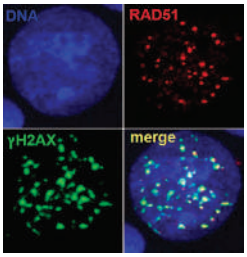
Breaking Advances
Highlights from Recent Cancer Literature

Overcoming PARP Inhibitor Resistance



Mutations in *BRCA1* or *BRCA2* that lead to defective homologous recombination (HR) are associated with familial breast and ovarian cancer. Issaeva and colleagues screened novel drugs for compounds that selectively killed BRCA2-defective cells and identified 6-thioguanine (6GT), which induces DNA double-strand breaks (DSB) that are repaired by HR. Moreover, the authors revealed that 6GT is as effective as a poly(ADP-ribose) polymerase (PARP) inhibitor in selectively killing BRCA2-defective tumor cells *in vivo* and efficiently kills BRCA1-defective tumor cells that have acquired PARP inhibitor resistance through genetic reversion of the *BRCA2* gene. These data indicate that HR is involved in repair of 6GT-induced DSBs as well as mismatch repair-independent 6GT-defective tumors and highlight a potential role for 6GT in treatment of advanced PARP inhibitor-resistant tumors.
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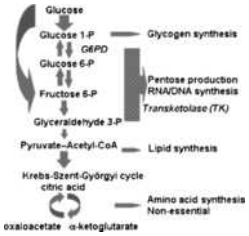
Issaeva N, Thomas H, Pedley N, et al. 6-thioguanine selectively kills BRCA2 defective tumors and overcomes PARP inhibitor resistance. Cancer Res 2010;70:6268–76.

Improving Adoptive Immunotherapy by Targeting Tumor Vasculature

Adoptive cell transfer (ACT)-based immunotherapies have been found to mediate objective cancer regression in some animal models and in some patients with metastatic melanoma. A major question that has been raised, however, is whether the chaotic nature of the tumor vasculature and/or high interstitial tumor pressure common to solid tumors impedes egress of tumor-specific T cells, thereby hindering therapy. Shrimali and colleagues have addressed this issue using vascularized B16 melanomas, in which they evaluated the effectiveness of ACT in combination with vascular endothelial growth factor antagonist. Results from this study indicate that "normalization" of tumor vasculature increases extravasation of adoptively transferred T cells into tumors, thereby improving the effectiveness of ACT-based immunotherapy and providing a rationale for exploring combinatorial antiangiogenic and ACT therapy for patients with cancer.

Shrimali RK, Yu Z, Theoret MR. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. Cancer Res 2010;70:6171–80.

Pancreatic Tumor Cells Choose Fructose



Glucose and fructose have long been thought of as interchangeable monosaccharide substrates with regard to metabolism. Liu and colleagues now report that fructose metabolism can result in enhanced pancreatic cancer cell proliferation by induction of thiamine-dependent transketolase flux and preferential metabolism via the nonoxidative pentose phosphate pathway to synthesize nucleic acids and increase uric acid production. Given the global increase in refined carbohydrate consumption, recognition of this important pathway may hold significance for cancer patients, whereby reducing dietary refined fructose consumption could lead to increased survival.
(*Image from cited article courtesy of publisher.*)

Liu H, Huang D, McArthur DL, et al. Fructose induces transketolase flux to promote pancreatic cancer growth Cancer Res 2010;70:6368–76.

Integrative Genomic Profiling Comes of Age

Annotation of cancer cell genomes provides a wealth of information to aid in our understanding of disease as well as identification of potential targets for therapy. Taylor and colleagues have conducted integrative genomic profiling of human prostate cancer using 218 tumor samples to assess DNA copy number, mRNA expression, and focused exon sequencing. Emerging from this endeavor is the surprise that somatic point mutations are relatively rare events in prostate cancers. Instead, genes often referred to as tumor suppressors, including *PTEN* and *TP53*, were commonly altered through copy-number loss rather than point mutation. Moreover, a significant role for the nuclear receptor coactivator *NCOA2* was identified and validated by showing that increased NCOA2 dosage amplifies androgen receptor pathway transcriptional output in primary tumors, thus providing a mechanism for its potential role as an oncogene. The authors provide this tremendous wealth of data to the community in the context of clinical outcome. This resource is now available through the portal http://cbio.mskcc.org/prostate-portal/ [cited July 1, 2010].

Taylor BS, Schultz N, Hieronymus H. Integrative genomic profiling of human prostate cancer. Cancer Cell 2010;18:11–22.

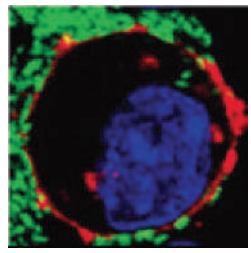
CD8$^+$ T cells Limit Melanoma Metastasis by Cytostatic Mechanisms

It has long been thought that metastases arise during the later stages of solid tumor development, a notion disputed in recent years as imaging and genomic technologies have improved. That said, what is clear is that timing of malignant cell dissemination and when productive metastases appear can be quite distinct. Thus, identification of the mechanisms controlling would-be tumor cell dormancy in ectopic tissues has emerged as a major question to address by cancer researchers. A recent study by Eyles and colleagues has revealed a surprising role for CD8$^+$ T cells in regulating malignant melanoma metastases by cytostatic, as opposed to cytotoxic, mechanisms involving interferon-γ- and tumor necrosis factor-α-dependent signals. These findings call into question the long-standing concept of tumor eradication by mechanisms solely reliant on tumor cell killing.

(*Image from Wikipedia [http://en.wikipedia.org/wiki/Disc_brake].*)

Eyles J, Puaux AL, Wang X. Tumor cells disseminate early, but immunosurveillance limits metastatic outgrowth, in a mouse model of melanoma. J Clin Invest 2010;120:2030–9.

CagA as a B-Cell Oncoprotein



Helicobacter pylori (H. pylori) is a common human pathogen that infects approximately 50% of the world's population and is associated with gastric ulcers. CagA$^+$ *H. pylori* infections are also associated with gastric carcinoma development and mucosa-associated lymphoid tissue (MALT) lymphomas. *H. pylori* colonization of gastric mucosa triggers a lymphocytic immune response and formation of acquired MALT. Sustained proliferation of B cells in MALT is partially mediated by antigenic stimulation and tumor-infiltrating T cells. Although involvement of CD40 and CD40L in sustaining B-cell proliferation has been recognized, the pathogenesis of how *H. pylori* induces development of B-cell MALT has not been clarified. Lin and colleagues found that, following translocation of the bacterial protein CagA into lymphoid B cells, CagA underwent tyrosine phosphorylation and bound intracellular SH-2, activating extracellular signal-regulated kinase (ERK) and p38 mitogen-activated protein kinase (MAPK), thereby upregulating expression of Bcl-2 and Bcl-x, resulting in prevention of apoptotic cell death. These data thus reveal an oncoprotein-type role for CagA in developing MALT lymphomas and identify a new target for therapy.

(*Image from cited article courtesy of publisher.*)

Lin WC, Tsai HF, Kuo SH. Translocation of Helicobacter pylori CagA into human B lymphocytes, the origin of mucosa-associated lymphoid tissue lymphoma. Cancer Res 2010;70:5740–8.

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.