FEATURES

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Osteosarcoma Cells Enhance Angiogenesis Visualized by Color-Coded Imaging in the In Vivo Gelfoam® Assay 1490

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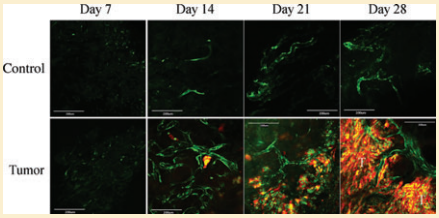
The authors report here that osteosarcoma cells promote angiogenesis in the Gelfoam® angiogenesis assay in ND-GFP mice. Gelfoam® was initially transplanted subcutaneously in the flank of transgenic ND-GFP nude mice. Seven days after transplantation of Gelfoam®, skin flaps were made and human 143B osteosarcoma cell expressing green fluorescent protein (GFP) in the nucleus and red fluorescent protein (RFP) in cytoplasm were injected into the transplanted Gelfoam®. The control group mice had only implanted Gelfoam®. Skin flaps were made at days 14, 21, and 28 after transplantation of the Gelfoam® to allow imaging of vascularization in the Gelfoam® using a variable-magnification small animal imaging system and confocal fluorescence microscopy. ND-GFP expressing nascent blood vessels penetrated and spread into the Gelfoam® in a time-dependent manner in both control and osteosarcoma-implanted mice. ND-GFP expressing blood vessels in the Gelfoam® of the osteosarcoma-implanted mice were associated with the cancer cells and larger and longer than in the Gelfoam®-only implanted mice ($P < 0.01$). The results demonstrate strong angiogenesis induction by osteosarcoma cells and suggest the process is a potential therapeutic target for the disease.



Correlation of Sprouty1 and Jagged1 With Aggressive Prostate Cancer Cells With Different Sensitivities to Androgen Deprivation 1505

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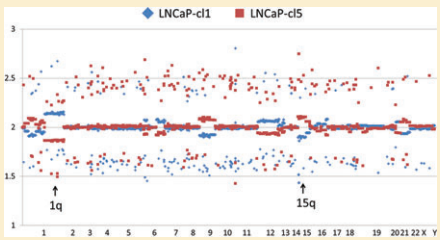
Prostate cancer is a heterogeneous disease and thus, it is important to understand whether among the heterogeneous collection of cell types, androgen-deprivation insensitive cells exist prior to hormonal manipulation. Several LNCaP subclones were established with distinct insensitivities to androgen deprivation from a parental LNCaP cell line. In the resulting clones, the sensitivity to androgen-deprivation negatively correlated with PSA expression levels. In two of these clones, an androgen insensitive clone, LNCaP-cl1, and an androgen sensitive clone, LNCaP-cl5, the DNA copy number differed significantly, indicating that these clones contain genetically distinct cells. LNCaPcl1 had higher PSA expression but lower invasiveness and tumor growth potential than LNCaP-cl5. The expression levels of two genes that are known to be regulated by miR-21, an androgen-regulated microRNA, Sprouty1 (SPRY1) and Jagged1 (JAG1) were significantly lower in LNCaP-cl1 than in LNCaP-cl5. Knocking down SPRY1 in LNCaP cells enhanced PSA expression and cell proliferation. JAG1 administration in LNCaP cells enhanced cell invasion and JAG1 knockdown in PC3 cells suppressed cell invasion and tumor formation. In summary, a random population of LNCaP cells comprises a heterogeneous group of cells with different androgen-deprivation sensitivities and potential for invasiveness.



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MiR-124 Inhibits Myogenic Differentiation of Mesenchymal Stem Cells Via Targeting Dlx5 1572

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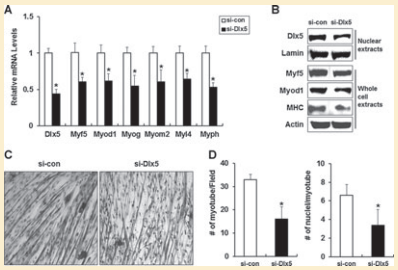

MicroRNAs (miRNAs), including miR-1, miR-133, and miR-206, play a crucial role in muscle development by regulating muscle cell proliferation and differentiation. The aim of the present study was to define the effect of miR-124 on myogenic differentiation of mesenchymal stem cells (MSCs). The expression level of miR-124 in skeletal muscles was much lower than those in primary cultured bone marrow-derived MSCs and the bone, fat and brain tissues obtained from C57BL/6 mice. Myogenic stimuli significantly decreased the expression levels of miR-124 in mouse bone marrow-derived MSCs and C2C12 cells. Forced expression of miR-124 suppressed the expression of myogenic marker genes such as Myf5, Myod1, myogenin and myosin heavy chain and multinucleated myotube formation. Blockade of endogenous miR-124 with a hairpin inhibitor enhanced myogenic marker gene expression and myotube formation. During myogenic differentiation of MSCs and C2C12 cells, the levels of Dlx5, a known target of miR-124, were inversely regulated with those of miR-124. Furthermore, overexpression of Dlx5 increased myogenic differentiation, whereas knockdown of Dlx5 using siRNA inhibited myogenesis in C2C12 cells. The results suggest that miR-124 is a negative regulator of myogenic differentiation of MSCs and that upregulation of Dlx5 accompanied with downregulation of miR-124 by myogenic stimuli is necessary for the proper progression of myogenic differentiation.

A Protease Storm Cleaves a Cell–Cell Adhesion Molecule in Cancer: Multiple Proteases Converge to Regulate PTPmu in Glioma Cells 1609

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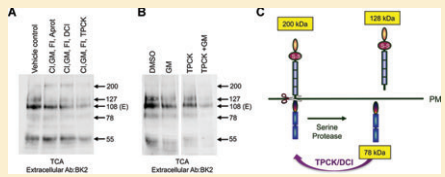

Cleavage of the cell–cell adhesion molecule, PTPμ, occurs in human glioblastoma multiforme brain tumor tissue and glioma cell lines. PTPμ cleavage is linked to increased cell motility and growth factor independent survival of glioma cells in vitro. The authors set out to biochemically analyze PTPμ cleavage in cancer cells. It was determined that a pool of 200 kDa full-length PTPμ exists at the plasma membrane that is cleaved directly by ADAM to generate a larger shed form of the PTPμ extracellular segment. Notably, in glioma cells, full-length PTPμ is also subject to calpain cleavage, which generates novel PTPμ fragments not found in other immortalized cells. Glycosylation and phosphorylation differences in the cancer cells were also observed. The data suggest that an additional serine protease also contributes to PTPμ shedding in glioma cells. It is hypothesized that a "protease storm" occurs in cancer cells whereby multiple proteases converge to reduce the presence of cell–cell adhesion molecules at the plasma membrane and to generate protein fragments with unique biological functions. As a consequence, the "protease storm" could promote the migration and invasion of tumor cells.