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Understanding of the activity of a protein involved in DNA repair by biochemical, structural and *in silico* approaches

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Introduction to the meeting

The repair of DNA from alkylation damage is generally performed by evolutionary conserved protein complexes. However, specific repair of O^6-alkylated-guanines is a task of a small class of proteins called AGTs (alkylated DNA-protein alkyl-transferases): by using a single-step reaction mechanism, the alkylic group is irreversibly transferred to a catalytic cysteine in the active site, inducing the *in vitro* and *in vivo* inactivation and destabilization of the protein. Although some conformational changes after the alkylation are supposed, a complete picture of structural rearrangements occurring during the reaction cycle is missing. The complete knowledge of these structural movements is a great challenge and a fundamental task for the development of new inhibitors of the human AGT, whose overexpression leads to a resistance in several types of tumor cells to the chemoterapic alkylating agents-based treatment.
We used the *Sulfolobus solfataricus* thermostable ortholog (*Ss*OGT) as a model for AGTs [1], by performing biochemical, structural, molecular dynamics and *in silico* analysis of ligand-free, DNA-bound and alkylated version of the protein. With this protein, we were able to highlight conformational changes and perturbations of intramolecular interaction occurring during lesion recognition and catalysis, confirming our previous hypothesis that coordination between the N- and C-terminal domains of *Ss*OGT is important for protein activity and stability [2]. All the data allowed us to propose a general model of structural rearrangements occurring during the reaction cycle of AGTs [3], and proposing it as a starting point to design strategies to modulate AGT activity in therapeutic settings.

References

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