Göteborg, 2021

A search for prognostic biomarkers in diffuse large B-cell lymphoma with proteomics and immunohistochemistry

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Karl Isaksson, Medicinaregatan 16, Göteborg, fredagen den 10 december, klockan 9.00

av **Susanne Bram Ednersson**

Fakultetsopponent:
Mats Ehinger, Universitetslektor
Lunds Universitet, Lund

Avhandlingen baseras på följande delarbeten

I. Bram Ednersson S, Stenson M, Stern M, Enblad G, Fagman H, Nilsson-Ehle H, Hasselblom S, Andersson P-O. Expression of ribosomal and actin network proteins and immunochemotherapy resistance in diffuse large B cell lymphoma patients. British Journal of Haematology 2018; 181: 770-781.

II. Bram Ednersson S, Stern M, Fagman H, Nilsson-Ehle H, Hasselblom S, Andersson P-O. TBLR1 and CREBBP as potential novel prognostic immunohistochemical biomarkers in diffuse large B-cell lymphoma. Leukemia & Lymphoma 2020; 61: 2595-2604.

III. Bram Ednersson S, Stern M, Fagman H, Nilsson-Ehle H, Hasselblom S, Thorsell A, Andersson P-O. Proteomic analysis in diffuse large B-cell lymphoma identifies dysregulated tumor microenvironment proteins in non-GCB/ABC subtype patients. Leukemia & Lymphoma 2021; 62: 2360-2373.

IV. Bram Ednersson S, Stern M, Fagman H, Nilsson-Ehle H, Hasselblom S, Andersson P-O. Increased expression of the interferon-inducible PYHIN proteins IFI16 and MNDA show prognostic impact in diffuse large B-cell lymphoma. Manuscript

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A search for prognostic biomarkers in diffuse large B-cell lymphoma with proteomics and immunohistochemistry

Susanne Bram Ednersson

Avdelningen för laboratoriemedicin, Institutionen för biomedicin, Sahlgrenska akademin, Göteborgs universitet, Sverige, 2021.

Abstract

Diffuse large B-cell lymphoma (DLBCL), the most common lymphoma in the Western world, can by gene expression profiling or immunohistochemistry (IHC), be divided into two subgroups according to its "cell-of-origin". The subgroup ABC (or non-GCB) with similarities to active post-germinal centre B-cells, is associated with worse outcome. In addition, patients with primary refractory disease or early relapse have a very dismal prognosis. The aim of this thesis has been to identify novel prognostic biomarkers in a large retrospective DLBCL patient cohort by mass-spectrometry (MS)-based proteomics and IHC. Quantitative MS-based proteomics (QMS) revealed several differentially expressed proteins between refractory/relapsed patients (REF/REL) and patients with progression-free survival ≥5 years (CURED). Many ribosomal proteins were up-regulated in REF/REL patients while numerous proteins associated with the actin cytoskeleton were up-regulated in CURED patients. By using QMS we also found several up-regulated proteins in non-GCB DLBCL related to the tumour microenvironment, including interferon (IFN)-stimulated proteins. By using IHC we found a prognostic association for two proteins (CREBBP and TBLR1) that are frequently mutated in DLBCL, and for IFI16 and MNDA, both belonging to the pyrin and hematopoietic IFN-inducible nuclear (PYHIN) family. In conclusion, we have found increased expression of several proteins or groups of proteins not previously described in DLBCL and with potential prognostic impact. Further functional studies are warranted to elucidate their role in immunochemotherapy resistance.

Keywords: Diffuse large B-cell lymphoma, cell-of-origin, proteomics, immunohistochemistry, ribosomal, PYHIN

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