

Genomic analysis of localised prostate cancer identifies AZIN1 as driver of metastatic progression

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Introduction & Objectives: High-risk PCa (HRPCa) remains very heterogeneous with an unacceptable variation in patient outcome after radical prostatectomy (RP) with cancer-specific mortality rates ranging from 4.6% to 20.3% at 10 years follow-up. Clearly, we need a better understanding of the tumor biology to enhance the sub-classification, enable the identification of lethal PCa and eventually allow a more precise decision-making regarding treatment.

Materials & Methods: We created a matched case-control study of two clinically identical HRPCa patient groups, both treated with RP but where one developed metastatic recurrence (n=19) and the other did not (n=25), despite very long-term follow-up. DNA and RNA of the primary tumor were extracted to perform somatic copy number aberration (CNA) and MicroArray based gene expression analyses. Further in vitro analyses were performed with standard molecular biology methodology.

Results: The integrated analysis of copy number aberrations and transcriptome analysis highlighted a focal amplification of 8q22.3, associated with a higher expression of antizyme inhibitor 1 (AZIN1) in the metastatic group. AZIN1 is involved in the polyamine biosynthesis pathway, which plays a central role in many cellular processes. Our in vitro analyses confirmed that modulation of AZIN1 expression determines both growth and migratory potential of PCa cells. RNA sequencing after knockdown of AZIN1 in PCa cells revealed several transcriptional programs, which are activated/deactivated upon AZIN1 knockdown. This showed among others a significant upregulation of genes involved in extracellular matrix composition, including genes encoding for subunits of the collagen IV which is an integral part of the basement membrane

Conclusions: The association of high AZIN1 levels with the metastatic HRPCa phenotype suggests a role for AZIN1 as possible predictor and/or target for metastatic HRPCa. Modulation of AZIN1 levels in PCa cells influences both proliferation and migration rate. The development of stable cell lines, mimicking our clinical findings to evaluate tumor growth and development of metastases in mice xenografts, are under development. Ongoing in vitro experiments will focus on identifying mechanisms by which AZIN1 regulates the extracellular matrix and creates a pro-metastatic environment.