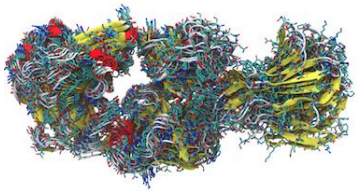

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Assessing VHHs Structural Dynamics and its Influence on their Binding Affinity to Antigens

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Abstract:

In addition to conventional full-length antibodies (Abs), where a heterodimer is formed between the variable domain of light and heavy chains, the camelid species can also produce a class of antibodies that only comprises the heavy-chains variable domain referred to as VHH or nanobodies (Nbs). Despite the absence of the light variable domain the VHHs are functionally equivalent to conventional Abs achieving nanomolar binding affinities and high specificities. Besides that, their reduced size and high solubility make them a promising tool for therapeutic, diagnostic and molecular research applications. Several VHHs are now being studied for use in various biomedical areas, including oncology, neurodegenerative diseases and viral infections, such as neutralizers for HIV-1. The recognition of antigen by VHH is achieve through three loops (H1, H2 and H3) which present a remarkable structural diversity. The affinity and diversity of recognition is given by the variation in sequence and extent of these loops. VHH dynamics constitute a still not thoroughly exploited area, however, it's invaluable its importance to clarify important structural features aiming at the identification and design of novel binders with improved characteristics. The present study aims to correlate binding affinities and structural properties, by means of elucidating the structural dynamics of recognition elements of the VHH. For this reason, a library containing 60 crystallographic structures of VHH available in the PDB was built and 100 ns Molecular Dynamics simulations have been carried out to each VHH in solution using the software suite Gromacs 4.6.7 and GROMOS53A6 force field. To map the contribution of each residue to VHHs stabilities alanine scanning using Rosetta v. 3.10 has been used. Moreover, metadynamics simulations were employed to calculate the binding free energy of each VHH to its antigen. Taken together, those data will deepen our comprehension on VHHs structural diversity of loops and its relation to binding affinities providing a consistent framework to rationalize the design of stable VHHs.

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