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3222 **Extracellular Vesicles from Cancer-Associated Fibroblasts Containing Annexin A6 Induces FAK-YAP Activation by Stabilizing β 1 Integrin, Enhancing Drug Resistance**
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These findings show that p38 γ links KRAS oncogene signaling and the Warburg effect through PFKFB3 and Glut2 to promote pancreatic tumorigenesis, which can be disrupted via inhibition of p38 γ and PFKFB3.
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Yixuan Li, Xiangyang Zhang, Shaoqi Zhu, Eden A. Dejene, Weiqun Peng, Antonia Sepulveda, and Edward Seto
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- 3305 A Genome-Wide Pooled shRNA Screen Identifies PPP2R2A as a Predictive Biomarker for the Response to ATR and CHK1 Inhibitors**
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This study reveals new approaches to specifically target PPP2R2A-deficient lung cancer cells and provides a novel biomarker that will significantly improve treatment outcome with ATR and CHK1 inhibitors.
- ## TUMOR BIOLOGY AND IMMUNOLOGY
- 3319 Extracellular-Regulated Protein Kinase 5-Mediated Control of p21 Expression Promotes Macrophage Proliferation Associated with Tumor Growth and Metastasis**
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These findings offer a new rationale for anti-ERK5 therapy to improve cancer patient outcomes by blocking the proliferative activity of tumor macrophages.
- 3331 Microenvironmental Activation of Nrf2 Restricts the Progression of Nrf2-Activated Malignant Tumors**
Makiko Hayashi, Ayumi Kuga, Mikiko Suzuki, Harit Panda, Hiroshi Kitamura, Hozumi Motohashi, and Masayuki Yamamoto
This study clarifies the importance of Nrf2 activation in the tumor microenvironment and in the host for the suppression of malignant Nrf2-activated cancers and proposes new cancer therapies utilizing inducers of Nrf2.
- 3345 Platelet-Specific PDGFB Ablation Impairs Tumor Vessel Integrity and Promotes Metastasis**
Yanyu Zhang, Jessica Cedervall, Anahita Hamidi, Melanie Herre, Kati Viitaniemi, Gabriela D'Amico, Zuoxiu Miao, Ragaseema Valsala Madhavan Unnithan, Alessandra Vaccaro, Luuk van Hooren, Maria Georganaki, Åsa Thulin, Qi Qiao, Johanna Andrae, Agneta Siegbahn, Carl-Henrik Heldin, Kari Alitalo, Christer Betsholtz, Anna Dimberg, and Anna-Karin Olsson
Conditional knockout of PDGFB in platelets demonstrates its previously unknown role in the maintenance of tumor vascular integrity and host protection against metastasis.

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3359 Oncogene-Induced Senescence Limits the Progression of Pancreatic Neoplasia through Production of Activin A

Yajie Zhao, Zhichong Wu, Marie Chanal, Fabienne Guillaumond, Delphine Goehrig, Sophie Bachy, Moitza Principe, Audrey Ziverec, Jean-Michel Flaman, Guillaume Collin, Richard Tomasini, Arja Pasternack, Olli Ritvos, Sophie Vasseur, David Bernard, Ana Hennino, and Philippe Bertolino

This study identifies activin A to be a beneficial, senescence-secreted factor induced in pancreatic preneoplastic lesions, which limits their proliferation and ultimately slows progression into pancreatic cancers.

3372 Pharmacokinetic Profiles Determine Optimal Combination Treatment Schedules in Computational Models of Drug Resistance

Itziar Irurzun-Arana, Thomas O. McDonald, Iñaki F. Trocóniz, and Franziska Michor

These findings introduce a computational modeling platform and software package for combination treatment strategies with flexible pharmacokinetic profiles and multidrug interaction curves that are estimated from data.

TRANSLATIONAL SCIENCE

3383 Senescent Stromal Cells Promote Cancer Resistance through SIRT1 Loss-Potentiated Overproduction of Small Extracellular Vesicles

AC Liu Han, Qilai Long, Shenjun Li, Qixia Xu, Boyi Zhang, Xuefeng Dou, Min Qian, Yannasitha Jiramongkol, Jianming Guo, Liu Cao, Y. Eugene Chin, Eric W.-F. Lam, Jing Jiang, and Yu Sun

Senescent stromal cells produce a large number of sEVs to promote cancer resistance in therapeutic settings, a process driven by SIRT1 decline in stromal cells and ABCB4 augmentation in cancer cells.

