Highlights from Recent Cancer Literature


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Genome-Based Classification of Lung Cancer

Seidel and colleagues asked whether genomic analyses could augment pathologic classification for adenocarcinoma, squamous carcinoma, small-cell lung carcinoma, and large-cell carcinoma. As expected, adenocarcinomas were enriched for \( \text{KRAS} \) and \( \text{EGFR} \) mutations, small-cell lung cancers for \( \text{MYCN} \), and squamous carcinomas for \( \text{NFE2L2} \). Large-cell carcinoma tumors showed alterations typical of all the other subtypes, enabling reclassification. An algorithm applied to 5,145 tumors provided a genome-based diagnosis in 75% of cases. Importantly, the incorporation of genomic alterations led to an improvement in patient outcome due to the identification of \( \text{EGFR} \)-mutant and \( \text{ALK} \)-rearranged cancers, both of which were amenable to effective targeted therapy. These findings support an integrated histologic-genomic approach to the classification of lung cancer. (Image courtesy of Wikimedia Commons.)


Role of AKT3 in Triple-Negative Breast Cancer

Using a short hairpin RNA screen to identify kinases frequently amplified and overexpressed in breast cancer, Chin and colleagues demonstrated that AKT3 kinase was required for growth in triple-negative breast cancers (TNBC). Silencing AKT3 in TNBC cells inhibited cell growth \textit{in vitro} and \textit{in vivo}, with dramatic inhibition in three-dimensional spheroid and xenograft growth (mediated by the cell-cycle inhibitor p27). Growth, migration, and invasion were selectively affected by AKT3, as compared with AKT1 or AKT2. Moreover, silencing AKT3 expression in TNBCs sensitized cells to a pan-AKT inhibitor. This study shows that AKT3 plays a significant role in TNBCs and might serve as a therapeutic target, increasing treatment options for patients. (Image from cited article courtesy of publisher.)


New Genetically Engineered Model for Ovarian Carcinoma

Perets and colleagues describe a new mouse model of high-grade serous ovarian cancer (HGSC). \( \text{Pax8} \), essential for development of fallopian tubes but not ovaries, that was used as a tissue-specific driver targeting \( \text{BrcA} \), \( \text{Trp53} \), and \( \text{Pten} \) deletions in fallopian tube secretory cells. The mice developed serous tubal epithelial carcinomas that spread to the ovary and peritoneum, recapitulating human disease. The lesions expressed key tumor and serum proteins used clinically in patients with HGSC. Genomic analysis revealed alterations that were similar to those in human HGSC tumors. This new model not only provides insights into the origin and pathogenesis of HGSC but also will be valuable in testing therapies and methods for early detection in women at risk. (Image courtesy of Wikimedia Commons.)

A Novel EGFR Inhibitor with Mutant Selectivity and Wild-type Sparing Properties

Lung cancer patients treated with inhibitors of EGFR often develop resistance due to gatekeeper mutations (T790). Walter and colleagues developed CO-1686 (orange), which covalently binds C797 in the EGFR-kinase domain (green). CO-1686 showed 22-fold selectivity for inhibiting EGFR\textsuperscript{T790M} over EGFR\textsuperscript{WT}, selectively blocking proliferation, EGFR phosphorylation, and mouse models of lung cancer driven by EGFR\textsuperscript{T790M}. CO-1686-resistant clones showed reduced dependence on EGFR for viability, and enrichment of genes driving epithelial–mesenchymal transition. CO-1686-resistant clones upregulated pAKT, and CO-1686 synergized with AKT inhibition in these clones. CO-1686 is in an early phase of clinical testing and shows promise for improved efficacy in patients with EGFR\textsuperscript{T790M}-resistant mutations and reduced toxicity due to relative sparing of EGFR\textsuperscript{WT}. (Image from cited article courtesy of publisher.)


Taking a Notch out of Wnt-Driven Cancers

Liu and colleagues identified a novel Wnt inhibitor, LGK974. LGK974 inhibited secretion of Wnt by attenuating palmitoylation via binding and inhibiting the O-acyltransferase Porcupine (PORCN). LGK974 inhibited Wnt-driven xenografts with good association among pharmacokinetics, efficacy, and decreased expression of Wnt biomarkers. Sustained pathway inhibition was not required for efficacy in vivo, perhaps explaining a favorable therapeutic index. Exome sequencing of LGK974-responsive head and neck squamous cell carcinoma cell lines revealed frequent loss-of-function mutations in NOTCH1, with expression of Notch inhibiting growth. Thus, in addition to describing a novel small-molecule Wnt inhibitor, this article describes a biomarker to identify patients most likely to benefit from clinical use of this inhibitor. (Image courtesy of Wikimedia Commons.)


Radiation and T-cell Immunotherapy

Using models for melanoma and pancreatic islet cell tumors, Klug and colleagues found that low-dose irradiation promoted infiltration by T cells as well as normalization of the vasculature, with antitumor response in an adoptive T-cell transfer model. Low-dose irradiation promoted proliferation and differentiation of macrophages into M1-like iNOS (NOS2)-expressing macrophages that orchestrated CTL recruitment, killing tumor cells by inducing endothelial activation and TH1 chemokines, while suppressing angiogenic, immunosuppressive, and tumor growth factors. These results were reproduced in samples from a clinical trial in pancreatic cancer. Larger studies are needed to confirm these results, which suggest low-dose irradiation as a means to enhance local antitumor immunity in pancreatic cancer. (Image courtesy of Wikimedia Commons.)


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.