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   2019G012

2. Title
   Epitranscriptional regulation of smoking-related detoxification and xenobiotic metabolism

3. Period
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4. Summary
   We evaluated the significance of N^6-methyladenosine (m^6A) modification in biological responses to cigarette smoking. First, we investigated the effects of cigarette smoking on the expression of m^6A modification-related genes. We found that treatment of cigarette smoke extract significantly decreased the expression of methyltransferase like 3 (METTL3) and METTL14, m^6A methyltransferases, in human lung cancer-derived A549 cells, indicating a possibility that smoking affects m^6A modification level. Next, we examined the possibility that METTL3 or METTL14 regulates expressions of cytochrome P450 1A1 (CYP1A1) and heme oxygenase 1 (HO-1). We revealed that the induction of CYP1A1 mRNA by 2,3,7,8-tetrachlorodibenzodioxin (TCDD) was attenuated by knockdown of METTL3 or AlkB homolog 5, RNA demethylase (ALKBH5). Consistent with the changes in the CYP1A1 induction, AHR nuclear translocator (ARNT) expression was significantly decreased by knockdown of METTL3 or ALKBH5, suggesting that that attenuation of CYP1A1 induction by knockdown of METTL3 or ALKBH5 is due to the decrease in ARNT expression. Furthermore, it was found that regulation of ARNT expression by knockdown of METTL3 or ALKBH5 would be due to the promotion of chromatin compaction in the ARNT promoter region. Moreover, we clarified that METTL3 and METTL14 positively regulate HO-1 expression by stabilizing its mRNA. In conclusion, we revealed that expression of CYP1A1 and HO-1 are regulated by m^6A modification-related genes, and m^6A modification is involved in the biological response to cigarette smoking.