using a combination of the biomarkers resulted in a ROC curve area of 0.806, which was significantly higher (p=0.0033) than that of PSA (0.58), or any of the variables alone. Our results show that the use of a combination of biomarkers in serum and urine improves the diagnosis of prostate cancer, which could avoid a significant number of unnecessary prostate biopsies.

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Proliferative/Angiogenic genetic profile is associated with progression-free-interval in androgen blockade treated prostate cancer patients

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Background: Androgen blockade therapy (ABT) is frequently used in prostate cancer (PC) advanced stages, albeit most men will eventually fail this therapy and die from recurrent hormone-resistant prostate cancer (HRPC). The epidermal growth factor (EGF), the transforming growth factor beta 1 (TGFβ1) and the vascular endothelial growth factor (VEGF) are key molecules in prostate cancer (PC) cell proliferation and tumoral angiogenesis. The combined effect of functional genetic variants in these genes (EGF +61G>A; TGFB1 +869T>C; VEGF +405G>C) in PC outcome are still uncovered. Their role in PC and HRPC oncobiology increases the rationale for selecting these molecular markers for studying PC prognosis and pharmacogenomics. We hypothesize that PC tumor microenvironment might be modulated through combined effect of EGF, TGFB1 and VEGF functional polymorphisms.

Methods: We conducted a case-control study in histopathologically confirmed PC patients (n=178) and healthy individuals without evidence of neoplastic disease (n=171). EGF +61G>A and VEGF +405G>C genotyping was performed through PCR-RFLP and the TGFB1 +869T>C polymorphism was analysed through allelic discrimination Real-Time PCR. Genotypes from the three polymorphisms were combined into 2 categories according to functional phenotype: low and intermediate/high risk profile (proliferative/angiogenic profile according to gene expression levels).

Results: Genotype frequencies are similar between patients and controls, according to the proliferative/angiogenic profile (P=0.173). The progression free interval (PFI) was significantly shorter in intermediate/high carriers, comparatively with low proliferative/angiogenic genetic profile carriers (36.3±6.5 and 56.4±6.5 months, respectively, P=0.007). Multivariate Cox-regression analysis showed that the proliferative/angiogenic genetic profile is an independent and significant variable for an earlier development of hormone-resistance, in the course of androgen-blockade therapy, even after adjustment for age, Gleason grade and clinical stage (HR=10.3, 95%CI=1.2-90.6, P=0.036).

Conclusion: Combined analysis of target genes from synergistic pathways may reveal interesting functional outcomes and help to define PC susceptibility and pharmacogenomic profile. Results from the present study show an independent effect of the proliferative/angiogenic genetic profile in the response to androgen blockade therapy. The genes studied may be included in further PC pharmacogenomic profiling.

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Relevance of autoantibody profiles in the early detection of cancer

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Circulating autoantibodies against tumour-derived proteins have been observed in the most if not all cancer patients hence they may serve as non-invasive biomarkers for the screening, diagnosis, prognosis or monitoring of cancer. We recently commenced a study aiming to identify a comprehensive set of antigens eliciting B cell responses in patients with melanoma, prostate and gastric cancer and to establish the relevance of autoantibodies for the early detection of cancer and prediction of response to immunotherapy. Nine T7 phage displayed cDNA expression libraries were constructed from testis, melanoma and gastric cancer tissues and prostate cancer cell lines, and the serum-reactive phage clones were selected via biopanning followed by the immunoscreening of the enriched libraries with sera from 76 cancer patients. This resulted in the identification of 1049 different serum-reactive phage clones. However, only ~10% of them represented known genes translated in their natural reading frame and included known TAAs such as CTAG1B, GAGE and Annexin XI-A, and several novel antigens. The remaining clones contained DNA fragments in non-natural reading frames that most likely represent mimotopes, nevertheless, they may turn out to be valid biomarkers. So far a panel of 750 serum-reactive phage clones was assembled and exploited for the production of phage-displayed antigen microarray that was applied to analyse the autoantibody profiles in the sera from 123 melanoma patients (not included in the screening set), 33 patients with systemic autoimmune disorders and 80 healthy controls. A cut-off value for defining melanoma specific antigens was set as >4SDs above the mean value for the healthy control sera. This revealed 194 antigens that reacted with serum from at least one melanoma patient and not with control sera with CTAG1B/CTAG2 being the most frequently recognised (p=0.0007) followed by two out-of-frame peptides (p=0.006). Based on this set of antigens we could classify the sera as “melanoma” or “normal” with 78% sensitivity and 100% specificity. Moreover, the sensitivity for the detection of stage I melanoma was 77% and 73, 77 and 82% for the stage II, III and IV, respectively that demonstrates the relevance of autoantibody profiling in the early detection of cancer.

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Diagnostic role of new circulating markers in bone metastases from breast cancer

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More than 50% of breast cancer patients who relapse with distant metastases present bone lesions, which are responsible for high morbidity. A diagnostic, non-invasive test to detect metastases is needed in order to provide patients with specific, effective treatments. The study was carried out on an overall 54 individuals: 18 healthy donors (median age 43 years [23-76]) and 36 breast cancer patients, 18 of whom were disease-free (median age 49 years [32-77]) and 18 at first diagnosis of bone metastases (median age 63 years [36-86]). OPG and RANKL transcripts were determined using quantitative PCR analysis. The diagnostic accuracy of each marker and their ratio were calculated using receiver operating characteristic (ROC) curves. OPG and RANK-L values were not significantly correlated in healthy donors, disease-free patients, or bone metastasis patients. Median values were independent of age in all the subgroups and, in patients with bone metastases, were not correlated with the number of bone lesions or the presence of visceral metastases. Although the median OPG value was lower in patients with lytic lesions than in those with osteoblastic/mixed lesions (0.3 vs. 1.5), the difference did not reach statistically significance. Moreover, whilst there was no statistically significant difference in median OPG or RANK-L/OPG values between healthy donors and the entire patient group, within the latter subgroup, median OPG was threefold lower (p <0.003) and the RANK-L/OPG ratio about threefold higher (p <0.003) in patients with bone metastases with respect to those who were disease-free. However, median RANK-L values were not statistically different in these two subgroups. The area under the curve (AUC) in disease-free patients was 0.88 for OPG and 0.83 for RANK-L/OPG, with 78% sensitivity and 89% specificity for OPG. The ratio between the two markers reached 44% sensitivity and 89% specificity. A parallel analysis showed about 100% specificity for CEA and CA153, but much lower sensitivity (57% and 50%, respectively) than that observed for RANK-L/OPG. Our preliminary results show that markers of bone damage, in particular OPG, could play a potentially important role in the diagnosis of bone metastases. Confirmation of these data is now required in a larger case series.

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The sodium-dependent phosphate transporter NaPi2b is a new target antigen in ovarian carcinoma and is recognized by the anti-cancer antibody MX35

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Epithelial ovarian cancer is the most common gynecologic cancer that is usually far advanced before it is diagnosed and thus patients have a poor prognosis and survival rate. Identification and characterization of novel ovarian cancer markers is important for understanding the molecular