Modular anatomy of the Ribokinase family fold.

Pablo Villalobos, Ricardo Cabrera, Mauricio Baez and Jorge Babul
Laboratorio de Bioquímica y Biología Molecular, Facultad de Ciencias, Universidad de Chile

The Ribokinase family includes ATP-dependent sugar kinases with a broad range of specificities. The ribokinase fold is composed by a major α-β-α domain, and a minor domain that performs as a lid over the active site. The ribokinase family fold is structurally diverse. For example, the minor domain shows insertion/deletions of complete secondary structure elements related to changes in dimeric packing and oligomeric state. On the other hand, significant variations in the length and packing of secondary structure elements, as well as unstructured regions are apparent from structural superposition of the major domains. In order to obtain a clearer description of the structural diversity and helping to define the importance of different regions in the ribokinase family fold on the folding and function of their members, a non-redundant set of 32 members was divided into modules.

A module is a contiguous segment of residues in the three-dimensional protein structure, representing a compact region. The modules are identified by its compactness, which is determined by calculating the centripetal distances profile over all the structure using different window sizes of residues. The mean square distances between residues are calculated for a fixed number of residues (window size). The resulting profile contains several minima and maxima, from which the boundaries of the module are defined. All the family members show a similar centripetal profile that could be divided into 9 modules.

For each module, all the members were compared in regard to its content of residues from the protein core atomic interaction network (PCAIN). These kind of residues are relevant for the stability of the protein fold and could be identified by searching for those residues within the atomic interaction network that are not accessible to the solvent. Thus, we quantified the distribution of PCAIN residues along the modular anatomy of the ribokinase family fold. For modules 1, 2, and 4 more than 35% of their residues belong to the PCAIN, suggesting that may contribute more to the stability of the ribokinase family fold. Also the mean percentage of identity was determined for each module.

Modular behavior was also observed in Phosphofructokinase-2, the most characterized
member in terms of allosteric regulation, through 20 ns trajectories of molecular dynamics simulations. The movements were analyzed by a correlation matrix showing coherent displacements of contiguous segments.

Structural diversity trees, built from distances matrices of pairwise quantification of the Qres index after structural superposition of individual modules, were compared to the phylogenetic bayesian tree of the 32 members multiple sequence alignment. Only the module 5 represented the phylogenetic topology. Interestingly, this module does not contain residues involved in substrate binding.