Editorial

Epigenetic regulator ARID1A and stem cell transcription factor SOX9 in the maintenance of pancreatic ductal cell differentiation state and development of intraductal papillary mucinous neoplasia (IPMN) and pancreatic ductal adenocarcinoma (PDAC)

Naipeng Cui[1], Jinsong Zhang[2], Huatian Huang[3], Lingeng Lu[4]

[1]Department of Breast Surgery, Affiliated Hospital of Hebei University, Baoding 071000, China; [2]Department of Pharmacology & Physiology, Saint Louis University School of Medicine, St. Louis, Missouri, USA; [3]Department of Imaging Diagnosis, Qian Xi Nan People's Hospital, Xingyi 652400, China; [4]Department of Chronic Disease Epidemiology, Yale School of Public Health, School of Medicine, Center for Biomedical Data Science, Yale Cancer Center, Yale University, New Haven, CT, USA

Correspondence to: Dr. Lingeng Lu. Department of Chronic Disease Epidemiology, Yale School of Public Health, School of Medicine, Center for Biomedical Data Science, Yale Cancer Center, Yale University, 60 College Street, New Haven, CT 06520-8034, USA. Email: lingeng.lu@yale.edu.

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Pancreatic ductal adenocarcinoma (PDAC) is one of the highest mortality malignancies, with average 5-year survival less than 3%. The etiology of pancreatic cancer has been investigated, and the identified risk factors including such as non-O ABO blood group (1), uncommon hereditary factors of germline mutations in *p16*, *BRCA1* and *BRCA2* (2), obesity, chronic pancreatitis, long-term diabetes mellitus (3,4), *Helicobacter pylori* colonization (5) and tobacco smoking (6). Somatic mutations of *KRAS* is a driver mutation with the frequency of over 90% in invasive PDAC (7,8), and with the frequency increasing from 36% to 87% according to disease progression from PanIN-1a to 2–3 preneoplastic lesions (9,10). Besides the *KRAS* mutations, there exist many other genes with somatic mutations in pancreatic cancer based on The Cancer Genome Atlas (TCGA) pancreatic cancer dataset (*Table 1*). However, our understanding on the molecular mechanisms of these mutated genes in the development of intraductal papillary mucinous neoplasia (IPMN) and consequently invasive PDAC is still limited (11,12), and the effective therapies against PDAC are lacking (13). In a recent study of *Gastroenterology*, Kimura and colleagues used available mouse models and clinical samples to investigate the functions of ARID1A (AT rich interactive domain 1A) in the development of IPMN and PDAC (14). Their investigation revealed that conditional *Arid1a* knockout (KO) mice had dilated pancreatic duct and acceleration of PDAC from IPMN when mutant *Kras* oncogene was also expressed. Eventually, multilocular cystic neoplasm developed. Interestingly, cystic neoplasm developed in these transgenic mice did not show aggressive cell proliferation, but manifested excessive intraductal mucin. Moreover, cystic neoplasms developed in these mice had the characteristics of IPMN in human, but not that of mucinous cystic neoplasms (MCN). About 20% (3 out of 15) of these IPMN lesions in the transgenic mice gradually developed into PDAC at 48 weeks of age. They observed decreased expression of Sox9 in *Arid1a* conditional KO mouse pancreas and marked decreased expression of p21, p53 and $p16^{INK4a}$ (*Cdkn2a*) in mouse IPMN-like cystic neoplasms. They concluded that ARID1A deficiency results in ductal cell dedifferentiation and ductal dilation due to reduced *SOX9* expression. This phenotype was rescued by overexpression of *SOX9* both in cell culture and *in vivo*. Their research illuminated an

important function of ARID1A which is the maintenance of differentiation of pancreatic ductal cells and the suppression of PDAC development, suggesting that ARID1A may be a target in the chemoprevention of PDAC. Their findings are encouraging and have implications beyond pancreatic cancer.

