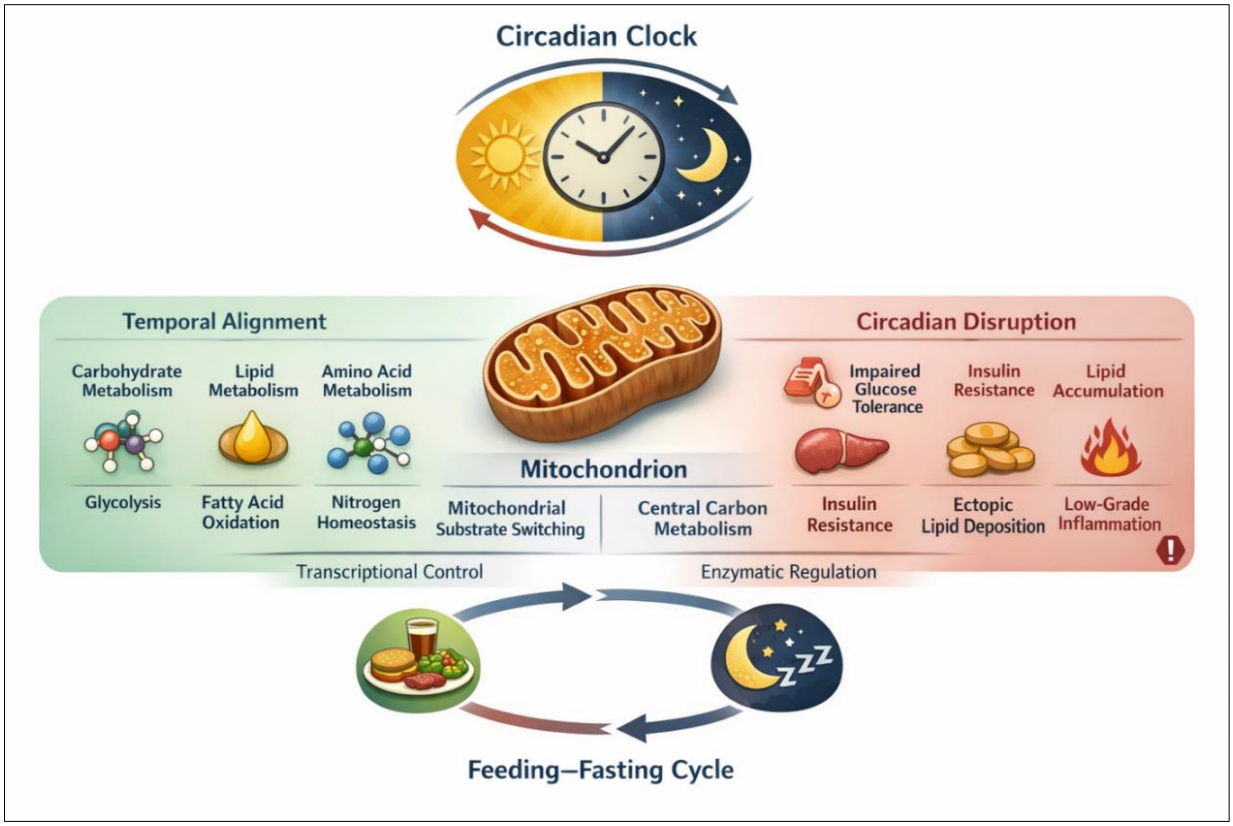


Fig. 1: Circadian clocks temporally orchestrate carbohydrate, lipid, and amino acid metabolism through coordinated transcriptional control, enzymatic regulation, and mitochondrial substrate switching. Temporal misalignment of nutrient intake disrupts metabolic flexibility, promoting insulin resistance, lipid accumulation, and metabolic dysfunction

4. Mitochondrial–Nuclear Crosstalk in Coordinating Macronutrient Fate

Mitochondria are becoming increasingly identified as dynamic signaling centers that combine cellular nutrient status with nuclear gene expression programs. In addition to their place in the canonical ATP generation, the mitochondria constantly monitor changes in carbohydrate, lipid, and amino acids and provide this data to the nucleus to optimally regulate the metabolic potential (Picard *et al.,* 2025). This mitochondrial and nuclear crosstalk is the reason why the flux of macronutrients is coupled with transcriptional, epigenetic and proteostatic responses to keep metabolic homeostasis. The impairment of this axis of communication adds to the inflexibility of the metabolism, the insulin resistance, and the dysfunction of mitochondria witnessed in metabolic disorders.

