Cancer Research
Breaking Advances
Highlights from Recent Cancer Literature
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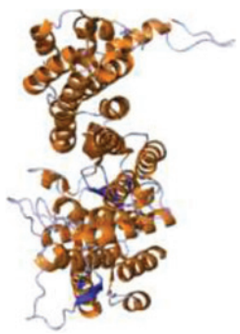
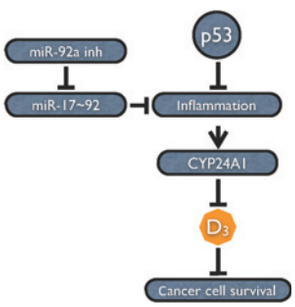
Developmental and Genetic Factors Interact in Pediatric Cancer



Funato and colleagues used human embryonic stem (hES) cells to model diffuse intrinsic pontine glioma (DIPG), a disease arising in a restricted location and developmental window. DIPGs are associated with $H3.3^{K27M}$ mutations in the histone variant *H3F3A* gene, loss of *p53*, and amplification of *PDGFRA*. Embryonic stem cells were differentiated into neural progenitor cells (NPC). While expression of $PDGFRA^{D842A}$ or $H3.3^{K27M}$ and knockdown of p53 individually promoted proliferation, the three (P5K) synergized in intracranial transformation and in blocking glial differentiation. Genes expressed in the neural plate during very early development were enriched, suggesting dedifferentiation of NPCs by P5K. Expression of menin, normally expressed in both hES cells and the neural plate, was upregulated in P5K cells. A menin inhibitor decreased tumor growth *in vivo*, supporting an oncogenic role in DIPG. (*Image courtesy of Wikimedia Commons.*)

Funato K, Major T, Lewis PW, Allis CD, Tabar V. Use of human embryonic stem cells to model pediatric gliomas with H3.3K27M histone mutation. Science 2014;346:1529–33.

Involvement of p53 and miR-17∼92 Cluster in Lung Cancer



Using a library of oligonucleotide inhibitors to miRNAs, Borkowski and colleagues identified novel synthetic lethal interactions between miRNA inhibition and p53 mutation in non–small cell lung cancer. Specifically, two inhibitors of miR-92a and miR-1226 were toxic in 27 cell lines that had lost expression of p53. Interestingly, depletion of p53 enhanced sensitivity of telomerase-immortalized bronchial epithelial cells that were otherwise resistant. The miR-17∼92 polycistron was downregulated by both inhibitors, but only when p53 was lost. Further studies showed that toxicity was caused by derepression of vitamin D signaling *via* suppression of CYP24A1. Additionally, CYP24A1 expression was correlated with poor patient outcome in lung cancer. Thus, the authors have identified clinically relevant synthetic lethal interactions that might be beneficial for patients with p53-negative lung cancer. (*Image from cited article courtesy of publisher.*)

Borkowski R, Du L, Zhao Z, McMillan E, Kosti A, Yang CR, et al. Genetic mutation of p53 and suppression of the miR-17∼92 cluster are synthetic lethal in non–small cell lung cancer due to upregulation of vitamin D signaling. Cancer Res; Published OnlineFirst December 17, 2014; doi:10.1158/0008-5472.CAN-14-1329.

A BCL6 Complex Represses Sonic Hedgehog Signaling

Tiberi and colleagues show that the lymphoma oncoprotein BCL6 controls neurogenesis during cerebellum development by regulation of granular neuron precursor cells. This activity of BCL6 required both the histone deacetylase SIRT1 and the BCOR corepressor, acting in a multiprotein complex to repress expression of the Sonic Hedgehog (SHH)–regulated transcription factors *Gli1* and *Gli2*. This multiprotein complex bound directly to BCL6 sites to remodel chromatin and repress gene expression. Using SHH-dependent medulloblastoma cells and models, the authors show that BCL6 acted via epigenetic suppression of *Gli1* and *Gli2*, doubling survival time in mice. Mice lacking both *Bcl6* and *Trp53*, but not either gene alone, developed medulloblastoma. Thus, *Bcl6* acts as either an oncogene or a tumor suppressor via epigenetic regulation of distinct subsets of genes in a context-dependent manner. (*Image from Sonic Generations courtesy of Wikimedia Commons.*)

Tiberi L, Bonnefont J, van den Ameele J, Le Bon SD, Herpoel A, Bilheu A, et al. A BCL6/BCOR/SIRT1 complex triggers neurogenesis and suppresses medulloblastoma by repressing Sonic Hedgehog signaling. Cancer Cell 2014;26:797–812.

Note: Breaking Advances are written by *Cancer Research* editors. Readers are encouraged to consult the articles referred to in each item for full details on the findings described.

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Cancer Res 2015;75:473.