Paxillin, microRNA-218, and Non–Small Cell Lung Cancer

Lung cancer is the leading cause of cancer death in industrial countries. Critical determinants of lung cancer progression that affect patient prognosis include tumor cell migration and metastasis. The focal adhesion protein paxillin (PXN) is associated with signal transduction pathways that regulate cell motility and migration. PXN mutations are associated with lung adenocarcinoma progression, and PXN has been identified as a target gene of microRNA-218 (miR-218). Based on this association, Wu and colleagues explored the hypothesis that PXN overexpression induced by miR-218 suppression might be an important promoter of lung cancer progression and metastasis. Using real-time PCR and immunohistochemical analyses, they found that expression levels of miR-218 and PXN in 124 surgically resected lung tumors revealed a negative association between miR-218 and PXN expression. Furthermore, patients with low miR-218 expression and high PXN positivity displayed the worst overall and relapse-free survival in the cohort of patients that were evaluated. The clinical sample evaluation outcome was supported by results from cell model systems showing that PXN was negatively regulated by miR-218 and that cell proliferation, invasion, and soft agar colony formation were enhanced by PXN overexpression induced by miR-218 suppression. These findings indicate diagnostic applications for PXN overexpression in non–small cell lung cancer. With further validation studies and additional experimentation, PXN may provide a viable therapeutic target to improve clinical outcomes in this disease. (Image from cited article courtesy of publisher.)


Aldehyde Dehydrogenase and Chemoresistance in Ovarian Cancer Stem Cells

Tumor recurrence and chemoresistance are common in patients with ovarian cancer. It is hypothesized that a potential source of these evolving tumor cells lies within a subpopulation of malignant cells termed cancer stem cells or tumor-initiating cells. In ovarian cancer, components of this subpopulation have been identified as CD44/c-kit positive, CD133-positive, and Hoechst-excluding. Landen and colleagues have focused on aldehyde dehydrogenase-1A1 (ALDH1A1)-positive ovarian cells as putative cancer stem cells. These authors revealed that the level of ALDH1A1 expression and activity were higher in taxane- and platinum-resistant cell lines. Moreover, approximately 73% of patients with ovarian cancer had ALDH1A1 expression in which the percentage of ALDH1A1-positive cells correlated negatively with progression-free survival. Experimentally, subpopulations of ALDH1A1-positive cells were approximately 50-fold more efficient in forming orthotopic tumors than were ALDH1A1-negative cells. Intriguingly, they also observed that tumors from ALDH1A1-positive cells gave rise to both ALDH1A1-positive and ALDH1A1-negative populations, but the opposite effect, that of ALDH1A1-negative to ALDH1A1-positive cells, was not observed. A role for ALDH1A1 in regulating chemotherapy resistance was supported by the observation that siRNA silencing of ALDH1A1 resulted in enhanced chemosensitivity in both taxane- and platinum-resistant ovarian cancer cell lines. These results indicate that ALDH1A1 may provide a useful means of identifying and targeting chemoresistant cell populations in ovarian cancer. (Image from cited article courtesy of publication.)


Genetics of Brain Tumors

Two recent articles identify new genetic alterations in brain tumors. Medulloblastoma is the most common malignant brain tumor of childhood, and consists of four transcriptomal groups. In the first article, Parsons and colleagues report on their sequencing of 22 medulloblastoma tumors. They found that genetic abnormalities in these childhood tumors occurred, on average, at one fifth to one tenth the frequency of those found in adult solid tumors sequenced in a similar manner. They subsequently sequenced mutant exons in an additional 66 tumors, identifying loss of function in a number of chromatin remodeling and transcriptional regulatory genes, including the histone-lysine N-methyltransferases, MLL2 and MLL3, in 16% of patients, not previously known to occur in medulloblastoma and not limited to any specific transcriptomal subgroup. Malignant gliomas comprise the most common brain tumors in adults, with high-grade glioblastoma multiforme tumors being the most aggressive and common of these. Amplification and activating mutations in epidermal growth factor receptor (EGFR) are common in glioblastoma multiforme, occurring an approximately two thirds of patients and acting in part to drive a transcriptional program regulated by NFkB. In the second article, Bredel and colleagues report on their sequencing of an inhibitor of NFkB (NFKBIA) in 790 glioblastoma tumors. They identified heterozygous deletions of NFKBIA in nearly one fourth of tumors that were mutually exclusive with amplification of
EGFR. Outcomes in patients with amplified EGFR or loss of NFKBIA were comparable and were worse compared with outcomes in patients with neither alteration. These data suggest NFKBIA as a haploinsufficient tumor suppressor gene with an effect similar to that of EGFR amplification in glioblastoma multiforme.


Resistance to BRAF Inhibition in Melanoma

A majority of malignant melanomas harbor activating mutations in the serine/threonine kinase BRAF, suggesting BRAF as a therapeutic target. Clinical studies using the inhibitor PLX4032 suggest remarkable activity in this disease, though patients treated with PLX4032 typically develop resistance. Three studies have now identified mechanisms contributing to therapeutic resistance to BRAF inhibitors, focusing largely but not exclusively on PLX4032. Villanueva and colleagues demonstrated that BRAF-dependent cells could switch to ARAF or CRAF dependence and also activated the receptor tyrosine kinase IGF-1R and downstream PI3K signaling as resistance mechanisms. In another study, Johannessen and colleagues identified MAP3K8 (encoding COT/Tpl2) as a MAP kinase pathway agonist that activated downstream MAP kinase signaling downstream of RAF signaling. In a third study, Nazarian and colleagues found that resistance could arise in a mutually exclusive manner through upregulation of the receptor tyrosine kinase PDGFRβ or through mutation of the Ras family member NRAS, activating MAP kinase downstream of RAF. Collectively, these studies indicate that resistance to BRAF inhibitors may occur through reactivation of MAP kinase signaling, or from RTK or PI3K-driven activation of alternative survival signaling. These results suggest a number of combination therapeutic strategies to block resistance to BRAF inhibition.


Immunogenic Tumor Apoptosis

Chemotherapy is generally assumed to induce apoptosis in tumor cells that is independent of an immune response. However, it has been shown that chemotherapy can also either stimulate or suppress various immune cell types depending upon specific circumstances. Schiavoni and colleagues identified two ways in which cyclophosphamide influences immunity that may play a direct role in tumor regression: first by influencing dendritic cell homeostasis through an interferon-regulated mechanism, and second through an immune-mediated apoptosis of tumor cells. These investigators used a mouse model to show that, upon treatment with cyclophosphamide, immune-mediated cell death occurs associated with translocation of calreticulin , downregulation of CD31, and release of HMGB1, promoting activation of dendritic cells followed by engulfment of tumor cells by activated dendritic cells. These results indicate that chemotherapies such as cyclophosphamide may mediate their antineoplastic properties through immune-regulated mechanisms of tumor cell elimination.


CD47 and Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is the most common tumor in children. Recently it was revealed that anti-CD47 therapy is a potentially effective modality for treatment of some cancers. Chao and colleagues describe a subset of human ALL that expresses high levels of CD47, and this expression predicts survival and resistance to therapy. Moreover, an antibody blocking CD47 regulates macrophage engulfment of tumor cells in vitro and growth of tumor cells in vivo. These results indicate that anti-CD47 antibody therapy may be useful for some patients with ALL. (Image from cited article courtesy of publisher.)

Highlights from Recent Cancer Literature


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