

Nuclear transport is essential for eukaryotic life. It proceeds through nuclear pore complexes (NPCs), which are embedded in the nuclear envelope (NE). Most nuclear transport pathways are mediated by importin β -type transport receptors, which include nuclear export receptors (exportins), as well as importins. In nuclear export, typically, a ternary complex is formed in the nucleus, consisting of the exportin, the cargo and the molecular switch RanGTP. This complex traverses the nuclear pore and is disassembled in the cytoplasm upon hydrolysis of the Ran-bound GTP molecule and the action of additional factors. CRM1 (exportin1 in yeast) is probably the most versatile exportin as it exports a huge variety of different RNAs, RNPs and proteins. Potential cargoes of CRM1 contain a so-called "leucine-rich" nuclear export signal (NES) that confers CRM1-mediated nuclear export. How CRM1 is able to recognize this wide range of different NESs has been unknown so far. Here, we present the 2.5 Å crystal structure of a CRM1-RanGTP-cargo ternary complex [1]. CRM1 exhibits an overall toroid-like structure that engulfs the Ran molecule and binds the cargo, snurportin1 (SPN1), through its outer surface. Three parts of SPN1 contact CRM1: The N-terminal α -helix, resembling a canonical nuclear export signal (NES), the m₃G-cap binding domain and the C-terminal tail. The structure shows how CRM1 can specifically return the RNA-free form of SPN1 to the cytoplasm and suggests that RanGTP promotes cargo-binding to CRM1 solely through long-range conformational changes in the exportin. Additionally, SAXS-experiments in combination with molecular dynamic simulations were performed to shed light on the structure of apo-CRM1. Unexpectedly and in contrast to other known nuclear transport receptors, the overall superhelical conformation of CRM1 does not change significantly when Ran and cargo are released.

[1] Monecke T., Güttler T., Neumann P., Dickmanns A., Görlich D., Ficner R., *Science*, 2009, 324, 1087.

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Structure and biochemical analysis of the heparin-induced E1 dimer of the amyloid precursor protein APP.

Manuel E. Than, Sven O. Dahms, Sandra Hoefgen, Dirk Roeser. *Leibniz Institute for Age Research – Fritz Lipmann Institute (FLI), Protein Crystallography Group, Jena, Germany.*

E-mail: than@fli-leibniz.de

The amyloid precursor protein (APP) is the key player in Alzheimer's disease pathology, yet APP and its analogues are also essential for neuronal development and cell homeostasis in mammals. We have determined the crystal structure of the entire N-terminal APP-E1 domain consisting of the growth factor like and the copper binding domains at 2.7 Å resolution and show for the first time that E1 functions as a rigid functional entity. The two subdomains interact tightly in a pH dependent manner via an evolutionarily conserved interface area. Two E1-entities dimerize upon their interaction with heparin, requiring eight to twelve sugar rings to form the heparin-bridged APP-E1-dimer in an endothermic and pH dependent process that is characterized by a low micromolar dissociation constant. Limited proteolysis confirms that the heparin-bridged E1 dimers obtained in solution correspond to

a dimer contact in our crystal, enabling us to model this heparin-[APP E1]₂ complex. Correspondingly, the APP based signal transduction, cell-cell- and/or cell-ECM interaction should depend on dimerization induced by heparin, as well as on pH, arguing that APP could fulfill different functions depending on its (sub)cellular localization.

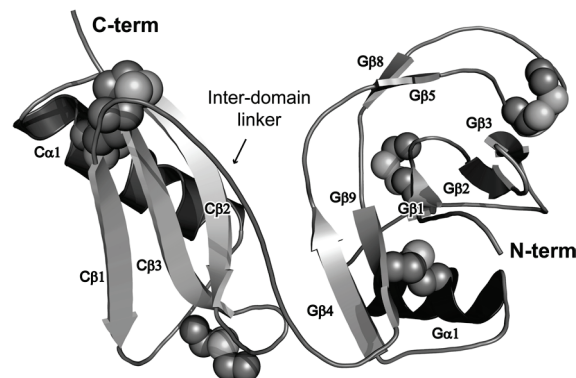


Fig. 1: Cartoon representation of the APP E1 domain, depicting the GFLD (right) and the CuBD (left). Secondary structure elements are labeled using the prefixes 'G' for the GFLD and 'C' for the CuBD.

[1] Dahms, S. O., Hoefgen, S., Roeser, D., Schlott, B., Gührs, K.-H. & Than, M. E. *Proc. Natl. Acad. Sci.* 2010, 107, 5381-5386.

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