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Structures of human m^{6}A RNA demethylases: FTO and ALKBH5

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Methylation at the N6 position of adenosine in mRNA (m^{6}A) was first observed around 40 years ago but little was known about the function of this modification at the time of discovery. Research over the last ten years has led to the identification of methyltransferases that produce or 'write' the m^{6}A RNA mark and recently demethylases that remove or 'erase' m^{6}A marks, thus indicating that the m^{6}A modification is reversible. Recent analyses have identified the motif and regions where m^{6}A marks are present within RNA transcripts as well as m^{6}A binding protein 'readers'. These studies have revealed a role for m^{6}A methylation in mRNA stability and demonstrated that sequence specific subsets of transcripts can be regulated in this manner. Like the histone lysine JmjC demethylases, nucleic acid demethylases are members of the 2-oxoglutarate and iron dependent oxygenase superfamily. The human nucleic acid oxygenases (NAOXs) with known structures include the TET enzyme that produces 5-hydroxymethylcytosine in DNA, ALKBH2 and 3 that demethylate 3-methylcytosine and 1-methyladenine in DNA, and ALKBH8 that modifies tRNA. We identified the fat mass and obesity associated protein, FTO, as a NAOX[1] and m^{6}A in RNA was recently reported to be a bona-fide substrate of FTO in in-vivo. Subsequently, ALKBH5 was also shown to be an m^{6}A demethylase. Here we present structural studies of FTO[2] and ALKBH5[3] as well as biochemical work that has led to structurally informed inhibitor design of the m^{6}A demethylases for the development of small molecules to probe biological function and for potential use as therapeutics.

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