FEATURES

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Integration and Distillation: Global Comparisons of Liver Regeneration and HCC

Zeynep Coban and Michelle Craig Barton

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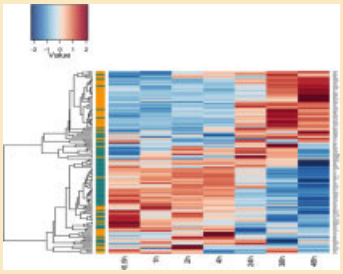

The modern arsenal of methodologies features computational analyses to assess, link and integrate large bodies of data. Genome-wide analyses of gene expression are widely used to ask how cancers, including hepatocellular carcinoma (HCC), compromise normal cellular functions, to determine significant pathways and specific factors active in cause or effect, and to develop gene signatures that may classify sub-types of tumors. The remarkable ability of liver to regenerate tissue mass and maintain metabolic function, even when highly compromised by toxins, injury or disease, parallels HCC in multiple ways: induced inflammation triggers proliferation, hyperplasia, vasculogenesis and architectural restructuring. In this "Prospects" Article, Coban and Barton integrate gene expression profiling of differentially regulated HCC-associated genes, filtered by comparisons of human HCC, mouse models of HCC and normal tissue, with profiles over a time course of liver regeneration. Hierarchal clustering reveals distinct groups of HCC-associated genes, up-regulated to function in cell cycle or down-regulated in metabolic functions, which segregate at specific phases of regeneration. These and other integrative analyses, expanded to a growing collection of comprehensive datasets, will offer new understanding of molecular mechanisms, held in common or unique to HCC or regeneration, and suggest new biomarkers, therapeutic targets or strategies for disease treatment.

Making Patient Tumors Glow in Mice

Atsushi Suetsugu, Matthew Katz, Jason Fleming, Mark Truty, Ryan Thomas, Hisataka Moriwaki, Michael Bouvet, Shigetoyo Saji, and Robert M. Hoffman

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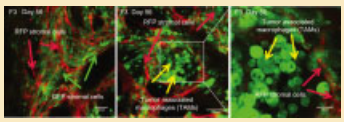

Cancer patient tumors have been grown in nude mouse models since 1969, but they are usually grown subcutaneously where they do not metastasize and are not readily imageable. Suetsugu *et al.* report in this issue on glowing pancreatic cancer patient tumors growing in nude mice. The patient tumors were first established in SCID-NOD mice, and then serially orthotopically implanted to three types of glowing transgenic nude mice: those expressing red fluorescent protein (RFP); those expressing green fluorescent protein (GFP); and finally to cyan fluorescent protein (CFP)-expressing transgenic nude mice. After growth and passage in the different colored transgenic nude mice, the patient tumors stably retained stroma of three colors, making the whole tumor brilliantly fluorescent. Confocal microscopy of the patient tumors after growth in 3 types of colored transgenic mice, visualized cancer-associated fibroblasts (CAFs), tumor associated macrophages (TAMs), and other stromal cells glowing either in RFP, GFP, or CFP, whose role in patient tumor progression can now be visualized. The glowing patient tumors will be ideal for noninvasive imaging of their growth, progression, and metatasis in non-transgenic nude mice, and will be a powerful tool for screening individualized patient therapeutics.

Journal of Cellular Biochemistry

Ups and Downs in Prostate Cancer Cell Gene Regulation

Daniel J. Purcell, Omar Khalid, Chen-Yin Ou, Gillian H. Little, Baruch Frenkel, Sanjeev K. Baniwal, and Michael R. Stallcup

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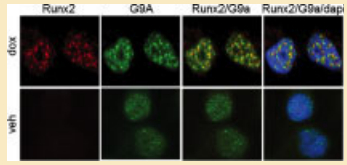
Increasing evidence indicates a critical role for Runx2 in a variety of cancers, including those originating from prostate and breast epithelia. While Runx2 was originally identified as a master transcriptional regulator of osteoblast maturation, its ectopic expression in cancer cells induces the expression of various cancer-related genes, including MMP9, SDF-1, CSF2, and IL6. Using prostate cancer cells that conditionally expressed Runx2, Purcell *et al.* established G9a, a histone methyltransferase, as a novel coregulator for Runx2-regulated gene expression. G9a binds to Runx2 in cultured cells and in cell-free conditions, and G9a is recruited to Runx2 binding sites on chromatin in a Runx2-dependent manner. Although G9a has been well characterized as a corepressor of gene expression, Purcell *et al.* showed that G9a contributes positively to Runx2-mediated expression of some genes, while limiting Runx2-mediated expression of other genes. Given the fact that both G9a and Runx2 are expressed by prostate as well as other metastatic cancer cells, these studies assert an important functional role for their crosstalk to regulate disease progression.



A New Mouse Model Sheds Light on PHEX and Rickets

Celeste Owen, Frieda Chen, Ann M. Flenniken, Lucy R. Osborne, Shoji Ichikawa, S. Lee Adamson, Janet Rossant, and Jane E. Aubin

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A long-standing puzzle in understanding X-linked hypophosphatemic rickets (XLH) has been whether the loss of Phex (phosphate-regulating gene with homologies to endopeptidases on the X chromosome) protein in osteoblasts leads directly to undermineralization of the bone matrix or whether undermineralization is a secondary effect following from renally-induced hypophosphatemia and/or changes in other serum factors. Owen *et al.* report a new mouse model for the disease, *Phex*^{Jrt}, in which a chemically induced nonsense mutation introduces a stop codon at amino acid 496 (K496X) effectively abrogating Phex protein production in the hemizygous males (*Phex*^{Jrt}/Y). *Phex*^{Jrt}/Y mice exhibit hypophosphatemic rickets, but *Phex*^{Jrt}/Y stromal osteoprogenitors in culture differentiate and form mineralized nodules indistinguishably from wild type mice, lending support for a cell non-autonomous effect of PHEX in the rachitic bone phenotype. The fact that expression levels of other phosphate-regulating factors, including FGF23, and several matrix proteins are altered in *Phex*^{Jrt}/Y bone suggests that the *Phex*^{Jrt}/Y mouse is an exciting new model in which to dissect the roles of these genes in XLH.