CANCER RESEARCH HIGHLIGHTS

1633  Mdm2 and MdmX: Partners in p53 Destruction
       James J. Manfredi

       See related article by Yang et al., Cancer Res 2021;81:898–909

1635  A Complementary Strategy to Mitigate Radiation-Induced Cognitive Decline
       Navynetaje Korimerla and Daniel R. Wahl

       See related article, p. 1732

1637  Beyond Stamp Collecting: Evolutionary and Functional Genomics Advance Our Understanding of Cancer Biology
       Joseph Lachance

       See related article, p. 1695

GENOME AND EPIGENOME

1639  Cancer-Associated Fibroblasts Promote Aggressive Gastric Cancer Phenotypes via Heat Shock Factor 1-Mediated Secretion of Extracellular Vesicles

       This study shows how HSF1 regulates a stromal transcriptional program associated with aggressive gastric cancer and identifies multiple proteins within this program as candidates for therapeutic intervention.

1654  Cancer-Specific Targeting of Taurine-Upregulated Gene 1 Enhances the Effects of Chemotherapy in Pancreatic Cancer

       Targeting TUG1 coupled with a cancer-specific drug delivery system effectively modulates 5-FU catabolism in TUG1-overexpressing PDAC cells, thus contributing to a new combinatorial strategy for cancer treatment.
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1758 RINT1 Regulates SUMOylation and the DNA Damage Response to Preserve Cellular Homeostasis in Pancreatic Cancer
These findings provide new insights into the aggressive behavior of PDAC, showing that RINT1 directly correlates with survival in patients with PDAC by disturbing the SUMOylation process, a crucial modification in carcinogenesis.

1775 Cooperative Targeting of Immunotherapy-Resistant Melanoma and Lung Cancer by an AXL-Targeting Antibody–Drug Conjugate and Immune Checkpoint Blockade
These findings show that targeting AXL-positive tumor fractions with an antibody–drug conjugate enhances anti-tumor immunity in several humanized tumor models of melanoma and lung cancer.

1788 Serial Stimulation of Invariant Natural Killer T Cells with Covalently Stabilized Bispecific T-cell Engagers Generates Antitumor Immunity While Avoiding Anergy
Covalently stabilized conjugates that engage the antigen receptors of iNKT cells and target a tumor antigen activate potent antitumor immunity without induction of anergy or depletion of the responding iNKT cells.

1802 Pan-Cancer Analysis of Ligand–Receptor Cross-talk in the Tumor Microenvironment
This study provides deconvoluted bulk tumor transcriptomes across multiple cancer types to infer cross-talk in the tumor microenvironment.

1813 Evasion of Innate Immunity Contributes to Small Cell Lung Cancer Progression and Metastasis
Mingrui Zhu, Yi Huang, Matthew M. Ender, Luc Girard, Rahul Kollipara, Buse Eglenen-Polat, Yujiro Naito, Trisha K. Savage, Kenneth E. Huffman, Shohei Koyama, Atsushi Kumanogoh, John D. Minna, Jane E. Johnson, and Esra A. Akbay
This study discovers in SCLC and neuroblastoma impairment of an inherent mechanism of recognition of tumor cells by innate immunity and proposes that this mechanism can be reactivated to promote immune surveillance.

1827 Survivin Expression Is Differentially Regulated by a Selective Cross-talk between RBM38 and miRNAs let-7b or miR-203a
Christopher A. Lucchesi, Jin Zhang, Buyong Ma, Ruth Nussinov, and Xinbin Chen
These findings show that RBM38 exerts opposing effects on survivin expression via two miRNAs, and disruption of the RBM38-AGO2 complex by an eight-amino acid peptide sensitizes tumor spheroids to survivin inhibitor YM155.

1840 Pan-Cancer Drivers Are Recurrent Transcriptional Regulatory Heterogeneities in Early-Stage Luminal Breast Cancer
Shambhavi Singh, Matthew D. Sutcliffe, Kathy Repich, Kristen A. Atkins, Jennifer A. Harvey, and Kevin A. Janes
Profiling intratumor heterogeneity of luminal breast carcinoma cells identifies a recurrent set of genes, suggesting sporadic activation of pathways known to drive other types of cancer.
See related articles, p. 1853 and p. 1868

1853 Fragmentation of Small-Cell Lung Cancer Regulatory States in Heterotypic Microenvironments
Dylan L. Schaff, Shambhavi Singh, Kee-Beom Kim, Matthew D. Sutcliffe, Kwon-Sik Park, and Kevin A. Janes
These findings demonstrate that the single-cell regulatory heterogeneity of small-cell lung cancer becomes increasingly elaborate in the liver, a common metastatic site for the disease.
See related articles, p. 1840 and p. 1868
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<td>1909</td>
<td>Delta-Like Ligand–Notch1 Signaling Is Selectively Modulated by HPV16 E6 to Promote Squamous Cell Proliferation and Correlates with Cervical Cancer Prognosis</td>
<td>Maryam Khelil, Heather Griffin, Maitake C.G. Bleeker, Renske D.M. Steenbergen, Ke Zheng, Taylor Saunders-Wood, Sanne Samuels, Jossie Rotman, Wim Vos, Brenda E. van den Akker, Renée X. de Menezes, Gemma G. Kenter, John Doorbar, and Ekaterina S. Jordanova</td>
<td>This study investigates cervical cancer cell-of-origin populations and describes a DLL-Notch1 phenotype that is associated with disease prognosis and that might help identify cells that are susceptible to HPV-induced carcinogenesis.</td>
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<td>1883</td>
<td>The Hydroxyquinoline Analogue YUM70 Inhibits GRP78 to Induce ER Stress–Mediated Apoptosis in Pancreatic Cancer</td>
<td>Soma Samanta, Suhui Yang, Bikash Debnath, Ding Xue, Yuting Kuang, Kavya Ramkumar, Amy S. Lee, Mats Ljungman, and Nouri Neamati</td>
<td>This study identifies a novel ER stress inducer that binds GRP78 and inhibits pancreatic cancer cell growth in vitro and in vivo, demonstrating its potential as a therapeutic agent for pancreatic cancer.</td>
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**CORRECTION**

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<td>1922</td>
<td>Local Targeting of NAD⁺ Salvage Pathway Alters the Immune Tumor Microenvironment and Enhances Checkpoint Immunotherapy in Glioblastoma</td>
<td>Ming Li, Ameya R. Kirtane, Juri Kiyokawa, Hiroaki Nagashima, Aaron Lopes, Zain A. Tirmizi, Christine K. Lee, Giovanni Traverso, Daniel P. Cahill, and Hiroaki Wakimoto</td>
<td>This study investigates cervical cancer cell-of-origin populations and describes a DLL-Notch1 phenotype that is associated with disease prognosis and that might help identify cells that are susceptible to HPV-induced carcinogenesis.</td>
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**AC** AC icon indicates Author Choice

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Immunofluorescent staining of DLL4 in a keratinocyte cell line, NIKS, highlights the high expression of this Notch1 ligand in migratory and proliferative cells of the leading edge of large monolayer gaps. This DLL4 phenotype is inherent to reserve cells in the normal, HPV-uninfected cervix, and HPV16 E6 expression sustains Notch1 ligand expression, likely facilitating a more durable skewing of squamous cell fate. Cervical tumors that show high DLL4 expression are associated with worse disease prognosis. For details, see Khelil and colleagues on page 1909.