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EPIGENETIC AND TELOMERE ANALYSES IN DIFFUSE LARGE B-CELL LYMPHOMA AND TELOMERE BIOLOGY DISORDERS

Olivia Carlund

Akademisk avhandling

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Fakultetsopponent: Professor, Colum Walsh,

Institutionen för biomedicinska och kliniska vetenskaper, Linköpings universitet, Sverige.

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Author
Olivia Carlund

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Abstract
Telomere biology and epigenetics are critical in cellular aging and malignant transformation. Telomeres at the end of chromosomes shorten during cellular replication which eventually induces cellular senescence. The telomeres can partially be restored by the telomerase enzyme, expressed by a few normal and most malignant cells. Telomere biology disorders (TBD) are caused by mutations (variants) in telomere-associated genes. However, several genetic variants in suspected TBD are classified as variants of unknown significance (VUS). VUS presents a dilemma since they are not actionable in clinical practice. Epigenetics involves chemical modifications of DNA, RNA, and proteins that alter the cellular phenotype without changing the DNA sequence. DNA methylation (DNAm) alterations are crucial in disease progression and malignant transformation. The overall aim of this thesis was to investigate alterations in telomere biology and epigenetics to improve the understanding of underlying factors contributing to TBD and large B-cell lymphoma.

We identified altered DNAm profiles in blood cells from TBD patients (n=35) compared to healthy controls (n=20). These changes were most prominent in symptomatic patients, regardless of telomere length, suggesting that DNAm alterations in blood cells could be involved in disease progression. Furthermore, seven genes of interest were identified. *PRDM8*, *SMC4, VARS*, and *WNT6* have previously been linked to TBD or telomere length. *MAS1L*, *NAV2*, and *TM4FS1* were novel in TBD. The functional relevance of these genes in terms of gene expression, telomere maintenance, and disease progression in TBD requires further evaluation.

We identified extensive DNAm alterations in tumor samples from patients with diffuse large B-cell lymphoma not otherwise specified (DLBCL, n=66), high-grade B-cell lymphoma (n=7), primary CNS lymphoma (n=8), and transformation from an indolent B-cell lymphoma to DLBCL (n=12). These entities had extensive semimethylation that was absent in normal cells and other B-cell neoplasms. Short telomere length and a high percentage of global hypomethylation were both independent prognostic factors for disease-specific survival in our cohort. The subpopulation with the highest percentage of global hypomethylation also had a high percentage of hypermethylated CGIs. These methylation alterations could potentially be targets for epigenetic therapy, including hypomethylating agents.

Telomerase activity (TA) was measured in activated T-cells from controls (n=100) and TBD patients (n=6). The genetic variants were classified as pathogenic (*TERT*, n=1) or likely-pathogenic (*TERT*, n=4 and *TERC*, n=1) following consensus guidelines from the American College of Medical Genetics and Genomics. TA was reduced in activated T-cells from TBD patients. Pathogenicity was supported for variants with a TA of more than 3 SD below the mean TA of controls (*TERT*, n=3). Functional analysis of TA in patient-derived cells could support pathogenicity evaluation and reduce the number of reported VUS in TBD.

Keywords
Telomere biology, epigenetics, DNA methylation, epigenetic age, telomere length, telomerase activity, telomere biology disorders, diffuse large B-cell lymphoma

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