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Human Prostate Cancer in a Clinically Relevant Xenograft Mouse Model: Identification of β(1,6)-branched Oligosaccharides as a Marker of Tumor Progression

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ABSTRACT: Purpose: To establish xenograft mouse models of metastatic and nonmetastatic human prostate cancer and to apply these models to the search for aberrant glycosylation patterns associated with tumor progression in vivo and in patients. Experimental design: Prostate cancer cells (LNCaP, PC-3, LuCaP 23.1, and DU-145) were xenografted subcutaneously into immunodeficient pfp(-/-)/rag2(-/-) mice. Tumor growth and metastasis formation were quantified and as altered glycosylation patterns have been associated with metastasis formation in several other malignancies, prostate cancer cells were profiled by a quantitative real-time PCR (qRT-PCR) glycosylation array and compared with normal human prostate cells. The activity of upregulated glycosyltransferases was analyzed by their sugar residues end products using lectin histochemistry on primary tumors and metastases in the animal experiments and on 2,085 clinical samples. Results: PC-3 cells produced the largest number of spontaneous lung metastases, followed by LNCaP and LuCaP 23.1, whereas DU-145 was nonmetastatic. qRT-PCR revealed an upregulation of β1,6-N-acetylglucosaminyltransferase-5b (Mgat5b) in all prostate cancer cell lines. Mgat5b products [β(1,6)-branched oligosaccharides] were predominantly detectable in metastatic xenografts as shown by increased binding of Phaseolus vulgaris leukoagglutinin (PHA-L). The percentage of prostate cancer patients who were PHA-L positive was 86.5. PHA-L intensity correlated with serum prostate-specific antigen and a cytoplasmic staining negatively affected disease-free survival. Conclusion: We show a novel xenograft mouse model for human prostate cancer respecting the complete metastatic cascade. Specific glycosylation patterns reveal Mgat5b products as relevant markers of both metastatic competence in mice and disease-free survival in patients. This is the first description of Mgat5b in prostate cancer indicating a significant biologic importance of β(1,6)-branched oligosaccharides for prostate cancer progression.

STATEMENT: *This is the first description of a clinically relevant mouse model of metastatic human prostate cancer respecting the entire metastasis cascade. Based on this model, β(1,6)-oligosaccharides were identified not only as a marker of metastatic competence in vivo, but also as a prognostic marker for patients. The relevance of the present work for the world-wide prostate cancer research community, which has so far been lacking a satisfying, clinically relevant metastasis mouse model, is indicated by publication in one of the top 10 % oncology journals." The article is featured in the journal as one of the four highlights of the issue.*

BACKGROUND: This work was performed at the Institute of Anatomy and Experimental Morphology in close collaboration with several other groups involved in prostate cancer research within the UKE [e. g., Institute of Pathology (Guido Sauter), Department of Urology, Section for Translational Prostate Cancer Research (Thorsten Schlomm)] and cancer research in general [Interdisciplinary Endoscopy (Mario Anders)] and therefore represents a truly interdisciplinary research effort. This is the world wide first experimental approach to model spontaneous prostate cancer metastasis in a xenograft model. This novel mouse model can now be used for the validation of the pathophysiological relevance of genes for metastasis formation identified by the above mentioned groups. In summary, the present work fills an important gap in prostate cancer research at UKE and displays a substantial improvement of the existing network.