IN THE SPOTLIGHT

A Role for ATM in Hereditary Pancreatic Cancer

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Summary: The genetic risk factors that contribute to pancreatic cancers are largely unknown. A new next-generation sequencing study by Roberts and colleagues now adds ATM to the list of pancreatic ductal adenocarcinoma predisposition genes. Cancer Discovery; 2(1); 14–5. ©2012 AACR.

Commentary on Roberts et al., p. 41 (3).

Pancreatic ductal adenocarcinoma is a devastating disease with a 5-year survival of less than 5%. For this reason, pancreatic cancers are the fourth most common cause of cancer-related deaths in the Western world. In approximately 10% of the pancreatic cancer cases, hereditary risk factors play a role. Germline mutations in BRCA2, PALB2, CDKN2A, STK11, and possibly BRCA1 have been associated with an increased risk of pancreatic cancer, but in the large majority the genetic risk factors are not known (1).

Next-generation sequencing techniques have launched a revolution in genetic research. Novel disease genes, including cancer predisposition genes, are uncovered by whole-genome and exome sequencing. Recently, next-generation sequencing was used to identify PALB2 as a pancreatic cancer susceptibility gene (2), and in this issue of Cancer Discovery, whole-genome and exome sequencing revealed pathogenic ATM mutations in patients with pancreatic cancer (3). Initially, 38 affected patients from 16 families with at least 3 cases of pancreatic ductal adenocarcinoma in the family were investigated. In 2 families, all 6 sequenced individuals with pancreatic cancer carried ATM mutations.

Subsequently, the ATM gene was screened in 166 familial pancreatic cancer patients and 190 healthy spouse controls. This screening revealed 4 additional pathogenic mutations and none in the controls. Two of these 4 families had 3 or more affected individuals, but cosegregation of the mutations with the disease is not reported for these 4 families. All the mutations identified in this study were identical to pathogenic ATM mutations previously reported in patients with ataxia-telangiectasia, an autosomal-recessive genetic instability syndrome with an increased risk for multiple cancer types (4). Analysis of one ATM-mutated pancreatic tumor showed loss of the wild-type ATM allele, supporting Knudson’s “2-hit model” for tumor suppressor genes. Unfortunately, tumor material from the remaining 9 pancreatic cancers was not available for analysis to further strengthen this observation. With these findings, the authors show that ATM mutations significantly contribute to the genetic susceptibility for pancreatic cancer. In their cohort, at least 2.4% of the familial pancreatic cases could be explained by ATM mutations.

ATM has an important multifunctional role in the DNA damage response. In the presence of DNA strand breaks, ATM regulates DNA repair, cell-cycle checkpoints, and apoptosis (5). There is strong evidence that ATM acts as an anticancer barrier in precancerous lesions (6, 7). The involvement of ATM in preventing tumorigenesis has been shown by the high incidence of cancer, especially of lymphoid cancers, in patients with ataxia-telangiectasia with both ATM alleles affected. In a retrospective analysis of heterozygous ATM mutation carriers in families with ataxia-telangiectasia, researchers showed an excess of female breast cancer with an overall relative risk of 2.23 (95% CI, 1.16–4.28) and a relative risk of 4.94 (95% CI, 1.90–12.9) in women younger than 50 years of age (8). An increased risk for other cancers, including pancreatic cancer (relative risk 2.41; 95% CI, 0.34–17.1), was also found, but for pancreatic cancer, this risk was not significant because of the low prevalence of this disease. An increased risk for breast cancer (relative risk 2.37; 95% CI, 1.51–3.78) in ATM mutation carriers was also found in a study on patients with hereditary breast cancer for which mutations in BRCA1 and BRCA2 were excluded (9). On the basis of these studies, ATM is considered to be a moderate-risk breast cancer susceptibility gene.

There is a striking overlap between breast and pancreatic cancer because mutations in several breast cancer susceptibility genes (BRCA1, BRCA2, and PALB2) or genes involved in cancer predisposition syndromes with increased breast cancer risk [CDKN2A (familial melanoma) and STK11 (Peutz-Jeghers syndrome)] also increase the risk for pancreatic cancer. The study by Roberts and colleagues (3) now adds ATM to this list of genes involved in both breast and pancreatic cancer. It remains to be seen whether CHK2, a moderate-risk breast cancer susceptibility gene and downstream target of ATM, also plays a role in familial pancreatic cancer.

This discovery may have implications for the surveillance of families with breast or pancreatic cancer and ATM mutations, but for good surveillance, more information about cosegregation of the mutation in families and the penetrance of the disease is essential. The rather high carrier frequency for ATM mutations in the general population (0.5%–1%) suggests that modifier genes also determine the risk for pancreatic cancer in ATM mutation carriers. At the moment there are no valid biomarkers to detect pancreatic cancer at an early stage, and imaging with computed tomography and magnetic resonance imaging is not able to detect small lesions.
However, imaging with endoscopic ultrasonography seems promising for high-risk families (10).

The results from the study by Roberts and colleagues (3) can be further translated into clinical practice. ATM-mutated pancreatic cancers could be treated with inhibitors of pathways that have become essential in the ATM-deficient tumors. This concept of synthetic lethality has been shown to be very effective in BRCA1- and BRCA2-deficient tumors, which can be specifically eradicated by PARP inhibitors (11). A study in ATM-deficient lymphoid tumor cells showed increased sensitivity to PARP-1 inhibition (12), indicating that PARP inhibitors may be effective in ATM-deficient pancreatic tumors as well.

Along similar lines, small-molecule inhibitors of DNA-PKcs, a kinase involved in the rejoining of DNA double-strand breaks, may be used, because mouse studies have demonstrated that the combined inactivation of DNA-PKcs and ATM has synthetic lethality (13). Several DNA-PKcs inhibitors for this purpose are already available. Research in Fanconi anemia pathway–deficient human and mouse cells showed that there is also a synthetic lethal interaction between the Fanconi anemia pathway and ATM (14). Interestingly, Fanconi anemia pathway–deficient pancreatic cancer cell lines were more sensitive to the ATM inhibitor KU-55933 than their corrected isogenic controls, indicating that Fanconi anemia pathway inhibitors may be used to treat ATM-deficient tumors. However, at the moment these inhibitors are still under development. Overall, the suggestion is that there are compensatory pathways involved in DNA damage response and repair, which could be used as targets for therapy in ATM-deficient tumors.

The study of Roberts and colleagues (3) also highlights the importance of functional studies. Next-generation sequencing techniques are leading to more and more data and more and more variants of unknown clinical significance. As the authors point out in their article, they only considered ataxia-telangiectasia related or truncating mutations to be pathogenic. The unclassified variants are excluded from their study, so the involvement of ATM in familial pancreatic cancer could be underestimated.

ATM, a key player in DNA damage response, is identified as a novel pancreatic ductal adenocarcinoma predisposition gene. This is an interesting finding that could lead to targeted treatment in familial pancreatic cancer and a more effective surveillance in these families.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

REFERENCES
