for unresectable HCC is even worse as chemotherapy response rate is low (less than 20%) with median survival duration less than a year. As HCC is highly malignant, there is an urgent need for an alternative novel therapeutic approach in addition to conventional clinical management.
Targeted cancer therapy is promising to limit non-specific toxicity and to improve therapeutic efficiency compared to conventional chemotherapy. Clinically approved therapeutic antibodies include trastuzumab (Herceptin) for metastatic breast cancer, bevacizumab (Avastin) for colorectal/lung cancer, and cetuximab (Erbitux) for colorectal cancer. However, no therapeutic antibody has been approved for HCC, and the research literatures on the molecular targets in HCC are limited. To address this issue, we have systematically examined the global gene expression profiles of various liver tissues by cDNA microarray to better understand the molecular signatures of liver cancers (Cancer Res 2002; Mol Biol Cell 2002). More than 200 liver samples have been examined, and genes differentially expressed between HCCs and their adjacent non-tumor liver tissues (chronic hepatitis and cirrhosis), and normal liver tissues have been identified. Differential expression of a number of genes was shown to associate with aggressive tumor features, including GPAA1, CLDN-10, AA454543, GEP and CYP2E1. Down-regulation of expression in some of these genes by anti-sense approach revealed inhibition of growth and invasion, and these genes would be promising novel therapeutic target for HCC.

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Membrane Type 1-Matrix Metalloproteinase (MT1-MMP) is overexpressed in lung cancer and can cleave peptide-conjugates

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Matrix metalloproteinase (MMP) activity is required for tumour growth and metastasis. This study assessed the expression of membrane-type 1 MMP (MT1-MMP) in human Non Small Cell Lung Cancer (NSCLC) specimens and paired histologically normal lung tissue. Analysis of cell lines, xenografts and NSCLC specimens (representative of all stages and grades), as well as corresponding histologically normal lung tissue, was undertaken by quantitative Real Time PCR (qRT-PCR). A statistically higher level of MT1-MMP expression was observed in tumour tissue relative to histologically normal lung samples. MT1-MMP activity, as measured in cell lines and xenografts by ELISA assay, demonstrated a strong correlation between MT1-MMP activity and gene expression levels. This indicates that qRT-PCR data gives a realistic indication of MT1-MMP activity in NSCLC. Following demonstration of selective expression, an MT1-MMP targeted peptide-conjugate was synthesised using solid-phase peptide synthesis. This targeted peptide conjugate is shown by liquid chromatography mass spectrometry techniques to be preferentially cleaved in MT1-MMP expressing tumour homogenates relative to mouse plasma and liver homogenates. Cell lines and xenografts expressing MT1-MMP (as determined by qRT-PCR and western blotting) efficiently cleave the peptide-conjugate to release the active agent, whilst those negative for MT1-MMP do not. Clinically derived NSCLC tumours expressing MT1-MMP are also able to release the active agent whereas the peptide-conjugate was stable in serum from the same patients. This study shows that MMPs are potential therapeutic targets in NSCLC.

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H_2O_2-associated DNA-damage induces acetylation-dependent upregulation of p21WAF1 expression in colorectal cancer cells

