examined differential gene expression over time as the human melanoma cell line VMM 5 degraded and contracted collagen lattices. We observed a correlation of ADAM 9 expression with the organizational state of the extracellular matrix. ADAM 9 is downregulated on organized matrix, as represented in our model system by growth in a collagen lattice compared with growth as a monolayer on unorganized matrix represented by gelatin or other single matrix components. This regulation is the opposite of that previously observed for MT1-MMP and MMP-9. ADAM 10, another proteolytically active reprolysin, showed a similar tendency. As the collagen lattice is contracted over time, upregulation of ADAM 10 occurs, which is the opposite of the regulation observed for MT1-MMP and MMP-2. Other proteins of interest, which were shown to be differentially expressed on the basis of matrix state, include TIMP 3, cadherin F1B1, and plasminogen activator inhibitor-1. The results of this study suggest a role for ADAM 9 and ADAM 10 in the invasion and migration of melanoma with their expression dependent on the organizational state of the matrix with which the cells are interacting.

Frengen, Eirik [59]

A high-resolution integrated map of the breast cancer loss of heterozygosity region on human chromosome 16q22.1

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Loss of heterozygosity on human chromosome 16q is frequently observed in both ductal and lobular invasive breast carcinomas. We have generated a 2.8-megabase PAC contig covering the smallest region of loss of heterozygosity overlap on 16q22.1 (SRO2). We established the contig orientation with two-color fluorescence *in situ* hybridization and verified that the contig faithfully represents the SRO2 region using long-range mapping. We have identified 68 transcripts in the map on the basis of expressed sequence tag screening and CpG island subcloning. One of the genes residing within SRO2 is the E-cadherin gene, *CDH1*. This gene is known to be mutated in lobular breast carcinomas, resulting in loss of E-cadherin expression. However, E-cadherin shows normal expression in most cases of ductal carcinoma, the major mammary cancer type. Thus other genes within 16q22.1 are expected to be involved in the development of this tumor subtype. A minimal-tiling path of the contig presented consists of PAC clones, which have the potential of being transferred to mammalian cells as stably replicating episomes. This feature might serve as the basis for a functional strategy in which PACs would be introduced into tumor cells for the identification, verification and characterization of the tumor suppressor gene expected to be present within SRO2.

Fruehauf, John [60]

New approaches to antiangiogenesis therapy of solid tumors

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Anticancer chemotherapy has produced only modest gains in the treatment of solid tumors. Anti-angiogenesis therapy on the basis of rationally designed therapies targeting the tumor vasculature is a new approach currently being pursued in clinical trials. This study is directed at the development of *in vitro* and *in vivo* strategies to measure the potential efficacy of anti-angiogenesis compounds. To characterize endothelial cells derived from malignant specimens, we have developed cell separation methods (flow sorting, magnetic immunobeads) to obtain selectively highly purified populations of resting ($CD105^{-}CD31^{+}CD45^{-}$) versus activated ($CD105^{+}CD31^{+}CD45^{-}$) endothelial cells. We assessed the functional characteristics of sorted endothelial cells in type I collagen and fibronectin cultures using flow cytometry immunostaining for CD31 and CD105, as well as Ac-low-density lipoprotein uptake monitored by fluoresence microscopy as a signature of vascular endothelial cells. We evaluated tubulogenesis in MATRIGEL-based cultures by phase contrast light microscopy. Docitaxel and thalidomide were employed as validation compounds to evaluate differential effects of drug exposure on morphology, cell-surface biomarker expression and apoptotic potential in HUVEC and HAEE1 endothelial cells grown on type I collagen. Annexin V binding was the apoptosis endpoint used for the flow cytometry assay. Research Genetics array technology was used to evaluate gene expression profiles in endothelial cells sorted on the basis of CD31 and CD105 expression or Annexin V binding and expanded in collagen I cultures.

Fung, Eric [61]

Ciphergen ProteinChip technology: A platform for protein profiling and biomarker identification

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ProteinChip proteomics technology can accelerate the discovery of protein biomarkers, including tumor markers. ProteinChip technology incorporates surface-enhanced laser desorption/ionization with mass spectrometry to allow for the rapid profiling and comparison of protein expression in normal and diseased tissues. I present examples of the use of ProteinChip technology to identify new markers of a variety of neoplasms, including bladder cancer, prostate cancer and leukemia. Efforts to identify and validate these biomarkers are under way. I also show that a biomarker panel has increased diagnostic sensitivity and specificity compared with a single biomarker.