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Genistein modulation of intricate signaling pathways underlying PC3 cells treatment

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To identify genes involved in the in vitro death of prostate cancer cells induced by the Genistein treatment, we analyzed gene expression profiles of the human prostate cancer cell lines PC3, androgen independent, using cDNA microarrays. Comparisson of expression patterns between Genistein untreated and treated PC-3 cells enabled us to identify several genes that were commonly up-regulated and/or down-regulated in the cell lines underlying intricate molecular pathways. Investigation of these genes should help us to decipher the molecular mechanism(s) underlying the death of prostate cancer cells treated with Genistein. In this paper, we propose a novel bioinformatics approach to predict the regulatory network of genes based on differential expressions of cDNA microarrays databases for Genistein treated human prostate cancer cells and untreated cells. The differences in regulatory networks of genes for treated and untreated prostate cancer cells reveal the information of finding possible Genistein-related genes. One exciting result of microarray technology has been the demonstration that patterns of gene expression can distinguish between Genistein treated and untreated human prostate cancer cells. Modification of existing statistical methodologies or development of new methodologies is needed for gene expression analysis. We proposed an evolutionary neural network that classifies gene expression profiles into Genistein treated and untreated prostate cancer cells. Such algorithms can play an important role in molecular profiling of underlying mechanism of Genistein treated prostate cancer cells. Neural networks can assist in the discovery of new Genistein-suppressing or -enhancing target genes, identify patterns of expression/alterations that correlate with biologically significant endpoints, and distinguish clinically meaningful outcomes (e.g., apoptosis, cell cycle arrest, signaling pathways).

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Signaling profile pathways involved in pancreatic cancer progression

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Background: The pathogenesis of pancreatic ductal adenocarcinoma (PDAC) involves multi-stage development of molecular aberrations affecting signaling pathways that regulate cancer growth and progression. This study was performed to gain a better understanding of the abnormal signaling that occurs in PDAC compared with normal duct epithelia.

Methods: Signaling profile was analyzed using xMAP array technology (Luminex 200) on samples derived from: Capan and MIA PaCa cell lines, cell cultures established from patients' tissue, tumoral and peritumoral tissue from PDAC patients and normal pancreas.

Results: Expression levels of signaling molecules were significantly increased in tumoral tissue from PDAC patients compared to normal tissue:
- cell receptors: c-KIT and EGFR were 1,5-2,0 fold increased;
- kinases: p70, p38, ERK/MAPK, JNK/SAPK were 1,7-4,0 fold increased;
- non-enzymatic signaling molecules: IRS1 was 2x increased while HSP27 over 100x;
- transcription modulators: STAT3 and CREB were around two times increased.

Similar variations were recorded in some of the peritumoral samples.

Cell cultures showed enhanced levels of expression, with a more pronunced increase in cell lines compared to primary cell cultures established from patients' tissue.

Conclusions: Our results indicate that multiple signaling proteins are over expressed and provide a higher amplification level of growth signals in PDAC. Increased levels of signaling molecules expression in peritumoral samples could be correlated with the invasivity of PDAC. Our study suggests that proteins form major cellular signaling pathways can be targets for pharmacological modulators developping thus new strategies in cancer therapy and improve the prognosis of pancreatic cancer.

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Trefoil Factor 1 (TFF1) function in cancer

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Trefoil Factor 1 (TFF1) is a small secreted protein that belongs to the Trefoil Factor Family (TFFs). It is synthesized and associated to mucin-secreting epithelial cells in the normal stomach mucosa and in damaged epithelial cells of the gastrointestinal tract. In these tissues, TFF1 plays a crucial role in mucosal defence and healing. TFF1 is essential to normal gastric mucosa differentiation and TFF1-deficient mice develop antropyloric adenomas (Lefebvre et al., Science. 1996;274:259-62). Moreover, in gastrointestinal cancer cells, TFF1 has double antiproliferative and antiapoptotic roles, which further support its function in cell differentiation (Bossenmeyer-Pourié et al., J cell Biol. 2002;157:761-70).

TFF1is frequently ectopically expressed in various human primary carcinomas as well as in their associated metastases (breast, bowel, prostate, and pancreas). In breast cancer, TFF1 overexpression is associated with a favorable prognosis (Spyratos et al., Br J Cancer. 1994;69:394-7) and is considered as a predictive factor of hormonotherapy response (Rio et al., PNAS, 1987;84:9243-7). Recent data however suggest that TFF1 could be involved in the metastatic process (Smid et al, J Clin Oncol. 2006;24:2261-7). In this context, the aim of our project is to study the role of TFF1 in breast and gastrointestinal cancer.

For this purpose, mutant and native recombinant TFF1 proteins are produced using a baculovirus/insect cell system and will be used to treat a variety of cell lines.. In parallel, breast cancer cells that show constitutive TFF1 overexpression will be silenced by a shRNA strategy.These models will be used to directly study TFF1 effect on proliferation, cell migration and apoptosis. A Transcriptome analysis of these cells will be performed to identify molecular and biological processes modulated by TFF1.

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Tumour phenotype and characteristics of metastatic brain involvement in breast cancer patient

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Background: Central nervous system metastases (CNS) occurs about 20% of patients with breast cancer. Despite of the fact that most of these patients die within a few months, substantial subgroup may survive a year or more. We performed this study to identify relations between the tumour phenotype and the incidence and characteristics of CNS dissemination, response to the local therapy and overall survival since the development of metastases in brain (OScns).

Methods: Our single institution study involved 187 breast cancer patients who developed brain metastases. Immunohistochemistry was performed on sections from primary tumors to determine following phenotypes: 1. triple-negative (negative expression of estrogen, progesterone and HER2 receptors), 2. triple-negative/basal-like (triple negative phenotype plus positivity of at least one of the basal cytokeratins and / or EGFR), 3. SHR+/HER2- (positivity at least one of the two studied steroid hormone receptors and negative expression of HER2 receptor), 4. HER2+/SHR-, 5. HER2+/SHR+, 6. SHR-/HER2? (unknown status of HER2 receptor).

Results: The incidence of monitored phenotypes was subsequent: 1. 19,4%; 2. 9,1%; 3. 21,5%; 4. 19,9%; 5. 16,7%; 6,9%, not determined 6,5%. An unambiguous dependence between the tumor's phenotype and the following attributes has been proven: a) interval between the disease diagnosis and the metastases in the CNS (TTPcns); b) interval between the first distant metastatic event and the metastases in the CNS (TTP1mts-cns); c) characteristics of CNS dissemination. The median TTPcns of monitored phenotypes was subsequent: 1. 23,6; 2. 38,0; 3. 56,4; 4. 27,7; 5. 34,6 (all in months, p=0,0111). Similarly medians of TTP1mts-cns: 1. 3,8; 2. 5,5; 3. 12; 4. 11,2; 5. 9,7 (p=0,0105). The CNS dissemination was the most