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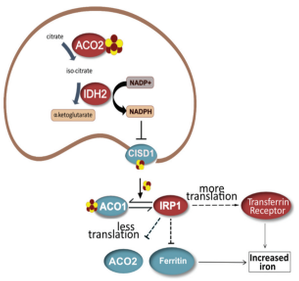
MOLECULAR CANCER RESEARCH
HIGHLIGHTS

Selected Articles from This Issue

An ACO2-Iron Axis Drives Aggressive NSCLC



Mirhadi *et al.* | Page 36

While several non-small cell lung cancer (NSCLC) oncogenic drivers have been identified and therapeutically targeted, many patients harbor aggressive NSCLC tumors lacking targetable oncogenic drivers. Patient-derived xenograft (PDX) models provide useful resources for novel oncogenic driver discovery, as PDX engraftment in immunocompromised mice is a prognostic indicator of poor disease outcomes. By defining engrafting and non-engrafting NSCLC proteomes using mass spectrometry, Mirhadi and colleagues discovered that engrafting tumors exhibit low mitochondrial aconitase (ACO2) and intracellular labile iron levels. Overexpressing ACO2 limits tumor growth *in vivo* and abrogating its expression using inducible shRNA enhances colony formation *in vitro*, underscoring the role of ACO2 as a tumor suppressor in NSCLC. Mechanistically, the authors found that ACO2-isocitrate dehydrogenase (IDH) reaction-generated NADPH inhibits mitoNEET (mNT), which could activate iron response element binding protein 1 (IRP1) to facilitate transferrin receptor stabilization and subsequent iron uptake. Correspondingly, iron supplementation or mNT inhibition using pioglitazone hydrochloride decreases viability in ACO2-ablated cells. Taken together, this study presents ACO2 as a tumor suppressor and mNT as a potential therapeutic target for NSCLC.

JAZF1 Regulates Sensitivity to BENSpm/MTDIA Therapy

Rosario *et al.* | Page 24

Previously, Rosario and colleagues demonstrated that the polyamine biosynthetic and methionine salvage pathways are augmented in prostate cancer. Targeting the pathways using N^1, N^{11}-bis(ethyl) norspermine (BENSpm) and Methylthio-DADMe-Immucillin-A (MTDIA), respectively, provides therapeutic efficacy, but only in a subset of prostate tumor samples. To identify biomarkers and elucidate regulators of BENSpm/MTDIA treatment responsiveness, Rosario and colleagues analyzed transcriptomic and metabolomic differences between BENSpm/MTDIA-sensitive and resistant prostate tumor samples. The authors found that intracellular polyamine levels decrease in BENSpm/MTDIA-sensitive tumor samples but not in resistant samples upon treatment. Correspondingly, spermidine/spermine N^1-acetyltransferase – which exports cellular polyamines and is stabilized by BENSpm – is more abundant in BENSpm/MTDIA-sensitive than resistant samples. RNA-sequencing analysis revealed that juxtaposed against zinc finger 1 (JAZF1) expression is enhanced in BENSpm/MTDIA-resistant samples. Stable JAZF1 transduction in prostate cancer cell lines corresponds with abrogated expression of polyamine biosynthesis and methionine salvage genes, as well as decreased BENSpm/MTDIA responsiveness. Altogether, this study demonstrates that JAZF1 transcriptionally regulates the polyamine biosynthetic and methionine salvage pathways and is a biomarker of BENSpm/MTDIA responsiveness in prostate cancer.

Metabolic Vulnerabilities in Prostate Cancer

Mossa *et al.* | Page 51

Androgen receptor-expressing prostate cancer (ARPC) and aggressive variant prostate cancer (AVPC) are castration-resistant prostate cancer subtypes characterized by low overall survival rates. ARPC and AVPC metabolic dynamics are poorly understood, such that potential metabolic therapeutic targets have not been defined in either subtype. In their study, Mossa and colleagues performed transcriptomic and reverse-phase protein array analyses using patient sample-derived datasets and xenografts to show that oxidative phosphorylation is prevalent in ARPC, whereas glycolysis in predominant in AVPC. *In vitro* metabolic analyses comparing C4-2B (ARPC) and PC3 (AVPC) cells demonstrated that C4-2B cells exhibit increased respiratory capacity and mitochondrial polarization, while PC3 cells display high levels of basal glycolysis. Accordingly, treatment with complex I inhibitor IACS-10759 inhibits C4-2B but not PC3 cell growth *in vitro*. Intriguingly, while IACS-10759 treatment *in vivo* inhibits C4-2B growth regardless of location, it inhibits PC3 growth in bone but not in other locations, suggesting ARPC and AVPC metabolic dynamics are responsive to cellular microenvironments. Overall, this study illuminates metabolic tendencies and associated therapeutic vulnerabilities in ARPC and AVPC.

GSTA4 Governs Melanoma Immune Resistance and Metastasis

Ucche *et al.* | Page 76

Tumor immune evasion is partially dependent upon resistance to interferon-γ (IFNγ)-mediated effects, and identifying IFNγ response regulators may inform more efficacious immunotherapeutic approaches. To that end, Ucche and colleagues created immunoselected tumor cell lines by harvesting B16OVA tumors that progressed after ovalbumin (OVA) immunization and contrasted them to non-immunoselected cell lines at the transcriptomic level. The authors found that glutathione-S-transferase-4 (GSTA4) expression is enhanced in immunoselected tumor cell lines. GSTA4 transduction into parental B16OVA cells decreases intracellular reactive oxygen species (ROS) and increases cell viability in the presence of IFNγ, and GSTA4 shRNA transduction into immunoselected tumor cell lines has the opposite effect. In *in vivo* models, GSTA4-overexpressing cells are resistant to PD-1 blockade, while immunoselected cells with abrogated GSTA4 expression are sensitive to PD-1 blockade and exhibit diminished invasion and metastasis. High GSTA4 expression portends decreased PD-1 blockade responsiveness in human melanoma patients as well. In sum, this study identifies a novel IFNγ response regulator, which could be leveraged to augment efficacy of future immunotherapeutic strategies.

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