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Protein Methylation, a Wrestler for Chromatin Structure, Modulates the Risk of Metabolic Disorders

Skeletal muscle is a critical organ in maintaining homeostasis against metabolic stress, and histone post-translational modifications are pivotal in those processes. However, the intricate nature of histone methylation in skeletal muscle and its impact on metabolic homeostasis have yet to be elucidated. Here, we report that mitochondria-rich slow-twitch myofibers are characterized by significantly higher levels of H3K36me2 along with repressed expression of Kdm2a, an enzyme that specifically catalyses H3K36me2 demethylation. Deletion or inhibition of Kdm2a shifts fuel use from glucose under cold challenge to lipids under obese conditions by increasing the proportion of mitochondria-rich slow-twitch myofibers. This protects mice against cold insults and high-fat-diet-induced obesity and insulin resistance. Mechanistically, Kdm2a deficiency leads to a marked increase in H3K36me2 levels, which then promotes the recruitment of Mrg15 to the Esrrg locus to facilitate its precursor messenger RNA splicing, thereby reshaping skeletal muscle metabolic profiles to induce slow-twitch myofiber transition. Collectively, our data support the role of Kdm2a as a viable target against metabolic stress.

Keywords: Kdm2a, H3K36me2, Histone post-translational modifications, mitochondria, myofiber transition, metabolic stress

Biography

Cong-Yi Wang, PhD, is the Director of the NHC Key Laboratory of Respiratory Diseases and a Professor at the Center for Biomedical Research, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. He received his PhD in Medical Immunology from Tongji Medical College and has established an internationally recognized research program in immunology, metabolism, and translational medicine. Prof. Wang has served on multiple prestigious study sections and review panels, including NIH, ADA, JDRF, the Wellcome Trust, and national funding agencies across Asia and Europe. He holds key editorial roles, including Editor-in-Chief of the International Journal of Molecular Epidemiology and Genetics and Associate Editor of Frontiers in Immunology. His research has been supported by major national and international grants and has resulted in 17 patents and over 210 peer-reviewed publications in leading journals such as NEJM, Cell Metabolism, Nature Communications, Diabetes, and Diabetologia.