From chromatin remodeling to metabolic reprogramming
a story about ARID1A

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The mutations in the SWI/SNF chromatin remodeling complex occur in nearly 25% of all human cancers and the ARID1A gene is the most frequently mutated component in the complex. ARID1A is dysregulated in many pancreatic cancer patients. However, its function in pancreas development, endocrine regulation and tumorigenesis remains largely uncharacterized. We generated mice that lack Arid1a expression in the pancreas. Our results showed that deletion of the Arid1a gene in mice caused a reduction in islet numbers and insulin production, both of which are associated with diabetes mellitus (DM) phenotype. RNA sequencing of isolated islets confirmed DM gene signature and decrease of developmental lineage genes. We identified neurogenin3, a transcription factor that controls endocrine fate specification, is a direct target of Aird1a. Our data suggest that Arid1a is required for the development of pancreatic islets by regulating Ngn3+-mediated transcriptional program and is important in maintaining endocrine function. Subsequently, we generated a genetically engineered mouse model harboring both K-ras mutation and Arid1a depletion (KAR mice) and showed that the combination of these two genetic alterations induces pancreatic tumor formation. Compared to the tumors developed in mice with K-ras mutation and Tp53 deficiency (KPC mice), KAR tumors exhibited a significant increase in fatty acid synthase (FASN) expression and lipid metabolism. Inhibition of FASN by chemical inhibitor reduced Arid1a-deficient tumor cell viability and slowed tumor progression in mice. Metabolomics analysis revealed a unique lipid reprogramming program in Arid1a-deficienct pancreatic cancer cells and sensitized the cells to ferroptosis induction. Collectively, ARID1A plays an important role in pancreas development and tumourigenesis by modulating cellular metabolism and tumor microenvironment.