

Metabolic health, disease, and therapeutic strategies

Meera S. Krishnan

Institute of Metabolic Health, Chennai Medical University, India

Corresponding Authors*

Meera S. Krishnan

Institute of Metabolic Health, Chennai Medical University, India

E-mail: meera.k@gmail.com

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Introduction

Cancer cells significantly alter their metabolism to fuel growth and survival, a process known as metabolic rewiring. This involves changes in how they process glucose, lipids, and amino acids. Targeting these distinct metabolic pathways, such as glycolysis or glutaminolysis, offers promising strategies for new cancer therapies and can help overcome resistance to existing treatments.[1]

Mitochondrial dynamics, encompassing fusion and fission, play a critical role in metabolic health. Dysregulation of these processes contributes significantly to obesity and insulin resistance by affecting energy metabolism, increasing oxidative stress, and promoting inflammation. Targeting mitochondrial dynamics presents a promising avenue for developing new treatments for these prevalent metabolic disorders.[2]

Metabolic flux analysis offers a dynamic view into the altered metabolic pathways underlying neurodegenerative diseases such as Alzheimer's and Parkinson's. By tracing the flow of nutrients through cells, researchers can identify specific dysregulations in glucose, amino acid, and lipid metabolism that contribute to neuronal dysfunction. This approach is crucial for uncovering new therapeutic targets to combat these devastating conditions.[3]

The gut microbiome profoundly impacts host metabolism, acting as a crucial determinant in the development of metabolic syndrome. This intricate relationship involves microbial metabolites influencing host glucose and lipid regulation, alongside inflammatory responses. Emerging research highlights the potential of therapeutically altering the gut microbiome to manage and prevent metabolic syndrome.[4]

NAD⁺ plays a pivotal role in cellular metabolism, yet its levels naturally diminish with aging, contributing to various age-related diseases. Understanding the complex pathways of NAD⁺ synthesis and degradation is essential. Boosting NAD⁺ levels through therapeutic interventions shows significant promise in counteracting age-related metabolic decline and improving overall health.[5]

Immune cells dynamically adjust their metabolism, a process known as metabolic reprogramming, which is crucial for their function in health and disease. These metabolic shifts dictate whether immune cells adopt inflammatory or immunosuppressive roles, influencing the progression of conditions like inflammatory diseases and cancer. Modulating immunometabolism presents a promising avenue for novel therapeutic strategies.[6]

The circadian rhythm is a powerful regulator of liver metabolism, and its disruption plays a key role in the development of nonalcoholic fatty liver disease (NAFLD). Alterations in the internal biological clock can severely impact hepatic lipid synthesis, glucose processing, and bile acid metabolism. Recognizing this connection opens doors for innovative chronotherapeutic strategies to manage and treat metabolic liver disorders.[7]

Exercise profoundly alters skeletal muscle metabolism, largely by driving crucial mitochondrial adaptations. Regular physical activity stimulates the creation of new mitochondria, boosts the muscle's capacity to use oxygen for energy, and improves metabolic flexibility. These changes are fundamental not only for enhancing athletic performance but also for maintaining overall metabolic health.[8]

Epigenetic modifications are key drivers of metabolic reprogramming in cancer cells, orchestrating the expression of genes involved in critical metabolic pathways. Changes in DNA methylation, histone modifications, and non-coding RNAs all contribute to the altered metabolism that fuels tumor growth. Targeting these epigenetic regulators represents a compelling strategy for new cancer therapies, aiming to disrupt abnormal metabolic processes and improve treatment outcomes.[9]

Personalized nutrition offers a tailored approach to diet, leveraging individual metabolic profiles, genetics, and lifestyle to optimize health. 'Omics' technologies, including genomics and metabolomics, are crucial in revealing the vast metabolic differences between individuals. This advanced understanding enables the creation of more precise dietary strategies to improve metabolic health and prevent chronic diseases effectively.[10]

Description

Metabolism forms the bedrock of cellular function, orchestrating how organisms process nutrients for growth, survival, and energy. Across diverse biological contexts, from the precise demands of immune cell function to the complex interplay within whole-body systems, metabolic processes are continually fine-tuned. Dysregulation in these pathways frequently underpins a wide array of diseases, making the study of metabolism crucial for understanding disease mechanisms and developing effective interventions. This area of research highlights the dynamic nature of metabolic responses to both internal and external stimuli, from genetic predispositions to environmental factors.

