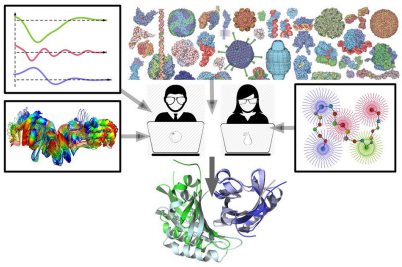

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Coupling X-ray crystallography and molecular modeling for the structural investigation of flexible antibody paratopes: A case study

By providing a precise snapshot of the structure of the interface between two protein partners, X-ray crystallography helps identifying point mutations that are likely to strengthen the interaction. However, this technique provides very little information about conformational flexibility, in particular in protein loop fragments. In cases where plasticity may be critical for protein function, the flexible fragments must be modeled using alternative methods that complete the partial view offered by X-ray crystallography. As part of a project to produce a strong anti-FGFR4 antibody, several crystal structures were obtained for the antibody, free or bound to FGFR4, after different steps of humanization or maturation. While the structures successfully identified point mutations to improve the affinity between the antibody and its antigen, they also revealed a conformational change happening in the CDR-H3 loop upon antigen binding that was not exploited. Using in silico modeling techniques, structural basis for the flexibility of this loop was clarified. Conformational stability in the absence of the antigen or of crystalline contacts was investigated. The results confirm that the loop presents two stable conformations, one of which is stabilized by the antigen, and by conformational changes in the loop surroundings.

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