How to predict a winning change

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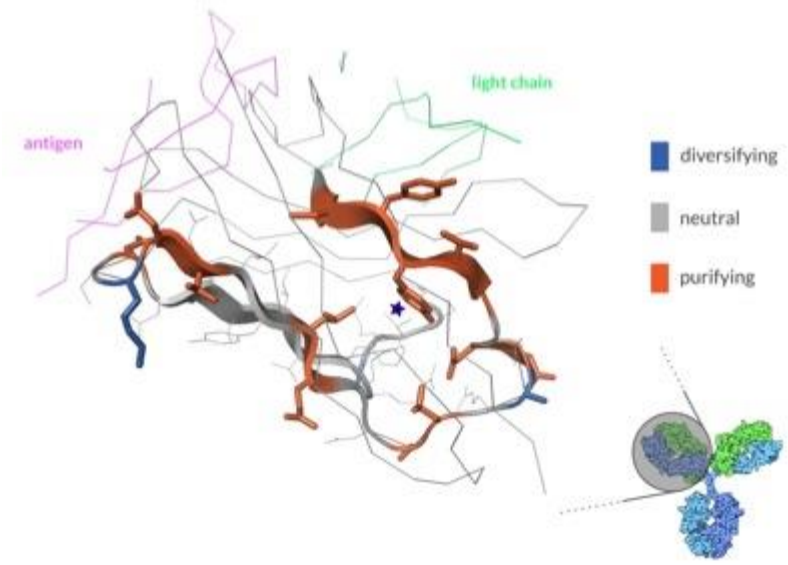

Schematics representing the distribution of mutations depending on the levels of surface exposure.

Image provided by Dr. Friedrick Matsen.

Most of us know that antibodies are key components of our immune system that protect us from infections by neutralizing pathogens as well as by activating other components of the immune system. Structurally, antibodies are Y-shaped molecules composed of two heavy and two light chains, each of which contains constant and variable regions; the latter responsible of antigen recognition. Each of us is capable of generating billions of antibodies with different specificities. How is such a wide pool generated?

First, genes encoding for antibodies contain several sequences encoding for the V, D and J components of antibody sequences. When a pluripotent cell differentiates into a B cell, recombination between different sequences occurs and originates an antibody with a V, a D and a J fragment. Recombination of different segments explains part of antibody diversity. Moreover, the antibody recognition of its cognate antigen initiates a process called somatic hypermutation, consisting in point mutations that can be selected for (positive selection) if they lead to an improved binding avidity and specificity. This process is controlled through Darwinian mutation and selection mechanisms. Understanding the forces that shape this process would have enormous implications for the design of antibody-based vaccines and treatments.

Previous studies addressed the effect of the identity of the surrounding nucleotides on a given nucleotide's mutation rate, but other aspects of the process, such as how the substitution differs

between different segments, have not been evaluated. Given the importance of the topic, Dr. Frederick Matsen and the Computational Biology group at Fred Hutch investigated this matter and reported the results of their study in a recent publication on the journal Philosophical Transactions of the Royal Society of London. Although they found a complex pattern of substitution, this pattern was surprisingly consistent among individuals.

Some somatic mutations cause the production of a non-functional antibody, for example by generating a stop codon or by an out-of-frame rearrangement. However, each B cell carries two copies of the antibody locus, and if a non-functional mutation occurs, the second locus undergoes rearrangement. Dr. Matsen and collaborators decided to use these out-of-frame sequences as a control for motif-driven mutations to infer per-residue selection pressures using high-throughput sequence data obtained from three individuals. In particular, the positive pressure was shown to be higher around the boundary between the V gene and CDR3, or third complementarity determining region, which is the region of the antibody recognizing the antigen. Furthermore, selective pressure correlated with the levels of surface exposure with highly conserved residues internally and positively selected more exposed.

"I certainly hope that this work could be useful for antibody design, although we need to repeat the analysis with many more samples. Vaccine design is yet one more step away—even if you know exactly what antibody you want, it's not at all easy to figure out what antigen to give to stimulate the development of that antibody. And we really need to do analysis with individuals of different genetic backgrounds." said Dr. Matsen. Although much research is still needed, the study published by Fred Hutch scientists advanced the complex field of B cell repertoire modeling.

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McCoy CO, Bedford T, Minin VN, Bradley P, Robins H, Matsen FA. 2015. Quantifying evolutionary constraints on B-cell affinity maturation. Philos Trans R Soc Lond B Biol Sci, 370