Structural characterization of the intrinsically disordered N-WASP domain V and its recognition by actin

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Intrinsically disordered proteins (IDP) are characterized by one or several regions which lack stable secondary and tertiary structure in their unbound state [1]. They frequently play crucial roles in the regulation of many biological processes and, to exert their functions, interact with several molecular partners. Formation of IDP-protein complexes can follow two limiting mechanisms, not necessarily exclusive [2]: the "induced fit" pathway, in which the disordered region binds to the protein partner and folded into an ordered structure on its surface, and the "conformational selection", in which the folded structure preexists in the IDP unbound state and is recognized by the protein partner. To gain insight into the structure and recognition mechanism of IDP-protein complexes, it is important to preliminary explore the conformational ensemble of IDP.

NMR experiments (CS and RDC) provide local information about their propensity to form transient secondary structures. On the other hand, small-angle X-ray scattering (SAXS) can deliver global information about their average size and shape. But, in order to infer a detailed conformational ensemble from NMR and SAXS data, it is most often necessary to use complementary *in silico* approaches to generate atomic scale structures, such as statistical coil generator or molecular dynamics (MD) simulations [3-7].

In the present study, we combined NMR, SAXS and *in silico* techniques to characterize the conformational ensemble of the fully disordered verprolin homology domain (V) of the Neural Wiskott-Aldrich Syndrome Protein (N-WASP), a pivotal protein in the regulation of the actin cytoskeleton dynamics [8]. Then, we used representative structure of the most populated clusters of its conformational ensemble to model the structure of N-WASP domain V in complex with actin.

References

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