ARID1A is an epigenetic regulator involved in chromatin remodeling (15). Its mutations occur at as high frequency as

Table 1 Mutation frequency of the top 72 genes in a TCGA pancreatic cancer data

Genes	Mutation frequency
KRAS	0.907
TP53	0.693
TTN	0.273
SMAD4	0.240
CDKN2A	0.147
MUC16	0.133
HMCN1	0.080
LRP1B	0.080
RYR1	0.080
OBSCN	0.080
FAT3	0.073
FLG	0.067
SCN5A	0.067
FAT2	0.067
USH2A	0.067
ASPM	0.060
CSMD2	0.060
DMD	0.060
CUBN	0.060
PLEC	0.060
DSCAM	0.060
DSCAML1	0.060
DNAH11	0.060
GNAS	0.060
TNXB	0.060
RYR3	0.060

Table 1 (*continued*)

Genes	Mutation frequency
SPTA1	0.060
GLI3	0.060
RNF43	0.053
SCN1A	0.053
CACNA1B	0.053
FAT4	0.053
HERC2	0.053
LRP2	0.053
CSMD3	0.053
ADAMTS16	0.053
SYNE1	0.053
MYO18B	0.053
RNF213	0.053
RELN	0.053
PCDH15	0.053
ZNF831	0.053
ADAMTS12	0.053
PRUNE2	0.053
SDK1	0.053
BTBD11	0.047
PCDH9	0.047
AKAP6	0.047
HECW2	0.047
FCGBP	0.047
RYR2	0.047
ATP10A	0.047
TGFBR2	0.047
HECW1	0.047
FAM71B	0.047
RBM12	0.047
TMEM132D	0.047
ARID1A	0.047
CSMD1	0.047
MKI67	0.047

Table 1 (*continued*)

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Genes	Mutation frequency
PSG6	0.047
SSPO	0.047
LRP1	0.047
AMOT	0.047
ANK3	0.047
GPR133	0.047
KCNA6	0.047
PKD1	0.047
HYDIN	0.047
RREB1	0.047
TPO	0.047
MYLK	0.047

TCGA, The Cancer Genome Atlas.

50% in a wide range of cancers, and lead to loss of ARD1A function (16,17). The frequency of somatic mutations of ARID1A in human pancreatic cancer is approximately 5% (*Table 1*), and the loss of ARIAD1A leads to poor prognosis in the patients (18). Recently, it has been shown that ARID1A promotes mismatch repair (MMR) by recruiting MSH2 to chromatin during DNA replication and promotes MMR (19). ARID1A deficiency enhances the efficacy of immune checkpoint blockade (19). In addition, a subunit of the SWI/SNF chromatin remodeling complex (20), ARID1A interacts with a variety of transcription factors and cofactors including p53, HDAC1/2, and SMAD2/3 (16). SOX9 is a stem cell transcription factor with the high-mobility-group box class DNA-binding motifs (21,22). Given that stem cell transcription factors in general have the potential of maintaining cells in the undifferentiated state (22), SOX9 mediation of ARID1A function is a novel finding in Kimura's study. But how ARID1A regulates *SOX9* expression, and how two factors orchestrate together and the nature of their partners in PDAC, remain to be answered. Many hypotheses can be made. A clear answer to these questions awaits further experimentations in the future.

It is not clear whether SOX9 KO leads to the same phenotype as ARID1A KO-induced one. The data in Kimura's study demonstrated that ARID1A KO in the KRAS mutant background accelerated the development of PDAC through the mTOR pathway. A previous study of this group showed that *Brg1* (another SWI/SNF complex component) KO mice has similar but stronger phenotypes compared to ARID1A KO-induced alterations in pancreatic ducts (23), suggesting that *BRG1* KO should also have stronger mTOR pathway activation.

As a chromatin remodeling factor, ARID1A should exert its functions by means of direct regulation of target gene expression. Immunohistochemistry results in Kimura *et al.*'s study showed that the levels of ARID1A and phosphorylated S6 (a marker of mTOR pathway activation) proteins were decreased in a parallel manner in both human IPMN and PDAC. There is also a positive correlation at the mRNA levels between ARID1A expression and the expression of several key mTOR pathway molecules such as mTOR, PIK3CA, AKT3 and RICTO, suggesting that activation of mTOR pathway is important for tumor progression in ARIAD-low PDAC. Taken together, these results raise the possibility of targeting mTOR pathway in the treatment of human PDAC when ARID1A or BRG1 expression levels are low in the patient tumor samples. Indeed, preclinical studies and clinical trials are in progress (24). It would be interesting to see whether mTOR pathway inhibitors have stronger therapeutic effects against human BRG1-low PDAC than ARID1A-low PDAC. Furthermore, would ARID1A or BRG1 or both be used as liquid biopsy-based biomarkers (for example, the presence of mutated genes in circulating exosomes as early detection of PDAC (25) in the future?

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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