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Project Title:

The immunomodulatory effects of the NR4A1/p53 axis in diffuse large B cell lymphoma

–a fascinating project of the LYMPHO-CHECK initiative in the field of bioinformatics

Background:

Diffuse large B cell lymphoma (DLBCL) is the most common lymphoid malignancy in the western world. While immune checkpoint blockade therapy is in clinical practice for a number of cancer types, the response rates for B cell lymphomas remain disappointingly low. Importantly, immune evasive mechanisms are still poorly investigated in B cell lymphomas, which has impeded the progress in developing new therapeutic approaches targeting the lymphoma immune landscape. This bioinformatics project aims to address this gap by investigating the immunomodulatory effects of the NR4A1/p53 axis, two pivotal transcription factors and tumour suppressors.

Hypothesis and Objectives:

Our preliminary data strongly suggests that NR4A1 and p53 build a functional axis to orchestrate immune evasive mechanisms in DLBCL. We therefore hypothesize that the NR4A1/p53 status results in distinct expression patterns of immunomodulatory factors (such as coinhibitory immune checkpoint receptors/ligands, MHC and cytokines), which in turn influences the anti-tumour response. Furthermore, we anticipate that the NR4A1/p53 status holds significant clinical relevance in human DLBCL. This bioinformatics project is part of a consortium initiative (LYMPHO-CHECK) with objectives that include the investigation of mouse models with Nr4a1 and/or p53 knockout and the exploration of treatment options. Additionally, the aim is to translate findings of the Nr4a1/p53 axis in mice into a clinical setting using the GRAZ lymphoma cohort (one of the largest clinically annotated cohorts in the world).

Methodology:

The PhD student will focus on the *in-silico* part of the consortium initiative by leveraging bioinformatics methods, data analysis and mining techniques. The analysis of transcriptomics data (qPRO-seq, (single-cell) RNA-seq) will serve as the foundation for investigating the expression patterns of immunomodulatory factors, anti-tumour response and tumour microenviroment. To explore the clinical relevance of the NR4A1/p53 axis and inter-patient heterogeneity, a comprehensively annotated DLBCL dataset will be processed and analyzed. This dataset includes multiple read-outs such as the NR4A1/p53 status, mutations, expression data of immunomodulatory factors, composition of tumour-infiltrating immune cells (based on imaging mass cytometry), *ex vivo* response rates and clinical parameters.

References:

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