4.1 Retrograde Signaling: Mitochondrial Metabolites as Epigenetic Modulators

Mitochondria are becoming known as active signaling platforms, which combine cellular nutrient state with programs of nuclear gene expression. In addition to their place in the canonical ATP generation, the mitochondria constantly monitor changes in carbohydrate, lipid, and amino acids and provide this data to the nucleus to optimally regulate the metabolic potential. This mitochondrial and nuclear crosstalk is the reason why the flux of macronutrients is coupled with transcriptional, epigenetic and proteostatic responses to keep metabolic homeostasis (Xu *et al.,* 2026). The impairment of this axis of communication adds to the inflexibility of the metabolism, the insulin resistance, and the dysfunction of mitochondria witnessed in metabolic disorders.

4.2 Citrate Export and Its Dual Role in Lipogenesis and Histone Acetylation

Citrate occupies a unique position at the crossroads of energy metabolism and gene regulation. When mitochondrial oxidative capacity exceeds immediate energetic demand, citrate is exported into the cytosol as a mechanism to redistribute excess carbon. In the cytosolic compartment, citrate-derived acetyl-CoA fuels fatty acid and cholesterol biosynthesis, promoting anabolic storage pathways during nutrient abundance. Simultaneously, citrate contributes to nuclear acetyl-CoA pools that support histone acetylation and transcriptional activation of lipogenic and anabolic genes (Chen*et al.,* 2024). This coordinated regulation ensures that lipid synthesis is transcriptionally reinforced, rather than occurring as an isolated metabolic event. By synchronizing metabolic output with chromatin remodeling, citrate-mediated signaling establishes a feed-forward mechanism that stabilizes nutrient-induced anabolic states while preventing metabolic imbalance.

4.3 α-Ketoglutarate-Dependent Dioxygenases Linking the TCA Cycle to Epigenetic Remodeling

α-Ketoglutarate functions as a critical metabolic cofactor for a class of dioxygenases that catalyze DNA and histone demethylation reactions. Through this role, mitochondrial tricarboxylic acid cycle activity becomes directly coupled to epigenetic remodeling and transcriptional plasticity. Elevated α-ketoglutarate availability favors an open chromatin configuration, supporting expression of genes involved in oxidative metabolism, mitochondrial biogenesis, and cellular differentiation (Carey *et al.,* 2015). Conversely, reduced α-ketoglutarate levels constrain demethylation capacity and promote transcriptional repression of metabolic genes. This mechanism allows cells to translate mitochondrial metabolic efficiency into long-term transcriptional outcomes. Importantly, this coupling ensures that nuclear gene expression remains aligned with mitochondrial functional capacity, preventing mismatches between metabolic demand and oxidative potential.

4.4 Mitochondrial Unfolded Protein Response and Amino Acid Transport Regulation

The mitochondrial unfolded protein response represents a stress-adaptive signaling pathway that safeguards mitochondrial proteostasis. When mitochondrial protein folding capacity is challenged by nutrient overload or oxidative stress, this response initiates a transcriptional program that extends beyond mitochondrial chaperones and proteases. Nuclear gene expression is reprogrammed to enhance amino acid transport, protein quality control, and mitochondrial turnover. Upregulation of amino acid transporters ensures a sufficient supply of substrates for mitochondrial protein synthesis and repair, while coordinated induction of proteostatic mechanisms prevents accumulation of misfolded proteins (Hansen *et al.,* 2019). This response aligns amino acid metabolism with mitochondrial functional status, reinforcing the integration of nitrogen metabolism into overall cellular energy homeostasis.

