1. **No.**

   FP01806084

2. **Title**

   The Effect of Smoking-associated Epigenetic Molecules on Mineralocorticoid Receptor Activity and its Clinical Impact

3. **Period**

   2016-2018

4. **Summary**

   In the analysis using our clinical database of primary aldosteronsim, the positive coorelation between severity of primary aldosteronism and progression of microalbumiuria was tighter in smoking group compared in non-smoking group, suggesting that smoking and mineralocorticoid excess were cooperatively involved in cardiovascular comorbidities.

   In *in vitro* experiment, among several candidates of novel MR-interacting epigenetic molecules, we identified lysine-specific demethylase 1 (LSD1) as a corepressor of MR through multiple assays including endogenous gene silencing by shRNA, co-immunoprecipitation, and chromatin immunoprecipitation.

   In *in vivo* experiments, we generated kidney-specific LSD1 knockout mice and demonstrated in this model that increased MR sensitivity was observed in short-term exogenous aldosterone treatment and that blood pressure was significantly elevated through increased MR activation in long-term high salt loading. This findings also supported the notion that LSD1 functions as a MR corepressor.

   In addition, we also demonstrated that nicotinic acetylcholine receptor (nAChR) expression was upregulated by MR activity and kidney-specific LSD1 knockout mice had aberrant nAChR expression, suggesting that LSD1 could be one of the key molecules in the cooperation of smoking and MR in the progression of cardiovascular risks.