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Loss of SWI/SNF component ARID1A associates with tumorigenesis, metastases and unfavorable prognosis of sporadic non-functional pancreatic neuroendocrine tumors

Xu HAN, Wenqi CHEN, Wentao ZHOU, Xuefeng XU, Wenhui LOU*

Department of Pancreatic Surgery, Zhongshan Hospital, Fudan University, China

Introduction : The molecular alterations and genetic profiles underlying sporadic non-functional pancreatic neuroendocrine tumors (NF-pNETs) remain largely unknown. Herein, we determined the clinicopathologic significance of SWI/SNF component ARID1A expression in NF-pNETs.

Methods : Exome capture, WES sequencing and bioinformatics analysis identified variants. Real-time PCR and immunohistochemistry were performed to verified gene mutation.

Results : In the current study, we sequenced the exomes of 7 surgically resected NF-pNETs (1 fresh and 6 FFPE samples). The results showed abundant chromosomal amplifications and deletions, and mutational signatures suggesting defective DNA repair. NF-pNETs harbored 264 somatic mutations in 228 different genes, affecting most commonly SWI/SNF component ARID1B (57.1%) and ARID1A (42.9%). We detected the mRNA level of ARID1A in 15 paired NF-pNETs tumors and adjacent non-cancerous tissues by quantitative real-time PCR, and protein expression of ARID1A in 40 paired NF-pNETs tumors, liver metastases tumors, and adjacent non-cancerous tissues by immunohistochemistry (IHC) tissue microarrays. Here, we identified ARID1A was remarkably downregulated in NF-pNETs and corresponding liver metastases tissue compared with adjacent normal pancreatic islets tissue. Low ARID1A/ARID1B expression was significantly related to the high grade level of NF-pNETs ($P<0.05$). Patients in the ARID1A low expression subgroup significantly presented a lower 5-year overall survival (OS) rate than those in the ARID1A high expression subgroup ($P<0.05$).

Conclusions : Taken together, these data suggested that loss of ARID1A/ARID1B expression may have a synergic effect on tumorigenesis and proliferation. Our findings indicate that alterations in chromatin-remodeling genes ARID1A/ARID1B contribute to tumorigenesis and metastasis of sporadic NF-pNETs.

Corresponding Author. : **Wenhui LOU** (lou.wenhui@zs-hospital.sh.cn)