The m6A demethylase FTO promotes esophageal cancer progression through YTHDF1-dependent posttranscriptional silencing of AKT3

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Abstract

Background : N⁶-methyladenosine (m⁶A) is the most abundant modification in eukaryotic messenger RNAs (mRNAs), and plays important roles in many bioprocesses. However, its functions in esophageal cancer remain elusive. **Methods :** Methylated RNA immunoprecipitation sequencing (MeRIP-seq) and transcriptomic RNA sequencing (RNA-seq) were used to screen the target genes of FTO. Western blot, quantitative real-time PCR (RT-qPCR) and immunohistochemical (IHC) were used to detect FTO expression in cell lines and patient tissues. The biological functions of FTO were investigated in vitro and in vivo . RNA pull-down and RNA immunoprecipitation assays were conducted to explore the specific binding of target genes. **Results :** We discovered that the RNA demethylase FTO was significantly up-regulated in esophageal cancer patients. Knockdown of FTO drastically reduced esophageal cancer cells (ESCCs) proliferation, migration, invasion, and apoptosis. On the other hand, overexpression of FTO significantly promoted ESCCs growth and invasion. Moreover, we found that the m⁶A methyltransferase METTL14 negatively correlates with FTO function on esophageal cancer progression. By using transcriptome-wide m⁶A-Seq and RNA-Seq assays, we identified AKT3 is the target of FTO, which acts in concert in esophageal cancer tumorigenesis and metastasis. Moreover, loss and gain functional studies confirm that YTHDF1 mediates m⁶A-increased translation of AKT3 mRNA. **Conclusion :** Our results uncovered an METTL14/FTO/YTHDF1/AKT3 signaling network that regulates the esophageal cancer progression.