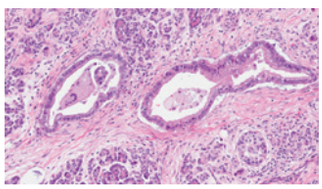
Breaking Advances
Highlights from Recent Cancer Literature

k-*Ras* and Subclinical Inflammation in the Pancreas



Long-term survival for patients with pancreatic ductal adenocarcinoma (PDAC) is limited, with only 5% of patients surviving 5 years. Although long-term survival statistics have not improved over the years, our understanding of the genetic anomalies underlying the disease has. Specifically, we now appreciate the role of several genetic drivers of PDAC, namely somatic mutations in the K-*Ras* oncogene in adulthood, and inactivation of tumor suppressor genes including *Trp53* and *p16Ink4a/P19Arf*. While patients suffering with chronic pancreatitis are at increased risk for PDAC, a majority of patients that develop PDAC have no prior clinical history of pancreatitis. That said, recent data indicate that subacute pancreatic inflammation may underlie a majority of human PDACs. Using a transgenic mouse model of PDAC, *KPC* mice, Geurra and colleagues induced subacute asymptomatic pancreatitis and revealed that when pancreatic ductal cells harboring K-*Ras* mutations were exposed to low levels of inflammatory stimuli, atrophy, fibrosis, and a persistent infiltration of macrophages and T lymphocytes resulted that was sufficient to induce neoplastic progression. Development of malignant lesions was dependent on the extent of tissue damage and the inflammatory response. Mechanistic evaluation revealed that inflammation abrogated the senescence barrier characteristic of low-grade premalignant lesions. Remarkably, malignant changes occurred even if the K-*Ras* mutation was switched on after inflammation-induced damage. Notably, treatment of mice with a nonsteroidal anti-inflammatory drug attenuated development of premalignant lesions and progression to PDAC. Relating the murine data to human pancreas biopsies, premalignant lesions in patients with chronic pancreatitis who had received anti-inflammatory drugs exhibited high expression of the senescence marker P16INK4A and had no evidence of cell proliferation. The opposite was observed in biopsies from patients untreated with anti-inflammatory drugs. These data from the mouse model and humans highlight the importance of inflammation in activating senescent premalignant lesions and suggest that anti-inflammatory therapies in people diagnosed with pancreatitis may reduce their risk of developing PDAC. *(Image courtesy of L. Coussens, University of California, San Francisco.)*

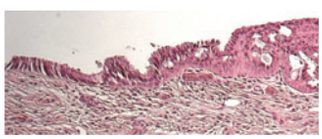
Guerra C, Collado M, Navas C, Schuhmacher AJ, Hernández-Porras I, Cañamero M, et al. Pancreatitis-induced inflammation contributes to pancreatic cancer by inhibiting oncogene-induced senescence. Cancer Cell 2011;19:728–39.

Genomics of Ovarian Cancer

Ovarian cancer is a common and frequently lethal cancer in women. A majority of cases are associated with mutation in the *p53* locus, and a significant minority also present with loss of the *BRCA1* and *BRCA2* tumor suppressors. In an effort to identify other genetic abnormalities, the Cancer Genome Atlas Research Network recently reported on genomic, transcriptomal, microRNA (miRNA), and epigenetic analysis of 489 ovarian cancers, with exome sequencing in 316. Over 95% of tumors showed mutations in *p53*, 20% showed mutation in *BRCA1* or *BRCA2*, and 50% showed defects in genes associated with homologous recombination. Other commonly dysregulated pathways included PI3K/RAS, RB, NOTCH, and FOXM1. Five recurrent chromosomal gains and 18 losses were found in more than half of the tumors, all of which had been reported previously. Transcriptomal profiling identified immunoreactive, differentiated, proliferative, and mesenchymal subtypes, with no significant survival differences among groups. Among 3 miRNA groups, the miRNA1 group was found to be enriched in proliferative tumors, and correlated with improved survival. A 193-gene signature was also identified that further stratified patient survival.

The Cancer Genome Atlas Research Network. Integrated genomic analysis of ovarian cancer. Nature 2011;474:609–15.

Opportunism Provided by p63 Loss



Population-based analyses of cancer incidence indicate that the relative incidence of adenocarcinoma is increasing. The malignancy arises progressively from metaplasia (Barrett esophagus), in which the normal stratified multilayered epithelium is converted, through poorly understood mechanisms, into a simple columnar epithelium. The p63 transcription factor is required for establishment of stratified epithelium during development, and expression of p63 is typically lost in Barrett esophagus. In a comparison of wild-type mice and mice deleted for p63, Wang and colleagues discovered a population of p63-negative columnar cells that were displaced during development by a local migratory population of p63-positive progenitor cells, giving rise to the normal stratified epithelium. A similar embryology was also observed in a sample of 21-week-old human fetal esophagus. Based on these observations, the authors postulated that a reservoir of opportunistic p63-negative progenitor cells is normally held in check by the p63-positive population. Indeed, injury to p63-positive cells provides an opportunity for p63-negative cells to repopulate "injured" tissue regions, and if followed by a chronic inflammatory insult (driven by gastroesophageal reflux, for example), progression to carcinoma is fostered. *(Image courtesy of L. Coussens, University of California, San Francisco.)*

Wang X, Ouyang H, Yamamoto Y, Kumar PA, Wei TS, Dagher R, et al. Residual embryonic cells as precursors of a Barrett's-like metaplasia. Cell 2011;145:1023–35.

