REVIEWs

Exploiting Tumor Neoantigens to Target Cancer Evolution: Current Challenges and Promising Therapeutic Approaches ........ 1024
R.G. Gupta, F. Li, J. Roszik, and G. Lizée

Therapeutic Targeting of Checkpoint Receptors within the DNAM1 Axis ........... 1040
Z. Alteber, M.F. Kotturi, S. Whelan, S. Ganguly, E. Weyl, D.M. Pardoll, J. Hunter, and E. Ophir

Mitochondrial and Metabolic Pathways Regulate Nuclear Gene Expression to Control Differentiation, Stem Cell Function, and Immune Response in Leukemia ............ 1052

Metabolic Codependencies in the Tumor Microenvironment ...1067
P. Dey, A.C. Kimmelman, and R.A. DePinho

RESEARCH ARTICLES

St. Jude Cloud: A Pediatric Cancer Genomic Data-Sharing Ecosystem ............... 1082

Précis: The St. Jude Cloud enables sharing, visualization, and analysis of large datasets on pediatric cancer and other catastrophic childhood illnesses; recent use cases include classification of and investigations of mutation rates in pediatric cancers.

Design and Efficacy of a Monovalent Bispecific PD-1/CTLA4 Antibody That Enhances CTLA4 Blockade on PD-1^ Activated T Cells ................................................. 1100

Précis: Combined blockade of CTLA4 and the PD-1–PD-L1 axis can be effective but is limited by immune-related adverse events, prompting the development of a bispeciﬁc antibody (MEDI5752) targeting PD-1 and CTLA4; this treatment limited tumor growth in vivo.

See commentary, p. 1008

Targeting the p300/CBP Axis in Lethal Prostate Cancer ................................................................. 1118

Précis: AR signaling depends on the transcription factors p300 and CBP; inhibition of which reduced tumor growth in xenograft models of prostate cancer, including enzalutamide-resistant prostate cancer with AR ampliﬁcation and expression of AR splice variants.

See commentary, p. 1011

A Procarcinogenic Colon Microbe Promotes Breast Tumorigenesis and Metastatic Progression and Concomitantly Activates Notch and β-Catenin Axes ........................................... 1138

Précis: The presence of the colon-dwelling microbe Bacteroides fragilis in the gut or breast duct was associated with breast tumorigenesis, and a toxin produced by enterotoxigenic B. fragilis promoted an invasive, migratory, stemlike phenotype in breast cancer cells.

SWI/SNF Complex Mutations Promote Thyroid Tumor Progression and Insensitivity to Redifferentiation Therapies ......................................................... 1158

Précis: Mutations in components of the BAF (mammalian SWI/SNF) complex promoted thyroid cancer, reduced expression of thyroid differentiation genes, blocked the re differentiation effects of MAPK inhibition, and reduced radioiodine treatment efﬁcacy in vivo.

DNA Polymerase and Mismatch Repair Exert Distinct Microsatellite Instability Signatures in Normal and Malignant Human Cells ................................................................. 1176

Précis: Deective DNA polymerase or mismatch repair proteins left distinct genomic signatures: Microsatellite mutations were most often multi-base pair deletions in the former and single-base pair deletions in the latter; this inﬂuenced immune checkpoint blockade efﬁcacy.

CRISPR Screening of CAR T Cells and Cancer Stem Cells Reveals Critical Dependencies for Cell-Based Therapies ......................................................... 1192

Précis: CRISPR−Cas9−based screens uncovered glioma stem cell vulnerabilities and possible ways to enhance chimeric antigen receptor (CAR) T-cell therapies for glioblastoma, potentially improving the so−far disappointing results of CAR−T−cell trials for this cancer.

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Metastasis and Immune Evasion from Extracellular cGAMP Hydrolysis ........ 1212


Précis: When expressed by cancer cells, the transmembrane glycoprotein ENPP1 hydrolyzed cGAS-generated extracellular cGAMP—which would otherwise elicit a STING-mediated antitumor response—to produce AMP that was processed into immunosuppressive adenosine.

MNK Inhibition Sensitizes KRAS-Mutant Colorectal Cancer to mTORC1 Inhibition by Reducing eIF4E Phosphorylation and c-MYC Expression ................. 1228


Précis: Loss-of-function APC mutations confer susceptibility to rapamycin in colorectal cancer, but oncogenic KRAS mutations circumvent this; however, blocking the MNK-eIF4E translation pathway restored sensitivity of these tumors to rapamycin.

Gut Microbiome Directs Hepatocytes to Recruit MDSCs and Promote Cholangiocarcinoma ................. 1248


Précis: In mice with impaired gut barrier function, liver exposure to Gram-negative commensal bacteria led to TLR4-dependent recruitment of immunosuppressive myeloid-derived suppressor cells, which promoted cholangiocarcinoma.

See commentary, p. 1014

Endogenous Retroviral Activation by Epigenetic Therapy Reverses the Warburg Effect and Elicits Mitochondrial-Mediated Cancer Cell Death ............... 1268


Précis: Epigenetic inhibitors cause transcription of endogenous retroviruses, causing ATP depletion via the double-stranded RNA helicases RIG-I and MDA5 and leading to tumor cell dependence on aerobic glycolysis, in contradiction to the Warburg effect.

Direct and Indirect Regulators of Epithelial–Mesenchymal Transition–Mediated Immunosuppression in Breast Carcinomas ............. 1286


Précis: Quasi-mesenchymal (qM) breast carcinoma cells produced immunomodulatory proteins, including CD73, which conferred resistance to anti-CTLA4; Cd73 knockout in minority populations of qM cells restored anti-CTLA4 sensitivity in entire tumors.

Retraction

Retraction: Increased Levels of COX-2 and Prostaglandin E2 Contribute to Elevated Aromatase Expression in Inflamed Breast Tissue of Obese Women ............. 1306

Pharmacologic disruption of epigenetic enzymes such as DNA methyltransferases, histone methyltransferases, and histone acetyltransferases has shown some efficacy in cancer, likely in part due to their ability to reactivate normally silenced genomic regions. Endogenous retroviruses are among the regions often activated, resulting in a RIG-I–MDA5-dependent innate immune response. Additionally, Fresquet and colleagues found that the helicase activity of RIG-I and MDA5 depleted intracellular ATP, reversing the Warburg effect and increasing cancer cell dependence on aerobic glycolysis. This was associated with succinate dehydrogenase hyperactivation and consequent production of reactive oxygen species, leading to caspase-independent tumor cell necroptosis that could be enhanced by blocking the programmed-cell-death inhibitor BCL2. For more information, see the article by Fresquet and colleagues on page 1268.