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Determination of the Regulon of CcpA, a Pleiotropic Regulator, in the Pathogen Streptococcus agalactiae

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Abstract

The commensal bacterium *Streptococcus agalactiae* is responsible for various infections in a wide variety of hosts including humans. Its broad spectrum of hosts shows its ability to acquire nutrients in variable conditions.The carbon catabolite repression allows bacteria to prioritize the uptake and the catabolism of the environmental sugars. In Gram-positive bacteria, CcpA (catabolite control protein A), a pleiotropic transcriptional regulator, plays a key role in catabolite repression. Complexed to its phosphorylated co-effector HPr (histidine-containing phosphocarrier protein), CcpA binds to a specific DNA consensus sequence named « *cre* » (for catabolite response element) in the regulatory region of the target genes, thereby causing their activation or repression.Studies have shown the involvement of carbon catabolite repression in the adaptation and stress resistance of pathogenic bacteria. The goal of this study is to determine the regulon and the role(s) of CcpA in the physiology and adaptation of *S. agalactiae*.

We studied the effect of CcpA deletion in *Streptococcus agalactiae* A909 by comparing, with an RNAseq analysis, the global transcription of the WT and Δ*ccpA* strains. We showed that 13.5% of the *S. agalactiae* genome was regulated by CcpA and that it acts mostly as a repressor.

In order to determine the direct targets of CcpA, we searched the genes harbouring a putative cre site in the *S. agalactiae* genome with an in-silico approach (RegPrecise, Virtual Footprint). Among the 274 genes significantly regulated by CcpA, 79 have at least one *cre* site. We are validating the consensus cre sequence with gelshift experiments on approximatively 20 putative direct targets.

In-silico and RNAseq analysis highlight the CcpA direct regulation of genes coding for proteins putatively involved in acidic and oxidative stresses. As an example, one of these proteins coded by the SAK_*1689* gene that is highly overexpressed in the Δ*ccpA* strain, has more than 50% identity with *lmo_1580*, an UspA protein of *Listeria monocytogene*s involved in the oxidative and stress responses. We are constructing transcriptional fusion vectors in order to confirm the implication of CcpA in their regulation and their expression in stress responses, and therefore the role of this regulator in the adaptation of *S. agalactiae*.