POST-TRANSLATIONAL MODIFICATIONS

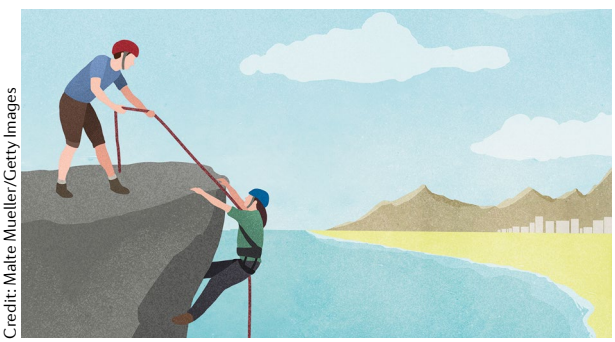
Histone serotonylation boosts neuronal transcription

> H3Q5ser promotes the transcription of neuronal genes … by potentiating the binding of the H3K4me3 reader TFIID

Serotonin (5-hydroxytryptamine) is known for its functions in the central nervous system and the gut as a neurotransmitter and a signalling molecule. Although serotonin can be found in the nucleus, its nuclear functions are unclear. Farrelly et al. now show that serotonin is a histone post-translational modification that promotes transcriptional permissiveness.

Serotonin can be covalently bound to proteins through transamidation by protein-glutamine γ-glutamyltransferase 2 (TGM2). Metabolic labelling and mutagenesis analyses in human and rodent cells revealed that TGM2 mediates the serotonylation of Gln5 of histone H3, but does not modify other histones.

Despite the close proximity of serotonylated H3 Gln5 (H3Q5ser) to trimethylated H3 Lys4 (H3K4me3; a modification associated with transcription activation) at the H3 tail, the presence of either modification did not hinder the catalysis of the other modification on nucleosomes in vitro. Labelling with H3Q5ser-specific or H3K4me3Q5ser-specific antibodies revealed that both H3Q5ser and H3K4me3Q5ser are found in cultured cells. However, only the dual modification was present in adult mouse and primate brain tissues and in fruit fly larvae. Overall, the dual modification was ubiquitously present in various mammalian serotonin-producing tissues and, especially in the brain, also in non-serotonergic cell types.



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To examine the role of H3K4me3Q5ser in cell differentiation, the levels of the dual modification were measured by chromatin immunoprecipitation and sequencing (ChIP–seq) in human pluripotent stem cell-derived serotonergic neurons, before and after differentiation. Differentiation led to a marked increase in H3K4me3Q5ser levels, especially at promoters of activated neuronal genes. This finding was corroborated in mouse embryonic brains examined at a time period in which serotonergic neurons become fully differentiated.

The role of H3Q5ser was further examined in the in vitro differentiation model of rat RN46A-B14 serotonergic cells. In differentiating cells, ChIP–seq signals of the antibody targeting the dual modification markedly increased at many gene promoters, without concomitant increase in signals of the antibody targeting H3K4me3 alone. This indicated that during differentiation, H3Q5ser levels increased without concomitant increase in H3K4me3 levels. Increased H3K4me3Q5ser again correlated with gene activation. Interestingly, H3K4me3Q5ser enrichment occurred at about two-thirds of genes that, in undifferentiated cells, had high levels of both H3K4me3 and the repressive modification H3K27me3 ('bivalent genes'), indicating that H3Q5ser may act to circumvent the repression of bivalent genes during differentiation.

TGM2 inhibition during RN46A-B14 cell differentiation decreased the expression of the H3K4me3Q5ser-regulated genes. Similarly, expressing a histone H3 mutant that cannot be serotonylated altered the expression patterns of many H3K4me3Q5ser-regulated genes and considerably reduced neurite length, suggesting that H3Q5ser is required for the differentiation of RN46A-B14 cells.

To investigate the effect of H3Q5ser on protein interactions of the H3 tail, synthetically modified H3-tail peptides were immunoprecipitated to identify their binding partners. The binding of dozens of known H3K4me3-binding proteins (H3K4me3 readers) was altered by the presence of Q5ser in the peptide. Among the H3K4me3 readers that exhibited Q5ser-enhanced binding were 15 members of the transcription factor IID (TFIID) complex, which functions in transcription initiation. ChIP–seq of a TFIID component in RN46A-B14 cells before and after differentiation revealed enrichment of H3K4me 3Q5ser compared with H3K4me3 in differentiated cells, suggesting that serotonylation of H3Q5 potentiates transcription initiation through TFIID during differentiation.

Serotonylation of H3Q5 is the first endogenous monoaminyl modification, and the first non-methyl post-translational modification of Gln, to be identified in histones. H3Q5ser promotes the transcription of neuronal genes during neuronal cell differentiation by potentiating the binding of the H3K4me3 reader TFIID at the gene promoters. Future studies will focus on identifying H3Q5ser readers and erasers and on other functions of H3Q5ser, for example, in the gut, and its possible contribution to pathophysiological conditions in the brain associated with aberrant serotonin function, such as mood-related disorders.

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ORIGINAL ARTICLE Farrelly, L. A. et al. Histone serotonylation is a permissive modification that enhances TFIID binding to H3K4me3. *Nature* **567**, 535–539 (2019)