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Unravelling the Primary Structural Determinants Essential for Proneurotrophins Biological Functions by a Combined Evolutionary and Structural Approach

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Nerve Growth Factor, Brain-Derived Neurotrophic Factor, Neurotrophin 3 and Neurotrophin 4 are known to play a range of crucial functions in the developing and adult peripheral and central nervous systems. Initially synthesized as precursors 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 initiate survival and differentiated responses. Recently all the proneurotrophins but proNT4 have been demonstrated to be not just inactive precursors, but signalling ligands that mediate opposing actions in fundamental aspects of the nervous system with respect to the mature counterparts through dual receptor complexes formation with sortilin, 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 function 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 behaviour 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).

1) Comput. Struct. Biotechnol. J. (2021) 19:2891-2904. doi: 10.1016/j.csbj.2021.05.007.

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