In the realm of pathology, metabolic alterations are profoundly implicated. Cancer cells, for instance, undergo significant metabolic rewiring, modifying their processing of glucose, lipids, and amino acids to sustain their rapid growth. This understanding paves the way for targeting specific metabolic pathways like gly-

colysis or glutaminolysis as innovative cancer therapies. Similarly, neurodegenerative conditions such as Alzheimer's and Parkinson's diseases are characterized by altered metabolic fluxes, where dysregulations in glucose, amino acid, and lipid metabolism contribute directly to neuronal dysfunction. Understanding these shifts through metabolic flux analysis is key to finding new therapeutic targets. Beyond individual cells, systemic metabolic disorders like obesity and insulin resistance are heavily influenced by mitochondrial dynamics; an imbalance in mitochondrial fusion and fission processes directly impacts energy metabolism and increases oxidative stress.

Several intrinsic and extrinsic factors profoundly regulate metabolic health. NAD⁺ metabolism, for example, is central to cellular processes, and its decline with aging contributes to various age-related diseases. Strategies to boost NAD⁺ levels show promise in counteracting this decline. The gut microbiome emerges as a critical determinant of host metabolism, with microbial metabolites influencing glucose and lipid regulation, directly impacting conditions like metabolic syndrome. Further, the body's internal clock, the circadian rhythm, exerts powerful control over organ-specific metabolism, particularly in the liver, where its disruption contributes to nonalcoholic fatty liver disease (NAFLD) by affecting lipid synthesis and glucose processing.

Metabolic reprogramming is also a core aspect of immune cell function, dictating whether cells adopt inflammatory or immunosuppressive roles, affecting diseases from chronic inflammation to cancer. Modulating this immunometabolism offers a novel therapeutic frontier. Furthermore, epigenetic modifications, including DNA methylation and histone changes, serve as key drivers of metabolic reprogramming in cancer, controlling gene expression in critical metabolic pathways and offering additional therapeutic targets.

Lifestyle interventions and personalized approaches represent significant avenues for promoting metabolic health. Regular physical activity, through exercise, induces crucial mitochondrial adaptations in skeletal muscle, enhancing oxygen utilization and metabolic flexibility, which are vital for overall health. On a more individualized level, personalized nutrition utilizes 'omics' technologies to consider genetic profiles, metabolic biomarkers, and lifestyle factors, enabling the creation of tailored dietary strategies. This precision approach allows for optimizing metabolic health and effectively preventing chronic diseases by addressing individual metabolic differences. These diverse research areas collectively underscore the pervasive influence of metabolism and the potential for targeted interventions.

Conclusion

Metabolic processes are fundamental to health, with dysregulation implicated in various diseases. Cancer cells, for example, exhibit metabolic rewiring, altering glucose, lipid, and amino acid processing for growth, suggesting metabolic

pathways as therapeutic targets. Mitochondrial dynamics play a critical role in metabolic health, with dysregulation contributing to obesity and insulin resistance. Neurodegenerative diseases like Alzheimer's and Parkinson's are linked to altered metabolic flux, highlighting the need for identifying new targets. The gut microbiome significantly impacts host metabolism and metabolic syndrome development through microbial metabolites. NAD⁺ levels decline with aging, affecting cellular metabolism and age-related diseases, making NAD⁺ boosting a promising intervention. Immune cells undergo metabolic reprogramming, influencing inflammatory conditions and cancer. The circadian rhythm regulates liver metabolism, and its disruption contributes to nonalcoholic fatty liver disease (NAFLD). Exercise induces beneficial mitochondrial adaptations in skeletal muscle, improving metabolic health. Epigenetic modifications drive metabolic reprogramming in cancer, offering therapeutic opportunities. Finally, personalized nutrition leverages individual metabolic profiles and 'omics' technologies to optimize health and prevent chronic diseases.

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