4.5 Integrated Model of Redox-Driven Nuclear Reprogramming

Mitochondrial redox state emerges as a central integrative signal governing mitochondrial–nuclear communication. Variations in NADH/NAD^+ ratios and reactive oxygen species production modulate both metabolic enzyme activity and transcriptional regulators. These redox-sensitive signals influence nuclear gene networks controlling glucose oxidation, lipid handling, amino acid catabolism, and antioxidant defense. In an integrated model, mitochondrial metabolites, redox cues, and stress-responsive pathways converge to reprogram nuclear transcription in a coordinated manner (Sanfrancesco *et al.,* 2025). This multilayered signaling architecture enables cells to dynamically adapt nutrient handling strategies in response to fluctuating metabolic environments. Effective mitochondrial–nuclear crosstalk

thus underpins metabolic flexibility, while its dysregulation contributes to the pathogenesis of metabolic disease.

Table 1: Overview of mitochondrial–nuclear crosstalk mechanisms that integrate macronutrient flux with transcriptional, epigenetic, and proteostatic regulation. The table summarizes how mitochondrial metabolites, redox signals, and stress responses coordinate nuclear gene expression to preserve metabolic flexibility and cellular homeostasis

Mitochondrial Signal or Process	Macronutrient Context	Mode of Nuclear Regulation	Cellular Outcome	Impact on Metabolic Homeostasis
Retrograde mitochondrial signaling	Mixed carbohydrate, lipid, and amino acid flux	Activation of nutrient-responsive transcriptional programs	Alignment of gene expression with substrate availability	Preserves metabolic flexibility
Mitochondrial metabolite export	Excess carbon availability	Metabolite-driven chromatin remodeling	Reinforcement of anabolic transcriptional states	Prevents uncoupled metabolism
Citrate efflux to cytosol and nucleus	Glucose-derived carbon surplus	Acetyl-CoA–dependent histone acetylation	Coordinated lipogenesis and gene activation	Stabilizes nutrient-induced anabolic balance
Cytosolic acetyl-CoA generation	High-energy nutrient states	Epigenetic regulation of lipid metabolism genes	Enhanced fatty acid and cholesterol synthesis	Enables efficient energy storage
TCA cycle activity modulation	Variable oxidative substrate input	Control of epigenetic enzyme activity	Adaptive transcriptional plasticity	Matches nuclear programs to mitochondrial capacity
α-Ketoglutarate availability	Oxidative metabolism intensity	DNA and histone demethylation	Expression of oxidative and mitochondrial genes	Supports long-term metabolic adaptation
Reduced α-ketoglutarate signaling	Impaired mitochondrial flux	Limitation of demethylation processes	Transcriptional repression of metabolic genes	Contributes to metabolic inflexibility
Mitochondrial unfolded protein response	Amino acid imbalance or proteotoxic stress	Stress-induced nuclear transcription	Enhancement of proteostasis machinery	Protects mitochondrial function
Amino acid transporter induction	Increased mitochondrial protein demand	Transcriptional upregulation of transport systems	Sustained mitochondrial repair and turnover	Integrates nitrogen metabolism
Proteostatic signaling to nucleus	Mitochondrial folding stress	Reprogramming of protein quality control genes	Prevention of protein aggregation	Maintains organelle integrity
Redox state fluctuation	Changes in nutrient oxidation rates	Redox-sensitive transcriptional regulation	Adjustment of metabolic enzyme expression	Enables rapid metabolic recalibration
$NADH/NAD^+$ ratio signaling	Energy abundance or deficit	Regulation of metabolic gene networks	Balanced glucose and lipid utilization	Prevents redox imbalance
Mitochondrial ROS signaling	Elevated oxidative metabolism	Activation of adaptive stress responses	Induction of antioxidant defenses	Limits oxidative damage
Integration of redox and metabolite signals	Dynamic nutrient environments	Coordinated transcriptional reprogramming	Optimized substrate handling	Enhances metabolic resilience
Mitochondrial–nuclear feedback loops	Long-term nutrient exposure	Sustained epigenetic and transcriptional changes	Stable metabolic phenotypes	Guards against chronic metabolic dysfunction

