Sumoylation of Neurofibromin and its SecPH domain plays a role in their functions and implies unexpected structural requirements

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Neurofibromin (Nf1) is a large, multi-domain protein encoded by the tumor-suppressor gene NF1. NF1 is mutated in a frequent genetic disease, Neurofibromatosis type I, which is mainly characterized by the development of tumors of the nervous system and it is also mutated in various types of cancers. The best described function of Nf1 is its Ras-GTPase activity, carried out by its central GRD (GAP related domain), which negatively regulates the Ras-MAPK pathway. But Nf1 exerts other functions in the regulation of cAMP production and actin cytoskeleton dynamics. Nf1 has been identified as highly regulated by post-translational modifications (PTM), particularly by phosphorylation and ubiquitination. Data of our team previously demonstrated a partial colocalisation of Nf1 with PML (ProMyelocytic Leukemia) nuclear bodies thereby suggesting a possible Nf1 sumoylation. In this work we demonstrated that endogenous Nf1 is preferentially sumoylated by SUMO-2. We then focused on a specific Nf1 domain, SecPH, a bipartite phospholipid binding module immediatly adjacent to GRD which connects Nf1 to diverse signaling pathways by interacting with different partners. We identified a typical SecPH sumoylation pattern and a specific lysine as a major SUMO acceptor site. We demonstrated that this sumoylation is important for Nf1 function because it affects the Ras-GAP activity of the adjacent GRD and the interaction of SecPH with one of its partners, furthermore SecPH sumoylation pattern is disrupted in different pathogenic NF1 missense mutations. We further characterized SecPH major sumoylation and demonstrated that it is independant of a consensus site but requires unexpected structural elements and could be used as a readout of SecPH folding or conformation to affect its stability and functions.