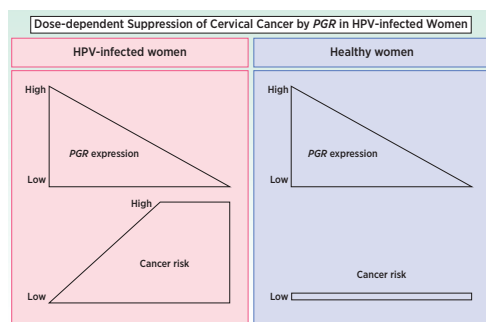


MOLECULAR CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

PGR Haploinsufficiency in Cervical Cancer

Park *et al.* | Page 42

Cervical cancer is largely driven by human papilloma virus (HPV) infections; however, several lines of evidence suggest a hormonal component to cervical cancer risk with estrogen and progesterone signaling playing opposing roles. In this study, Park and colleagues extend these observations and identify progesterone receptor (PR) as a key tumor suppressor in the cervix. Using genetically engineered mouse models of tissue-specific PR knockout, the authors show that disruption of a single PR allele resulted in significantly increased HPV oncogene-mediated tumor development. Moreover, homozygous loss of PR expression did not result in significantly more tumor development than in the PR-heterozygous animals, indicating that PR's tumor suppressor function is haploinsufficient in the cervix. These observations were supported by clinical data showing that biallelic PR loss is rare in human disease and that low PR expression is associated with worse cervical cancer outcomes, particularly in young patients. Taken together, the data indicate that tightly controlled PR expression is essential for its tumor suppressor function in the cervix and that its loss may increase cervical cancer risk in HPV-infected women.

CIN-induced Tumor Suppression Is p53 Independent

Funk *et al.* | Page 112

Chromosomal instability (CIN) is a known feature of cancer cells resulting from mitotic defects and asymmetric division of chromosomes. Low levels of CIN, which stem from missegregation of chromosomes during mitosis, can have tumorigenic effects. By contrast, induction of a high level of CIN has deleterious effects on tumors, either through the loss of indispensable genes on chromosomes that segregate asymmetrically or by activation of cell death pathways through p53. This mechanism is key to the function of paclitaxel, a microtubule inhibitor whose therapeutic efficacy in human cancer relies on induction of CIN. However, as p53 is one of the most frequently mutated genes in human cancer, it remains unclear whether its intact function is necessary to derive clinical benefit from CIN-inducing therapies. Here, Funk and colleagues demonstrate that genetic or pharmacological induction of high CIN did not require normal p53 function to induce tumor cell death. This observation confirms that clinical interventions that rely on induction of CIN, such as paclitaxel, may still benefit patients with loss or mutation of p53.

Coordinate Regulation of ACSLs by AR in PCa

Ma *et al.* | Page 124

Androgen receptor (AR)-targeted therapy is a cornerstone of the clinical management of prostate cancer (PCa), but sustained suppression of AR signaling can lead to the development of AR pathway-independent PCa. Given the central role AR plays in prostate cell metabolism, it remains unknown how AR pathway-independent PCa cells maintain fatty acid homeostasis to drive cancer progression. Here, Ma and colleagues describe coordinate regulation of long-chain Acyl-CoA synthetases (ACSL) 3 and 4 by AR. Specifically, AR signaling activated the expression of ACSL3 while suppressing ACSL4 in the normal prostate and androgen-dependent PCa. Suppression of the AR pathway resulted in reversal of ACSL3/4 expression dynamics, with ACSL4 assuming regulatory control of fatty acid metabolism in PCa cells. Importantly, ablation of ACSL4 in AR pathway-independent PCa cells significantly impeded their migratory capacity *in vitro*, as well as their proliferative capacity both *in vitro* and *in vivo*. These data highlight a crucial feedback loop sustaining lipid metabolic function under androgen deprivation, which may highlight a new means of treating AR pathway-independent PCa or delaying its onset.

The ECM Mediates FGF-Induced ER Activity

DiGiacomo *et al.* | Page 136

Fibrotic microenvironments have been shown to promote tumorigenesis as well as tumor progression. However, the extracellular matrix (ECM)—a network of fibrous filaments and growth factors that bridge the interactions between cells in a tissue compartment or tumor microenvironment—is frequently omitted from studies of tumor-stroma crosstalk. Here, DiGiacomo and colleagues employ fibroblast-derived ECM scaffolds as a tissue culture platform and identify key interactions that support breast cancer cell growth and survival. Specifically, FGF2 sequestered within the ECM caused activation of intracellular MAPK signaling, which in turn promoted increased estrogen receptor (ER) activity independent of intracellular estrogen levels. This FGF2-FGFR1-MAPK-ER signaling axis promoted the accumulation of Cyclin D1, driving cells past the G1/S cell cycle checkpoint and rendering them resistant to antiestrogen therapy. Taken together, the data highlight a key role for ECM and ECM-derived growth factors in the response to endocrine therapy in breast cancer and suggest new avenues to enhance patient outcomes in the clinic.