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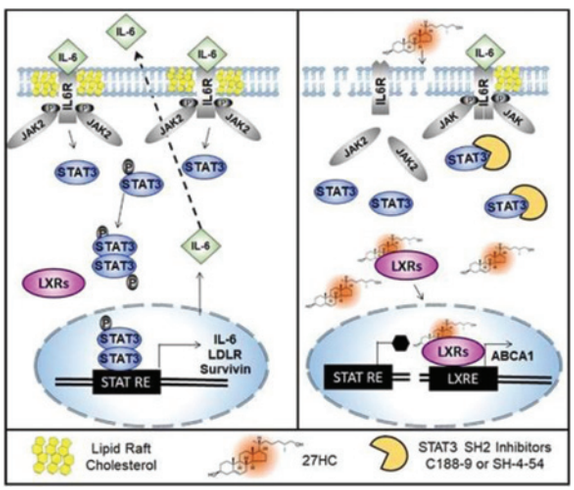
MOLECULAR CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

27HC Disrupts Lipid Raft IL6–JAK–STAT3 in Prostate Cancer



Dambal *et al.* | Page 671

Lipid rafts in the plasma membrane have tightly regulated phospholipid and cholesterol content, serving to nucleate surface receptors and intracellular signaling mediators. Disruption of lipid raft composition can have significant bearing on the strength and efficiency of signal transduction from the extracellular space. Here, Dambal and colleagues expand upon their previous work, demonstrating that inhibition of prostate cancer cell growth by the CYP27A1-derived cholesterol metabolite 27-hydroxycholesterol (27-HC) is largely due to disruption of lipid rafts. Single-molecule imaging of prostate cancer cell membranes revealed that 27-HC reduced cholesterol density in the plasma membrane and disrupted key signaling pathways. In particular, IL-6/JAK/STAT3 signaling—a known pro-tumorigenic axis contributing to prostate cancer progression and recurrence—was suppressed by 27-HC, with reductions observed in STAT3 activation, dimerization, and transcriptional activity. Finally, delivery of 27-HC combined with a STAT3 inhibitor showed combinatory effects in suppressing prostate cancer proliferation and motility, suggesting that this axis may be therapeutically exploitable in advanced or castration-resistant prostate cancer.

JM6JD1A Promotes Prostate Cancer Progression via Snail

Tang *et al.* | Page 698

Epigenetic control of gene expression is mediated partially by Jumonji (JMJ)-family histone demethylases, and aberrant expression or activity of these enzymes has been linked to aggressive phenotypes in a variety of cancers. In this study, Tang and colleagues detail new findings for the role of JMJD1A, which is overexpressed in prostate cancer compared to normal prostate tissue. JMJD1A was shown to directly interact with the promoter region of Snail—a key regulator of stem cell-like characteristics linked with disease progression—mediating removal of mono- and dimethyl marks on H3K9 residues and increasing Snail expression at the transcriptional level. This regulatory axis was directly tied to the proliferative capacity of prostate cancer cells and represents a potential target to impede prostate cancer progression.

Endogenous PAD4 Mediates CECN Formation and Promotes Metastasis

Shi *et al.* | Page 735

Neutrophil extracellular traps are a recently characterized phenomenon in which hypercitrullinated chromatin is released into the extracellular space to trap microbes. Now, new data from Shi and colleagues suggest a role for citrullinated chromatin released from breast cancer cells in promoting cell motility and metastasis. Mechanistically, peptidyl arginine deaminase 4 (PAD4)—the same enzyme that citrullinates chromatin in neutrophils—was shown to be overexpressed in murine breast cancer 4T1 cells, and its expression was essential for the establishment of cancer extracellular chromatin networks (CECN). Genetic ablation of PAD4 from breast cancer cells using CRISPR resulted in loss of CECN formation and significant reductions in both tumor growth and metastatic spread to the lungs. Similarly, disruption of CECN with DNase I also inhibited lung metastasis. Taken together, the data suggest that endogenous PAD4 exerts a pro-metastatic effect in breast cancer by causing extrusion of citrullinated chromatin from tumor cells, forming an extracellular chromatin network and thus facilitating metastatic spread.

c-Src Tyrosine Phosphorylates CIC

Bunda *et al.* | Page 774

Capicua (CIC) is a key suppressor of gene transcription that counters the oncogenic stimuli transduced by receptor tyrosine kinase (RTK) signaling: phosphorylation of CIC by activated ERK causes its dissociation from gene promoters, thereby allowing transcription of downstream targets such as *ETV1* and *5*. However, pharmacological suppression of downstream signaling is not always sufficient to re-engage CIC in glioblastoma (GBM) patients. In this study, Bunda and colleagues describe a novel Src-mediated phosphorylation site at CIC tyrosine 1455, which causes nuclear export of CIC and continued expression of ETV family members even when RTK/Ras/ERK signaling is suppressed. Inhibition of Src activity with dasatinib or expression of the CIC-Y1455F mutant reestablished CIC nuclear localization and suppression of oncogenic signaling in GBM cells. Importantly, cells expressing the CIC-Y1455F isoform lost sensitivity to dasatinib, suggesting that the pro-tumorigenic effects of Src in these cells are mediated primarily through CIC. Taken together, the data describe important regulatory mechanisms governing CIC activity in GBM and nominate a combinatorial strategy to enhance the efficacy of RTK inhibitor-based therapy in GBM patients.

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