1. **No.**

   FP01901018

2. **Title**

   Deregulation of mTOR / Trefoil Factor Pathway and its Relation with Smoking History

3. **Period**

   2018-2020

4. **Summary**

[Background] By microarray, we identified trefoil factor-1 (TFF-1) which is suppressed by pmTOR. TFF is the protein family (TFF-1-3) in which TFF-1 exhibits bivalent functions on the cancers. The purpose was to clarify the function of TFF-1 and the utility of TFF1-3 as biomarkers of lung carcinoma. [Methods] In 200 cases of cancer and healthy control, TFF-1-3 in the serum and the urine was quantified by ELISA and the relation with smoking habit was analyzed. In cultured lung carcinoma cells, TFF-1 expression and secretion were evaluated by immunoblot, quantitative RT-PCR and ELISA. The transcriptional regulation of TFF-1 promoter was analyzed by luciferase assay. In cells overexpressing TFF-1, proliferation rate was quantified and cell cycle profiles were assessed by flow cytometry. Migration and invasion were evaluated by wound healing assay and Transwell assay, respectively. [Results] TFF-1-3 in the serum in cancer patients was significantly higher than control, but lower in the urine. Heavy smoker exhibited higher TFF-1/3 in the serum, but lower TFF-2. In cultured cells, expression of TFF-1 was detected only in adenocarcinoma in the cell lysate and in cultured medium. Suppression of pmTOR enhanced promoter activity and expression of TFF-1. Overexpression of TFF-1 drove cell cycle transition, but decreased proliferation due to enhanced cell death and significantly suppressed the proliferation, migration/invasion, which were rescued by siRNA of TFF-1. [Conclusions] TFFs are potential biomarkers for lung carcinomas, and TFF-1 drives abortive cell cycle, and functions as suppressor of cancer proliferation/migration/invasion. Thus, TFF-1 may provide treatment strategies as anti-cancer molecule.