MS11-P09

DPP8 and DPP9 structure, mechanism and interaction with SUMO1

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Cells require specific molecular entities to regulate biological processes, which are often out of balance in diseases. Once these entities are identified, their activities may be modulated by specific ligands. DPP4 protein is an example of a target to successfully treat type II diabetes by small molecule ligands [1]. Other members of the DPP4 family are similarly interesting. **DPP8 and DPP9, are active serine proteases located inside cells. They are relevant in immune response and cancer [2]. It is crucial to understand their structures, enzymatic mechanisms and interactions to enable structure-based drug development.** DPP8 and DPP9 activity can be modulated by inhibitors like SLRFLYEG, 1G244, and Val-BoroPro. SLRFLYEG is a specific peptidic DPP8 and DPP9 inhibitor with allosteric properties. This inhibitor was designed using a segment of SUMO1. 1G244 is a strong specific competitive inhibitor of DPP8 and DPP9. Val-BoroPro is a non-specific covalent inhibitor of DPP4, DPP8 and DPP9. Regarding binding partners, SUMO1 has been described to form complex with either DPP8 or DPP9 during pulldown experiments using SUMO1-tagged beads. While the complexes are not stable in solution this binding may regulate important signaling in cells.

We hereby reveal DPP8 and DPP9 molecular structures and substrate binding features. Moreover, we clarify how structural differences in inhibitor binding lead to differences in potency and binding mechanisms. DPP8 and DPP9 are structurally related to DPP4, with a conserved α-hydrolase domain and β-propeller domain. However, the mechanism underlying the enzymatic activity differs significantly. We observed a disorder-order transition of a 26 aa segment upon substrate binding. This segment partially folds into an α-helix, which is required to fix the incoming substrate, allowing enzyme activity [3]. Furthermore, we characterize the SUMO1-DPP9 complex using protein-protein interaction assays. We observed a stable complex between DPP9 and oligomeric forms of SUMO1. Therefore, a bis-sumoylated substrate might be the minimal requirement for interaction in a physiological context. The determination of DPP8 and DPP9 crystallographic structures as well as their interaction with SUMO1 can be of paramount relevance in immunological regulation or drug design when treating diseases like cancer.

References:

[1] Lambeir, A. M. et al. (2008). Biochem Pharmacol, 76 (12), 1637–1643.
[2] Okondo, M. C. et al. (2017). Nat Chem Biol, 13 (1), 46–53.
[3] Ross, B. et al. (2018). PNAS, 115 (7), E1437–E1445.

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Revealing the properties of small local folds with ALEPH: from structure annotation to *ab initio* phasing

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Software for structure annotation has become a key aspect for any functional study, as structure is highly conserved and a vast amount of structural data is available. Implemented in software like DSSP, Cablam or Gesamt, algorithms employed for structure analysis are based either on sequence features, geometrical parameters or a combination of them. For the validation context, algorithms based on geometry descriptors have been developed, such as C-Alpha Based Low-resolution Annotation Method (CABLAM)[1]. ALEPH addresses two challenges:

- Revealing structure properties of small local folds, of immediate application to produce models for *ab initio* phasing.
- Flexibly tuning the annotation to the purpose for which it will be used.

ALEPH, which incorporates the previous algorithm Borges [2], has been developed to analyze small local folds. ALEPH is integrated in the ARCIMBOLDO software for *ab initio* phasing, especially in ARCIMBOLDO_SHREDDER [3] for identification of compact folds. The software uses *ad hoc* parameters called Characteristic Vectors (CV's) for retrieving tridimensional properties of the main chain. CV's exploit the fact that carbonyl oxygens are differently oriented for each secondary structure. Properties of the CV such as their modulus or direction, the angles between them or the distances that separates them, allow to identify different secondary structures and describe their environment. Recent developments, including an increase in the number of parameters used for main chain description and the addition of new mathematical algorithms has allowed not only to improve the precision in the annotation but also its flexibility.

Beyond secondary structure annotation, ALEPH can also optimally superpose very small structures, annotate and extract folds from a model or generate libraries of a given fold. A general description of the performance of ALEPH for validation of non ideal main chains, identification of a fold from an unknown solution and identification of compact