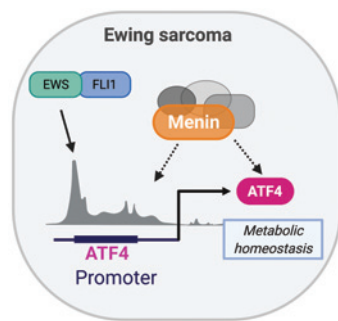


## MOLECULAR CANCER RESEARCH

## HIGHLIGHTS

Selected Articles from This Issue

## EWS-FLI1 and Menin Converge on ATF4

Jiménez *et al.* | Page 1182

Ewing sarcoma is largely driven by pathognomonic gene fusions involving *EWSR1*, particularly the *EWS-FLI1* fusion, which are chiefly responsible for driving the transcriptional and metabolic rewiring associated with these cancers. However, previous work has also uncovered an oncogenic role for the scaffold protein menin in metabolic rewiring of Ewing sarcoma and other tumors, though the mechanism underlying this role is undefined. In this study, Jiménez and colleagues show that *EWS-FLI1* and menin serve as upstream regulators of ATF4, a master regulator of the serine biosynthesis pathway. *EWS-FLI1* directly binds the *ATF4* promoter and both *EWS-FLI1* and menin are integral for the induction of serine synthesis pathway downstream of ATF4, as inhibition of either gene resulted in loss of ATF4 expression and reduced activation of the serine biosynthesis gene program. Interestingly, menin inhibition also caused reduced ATF4 activity in B-cell acute lymphoblastic leukemia bearing *MLL* rearrangement, suggesting a broader role for menin in metabolic regulation. Taken together, the data uncover new mechanisms underlying the metabolic reprogramming observed in Ewing sarcoma and elucidate a pro-tumorigenic metabolic role for menin that may span a variety of different cancers.

## DMAPT Delays Prostate Cancer Resistance to AR Inhibition

Morel *et al.* | Page 1137

Prostate cancer is clinically managed by ablation of circulating testosterone and/or blockade of androgen receptor (AR) signaling, but invariably tumors progress to a castrate-resistant (CRPC) state. Numerous molecular drivers of castration resistance have been described, including hyperactivation of NF- $\kappa$ B signaling. However, strategies to overcome this resistance mechanism have proven elusive due to poor oral bioavailability of NF- $\kappa$ B pathway inhibitors. Here, Morel and colleagues demonstrate effective targeting of the NF- $\kappa$ B axis in CRPC *in vivo* using a novel orally bioavailable small molecule, dimethylamino-parthlide (DMAPT). Castration of mice bearing prostate tumors caused an increase in NF- $\kappa$ B signaling, leading to increased expression of AR and AR splice variants associated with a CRPC state. However, combination of castration with DMAPT prevented the induction of constitutively active AR variants. The authors show that this effect was specifically reliant on the effective inhibition of phosphorylated p65 NF- $\kappa$ B activity. Taken together, the data support the development of DMAPT as a therapeutic strategy to extend the efficacy of AR-targeted therapy by preventing or delaying the onset of castration resistance.

## Genomics and Transcriptomics of DSRCT

Slotkin *et al.* | Page 1146

Desmoplastic small round cell tumors (DSRCT) are rare, poorly differentiated cancers that are thought to arise from the peritoneum and which are marked by a pathognomonic *EWSR1-WT1* gene fusion. The rarity of this tumor type has thus far precluded randomized trials and few laboratory models are available, highlighting an urgent need for additional insights and potential therapeutic targets. Here, Slotkin, Bowman, and their colleagues report genomic and transcriptomic data from a cohort of 78 DSRCT patients as well as a new bank of patient-derived xenografts for the study of DSRCT biology. The authors found that, aside from the pathognomonic fusion, DSRCT has a relatively stable genome with few recurrent mutations. Notably, however, *FGFR4* was found to be highly expressed in DSRCT overall, with additional cases bearing *FGFR4* amplification and/or activating mutations. These data provide new insights into the biology of DSRCT, including the role of *FGFR4* as a potential therapeutic target, and present the first available bank of DSRCT laboratory models to the research community.

## Mechanism of Resistance to Dasatinib in KIT-Altered Melanoma

Sabbah *et al.* | Page 1221

c-Kit is a frequently activated proto-oncogene in acral and mucosal melanoma, but the c-Kit inhibitor dasatinib has limited efficacy in the clinic. In this study, Sabbah and colleagues perform pathway analysis to elucidate mechanisms of dasatinib resistance in melanoma. The authors report that dasatinib treatment achieves the goal of silencing the MAPK and PI3K/Akt pathways downstream of c-Kit, indicating an on-target effect. However, at pharmacological doses of dasatinib, the authors also observed activation of CREB transcriptional activity leading to induction of MITF and Bcl-2 expression via the CRTC3 pathway. Indeed, forced expression of MITF prevented any response to dasatinib in c-Kit mutant/amplified melanoma models, but inhibition of Bcl-2 using pharmacological agents restored sensitivity to dasatinib. Taken together, these data suggest that dasatinib treatment stimulates its own mechanism of resistance via induction of the pro-survival protein Bcl-2 and may also explain the modest benefits observed in dasatinib clinical trials.