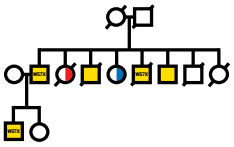
ATM is a Familial Pancreatic Ductal Adenocarcinoma Predisposition Gene

- Inactivating mutations of *ATM* were identified in kindreds with familial PDA.
- *ATM* is inactivated by a classic 2-hit model in patients with PDA.
- 4.6% of families severely affected by PDA carry deleterious *ATM* mutations.



Pancreatic ductal adenocarcinomas (PDA) are extremely lethal cancers, with a 5-year survival rate of less than 5%. Up to 10% of PDA cases are hereditary, but the basis for genetic predisposition in the vast majority of familial cases remains unknown. To identify familial PDA predisposition genes, Roberts and colleagues performed whole-genome or whole-exome sequencing of blood from affected individuals in families with at least 3 members with PDA. Inherited, inactivating variants of *ATM* (*ataxia-telangiectasia mutated*) segregated with disease in 2 affected kindreds. In one affected individual harboring a germline *ATM* mutation, LOH was observed in their pancreatic tumor tissue, suggesting that *ATM* is a classic tumor suppressor gene inactivated by a 2-hit mechanism in PDA. Sequencing of the *ATM* coding region in a larger panel of 166 pancreatic cancer patients revealed the presence of 4 germline *ATM* variants. Importantly, these variants were known to be deleterious because they have also been reported in patients with ataxia-telangiectasia (A-T), an autosomal-recessive cancer predisposition syndrome, and were also specifically found in individuals from the highest risk families (i.e., 3 or more family members with PDA). Of note, the authors found additional *ATM* germline mutations not previously characterized in A-T in other cases of familial PDA, suggesting that *ATM* mutations may play an even greater role in PDA susceptibility. ■

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Ultra-Sensitive Sequencing Maps the Clonal Evolution of Follicular Lymphoma

- A donor–recipient pair developed follicular lymphoma after hematopoietic cell transplantation.
- Identification of shared mutations revealed early oncogenic events in lymphomagenesis.
- Genetic inactivation of *ARID1A* can be a late event in lymphomagenesis.

Weigert and colleagues report the case of a patient with chronic myelogenous leukemia (CML) who received a bone marrow transplant and subsequent donor lymphocyte infusions (DLI) from her sister and ultimately achieved complete hematologic remission. Remarkably, more than 7 years later, both the patient and her sister were diagnosed with follicular lymphoma. The availability of genomic DNA from both the donor and recipient follicular lymphomas as well as the DLI, representing a common ancestor population, provided a unique opportunity to study shared and divergent genetic events during lymphomagenesis. The donor and recipient follicular lymphomas exhibited an identical *B-cell lymphoma 2/immunoglobulin heavy locus* (*BCL2/IGH*) gene rearrangement, which was also present in a rare population of cells in the DLI, indicating that transplantation of malignant precursors occurred more than 7 years prior to follicular lymphoma presentation. Exome sequencing identified 15 mutations that were shared between the 2 follicular lymphomas, 14 of which were also identified in the DLI using ultrasensitive deep sequencing. Collectively, these alterations likely represent early genetic events. Several other mutations were identified in only one follicular lymphoma, including a nonsense mutation in the putative tumor suppressor gene *adenine-thymine–rich interactive domain-containing protein 1A* (*ARID1A*) in the recipient follicular lymphoma. Interestingly, both follicular lymphomas had reduced ARID1A protein expression, and qPCR analysis revealed *ARID1A* copy number loss in the donor follicular lymphoma, suggesting that *ARID1A* loss-of-function mutations may occur at later stages of lymphomagenesis. ■

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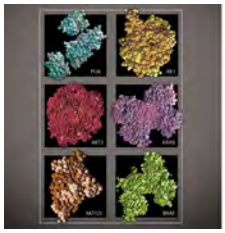
Ovarian Cancers Exhibit Differential Sensitivity to AKT Inhibition

- Genetic heterogeneity among ovarian cancers underlies variable AKT dependence.
- The effectiveness of selective AKT inhibitors depends on the AKT isoforms expressed.
- Cells with *RB1* deletion or *RAS*/*RAF* mutation are resistant to AKT inhibition.

