Contribution ID: **73** Type: **Posters**

How much do we need to focus? Advantages of high resolution crystal structures

Tuesday, 16 June 2015 17:40 (1h 50m)

Last decade, advances in synchrotron facilities have allowed an exponential increase on the number of protein structures solved at atomic resolution. Last year, the Protein Data Bank reached the 100k structures but less than 10 % of these can be considered "atomic-resolution structures". These structures show more detailed and accurate information of the proteins. The presence of alternate conformations in some residues or modified residues is only noticeable in those high-resolution structures. Besides, these structures allow a better modeling of water molecules. Our group is interested in the solution of the structures of modular domains that interacts with proline rich motifs (PRMs) to study the anomalous thermodynamic signature of these complexes. The binding site of these domains is characterized by the presence aromatic residues where the proline residues are buried upon binding. Unexpectedly, most of the times, the binding is driven by a negative value of the enthalpy that might be addressed to the burial of water molecules. We have solved the structures of PRMs-binding modular domains (WW, TSG101-UEV and SH3) and we were able to determined special features related with their binding behavior that are only visible in high resolution structures [1-3]. For example the binding orientation of these PRMs to some SH3 domains is conducted by the formation of a salt bridge between an arginine/lysine residue flanking the canonical binding motif PxxP and an aspartate/glutamate residue located at the specificity pocket. High resolution structures have allowed us to identify alternate conformation of a leucine residue next to the acidic residue that forms the salt bridge, which might be correlated to the orientation of the PRMs binding. This residue is well conserved among the SH3 domains. Here we show how high resolution structures can help to solve the ambiguity in the modeling of some residues that might participate in the binding of PRMs through conformational changes that promotes long distant interactions. We compared these high resolution structures with lower resolution ones to show how these alternate residues cannot be modeled at lower resolution, although some clues are already present.

References

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Session Classification: Special Session - Coffee and poster discussion: ALBA users and AUSE members

Track Classification: VII AUSE Congress