Breaking Advances
Highlights from Recent Cancer Literature

Circuitry of the RAS-RAF-MEK-ERK Signaling Pathway

Abnormal activation of the RAS-RAF-MEK-ERK signaling pathway is a common feature of many human solid tumors. Based on this observation, several RAF and MEK inhibitors have been developed and are currently being evaluated in clinical trials; however, an unexpected, albeit not entirely surprising complication has emerged. Clinical trials in patients with metastatic melanoma have shown positive therapeutic effects following treatment with PLX4032, a compound that is thought to selectively inhibit BRAF\(^{58}\), a common mutation found in melanoma associated with increased BRAF activity. However, it is now clear that, despite the positive response to PLX4032, some patients have developed hyperproliferative skin lesions, and in a few instances, squamous cell carcinomas, which regressed after drug cessation. Three recently published studies have begun to unravel the complexity of this signaling conundrum and now provide an explanation for the unanticipated outcomes. These authors and their colleagues have found that, whereas selective BRAF inhibitors suppress RAF-MEK-ERK signaling in BRAF-mutant melanoma cells, they unexpectedly activate the pathway in cells carrying an oncogenic KRAF mutation, common to squamous carcinomas, but which possess a wild-type BRAF gene that favors activity of the MEK-ERK pathway.


Long-term COX-2 Inhibition Leads to Increased COX-2 Expression

Numerous experimental and clinical studies have revealed that intestinal tumor formation is prevented by treatment with anti-inflammatory drugs targeting cyclooxygenase 2 (COX-2). In Min/" mouse treated with selective COX-2 inhibitors, intestinal tumors rapidly regress; however, drug-resistant tumors appear after long-term treatment. In a new study from the Bertagnolli lab, stroma from resistant tumors was found to contain expanded populations of bone marrow-derived myofibroblasts exhibiting increased expression of transforming growth factor β (TGF-β) and COX-2, concomitant with decreased expression of syndecan-1 in enterocyte membranes. These changes in gene expression were associated with increased tissue fibrosis and an environment favoring chronic inflammation. Thus, the chemopreventive benefit of COX-2 inhibition was overcome by a compensatory increase in stromal myofibroblasts, the cellular sources of COX-2, PGE2 and TGF-β in the intestinal mucosa. This study highlights the complex level of interactions in tissues where paracrine interactions between cells must be taken into account in treatment of any chronic diseases.


Statins and Prostate Tumor Inflammation

Statins are cholesterol-lowering drugs harboring significant anti-inflammatory activity. Because chronic presence of infiltrating leukocytes (chronic inflammation) is associated with advanced prostate cancer, Bahez and colleagues investigated if statin use was associated with reduced intratumoral inflammation in men undergoing radical prostatectomy. In a cohort of 236 men, preoperative statin use was indeed found to coincide with a significantly lower risk for any grade of intratumoral inflammation. Along with increasing evidence that statin use reduces the risk of advanced prostate cancer, results from this study indicate that some of the chemopreventive value of statin use may be in inhibiting (or limiting) chronic prostate inflammation. (Image courtesy of L. Coussens, University of California, San Francisco.)


Meat Consumption and Colorectal Cancer

Whereas the relationship between red and processed meat consumption and colorectal cancer has been described in multiple epidemiologic studies, mechanisms underlying this risk have not been defined. Cooking meat at high temperatures increases uptake of several mutagens, including heterocyclic amines and polycyclic aromatic hydrocarbons, as well as heme iron, nitrate, and nitrite. In a 7-year follow-up study performed by Sinha and colleagues, cooking practices and meat type were surveyed in a cohort of 300,948 men and women who reported 2,719 cases of diagnosed colorectal cancer. The study revealed a positive correlation between colorectal cancer and processed meat intake linked to heme iron, nitrate, and heterocyclic amines formed when meat was cooked at high temperatures, as opposed to correlating with consumption alone.


