456c An Informatics Analysis of the in Vivo Affinity Maturation Process -- Learning from Nature's Evolution of Protein-Protein Interfaces

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The mammalian adaptive immune system uses a gene fragment mixing process (VDJ recombination) to provide a large repertoire of naive antibody precursors. When activated, those that are capable of recognizing a specific new antigen undergo a series of single point mutations (somatic hypermutations) eventually resulting in high-affinity soluble antibodies. It is possible to derive the sequence of the germline precursor from a given mature sequence. With this information, we have analyzed the location and type of mutations that occur for thousands of antibodies during the affinity maturation process. Coupled with structural data for a smaller number of antibody-antigen complexes, it is possible to gain considerable insight into how protein-protein interactions evolve in vivo. One striking feature is a very high abundance of tyrosine residues in certain regions of the germline precursor. Many of these residues mutate to residues of other character, but mature antibody-antigen interfaces are still tyrosine-dominated. Nature "stacks the decks" with a certain residues types, presumably to facilitate generic antigen recognition. These and other insights and their practical application to design of protein-protein interactions will be described.