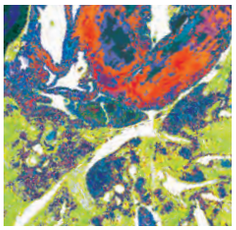
IN THIS ISSUE

C-Raf Is Required for K-Ras–Induced Lung Cancer

- C-Raf but not B-Raf is required for K-Ras^{G12D}–mediated cell transformation *in vitro* and *in vivo*.
- Oncogenic signaling through the Ras pathway is mediated by C-Raf.
- C-Raf is a potential therapeutic target in K-Ras–mediated cancers.



Increased signaling through the Ras/Raf/Mek/Erk pathway occurs frequently in cancer, and is often mediated by activating mutations in *Ras* genes. Because targeted therapies against Ras have proved to be unsuccessful, targeting downstream effectors of Ras has become a focus of investigation. To determine the relative contribution of 2 such effectors, B-Raf and C-Raf, to the proliferative effects of the oncogenic K-Ras^{G12D} mutant, Karreth and colleagues used a Cre-Lox recombinase system to genetically ablate either B-Raf or C-Raf in a Ras^{G12D} background. In transformed mouse embryonic fibroblasts, combined deletion of both Raf proteins was required to inhibit proliferation, and loss of either protein individually was insufficient to curtail cell growth. However, in both K-Ras^{G12D}–transformed primary epithelial cells and in a mouse model of K-Ras^{G12D}–induced lung cancer, C-Raf but not B-Raf was required for cell proliferation and appearance of tumors, respectively. This study demonstrates that oncogenic signaling through the Ras pathway is mediated by C-Raf and not B-Raf, suggesting that C-Raf represents an important therapeutic target in the prevention and treatment of K-Ras–mutant lung cancer. ■

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The Temporal Evolution of Cancer

- Integration of mutation and copy number information allows inference of timing of genetic alterations.
- In cSCCs, *TP53* inactivation occurs early, followed by increased mutational burden.
- Notch pathway members are inactivated late, suggesting a role as a suppressor of progression.

Advances in sequencing technology have enabled the collection of large catalogs of mutations in clinical tumor specimens and cancer cell lines. However, it remains a challenge to determine the order of occurrence of genetic abnormalities during the evolution of a tumor. Such information might allow identification of mutations that directly lead to tumor progression. Durinck and colleagues hypothesize that occurrence can be inferred by integrating mutation and copy number data obtained by exome-level sequencing. In 8 primary cutaneous squamous cell carcinomas (cSCC), the authors show that *TP53* mutation was an early event and was followed by a significant increase in the number of simple mutations. These results were confirmed in ovarian serous adenocarcinoma samples sequenced by the Cancer Genome Atlas Project. Further, the authors identified loss or mutation in *Notch1, Notch2,* and *PKHD1* later in the evolution of cSCCs, suggesting that these are tumor suppressors that play a role in progression. ■

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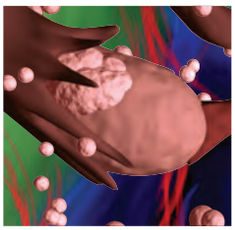
Ovarian Cancer Spheroids Use Myosin-Generated Force to Clear the Mesothelium

- Ovarian cancer spheroids attach to and clear the mesothelial cell layer to access the underlying connective tissue.
- Mesothelial cell clearance requires actomyosin contractility and is myosin-, talin-, and integrin-dependent.
- Ovarian cancer cells exert a contractile force on the extracellular matrix that physically displaces mesothelial cells.

Ovarian cancer metastasizes through the formation and subsequent implantation of spheroids, cell clusters that detach from the primary tumor. To successfully attach to the surface of peritoneal organs, the spheroids need to penetrate the mesothelial cell layer and gain access to the connective tissue under the mesothelial cells. Using a live, image-based *in vitro* model,