See related commentary, p. 3193

3399 Engineering the Human Fc Region Enables Direct Cell Killing by Cancer Glycan-Targeting Antibodies without the Need for Immune Effector Cells or Complement

AC Mireille Vankemmelbeke, Richard S. McIntosh, Jia Xin Chua, Thomas Kirk, Ian Daniels, Marilena Patsalidou, Robert Moss, Tina Parsons, David Scott, Gemma Harris, Judith M. Ramage, Ian Spendlove, and Lindy G. Durrant

Fc engineering enhances avidity and direct cell killing of cancer-targeting anti-glycan antibodies to create superior clinical candidates for cancer immunotherapy.

3413 NRAS Status Determines Sensitivity to SHP2 Inhibitor Combination Therapies Targeting the RAS-MAPK Pathway in Neuroblastoma

Ivette Valencia-Sama, Yagnesh Ladumor, Lynn Kee, Teresa Adderley, Gabriella Christopher, Claire M. Robinson, Yoshihito Kano, Michael Ohh, and Meredith S. Irwin

These findings suggest that conventional therapy-resistant, relapsed neuroblastoma may be effectively treated via combined inhibition of SHP2 and MEK or ERK of the RAS-MAPK pathway.

CONVERGENCE AND TECHNOLOGIES

3424 Noninvasive MRI Native T₁ Mapping Detects Response to MYCN-targeted Therapies in the Th-MYCN Model of Neuroblastoma

AC Konstantinos Zormpas-Petridis, Evon Poon, Matthew Clarke, Neil P. Jerome, Jessica K.R. Boulton, Matthew D. Blackledge, Fernando Carceller, Alexander Koers, Giuseppe Barone, Andrew D.J. Pearson, Lucas Moreno, John Anderson, Neil Sebire, Kieran McHugh, Dow-Mu Koh, Louis Chesler, Yinyin Yuan, Simon P. Robinson, and Yann Jamin

This study shows that MRI-based functional imaging can detect apoptotic responses to MYCN-targeted small-molecule inhibitors in a genetically-engineered murine model of MYCN-driven neuroblastoma.

POPULATION AND PREVENTION SCIENCE

3436 Psychiatric Disorders Are Associated with Increased Risk of Sepsis Following a Cancer Diagnosis

Qianwei Liu, Huan Song, Therese M.-L. Andersson, Patrik K.E. Magnusson, Jianwei Zhu, Karin E. Smedby, and Fang Fang

These results call for extended prevention and surveillance of sepsis among patients with cancer psychiatric comorbidities.

RESOURCE REPORT

3443 LDtrait: An Online Tool for Identifying Published Phenotype Associations in Linkage Disequilibrium

AC Shu-Hong Lin, Derek W. Brown, and Mitchell J. Machiela

The new GWAS search tool LDtrait will expedite discovery of shared genetic components underlying seemingly unrelated diseases and may offer novel insights into cancer research.

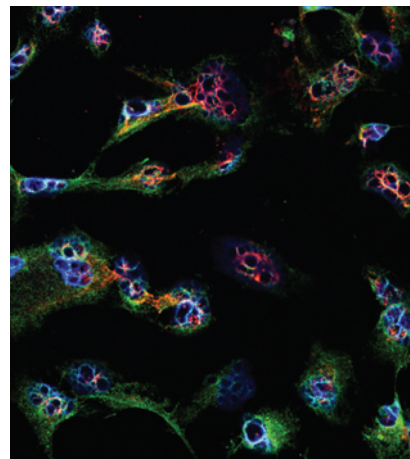
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ABOUT THE COVER

Neoadjuvant chemotherapy provides long-term clinical benefits to patients, especially when the primary tumor fully regresses before surgery. However, therapeutic benefits of these anticancer drugs may be limited by tumor-promoting host responses, which are frequently elicited by off-target effects of chemotherapy and are manifested as stromal cell senescence in the tumor microenvironment. Senescent stromal cells produce a large number of small extracellular vesicles (sEV) responsible for development of acquired cancer resistance. With confocal microscopy, active biosynthesis of sEVs by senescent stromal cells can be observed, as evidenced by remarkable expression of CD63 (green), a tetraspanin protein, and TSG101 (red), both typical biomarkers of sEVs. Nuclei were stained with DAPI (blue). For details, see article by Han and colleagues on page 3383.



Cancer Research

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