Tumor-Induced Erythropoietin and Erythroid Cells

Sano et al. | Page 507

Hematopoietic cells have well-documented roles in guiding the establishment and progression of cancer, with myeloid and lymphoid cells among the best-characterized in this setting. The role of erythroid cells in tumor biology has received less attention, but emerging evidence suggests that they too are involved. In this study, Sano and colleagues detail a series of multi-organ tumor-host interactions that result in increased erythropoietin production in the kidneys and subsequent expansion of immature red blood cell populations in mice. These cells harbor intact nuclei and markers of incomplete differentiation, as well as expression of multiple immunosuppressive markers including the immune checkpoint protein PD-L1. The authors noted that the immature erythroid cells localized to tumor tissue, where they exerted a pro-tumorigenic effect: blockade of erythropoietin with neutralizing antibodies ablated the induction of the tumor-responsive immature erythroid cells and impeded tumor growth. These observations support a functional role for erythroid cells in the control of tumor progression which could feasibly be targeted for clinical benefit.

DNA Sequencing in Phase I mBC Trials

Alhalabi et al. | Page 395

Metastatic bladder cancer (mBC) patients face dismal outcomes and lack options for targeted therapy, particularly those that are resistant to platinum-based chemotherapy. Here, Alhalabi and colleagues employ genome sequencing of tumor tissue and/or circulating tumor DNA in Phase 1 mBC clinical trial participants whose tumors had progressed to a platinum-refractory stage. Recurrent mutations were discovered in TP53, ERBB2, PIK3CA, FGFR3, and ARID1A, some of which were targetable with experimental therapeutics. Notably, TP53 and FGFR3 mutations were nearly mutually exclusive and represented divergent outcomes: patients harboring TP53 mutations experienced faster disease progression, whereas FGFR3- and ERBB2-mutant tumors responded to targeted therapeutics and were associated with longer progression-free survival. Taken together, the data indicate an effective prognostic role for genome sequencing and personalized medicine in mBC patients whose tumors have progressed following platinum-based chemotherapeutic regimens.

Metabolomics of Prostate Cancer in Tissue and Serum

Penney et al. | Page 475

The Gleason score is a longstanding histological tool used in the diagnosis and monitoring of prostate cancer. While informative, Gleason grading requires multiple invasive biopsies which are subject to sampling bias and subjective grading of histological features. Thus, next-generation pathobiological screening techniques are needed to guide treatment decisions—particularly during active surveillance of indolent prostate cancer. Here, Penney and colleagues report on the metabolomic features of prostate cancer tissue and patient serum, employing artificial intelligence and machine learning to establish metabolite profiles associated with Gleason grade. The authors found that computational analysis was able to effectively differentiate between tumor and normal tissue based on a 25-metabolite signature. While some metabolites were differentially enriched in low versus high Gleason scores, larger studies will be needed to refine signatures to infer the presence of occult high-grade prostate tumors. The authors therefore suggest that it is feasible to incorporate metabolomic profiles and machine learning in prostate cancer diagnosis. They further propose that key analytical challenges remain which should be addressed in future studies of metabolomic pathobiology.

Neoantigen Pipeline Predicts Response to ICB

Lazdun et al. | Page 498

Mutations arising in endogenous genes over the course of tumor development and progression—termed “neoantigens”—are key to the proper function of tumor immunosurveillance and clearance. However, not all neoantigens provoke a robust immune response: because of the differences in how peptides interact with a patient’s antigen presentation machinery, only certain neoantigens are predicted to be immunogenic enough to efficiently activate the immune system. In this study, Lazdun and colleagues reveal a new pipeline for predicting and validating immunogenic mutations using exome sequencing. Peptide neoantigens identified from sequencing data were modeled in the context of the antigen presentation machinery, then pulsed onto antigen-presenting cells. Co-culture experiments with CD8+ T cells and downstream functional assays were then performed for each neoantigen. The authors report that this pipeline efficiently identified immunogenic neoantigens whose expression in bladder tumors marked patients who were likely to respond to anti-PD-L1 immune checkpoint blockade.