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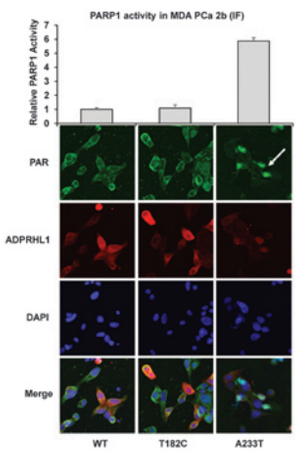
MOLECULAR CANCER RESEARCH
HIGHLIGHTS

Selected Articles from This Issue

ADPRHL1 Mutation Confers Prostate Cancer Risk and Tumorigenesis



Zhang *et al.* | Page 1776

African American men are particularly susceptible to prostate cancer incidence, but genetic factors mediating prostate cancer risk in African American men remain poorly defined. To search for genetic contributors to prostate cancer occurrence in African American men, Zhang and colleagues performed whole exome sequencing using blood samples from men from 20 families affected by hereditary prostate cancer. Sequencing revealed a rare non-synonymous *ADPRHL1* variant, c.A233T, encoding a p.D78V amino acid conversion, that was present in men affected by prostate cancer in four of the families but not present in 170 unrelated healthy African American men. Functional studies demonstrated that the A233T variant increases prostate cancer cell growth and induces PARP activation. A233T variant-mediated PARP activation renders prostate cancer cells resistant to DNA damaging agents but susceptible to PARP inhibitor olaparib. The authors also found that ADPRHL1 abundance decreases during prostate cancer progression, suggesting A233T is a loss-of-function variant. Altogether, this study identifies a potential genetic contributor to prostate cancer predisposition in African American men, as well as an associated therapeutic vulnerability.

USP27X Regulates CCND1 Degradation

Alam *et al.* | Page 1751

Cyclin D1 (CCND1) is critical for HER2-driven tumorigenesis and therapeutic resistance. CCND1 is not therapeutically targetable, making identifying and targeting proteins that regulate its abundance an appealing therapeutic approach. USP27X also promotes tumorigenesis, but mechanisms by which USP27X underlies tumor growth have not been fully elucidated. In this study, Alam and colleagues observed that abrogating USP27X expression using shRNA or Cre-lox recombination ablates CCND1 expression in non-small cell lung cancer and breast cancer cells. The authors demonstrated that endogenous USP27X and CCND1 interact, and that wild-type, but not catalytically inactive, USP27X deubiquitinates and stabilizes CCND1. Furthermore, shRNA-mediated USP27X silencing sensitizes breast cancer cells to HER2 inhibitor lapatinib *in vitro* and decreasing USP27X using doxycycline-inducible shRNA inhibits tumor cell proliferation and tumor growth *in vivo*. Overall, this study presents USP27X as a novel CCND1 regulator, and suggests that targeting USP27X may be a promising therapeutic strategy for HER2-driven cancers.

C-terminal Domain of mtp53 Associates with PARP1

Lundine *et al.* | Page 1799

p53 harboring an oncogenic R273H mutation is commonly expressed in triple-negative breast cancer (TNBC), but whether the C-terminal domain in R273H mutant p53 (mtp53) is important for established poly-ADP-ribose polymerase 1 (PARP1) and poly-ADP-ribose (PAR) interactions is not known. In their study, Lundine and colleagues endogenously expressed 2 R273H mtp53 C-terminal domain deletion mutants – R273HΔ381-388 and R273HΔ347-393 – in TNBC cells using CRISPR/Cas9 to assess the function of the R273H mtp53 C-terminal domain. Using proximity ligation assays, the authors found that R273HΔ381-388 and R273HΔ347-393 both disrupt R273H mtp53 interactions with PARP1, and that R273HΔ347-393 uniquely disrupts R273H mtp53 interactions with PAR. Accordingly, R273HΔ347-393 limits sensitivity to PARP inhibition via temozolomide plus talazoparib treatment and hydroxyurea-mediated DNA replication stress. Cells expressing R273HΔ381-388 display delayed cell cycle progression and corresponding increases in 53BP1 foci, a marker of incomplete replication due to single-stranded DNA gaps. Taken together, this study demonstrates the importance of the R273H mtp53 C-terminal domain in R273H mtp53 associations with PARP1 and PAR as well as subsequent DNA replication and cell cycle progression in tumor cells.

Raptinal Induces Pyroptosis in Melanoma

Vernon *et al.* | Page 1811

While targeting oncogenic tyrosine kinases such as BRAF and MEK typically displays clinical effectiveness upon initial treatment, its overall efficacy is often limited by drug resistance development. Given pyroptosis – an immunogenic form of programmed cell death – can elicit anti-tumorigenic immunity, inducing pyroptosis alongside BRAF/MEK inhibition may augment therapeutic responsiveness and abrogate drug resistance. To test that hypothesis, Vernon and colleagues treated human and mouse melanoma cells bearing BRAF mutations with raptinal, an activator of caspase-3 and pyroptosis. The authors found that raptinal induces pyroptosis in BRAF mutant melanoma cells *in vitro* and slows tumor growth and prolongs overall survival *in vivo*. Using pharmacologic caspase-3 inhibitors and CRISPR/Cas9-mediated ablation of gasdermin E – a pyroptotic effector activated by caspase-3 – the authors showed that raptinal-mediated pyroptosis is caspase-3- and gasdermin E-dependent. Furthermore, combination treatment with BRAF/MEK inhibitors and raptinal enhances therapeutic effectiveness in BRAF/MEK inhibitor naïve and resistant melanoma cells *in vitro* and *in vivo*. In sum, this study demonstrates that pyroptosis may be a leverageable cellular phenomenon capable of augmenting BRAF/MEK inhibition efficacy and preventing drug resistance.

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