

Cellular Signaling Dysregulation in Metabolic Syndromes

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ABOVE THE STUDY

Metabolic syndromes represent a cluster of interconnected disorders, including insulin resistance, central obesity, dyslipidemia, and hypertension, which collectively increase the risk of cardiovascular disease and type 2 diabetes. At the molecular level, these conditions are increasingly recognized as disorders of cellular signaling rather than isolated metabolic defects. Dysregulation of key signaling pathways disrupts energy homeostasis, inflammation control, and metabolic flexibility, ultimately driving disease progression.

One of the central pathways implicated in metabolic syndrome is the insulin signaling cascade. Under normal physiological conditions, insulin binds to its receptor and activates downstream signaling through Insulin Receptor Substrates (IRS), phosphoinositide 3-kinase (PI3K), and Akt, leading to glucose uptake and glycogen synthesis. In metabolic syndrome, this pathway becomes impaired due to serine phosphorylation of IRS proteins, lipid accumulation, and chronic inflammation, resulting in insulin resistance [1]. This resistance is a hallmark feature linking obesity to hyperglycemia and type 2 diabetes.

Chronic low-grade inflammation plays a crucial role in disrupting cellular signaling networks. Adipose tissue in obese individuals secretes pro-inflammatory cytokines such as TNF- α and IL-6, which interfere with insulin signaling pathways [2]. These cytokines activate stress-related kinases such as JNK and IKK β , which further inhibit insulin receptor signaling, creating a self-amplifying loop of metabolic dysfunction. This inflammatory signaling is now considered a key driver of systemic insulin resistance [3].

AMP-Activated Protein Kinase (AMPK), a master regulator of cellular energy homeostasis, is also significantly altered in metabolic syndrome. AMPK normally promotes glucose uptake and fatty acid oxidation while inhibiting lipogenesis. However, its activity is often reduced in obesity and insulin resistance, leading to impaired energy balance and lipid accumulation in tissues such as liver and muscle [4]. Restoration of AMPK signaling is therefore considered a potential therapeutic strategy for metabolic disorders.

Another critical pathway involved is the Mechanistic Target of Rapamycin (mTOR) signaling cascade. mTOR integrates nutrient and growth factor signals to regulate protein synthesis and cellular growth. In metabolic syndrome, overactivation of mTOR contributes to insulin resistance and lipid dysregulation [5]. The interplay between mTOR and insulin signaling highlights the complexity of metabolic regulation and the importance of pathway crosstalk.

Mitochondrial signaling dysfunction further exacerbates metabolic imbalance. Impaired oxidative phosphorylation and increased Reactive Oxygen Species (ROS) production disrupt cellular energy metabolism and activate stress signaling pathways [6]. ROS-mediated activation of NF- κ B enhances inflammatory gene expression, linking mitochondrial dysfunction to systemic inflammation and metabolic deterioration.

Adipokines, such as adiponectin and leptin, also play important roles in cellular signaling regulation. Adiponectin enhances insulin sensitivity through activation of AMPK, whereas leptin regulates appetite and energy expenditure through hypothalamic signaling pathways. In metabolic syndrome, reduced adiponectin levels and leptin resistance contribute to dysregulated energy balance and insulin resistance [7].

Emerging evidence also highlights the role of gut-derived signaling molecules in metabolic regulation. Short-chain fatty acids and bile acid metabolites influence host metabolism through G-protein coupled receptors and nuclear receptors such as FXR and TGR5. Dysbiosis of the gut microbiota alters these signaling pathways, contributing to metabolic inflammation and insulin resistance [8].

At the epigenetic level, DNA methylation and microRNA expression further modulate cellular signaling pathways involved in metabolism. Specific microRNAs regulate insulin signaling components and lipid metabolism genes, thereby influencing disease progression [9]. These epigenetic modifications provide a mechanistic link between environmental factors and metabolic dysfunction.

Therapeutically, targeting dysregulated signaling pathways offers promising opportunities. Drugs such as metformin activate

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Received: 24-Feb-2025, Manuscript No. JMPB-25-41750; **Editor assigned:** 26-Feb-2025, PreQC No. JMPB-25-41750 (PQ); **Reviewed:** 12-Mar-2025, QC No. JMPB-25-41750; **Revised:** 19-Mar-2025, Manuscript No. JMPB-25-41750 (R); **Published:** 26-Mar-2025. DOI: 10.35248/jmpb.25.6.212.

Citation: Nakamura H (2025). Cellular Signaling Dysregulation in Metabolic Syndromes. *J Mol Pathol Biochem*.6:212.

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AMPK signaling, improving insulin sensitivity, while emerging agents target inflammatory kinases and mTOR pathways [10]. However, given the interconnected nature of these signaling networks, combination therapies may be required for effective disease management.

In conclusion, metabolic syndromes are fundamentally disorders of cellular signaling dysregulation involving insulin resistance, inflammatory activation, mitochondrial dysfunction, and nutrient-sensing pathways. A deeper understanding of these interconnected networks is essential for developing targeted and effective therapeutic strategies.

References

1. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature*. 2001;414(6865):799-806.
2. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006;444(7121):860-7.
3. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *The Journal of clinical investigation*. 2006;116:1793-801.
4. Hardie DG, Ross FA, Hawley SA. AMP-activated protein kinase: a target for drugs both ancient and modern. *Chemistry & biology*. 2012;19:1222-36.
5. Laplante M, Sabatini DM. mTOR signaling in growth control and disease. *cell*. 2012;149:274-93.
6. Di Donfrancesco A, Massaro G, Di Meo I, Tiranti V, Bottani E, Brunetti D, et al. Gene therapy for mitochondrial diseases: Current status and future perspective. *Pharmaceutics*. 2022;14:1287.
7. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. *Endocrine reviews*. 2005;26:439-51.
8. Canfora EE, Jocken JW, Blaak EE. Short-chain fatty acids in control of body weight and insulin sensitivity. *Nature Reviews Endocrinology*. 2015;11:577-91.
9. Zhang X, Ho SM. Epigenetics meets endocrinology. *Journal of molecular endocrinology*. 2011 Feb;46(1):R11.
10. Violette B, Guigas B, Garcia NS, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. *Clinical science*. 2012;122:253-70.