Computational analysis of human heavy chain CDR3 repertoires

The paradox of tyrosine rich antibodies in memory B cell repertoires

Simon Schäfer[a,b], Thomas Winkler[a] and Heinrich Sticht[b]

[a]Chair of Genetics and [b]Division of Bioinformatics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

Next generation sequencing analysis of distinctive B cell subsets from leukapheresis products of hematopoietic stem cells from healthy donors [1] proved to be a powerful tool to characterize the human antibody repertoire. The antibodies produced by human naïve and memory B cells show significant differences in their heavy chain CDR3 repertoires. We prove that human heavy chain CDR3 loops are shorter in their memory repertoire compared to the naïve repertoire of the same donor and show a shift in the usage of an important J gene responsible for the creation of long CDR3 (J6) [2].

In addition, the quantification of specific amino acid motifs observed among all healthy donors hint that positive and negative selection shape the antibody memory CDR3 repertoire as opposing principles very specifically. These effects are highlighted by the observation of the paradox role of tyrosine repeats introduced by J gene 6. The usage of J6 is decreased in memory repertoire of healthy donors compared to the naïve repertoire of the same donor.

For the CDR regions Tyr is described by previous studies to be beneficial for antigen recognition and is expected to be positively selected [3]. In contrast, we show the decrease of Tyr motifs and Tyr rich J genes (J6) in all analyzed memory repertoires. Previous and current studies describe the prevalence of antibodies containing J6 in patients with autoimmune disease and the usage of J6 in antibodies against neo antigens in cancer patients [4,5]. We therefore suggest that tyrosine rich antibodies with long CDR3 are negatively selected and are an important future research subject in understanding autoimmunity.

[1] Tittlbach, Hannes; Schneider, Andrea; Strobel, Julian; Zimmermann, Robert; Maas, Stefanie; Gebhardt, Bernd et al. (2017): *Journal of translational medicine* 15 (1), S. 228. DOI: 10.1186/s12967-017-1330-5.

[2] Briney, Bryan S.; Willis, Jordan R.; Crowe, James E. (2012): *PloS one* 7 (5), e36750. DOI: 10.1371/journal.pone.0036750.

[3] Birtalan, Sara; Zhang, Yingnan; Fellouse, Frederic A.; Shao, Lihua; Schaefer, Gabriele; Sidhu, Sachdev S. (2008): *Journal of Molecular Biology* 377 (5), S. 1518–1528. DOI: 10.1016/j.jmb.2008.01.093.

[4] Foster, Mary H.; Buckley, Elizabeth S.; Chen, Benny J.; Hwang, Kwan-Ki; Clark, Amy G. (2016): *Molecular immunology* 76, S. 123–133. DOI: 10.1016/j.molimm.2016.07.004.

[5] Liu, Song; Zhu, Ying; Lin, Lie-Wen; Ding, Shun-Kai; Lin, Xiao-Cong; Zhong, Ke-Li et al. (2018): *Oncology letters* 16 (1), S. 239–246. DOI: 10.3892/ol.2018.8677.

Keywords: Next generation sequencing, CDR3, J6, Tyrosine