Structural basis of the addiction of toxin-antitoxin systems to molecular chaperones
Team "Structural biophysics" – IPBS (Lionel MOUREY)

Supervisors: Valérie GUILLET, email: valerie.guillet@ipbs.fr, phone: 05 61 17 54 37; Lionel MOUREY, email: lionel.mourey@ipbs.fr, phone: 05 61 17 54 36

Summary

Toxin-antitoxin systems are genetic elements capable of controlling bacterial growth in response to certain stresses. They are usually composed of a toxin and an antitoxin that inhibits the deleterious effect of the toxin. Under certain stress conditions, the less stable antitoxin is degraded and the released toxin can control bacterial growth by targeting replication or *de novo* protein synthesis, for example. The involvement of some of these systems in bacterial persistence and in the virulence of certain pathogens makes them therapeutic targets of interest. *Mycobacterium tuberculosis*, the bacterium responsible for tuberculosis, causes nearly two million deaths each year worldwide and remains a major public health problem. *M. tuberculosis* has a very large number of toxin-antitoxin systems and it has been proposed that these systems may be involved in the establishment of the persistence phase in this bacterium.

Among these toxin-antitoxin systems, the TAC (Toxin-Antitoxin-Chaperone) system is atypical in that it is controlled by a third obligatory partner: a molecular chaperone that facilitates folding and prevents degradation of the antitoxin. Remarkably, the chaperone dependence of this toxin-antitoxin system is determined by a small region of the antitoxin, called ChAD (for chaperone addiction), which interacts specifically with the chaperone and induces the aggregation of the antitoxin in its absence [1].

We have been working for many years with Pierre Genevaux's team (LMGM-CBI, Toulouse) on the characterization of the TAC system. In particular, we characterized the interactions of the chaperone with its partners and solved its structure in complex with a peptide derived from ChAD [2]. Our current efforts are directed towards the resolution of the structure of bipartite chaperone-antitoxin and chaperone-ChAD complexes as well as tripartite chaperone-antitoxin-toxin and chaperone-antitoxin-DNA complexes using X-ray crystallography and cryo-EM techniques.

The aim of the internship will be to contribute to the structure determination of these complexes. Protocols for the production and purification of TAC proteins and sub-complexes have been developed. The focus will be on crystallization, structure determination by X-ray crystallography and possibly the preparation of samples for cryo-electron microscopy.

References

1. Bordes, P., Sala, A., Ayala, S., Texier, P., Slama, N., Cirinesi, A.-M., Guillet, V., Mourey, L., and Genevaux, P. **(2016)**. Chaperone addiction of toxin-antitoxin systems. ***Nat Commun*** 7:13339.

2. Guillet, V., Bordes, P., Bon, C., Marcoux, J., Gervais, V., Sala, A.J., Dos Reis, S., Slama, N., Cirinesi, A.M., Maveyraud, L., Genevaux, P., and Mourey, L. **(2019)**. Structural insights into chaperone addiction of toxin-antitoxin systems. ***Nat Commun*** 10:782.