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The Role of Post-translational Modifications in Diabetes: Unveiling the Molecular Complexity

Daniela María*

Department of Physical Chemistry, Faculty of Chemistry, University of Bialystok, Ciołkowskiego 1K Street, 15-245 Białystok, Poland

Introduction

Diabetes mellitus, a metabolic disorder characterized by hyperglycemia, affects millions worldwide, posing a significant health challenge. While genetic predisposition and lifestyle factors contribute to its pathogenesis, emerging evidence suggests a pivotal role of post-translational modifications (PTMs) in the development and progression of diabetes. PTMs, intricate molecular alterations occurring after protein synthesis, modulate protein structure, function and localization, exerting profound effects on cellular signaling pathways. This article explores the diverse landscape of PTMs implicated in diabetes, unraveling their mechanistic insights and therapeutic implications [1].

Description

Glycosylation, the enzymatic addition of carbohydrate moieties to proteins, profoundly influences protein structure and function. In diabetes, aberrant glycosylation disrupts cellular homeostasis, contributing to disease pathogenesis. Notably, advanced glycation end products (AGEs), formed by non-enzymatic glycation of proteins, accumulate in diabetic tissues, promoting inflammation and oxidative stress. Additionally, hyperglycemia-induced glycosylation impairs the function of vital proteins, including insulin receptors and extracellular matrix components, exacerbating insulin resistance and vascular complications [2].

Phosphorylation, the addition of phosphate groups to proteins, serves as a pivotal regulatory mechanism in cellular signaling cascades. Dysregulated phosphorylation events underlie insulin resistance and pancreatic β-cell dysfunction in diabetes. In insulin signaling pathways, aberrant phosphorylation of insulin receptor substrates (IRS) disrupts downstream signaling, impairing glucose uptake and metabolism. Moreover, dysregulated phosphorylation of transcription factors, such as FoxO1 and PPARγ, perturbs gene expression profiles, exacerbating metabolic abnormalities in diabetes [2].

Acetylation, the addition of acetyl groups to lysine residues, dynamically modulates protein function and stability. Altered protein acetylation profiles are implicated in the pathogenesis of type 2 diabetes mellitus (T2DM), linking nutrient sensing pathways with metabolic dysregulation. In diabetes, dysregulated acetylation of metabolic enzymes, such as PGC-1α and SIRT1, disrupts mitochondrial function and energy metabolism, contributing to insulin resistance and β-cell dysfunction. Moreover, aberrant acetylation of histones and transcription factors dysregulates gene expression programs, exacerbating diabetic complications [3].

Ubiquitination, the covalent attachment of ubiquitin molecules to proteins, regulates protein turnover and cellular signaling. Dysregulated ubiquitination pathways are implicated in the pathogenesis of diabetes, influencing insulin sensitivity and pancreatic β-cell function. In diabetes, aberrant ubiquitination of insulin signaling components, including IRS and Akt, disrupts insulin receptor trafficking and downstream signaling, exacerbating insulin resistance. Furthermore, dysregulated ubiquitination of transcription factors, such as PDX-1 and HNF1α, impairs β-cell development and function, contributing to impaired insulin secretion in diabetes [4].

SUMOylation, the reversible attachment of small ubiquitin-like modifier (SUMO) proteins to target proteins, modulates protein-protein interactions and subcellular localization. Emerging evidence suggests a role of dysregulated SUMOylation in diabetes pathogenesis, influencing insulin signaling and βcell function. In diabetes, aberrant SUMOylation of IRS and Akt disrupts insulin receptor signaling and glucose homeostasis, contributing to insulin resistance. Moreover, dysregulated SUMOylation of transcription factors, such as PPARγ and NF-κB, alters gene expression profiles, exacerbating inflammatory responses and metabolic abnormalities in diabetes [5].

Conclusion

Post-translational modifications intricately regulate protein function and cellular signaling pathways, exerting profound effects on diabetes pathogenesis. Glycosylation, phosphorylation, acetylation, ubiquitination and SUMOylation represent key PTMs dysregulated in diabetes, contributing to insulin resistance, pancreatic β-cell dysfunction and diabetic complications. Understanding the molecular mechanisms underlying PTM dysregulation in diabetes offers novel insights into disease pathogenesis and therapeutic strategies. Targeting PTMs and their regulatory enzymes holds promise for developing precision therapies to mitigate diabetes-associated complications and improve patient outcomes. Further research elucidating the intricate interplay of PTMs in diabetes will pave the way for innovative therapeutic interventions, ushering in a new era in diabetes management.

Acknowledgement

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Conflict of Interest

None.

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***Address for Correspondence:** Daniela María, Department of Physical Chemistry, Faculty of Chemistry, University of Bialystok, Ciołkowskiego 1K Street, 15-245 Białystok, Poland; E-mail: mariajose456@gmail.com*

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