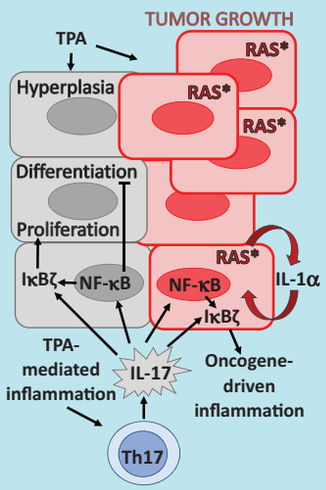
Molecular Cancer Research

Highlights

August 2019 • Volume 17 • Number 8

Selected Articles from This Issue



RAS Oncogenesis Is Mediated by IκBζ Signaling

Cataisson *et al.* **Page 1759**

Chronic tissue inflammation is known to exert a strong pro-tumorigenic effect, but the specific molecular pathways leading from inflammation to carcinogenesis are poorly defined. Here, Cataisson and colleagues demonstrate that normal and precancerous cells activate NF-κB and IκBζ in response to carcinogenic stimuli, promoting cytokine and chemokine release and the MyD88-dependent recruitment of Th17 cells to the site of insult. IL17 released by Th17 cells reprograms the microenvironment to a tumor-permissive state, promoting the development of cancer-associated molecular features and allowing for the eventual eruption of precancerous lesions.

Differential Regulation of Mitotic DNA Synthesis

Graber-Feesl *et al.* **Page 1687**

Replication stress is a major hurdle that cancer cells must overcome in order to proliferate rapidly without catastrophic genomic events. Recently, mitotic DNA synthesis has been identified as a mechanism to repair late replication intermediates during mitosis, though it is unknown how this can occur in the absence of key proteins in recombination repair like RAD51 and BRCA2. Here, Graber-Feesl and colleagues demonstrate that mitotic DNA synthesis in cancer cells is critically reliant on FANCD2 and RAD52, whereas normal cells use exclusively FANCD2 for the process. The authors suggest that this may present a novel, selective approach to promoting cancer cell death by RAD52 inhibition under a sensitized condition that exacerbates replication stress in cancer cells.

Targeting IDH1 in Ovarian Cancer

Dahl *et al.* **Page 1710**

Cancer cells rewire their metabolic networks to meet increased demand for energetics and nutrients, and to support aberrant proliferation. In this study, Dahl and colleagues identify isocitrate dehydrogenase (IDH)1, a key regulator of the citric acid cycle, as commonly upregulated in high grade serous ovarian carcinoma (HGSOC) cells, spheroids, and patient samples compared with normal fallopian tube epithelial cells. IDH1 expression was inversely correlated with progression-free survival in HGSOC patients, and its ablation was associated with decreased cellular proliferation and the onset of senescence *in vitro* due to epigenetic silencing of E2F target genes. The authors argue that IDH1 is uniquely positioned to influence both cellular metabolism and epigenetic states in HGSOC, and as such represents a promising therapeutic target.

SPCA2 Regulates EMT in Breast Cancer

Dang *et al.* **Page 1735**

Loss of E-cadherin expression is a major contributor to epithelial-mesenchymal transition, the acquisition of stem cell-like characteristics, and induction of a migratory phenotype. Here, Dang and colleagues demonstrate that disruption of post-translational E-cadherin biogenesis is a key mechanism underlying loss of its expression in breast cancer cells. Specifically, calcium signaling through the Ca2+-ATPase SPCA2 was shown to stabilize E-cadherin, thereby preserving Hippo pathway signaling for nuclear exclusion of YAP. Conversely, loss of SPCA2 resulted in decreased expression of E-cadherin, loss of tight junction signaling, and induction of YAP activity, leading to increased EMT and cellular migration. Taken together, the data suggest that modulating calcium signaling could provide a new avenue to mitigate breast cancer metastatic potential.

Molecular Cancer Research

Highlights of This Issue

Mol Cancer Res 2019;17:1595.