IN THIS ISSUE  Highlighted research articles .................................. 591

NEWS IN BRIEF  Important news stories affecting the community .......................... 594

NEWS IN DEPTH  Q&A: Ashok Venkitaraman on “Undruggable” Targets ........ 597

SECOND CHANCES FOR SHELVED COMPOUNDS .................................. 598

RESEARCH BRIEFS  Illuminating Cancer Systems with Genetically Engineered Mouse Models and Coupled Luciferase Reporters In Vivo ............... 616

B. Kocher and D. Piwnica-Worms

Response to Cabozantinib in Patients with RET Fusion-Positive Lung Adenocarcinomas .................. 630


See commentary, p. 604

Précis: Preliminary data from a prospective phase II trial shows cabozantinib elicits prolonged partial responses and disease stabilization in non-small cell lung cancers harboring RET fusions.

Identification of Targetable FGFR Gene Fusions in Diverse Cancers .................. 636


See commentary, p. 607

Précis: FGFR gene fusions that encode for active kinases are present in multiple cancer types and confer enhanced sensitivity to FGFR inhibitors.

Succinate Dehydrogenase Mutation Underlies Global Epigenomic Divergence in Gastrointestinal Stromal Tumor .................. 648


Précis: SDH-deficient tumors of various lineages are characterized by a divergent DNA hypermethylation profile comparable to that of other Krebs cycle-defective tumors.
Amplification of the MET Receptor Drives Resistance to Anti-EGFR Therapies in Colorectal Cancer 658
Précis: MET amplification underlies acquired resistance to cetuximab or panitumumab in colorectal cancers that have not developed secondary KRAS mutations.

Canonical Wnt/β-catenin Signaling Drives Human Schwann Cell Transformation, Progression, and Tumor Maintenance 674
Précis: WNT pathway activation induces oncogenic properties in Schwann cells and promotes growth of malignant peripheral nerve sheath tumors.

GSK-3α Promotes Oncogenic KRAS Function in Pancreatic Cancer via TAK1–TAB Stabilization and Regulation of Noncanonical NF-κB 690
D. Bang, W. Wilson, M. Ryan, J.J. Yeh, and A.S. Baldwin
Précis: GSK3α but not GSK3β enhances pancreatic cell growth downstream of mutant KRAS via coordinate activation of both canonical and noncanonical NF-κB signaling.

Killian and colleagues found that gastrointestinal stromal tumors (GIST) with mutations in succinate dehydrogenase (SDH) complex genes exhibited a distinct methylation signature relative to the profile of KIT-mutant tumors and normal reference tissues. This methyl-divergent profile was distinguished by increased global DNA hyper-methylation, particularly at DNase hypersensitive sites, and was also present in other SDH-mutant tumor lineages, including paraganglioma and pheochromocytoma, supporting the oncogenotype dependence of this signature. In addition, a similarly perturbed methylation profile was detected in gliomas harboring mutations in another Krebs cycle enzyme, isocitrate dehydrogenase (IDH). These findings identify a strong association between the mitochondrial Krebs cycle and cancer epigenomic reprogramming. For details, please see the article by Killian and colleagues on page 648.

ON THE COVER
Killian and colleagues found that gastrointestinal stromal tumors (GIST) with mutations in succinate dehydrogenase (SDH) complex genes exhibited a distinct methylation signature relative to the profile of KIT-mutant tumors and normal reference tissues. This methyl-divergent profile was distinguished by increased global DNA hyper-methylation, particularly at DNase hypersensitive sites, and was also present in other SDH-mutant tumor lineages, including paraganglioma and pheochromocytoma, supporting the oncogenotype dependence of this signature. In addition, a similarly perturbed methylation profile was detected in gliomas harboring mutations in another Krebs cycle enzyme, isocitrate dehydrogenase (IDH). These findings identify a strong association between the mitochondrial Krebs cycle and cancer epigenomic reprogramming. For details, please see the article by Killian and colleagues on page 648.

Updated version Access the most recent version of this article at: http://cancerdiscovery.aacrjournals.org/content/3/6

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.