Highlights of This Issue

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PKA Regulates AA-Activated Calcium Entry

Fiorio Pla et al. __________ Page 1466

Intracellular calcium ($Ca^{2+}$) increase is a widely distributed response to growth factors and its alteration impairs EC proliferation, migration, and differentiation. Arachidonic acid (AA), released upon bFGF or VEGF stimulation, mediates $Ca^{2+}$ entry, playing a key role in the initial stages of tumor angiogenesis in vitro. Here Fiorio Pla and colleagues show that AA-mediated $Ca^{2+}$i signal and cell migration are dependent on cAMP/PKA and NO pathways in breast tumor–derived EC (B-TEC), but not in EC from normal tissues. This finding suggests a possible role for an AA-mediated $Ca^{2+}$i signaling pathway as a molecular target to selectively interfere with tumor angiogenesis.

Caveolin-1 Modulates the Ability of Ewing’s Sarcoma to Metastasize

Sáinz-Jaspeado et al. __________ Page 1489

Caveolin-1 (CAV1) is a multifunctional scaffolding protein with multiple binding partners that associates with cell surface caveolae. CAV1 was previously identified as a key determinant of the oncogenic phenotype and tumorigenic activity of cells from tumors of the Ewing’s sarcoma family (ESFT). Sáinz-Jaspeado and colleagues showed the implication of CAV1 in the migratory and invasive capabilities of ESFT cells and in its potential to develop lung metastases. The molecular mechanism by which CAV1 carries out its key role in ESFT metastasis involves MMP and SPARC regulation. Their results add relevance to the key roles that CAV1 plays in ESFT biology.

Glucose Transporter 3 Mediates DNA Damage–Induced Cell Death

Watanabe et al. __________ Page 1547

Because the increased uptake of glucose is well characterized in many cancer cells, targeting glucose transporter at the cell membranes to modulate the uptake may bring a new strategy for cancer chemotherapy. Watanabe and colleagues found a selective inhibition by DNA-damaging anticancer agents of the GLUT3 expression in HeLa cells. This effect seemed to be induced through activation of the MEK-ERK pathway independently of p53. Overexpression of GLUT3 increased resistance to these drugs, whereas depletion of the gene rendered the cells more sensitive. These data suggest that the GLUT3-dependent metabolism of glucose has a crucial role in DNA damage–induced cell death.

Mutation and Function of ADAMTS18 in Melanoma

Wei et al. ___________ Page 1513

The disintegrin-metalloproteinases with thrombospondin domains (ADAMTS) genes, which belong to the superfamily of zinc-based proteinases, the metzincins, have been suggested to function as tumor suppressors in various cancers. Through a systematic mutational analysis of the ADAMTS gene family in human cutaneous melanoma, we identified ADAMTS18 to be mutated in 18% of the cases analyzed. Reevaluation of ADAMTS18 in a separate independent melanoma tumor panel detected ADAMTS18 mutations in 14% of the cases analyzed. Functional evaluation of six somatic mutations showed reduced growth factor dependence, reduced adhesion on laminin-1, and increased migration in vitro and metastasis in vivo. The frequency and functional evaluation of the discovered alterations suggest that ADAMTS18 is a driver in melanoma.