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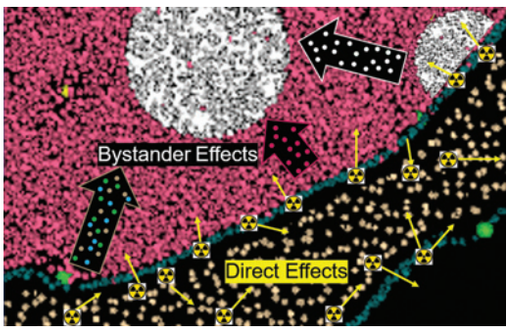
MOLECULAR CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

Radium-223–Induced Bystander Effects



Canter *et al.* | Page 1739

Radium-223 dichloride is a radiopharmaceutical used to treat cancer that has metastasized to the bones, and whose effects are derived from both direct action of radiation on tumor cells as well as bystander effects caused by irradiation of both tumor and non-tumor cells in the bone microenvironment. Here, Canter and colleagues quantify the biological effects derived from both of these mechanisms of action. *Direct effects* from alpha particle irradiation (yellow arrows in the image at left) contribute to biological changes detected histologically in disseminated tumor cells and osteocytes within the range of the alpha particles. *Bystander effects* also contribute to biological changes in tumor cells beyond the range of the alpha particles emitted from the endosteal surface of the bone. These radiation-induced bystander effects can arise from tumor cells (white outlined arrow) and marrow cells (pink outlined arrow) within the range of alpha particles, and from bone cells (brown outlined arrow). The data suggest that bystander effects in the bone environment likely contribute to growth delay of disseminated tumor cells in bone marrow.

Mir-324-5p Promotes Cancer Stemness

Ghatak *et al.* | Page 1635

Regulation of cancer stemness has emerged as a key tumor-intrinsic property underlying disease progression and therapy resistance. Recently, gain-of-function (GOF) mutations in p53 have been shown to promote increased stemness characteristics, but the mechanism for this is not well understood. Here, Ghatak and colleagues identify the microRNA miR-324-5p as the key effector of GOF mutant p53 that controls this phenomenon in non–small cell lung cancer (NSCLC) cells. GOF p53 isoforms expressed in NSCLC cells caused upregulation of c-Myc, which bound to and activated transcription of miR-324. The authors demonstrate that expression of CUEDC2—the direct target of miR-324-5p in this context—was ablated in cells expressing GOF p53 isoforms, and the loss of CUEDC2 expression was associated with activation of NF-κB and increased expression of stemness markers. CUEDC2 downregulation was further shown to be characteristic of human tumors bearing GOF p53 mutations. The authors conclude that *TP53* mutations coupled with high miR-324-5p expression is associated with worse prognosis in lung cancer patients. Taken together, the data identify miR-324-5p as a novel epigenetic regulator of stemness properties in NSCLC.

Zfp871 Regulates Development and Lipid Metabolism in Mice

Mohibi *et al.* | Page 1751

Balanced MDM2:p53 expression maintains proper cell cycle progression, whereas aberrant p53 activity is associated with developmental defects and pathologic states. Here, Mohibi and colleagues demonstrate that the RNA binding protein Zfp871 is a direct transcriptional target of *p53 in vivo*. Zfp871 functions to provoke a negative feedback loop regulating p53 activation by binding to the 3′UTR of *MDM2* mRNA and stabilizing it. This interaction increases MDM2 expression and, by consequence, promotes degradation of p53. Mice deficient in Zfp871 were prone to early death, and heterozygous mice experienced a shortened lifespan and prominent steatohepatitis. The early death seen in *Zfp871*-KO mice, however, was ameliorated by ablation of *Trp53*. Gene expression analyses unveiled that p53 hyperactivation caused by Zfp871 loss was associated with alterations in lipid metabolism and inflammatory signaling as well as key developmental pathways. While the precise mechanism underlying the control of these pathways is yet to be determined, the data clearly demonstrate that precise control of p53 expression and activity—in part through the novel Zfp871-MDM2-p53 axis—is required to prevent the onset of pathologic conditions.

EO-Derived EVs Suppress Breast Cancer Proliferation

Shupp *et al.* | Page 1763

Micro-metastatic lesions in the bone are often latent and can persist undetected for years in a quiescent state. However, the mechanisms by which rapidly proliferating tumor cells suddenly become quiescent upon metastasis are poorly defined. Here, Shupp and colleagues demonstrate that soluble signals from the bone metastatic microenvironment may play a key role in regulating this process. In particular, small extracellular vesicles (sEV) released by osteoblasts in proximity to breast cancer cells were shown to harbor factors such as miR-148a-3p, which had implications for breast cancer cell biology. Among other effects, the uptake of these sEV by metastatic breast cancer cells resulted in disruptions of both ERK1/2 signaling and cell cycle progression, thereby slowing cancer cell proliferation and contributing toward their latency. Taken together, the data elucidate a novel mechanism by which stromal cells influence cancer cell progression in the metastatic niche and underscore the importance of extracellular vesicles in mediating tumor–stromal cell interactions.

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