BacTyrKin

BIOLOGIE & SANTÉ 2011

Bacterial tyrosine kinases: a new class of enzymes as innovative therapeutic targets

Programme Jeunes Chercheurs – Jeunes chercheuses 2007

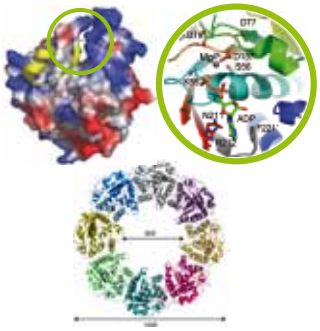
State of the art and scientific goals

A decade ago, bacteria were thought to be devoid of tyrosine-kinases. However, evidence has accumulated over the years and today it is clear that bacteria do possess idiosyncratic tyrosine-kinases, named BY-kinases, that are unrelated to their eukaryotic counterparts. Recent advances in phosphoproteomics provided snapshots of several bacterial phosphoproteomes and suggest that BY-kinases would be involved in a number of regulatory processes. However, their mode of action is still elusive and the underlying regulatory mechanisms remain largely unknown.
In this project, we develop an integrative approach combining biochemistry, molecular biology, microbiology, crystallography and bioinformatics toward the structural and functional characterization of BY-kinases Wzc and CapB in *Escherichia coli* and *Staphylococcus aureus*, respectively. We showed that BY-kinases regulate not only the export of extracellular polysaccharides, but also the biosynthesis of these compounds by phosphorylation of endogenous proteins. Extracellular polysaccharides are important virulence factors. BY-kinases constitute therefore original and attractive targets for the development of new drugs to treat infectious deseases.

First BY-kinase 3D structure

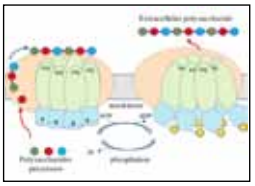
In firmicutes, BY-kinases alone are inactive and interaction with the cytoplasmic C-term end of a membrane protein activator (yellow helix) is required to promote their tyrosine-kinase activity. Activation is performed by a hydrophobic residue, which complements the active site of the BY-kinase and interacts with the base moeity of ATP.

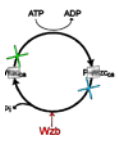
Unphosphorylated BY-kinases form transmembrane octamers.

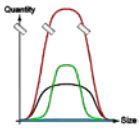


Functional analysis of the BY-kinase Wzc

Phosphorylation and dephosphorylation of BY-kinases control association/dissociation of the octamer and polysaccharide export.





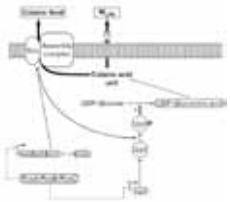


BY-kinases-mediated phosphorylation of endogenous UDP-sugar dehydrogenases

BY-kinases are able to phosphorylate and activate UDP-sugar dehydrogenases.

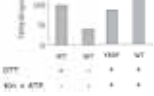
UDP-sugar dehydrogenases participate in the production of polysaccharide subunits.

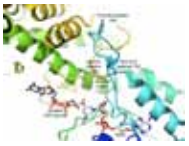
UDP-sugar dehydrogenases phosphorylation controls the amount of polysaccharides produced.

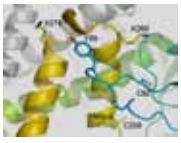


The structural and functional analysis of the UDP-sugar dehydrogenase CapO from *S. aureus* reveals that its activity is regulated by tyrosine phosphorylation and a redox-switch mechanism.

P-Tyr89 could participate in the stabilization of helix αJ and correct positioning of the catalytic Cys 258 in the active site.

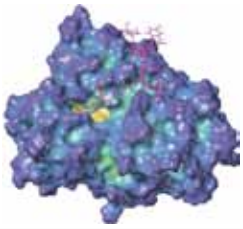






BY-kinase inhibitors

We design drugs in order to target and affect BY-kinases activity and thus polysaccharides production. Inhibitors are modified peptides with a moiety that can mimic the ATP molecule (PNA-A), the peptide part having a great affinity and specificity for the protein kinase.



Publications - Patents

Gruszczyk et al., J. Biol. Chem.,(2011), 286, 17112-21.
Bechet et al., Mol. Microbiol., (2010), 77, 1315-1325.
Grangeasse et al., International Patent (2009) (WO 2009/133209 A1).
Olivares-Illana et al., PLoS Biol., (2008), 10, E143.
Lacour et al., PLoS ONE, (2008), 3 : e3053.
Jadeau et al., Bioinformatics, (2008), 21 : 2427−30.
Grangeasse C, et al. Trends Biochem. Sci., (2007), 32, 86-94.

CONTACT : C. GRANGEASSE
Institut de Biologie et Chimie des Protéines
UMR5086 - BMSSI - CNRS/Université Lyon I
7, passage du Vercors – F-69367 Lyon Cedex 07
Tel: +33 (0)4 72 72 26 88 - c. grangeasse@ibcp.fr