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Background: Tumor cells are frequently subjected to oxyradicals generated by immune cells or after treatment with anticancer drugs. It is only poorly understood how oxidative stress contributes to histone modifications and associated alterations of gene expression
Material and Methods: To address this question, we studied the p53 target gene and cell cycle regulator $p21^{WAF1}$ after H_2O_2 treatment (30mM, 3min) with and without pre-treatment with the histone deacetylase inhibitor trichostatin A (TSA) in HCT116 colorectal cancer cells. The MTT and cytotoxicity assay was used to measure cell viability and cytotoxicity. mRNA expression was determined by *real-time* RT-PCR on a LightCycler, and protein expression was detected by Western Blotting. Promoter status of the $p21^{WAF1}$ gene was analyzed by chromatin immunoprecipitation (ChIP). HDAC activity was determined using a HDAC fluorimetric assay.
Results: In HCT116 cells, H_2O_2 caused G_2/M arrest that was accompanied by a strong increase in p53 and $p21^{WAF1}$ expression. Chromatin immunoprecipitation experiments demonstrated that the oxidative stress induced the recruitment of p53 to the $p21^{WAF1}$ promoter and concomitant histone H4 acetylation. Pretreatment of the cells with TSA reinforced these effects through several pathways. Firstly, TSA prevented H4 deacetylation. Secondly, it caused the dissociation of HDAC1 from the $p21^{WAF1}$ promoter, thus allowing for higher p53 binding efficiency. Finally, TSA enhanced acetylation of p53, increasing its binding efficiency at the $p21^{WAF1}$ promoter. All these mechanisms contributed to the increase in $p21^{WAF1}$ expression and to the ensuing G_2/M arrest.
Conclusions: These results suggest that the acetylation-dependent up-regulation of $p21^{WAF1}$ seems to be a common principle after H_2O_2-based DNA damage. TSA in combination with a H_2O_2-based anticancer drug might have remarkable antiproliferative activity in colorectal cancer cells.

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Defining Hsp90 as inhibitor of apoptosis in small cell lung cancer

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Apoptosis plays an essential role in the elimination of mutated or transformed cells from the body. In order to survive, cancer cells and their precursors must develop highly efficient, and usually multiple, mechanisms to avoid apoptosis. The complexity of apoptosis resistance in lung cancer is especially apparent; in many such cancers there is not only loss of proapoptotic proteins, but also activation or overexpression of anti-apoptotic molecules. Among these, several caspases including caspase-1, -4, -8 and -10 are either not expressed or are inactivated in small cell lung cancer (SCLC) cell lines and tumors, suggesting that major perturbations in the death receptor pathway and other aspects of apoptosis characterize this tumor type. These defects ultimately result in resistance to routine chemotherapy accounting for the poor prognosis of SCLC. Whereas this disease often initially responds well to chemotherapy, relapses occur almost without exception, and these are usually resistant to cytotoxic treatment. It is thus of major importance for SCLC treatment to identify novel targets whose sensitivity is not perturbed in chemotherapy-resistant tumors. We identify Hsp90 as one such target in SCLC. Probing selective Hsp90 inhibition in SCLC cells by pharmacological means, we show that both chemotherapy naive and resistant SCLC cells exhibit a strong apoptotic response when challenged with an Hsp90 inhibitor. Apoptosis in SCLC cells is independent of upstream caspase activity and occurs through a mitochondrion-mediated pathway, via caspase-9 activation and employing caspase-3 as effector caspase. Induction of apoptosis is restricted to SCLC cells, as normal lung fibroblasts are unaffected by Hsp90 inhibition. These effects of Hsp90 inhibitors are maintained in animal models of SCLC. Further, treatment of mice bearing xenografted tumors established from SCLC cells harvested from a patient whom had failed several lines of chemotherapy, resulted in both tumor growth inhibition and reduction of metastasis. With several Hsp90 inhibitors, such as 17AAG, 17DMAG and the purine-scaffold CNF2024 currently in clinic in Phase I and II evaluations, and with more novel scaffold small molecules to soon follow, these findings provide a strong platform for the introduction of Hsp90 in clinic as a novel target in the treatment of patients with SCLC.

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Measuring alpha-folate receptor expression levels on ascites tumour cells may help to identify patients that are more likely to respond to alpha-FR targeted therapy

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The alpha-folate receptor (α-FR) is a folate transporter with very restricted expression levels in normal tissues but is overexpressed in several cancers, particularly epithelial carcinomas. This offers a novel therapeutic target for new selective imaging and cytotoxic agents including BGC 945, an α-FR targeted TS inhibitor. Tumour specimens from >90% of patients with non-mucinous ovarian cancer homogenously overexpress α-FR. However, tumour samples are often unavailable if patients subsequently relapse. A number of these patients develop ascites that is often rich in tumour cells. A novel three antibody flow cytometric method to assess α-FR expression on tumour cells from ascites has been developed. An antibody to BerEP4, an epithelial cell marker expressed on >90% of ovarian cancers, and an α-FR