Conference

Disclosing the Major Structural Determinants Essential for Proneurotrophins Biological Functions.

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Nerve Growth Factor, Brain-Derived Neurotrophic Factor, Neurotrophin 3 and Neurotrophin 4 play a range of crucial functions in the developing and adult peripheral and central nervous systems. Initially synthesized as precursors, named proneurotrophins (proNTs), that are cleaved to release C-terminal mature forms, they act through two types of receptors, the specific Trk receptors and the pan-neurotrophin receptor p75NTR, to promote differentiation, neuronal survival, synaptogenesis and modulating synaptic plasticity. Recently, all the proNTs but proNT4 have been demonstrated to be not just inactive precursors, but biologically active signaling ligands that mediate opposing actions in fundamental aspects of the nervous system with respect to the mature counterparts through dual receptor complexes formation, involving a member of the VPS10 family and p75NTR. Despite the functional relevance, the molecular determinants underpinning the interactions between the pro-domains and their receptors are still elusive probably due to their intrinsically disordered nature. Here we present an evolutionary approach coupled to an experimental study aiming to uncover the structural and dynamical basis of the biological functions displayed by proNGF, proBDNF and proNT3 but missing in proNT4. A bioinformatic analysis allowed elucidating the functional adaptability of the proNTs family in vertebrates, identifying conserved key structural features. The combined biochemical and SAXS experiments shed lights on the structure and dynamic behavior of the human proNTs in solution, giving insights on the evolutionary conserved structural motifs, essential for the multifaceted roles of proNTs in physiological as well as in pathological contexts.[1]

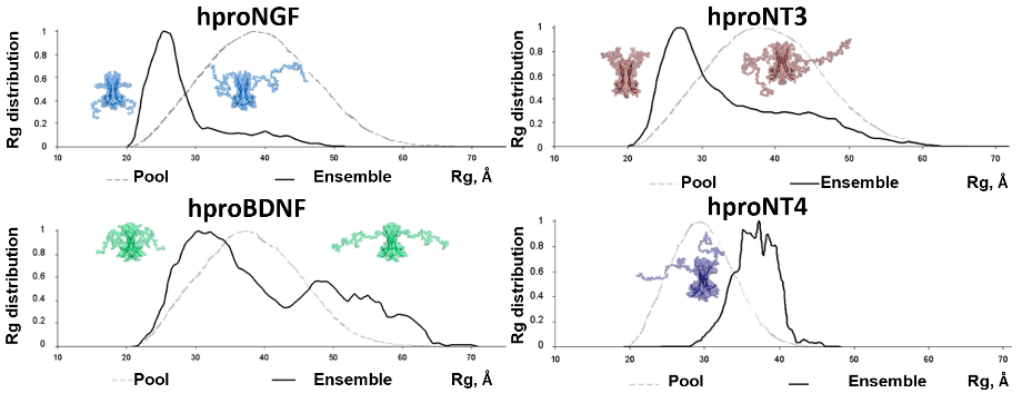

Fig. 1 The distributions of the radius of gyration (R_g) obtained by the Ensemble Optimization Methos for hproNGF, hproBDNF, hproNT3 and hproNT4. Initial random pools of the models (grey dot lines) and for the selected ensembles (black solid lines) are shown as well as the representative compact (on the left) and extended (on the right) conformations (semitransparent surfaces).

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References

1 S. Covaceuszach, L. Peche, P. Konarev, D. Lamba, A combined evolutionary and structural approach to disclose the primary structural determinants essential for proneurotrophins biological functions, Computational and Structural Biotechnology Journal 19 (2021) 2891–2904. doi:https://doi.org/10.1016/j.csbj.2021.05.007.