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B Cell Differentiation in the Germinal Centre Reaction

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The differentiation of B cells during germinal centre (GC) reactions is a highly complex and dynamic process characterised by continuous transitions between two transcriptional poles of functionally distinct dark zone (DZ) and light zone (LZ) populations, eventually resulting in the formation of long-lived plasma (PC) and memory B cells (MBC) that produce immunoglobulins of higher affinity. Processes such as clonal expansion and the acquisition of somatic mutations within the B cell receptor V genes, both occurring in DZ B cells, as well as affinity-based selection of LZ B cells profoundly impact the structure of the resulting MBC and PC clones.

Ongoing DNA damage during somatic hypermutation and class switching but also the highly proliferative capacity of DZ cells, mechanisms involved in normal B cell differentiation, form the basis for possible malignant transformations and tumorigenesis, for example through off-target mutations and failure of selection mechanisms.

The heterogeneity of GC-derived lymphomas is reflected by the complex dynamics of normal GC B cells, including a switch from highly proliferative to quiescent cells, interaction with a complex environment and distinct fate decisions. Consequently, understanding the mechanisms of normal B cell differentiation might be beneficial for examining aberrations of lymphoma cells compared to their non-malignant counterpart.

The mechanisms implicated in the differentiation of human tonsillar GC B cells and their heterogeneity was examined by single cell RNA-, V(D)J- and feature barcode sequencing.

Several DZ and LZ, as well as intermediated stages of GC B cells were identified by transcriptome-based dimensional reduction and clustering. In addition to precursors destined to eventually differentiate into PCs or MBCs, respectively, as well as positively selected cells designated to remain in the GC reaction, various populations were identified that presumably represent different stages of affinity-based selection. Furthermore, the heterogeneity of the CCR6-positive population, which was previously described as exclusively comprising MBC precursors, was resolved at a higher resolution.

Based on the integrated transcriptome and V gene data, it was further demonstrated that GC B cells indeed fulfil the requirements for the event of isotype class switching and that class switch recombination occurs frequently during the clonal evolution of GC B cells.