Abstract: PB3116

Title: INVESTIGATION OF THE DLBCL TUMOUR MICROENVIRONMENT USING CIBERSORT

Abstract Type: Publication Only

Topic: Lymphoma biology & translational research

Background:

Diffuse large B-cell lymphoma (DLBCL) is the most common blood cancer and demonstrates a remarkable degree of clinical and genetic heterogeneity. First line treatment of DLBCL combines rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). However, up to 50% of all patients have refractory disease or relapse, and the majority of these patients will fail to achieve remission and have a very poor prognosis. It is now understood that the tumour microenvironment (TME), comprised of the extracellular matrix, blood vessels and host immune cells, interacts with malignant B-cells and may play a role in DLBCL pathogenesis. However, the TME in DLBCL remains poorly understood.

Aims:

The aims of this study were to predict the immune cell landscape of the TME of 624 DLBCL patients using the computational algorithm CIBERSORT, and to investigate whether the presence of host immune cell subsets is associated with survival.

Methods:

CIBERSORT (https://cibersortx.stanford.edu) Digital Cytometry was performed on the DLBCL RNA-Seq dataset. The selected signature matrix, LM22, is composed of 547 genes which are distinctly expressed across 22 human leucocytes including B Cells, T Cells, plasma cells, granulocytes, natural killer cells, and dendritic cells. The presence of statistically significant differences in the proportions of immune cell infiltrates in the DLBCL tumour microenvironment was inferred using the student's t-test and the single-factor analysis of variance (ANOVA) test. Kaplan Meier survival curves were constructed correlating clinical data with overall survival of the DLBCL cohort using R software and Cox proportional-hazard models were constructed for each cell subset to investigate the association between the DLBCL RNA-Seq CIBERSORT deconvolution analysis and predicted survival times.

Results:

Results of CIBERSORT analysis predicted that resting CD4+ memory T-cells, M0/M1/M2 macrophages and follicular helper T-cells are the most prominent components in the TME, whilst neutrophils, activated mast cells, plasma cells and resting dendritic cells are rare. Natural killer cells and mast cells in the TME are predominantly inactive, whilst active dendritic cells were more common than inactive forms. Kaplan-Meier and multivariate Cox regression analyses revealed that the presence of certain immune cell subsets is associated with prognosis. Infiltrations of resting CD4+ memory T-cells ($p=0.001$), follicular helper T-cells ($p=0.032$) and M0 macrophages ($p=0.021$) are associated with increased survival whilst the presence of monocytes ($p<0.001$) is strongly associated with a poor prognosis.

Summary/Conclusion:

Overall, this study demonstrated that host immune cells are predicted to infiltrate the TME of DLBCL, and these immune cell subsets may be important determinants of patient outcome. Further investigation and profiling of the TME immune infiltrate may inform patient prognosis and present new therapeutic targets and opportunities.

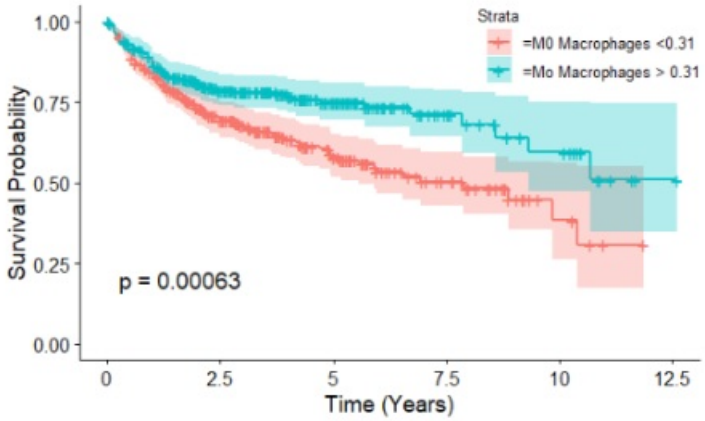

Image 1:

Kaplan-Meier plots of the M0 macrophages, one of the immune cell subsets which demonstrated significance in univariate Cox regression analysis, stratified by the median value. + symbols present along each curve represent censored data. Increased proportions of naïve M0 macrophages were strongly associated with increased survival across the patient cohort ($p < 0.001$).

Keywords: Microenvironment, RNA-seq, Diffuse large B cell lymphoma, Prediction