Extratumoral Effects of Highly Aggressive Prostate Cancer

Kerstin Strömvall

Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i hörsal Betula, byggnad 6M NUS (målpunkt L) torsdagen den 26 oktober, kl. 13:00.
Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent: Professor/överläkare, Göran Landberg,
Institutionen för biomedicin, Sahlgrenska Cancer Center, Göteborgs University/Sahlgrenska universitetssjukhuset, Göteborg, Sverige.

Department of Medical Biosciences
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Abstract
Prostate cancer (PC) is the most common cancer in Sweden. Most patients have slow growing tumors that will not cause them any harm within their lifetime, but some have aggressive tumors and will die from their disease. The ability of current clinical practice to predict tumor behavior and disease outcome is limited leading to both over- and undertreatment of PC patients. The men who die from their disease are those that develop metastases. It is therefore of great value to find better and more sensitive prognostic techniques, so that metastatic spread can be detected (or predicted) at an early time point, and so that appropriate treatment can be offered to each subgroup of patients.

The aim of this thesis was to investigate if, and by what means, highly aggressive prostate tumors influence extratumoral tissues such as the non-malignant parts of the prostate and regional lymph nodes (LN), and also if any of our findings could be of prognostic importance. Gene- and protein expression analysis were the main methods used to address these questions.

Our research group has previously introduced the expression Tumor Instructed (Indicating) Normal Tissue (TINT), and we use the term TINT-changes when referring to alterations in non-malignant tissue due to the growth of a tumor nearby or elsewhere in the body.

In the Dunning rat PC-model we found that MatLyLu (MLL)-tumors, having a high metastatic ability, caused pre-metastatic TINT-changes that differ from those caused by AT1-tumors who have low metastatic ability. Prostate-TINT surrounding MLL-tumors had elevated immune cell infiltration, and gene ontology enrichment analysis suggested that biological functions promoting tumor growth and metastasis were activated in MLL- while inhibited in AT1-prostate-TINT. In the regional LNs we found signs of impaired antigen presentation, and decreased quantity of T cells in the MLL-model. One of the downregulated genes in the MLL-LNs was Siglec1 (also known as Cdi169), expressed by LN resident macrophages that are important for antigen presentation. When examining metastasis-free LN tissue from PC patients we found CD169 expression to be a prognostic factor for PC-specific survival, and reduced expression was linked to an increased risk of PC-specific death.

Some of our findings in prostate- and LN-TINT could be seen already when the tumors were very small suggesting that differences in TINT-changes between tumors with different metastatic capability can be detected early in tumor progression. However, before coming of use in the clinic more research is needed to better define a suitable panel of prognostic TINT-factors as well as the right time window of when to use them.

Keywords
Prostate cancer; tumor instructed normal tissue; TINT; non-malignant prostate tissue; lymph nodes; lymph node metastasis; pre-metastatic niche; tumor microenvironment; tumor macroenvironment; tumor immunoediting; Dunning rat model of prostate cancer.