FtsH4-Mediated Control of Carbon Uptake in *Synechocystis* sp. PCC 6803

Abstract:

Membrane-bound FtsH proteases are universally present in prokaryotes and in the mitochondria and chloroplasts of eukaryotic cells. These metalloproteases are often critical for the viability of the cell and play both protease and chaperone roles to maintain cellular homeostasis. In contrast to most bacteria having a single ftsH gene, cyanobacteria typically possess four FtsH proteases (FtsH1-4) that form heteromeric (FtsH1/3 and FtsH2/3) and homomeric (FtsH4) complexes. The function and substrate repertoire of each complex is poorly understood. Recent data showed that FtsH4 plays a role in stress acclimation by regulating high light inducible proteins. To identify new substrates of the FtsH4 protease complex, we established a trapping assay in the cyanobacterium *Synechocystis sp.* PCC 6803 utilizing a proteolytically inactivated trapFtsH4-His. This approach revealed several carbon concentrating mechanism (CCM) proteins, including SbtA, SbtB, and CupA. Notably, SbtB, a PII-like signaling protein involved in carbon acclimation via cAMP, was exclusively captured by the inactive trap**.** Our work shows that SbtB is directly regulated by FtsH4, with in vivo assays confirming its proteolytic degradation. By controlling SbtB levels, FtsH4 enables the cell to dynamically adjust bicarbonate uptake and carbon assimilation, positioning SbtB degradation as a central regulatory switch in cyanobacterial carbon homeostasis.