

FEATURES

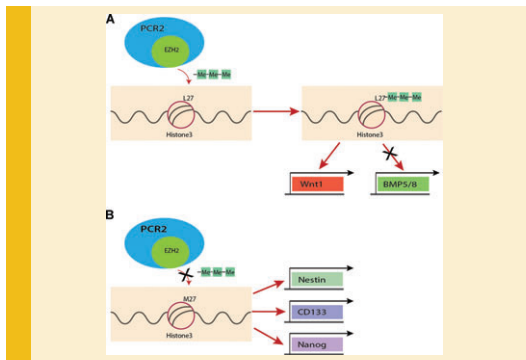
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Epigenetic Pathways and Glioblastoma Treatment: Insights From Signaling Cascades

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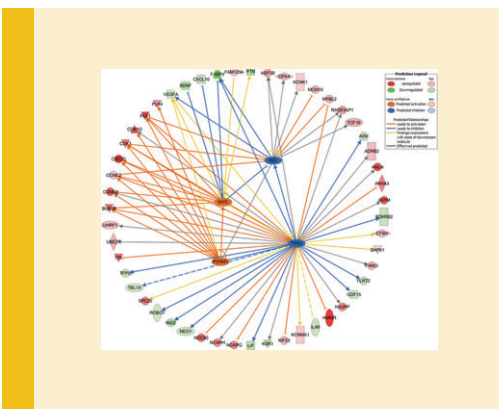
There is an urgent need to identify novel therapies for glioblastoma (GBM) as most therapies are ineffective. A first step is to identify and validate targets for therapeutic intervention. Epigenetic modulators have emerged as attractive drug targets in several cancers including GBM. The epigenetic regulators 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 Wntless (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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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.

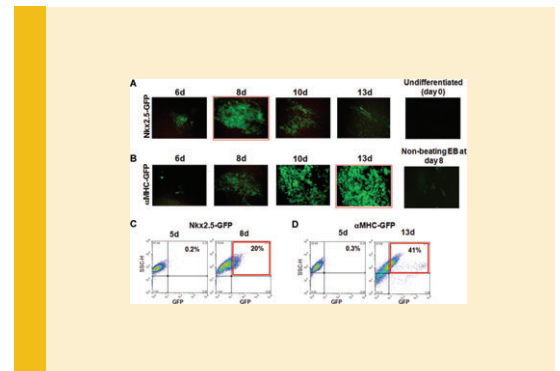
EphB4 Forward-Signaling Regulates Cardiac Progenitor Development in Mouse ES Cells

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Eph receptor (Eph)-ephrin signaling plays an important role in organ development and tissue regeneration. Bidirectional signaling of EphB4-ephrinB2 regulates cardiovascular development. To assess the role of EphB4-ephrinB2 signaling in cardiac lineage development, the authors utilized two GFP reporter systems in embryonic stem (ES) cells, in which the GFP transgenes were expressed in Nkx2.5⁺ cardiac progenitor cells and in α -MHC⁺ cardiomyocytes, respectively. Both EphB4 and ephrinB2 were expressed in Nkx2.5-GFP⁺ cardiac progenitor cells, but not in α -MHC-GFP⁺ cardiomyocytes during cardiac lineage differentiation of ES cells. An antagonist of EphB4, TNYL-RAW peptides, that block the binding of EphB4 and ephrinB2, impaired cardiac lineage development in ES cells. Inhibition of EphB4-ephrinB2 signaling at different time points during ES cell differentiation demonstrated that the interaction of EphB4 and ephrinB2 was required for the early stage of cardiac lineage development. Forced expression of human full-length EphB4 or intracellular domain-truncated EphB4 in EphB4-null ES cells was established to investigate the role of EphB4-forward signaling in ES cells. Interestingly, while full-length EphB4 was able to restore the cardiac lineage development in EphB4-null ES cells, the truncated EphB4 that lacks the intracellular domain of tyrosine kinase and PDZ motif failed to rescue the defect of cardiomyocyte development, suggesting that EphB4 intracellular domain is essential for the development of cardiomyocytes. The study provides evidence that receptor-kinase-dependent EphB4-forward signaling plays a crucial role in the development of cardiac progenitor cells.



MBD4 Interacts With and Recruits USP7 to Heterochromatic Foci

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MBD4 is the only methyl-CpG binding protein that possesses a C-terminal glycosylase domain. It has been associated with a number of nuclear pathways including DNA repair, DNA damage response, the initiation of apoptosis, transcriptional repression, and DNA demethylation. However, the precise contribution of MBD4 remains elusive. The authors identified UHRF1 and USP7 as two new interaction partners for MBD4. Both UHRF1, a E3 ubiquitin ligase, and USP7, a de-ubiquinating enzyme, regulate the stability of the DNA maintenance methyltransferase, Dnmt1. The ability of MBD4 to directly interact with and recruit USP7 to chromocenters implicates it as an additional factor that can potentially regulate Dnmt1 activity during cell proliferation.

