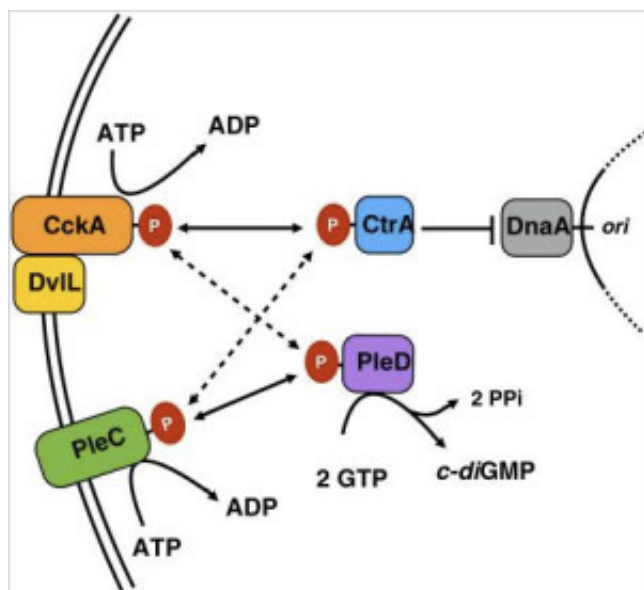


Genes regulating *Wolbachia* cell division

Bacterial infection underlies many devastating diseases, yet bacteria also play a central role in the maintenance of human health and well-being. From aiding in host food digestion and limiting unfavorable bacterial growth to causing paralysis or even death, the principles that govern host-microbe interactions are fundamentally important for understanding human health. Chief among these are the basic signals, such as physical and chemical stimuli provided by the host, which bacterial species use to regulate growth and division. These signals, interpreted by an array of environmental sensors, are integrated through signaling cascades that ultimately lead to changes in parameters such as bacterial motility, virulence and cell density.



Model for interaction of cell-cycle regulatory proteins in *Wolbachia*. Interaction of sensor kinases and response regulators for most strains investigated in this study. Arrows indicate the predominant direction of signaling or substrate flow. CtrA output is represented as the inhibition of chromosome replication only.

An organism of emerging importance in the field of host-microbe interactions is *Wolbachia pipientis*, intercellular bacteria found in insects and nematode worms. *Wolbachia* both cause human disease (lymphatic filariasis and African river blindness, via association with filarial worms) and prevent human diseases (Dengue fever and Chikungunya, via association with *Aedes* mosquitoes). Despite an expanding interest in its potential, relatively little is known about the diverse biology of *Wolbachia* bacteria. For example, while many of the genes governing regulation of cell division are known for important model organisms, such as *E. coli* and *C. crescentus*, little was known about the basis for *Wolbachia* cell division.

To gain insight into the host factors regulating division, we compared the completely sequenced and annotated genomes of *Wolbachia* from a variety of invertebrate hosts, focusing on known cell-cycle regulatory genes. Central regulators are primarily ‘sensor kinases’ like CckA and PleC; and ‘response regulators’ like CtrA and PleD. Although the relative position of these genes is not well conserved between *Wolbachia* variants, our analysis indicated that these key genes generally lie within clusters that do not vary substantially between *Wolbachia* from different worm, mosquito or fruit fly hosts. We next asked whether *Wolbachia* sensors and their signaling partners, known as ‘two-component’ systems (TCSs) might interact through phosphotransfer as shown for other systems. A general model for *Wolbachia* TCS interaction can be seen in Fig. 1. Analysis of deduced protein sequences suggest that TCS proteins are functional in most *Wolbachia* strains, though they may interact in a flexible manner with ‘cross-talk’ between partners. Comparison of the *Wolbachia* ‘sensor’ domains with existing 3-D models also suggested that the sensor CckA binds heme, an important iron-coordinated ligand.

In comparison to other bacterial models that have multitudes of TCS proteins, small symbiotic *Wolbachia* have only two such TCS pairs. As some of the variants have lost portions of these genes, this study can help to define a minimal functional set necessary to regulate cell division. This information not only informs *Wolbachia* host-symbiont studies, but can be useful in efforts toward creating regulated synthetic biological systems.

Laura R. Serbus and Steen Christensen

*Department of Biological Sciences and Biomolecular Sciences Institute
Florida International University
Miami, USA*

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