



Mitogenic Hedgehog Signaling and Mitochondria Form

Malhotra *et al.* _____ Page 114

Sonic hedgehog (Shh) signaling is closely coupled with bioenergetics of medulloblastoma. In this study, effects of Shh on mitochondrial dynamics were investigated. Exposure of cerebellar granule neuron precursors, the cells-of-origin for medulloblastoma, to Shh, their obligate mitogen, altered mitochondria structurally, blocking their fusion through suppression of mitofusins. This resulted in reduced mitochondrial membrane potential and overall ATP production. Similar findings were observed in tumor tissue and mouse medulloblastoma cells. Ectopically expressed mitofusins rescued the metabolic profile of tumor cells to that of non-transformed, non-proliferating cells. Regulation of mitochondrial dynamics by Shh represents a potential avenue to generate improved medulloblastoma therapeutics.

BRCA2 and RAD51 Promote Oncolytic Adenovirus Activity

Tookman *et al.* _____ Page 44

Oncolytic adenoviruses hold therapeutic promise; however, their interactions with stress response pathways are still being studied. Tookman and colleagues investigated the interplay between oncolytic adenovirus and the Homologous Recombination (HR) pathway of DNA double strand break repair in high grade serous ovarian cancer (HGSOC). Half of HGSOC retained normal HR function, which is associated with poor response to chemotherapy and reduced overall survival. In addition, the data indicate that adenovirus type 5 vectors utilize HR components to enhance their own replication, and that both BRCA2 and RAD51 localize to virus replication centers in the infected cell nucleus. Thus, oncolytic adenoviral therapy may specifically benefit patients whose tumors have an intact HR pathway.

p53 Activity Dominates that of p73 Caused by Mdm4 Loss

Tashakori *et al.* _____ Page 56

Mdm4 negatively regulates p53 activity in embryogenesis and tumorigenesis. p73 is a transcription factor with structural and functional homology to p53. Unlike p53, this tumor suppressor lacks mutations in most cancers. Mdm4 has higher affinity for p73 than p53, which suggests a mechanism for p73 inactivation in cancer development. In this study, p73 loss did not rescue any *Mdm4*-deficient phenotypes as did p53 deletion, despite evidence for p73-specific transcriptional activity. In addition, *Mdm4* overexpression and p73 heterozygosity did not synergize in tumor development demonstrating that the Mdm4-p73 axis cannot override the dominant role of p53 in development and tumorigenesis.

Periostin-ITGB3 Signaling Maintains Breast CSCs

Lambert *et al.* _____ Page 103

Basal-like breast cancer is an aggressive subtype of breast cancer that is often enriched with cancer stem cells, which contribute to metastasis, resistance to chemotherapy, and disease recurrence. Here, Lambert and colleagues find that periostin, a matricellular protein, is secreted by basal-like breast cancer cells and mechanistically acts through integrin $\beta 3$ to control the production of key cytokines that regulate the stem cell state. This work highlights the idea that tumor cell-derived factors allow basal-like breast cancer cells to establish their own functional niche, which acts to maintain a population of cancer stem cells.

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