or pharmacological inhibition of this enzyme induced profound apoptosis, which coupled with significant elevation of intracellular ceramide and loss of sphingosine 1-phosphate. *In vivo*, both docetaxel and camptothecin treatment of fluorescent tumors consistent of PC-3/GFP cells o.t. implanted in nude mice induced primary tumor and lymph nodes' volume regression, markedly docetaxel being twice more potent than camptothecin. These events were coupled to sphingosine kinase inhibition and elevation of ceramide/sphingosine 1-phosphate ratio both in primary tumors and in lymph nodes. Markedly, docetaxel treatment abrogated migration of cancer cells and formation of micrometastases.
Collectively our results show that apoptosis induction by chemotherapy in prostate cancer cells is correlated with sphingosine kinase inhibition. Ability of sphingosine kinase to determine the resistance of cancer cells to chemotherapy might propose its role as a responsive element in proapoptotic signaling. Thus modulation of SK activity and thus of ceramide/S1P balance might find an application in cancer treatment.

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Different expression of tight junction proteins in HCC and metastatic liver tumours

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Background: Tight junction (TJ) proteins have already been found implicated in carcinogenesis. A group of integral membrane proteins – occludin, claudins and junctional adhesion molecules – interact with cytoplasmatic tight junction proteins to integrate diverse processes (e.g. tumour suppression, gene transcription, cell polarity).
Material and methods: Expression of claudins, occludin, junctional adhesion molecule (JAM)-1, -2, -3 and zonula occludens (ZO)-1, -2, -3 was analysed in 15 human hepatocellular carcinoma (HCC) and 15 colorectal metastasis in liver to study TJ in liver malignancies. Gene expression levels were measured by real-time PCR, protein expression was determined by immunohistochemistry and Western blot comparing tumours to surrounding parenchyma and to normal liver samples (7).
Results: ZO-1, -2, -3, JAM-1, -2, -3 and occludin mRNAs were significantly downregulated in HCC compared to normal liver (4.6×; 15.3×; 18.2×; 12.9×; 5.9×; 3.3× and 8.2×) and ZO-2, -3, JAM-2 and occludin mRNAs were also significantly downregulated compared to surrounding tissues (3.4×; 5×; 3.2× and 2.2×). In metastasis claudin-4 was significantly upregulated (12.7×), while ZO-1, -2, JAM-1, -2 and occludin were downregulated (6.4×; 9.6×; 9.4×; 18.6× and 12.1×) with respect to normal liver. Immunohistochemistry basically supported RNA expression data. Claudin-3, -4 and -7 staining were very strong in metastasis, while only scattered weak in HCC. TJ proteins were generally weakly expressed on hepatocytes, while strongly on bile canaliculi and arterioles in normal liver.
Conclusions: HCC and metastasis show different pattern of expression of TJ components. Differences in ZO-3, claudin-3 and -4 could be used for differentiation of the primary and secondary tumour. The origin of metastatic tumour could influence TJ protein expression, especially different organs can be characterized by their claudin expression.
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Characterization of genes with increased expression in glioblastomas

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Background: In the present study, we have used the gene expression data available in the SAGE database in an attempt to identify *glioblastoma molecular* markers.
Material and methods: Nine SAGE libraries of human glioblastoma (GB), six SAGE libraries of GB cell lines, and five SAGE libraries of normal human brain (NB) were analyzed to compare gene expression in GB with that of NB by accessing SAGE NCBI web site http://www.ncbi.nlm.nih.gov/SAGE and using the search tool cDNA Digital Gene Expression Displayer (DGED) provided by the SAGE Genie database. Northern blot analysis was performed for confirmation of enhanced expression of activated genes in glioblastoma.
Results: Of 129 genes with more than 5-fold difference ($P \leqslant 0.05$) found by comparison of nine *glioblastoma* vs. five normal brain SAGE libraries, 44 increased their expression in *glioblastomas*. High expression of 21 genes in *glioblastomas* as well as in *glioblastoma* cell lines suggested that expression in the bulk tumors was from transformed cells. Increasing of expression of 23 other genes only in *glioblastomas* but not in *glioblastoma* cell lines suggested that expression in the bulk tumors was from macrophages/microglial cells. Many of the latter genes are among of the top transcripts in activated macrophages and are involved in the immune response and angiogenesis.
Conclusion: Since constituent parts of tumor, *primary tumor tissue and microglia*, both participate in the tumor growth and development, all genes with highest levels of expression in glioblastomas can be used as molecular markers in the analysis of malignant progression of astrocytic tumors. Moreover, several of genes overexpressed in glioblastomas, produce extracellular proteins, thereby providing opportunities for clinical application. Further characterization of these genes will allow them to be exploited in molecular classification of glial tumors, diagnosis, prognosis, and anticancer therapy.

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Pramanicin induces apoptosis in Jurkat leukemia cells: a role for JNK, p38 and caspase activation

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The improvement in our understanding of the regulation of the molecular machinery of apoptosis reveals that the suppression of apoptosis in the presence of a proliferative stimulus is critical for tumour development. It has been clarified that new therapeutic approaches based on drug targets in apoptotic pathways will improve the response of patients to "target specific" therapeutic approaches. Pramanicin is a novel anti-fungal drug with a wide range of potential application against human diseases. In the present study, we showed that pramanicin induced apoptosis in Jurkat T leukemia cells in a dose- and time-dependent manner.
Our data reveal that pramanicin induced the release of cytochrome *c* and caspase-9 and caspase-3 activation, as evidenced by detection of active caspase fragments and fluorometric caspase assays. Pramanicin also activated c-jun N-terminal kinase (JNK), p38 and extracellular signal-regulated kinases (ERK 1/2) with different time and dose kinetics. Treatment of cells with specific MAP kinase and caspase inhibitors further confirmed the mechanistic involvement of these signalling cascades in pramanicin-induced apoptosis. JNK and p38 pathways acted as pro-apoptotic signalling pathways in pramanicin-induced apoptosis, in which they regulated release of cytochrome *c* and caspase activation. In contrast the ERK 1/2 pathway exerted a protective effect through inhibition of cytochrome *c* release from mitochondria and consequent caspase activation, which were only observed when lower concentrations of pramanicin were used as apoptosis-inducing agent.
These results suggest pramanicin as a potential apoptosis-inducing small molecule, which acts through a well-defined JNK- and p38-dependent apoptosis signalling pathway in Jurkat T leukemia cells. Studies focusing on different cancer cell lines and/or experimental animal models will further extend our understanding of mechanisms involved in apoptotic response to pramanicin and will allow us to better evaluate the anti-cancer potential of this molecule.

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MDGA1, a novel human protein with a functional role related to cellular adhesion

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Background: We have reported the characterization of the novel human protein MDGA1 (MAM Domain containing Glycosylphosphatidylinositol Anchor-1 protein). The deduced polypeptide exhibits structural features found in different types of Cell Adhesion Molecules (CAMs), such as the presence of both immunoglobulin domains and a MAM domain or the capacity to anchor to the cell membrane by a GPI (GlycosylPhosphatidylInositol) motif. *MDGA*1 encodes a 955 aminoacids protein containing an N-terminal signal peptide followed by six immunoglobulin-like (Ig) domains, one single fibronectin type III (FnIII) domain, a MAM (meprin, A5 protein, receptor protein-tyrosine phosphatase μ) domain and a C-terminal containing a cleavage site for GPI (GlycosylPhosphatidylInositol) anchoring to the cell membrane. The presence of multiple Cell Adhesion Molecule-like domains in MDGA1, lead us to hypothesize a functional role related to cellular adhesion for this protein.