DNA methylation as a prognostic marker in acute lymphoblastic leukemia

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt förvar i Sal B, 9tr., Tandläkarhögskolan, Norrlands Universitetssjukhus. fredagen den 25 november, kl. 09:00.
Avhandlingen kommer att förvaras på engelska.

Fakultetsopponent: Docent, Kim Vettenranta, Hospital for Children and Adolescents, Helsinki, Finland.
Abstract: Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy. Most ALL cases originate from immature B-cells (BCP-ALL) and are characterized by reoccurring structural genetic aberrations. These aberrations hold information of the pathogenesis of ALL and are used for risk stratification in treatment. Despite increased knowledge of genetic aberrations in pediatric T-cell ALL (T-ALL), no reliable molecular genetic markers exist for identifying patients with higher risk of relapse. The lack of molecular prognostic markers is also evident in patients with relapsed ALL. During the last decades, aberrant epigenetic mechanisms including DNA methylation have emerged as important components in cancer development. Telomere maintenance is another important factor in malignant transformation and is crucial for long-term cell survival. Like DNA methylation, telomere length maintenance has also been implicated to reflect outcomes for patients with leukemia.

In this thesis, the prognostic relevance of DNA methylation and telomere length was investigated in pediatric ALL at diagnosis and relapse. The telomere length (TL) was significantly shorter in diagnostic ALL samples compared to normal bone marrow samples collected at cessation of therapy, reflecting the proliferation associated telomere length shortening. Prognostic relevance of TL was shown in low-risk BCP-ALL patients were longer telomeres at diagnosis were associated with higher risk of relapse. Genome-wide methylation characterization by arrays in diagnostic T-ALL samples identified two distinct methylation subgroups denoted CIMP+ (CpG Island Methylator Phenotype high) and CIMP- (low). CIMP- T-ALL patients had significantly worse outcome compared to CIMP+ cases. These results were confirmed in a Nordic cohort treated according to the current NOPHO-ALL2008 protocol. By combining minimal residual disease (MRD) status at treatment day 29 and CIMP status at diagnosis we could further separate T-ALL patients into risk groups. Likewise, the CIMP profile could separate relapsed BCP-ALL patients into risk groups, where the CIMP- cases had a significantly worse outcome compared to CIMP+ cases. From these data we conclude that DNA methylation subgrouping is a promising prognostic marker in T-ALL, as well as in relapsed BCP-ALL two groups where reliable prognostic markers are currently missing. By elucidating the biology behind the different CIMP profiles, the pathogenesis of ALL will be further understood and may contribute with new treatment strategies.