The discovery of cystosine 5-hydroxymethylation, and of the Ten-Eleven Translocation family of enzymes (TET1, TET2, and TET3) that catalyze conversion of mC to hmC has sparked great interest in uncovering the roles played by this mark and these proteins.

In attempts to better understand the mechanisms by which TETs function, we searched for their protein partners. We found a strong association of TET2 and TET3 with the O-GlcNAc transferase OGT. This enzyme is known to catalyze the addition of an O-GlcNAc residue to serine and threonine of a large number of proteins. Its implication in the epigenetic control of transcription is emerging but information is scant on how OGT and epigenetic mechanisms are linked. After validation of the TET2- or TET3-OGT interaction, cellular depletion of TET2 or TET3 by RNAi experiments revealed reduced OGT-mediated O-linked glycosylation. In agreement with these data, western blotting with anti-GlcNAc antibody in RNAi TET2 and TET3 cells showed a decrease in global O-GlcNac levels. Further, ChIP-Seq analysis indicated that TET proteins colocalize with OGT on a significant number of target genes. Experiments are under way to evaluate the relationship between TET-OGT and gene expression as well the underlying mechanisms.

Our results thus suggest that TET2 and TET3 may regulate OGT-mediated GlcNAcylation, uncovering a direct mechanistic link between the O-GlcNAc transferase OGT and the 5-hydroxymethylation protein machinery.