5. Microbiota-Derived Metabolites as Modulators of Host Nutrient Metabolism

The metabolic influence of the gut microbiota extends far beyond nutrient extraction, positioning microbial communities as active regulators of host metabolic decision-making. Through fermentation, biotransformation, and redox reactions, gut microbes generate a diverse metabolite pool that intersects with host metabolic pathways at multiple regulatory levels. These microbial products influence enzyme activity, transcriptional programs, epigenetic states, and hormonal signaling, thereby shaping how carbohydrates, lipids, and amino acids are partitioned across tissues (Cox *et al.,* 2022). Importantly, microbial metabolites act as context-dependent signals, allowing the host to adapt metabolic strategies according to dietary composition, feeding state, and environmental cues.

5.1 Short-Chain Fatty Acids as Energetic Substrates and Metabolic Signals

Short-chain fatty acids represent a primary interface between microbial fermentation and host energy metabolism. Following absorption, these metabolites contribute directly to central carbon metabolism by entering pathways that support oxidative phosphorylation and biosynthesis. However, their physiological relevance extends beyond their caloric contribution. Short-chain fatty acids influence metabolic flexibility by modulating nutrient sensing and substrate preference in metabolic tissues. In skeletal muscle and liver, they alter the balance between glucose oxidation and lipid utilization, promoting efficient energy use under varying nutrient conditions. In adipose tissue, they influence lipid storage dynamics and adipocyte function, linking intestinal fermentation activity to peripheral energy handling (Canfora *et al.,* 2015). Beyond their tissue-specific effects, short-chain fatty acids act as systemic signaling molecules that coordinate energy balance across organs. By integrating dietary fiber availability with host metabolic responses, they enable the microbiota to indirectly regulate energy expenditure, insulin responsiveness, and metabolic resilience during nutrient fluctuations.

5.2 Butyrate-Driven Epigenetic Remodeling and Glucose Metabolic Control

Butyrate exerts a unique influence on host metabolism through its capacity to reshape chromatin structure and transcriptional accessibility. By modulating histone acetylation status, butyrate alters the expression of genes involved in glucose production, mitochondrial function, and oxidative metabolism. This epigenetic regulation ensures that hepatic gluconeogenesis is tightly coupled to nutritional state, preventing maladaptive glucose overproduction during periods of nutrient abundance (Rui *et al.,* 2014). In addition to hepatic effects, butyrate-induced epigenetic changes influence metabolic pathways in peripheral tissues, enhancing insulin sensitivity and promoting metabolic efficiency. Through sustained transcriptional reprogramming rather than acute signaling alone, butyrate enables long-term adaptation of host metabolism to dietary patterns, highlighting the microbiota's role in shaping metabolic memory.

5.3 Secondary Bile Acids as Integrators of Lipid and Glucose Metabolism

Microbial modification of bile acids represents a critical mechanism by which the gut microbiota regulates lipid handling and systemic metabolic signaling. Secondary bile acids function as metabolic messengers that coordinate intestinal lipid absorption with hepatic lipid processing and peripheral insulin sensitivity. These metabolites influence the timing and efficiency of dietary fat assimilation while simultaneously modulating pathways involved in glucose homeostasis (Xiong *et al.,* 2023). Through this bile acid signaling network, microbial activity synchronizes lipid availability with host energy requirements, ensuring that lipid storage and oxidation are matched to metabolic demand. Disruption of this regulatory axis can uncouple lipid and glucose metabolism, contributing to metabolic inefficiency and insulin resistance.

