Breaking Advances
Highlights from Recent Cancer Literature

Vascular Endothelial Growth Factor and Endothelial Growth Factor Cooperate as Mitogens for Epithelial Cancers

Vascular endothelial growth factor receptor (VEGFR) and endothelial growth factor receptor (EGFR) family members are critical to the development of epithelial cancers. Vascular endothelial growth factor (VEGF) is a ligand secreted by these cancers and is known to drive angiogenesis. Lichtenberger and colleagues recently reported that deletion of VEGF or its receptor Flt1 impairs tumorigenesis and proliferation in mouse skin tumors driven by SOS (which signals downstream of Ras) under control of the keratin 5 promoter. The results showed that VEGF and VEGFR are upregulated in these cancers, EGFR plays a role in blocking apoptosis, and tumors are completely blocked in mice doubly mutant for VEGF and EGFR. These findings, along with observations that VEGFR is upregulated in human squamous cancers, establish a role for VEGF as a growth factor for epidermal tumors.


Deubiquitinating p53

The half life of wild-type p53 is quite short, with the ubiquitin ligase Mdm2 driving ubiquitination, nuclear export, and degradation of p53. Recent work from Yuan and colleagues identified USP10 as a p53 deubiquitinase capable of reversing Mdm2-induced nuclear export and degradation of p53. In response to DNA damage, USP10 is phosphorylated and stabilized by ATM, enabling USP10 to translocate to the nucleus to activate p53. Expression of USP10 is low in renal cell cancers with wild-type p53 and can suppress the growth of renal cell cancer cells in vitro. These findings demonstrate that USP10 is a regulator of p53.


An Apoptosis-Independent Role for p53 in Radiation-Induced Gastrointestinal Syndrome

Gastrointestinal injury in response to radiation is common but poorly understood. Kirsch and colleagues irradiated wild-type mice or mice deleted for Bax and Bak, gatekeepers for the intrinsic pathway of apoptosis. Mice developed the gastrointestinal syndrome irrespective of Bax/Bak mutational status, suggesting that the intrinsic pathway for apoptosis in endothelial and epithelial cells does not contribute to this syndrome. In contrast, overexpression of p53 in epithelial cells was protective, whereas ablation of p53 in epithelia, but not endothelia, sensitized mice to the gastrointestinal syndrome. These data suggest that the gastrointestinal syndrome arises from radiation-induced death of gastrointestinal epithelial cells, and that the death of these cells is dependent on p53 and independent of the intrinsic pathway of apoptosis. This study also raises the question of whether emerging clinical inhibitors of p53 may exacerbate the late effects of radiation therapy.


Lmo2 and Self Renewal

Relapse is common in pediatric T-cell acute lymphocytic leukemia, with activation of the transcriptional modulator Lmo2 implicated in 10% of relapsed patients. Lmo2 was also activated by retroviral insertional mutagenesis and shown to contribute to leukemia in a subset of patients receiving gene therapy for X-linked severe combined immunodeficiency. McCormack and colleagues studied fate mapping in mice prone to T-cell leukemia. These mice carry an Lmo2 transgene driven by the CD2 promoter in the thymus. Lmo2 induced self renewal and activated hematopoietic stem cell markers in T cells months before animals developed leukemia. These and supporting data suggest that Lmo2 induces self renewal of preleukemic thymocytes as an initiating event, enabling these cells to accumulate additional genetic mutations needed to develop leukemia.


Oncogenic Mutations in Adjacent Epithelial Cells Cooperate in Transformation

Checkpoint control contributes to protection against cancer, with loss of checkpoint control typically thought to occur early in oncogenesis, enabling genetic lesions to accumulate and resulting in full-blown malignancy. Using antennal discs from the fruit fly Drosophila melanogaster, Wu and colleagues showed that cells carrying the RasV12 mutation can
cooperate with adjacent cells carrying the tumor suppressor scribbled (implicated in epithelial polarity and mammary cancer) to promote metastasis. Scribbled mutant clones propagate damage through Jnk signaling and Jak/Stat regulated cytokines, with similar signaling activated in response to tissue damage. This paper suggests a role for inflammation-induced Jnk signaling contributing to the development of RasV12 tumors.


Small Molecule Inhibitors of Therapy-Resistant Abl Mutations in CML

The gatekeeper is a conserved threonine residue in kinases that serves as a selectivity filter, as its bulky side-chain creates a size barrier that keeps molecules larger than ATP from fitting into the ATP-binding pocket. Mutations at the gatekeeper residue generate a selectivity filter that blocks the binding of small molecule inhibitors. The T315I mutation in Bcr-Abl represents a particularly troublesome mutation that remains resistant even to the newest small molecule inhibitors of Abl, nilotinib and dasatinib. Zhang and colleagues recently described a new class of small molecule inhibitors of Abl that binds to the myristate-binding site rather than to the ATP-binding pocket of Abl. One member of this group, GN5, could only weakly inhibit the T315I mutant protein but finessed an allosteric change in the ATP-binding site. When GN5 was used in combination with nilotinib, improved inhibition of the T315I mutant was observed in cells and in a mouse transplant model. Thus, combining allosteric and ATP-competitive inhibitors of Abl represents a promising new strategy to block development of resistance.


Chronic B-cell-Receptor Signaling Drives Survival of Diffuse B Lymphoma Cells

Diffuse large B-cell lymphomas (DLBCLs) comprise a mixture of diseases with differing genetic profiles and clinical outcomes. B-cell-receptor (BCR) signaling has long been hypothesized to be a common driver in DLBCLs, but direct evidence in human tumors has been lacking. RNAi screens performed by Davis and colleagues now provide genetic support for this hypothesis, defining elements of “chronic active” BCR signaling that are needed for survival of DLBCL cells. These findings implicate the nerve growth factor κ-B (NF-κ-B) pathway, identifying upstream regulators including signaling adapter CARD11, Bruton’s tyrosine kinase, and BCR subunits as essential elements for cell survival. By establishing dysregulated BCR signaling as a pathogenetic mechanism in DLBCLs, the results of this study suggest several new therapeutic strategies to disrupt this core survival pathway.


