Diffuse large B-cell lymphoma – proteomic and metabolomic studies on prognosis and treatment failure

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Patologens föreläsningssal, Ehrenströmsgatan 1, den 23 november 2018, klockan 09.00

av **Martin Stenson**

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Avhandlingen baseras på följande delarbeten

I.   Rüetschi U*, **Stenson M***, Hasselblom S, Nilsson-Ehle H, Hansson U, Fagman H, Andersson P-O. SILAC-Based Quantitative Proteomic Analysis of Diffuse Large B-Cell Lymphoma Patients. Int J Proteomics vol. 2015: Article ID 841769, 12 pages. *These authors contributed equally.*

II. **Stenson M**, Pedersen A, Hasselblom S, Nilsson-Ehle H, Karlsson G, Pinto R, Andersson P-O. Serum nuclear magnetic resonance-based metabolomics and outcome in diffuse large B-cell lymphoma patients - a pilot study. Leukemia and Lymphoma 2016; 57:8, 1814-1822.

III. 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. Br J Haematol 2018; 181: 770-781. *These authors contributed equally.*

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Abstract

Background and aim: Every year almost 600 patients in Sweden are diagnosed with diffuse large B-cell lymphoma (DLBCL), the most common lymphoma, and with immunochemotherapy, approximately 60 % are cured. Yet, for patients with primary refractory disease or early relapse, the prognosis is very poor. Despite advances in molecular subclassification of DLBCL, the major tool used to risk stratify patients is the clinically based International Prognostic Index (IPI). However, there is still no available system that with precision can identify the individual patients at highest risk of treatment failure. The aim of this thesis was to search for novel prognostic and predictive biomarkers, and also investigate the mechanisms behind chemoresistance in DLBCL.

Patients and methods: In paper I and III, tumor tissue from two groups of DLBCL patients; (i) patients with primary refractory disease or early relapse (REF/REL; paper I: n=5, paper III: n=44); and (ii) long-term progression-free patients, clinically considered cured (CURED; paper I: n=5, paper III: n=53), was examined with mass spectrometry proteomic approaches to explore possible differences in global protein expression, but also with the aim to reveal new mechanisms involved in immunochemotherapy resistance. In paper II, metabolomic examination with nuclear magnetic resonance spectroscopy was performed on serum from REF/REL (n=27) and CURED (n=60) DLBCL patients, to determine if differences in clinical outcome could be correlated to diverse metabolomic profiles.

Results and Conclusions: In paper I, a large number of proteins could be identified and quantified. Overexpression of actin-related proteins was found among the CURED patients, a finding that appeared to be confirmed in paper III, where in addition a novel discovery regarding overexpression of multiple ribosomal proteins in the REF/REL group was made. The findings suggest previously undescribed mechanisms for immunochemotherapy resistance in DLBCL patients. In paper II, differences in the serum metabolome was found between the two groups, that could be separated with multivariate statistical analyses. Even though the results are encouraging they need to be confirmed in larger unselected studies, with aims of further exploring actin-related and ribosomal proteins, not only as possible prognostic/predictive biomarkers, but also regarding their functional role in treatment resistance in DLBCL.

Keywords: DLBCL, prognostics, proteomics, metabolomics