Delineating the effects \textit{BRCA1} and \textit{BRCA2} loss of heterozygosity in pancreatic cancer progression

References


Nearly two decades have passed since the research groups of Mark Skolnick and Michael Stratton independently discovered the breast cancer susceptibility genes \textit{BRCA1} and \textit{BRCA2}. The identification of these genes,
although initially spurred by the heavy interest in identifying the genetic bases of breast and ovarian cancers, have gradually come under the intense investigation of scientists and clinicians probing the genetic underpinnings in other common cancers. Pancreatic cancer, otherwise known as pancreatic ductal adenocarcinoma (PDAC), is no exception to this scrutiny. Among the most lethal of solid malignancies, it is predicted that over 45,000 Americans will be diagnosed with PDAC in 2013 and over 38,000 will die from this disease, with 5-year survival rates hovering at a grim 5%.

A previous study by Ferrone et al. showed that approximately 4% to 10% of Ashkenazi Jews with PDAC carry a common $BRCA1$ or $BRCA2$ founder mutation, and that $BRCA2$ mutations are associated with a higher incidence of PDAC (1). Many patients with germline $BRCA1$ or $BRCA2$ mutations report no breast, ovarian or pancreatic cancer in other members of the immediate family, suggesting incomplete penetrance of these genes. This study by Lucas et al. aims to elucidate a genetic mechanism that might explain the pathogenesis of PDAC with the hypothesis that $BRCA1$ and $BRCA2$ mutations lead to PDAC through loss of heterozygosity (LOH).

Frozen, resected pancreatic tissues from a cohort of 63 unique Ashkenazi Jewish patients were genotyped for the three common Ashkenazi Jewish mutations ($BRCA1$ 185delAG, $BRCA1$ 5382insC and $BRCA2$ 6174delT). This revealed that a $BRCA1$ or $BRCA2$ founder mutation was present in 19% of the surgical cohort of 63 individuals. Among the subset of 39 patients who underwent pancreatic resection for PDAC, 21.6% were found to carry a germline $BRCA$ mutation ($BRCA1$ 185delAG, 8.1%; $BRCA1$ 5382insC, 2.7%; and $BRCA2$ 6174delT, 10.8%). In another subset of seven individuals who had surgery to remove intraductal papillary mucinous neoplasms (IPMNs), benign tumors that may progress into PDACs, 28.6% carried a $BRCA1/2$ mutation (one patient had a $BRCA1$ 185delAG mutation, the other a $BRCA2$ 6174delT mutation).

Further analysis revealed LOH in 50% of $BRCA1$-associated PDACs and 75% of $BRCA2$-associated PDAC. The authors did not find a significant correlation between disease stage, histology or overall survival and $BRCA1/2$ carrier status among the patient cohort. Likewise, the presence or absence of LOH among $BRCA1/2$ carriers did not seem to factor into disease pathophysiology. These suggest that genetic factors other than $BRCA1/2$ likely cooperate in the pathogenesis of PDAC. Remarkably, microdissection of a PDAC sample arising from an IPMN (IPMN microdissected separately from the PDAC) revealed partial LOH in the IPMN and complete LOH in the PDAC. As IPMNs progress into malignant carcinomas, biallelic loss-of-function in $BRCA2$ is a plausible contributor to disease. Further, this study also suggests that the onset of sporadic and hereditary pancreatic cancer may vary, as Ashkenazi Jewish patients with PDAC who are $BRCA1/2$ carriers have a lower mean age of diagnosis compared with non-carriers, although the results are not statistically significant ($p=0.15$), due to a small sample size.

As $BRCA1/2$ mutations alter DNA repair fidelity and lead to perturbations of the cell cycle that give rise to oncogenesis, Lucas et al. stained $BRCA1/2$-positive PDAC tumors for the tumor suppressor p53 and observed increased nuclear staining in 62.5% of the tissues analyzed. Using this as a surrogate marker for P53 mutation, the authors state that P53 mutations are present in patients with $BRCA1/2$ LOH, citing varied nuclear p53 staining in some regions of tumor tissue. Murine models of PDAC suggest that P53 mutations are required before $BRCA1/2$ LOH in the progression

![Fig. 3. A simplified model of pancreatic cancer progression implicating $BRCA1$ and $BRCA2$ loss-of-function. Gain of KRAS expression promotes cellular growth. This, coupled with loss of tumor suppressor function mediated by P53 regulation of the cell cycle could lead to tumorigenesis and IPMN. Further loss of DNA repair and cell cycle regulation through dysfunction in $BRCA1/2$ could expedite cancer growth and lead to metastasis. Other factors that predispose to oncogenesis and tumor evolution remain to be elucidated. This figure is meant to illustrate a plausible mechanism described by Lucas et al. and not an exhaustive representation of the various clinically and pathologically distinct neoplasms that arise in the pancreas.](image-url)
HotSpots
to PDAC, and that monoallelic loss-of function in
BRCA2 was sufficient to promote p53 and Kras-driven
tumorigenesis (2, 3) (Fig. 3). Whether or not BRCA1/2
LOH is critical to PDAC in humans remains to be
answered. From a therapeutic perspective, BRCA1/2
tumors may be subjected to synthetic lethality by poly-
ADP ribose polymerase (PARP) inhibitor treatment that
has proven to be highly effective against BRCA1/2
breast and ovarian tumors. Ultimately, the evolution of
pancreatic cancer needs to be probed at a single-cell
level using representative tissue samples to decipher the
molecular changes over time. This will allow greater
insight into the involvement of BRCA1/2 in PDACs.

HK Fam
Department of Medical Genetics, University of British Columbia, 950
West 28th Avenue, Vancouver, British Columbia V5Z4H4, Canada
e-mail: hfam@cfri.ca