Novel Route to Destabilize MCL1, a Potent Cousin of BCL2 in Human Cancers

Drug resistance is an inherent problem with any new cancer therapy. Indeed, drug resistance to the more specifically targeted molecular therapies may arise more readily relative to traditional, standard-of-care, broad-spectrum cytotoxic drugs. One important mechanism of resistance that arises in small molecule inhibitors of BCL-xl that are in clinical development is activation of the BCL2-related protein MCL1, a potent oncogene that is itself dysregulated in certain human cancers. Recent work from Schwickart and colleagues identified a regulatory pathway for MCL1 protein turnover that involves the deubiquitinase USP9X. These findings suggest that therapeutic targeting of USP9X or other elements of this pathway is a rational strategy to destabilize MCL1, thereby thwarting an important avenue of resistance to BCL2/BCL-xl inhibitors, and more generally, providing a route to disrupt survival of human tumor cells where MCL1 is dysregulated.


PARP1 Inhibitors Selectively Destroy Tumor Cells with BRCA1 or ATM Lesions

One concept in cancer therapy receiving a great deal of consideration relates to applications of synthetic lethality, which in genetics refers to the lethal phenotype produced by a combination of lesions that by themselves are harmless. In cancers that are driven by a root lesion, an application of this concept would be to define chemical genetic strategies to attenuate a function that cooperates with the root lesion to trigger lethality of the cancer cell, while leaving normal cells lacking the lesion unaffected. In a demonstration of the potential of this idea, the fundamental elements of which have been credited to Hartwell, preclinical and clinical studies of a small molecule inhibitor of the DNA repair-related enzyme PARP1 showed that this inhibitor is unexpectedly efficacious against breast cancer tumors with BRCA1 mutations.
Presumably, breast cancer cells lacking BRCA1 are defective in DNA repair pathways that require this tumor suppressor gene (e.g., DNA recombination), such that they are highly reliant on enzymes such as PARP1 that support alternate repair pathways (e.g., nonhomologous end joining). PARP1 inhibitors resulting in the loss of both pathways cripple BRCA1-defective breast cancer cells but not normal cells, which continue to have access to the BRCA1 pathways as backup. Recent work suggests that PARP1 inhibitors will also be effective in killing cancer cells with deficiencies in the ATM pathway of DNA repair. Exciting progress in this area provides a strong rationale for continued exploration of genetic and synthetic lethal approaches as therapeutic strategies for selective destruction of tumors.


Emergence of ‘Onco-Metabolite’ 2-Hydroxyglutarate in Cancer

Therapeutic exploitation of cancer metabolism has mainly focused on glycolysis and the mammalian target of rapamycin (mTOR) pathway, but rapidly increasing interest has been expressed in other metabolic realms, such as the tricarboxylic acid (TCA) cycle, the pentose phosphate cycle, and amino acid catabolism pathways. One enzyme in the TCA cycle that has garnered major attention recently is isocitrate dehydrogenase (IDH1/2) on the basis of glioma studies that identified genetic alterations in IDH1/2 as tumor suppressor mutations. A new development in this story has emerged due to the finding that IDH1 mutations may represent gain-of-function changes that lead to increased production of 2-hydroxyglutarate, which has been termed an onco-metabolite. Other recent work suggests that IDH1 mutations found in AML also elevate production of 2-hydroxyglutarate. These findings represent an important new convergence of cancer genetics and metabolism, likely heralding more intensive study of 2-hydroxyglutarate and TCA cycle dysfunction in cancer.


Convergence on ‘Onco-Fetal’ Metabolic Regulator Pyruvate Kinase-M in Cancer

Pyruvate kinase (PK) is a pivotal enzyme connecting glycolysis and the TCA cycle. Broad activation of glycolysis in cancer cells (the Warburg effect) means that PK lies at a key intersection of metabolic activity for which the pathophysiologic impact is not yet fully understood. Recent studies have revealed a common mechanism of PK alteration in tumor cells and tumor-infiltrating antigen-presenting cells (dendritic cells) yielding an alternately spliced isoform known as PK-M. This event has several important implications. PK-M upregulation occurs in both fetal development and cancer, where it confers a proliferative advantage. Additionally, PK-M formation is mediated by alternate RNA splicing factors that are controlled by Myc, a pivotal oncogene in cancers that also alters glycolytic status. Lastly, and perhaps most provocatively, PK-M has also been associated with reduced antigen presenting capability of immune cells in cancer, suggesting an important role in tumor dormancy and immune escape. The convergence on PK-M represents an important new development in studies of the impact and meaning of dysregulated glycolysis in cancer.


Attacking the STAT3 Pathway in Cancers via JAK2 Inhibition

A compelling number of preclinical studies have underscored the importance of STAT3 pathway activation in cancer pathophysiology, both at the level of the tumor cell and the supportive immune tumor microenvironment. Given the great interest in STAT3 signaling as a target for therapeutic attack, considerable efforts have been devoted in academic and pharmaceutical laboratories in developing small molecule inhibitors of this pathway. One of the potentially promising directions is...
the development of inhibitors of the Jak2 tyrosine kinase, which responds to chronic upstream receptor activation by stimulating STAT3 function. Results from recent studies suggest that Jak2 inhibitors might be efficacious in various solid tumors and myeloproliferative diseases, acting at possibly two levels to block STAT3-driven growth and survival of tumor cells as well as immunosuppressive cells in the tumor microenvironment.


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.