Tumor Indicating Normal Tissue
New field of diagnostic biomarkers for prostate cancer

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ABSTRACT

Background
Prostate cancer is the most common cancer in Sweden. Due its highly variable behavior, multifocal nature, and insufficient diagnostic methods, prostate cancer is difficult to diagnose and prognosticate. Some patients have an aggressive lethal disease, but the majority of prostate cancer patients have slow-growing, non-lethal disease with long expected survival without treatment. Current diagnostic methods—serum levels of prostate-specific antigen (PSA) and histological grading of biopsied prostate tissue—often do not give the information required to be able to safely differentiate indolent tumors from potentially lethal ones. Many prostate cancers are difficult to detect by imaging, so tissue biopsy cannot be safely guided towards the tumor, and particularly not towards the most aggressive forms.

To overcome this problem, multiple needle biopsies are taken from the organ, but biopsies are small and they sample less than 1% of the whole prostate. In this thesis, we explore the non-malignant prostate tissue adjacent to tumors, which is always sampled in biopsies, and we study adaptive changes in this tissue, which may provide new diagnostic and prognostic markers for prostate cancer. We have therefore proposed that this type of tissue should be termed TINT (Tumor Instructed/indicating Normal Tissue).

Methods
In our studies, we used orthotopic rat prostate cancer models with tumors of different aggressiveness. We also used clinical materials from patients diagnosed with prostate cancer at transurethral resection (1975-1990); the majority of these men were followed with watchful waiting. Analyses were performed with whole-genome expression array, quantitative real-time PCR, immunohistochemistry, and western blotting.

Results
Using the animal model, we found that the presence of a tumor induces changes in gene expression in the surrounding tumor-bearing organ (TINT). The gene signature of TINT was linked to processes such as extracellular matrix organization, immune responses, and inflammation. We also showed that some of these adaptive TINT changes appear to be related to the aggressiveness and metastatic potential of the growing tumor, such as increases in macrophages, in mast cells, in vascular densities, and in vascular cell-proliferation. Some of these findings were confirmed by our observations in patient samples. We found that high staining of the extracellular matrix component hyaluronan in the stroma of the non-malignant prostate tissue was prognostic for short cancer-specific survival. We also found that an elevated proportion of C/EBP-beta positive epithelial cells in non-malignant (TINT) prostate tissue was associated with a good prognosis.

Conclusions
Using animal experiments and patient samples, we showed that the presence of prostate cancer induces changes in the tumor-bearing organ, alterations associated with tumor aggressiveness, and that grading of these changes in TINT can be used to predict outcome in prostate cancer patients.

Keywords: Prostate cancer, TINT, biomarkers, orthotopic rat model, gene expression, hyaluronan, C/EBPbeta.