Acetylation of AML-ETO in Leukemia

Oncogenic fusion proteins are frequently found in leukemias, with fusion of the *AML1* transcription factor to the Eto gene

(AML-ETO) resulting in deletion of the C-terminus of *AML1*. This deleted region typically binds to the p300 protein, enabling p300 to acetylate the N-terminus of AML. How does AML-ETO drive myeloid leukemia? To address this question, Wang and colleagues analyzed the interaction of p300 with AML-ETO, demonstrating that p300 was still able to bind through a domain in ETO, and that the NHR1 domain of ETO was required for transcriptional activation, driving a self-renewal program. They went on to show that p300 binding to AML-ETO drives acetylation of a 1ysine-43 residue in AML1, and that this acetylation was critical to the both activation of gene expression and self-renewal. Inhibition of p300 led to increased survival in mouse models for leukemia, suggesting a role for inhibitors of acetylation in the treatment of myeloid leukemia.

Wang L, Gural A, Sun XJ, Zhao X, Perna F, Huang G, et al. The leukemogenicity of AML1-ETO is dependent on site-specific lysine acetylation. Science 2011 Jul 14. [Epub ahead of print].

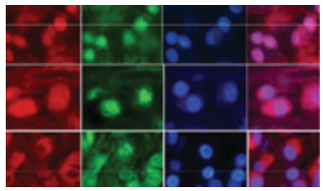
Force-Dependent Mechanisms Facilitate Ovarian Cancer Dissemination

High-grade serous ovarian cancer does not spread in the same manner as other malignancies. Instead of using lymph and blood vessels, ovarian cancer cells disseminate in the peritoneum, forming multiple deposits on areas such as the omentum and bowel mesentery. Primary tumors, no larger than 2 to 3 cm, can give rise to multiple peritoneal colonies and thereby cause a serious and significant clinical problem. In the second issue of *Cancer Discovery*, Iwanicki and colleagues describe their use of a live image–based *in vitro* model to study interactions between ovarian cancer spheroids and mesothelial cells that usually line the peritoneum, providing a spatial and temporal understanding of the process by which spheroids "clear" mesothelial cells to obtain access to submesothelial compartment. Initially, tumor spheroids adhere to dorsal surfaces of mesothelial cells to initiate spreading. Then, protrusions from spreading cells penetrate underneath mesothelial cells, causing localized breakdown of mesothelial cell-matrix adhesions and provoking their migration away from the spheroid. Traction force generated by spreading cancer cell clusters via integrin- and talin-dependent activation of myosin II leads to clearance of the mesothelial cells. Thus, acquisition of a contractile phenotype may be one step in the progression of high-grade serous ovarian cancer. This *in vitro* model may be relevant to the human disease since mesothelial cells are not present under ovarian tumor masses found attached to peritoneal tissues in women with advanced disease.

Iwanicki MP, Davidowitz RA, Ng MR, Besser T, Muranen T, Merritt M, et al. Ovarian cancer spheroids use myosin-generated force to clear the mesothelium. Cancer Discovery 2011;1:144–57.

p53 Controls DNA Repair through Regulation of BCRCA1 Nuclear Export

Subcellular localization of BRCA1 is an important aspect of BRCA1 functionality. Following DNA damage, p53 is required for BRCA1 export to the cytoplasm. A lingering question in breast cancer has been the degree to which mutant p53 alters



nuclear-cytoplasmic translocation of genetically wild-type BRCA1. To address this question, Jiang and colleagues investigated the influence of mutant p53 on proper BCRCA1 localization. They revealed that p53 regulates BRCA1 nuclear export via protein interactions involving the C-terminal BRCT region of BRCA1 and interruption of BRCA1–BARD1 interaction, resulting in enhanced susceptibility to ionizing radiation. Thus, loss-of-function mutations in p53 may contribute to genomic destabilization by interfering with nuclear export of BRCA1. Importantly, these data also indicate that altering BRCA1 transport mechanisms may be a viable strategy for increasing the susceptibility of breast cancers to therapies by enhancing DNA damage, and that nongenetic mechanisms suppressing BRCA1 activity may also play an important role in the pathogenesis of breast cancer. *(Image from cited article courtesy of publisher.)*

Jiang J, Yang ES, Jiang G, Nowsheen S, Wang H, Wang T, et al. p53-dependent BRCA1 nuclear export controls cellular susceptibility to DNA damage. Cancer Res 2011:71:5546–57.

Reverse Engineering of Signal Transduction Pathways

A major limitation of "omic"-based platforms that identify gene and protein networks is their inability to appropriately evaluate the significance of "context" or their ability to predict responses based on different stimuli. To overcome this limitation, Saez-Rodriguez and colleagues examined the dynamics of immediate-early signal transduction pathways using primary human hepatocytes, and 4 hepatocellular carcinoma (HCC) cell lines treated with interleukin (IL)-1α, IL-6, TGF-α, TNF-α, and insulin, in the presence and absence of small-molecule kinase inhibitors (e.g., IκB kinase, MAP/ERK kinase, and phosphoinositide 3-kinase), followed by examination of 16 intracellular signaling proteins using Luminex-based assays. With the aid of Boolean logical models of immediate early signaling, normal human hepatocytes were easily distinguished from malignant HCC cells. Importantly, the Boolean models also revealed Jak-Stat as a novel target for TPCA-1, an IκB kinase inhibitor. Thus, this modeling approach provides an elegant proof-of-concept that similar methods could be applied to examine other types of proteomic data to distinguish normal from malignant cells, as well as to potentially identify therapeutic agents. It will be interesting going forward to apply these approaches to other types of "biochemical" assays and in particular to obtain data on network interactions and response from *in vivo* multicellular models and/patients receiving different therapies.

Saez-Rodriguez J, Alexopoulos L, Zhang M, Morris MK, Lauffenburger DA, Sorger PK. Cancer Res 2011:71:5400–11.

Note: *Breaking Advances* are written by *Cancer Research* Editors. Readers are encouraged to consult the articles referred to in each item for full details on the findings described.