Genome-wide gene expression profiling of early bladder cancer, and functional characterization of target genes, using microarrays

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ABSTRACT

This PhD dissertation consists of four articles and one submitted manuscript. The studies have been conducted at the Molecular Diagnostic Laboratory, Department of Clinical Biochemistry, Skejby Sygehus.

At present, the mechanism leading to bladder cancer is still poorly understood, and our knowledge about early events in tumourigenesis is limited. Our approach in this study was to describe the changes in gene expression occurring during the neoplastic transformation of normal bladder urothelium into non-invasive tumours. And to identify new genes involved in the progression of bladder cancer.

Our data showed that the early neoplastic process was accompanied by changes in expression of genes related to functional important classes, such as cytoskeleton, protein folding, transferase activity, and transcription. The genes that were identified seemed relevant based on their purported function.

The human transcription factor SOX4, was selected for further analysis as it was 5-fold up-regulated in tumours compared to normal urothelium. By immunohistochemical staining we found cancer cells to express SOX4 protein in tumours, and tissue microarray analyses reveal a significant correlation ($p<0.05$) between strong SOX4 expression and increased patient survival. We did a thorough examination of the in-vitro functional properties of the gene SOX4 by a time-course global expression approach, to identify target genes and SOX4-induced pathways. When induced in bladder cells SOX4 promoted apoptosis. Analyses of microarray data revealed the existence of 130 novel SOX4 associated genes.

Another interesting gene was ISG15, which was found highly expressed in bladder tumours not only of benign tumours but also of muscle-invasive tumours. By immunohistochemical stainings, we found expression of ISG15 protein localized in both cancer cells and in stromal immune cells. Only a minor subgroup of the normal urothelium samples stained positive for ISG15. Our findings indicate that ISG15 over-expression does not reflect a generalized inflammatory response as changes in expression of well-known pro- and anti-inflammatory markers were not seen. The present data suggest a role for ISG15 in host immune response to bladder cancer.