Nature Reviews Gastroenterology & Hepatology | Published online 25 Jan 2017; doi:10.1038/nrgastro.2017.9

PANCREATIC CANCER

PDAC metastases show identical known driver gene mutations

In new research published in *Nature Genetics*, sequencing of treatment-naive metastases from patients with pancreatic ductal adenocarcinoma (PDAC) has revealed identical known driver gene mutations in all lesions from each patient. These findings could have important clinical implications for future therapies in advanced-stage PDAC.

Intratumoural genetic heterogeneity is an important topic in cancer biology with direct implications for targeted or immunotherapeutic interventions. Although prior studies have observed similar gene mutations in PDAC primary tumours and matched metastases, those insights were not quantitative and did not establish if heterogeneity occurs in known driver genes such as *KRAS*, *CDKN2A*, *TP53* and *SMAD4*. "We wanted to know whether pancreatic cancer metastases independently acquired driver gene mutations," explains author Alvin Makohon-Moore.

Genetic heterogeneity in PDAC was evaluated using whole-genome, multiregion sequencing of patient-derived primary tumours and matched metastatic lesions from various organs. "We had a unique opportunity afforded by the autopsy tissues we collected … from patients diagnosed with metastatic pancreatic cancer and who were not treated," says author Christine Iacobuzio-Donahue. "We focused on untreated pancreatic cancers to ensure that the patterns we observed were specific to baseline evolution and not affected by various treatments," explains Makohon-Moore.

To quantitatively analyse the sequencing data, the investigators used a novel phylogenetic tool called Treeomics, as well as a mathematical model of normal tissue evolution. "We found that there was no heterogeneity for driver genes among the primary tumour and all matched metastases," reports Iacobuzio-Donahue. This finding is important for patients with metastatic PDAC as the same driver gene mutations occurred in cancer cells that seeded the metastases so a therapy targeted to that mutation could provide a clinical benefit. Genetic heterogeneity was found, but only in passenger genes that do not have known functional effects. Furthermore, the heterogeneity of metastases in a patient with PDAC was found to be lower than that of normal tissue in the same patient, suggesting that end-stage treatment-naive PDAC is a relatively homogenous population at the genetic level.

"These findings are just the beginning. We now know how the genetic evolution of pancreatic cancer ends, but we do not know how it gets there," explains Iacobuzio-Donahue. "Studying patients with pancreatic cancer diagnosed at earlier stages and who are being treated will reveal these answers." The investigators also plan to examine additional types of variation. "While our current work focused on genetic mutations, we did not study other potentially important types of alterations such as epigenetic, post-translational or microenvironmental," concludes Makohon-Moore.

Iain Dickson

ORIGINAL ARTICLE Makohon-Moore, A. P. *et al.* Limited heterogeneity of known driver gene mutations among the metastases of individual patients with pancreatic cancer. *Nat. Genet.* http://dx.doi.org/10.1038/ng.3764 (2017)