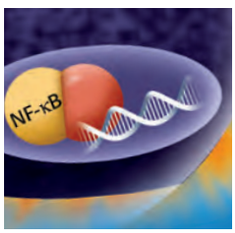


Iwanicki and colleagues demonstrate that tumor spheroids generate a force to physically displace mesothelial cells from the underlying extracellular matrix, a process termed *cell clearance*. Time-lapse microscopy allowed the authors to visualize the attachment of spheroid cells to a mesothelial cell layer, disassembly of mesothelial cell matrix adhesion, intercalation of tumor cells, and mesothelial clearance. The authors next demonstrated that signaling through the α_5 integrin fibronectin receptor activated myosin in the ovarian tumor cells, while knockdown of either myosin II or talin I, molecules involved in myosin contractility and force generation, attenuated mesothelial cell clearance. Further, the spreading spheroid was shown to generate a measurable contractile force; it is this unique contractile phenotype of tumor cells that drives mesothelial cell clearance and most likely promotes metastatic disease progression in ovarian cancer. ■

See article, p. 144.

PTEN Is a Tumor Suppressor in Human Pancreatic Ductal Adenocarcinoma

- PTEN is a haploinsufficient tumor suppressor in human PDAC.
- PTEN controls NF-κB–dependent transcription and cytokine expression.
- The PI3K/AKT axis and NF-κB may be targets for therapeutic intervention in PDAC.

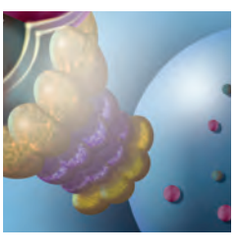


The PTEN tumor suppressor is a lipid phosphatase that dephosphorylates phosphatidylinositol-3, 4, 5-trisphosphate and negatively regulates the PI3K/AKT pathway. Although *PTEN* aberrations are present in many cancer types, it is thought to play little role in pancreatic ductal adenocarcinoma (PDAC), a disease with very low 5-year survival rates. Now, Ying and colleagues show loss of PTEN expression and deletion of the *PTEN* locus in a significant percentage of human PDAC tumor samples. The authors turn to a mouse model in which activated Kras is expressed in the pancreas and one allele of *Pten* is deleted. Interestingly, these mice present with invasive pancreatic tumors that exhibited infiltration of inflammatory cells. Gene expression analysis of primary cells derived from the tumors showed activation of NF-κB transcription that was dependent on PI3K signaling. Further, inhibition of NF-κB activity reduced tumor growth when such cells were implanted into nude mice. Finally, the authors showed upregulation of NF-κB–dependent cytokine expression in the mouse model; in publicly available human expression data, 4 of 5 cytokines were upregulated in PDAC, negatively correlating with PTEN expression. These data indicate PTEN is a haploinsufficient tumor suppressor in PDAC and it regulates an NF-κB–cytokine network that may be responsible for immune cell infiltration. In addition, the PTEN/PI3K/AKT axis and NF-κB itself may be drug targets in pancreatic cancer. ■

See article, p. 158.

PI3K Pathway Mutations in Endometrial Cancer

- Endometrial cancer displays a high frequency of PI3K pathway mutations and pathway activation.
- PI3K mutations lead to pathway activation.
- p85α (*PIK3R1*) regulates PI3K pathway through stabilization of PTEN.



Members of the PI3K and Ras signaling pathways are frequently deregulated in cancers, including endometrial cancer. However, the functional relevance of these alterations in endometrial cancer has not been fully explored, impeding the development of pathway-targeted therapy. Cheung and colleagues conducted mutational analysis of a large set of endometrial tumors and found high frequencies of aberrations in the PI3K pathway and *KRAS*. Integrated proteomic analysis suggests a lack of functional redundancy among PI3K pathway and *KRAS* mutations in these tumors. Coordinated mutations of multiple PI3K pathway members occur more commonly than predicted by chance with mutations in *PIK3R1* (encodes p85α) occurring at a higher rate in endometrial cancer than in any other tumor lineage. They also found that *PIK3R2* (encodes p85β), not previously demonstrated to be a cancer gene, is also frequently mutated. PI3K pathway mutations phenocopy PTEN loss, resulting in pathway activation. Their study also unveils a novel function of p85α in regulating the PI3K pathway by stabilizing PTEN. The PI3K pathway is shown to be a driver of endometrial carcinogenesis and a novel therapeutic target. ■

See article, p. 170.

Note: *In This Issue* is written by *Cancer Discovery* Editors. Readers are encouraged to consult the articles referred to in each item for full details on the findings described.

AACR American Association for Cancer Research

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