



TIE2 Inhibition Reverses Chemotherapy-induced Tumor Dissemination and Metastasis

Harney and Karagiannis *et al.* _____ Page 2486

Cytotoxic chemotherapy is known to induce pro-metastatic changes resulting in poor survival. Harney, Karagiannis and colleagues show that the TIE2 kinase inhibitor rebastinib reduces primary tumor growth and metastasis in a preclinical breast cancer model, and is synergistic in combination with taxane chemotherapy. They demonstrate that taxane chemotherapy is associated with metastasis through recruitment of tumor-infiltrating TIE2⁺ macrophages that promote angiogenesis, TMEM-dependent tumor cell intravasation and lung metastasis, events reversed by rebastinib. In an adjuvant study, rebastinib in combination with eribulin led to a significant improvement in survival compared to single agent eribulin. Thus, rebastinib is a promising therapy for inhibiting pro-metastatic microenvironments in cancer patients.

Inhibition of EMT by Archazolid

Merk *et al.* _____ Page 2329

Epithelial-mesenchymal transition (EMT) plays an important role in cancer progression, relapse, and metastasis. By using the myxobacterial natural compound Archazolid A as a tool, Merk and colleagues discovered the V-ATPase, a multimeric proton pump that regulates lysosomal acidification, as a crucial player in EMT and Archazolid A as a promising strategy to block EMT through the inhibition of V-ATPase. Mechanistic studies found that Archazolid A disrupts the process of EMT, the generation of tumor-initiating cells and the turnover of E-cadherin. These evidences suggest that Archazolid A is a promising cancer therapeutic agent that is worth further investigation.

DDR1 Inhibition Enhances Chemotherapy in PDA

Aguilera and Huang *et al.* _____ Page 2473

The extracellular matrix limits the efficacy of chemotherapy in pancreatic ductal adenocarcinoma (PDA) in part by active cell signaling. Discoidin domain receptor 1 (DDR1) is a receptor tyrosine kinase that binds fibrillar collagens and is expressed by PDA tumor cells. Aguilera, Huang and colleagues demonstrate that pharmacologic inhibition of DDR1 with the small molecule 7rh substantially improves the efficacy of standard chemotherapy in robust preclinical models of PDA in the absence of additional normal tissue toxicity. These results suggest that inhibition of collagen signaling with 7rh has the potential to improve efficacy of conventional chemotherapy in PDA patients.

TMB Predicts Response to Immunotherapy in Diverse Cancers

Goodman *et al.* _____ Page 2598

High tumor mutational burden (TMB) predicts response to checkpoint blockade in lung cancer and melanoma. Our study demonstrates that TMB can be used to predict response to checkpoint blockade independent of tumor histology. Higher TMB was independently and linearly associated with improved response rates and progression-free survival on multivariate analysis. Response rates were 67% with very high TMB (>50 mutations/mb). Further, the median TMB was significantly higher for patients who responded to anti-PD-1/PD-L1 monotherapy compared to those who did not. Interestingly, benefit from dual checkpoint blockade did not show a similarly strong dependence on TMB.

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