Editorial

# ARID1A: guardian of normal pancreatic ducts

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*Comment on:* Kimura Y, Fukuda A, Ogawa S, *et al.* ARID1A Maintains Differentiation of Pancreatic Ductal Cells and Inhibits Development of Pancreatic Ductal Adenocarcinoma in Mice. Gastroenterology 2018;155:194-209.e2.

Submitted Sep 11, 2018. Accepted for publication Nov 30, 2018.

doi: 10.21037/tcr.2018.12.02

**View this article at:** http://dx.doi.org/10.21037/tcr.2018.12.02

Pancreatic cancer will likely become the second leading cause of cancer deaths in the United States in the next few years and has a dismal single digit 5-year survival. Given the severity and poor prognosis of this disease, it is imperative to gain a better understanding of the molecular mechanisms that contribute to pancreatic ductal adenocarcinoma (PDAC). Fortunately, we have well-defined key molecular mutations involved in pancreatic tumorgenesis including *Kras*, p53, and TGFβ. Indeed, much interest in complementary genetic changes has risen from genome-wide sequencing studies, and one such effort has reported mutations in the subunit genes of the SWItch/sucrose non-fermentable (SWI/SNF) chromatin remodeling complex (1). In addition, other studies have shown that 12–23% of human PDAC cases have alterations in the SWI/SNF complex subunit genes such as *ARID1A* (2). This current study (3) expands our understanding of tumorigenesis in the exocrine compartment via extensive investigation of the role *ARID1A* plays in the initiating stages of pancreatic acinar-ductal metaplasia (ADM) including the identification of possible key events in the development and progression of PDAC. This work utilized several mouse models including those with single mutations in *Arid1a* or *Kras* and accumulation of these mutations which led to the development of intrapapillary mucinous neoplasia (IPMN), fueling more aggressive PDAC in these models.

This work demonstrates the means by which ARID1A maintains pancreatic duct integrity in adult mice. Conditional *Arid1a* KO mice show distinct signs of pancreatic ductal cell metaplasia and duct dilation, as evidenced by multifocal fluid filled mucinous cysts lined with epithelial cells that express ductal cell markers (cytokeratins and acetylated tubulin). Indeed, these cysts developed exclusively from dysplastic changes in pancreatic ducts and not ADM, implicating a ductal cell of origin. In the context of mutant *Kras* expression, some of these lesions advance to neoplasms resembling IPMN concomitant with expression of ductal cell markers (including mucins). This supports a critical role of ARID1A in quelling pancreatic IPMN formation, though loss of *Arid1a* did not inhibit PanIN formation. Reduced or absent levels of p21, p16, and p53 were observed in these mouse IPMNs, which at a lower penetrance could progress to PDAC at about 1 year of age. Specific targeting of adult acinar or ductal cells with both mutant *Kras* and deleted *Arid1a* alleles did not produce IPMNs or any advanced disease, demonstrating that IPMNs do not arise from acinar cells. ARID1A likely prevents ductal dysplasia in adult mouse pancreatic ductal cells, though it is not entirely clear if IPMNs can form from this cell population.

Further investigation into the mechanism of ARID1A provided evidence that it can directly regulate SOX9, preventing the dedifferentiation of pancreatic ductal cells *in vitro* and *in vivo*. In addition, SOX9 over expression prevented pancreatic duct dilation when *Arid1a* was deleted *ex vivo* and *in vivo*. However, SOX9 is not capable of compensating for the deletion of *Arid1a* in the presence of mutant *KRAS*-induced IPMNs. Though ARID1A may prevent IPMN formation in the context of mutant KRAS, ARID1A appears to have tumor promoting properties and is capable of activating the mTOR pathway. However, in advanced disease, *Arid1a* expression was shown to be absent in mouse models of PDAC. These findings were corroborated to some extent with a large number of human IPMN and PDAC samples, which showed that reduced ARID1A in human PDAC was consistent with reduced

mTOR signaling and thus improved prognosis.

Indeed, this report provides a keen approach to better understand the role ARID1A plays in exocrine cell fate and tumorgenesis in pancreas with and without expression of mutated *Kras*. ARID1A demonstrated tumor-suppressive functions by preserving normal pancreatic ducts, as its loss promoted a tumorigenic switch from pancreatic ductal cells to IPMN and progression to PDAC. However, intact ARID1A can increase activated mTOR to drive pro-tumorigenic signals, highlighting its paradoxical nature. In a separate study which corroborates several of these findings, inducible control of *Arid1a* expression demonstrated that regulation of acinar cell identity in response to oncogenic *Kras* was both temporal and context-dependent (4). Also, loss of *ARID1A* was associated with rapid transcriptional shifts in cell identity (4), which may be attributed to pausing of RNA Pol II (5) or mTOR. Future investigations should consider restoration of ARID1A in mouse pancreatic ductal cells in the neoplastic setting, therefore providing insight into possible ARID1A chemoprevention. Since mTOR activity increased in the presence of oncogenic KRAS, another consideration includes inhibition of mTOR in *Arid1a* deficient mouse IPMNs. Indeed, a dual approach with ARID1A supplementation and mTOR inhibition in patients with IPMNs might prove to reduce the advancement of these neoplastic lesions and restore more normal pancreatic ductal cells and duct architecture.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned and reviewed by the Section Editor Xiaoping Yi, MD (Department of Radiology, Xiangya Hospital, Central South University, Changsha, China).

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.12.02). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



## References

1. Shain AH, Pollack JR. The spectrum of SWI/SNF mutations, ubiquitous in human cancers. PLoS One 2013;8:e55119.
2. Witkiewicz AK, McMillan EA, Balaji U, et al. Whole-exome sequencing of pancreatic cancer defines genetic diversity and therapeutic targets. Nat Commun 2015;6:6744.
3. Kimura Y, Fukuda A, Ogawa S, et al. ARID1A Maintains Differentiation of Pancreatic Ductal Cells and Inhibits Development of Pancreatic Ductal Adenocarcinoma in Mice. Gastroenterology 2018;155:194-209.e2.
4. Livshits G, Alonso-Curbelo D, Morris JP 4th, et al. Arid1a restrains Kras-dependent changes in acinar cell identity. Elife 2018. doi: 10.7554/eLife.35216.
5. Trizzino M, Barbieri E, Petracovici A, et al. The Tumor Suppressor ARID1A Controls Global Transcription via Pausing of RNA Polymerase II. Cell Rep 2018;23:3933-45.

**Cite this article as:** Castellanos KJ, Grippo PJ. ARID1A: guardian of normal pancreatic ducts. Transl Cancer Res 2019;8(Suppl 2):S133-S134. doi: 10.21037/tcr.2018.12.02

 