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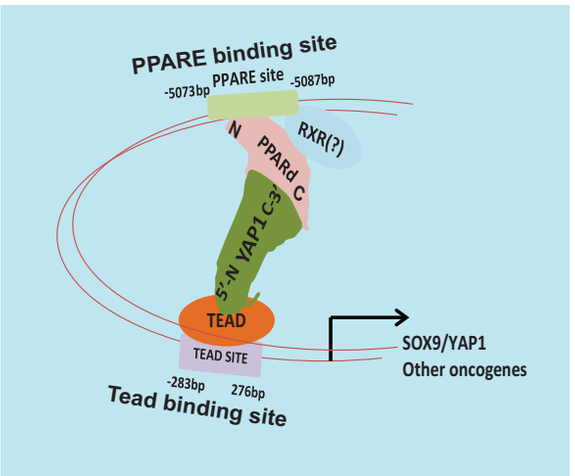
MOLECULAR CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

PPARδ–YAP1–SOX9 Axis in GC Progression



Song *et al.* | Page 390

Peroxisome Proliferator-Activated Receptors (PPARs), including PPARδ, are nuclear receptor transcription factors with well-appreciated roles in regulation of cellular lipid metabolism. However, their precise roles in either promoting or repressing tumorigenesis have remained elusive. Here, Song and colleagues provide clear evidence for a pro-oncogenic axis controlled by PPARδ in gastric cancer. Activated PPARδ in gastric cancer cells bound directly to the Hippo coactivator YAP1, thereby driving YAP1 signaling and promoting expression of the oncogenic transcription factor SOX9, whereas ablation of PPARδ inhibited YAP1/SOX9 pathway activity and reduced gastric cancer cell migration and sphere formation. Crucially, disruption of YAP1 or SOX9 expression via CRISPR/Cas9 abolished the oncogenic potential of PPARδ, indicating that its tumor-promoting functions are largely restricted to this axis and are not derived from its other cell biological functions. These data highlight a key regulatory role for PPARδ in maintaining an aggressive phenotype in gastric tumors via YAP1 and SOX9, thus identifying a new strategy for clinical management of gastric cancer.

YAP1/TEAD in Mesothelioma

Kandasamy *et al.* | Page 343

Exposure to environmental carcinogens such as asbestos is the primary cause of mesothelioma, and due to its highly aggressive nature, patients face a difficult disease course with poor outcomes. Mesotheliomas harbor a subpopulation of cancer stem cells ("MCS" cells) which maintain the tumor through chemotherapy, and therefore represent a key target for intervention. Here, Kandasamy and colleagues report that mesothelioma cells are critically reliant on Hippo pathway signaling to sustain the MCS cell niche and, by extension, an aggressive cancer phenotype. The authors demonstrate that pharmacological inhibition of YAP1 with verteporfin or CA3 resulted in reduced migration, invasion and sphere formation *in vitro* and greatly reduced tumor growth *in vivo*, owing to an observed increase in apoptotic signaling. Importantly, this observation held true in MCS cells of both pleural and peritoneal origin, suggesting that the YAP1/TAZ/TEAD pathway may represent a novel target for clinical intervention to supplement the current standard of care for mesothelioma patients.

Zebrafish-Based Screening for Antimetastasis Drugs

Nakayama *et al.* | Page 477

Cancer cell metastasis is a multi-step process that is controlled by myriad factors, both cell-intrinsic and -extrinsic. Given this complexity, appropriate model selection is critical to ensure the success and fidelity of pharmacologic screens for metastasis-inhibiting compounds. In this study, Nakayama and colleagues present a new transgenic zebrafish platform for the analysis of potential anti-metastatic drugs, and further report their findings that adrenosterone is one such compound. Functioning to inhibit hydroxysteroid 11-β dehydrogenase 1 (HSD11β1), adrenosterone was shown to suppress the metastatic spread of xenotransplanted hepatocellular carcinoma cells through the abdomen and tail of zebrafish embryos. Concordantly, HSD11β1 ablation had the same effect as chemical inhibition with adrenosterone, with both approaches resulting in decreased expression of mesenchymal/metastatic markers such as the transcription factors Snail and Slug. Taken together, the data provide proof of utility for the authors' novel anti-metastatic drug screening platform and nominate adrenosterone for further preclinical development.

PSCA/PGRN Promotes Prostate Cancer Bone Metastasis

Zhao *et al.* | Page 501

Prostate cancer exhibits a marked propensity for metastasis to the bone, and the factors underlying this longstanding observation are of considerable clinical interest. In this study, Zhao and colleagues detail a novel mechanism for the interaction between prostate cancer cells and the bone endothelium. Prostate cancer cells expressing high levels of prostate stem cell antigen (PSCA) were shown to adhere more tightly to bone marrow endothelial cells (BMECs) *in vitro*. Functional analysis of the interaction revealed that PSCA interacted with progranulin in this model, leading to enhanced activation of NF-κB and upregulation of Integrin-α4. Ablation of any of these factors weakened adhesion of prostate cancer cells to BMECs, and depletion of PSCA significantly reduced osteotropic metastasis in a mouse model of prostate cancer. Finally, PSCA expression in clinical samples is tightly correlated with both bone metastasis and poor outcomes, suggesting that this axis is likely intact in human patients and may represent a means to impede metastatic spread.

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