5.4 Microbial Amino Acid Metabolism and Disruption of Insulin Signaling Networks

Dietary amino acids serve not only as substrates for protein synthesis but also as precursors for microbial metabolite production. Microbial processing of amino acids generates nitrogen-containing compounds that exert potent effects on host signaling pathways. Certain metabolites interfere with insulin signal transduction, impairing glucose uptake and utilization despite adequate insulin availability. This mechanism introduces a layer of metabolic regulation that is independent of energy intake, emphasizing the importance of metabolite quality over caloric quantity (Efeyan *et al.,* 2015). These interactions highlight the capacity of microbial amino acid metabolism to reshape host metabolic priorities, diverting substrates away from oxidative pathways and altering insulin responsiveness. As such, nitrogen metabolism by the microbiota emerges as a critical, yet often underappreciated, determinant of metabolic health.

5.5 Host Microbe Metabolic Co-Metabolism as a Systems-Level Framework

Taken together, microbiota-derived metabolites establish a systems-level regulatory framework in which host and microbial metabolic processes are tightly interwoven. Rather than acting in isolation, microbial metabolites converge with host transcriptional, epigenetic, and hormonal networks to regulate macronutrient partitioning across tissues. This co-metabolic architecture allows the host to dynamically allocate nutrients toward oxidation, storage, or biosynthetic pathways based on microbial composition and metabolic output (Fan *et al.,* 2021). This framework provides a mechanistic explanation for interindividual variability in metabolic responses to identical diets and

underscores the microbiota as a modifiable determinant of metabolic phenotype. Understanding host–microbe metabolic co-metabolism offers new perspectives on nutritional adaptation, metabolic flexibility, and the development of metabolic disorders.

6. Substrate Competition and Metabolic Inflexibility in Cellular Energetics

Efficient cellular energy metabolism depends on the ability of cells to dynamically adjust substrate utilization in response to nutrient availability, hormonal signals, and energetic demand. Carbohydrates, lipids, and amino acids converge at shared mitochondrial and cytosolic pathways, where competitive interactions determine substrate priority. While this competition enables metabolic efficiency under physiological conditions, its dysregulation leads to metabolic inflexibility, a hallmark of insulin resistance and metabolic disease. Understanding the molecular basis of substrate competition provides critical insight into how energetic homeostasis is maintained and how it becomes pathologically impaired.

6.1 Molecular Basis of Glucose Fatty Acid Antagonism

The reciprocal regulation of glucose and fatty acid oxidation represents a central organizing principle of cellular energetics. When fatty acid availability is high, enhanced β-oxidation generates reducing equivalents and lipid-derived intermediates that suppress glucose uptake and oxidation. This antagonism operates at multiple levels, including inhibition of key glycolytic enzymes, reduced pyruvate flux into mitochondria, and diminished glucose transporter activity at the plasma membrane. At the mitochondrial level, elevated fatty acid oxidation increases NADH and acetyl-CoA concentrations, signaling sufficient energy supply and reducing the requirement for carbohydrate-derived ATP production (Sugden *et al.,* 2008). This shift ensures efficient utilization of the most abundant substrate while preventing simultaneous overactivation of parallel energy-producing pathways. Such substrate prioritization is particularly evident in oxidative tissues such as skeletal muscle and liver, where rapid adaptation to fasting–feeding cycles is essential for systemic metabolic balance.

6.2 β-Oxidation–Derived Acetyl-CoA and Pyruvate Dehydrogenase Inhibition

A critical molecular node linking fatty acid oxidation to carbohydrate suppression is the pyruvate dehydrogenase complex, which controls the entry of glycolytic carbon into the tricarboxylic acid cycle. Excess acetyl-CoA generated from β-oxidation acts as both a direct allosteric inhibitor and an upstream signal that promotes phosphorylation-dependent inactivation of this complex. This regulatory mechanism effectively limits glucose-derived acetyl-CoA production when lipid-derived energy is abundant (Muoio *et al.,* 2014). Sustained activation of this inhibitory axis reinforces a metabolic state favoring lipid oxidation while restricting carbohydrate utilization, even in the presence of glucose. Over time, this biased substrate selection contributes to impaired glucose disposal and reduced metabolic adaptability. Importantly, this regulation reflects an integrated response involving transcriptional control, post-translational modification, and metabolite-mediated feedback, underscoring the complexity of substrate competition at the mitochondrial interface.

