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PANCREATIC CANCER

KRAS dosage key in PDAC

Oncogenic gene dosage is a key factor in pancreatic adenocarcinoma (PDAC), according to new research.

Work to associate the mutational landscape of PDAC with tumour phenotypes has been largely unsuccessful. Factors hindering these studies include the complexity of PDAC genomes, high stromal content (impairing gene-dosage and transcriptome analyses) and a lack of cell culture resources.

To address these limitations, Roland Rad and colleagues derived cancer cell cultures from untreated mouse PDAC tumours, driven by pancreatic $Kras^{G12D}$ mutation. These cell cultures were characterized on the basis of genomic, transcriptomic and phenotypic features.

The first key finding was that two-thirds of cancers had increased $Kras^{G12D}$ gene dosage (termed $Kras^{iGD}$). By analysing human pancreatic intraepithelial neoplasias, the researchers showed that, after initial *KRAS* mutation, additional oncogenic gene dosage gain is required for cancer evolution, via amplification of either mutated *Kras* or other oncogenes, such as *Yap1* or *Nfkb2*. $Kras^{iGD}$ was also shown to promote metastasis, providing a mechanism for the frequent early metastasis of PDAC in humans.

Next, using a variety of mouse models, Rad and colleagues demonstrated that the nature of oncogenic gene dosage gain is dependent on the inactivated tumour suppressor. For instance, homozygotic inactivation of *Tp53* or *Cdkn2a* predisposed tumours to $Kras^{iGD}$; conversely, *Yap1* or *Nfkb2* amplifications resulted from heterozygotic *Cdkn2a* loss.

Finally, integration of cellular phenotypes showed that *Kras* mutational status and gene dosage was associated with epithelial-to-mesenchymal transition and the degree of dedifferentiation. "The current progression model considers the *KRAS* mutations, but not its dosage variation," concludes Rad. "We have introduced oncogenic dosage increase as a fundamentally important process."

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ORIGINAL ARTICLE Mueller, S. *et al.* Evolutionary routes and *KRAS* dosage define pancreatic cancer phenotypes. *Nature* http://dx.doi.org/10.1038/nature25459 (2018)