PlzA is a unique dual function c-di-GMP effector protein required for survival of the Lyme disease spirochete, *Borrelia burgdorferi*, within its arthropod vector and mammalian host

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Our hypothesis is that PlzA suffers a conformational change after c-di-GMP binding that allows the dual function (tick vs. mammal). Electrostatics analysis suggests a DNA binding function.

C-di-GMP exert its effector function, either allosterically or transcriptionally (riboswitches) as part of a wide range of diverse adaptive programs, including biofilm formation, motility and virulence. The only known c-di-GMP effector protein in *Bb* is PlzA (BB0733), which contains a prototypical "Plz"-c-di-GMP binding domain.

In order to maintain this enzootic cycle, *Bb* must sense and respond to a myriad of signals encountered in these vastly different niches. Two-component systems (TCS) are important mechanisms by which bacteria adapt to their surroundings. *Bb* encodes only two TCSs, Hk1/Rrp1 and Hk2/Rp2. While the contribution of Hk2 remains unclear, Rp2 is part of a regulatory pathway involving the spirochete's alternative sigma factors, RpoN and RpoS. Genes within the Rpo2/RpoN/RpoS regulon function to promote tick transmission and early infection. Activation of the other TCS, Hk1/Rrp1 results in production of the second messenger cyclic dimeric guanosine monophosphate (c-di-GMP) by Rrp1, a diguanylate cyclase (DGC). Hk1/Rrp1 is thought to work exclusively in ticks.

The tick is a "c-di-GMP bound-PlzA" environment, while the mammal is an "unbound-PlzA" environment.

Western blots of whole cell lysates from *Bb* cultivated in DMCs

Bound PlzA regulates tick phase genes (directly or indirectly)

continued synthesis of c-di-GMP in the mammal prevents infection

Unbound PlzA has a c-di-GMP independent function in mammals

Secondary structure of proteins with bipartite domain organization including a C-terminal PilZ-like domain in the N-terminal region.

PlzA structural models