AFC 2008 Rennes

(www.afc2008.univ-rennes1.fr)

Colloque IVB : Signalisation et réaction cellulaire

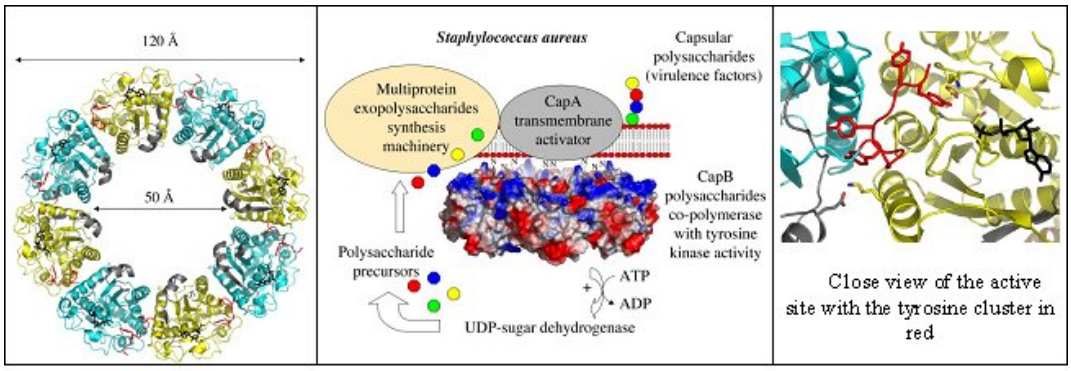
V. Olivares-Illana[1], P. Meyer[1], E. Bechet[2], V. Gueguen-Chaignon[1], S. Lazereg-Riquier[3], Alain J. Cozzone[2], O. Laprévotte[3], S. Morera[1], C. Grangeasse[2] and S. NESSLER[1]

[1] Laboratoire d'Enzymologie et Biochimie Structurales, CNRS, 91198 Gif sur Yvette, France
[2] Institut de Biologie et Chimie des Protéines, CNRS, Université Lyon 1, Université de Lyon, 69367 Lyon
[3] Institut de Chimie des Substances Naturelles, CNRS, 91 198 Gif sur Yvette, France

Crystal structure of CapB, a tyrosine kinase from the pathogen *Staphylococcus aureus*

Bacteria were thought to be devoid of tyrosine-phosphorylating enzymes. However, several tyrosine kinases without similarity to their eukaryotic counterparts have recently been identified in bacteria [1]. They undergo an autophosphorylation process on a C-terminal tyrosine cluster and phosphorylate endogenous protein substrates. They are involved in many physiological processes but their accurate functions remain poorly understood, due to slow progress in their structural characterization. They have been best characterized as co-polymerases involved in the synthesis and export of extracellular polysaccharides. These compounds play critical roles in the virulence of pathogenic bacteria and bacterial tyrosine kinases can thus be considered as potential therapeutic targets.

Here we present the crystal structures of the phosphorylated and unphosphorylated states of the tyrosine kinase CapB from the human pathogen *Staphylococcus aureus* together with the activator domain of its cognate transmembrane modulator CapA [2]. This first high-resolution structure of a bacterial tyrosine kinase reveals a 230kDa ring-shaped octamer that dissociates upon intermolecular autophosphorylation. Our data provide a molecular basis for the activation mechanism of CapB by CapA and allow us to propose a regulatory mechanism, that was further investigated by mutational and biochemical approaches.



These results further give new insights into the co-polymerase function of the bacterial tyrosine kinases and onto the phosphorylation of their endogenous substrates like CapO, an UDP-sugar dehydrogenase involved in the synthesis of polysaccharide precursors in *S. aureus* [3]. We finally propose a molecular model for the regulation of extracellular polysaccharide synthesis.

[1] Grangeasse C, Cozzone AJ, Deutscher J, Mijakovic I., Trends Biocem. Sci., 32 (2007) 86-94.

[2] Soulat D, Jault JM, Duclos B, Geourjon C, Cozzone AJ, Grangeasse C., J Biol Chem., 281 (2006) 14048-4056.

[3] Soulat D, Grangeasse C, Vaganay E, Cozzone AJ, Duclos B., J Mol Microbiol Biotechnol., 13 (2007) 45-54.