Pathways of cellular signalling in energy metabolism: Physiology to pathology.

Ashton Nie*

Department of Gastroenterology and Hepatology, Shenzhen University General Hospital, Shenzhen, China

Introduction

Cellular energy metabolism is a highly regulated process that involves the conversion of nutrients into usable energy in the form of ATP. It plays a crucial role in maintaining cellular homeostasis and supporting various physiological functions. Energy metabolism is governed by intricate signaling pathways that sense nutrient availability, energy demands, and cellular stress. Dysregulation of these signaling pathways can lead to metabolic disorders and contribute to the development of various pathologies. This article explores the pathways of cellular signaling in energy metabolism, highlighting their physiological roles and implications in pathological conditions.

Insulin signaling pathway

The insulin signaling pathway is a central regulator of energy metabolism, particularly in the context of glucose homeostasis. Insulin, a hormone secreted by the pancreas, acts on target tissues such as liver, muscle, and adipose tissue to regulate glucose uptake, utilization, and storage. Upon binding to its receptor, insulin activates a cascade of intracellular signaling events. Insulin signaling pathway activates phosphatidylinositol 3-kinase (PI3K), which phosphorylates and activates Akt (also known as protein kinase B). Akt regulates glucose transport by promoting the translocation of glucose transporters, such as GLUT4, to the plasma membrane. It also stimulates glycogen synthesis by inhibiting glycogen synthase kinase 3 (GSK3) and activating glycogen synthase. Additionally, insulin signaling inhibits gluconeogenesis, the process of glucose production from non-carbohydrate sources, in the liver. It suppresses the expression of key gluconeogenic enzymes, such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), through the inactivation of transcription factors, including forkhead box protein O1 (FoxO1) [1].

AMP-Activated Protein Kinase (AMPK) pathway

AMP-Activated Protein Kinase (AMPK) is a master regulator of cellular energy status. It functions as an energy sensor, activated under conditions of low energy, such as low ATP levels or increased AMP-to-ATP ratio. AMPK activation stimulates catabolic pathways that generate ATP while inhibiting anabolic processes that consume ATP. When activated, AMPK phosphorylates and inhibits enzymes involved in ATP-consuming processes, such as fatty acid synthesis (e.g., acetyl-CoA carboxylase, ACC) and protein synthesis (e.g., mammalian target of rapamycin, mTOR). Conversely, it activates enzymes involved in ATP-generating processes, such as fatty acid oxidation (e.g., carnitine palmitoyltransferase 1, CPT1) and glucose uptake (e.g., translocation of GLUT4). AMPK also plays a role in mitochondrial biogenesis and function. It stimulates mitochondrial biogenesis by activating peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), a master regulator of mitochondrial biogenesis. AMPK activation also enhances mitochondrial oxidative capacity and improves mitochondrial quality control through the regulation of mitophagy, a process that selectively degrades damaged mitochondria [2].

Sirtuin pathways

Sirtuins, a family of NAD+-dependent deacetylases, have emerged as critical regulators of cellular energy metabolism. They modulate energy metabolism through the deacetylation of various substrates, including transcription factors, metabolic enzymes, and histones. One of the well-studied sirtuins is Sirtuin 1 (SIRT1), which is involved in the regulation of multiple metabolic processes. SIRT1 deacetylates and activates PGC-1α, promoting mitochondrial biogenesis and oxidative metabolism. It also deacetylates and inhibits the activity of the transcription factor peroxisome proliferator-activated receptor gamma (PPARγ) coactivator-1 alpha (PGC-1α), which leads to enhanced gluconeogenesis in the liver. Moreover, SIRT1 influences cellular metabolism through its interactions with other signaling pathways. For example, SIRT1 can deacetylate and activate AMPK, synergistically regulating cellular energy balance. SIRT1 also interacts with insulin signaling by deacetylating insulin receptor substrate 2 (IRS2), enhancing insulin sensitivity, and promoting glucose uptake [3].