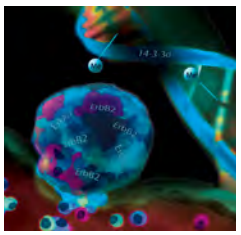


Increased AKT activation is common in high-grade serous ovarian tumors, suggesting that targeted inhibition of AKT might be an effective therapeutic strategy. Hanrahan and colleagues analyzed a panel of ovarian cancer cell lines to identify molecular determinants of sensitivity to AKT inhibition. Four major groups of cell lines were identified: those with PI3K/AKT pathway alterations; those with mutations in *RAS* or *RAF* or their downstream effectors; those with *RB1* deletions; and those with no alterations in these pathways. Despite rapid inactivation of AKT, treatment with allosteric AKT inhibitors failed to elicit a response in the majority of the cell lines, particularly those with *RB1*, *RAS*, or *RAF* mutations. The cell lines that were hypersensitive to AKT inhibition all harbored PI3K/AKT pathway mutations, though this was insufficient to confer sensitivity. Of the sensitive cell lines, a pan-AKT inhibitor was more effective when AKT3 was expressed, but an AKT1/AKT2-selective inhibitor was sufficient to kill AKT3-deficient cells. Together, these findings suggest that AKT inhibitor monotherapy will elicit a low response rate in high-grade serous ovarian tumors, although a subset of patients with PI3K/AKT pathway mutations may benefit and combination therapy may be effective in others. Given the genetic heterogeneity of ovarian cancers, the authors argue that genomic and proteomic characterization on a case-by-case basis will be required to identify patients who may benefit from AKT inhibition. ■

See article, p. 56.

14-3-3σ Is a Tumor Suppressor in ErbB2-Driven Breast Cancers

- Inactivation of 14-3-3σ accelerates the formation of ErbB2-induced tumors.
- Heterozygous tumors silence the remaining *14-3-3σ* allele by CpG hypermethylation.
- 14-3-3σ loss increases the metastatic potential of ErbB2-expressing tumor cells.

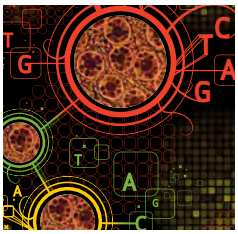


Amplification or overexpression of V-erb-b2 erythroblastic leukemia viral oncogene homolog 2 [*ERBB2*, also known as *human epidermal growth factor 2* (*HER2*)] is observed in 20% to 30% of human breast cancers. Previous studies with ErbB2 transgenic breast cancer models identified recurrent deletions encompassing the gene encoding 14-3-3σ, a mammary epithelial protein that regulates cell polarity and proliferation. Consistent with a potential role for 14-3-3σ in tumor suppression, a large proportion of human breast cancers do not express 14-3-3σ. However, targeted disruption of 14-3-3σ alone in the mouse mammary gland does not induce tumor formation within an observation time of 1 year. Ling and colleagues therefore hypothesized that 14-3-3σ may specifically act as a tumor suppressor in ErbB2-driven tumors. In 2 independent mouse models in which 14-3-3σ was conditionally inactivated and ErbB2 was conditionally activated in the mammary epithelium, 14-3-3σ loss dramatically accelerated the formation of mammary tumors. Notably, in the majority of heterozygous tumors, expression of the remaining wild-type *14-3-3σ* allele was epigenetically silenced, a "second hit" indicating that 14-3-3σ acts as a tumor suppressor in ErbB2-driven cancers. 14-3-3σ deficiency also increased the metastatic potential of ErbB2-induced mammary tumors, and *in vitro* transwell and immunofluorescence assays showed that 14-3-3σ–deficient ErbB2 tumor cells displayed increased migratory and invasive potential that was associated with dissolution of adherens and tight junctional complexes. Together, these data suggest that 14-3-3σ inactivation may be a critical event in the initiation and progression of HER2-positive breast cancers. ■

See article, p. 68.

Genetic Profiling of FFPE Tumor Samples Identifies Actionable Mutations

- A sequencing-based platform identifies genetic alterations in archival clinical samples.
- Deep sequencing allows detection of tumor mutations regardless of stromal admixture.
- Identification of actionable genomic alterations can direct personalized cancer treatment.



Current genotyping-based tumor mutation profiling platforms have several inherent weaknesses that may ultimately preclude their widespread use in guiding individualized therapy. Only a finite number of pre-specified point mutations can be assayed, which of necessity are largely restricted to oncogenic mutations occurring in known hotspots, not tumor suppressor loss-of-function mutations that can occur anywhere throughout the gene. Further, these mass spectrometric- or PCR-based approaches cannot detect other classes of mutation such as insertions, deletions, or amplifications, and are less sensitive in tumor samples with high degrees of stromal contamination. To circumvent these limitations in a robust, cost-effective manner, Wagle and colleagues utilized a targeted exon capture/massively parallel sequencing-based approach that reduced the complexity of tumor genomic DNA through enrichment for the coding regions of frequently mutated oncogenes and tumor suppressor genes and for pharmacogenomic polymorphisms. In a proof-of-principle analysis of formalin-fixed, paraffin-embedded (FFPE) breast and colon tumors, this technique allowed the identification of single-nucleotide variants, insertions, deletions, and copy-number alterations with greater sensitivity than existing profiling methods, even in low-purity samples. These genetic alterations included "actionable" mutations known to predict response to U.S. Food and Drug Administration–approved or experimental therapies, prognostic or diagnostic gene variants, and previously uncharacterized variants presumed to have clinical relevance. This approach will allow retrospective and prospective profiling of tumor cohorts in a clinical setting and has the potential to guide use of targeted or cytotoxic therapy. ■

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Note: *In This Issue* is written by *Cancer Discovery* Science Writers. Readers are encouraged to consult the original articles for full details.

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