BRAF-Mutant Melanoma Depends on ERK2

BRAF mutation is a common driver event in melanoma, rendering the tumors reliant on constitutive signaling through the MAPK pathway and the extracellular signal-regulated kinases (ERK) 1 and 2. Thus, MAPK pathway inhibitors that act through both ERK1 and ERK2 have become a key component of the therapeutic arsenal against melanoma, but their use is associated with dose-limiting toxicities. Here, Crowe and colleagues demonstrate that BRAF-mutant melanoma is specifically reliant on ERK2 signaling. Targeted ERK2 ablation resulted in transcriptomic and proteomic alterations that aligned with those effected by full MAPK pathway inhibitors, whereas targeted ERK1 ablation produced a distinct set of responses. Both isoforms promoted cell viability, but ERK2 loss suppressed MAPK pathway activity and cell proliferation more effectively than ERK1 loss. Moreover, ERK2 was shown to compensate for ERK1 depletion in the context of BRAF mutation, whereas ERK1 was not able to compensate for loss of ERK2 activity. The authors argue that these findings support the development of ERK2-selective inhibitors, which could potentially be achieved through the targeting of protein-protein interaction domains that are differentially utilized between the two isoforms.

Functional Analysis of FANCJ Mutations

Calvo et al. | Page 1015

Mutation of DNA damage-responsive Fanconi Anemia family members (FANC) is associated with hereditary cancer syndromes and familial cancers, particularly breast and ovarian cancer, due to their role in mediating homologous recombination repair. In particular, FANCJ has been nominated as a key tumor suppressor in several cancer types, though functional data on the many clinically identified FANCJ mutations are lacking. Here, Calvo and colleagues employ a mutation library to screen for loss-of-function (LOF) mutations that confer sensitivity to interstrand crosslinking (ICL) agents. They find that missense and nonsense mutations in the helicase domain are associated with FANCJ LOF, whereas mutations outside this domain did not affect the response to ICL chemotherapeutics. Notably, mutations in the carboxy-terminal domain, which mediates protein-protein interactions with other homologous recombination mediators such as BRCA1, did not significantly affect FANCJ function in response to ICL agents. Finally, while only a minority of FANCJ mutations (~12%) exhibited LOF in response to ICL, the authors note that the comprehensive mutation library developed here will continue to be useful in characterizing FANCJ mutants and their functionality in response to other stimuli and other types of genomic lesions.

CTC Genomics Predict mCRPC Treatment Outcomes

Gupta et al. | Page 1040

Circulating tumor cells (CTC) provide important prognostic information in metastatic castration-resistant prostate cancer (mCRPC), in which the expression of androgen receptor (AR) splice variants is a key prognostic indicator of patient response to enzalutamide and/or abiraterone (enza/abi). However, most patients do not express AR variants, and therefore additional markers are needed. In this study, Gupta et al. leverage CTC exome sequencing and copy number alteration profiles from men with mCRPC undergoing therapy with enza/abi to identify genomic events associated with therapy resistance. The authors identify a subset of patients who progressed rapidly on enza/abi and bore genomic lesions that were detectable in pooled CTC DNA, including gain of MYCN, BRCA2, and AR, and loss of CHD1, NCOR2, and PTEN. In patients who initially responded and later acquired resistance, CTC sampling uncovered mutations and copy number alterations which converged on genes linked to proliferation, hormone signaling, lineage plasticity and epigenetic signaling, and resistance to cell death. Taken together, these data could form the molecular basis for more effective therapeutic decision making in mCRPC.

HLA-E Suppresses Immunity in TAPI-Deficient Tumors

Zhang et al. | Page 1076

Tumors commonly down-regulate antigen processing and presentation pathways in order to evade the anti-tumor immune response, which can undermine the efficacy of immune checkpoint blockade. Here, Zhang and colleagues show that Qa-1b—the mouse homolog of the human major histocompatibility complex class I molecule HLA-E—is a key player in how tumors and the immune system interact when antigen presentation is defective. Loss of TAP1 resulted in the establishment of an immunosuppressive tumor microenvironment, but loss of both TAPI and Qa-1b restored sensitivity to immunotherapy. This effect was mediated at least in part through direct interactions between Qa-1b and natural killer cells, likely through the inhibitory NKG2A receptor through which Qa-1b and HLA-E normally act. Concurrent disruption of TAPI and Qa-1b reversed immunoresistance by causing increased CD8\(^{+}\) T cell to Treg ratios, increased natural killer cell infiltration and activity, and sensitization to immune checkpoint blockade with anti-PD-1 antibodies. The data suggest that Qa-1b and HLA-E engage in crosstalk with the antigen presentation machinery and represent a key control node that governs the immune response to antigen presentation by tumor cells.