The T-cell-receptor repertoire of splenic germinal centers and its distribution within and between lymphoid organs

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Abstract

The GC reaction depends on T follicular helper (Tfh) cells and there are indications that the T-cell-receptor repertoire (TCRR) within GCs is important for the generation of broadly neutralizing antibodies. However, data on the TCRR of single GCs are rare. To address this question we induced an immune response by injecting sheep red blood cells and 7 days later we isolated GCs from splenic cryo-sections by laser-microdissection and determined the number of T-cell clonotypes (GC Tfh clonotypes, GC-Tfh) by next generation sequencing of the CDR3β region of the T cell receptor. In addition, we determined the number of those GC-Tfh within i) the neighboring B and T cell zone, ii) a distant GC and iii) the mesenteric lymph node.

At day 7 post immunization each GC harbored 7552±1462 (n=6) different GC-Tfh of which 15.8±3.0% were found also outside the GC. The number of different GC-Tfh was comparable in the adjacent B cell zone (513±74), T cell zone (398±153) and even in the distant GC (463± 68), where they account for 6.5±2.0% of the GC-Tfh. Since the analyzed GCs are far apart, migration within the tissue from one GC to the other GC seems rather unlikely. Alternatively, GC Tfh clonotypes might leave the spleen into the blood and return from there into the spleen and subsequently into the distant GC. Support for such a scenario comes from the observation that GC-Tfh were also found within the mesenteric lymph node (424±92; n=6).

Taken together, our data show that a GC harbors several thousand different Tfh clonotypes which are able to leave the GC migrating both into various splenic compartments and even into the mesenteric lymph node. Our non-invasive approach will be used to further elucidate the biological role of the T cell receptor repertoire of GCs.