6.3 Amino Acid-Driven Anaplerosis and Carbon Competition

Beyond glucose and fatty acids, amino acids contribute significantly to cellular energetics through anaplerosis, replenishing tricarboxylic acid cycle intermediates withdrawn for biosynthesis. Catabolism of glucogenic and ketogenic amino acids introduces carbon skeletons that compete with glycolytic pyruvate for mitochondrial entry and oxidative processing. This competition becomes particularly pronounced under conditions of high protein intake, fasting, or metabolic stress, where amino acid oxidation supports energy production and redox balance. Anaplerotic flux alters the relative contribution of carbohydrate-derived carbon to mitochondrial metabolism, reshaping substrate hierarchy within the cell (Ahuja et al.., 2026). While this flexibility supports survival during nutrient fluctuations, excessive reliance on amino acid oxidation can suppress glucose oxidation and alter nitrogen balance. Thus, amino acids function not merely as building blocks for protein synthesis but as active regulators of metabolic prioritization within the central energy network.

6.4 Metabolic Inflexibility in Insulin-Resistant States

Metabolic inflexibility arises when cells lose the capacity to switch efficiently between substrates in response to changing physiological conditions. In insulin-resistant states, persistent fatty acid oxidation dominates mitochondrial metabolism, even when carbohydrate availability is high. This rigidity suppresses glucose uptake, glycolysis, and oxidation, contributing to hyperglycemia and impaired insulin signaling. Rather than reflecting isolated enzymatic dysfunction, metabolic inflexibility represents a systems-level reprogramming of energy metabolism (Goodpaster *et al.,* 2017). Altered hormonal signaling, chronic lipid oversupply, and mitochondrial signaling disturbances converge to lock cells into a lipid-centric metabolic state. This maladaptive substrate preference exacerbates oxidative stress, disrupts redox balance, and reinforces insulin resistance, creating a self-sustaining cycle of metabolic dysfunction.

6.5 Therapeutic Targeting of Substrate-Switching Nodes

Restoring metabolic flexibility requires intervention at regulatory nodes that govern substrate entry and mitochondrial fuel selection. Enzymes and transporters controlling fatty acid uptake, mitochondrial import, and pyruvate oxidation represent strategic targets for rebalancing substrate utilization. Modulation of these

nodes can relieve excessive lipid dominance, re-enable glucose oxidation, and improve insulin responsiveness (Samuel *et al.,* 2012). From a therapeutic perspective, targeting substrate-switching mechanisms offers a means to correct metabolic dysfunction without globally suppressing energy production. By reinstating the capacity for adaptive fuel selection, such strategies aim to restore energetic efficiency, reduce metabolic stress, and improve systemic glucose homeostasis. This approach emphasizes metabolic plasticity as a core determinant of cellular and organismal health.

CONCLUSION

Cellular nutrient metabolism represents a highly integrated biochemical network that enables precise coordination of carbohydrate, lipid, and protein utilization in response to fluctuating energetic and environmental demands. At the molecular level, metabolic flexibility emerges from dynamic regulation of enzymatic flux, mitochondrial function, and signaling pathways that collectively determine substrate prioritization and energy efficiency. The interplay between central carbon metabolism, redox balance, and epigenetic regulation underscores the role of metabolites not only as fuels but also as regulators of gene expression and cellular adaptation. Disruption of these finely tuned processes leads to metabolic inflexibility, a defining feature of insulin resistance and related metabolic disorders. Advancing our understanding of the molecular mechanisms governing nutrient sensing, substrate competition, and mitochondrial–nuclear communication provides critical insight into the biochemical basis of metabolic health. Such knowledge establishes a foundation for developing targeted strategies aimed at restoring metabolic plasticity and improving cellular resilience in metabolic disease states.

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