mTOR signaling pathway

The mechanistic target of rapamycin (mTOR) is a central regulator of cell growth and metabolism. It integrates various signals, including nutrient availability, energy status, and growth factors, to coordinate cellular processes involved in energy metabolism and protein synthesis. mTOR functions through two distinct complexes: mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2). mTORC1 is sensitive to

***Correspondence to:** Ashton Nie, Department of Gastroenterology and Hepatology, Shenzhen University General Hospital, Shenzhen, China. E-mail: ashtom_n74@cuhk.edu.hk

***Received:** 22-May-2023, Manuscript No. AACBM-23-101826; **Editor assigned:** 25-May-2023, PreQC No. AACBM-23-101826(PQ); **Reviewed:** 08-Jun-2023, QC No AACBM-23-101826; **Revised:** 12-Jun-2023, Manuscript No. AACBM-23-101826(R); **Published:** 20-Jun-2023, DOI:10.35841/aacbm-5.3.152*

***Citation:** Nie A. Pathways of cellular signalling in energy metabolism: Physiology to pathology. J Cell Biol Metab. 2023;5(3):152*

nutrient availability and regulates processes such as protein synthesis, lipogenesis, and autophagy. It is activated by amino acids, insulin, and growth factors. mTORC1 promotes anabolic processes by activating key regulators of protein synthesis, including ribosomal protein S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E-binding protein 1 (4EBP1). It also stimulates lipogenesis by promoting the expression of lipogenic genes through the activation of transcription factors, such as sterol regulatory element-binding proteins (SREBPs) [4].

Pathological implications

Dysregulation of cellular signaling pathways in energy metabolism can lead to metabolic disorders and contribute to the development of various pathologies. For example:

Insulin resistance: Impaired insulin signaling can lead to insulin resistance, a key feature of type 2 diabetes. Insulin resistance is characterized by reduced glucose uptake and impaired glycogen synthesis, contributing to hyperglycemia.

Obesity: Dysregulated signaling pathways, such as mTOR and AMPK, are implicated in the development of obesity. Excessive activation of mTORC1 promotes adipogenesis and inhibits lipolysis, leading to increased fat accumulation. Conversely, impaired AMPK activity reduces fatty acid oxidation and promotes lipid storage.

Cancer: Dysregulation of energy metabolism is a hallmark of cancer cells. Altered signaling pathways, including increased mTORC1 activity and enhanced aerobic glycolysis, support the metabolic demands of rapidly proliferating cancer cells [5].

Conclusion

Cellular signaling pathways play critical roles in the regulation of energy metabolism. Insulin signaling pathway ensures glucose homeostasis, AMPK pathway coordinates energy balance, sirtuin pathways integrate metabolic and epigenetic regulation, and mTOR signaling pathway controls cell growth and anabolic processes. Dysregulation of these pathways can contribute to metabolic disorders, such as diabetes and obesity, as well as pathological conditions, including cancer. Understanding the intricate signaling networks in energy metabolism provides insights into potential therapeutic targets for the treatment of metabolic diseases and related pathologies. Further research is needed to unravel the complexities of these pathways and develop effective interventions to restore metabolic balance and improve human health.

References

1. Metallo CM, Vander Heiden MG. Metabolism strikes back: Metabolic flux regulates cell signaling. Genes Dev. 2010;24(24):2717-22.
2. Mihaylova MM, Shaw RJ. The AMPK signalling pathway coordinates cell growth, autophagy and metabolism. Nat Cell Biol. 2011;13(9):1016-23.
3. Semenza GL. Hypoxia-inducible factors in physiology and medicine. Cell. 2012;148(3):399-408.
4. Cai L, Tu BP. Driving the cell cycle through metabolism. Annu Rev Cell Dev Biol. 2012;28:59-87.
5. Choi AM, Ryter SW, Levine B. Autophagy in human health and disease. N Eng J Med. 2013;368(7):651-62.

Citation: *Nie A. Pathways of cellular signalling in energy metabolism: Physiology to pathology. J Cell Biol Metab. 2023;5(3):152*