Molecular Therapy
Nucleic Acids
Commentary

RNA modifications at the heart of oral inflammation

Nicola Guzzi[1]

https://doi.org/10.1016/j.omtn.2025.102528

In the March issue of *MTNA*, Fan et al. described a novel molecular pathway involved in the development of oral lichen planus (OLP), regulated by the RNA modification N6- methyladenosine (m6A).[1] RNA modifications are critical in controlling gene expression, and their implications in various diseases are well established.[2] m6A is the most abundant mRNA modification, influencing several aspects of the mRNA life cycle, including mRNA stability and translation.[3] Fan et al. uncover a role of m6A in OLP, a chronic mucocutaneous inflammatory disorder characterized by T cell infiltration and an increased risk of malignant transformation. The molecular mechanisms underlying OLP remain largely unknown; therefore, the standard of care primarily focuses on symptom management.[4] This study underscores the role of RNA modifications in regulating the expression of key genes involved in OLP development, such as the vitamin D receptor (VDR). It is intriguing to speculate that other genes implicated in OLP etiology might also be regulated by m6A. Further research is required to explore the transcriptome-wide effects of m6A dysregulation in OLP.

Previous findings from the same lab have shown dysregulation of m6A in OLP and an increased level of the m6A methyltransferase METTL14.[5] In the current study, the authors report alterations in the fat mass and obesity-associated protein (FTO), an m6A eraser, in patient-derived OLP cells. Specifically, increased level of GSK-3β lead to the phosphorylation of FTO at Serine256 and its subsequent degradation. Using recombinant FTO and its catalytically inactive mutant, the authors demonstrated FTO-dependent regulation of m6A levels in *VDR* mRNA. The protective role of Vitamin D in OLP has been widely discussed, as has the downregulation of VDR in OLP development.[6] However, the molecular mechanisms modulating VDR levels are less understood. In this study, GSK-3β-mediated loss of FTO resulted in decreased *VDR* stability and increased cytokine activation and cellular apoptosis via the caspase-3 pathway. Notably, previous studies have reported post-transcriptional control of *VDR* stability through microRNA (miRNA)-mediated degradation.[7] Similarly, m6A-mediated regulation of *VDR* also occurs post-transcriptionally. Taken together, these data suggest an intricate program involving multiple post-transcriptional checkpoints to ensure the precise modulation of VDR levels. Future research should focus on better understanding the interconnections between distinct post-transcriptional programs.

The finding that both a writer (METTL14) and an eraser (FTO) of m6A are dysregulated in OLP underscores the significance of m6A biology in OLP and highlights the molecular complexity of the m6A molecular program. Discerning whether the increased m6A levels are primarily due to METTL14 upregulation or FTO downregulation is complex but crucial for advancing our understanding of OLP's molecular etiology and developing a curative strategy. The authors offer compelling evidence that FTO's catalytic activity is essential for erasing m6A from VDR and promoting VDR destabilization. However, future studies are required to better characterize the global changes in the m6A profile in FTO-deficient OLP cells. Given m6A's central role in regulating the mRNA life cycle, it is likely that additional mRNAs are impacted by the loss of FTO. Conducting m6A profiling and transcriptome-wide analysis of mRNA stability would provide a deeper understanding of the molecular programs overseen by FTO.

The ability of FTO to demethylate m6A *in vivo* has been a subject of considerable debate in the field.[8] While FTO was initially identified as the first m6A eraser, demonstrating the reversibility of this modification and sparking significant interest in m6A biology, later studies revealed that ALKBH5 is the primary m6A eraser in cells. Conversely, FTO's main substrate is N^6,2′-*O*-dimethyladenosine (m6Am), found at the second nucleotide position following the cap structure at the 5′ end of mRNA transcripts. Nevertheless, FTO has been shown to erase m6A on specific transcripts *in vivo*.[8] To fully understand the transcriptome-wide impact of FTO loss, future studies should aim to investigate m6A and m6Am levels in OLP cells in parallel and characterize their functional impact on transcript stability.

GSK-3β plays a significant role in regulating the proliferation and differentiation of epithelial cells, and its dysregulation is strongly associated with the development of oral and skin cancers.[9] Fan et al. describe a novel molecular mechanism linking GSK-3β and vitamin D pathways through the post-transcriptional modification of RNA.[1] Using an elegant co-culture system of human oral keratinocytes and OLP-derived T cells to mimic the pro-inflammatory environment typical of OLP patients, the study demonstrates the upregulation of GSK-3β, resulting in the phosphorylation and subsequent degradation of FTO. These findings were confirmed in OLP-derived oral keratinocytes. Fan et al. build on previous evidence that FTO decay is regulated through GSK-3β and show that reduced FTO levels lead to increased m6A modification of VDR, which, in turn, causes its destabilization.

