EDITORIAL ASIAN JOURNAL OF MEDICAL SCIENCES

Protein lactylation: A new jewel in the crown

Submission: 28-04-2025 Revision: 08-05-2025 Publication: 01-06-2025

Access this article online

Website:
https://ajmsjournal.info/index.php/AJMS/index

DOI: 10.71152/ajms.v16i6.4587

E-ISSN: 2091-0576

P-ISSN: 2467-9100

Lactylation is a newly identified post-translational modification that has emerged as a crucial epigenetic regulator, significantly influencing cellular functions and disease processes.[1] Lactylation involves the addition of lactate, a glycolysis byproduct, to lysine residues in proteins, particularly histones. This modification, which leads to lactyl-lysine formation, was first discovered in 2019 by Zhang et al. and reported in Nature.[2]

WHAT IS THE BIOCHEMICAL PROCESS

In the lactylation process, lactyl-CoA (derived from lactate) acts as the donor molecule that transfers the lactyl group to the ε-amino group of lysine residues.[3] This marks a unique epigenetic signature that affects gene expression in ways distinct from other histone modifications, such as acetylation or methylation. Lactylation signifies a direct link between cellular metabolism and gene regulation. When cells execute glycolysis and generate lactate, especially under low-oxygen conditions, this triggers histone lactylation.[4] Histone lactylation usually encourages gene expression, akin to acetylation, by facilitating a more accessible chromatin structure. In macrophages, histone lactylation is vital for the late-phase immune response, aiding homeostasis and tissue repair by regulating genes associated with wound healing and bacterial clearance.[5] Abnormal lactylation has been linked to several pathological conditions such as cancer, inflammatory diseases, and metabolic disorders.[6-8]

RECENT RESEARCH DEVELOPMENTS

Recent investigations have broadened our knowledge of lactylation beyond histones to non-histone proteins. Researchers have discovered lactylation sites on enzymes associated with glycolysis, the tricarboxylic acid cycle, and additional metabolic pathways, implying a more extensive regulatory network. Advanced mass spectrometry methods have facilitated the mapping of lactylomes across different cell types and tissues, uncovering hundreds of proteins subject to this modification.[9,10]

The identification of lactylation has paved the way for new research opportunities at the crossroads of metabolism and epigenetics. Understanding the enzymes (writers, erasers, and readers) involved in regulating lactylation may unveil new therapeutic targets for interventions in diseases linked to metabolic dysregulation and altered gene expression.

Ruby Dhar[1], Arun Kumar[2], Subhradip Karmakar[3]

[1]Scientist, Room 3020, [3]Additional Professor, Department of Biochemistry, All India Institute of Medical Sciences, New Delhi, [2]Professor, Department of Biochemistry, Jagannath Gupta Institute of Medical Sciences, Kolkata, West Bengal, India

Address for Correspondence:
Dr. Subhradip Karmakar, Additional Professor, Department of Biochemistry, All India Institute of Medical Sciences, New Delhi, India. **Mobile:** +91-9999612564. **E-mail:** subhradipaiims@gmail.com
Dr. Arun Kumar, Professor, Department of Biochemistry, Jagannath Gupta Institute of Medical Sciences, Budge Budge, Kolkata, West Bengal, India. **Mobile:** +91-7584089886. **E-mail:** editor@ajmsjournal.info

REFERENCES

1. Zhang W, Shan G, Bi G, Hu Z, Yi Y, Zeng D, et al. Lactylation and regulated cell death. Biochim Biophys Acta Mol Cell Res. 2025;1872:119927.
https://doi.org/10.1016/j.bbamcr.2025.119927
2. Zhang D, Tang Z, Huang H, Zhou G, Cui C, Weng Y, et al. Metabolic regulation of gene expression by histone lactylation. Nature. 2019;574:575-80.
https://doi.org/10.1038/s41586-019-1678-1

3. Tsusaka T, Najar MA, Sharma I, Marcinkiewicz MM, Crispim CV, Snyder NW, et al. Class I histone deacetylases catalyze lysine lactylation. bioRxiv; 2025.
https://doi.org/10.1101/2025.02.25.640220
4. Vander Heiden MG, Cantley LC and Thompson CB. Understanding the Warburg effect: The metabolic requirements of cell proliferation. Science. 2009;324:1029-33.
https://doi.org/10.1126/science.1160809
5. Dichtl S, Lindenthal L, Zeitler L, Behnke K, Schlösser D, Strobl B, et al. Lactate and IL6 define separable paths of inflammatory metabolic adaptation. Sci Adv. 2021;7:eabg3505.
https://doi.org/10.1126/sciadv.abg3505
6. Goldberg EL, Letian A, Dlugos T, Leveau C and Dixit VD. Innate immune cell-intrinsic ketogenesis is dispensable for organismal metabolism and age-related inflammation. J Biol Chem. 2023;299:103005.
https://doi.org/10.1016/j.jbc.2023.103005
7. Tannahill GM, Curtis AM, Adamik J, Palsson-McDermott EM, McGettrick AF, Goel G, et al. Succinate is an inflammatory signal that induces IL-1β through HIF-1α. Nature. 2013;496:238-42.
https://doi.org/10.1038/nature11986
8. Colegio OR, Chu NQ, Szabo AL, Chu T, Rhebergen AM, Jairam V, et al. Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. Nature. 2014;513:559-63.
https://doi.org/10.1038/nature13490
9. Semenza GL. Oxygen sensing, hypoxia-inducible factors, and disease pathophysiology. Annu Rev Pathol. 2014;9:47-71.
https://doi.org/10.1146/annurev-pathol-012513-104720
10. Sabari BR, Zhang D, Allis CD and Zhao Y. Metabolic regulation of gene expression through histone acylations. Nat Rev Mol Cell Biol. 2017;18:90-101.
https://doi.org/10.1038/nrm.2016.140

Authors' Contributions:
RD, AK, and SK- Contributed equally toward the scripting of this editorial.

Work attributed to:
Department of Biochemistry, All India Institute of Medical Sciences, New Delhi, India, and Department of Biochemistry, Jagannath Gupta Institute of Medical Sciences and Hospital, Budge Budge, Kolkata, West Bengal, India.

Orcid ID:
Dr. Ruby Dhar - https://orcid.org/0000-0003-3600-6554
Dr. Arun Kumar - https://orcid.org/0000-0002-8800-0296
Dr. Subhradip Karmakar - https://orcid.org/0000-0002-4757-8729

Source of Support: Nil, **Conflicts of Interest:** None declared.