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DNA Methylation Signatures in Precursor Lymphoid Neoplasms

-with focus on clinical implications and the biology behind.

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i Betula, byggnad 6M, Norrlands universitetssjukhus, fredagen den 15 mars, kl. 09:00.
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Title
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Abstract
Precursor lymphoid neoplasms, namely acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL), are characterized by an aggressive proliferation of malignant progenitor B- or T-cells. To improve risk classification at diagnosis, better prognostic and treatment stratifying biomarkers are needed. Altered DNA methylation pattern is a hallmark of neoplastic transformation, and has been employed as a molecular prognostic and predictive marker in various cancers, including hematological malignancies. Our research group previously identified a CpG island methylator phenotype (CIMP) panel that classified pediatric T-ALL patients into prognostic subgroups.

The aim of this thesis was to evaluate distinct DNA methylation signatures in precursor lymphoid neoplasms, and to validate the prognostic value of CIMP classification in separate patient cohorts. Additionally, the biological mechanisms underlying the distinct CIMP methylation signatures in these malignancies were investigated.

The prognostic relevance of CIMP classification was validated in an independent Nordic cohort of pediatric T-ALL patients. Combination of CIMP status with minimal residual disease (MRD) status, could further dissect the high-risk MRD positive T-ALL patients into two CIMP subgroups with significantly distinct outcomes. Furthermore, CIMP classification at diagnosis was shown to predict overall survival in relapsed BCP-ALL patients. CIMP methylation signatures were also identified in T-LBL patients, indicating a broader relevance of CIMP based classification in lymphoid malignancies. Investigating the biology behind CIMP methylation signatures showed the association of CIMP status with the proliferative history of the leukemic cells. A differential transcriptomic analysis revealed a correlation of CIMP subgroups with known T-ALL drivers, as well as with novel genes in T-ALL biology. Finally, we identified distinct DNA methylation patterns and genetic aberrations in T-ALL and T-LBL that might contribute to the different clinical presentation of these two diseases. In conclusion, we validated the prognostic significance of CIMP methylation signature in precursor lymphoid malignancies and identified transcriptomic profiles that associated with the subgroups. DNA methylation is a strong candidate for further risk classification in lymphoid neoplasms, and our findings can contribute to the identification of new potential targets for treatment.

Keywords
Acute Lymphoblastic Leukemia, Lymphoma, T-ALL, BCP-ALL, T-LBL, DNA methylation, CIMP, Prognosis, TAL1, HOX.

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