Homology Modeling of Human Septins

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Septins are filament forming GTPases involved in a series of essential cellular processes, such as cell division and exocytosis. The human genome indicates the presence of at least fourteen different septins, many of which have tissue-specific expression profiles. They can be divided into four groups based on the sequence similarity of the GTPase domain. Until recently, little was known about the 3D structure of septins and their associated filaments. However, a publication of the crystal structure of heterotrimeric complex of septins 2, 6 and 7 together with higher resolution structures for septin 2 dimer, opened up the possibility for bioinformatics studies of the entire family. We have generated homology models for sept1, sept4 and sept5, which belong to the same group as sept2, and subsequently characterized their structures. Considering both the well-known conserved GTPases motifs (designated G1 to G5 in the literature) as well as more recently described septin-specific motifs, our models lead us to conclude that septins 1, 4 and 5 are expected to form homodimers in solution similar to those observed experimentally for sept2. This is based on the observation of conserved interfacial residues and is consistent with experimental data from our own laboratory on sept4. Furthermore, the models are consistent with Kinoshita's proposal that septins 1, 2, 4 and 5 are substitutable within heterofilaments. A full sequence alignment of all human septins also provides clues as to why sept6 (and its group members) are less efficient in the hydrolysis of GTP, presumably due to alterations in the G3 motif. Bioinformatics analysis will be useful, together with ongoing yeast two-hybrid experiments, in defining new constructs for the crystallization of novel heterotrimeric complexes.