of genes such as *BNIP3, EGFR, AATF* and *NDRG1* did not change with telomere status, however genes such as *p53, p16, DAPK1, GADD45A* and *SHC1* showed a significant overexpression in the group of tumours in which telomere shortening was not 20% higher than in corresponding non tumour tissues.
Conclusion: Our data suggest a differential impact for senescence and cell death pathways in CRC and NSCLC, in relation to telomere function.

143 Expression and clinical significance of the Kv3.4 potassium channel subunit during the development and progression of head and neck squamous cell carcinomas

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Background: Increasing evidences indicate that ion channels are involved in tumour cell biology and the concept of ion channels as membrane therapeutic targets and diagnostic/prognostic biomarkers is attracting growing interest. Dysregulation of the voltage-gated potassium channel Kv3.4 has been linked to a human neuromuscular disease, periodic paralysis and Alzheimer's. In addition, increased Kv3.4 mRNA expression has been reported in oral and oesophageal squamous cell carcinomas. This prompted us to investigate the expression pattern and clinical significance of the Kv3.4 channel subunit in the development and progression of HNSCC.
Material and Methods: Kv3.4 mRNA levels were determined by real-time RT-PCR in both HNSCC tissue specimens and derived cell lines. Kv3.4 protein expression was evaluated by immunohistochemistry in paraffin-embedded tissue specimens from 84 patients with laryngeal/pharyngeal squamous cell carcinomas and 67 patients with laryngeal dysplasias. Molecular alterations were correlated with clinicopathological parameters and patient outcome.
Results: Increased Kv3.4 mRNA levels were found in 15 (54%) out of 28 tumours, compared to the corresponding normal epithelia and varied mRNA levels were detected in 12 HNSCC-derived cell lines. Increased Kv3.4 protein expression was observed in 34 (40%) of 84 carcinomas and also at early stages of HNSCC tumourigenesis. Thus, 35 (52%) of 67 laryngeal lesions displayed Kv3.4-positive staining in the dysplastic areas, whereas both stromal cells and normal adjacent epithelia exhibited negligible expression. No significant correlations were found between Kv3.4-positive expression in HNSCC and clinical data, however Kv3.4 tended to diminish in advanced-stage tumours. Interestingly, patients carrying Kv3.4-positive dysplasias experienced a significantly higher laryngeal cancer incidence than did those with negative lesions ($p = 0.0209$). In addition, functional studies using HNSCC cells revealed that Kv3.4 blockade by siRNA leads to the inhibition of cell proliferation via selective G2/M cell cycle arrest without affecting apoptosis.
Conclusions: These data demonstrate for the first time that Kv3.4 expression is frequently increased during HNSCC tumourigenesis and significantly correlated with a higher cancer risk. Our findings support a role for Kv3.4 in malignant transformation and provide original evidence for the potential clinical utility of Kv3.4 expression as a biomarker for cancer risk assessment.

144 UGT-expression in breast tissue from healthy women is associated with mammographic density

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Introduction: Mammographic density (MD) is one of the strongest risk factors for breast cancer and confers a four to six fold risk elevation of developing breast cancer, even after adjustment for other known breast cancer risk factors. The relative content of adipose, connective and epithelial tissue in the female breast determines the MD which in turn is assessed from film screen mammograms. Today, little is known about the biologic correlates of MD.
Material and Methods: Gene expression analysis using whole genome arrays was performed on breast biopsies from 79 women with no malignancy (healthy women) recruited through mammographic centres. To compare with findings in tumour samples, 64 newly diagnosed breast cancer patients were recruited. MD percentage was determined using a previously validated, computerized method on scanned mammograms. Significance analysis of microarrays (SAM) was performed to identify genes associated with MD.
Results: SAM identified 24 genes differentially expressed between high and low MD in the healthy women, including three uridine 5′-diphospho-glucuronosyltransferase (*UGT*) genes: *UGT2B7*, *UGT2B10* and *UGT2B11*. These genes had a reduced expression in samples from breasts with high MD compared with samples from breasts with low MD and reduced expression in breast cancers compared with healthy breasts. These *UGT* genes were the only genes among the 24 differentially expressed which had a similar expression in breasts with high MD and in breast cancers. The UGT enzymes inactivate several endogenous and exogenous compounds, including sex hormones. The reduced expression in breasts with high compared with low MD was most significant in the subpopulation with higher levels of female sex hormones (premenopausal women and postmenopausal women on hormone replacement).
Conclusions: Twenty-four genes associated with MD were identified. Three UGT2B genes had reduced expression in breasts with higher MD and breast cancers compared with healthy breasts. We hypothesise that reduced expression of *UGT* genes in women exposed to female sex hormones, increase MD and that this may be associated with an increased risk of breast cancer. Validation and further analysis of these genes is ongoing.

145 Role of collagen in the anti-metastatic activity of a ruthenium-based drug

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Background: NAMI-A, namely imidazolium tetrachorido (S-dimethylsulfoxide) imidazoleruthenate (III) is an anti-metastasic drug independent of conventional cell cytotoxicity. Interactions of NAMI-A with the components of extracellular matrix, including collagen, are thought to be crucial for its anti-metastatic action.
Materials and Methods: Structural changes in collagen and cultured cancer cells treated with NAMI-A were investigated by using a combination of X-Ray absorption spectroscopy (XAS), field-emission scanning electron microscopy (FE-SEM), Fourier transform infrared spectroscopy (FTIR), transmission electron microscopy (TEM), X-Ray photoelectron spectroscopy (XPS) and gel electrophoresis.
Results: The *XAS* results showed that the incubation of collagen with NAMI-A at pH 7.4 resulted in a significant change in coordination environment, most of the Cl^- ligands being replaced with N- and O- donor ligands of the protein. The *SEM* observation demonstrated that the Ru treatment leads to the formation of Ru clusters of 25−35 nm between collagen fibrils, where the thin fibrils exhibit an increased axial D periodicity. The secondary structure of collagen was monitored by *FTIR*. When the native form of collagen was subjected to Ru treatment, the amide I band attributed to helical protein structures increased, and that attributed to random coil formation decreased. *Gel electrophoresis* confirmed the formation of crosslinks between collagen chains in Ru-treated collagen, as well as matrix metallo-proteinase (MMP) inhibition. The *TEM* results showed that the co-culture of lung cancer cells (A549) with Ru-treated collagen resulted in the formation of 20−35 nm particles along the plasma surface of cells' invasive protrusions. *XPS* revealed that these particles contained Ru.
Conclusion: Combination of the above results points to the formation of Ru clusters deposited among collagen fibrils, as well as of Ru-induced intra- and inter-molecular cross-links. The binding of Ru to collagen leads to an increase in the structural order, but does not destroy the triple helices of collagen. These changes cause inhibition of matrix metallo-proteinase (MMP) interactions with collagen, which is expected to contribute to the anti-metastatic activity of NAMI-A.

146 Identification of novel tumour-associated autoantibody signatures in gastric cancer

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Background: Gastric cancer, despite an overall global decrease in incidence, remains the third most common malignancy in Eastern Europe, and in more than 80% of the cases it is diagnosed at late stages when therapy is ineffective. Thus, the identification and validation of novel biomarkers for the early detection of gastric cancer would contribute significantly to the decrease of gastric cancer-related morbidity and mortality.
Material and Methods: We applied the T7 phage display-based SEREX technique to identify a representative set of antigens eliciting humoral responses in gastric cancer and gastritis patients. All identified antigens