Mousses, Spyro [61]

Gene expression changes during hormonal therapy for prostate cancer reveal candidate diagnostic and drug targets

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Although prostate cancers initially respond favorably to androgen deprivation, regrowth of androgen-independent tumors is very common. The molecular mechanisms involved in the regression and regrowth of prostate cancers are unknown. We applied complementary DNA microarrays containing 6,605 genes to identify gene expression changes in the CWR22 human prostate cancer xenograft model system 12 h to 16 d after androgen deprivation, as well as in recurrent androgen-independent CWR22R tumors. We identified 59 genes whose expression levels decreased threefold in response to castration, including several cell cycle regulators. In the recurrent tumors, expression levels of 57 of these genes (96.6%) were restored, suggesting reactivation of androgen signaling in the absence of ligand. Of the 6,605 genes, 251 (3.8%) were differentially expressed between primary and recurrent prostate cancers. These genes included those coding for transcription factors, signal transducers, growth and survival factor receptors and cell cycle regulators. One of the most overexpressed genes in the recurrent tumors was *S100P,* which encodes a calcium-binding signaling protein. The role of *S100P* in the progression of prostate cancers *in vivo* was further suggested by *in situ* hybridization of messenger RNA and protein immunostaining of 440 clinical tumor specimens in a tissue microarray format. Tissue microarray analysis indicated that *S100P* expression increased significantly ($P<0.0001$) during the progression of prostate cancers *in vivo,* with the highest levels seen in hormone-refractory and metastatic prostate cancers. The cDNA microarray data may also suggest targets for therapeutic intervention. For example, several direct and indirect rapamycin targets were differentially expressed in recurrent tumors. Rapamycin also inhibited CWR22R prostate cancer cell growth *in vitro.* Tissue and cDNA microarrays enable rapid identification, prioritization and validation of gene targets that may have diagnostic and therapeutic significance in the management of patients with hormone-refractory human prostate cancer. Hormone-independent prostate cancer growth seems to require re-expression of androgen-dependent signaling pathways as well as altered expression of several other genes.

Mutter, George L. [62]

Expression signatures of high- and low-metastatic-risk lymph-node-negative premenopausal breast cancers

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Breast cancer metastasis can be predicted by morphometric quantification of mitotic activity in the tumor perimeter according to the Mitotic Activity Index (MAI). We used Affymetrix HuFL GeneChips to compare approximately 6,000 RNAs from 12 high-MAI (10 mitoses per 10 h.p.f., high metastatic risk) and 11 low-MAI, premenopausal, lymph-node-negative, primary breast cancers. We identified 51 discriminating genes as having *t*-statistics above the randomly permuted data set background (Permax 0.96) and means differing by 100 expression units, and a twofold ratio. The largest category consisted of cell cycle and division genes, usually (12/13) those with the highest levels of expression in high-MAI tumors. Internal validation of the list was provided by the following: one gene independently selected by two probe sets during analysis; five pairs of genes known to be co-expressed and one instance of reciprocal regulation of ligand and receptor. Genes that may contribute to divergent aggressiveness between groups include seven membrane-associated genes participating in cell–cell interactions, five extracellular matrix genes, and five genes encoding matrix-modifying proteolytic enzymes. A graphical classification model was tested using a 10% jackknife and 50 genes selected in each cycle. The mean level of expression in the low-MAI group and the difference of means between the groups were rank-ordered. These two variables were plotted on a triangular coordinate system against actual expression values for each tumor. Distinctive bimodally shifting cloud patterns of data points were used to assign 78% (18/23) of jackknifed tumors to their correct MAI groups. Expression profiling can be used to discover genes associated with breast cancer metastasis, and these may be of practical use in prospective risk classification.

Myklebost, Ola [63]

Microarray-based analysis of gene activity patterns in osteosarcoma

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Using spotted complementary DNA microarrays on glass slides, we have analyzed the gene expression patterns in human osteosarcomas, mesnchymal tumors of the bone. We determined the expression patterns of cell lines, tumors transplanted to immunodeficient mice and one patient sample. We compared the patterns of the same sample grown *in vitro* and *in vivo,* as well as one patient sample and its corresponding xenograft. The results indicate genes that may be important in osteosarcoma development or progression, as well as those expressed differentially *in vivo* and *in vitro.* We compared the expression patterns of osteosarcomas with those obtained from Ewing sarcoma cell lines.