Breaking Advances
Highlights from Recent Cancer Literature

**Modification of Chemotherapy Resistance in Pancreatic Cancer Cells**

Pancreatic cancers are inherently refractory to conventional chemotherapies. Gemcitabine [2’,2’-difluoro-20-deoxyctydine (dFdC)] is currently used as a first-line treatment against locally advanced and metastatic adenocarcinoma of the pancreas. Gemcitabine is phosphorylated intracellularly to its active diphosphate (dFdC-DP) and triphosphate (dFdC-TP) forms that inhibit DNA and RNA replication. Membrane-bound nucleoside transporters are prerequisites for hydrophilic gemcitabine to enter cells because cells deficient in nucleoside transporter are resistant to gemcitabine cytotoxicity. Studies to date suggest 2 transporters from each of the human concentrative nucleoside transporter family (hCNT1 and hCNT3) and the equilibrative nucleoside transporter family (hENT1 and hENT2) are capable of translocating gemcitabine across the cell surface. Despite the expression of one or more of the aforementioned transporters in most cells types, hENT1 is generally considered to be predominantly involved in gemcitabine transport in tumors as its expression correlates with cellular proliferation. Clinical evidence also shows that pancreatic tumor cells with high hENT1 expression exhibit increased gemcitabine chemosensitivity. The present study establishes a role for the human concentrative nucleoside transporter-1 (hCNT1) in regulating the chemosensitivity of human pancreatic cancer cells to gemcitabine. Pharmacologic inhibition of hCNT1 degradation moderately increased cell surface hCNT1 expression and cellular gemcitabine transport in Mia PaCa-2 cells. Constitutive hCNT1 expression reduced clonogenic survival of Mia PaCa-2 cells and steeply augmented gemcitabine transport and chemosensitization. In addition to supporting a putative tumor suppressor role for hCNT1, the present findings highlight hCNT1 as a potential candidate to render drug-resistant pancreatic cancer cells amenable to chemotherapy. *(Image from cited article courtesy of publisher.)*

**Humoral Immune Response Regulates Tumor Angiogenesis**

Targeted inhibition of angiogenesis represents a potentially useful approach for therapy in solid tumors. Indeed, bevacizumab, a humanized monoclonal antibody blocking VEGF-A, is used for treatment of some human cancers. However, targeting VEGF-A alone is not sufficient to induce sustained tumor regression, suggesting that additional approaches (or targets) are required. Schoenfeld and colleagues report a provocative finding—that as part of successful immune therapy, patients develop antibodies against angiogenic vessels. This approach uses lethal irradiation and autologous tumor cells engineered to secrete granulocyte macrophage colony-stimulating factor combined with anticytotoxic T-lymphocyte antibody blockade. The authors observed that some patients receiving this therapy exhibited an immune response apparently directed at tumor angiogenesis. From one patient exhibiting a favorable response to therapy, sera were isolated and screened for vascular interactions using a B16 melanoma cDNA library. VEGF-A, angiopoietin-1 and 2, and macrophage inhibitory factor identified from the screen were functionally evaluated for effects on angiogenesis, macrophage chemotaxis, and metalloproteinase production. These findings raise questions about the role of humoral response as a physiologic regulator of angiogenesis, and about other aspects of the important microenvironmental processes that influence response to therapy.

**Inhibition of MAP Kinase Interacting Kinase Suppresses Experimental Lung Metastases by Inhibiting Initiation Factor 4E Phosphorylation**

Initiation factor 4E (eIF4E) regulates mRNAs that generally encode proteins involved in key components of malignancy including proteins involved in cell growth, angiogenesis, invasion, and survival. Overexpression of eIF4E transforms cells by selectively upregulating translation of these malignancy-related mRNAs. Moreover, in transgenic mice, ectopic eIF4E expression increases the incidence of multiple cancers, including lymphomas, lung adenocarcinomas, angiosarcomas, and hepatomas, and accelerates the Eμ-myc mouse lymphoma model. Signaling through the AKT-mTOR pathway activates eIF4E by phosphorylating the inhibitory 4E binding proteins. This liberates eIF4E and allows binding to eIF4G; eIF4G can then be phosphorylated at serine 209 by the MAPK-interacting kinases (Mnk), which also interact with eIF4G. In the present study, Konicek and colleagues provide convincing evidence that Mnk inhibition may represent a viable cancer therapeutic. They describe a potent, selective, and orally available Mnk inhibitor that induces apoptosis and suppresses proliferation and soft agar colonization of cancer cells. Oral dosing with the Mnk inhibitor significantly suppressed outgrowth of experimental B16 melanoma pulmonary metastases as well as growth of subcutaneous HCT116 colon carcinoma xenograft tumors, without affecting body weight. This interesting article provides initial support for a potentially novel targeted therapeutic approach for cancer therapy exploiting the Mnk pathway. *(Image from cited article courtesy of publisher.)*


