Molecular Cancer Therapeutics

Highlights

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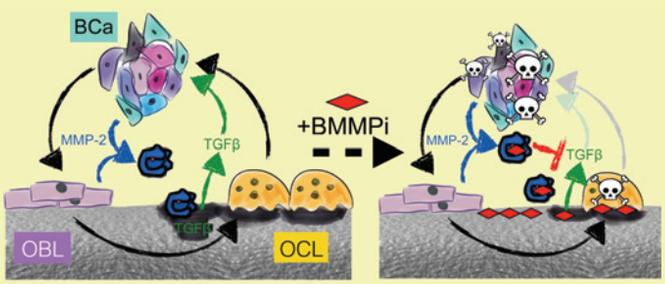
Selected Articles from This Issue



BMMPIs inhibit MMP-2 in bone metastatic breast cancer

Tauro *et al.* Page 494

Since the failure of matrix metalloproteinase (MMP) inhibitor in clinical trials, highly selective reagents that target individual MMPs have been the new focus. MMP-2 is highly expressed in bone metastatic breast cancer and drives the progression of the disease. Here, Tauro and colleagues have generated MMP-2 highly selective bone seeking MMP inhibitors (BMMPIs) based on bisphosphonates. *In vivo* studies reveal BMMPIs are effective in promoting the apoptosis of bone metastatic breast cancer cells and protecting against cancer induced bone disease. Given the well-tolerated nature of bisphosphonates, BMMPIs could be rapidly translated to the clinic for the treatment of skeletal malignancies such as bone metastatic breast cancer.

Selinexor and T cell checkpoint inhibitors

Farren *et al.* Page 417

Immune checkpoint blockade has shown promise in melanoma, with a subset of patients experiencing complete durable responses. However, the majority of patients still do not receive long-term benefit. Farren and colleagues combined immune checkpoint blockade with selinexor, a small molecule inhibitor of exportin-1 that has anti-melanoma activity of its own. This treatment combination skewed immune responses toward a Th1 type, and proved more effective in controlling tumor growth when administered at multiple schedules in a murine model. These results support further development of this novel combination of immune checkpoint blockade and small molecule nuclear export inhibitors.

Effects of selinexor on immune homeostasis

Tyler and Servos *et al.* Page 428

Selinexor (KPT-330) is a first in class nuclear transport inhibitor currently in clinical trials as an anti-cancer agent. Tyler, Servos and colleagues analyzed immune homeostasis in mice treated with selinexor and found disruptions in T cell development, a progressive loss of CD8 T cells and increases in inflammatory monocytes. Altering the frequency of drug dosing preserved normal immune function better than decreasing the dose. Overall, selinexor treatment leads to transient inhibition of T cell activation but clinically relevant once and twice weekly dosing schedules that incorporate sufficient drug holidays allow for normal CD8 T cell functioning and development of anti-tumor immunity.

The FA/BRCA pathway predicts cisplatin response in HNSCC

Martens-de Kemp *et al.* Page 540

Stage III/IV head-and-neck squamous cell carcinomas (HNSCCs) are often treated with cisplatin-containing chemoradiation protocols. However, not all tumors respond well and biomarkers to personalize chemoradiotherapy are not available. Martens-de Kemp and colleagues performed an unbiased genome-wide functional genetic screen to identify genes that influence cisplatin response. Pathway analysis on cisplatin-sensitizing genes identified the FA/BRCA pathway as the predominant cisplatin response pathway in HNSCC cells. Expression of genes involved in this pathway predicted prognosis of (chemo-) radiation treated HNSCC patients. Biomarkers that indicate FA/BRCA pathway activity in tumors are prime candidates to predict cisplatin response in HNSCC.

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