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# ANLN, TLE2 and MIR31HG transcripts in muscle invasive bladder cancer: a functional and clinical analysis based on molecular subtypes

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Diagnostic, risk stratification and therapy of muscle-invasive bladder cancer (MIBC) has barely changed over the last decades. Limitations in histopathological and molecular classification might lead to inadequate treatment decisions of MIBC. Besides, growing evidence supports the pivotal role of long non-coding RNAs (lncRNAs) in the regulation of cancer development and progression. Their expression patterns and biological function in MIBC remain elusive. In addition, the expression and function of coding genes ANLN, TLE2 and non-coding gene MIR31HG in MIBC are remain unknown. Therefore, the aim of the study was the analysis of gene expression, clinical association and function of ANLN and TLE2, and lncRNA MIR31HG in bladder cancer (BLCA) cells and tissues.

On one hand, this study provides preclinical *in silico* and *in vitro* evidence supporting the prognostic potential of ANLN and TLE2 for patients with MIBC. In a MIBC cohort from the Medical Faculty Mannheim, tumors with high ANLN expression were associated with lower overall survival (OS) and disease-specific survival (DSS), while high TLE2 expression was associated with a favorable OS. Data from the published The Cancer Genome Atlas (TCGA) cohort confirmed that high ANLN and low TLE2 expression was associated with shorter OS and disease-free survival (DFS). In both cohorts, multivariable analyses showed ANLN and TLE2 expression as independent outcome predictors. Furthermore, ANLN was more highly expressed in cell lines and patients with the basal subtype, while TLE2 expression was higher in cell lines and patients with the luminal subtype.

On the other hand, this study showed that a decreased expression of lncRNA MIR31HG was found in BLCA cells and tissues, except in the basal subtype. Knockdown of MIR31HG inhibits cell proliferation, colony formation and migration in BLCA cell lines. Survival analysis showed that high expression of MIR31HG was associated with poor OS and DFS in patients with MIBC of basal subtype. Two splice variants of MIR31HG lacking exon 1 (MIR31HGΔE1) and exon 3 (MIR31HGΔE3) were identified to have specific expression patterns in different subtypes of both MIBC cohorts. MIR31HGΔE3 was highly expressed in tumors with basal subtype. After knockdown of splice variants of MIR31HG, cell proliferation and migration assays showed corresponding roles for the full-length transcript. A high expression of MIR31HGΔE1 and MIR31HGΔE3 was associated with worse OS and DFS in the MIBC cohort.

In conclusion, this thesis identified three RNA transcripts ANLN, TLE2, MIR31HG - and its splicing variants - expressed in cells and tissues of MIBC with subtype specificity. Evidences from different MIBC cohorts supported the prognostic potential of ANLN, TLE2 and MIR31HG as well as its splice variants for patients with MIBC. Furthermore, MIR31HG and its splice variants could regulate proliferation and migration of corresponding BLCA cells. This thesis provides new biomarkers into studies for MIBC, and will facilitate to further optimize personalized therapy for these patients.