The antagonistic relationship between GSK-3β and vitamin D pathways through the

[1]Translational Genomics, Centre for Genomics Research, Discovery Sciences, R&D, AstraZeneca, Gothenburg, Sweden

Correspondence: Nicola Guzzi, Translational Genomics, Centre for Genomics Research, Discovery Sciences, R&D, AstraZeneca, Gothenburg, Sweden.
E-mail: nicola.guzzi@astrazeneca.com

regulation of VDR levels has been described previously in liquid and solid tumors.[7,10] VDR regulation downstream of GSK-3β activation occurs at both transcriptional and post-transcriptional levels. For instance, key transcription factors downstream of the Wnt pathway (e.g., Snail1 and Snail2) directly regulate *VDR* mRNA expression.[7] Additionally, a cluster of miRNAs activated by Wnt signaling targets *VDR* and promotes its degradation.[7] In the context of OLP, GSK-3β is transcriptionally upregulated rather than activated through Wnt signaling. It is likely that GSK-3β upregulation is driven by cytokines released by the T cell as part of the pro-inflammatory OLP microenvironment. To gain deeper insights into the molecular pathogenesis of OLP, it will be necessary to dissect the contributions of these various transcriptional and post-transcriptional events toward the repression of the vitamin D pathway.

Overall, these findings emphasize the significance of RNA modifications, particularly m6A, in disease. It is intriguing to speculate on why cells have evolved such complex molecular mechanisms to control the expression of vital genes. m6A-mediated RNA degradation allows for the rapid turnover of key mRNAs in response to external stimuli, enabling the fine-tuning of gene expression. Given the essential role of the GSK-3β pathway in regulating cell proliferation and differentiation and the need to swiftly adjust gene expression programs in response to stimuli, it is plausible that FTO acts as a key node to sense GSK-3β activation status and regulates the gene expression levels of crucial transcripts accordingly. These findings align with previous evidence indicating that FTO downregulation downstream of Wnt signaling is necessary for triggering an epithelial-to-mesenchymal transition program in a m6A-dependent fashion. Are other RNA modifications regulated downstream of GSK-3β signaling, and if so, what is their impact on cellular fate? The emergence of novel therapeutic approaches that target RNA modifications and modulate their abundance necessitates a deeper understanding of their molecular pathways and their involvement in disease pathogenesis.

DECLARATION OF INTERESTS

N.G. is an employee and shareholder of AstraZeneca.

REFERENCES

1. Fan, Y., Hao, Y., Ding, Y., Wang, X., and Ge, X. (2025). FTO deficiency facilitates epithelia dysfunction in oral lichen planus. Mol. Ther. Nucleic Acids *36*, 102463.
2. Delaunay, S., Helm, M., and Frye, M. (2024). RNA modifications in physiology and disease: towards clinical applications. Nat. Rev. Genet. *25*, 104–122.
3. Sendinc, E., and Shi, Y. (2023). RNA m6A methylation across the transcriptome. Mol. Cell *83*, 428–441.
4. Kurago, Z.B. (2016). Etiology and pathogenesis of oral lichen planus: an overview. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. *122*, 72–80.
5. Wang, X., Li, S., Song, H., Ding, Y., Gao, R., Shi, X., Li, R., and Ge, X. (2023). METTL14-upregulated miR-6858 triggers cell apoptosis in keratinocytes of oral lichen planus through decreasing GSDMC. Commun. Biol. *6*, 976.
6. Zhao, B., Li, R., Yang, F., Yu, F., Xu, N., Zhang, F., Ge, X., and Du, J. (2018). LPS-induced Vitamin D Receptor Decrease in Oral Keratinocytes Is Associated With Oral Lichen Planus. Sci. Rep. *8*, 763.
7. Gonzalez-Sancho, J.M., Larriba, M.J., and Munoz, A. (2020). Wnt and Vitamin D at the Crossroads in Solid Cancer. Cancers *12*, 3434.
8. Wei, J., Liu, F., Lu, Z., Fei, Q., Ai, Y., He, P.C., Shi, H., Cui, X., Su, R., Klungland, A., et al. (2018). Differential m(6)A, m(6)A(m), and m(1)A Demethylation Mediated by FTO in the Cell Nucleus and Cytoplasm. Mol. Cell *71*, 973–985.e5.
9. Mishra, R. (2010). Glycogen synthase kinase 3 beta: can it be a target for oral cancer. Mol. Cancer *9*, 144.
10. Gupta, K., Stefan, T., Ignatz-Hoover, J., Moreton, S., Parizher, G., Saunthararajah, Y., and Wald, D.N. (2016). GSK-3 Inhibition Sensitizes Acute Myeloid Leukemia Cells to 1,25D- Mediated Differentiation. Cancer Res. *76*, 2743–2753.