ABSTRACT

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic disorders with a risk of transformation into acute myeloid leukemia (AML). The International Prognostic Scoring Systems integrate clinical data and cytogenetics to determine the risk of AML transformation for individual patients. Precise risk assessment is crucial for treatment decision-making.

The aim of this thesis was to identify molecular markers for the early detection of disease progression in MDS patients. Using cDNA microarrays and next-generation sequencing, we targeted long noncoding RNAs (lncRNAs) and recurrently mutated genes in bone marrow cells. In addition, we focused on the identification of pathways related to the progression of MDS and understanding how the identified biomarkers participate.

In the transcriptome study, we identify 4 candidate lncRNAs that may serve as prognostic biomarkers of the adverse course of MDS: *H19*, *WT1-AS*, *TCL6*, and *LEF1-AS*. Using various statistical approaches, we determined the level of *H19* to be a strong independent prognostic marker. Furthermore, our data showed that disruption of transcriptional coregulation of the imprinting locus *H19/IGF2* and miR-675, which directly regulates *H19* and plays a role in tumorigenesis, accompanies disease progression.

In the genomic study aimed at lower-risk MDS patients, we identified mutated *RUNX1*, *SETBP1*, *STAG2*, *TP53*, and *U2AF1* genes to have a significant effect on progression-free survival by univariate analysis. In multivariate analysis, the mutated *RUNX1* gene was determined to be the strongest predictive marker of rapid progression. We showed how the implementation of the *RUNX1* mutational status into the Revised International Prognostic Scoring System may improve patient stratification. We described an association of *RUNX1* with the DNA damage response (DDR) and cellular senescence and that its loss-of-function mutations lead to escape from these cellular protection barriers and to progression. The deregulation of DDR and cellular senescence in *RUNX1*-mutated patients was verified at the functional level by the detection of γH2AX protein expression and senescence-associated β-galactosidase activity.

In conclusion, we identified mutated and deregulated genes that can be used as predictive markers of rapid progression in MDS. Our results may contribute to the early detection of patients at risk of disease progression and the initiation of appropriate treatment. Simultaneously, we described cellular processes in which the biomarkers are involved and suggested their role in disease pathogenesis.