FEATURES

VOLUME 116 • NUMBER 3

Epigenetic Pathways and Glioblastoma Treatment: Insights From Signaling Cascades

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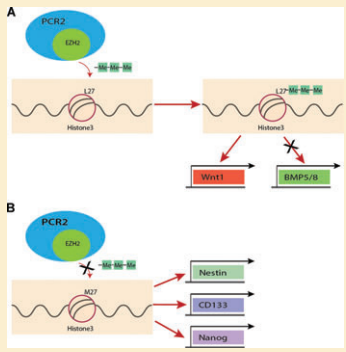
ACCEPTED MANUSCRIPT ONLINE 7 OCTOBER 2014



There is an urgent need to identify novel therapies for glioblastoma (GBM) as most therapies are ineffective. A first step is to identify and validate targets for therapeutic intervention. Epigenetic modulators have emerged as attractive drug targets in several cancers including GBM. The epigenetic regulators affect gene expression without changing the DNA sequence. Recent studies suggest that epigenetic regulators interact with drivers of GBM cell and stem-like cell proliferation. The drivers include components of the Notch, Hedgehog, and Wingless (WNT) pathways. The authors highlight recent studies connecting epigenetic and signaling pathways in GBM. In addition, review systems and big data approaches for identifying patient specific therapies in GBM. Collectively, the studies will identify drug combinations that may be effective in GBM and other cancers.

DNA Microarray and Signal Transduction Analysis in Pulmonary Artery Smooth Muscle Cells From Heritable and Idiopathic Pulmonary Arterial Hypertension Subjects

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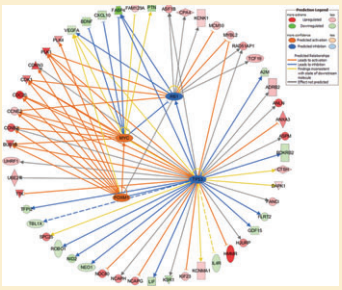
ACCEPTED MANUSCRIPT ONLINE 7 OCTOBER 2014



Pulmonary arterial hypertension (PAH) is characterized by increased pulmonary vascular smooth muscle contraction and proliferation. The authors analyze genome-wide mRNA expression in human pulmonary arterial smooth muscle cells (HPASMC) isolated from three control, three hereditary (HPAH), and three idiopathic PAH (IPAH) subjects using the Affymetrix Human Gene ST 1.0 chip. The microarray analysis reveals the expression of 537 genes in HPAH and 1024 genes in IPAH changed compared with control HPASMC. Among those genes, 227 genes show similar directionality of expression in both HPAH and IPAH HPASMC. Ingenuity™ Pathway Analysis (IPA) suggests that many of those genes are involved in cellular growth/proliferation and cell cycle regulation and that signaling pathways such as the mitotic activators, polo-like kinases, ATM signaling are activated under PAH conditions. Furthermore, the analysis demonstrates downregulated mRNA expression of certain vasoactive receptors such as bradykinin receptor B2 (*BKB2R*). Using real time PCR, the downregulated *BKB2R* expression in the PAH cells was verified. Bradykinin-stimulated calcium influx also decreased in PAH PASMC. IPA also identified transcriptional factors such p53 and Rb as downregulated, and FoxM1 and Myc as upregulated in both HPAH and IPAH HPASMC. The decreased level of phospho-p53 in PAH cells was confirmed with a phospho-protein array; and dysregulated proliferation of both HPAH and IPAH PASMC is experimentally shown. Together, the microarray experiments and bioinformatics analysis highlight an aberrant proliferation and cell cycle regulation in HPASMC from PAH subjects. The newly identified pathways may provide new targets for the treatment of both hereditary and idiopathic PAH.

Journal of Cellular Biochemistry