The Combination of MYC and MCL1 Contributes to the Genesis and Outcome of Non–Small Cell Lung Cancer

The proto-oncogene MYC is documented to play a major role in the development of multiple human cancers. MYC encodes a transcription factor that modulates expression of multiple gene networks involved in important cellular processes, including proliferation, metabolism, and ribosome biogenesis. In addition, MYC activates the proapoptotic BCL2 family protein BAX culminating in cytochrome C release from mitochondria and apoptosis. MCL1 is an antiapoptotic member of the BCL2 family of proteins that localizes in the outer membrane of mitochondria and other intracellular membranes, inhibiting events that lead to cytochrome C release. MCL1 is amplified in human non–small cell lung carcinomas (NSCLC) and cooperates with MYC in experimental leukemogenesis. Although previous studies have argued that MCL1 overexpression does not correlate with prognosis in NSCLC, studies by Allen and colleagues now dispute this finding. These investigators have found that MCL1 overexpression does correlate with poor patient survival, but only when this alteration is accompanied by overexpression of the MYC protein. These results support the suggestion that combined overexpression of MCL1 and MYC may provide a useful biomarker for both prognosis and treatment in human NSCLC. Moreover, these studies suggest the intriguing possibility that inhibition of MCL1 might have a synthetic lethal effect by unleashing the proapoptotic effect of MYC. (Image from cited article courtesy of publisher.)


Novel Inhibitors of Carbonic Anhydrase Suppress Breast Tumor Growth and Metastasis

Although multiple factors contribute to tumor dissemination to secondary sites in distant organs, an increasing body of evidence indicates that hypoxia plays a seminal role in cancer progression and metastasis. In this context, mounting data suggest an important role for altered tumor metabolism and hypoxia-inducible factor 1α (HIF-1α)–regulated enzymes such as carbonic anhydrase IX (CAIX) and CAIXII in tumor evolution and spread. CAIX regulates intra- and extracellular pH under hypoxic conditions and promotes tumor cell survival and invasion in hypoxic microenvironments. Moreover, CAIX has been suggested to be an independent poor prognostic biomarker for distant metastases and survival. Depletion of CAIX expression in 4T1 mouse metastatic breast cancer cells and MDA-MB-231 human metastatic breast cancer cells, using short hairpin RNA and stable depletion approaches, significantly attenuated lung metastases and primary tumor growth, respectively. Moreover, treatment of mice containing CAIX-positive 4T1 mammary tumors with novel CAIX-specific small molecule inhibitors that replicated the effects of CAIX depletion in vitro resulted in significant inhibition of tumor growth and metastasis formation in both spontaneous and experimental models of metastasis without a significant inhibitory effect on CAIX-negative tumors. A similar inhibitory phenomenon was observed in mice harboring orthotopic tumors comprised of lung metastatic MDA-MB-231 LM2-4Luc+ cells. The take-home message from this report is that CAIX is vital for growth and metastasis of hypoxic breast tumors and may provide a specific, targetable biomarker for breast cancer metastasis. (Image from cited article courtesy of publisher.)


Genomic Instability: Help or Hindrance for Tumorigenesis?

Genomic instability is a hallmark of cancer. Generally, it is presumed that circumstances promoting genomic instability contribute to tumorigenesis. Birbak and colleagues examined chromosomal instability for correlations with clinical outcome. Paradoxically, they found that chromosomal instability can correlate with a better clinical outcome. They examined profiles of 2,125 breast cancers for a CIN70 expression signature that correlates with structural chromosomal complexity. They found that tumors with extreme chromosomal instability were associated with an estrogen receptor–negative, basal-like phenotype and had an improved prognosis compared with tumors with intermediate chromosomal instability. Similarly, a paradoxical relationship between chromosomal instability and prognosis in other solid tumors including ovarian, gastric, and non–small cell lung carcinoma was revealed. The authors postulate that, although chromosomal instability can enhance the opportunity for biological fitness, this comes at the cost of decreased viability. Hence, tumors appear to make a trade-off between genetic adaptability and intrinsic proliferative ability. These results have provocative implications, as they highlight the existence of an optimal amount of genomic instability during tumor evolution. One question raised by these results is whether this generally applies to any form of genomic destabilization or is instead specific to particular types of genomic instability that are more likely to result in altered gene expression. Another implication of these results is that cancer treatments exploiting genomic damage are similarly likely to have evolutionary consequences for a tumor that, in a predictable manner, may lead to tumor regression as well as tumor escape.


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.
Highlights from Recent Cancer Literature

Cancer Res 2011;71:3173-3174.

Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/71/9/3173

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, use this link http://cancerres.aacrjournals.org/content/71/9/3173. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.