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Towards Understanding the Structure Function Relationship in Highly Conserved Endocytic Protein Machinery: P5 Protein Complex

Vijay Kumar Srivastava*

Amity Institute of Biotechnology, Amity University, India

P5- a multi protein complex present in human, consist of five proteins viz. P100, P95, P60, P45, P25 conserved from nematodes to humans. In *C. elegans* and *Drosophila*, complex contains only P100, P95 and P60: P3 complex. P95 in Drosophila is truncated and is 406 amino acids long. Sequence analysis of the P5 components revealed that P100 contains a TBC domain which is known to be the signature domain for Rab GAPs. P95 has a vacuolar ATPase domain and hence it might be involved in pH regulation of the intracellular vesicles. P60 has a transcription factor like domain. On the other hand the two less conserved components, P45 and P25 have a RNA helicase and an intracellular protease like domain, respectively. On the basis of the domain organization in the individual components of P5 complex, several models have been proposed to describe function of P5 complex in mammalian cell. They include vesicular tethering and fusion, RNA transport, pH regulation of the intracellular vesicles, cellular signaling processes. The validities of these models are yet to be established experimentally. The molecular assembly process is essential for the function of the complex and therefore understanding its molecular basis would be the first step towards explaining structure-function relationship for this complex. Moreover, P100 harbors a TBC domain which is known to acts as GTPase activating protein (GAP) for Rab GTPases. The Rabs containing a specific GAP domain is known as TBC that catalyze the inactivation of the Rabs. The sequence and structural divergence of Rab GAPs also suggests a possible existence of other structural classes of Rab GAPs in eukaryotes that have escaped from identifcation by conventional sequence and domain analyses. Most known GAPs for Rab GTPases share a homologous catalytic domain of 200 residues, termed the TBC (Tre-2/Bub2/Cdc16) domain. The TBC domain containing protein is not identical to the GAPs which are already known for the Ras and Rho GTPases. They share similar characteristics to catalyze GTP hydrolysis by the conserve Arg residue throughout the evolution. Structural studies of yeast Gyp1p reveal a unique catalytic glutamine residue ("glutamine finger") in the TBC domain GAPs. Therefore, an atomic detail of RabGAP-mediated catalysis is of great interest, and is an important in the field of drug discovery. In all small GTPases the nucleus loving water molecule get the stability by the carboxylic group of a Gln or Asn residue that is crucial for the hydrolysis of small GTPases. The conserved glutamine residue of "switch II" provides $CONH_2$ goup in the Ras, Ran, and Rho families. In Rap, having Thr at the conserved position 61, the NH_2 group is provided by the Asn of RapGap or in a dual specificity GAPs it is given by Gln63 of Rap itself. In addition to that the catalytic Arg finger which is used by the Ras, Rho, and RabGAPs is not essential in Ran and Rap for catalysis. Thus identification of its substrate could further help us to understand its cellular role.

***Corresponding author:** Vijay Kumar Srivastava, Amity Institute of Biotechnology, Amity University, India, Tel: +91 9140434996; E-mail: vksrivastava@jpr.amity.edu

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