1. **No.**

   FP01801022

2. **Title**

   Establishment of the treatment paradigm based on the genetic mutation the patients with renal cell cancer

3. **Period**

   2016-2018

4. **Summary**

Smoking causes not only hypoxia but also atherosclerosis, which also causes various deprivation for cancer cells and associates efficacies of cancer therapy. In this study period, we demonstrated the following results. In the first experiment, we found that the resistant type possessed higher activities for both mitochondrial oxidative phosphorylation and glycolysis than the sensitive types. These higher activities were supported by the stored carbon, lipid and carbohydrate sources, and by a low level of mitochondrial ROS due to sustained SOD2 expression in the resistant RCC cells. In metastatic RCC cases, higher SOD2 expression was associated with a significantly shorter survival period. Next, the hypoxia-inducible factors (HIF) transcription factor network was significantly enhanced in deprivation-resistant RCCs compared to the sensitive RCCs. Deprivation-resistant RCC, that had lost von Hippel-Lindau (VHL) tumor suppressor expression, expressed hydroxyl-HIF2-alpha in the nucleus, but not sensitive- RCCs. Knockdown for HIF2-alpha, but not HIF1-alpha, induced cell death related to a reduction in HIF-related gene expression in deprivation-resistant RCC cells. Therefore, hydroxyl-HIF2-alpha might be a potential therapeutic target for RCCs. At last, using the discovery cohort and the validation cohort, ARL4C was shown to be a predictive biomarker for poor prognosis in patients with RCC and may be a novel target in the treatment of RCC. In this study, global transcriptomics were used in the discovery cohort (43 patients with RCC) to identify biomarker genes. Each identified biomarker was subsequently analyzed using immunohistochemistry in the second cohort (97 patients with RCC).