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EDITORIAL

On the Effects of Gene Mutations in Pancreatic Tumorigenesis, Depending on the Cell Types and Times When They Are Induced

Pancreatic ductal adenocarcinoma (PDAC) is one of the cancers that currently has one of the worst prognoses. It appears mainly from 2 precursor lesions, the pancreatic intraepithelial neoplasia (PanIN), of microscopic appearance, and the intraductal papillary mucinous neoplasms (IPMN), appearing as an association of papillary lesions and large cysts.[1,2] Its name comes from the fact that it presents ductal structures that recall that of the pancreatic ducts, whose function is to drive the pancreatic secretions produced by the acinar cells to the duodenum. For this reason, physicians have long thought that the cells bordering these ducts were those at the origin of the PDAC. The development of genetically engineered mouse models (GEMM) of PDAC has shattered this idea and shown that the acinar cells could generate PanIN evolving in PDAC.[3] In addition, other GEMM have also shown that ductal cells could form IPMN.[4]

Genetically, PDAC is associated with a very broad mutational spectrum, dominated by the presence of mutations in the KRAS, TP53, SMAD4, and CDKN2A genes.[1] Of these, KRAS is the most frequently mutated. From there, almost all GEMM of PDAC are based on an activating mutation in the Kras gene, frequently associated with a mutation in an additional gene, to characterize the mechanisms of pancreatic tumorigenesis. Although inducing these mutations in adult acinar or ductal cells can be performed, most studies induce these mutations at the embryonic stage in the multipotent pancreatic precursors, which will later give rise to the different specific cell types of the pancreas. The major advantage of this approach is the ease and speed of obtaining PDAC, although this is obscured by the inability to determine the cell type(s) that drive tumorigenesis. This is reinforced by the fact that studies comparing the effects of gene mutations depending on whether they are induced in pancreatic precursors, ductal cells, or acinar cells are not carried out.

In a study published in this issue, Saeki et al tackle the question of whether genes important for PDAC can induce tumors from both acinar and ductal cells.[5] In a previous study, the authors showed that inducing mutations of Kras and Activin A receptor type 1B (Acvr1b), which encodes a serine/threonine kinase upstream of SMAD4, in multipotent pancreatic precursors led to the development of PanIN, IPMN-like lesions, and PDAC.[6] This approach did not allow to determine which cell types contributed to the development of these lesions. By inducing the combination of mutations either in acinar cells or in ductal cells, and then phenotypically characterizing the corresponding GEMM, they now show that this combination of mutations induces the formation of cysts and PanIN from both cell types.[5] This also indicates that papillary IPMN-like lesions are only obtained when Kras and Acvr1b mutations are induced during pancreas development, as potentially the result of a complex interplay of events occurring only during embryonic stages.

Importantly, these results show that mutations in acinar cells can lead to the formation of cysts, even if the authors of the study did not carry out genetic lineage tracing that would have definitively supported these results. Coupled with the result of another study that indicates that IPMN can be generated from mutations present in acinar cells,[7] they suggest that in humans, acinar cells could be the origin of a particular type of IPMN called branch duct-IPMN (as opposed to main duct-IPMN), where the neoplastic lesions are associated with secondary branches of the ductal system. Even more importantly, they also highlight that the consequences of mutations favoring PDAC are not the same depending on whether they appear at an embryonic or postnatal stage. Furthermore, the authors emphasize that, when mutations are present in different pancreatic cell types following their induction in embryonic multipotent precursors, the effects of the mutations in one cell type could exacerbate the phenotype generated in the other cell type. Better yet, endocrine cells, which also have the mutations and which have been shown to affect initiation of neoplastic lesions in acinar cells,[8] could also be involved in the tumorigenic process. Beyond these considerations, these results force us to think about the relevance of the embryonic model in view of its use as a preclinical model of PDAC. Is it a correct reflection of the tumorigenic process in humans? And does its intratumoral heterogeneity come more from dynamic interconversion mechanisms between various pancreatic cancer differentiation states[9] or from the fact that tumors develop from several cell types? The answers to these questions could influence how we study PDAC and consider treating it.

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