Shifting the Balance: T\(_{H}1\) Programming of Tumors Enhances Radiation Therapy

A great deal has been written on the association between chronic inflammation and cancer development. Although progress has been made with elucidating critical molecular and cellular pathways that demonstrate this link, turning these molecular and cellular candidates into anticancer therapy remains more of a hope than a reality. That said, many tumors harbor cytotoxic T lymphocytes (CTLs) that are insufficient in combating tumor development, likely due to their limited durability in prominent protumor T\(_{H}2\)-rich microenvironments. Cytotoxic therapies are known to induce leukocyte activation and transient infiltration of tissue by CTLs - bolstering these responses or programming them in such a way that they are more durable and effective.
able to enhance the efficacy of cytotoxic therapy. Two recent papers have investigated this hypothesis. Sims and colleagues found that type I cytokine therapy, in combination with ionizing radiation therapy (RT), significantly reduced tumor size by improving oxygenation of tumors and altering tumor vasculature. In contrast, the Nishimura group found that T_{H1}-based cell therapy, in combination with RT, led to increased presence of tumor-specific CTLs in tumors and tumor draining lymph nodes that was associated with tumor regression. Together, these studies support the hypothesis that reprogramming the immune microenvironment represents a rational approach for enhancing response to cytotoxic-based anticancer therapies.


**Cell Lineage Identification for Basal Cell Carcinoma**

Elegant use of mouse genetics has identified the cell of origin in basal cell carcinoma (BCC) that can result from activation of the Hedgehog signaling pathway. Blanpain and colleagues activated Hedgehog signaling in multiple cellular compartments of skin by using mice expressing a conditionally active Smoothened mutant (SmoM2). Interestingly, BCCs only arose when SmoM2 was activated in long-term resident progenitor cells of interfollicular epidermis and the upper infundibulum, as opposed to hair follicle bulge stem cells or their transient amplifying progenitors. These realizations are significant, as they illustrate that expression of differentiation markers in neoplastic cells alone is not predictive of cancer initiating cells.


**In vivo Imaging of Inflammation**

Chronic inflammation is a common feature of most adult solid tumors. On the other end of the spectrum, activation of acute inflammation and infiltration of tissues by cytotoxic cells is a common response to cytotoxic therapies. Thus, imaging biomarkers associated with these distinct forms of inflammation could be of significant clinical relevance. Two studies using different approaches now provide evidence that imaging inflammation as a biomarker is feasible. Ross and colleagues used diffusion magnetic resonance imaging and 2-[18F]-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) to reveal treatment-associated inflammatory responses in rats bearing gliosarcomas following various treatment regimens and found that increased presence of glucose-consuming activated macrophages corresponded with increased FDG uptake in tumors. Marnett and colleagues took a different approach and instead targeted the proinflammatory enzyme cyclooxygenase-2 (COX-2). The Marnett team designed novel fluorescent imaging agents that target active COX-2 and demonstrated that due to their high specificity, contrast, and detectability, the "COX-2 beacons" have significant utility as a noninvasive means to detect inflammation in tissues.


**To B or not to B**

B lymphocytes constitute a central component of humoral immunity. They not only serve in antibody production but also have a role in antigen presentation and cytokine secretion. In particular, B lymphocyte expression of MHC and costimulatory molecules, along with secretion of proinflammatory cytokines, is critical for regulating CD4+ and CD8+ T-cell activation, expansion, antigenic spreading, and memory T-lymphocyte formation. In addition to this diverse repertoire of functions, B lymphocytes have also recently gained recognition for representing significant components of tumor immunity. Two recent publications highlight this role and reveal unexpected molecular mechanisms whereby chronic inflammation potentiates solid tumor development. Andreu and colleagues report that, during squamous carcinogenesis, circulating immune complexes (CICs) containing antigen-specific immunoglobulins activate protumor programming of myeloid cells by activating Fcγ receptors (FcγR) on recruited macrophages, mast cells, and dendritic cells. This process, in turn, enhances angiogenesis and tissue remodeling programs to potentiate primary tumor progression. Ammirante and coworkers also recognized a critical role for B cells independent of immunoglobulin expression and FcγR signaling. Using a mouse model of castration-resistant prostate cancer metastasis, they found that recruited B cells secrete high levels of lymphotxin that regulate IKK-α and STAT3 activation and together stimulate metastasis by NF-κB-independent and cell autonomous mechanisms.