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Fighting the Beast by Knowing it Better: Advances in *Vibrio Cholerae* Studies Leading to Novel Drugs against *Cholera*

"Genetics studies advance development of novel drugs against cholera"

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COLUMN ARTICLE

The World Health Organization warns about frequent outbreaks of the deadly disease *cholera* world-wide. Warm standing waters, raw seafood, fruits and vegetables, are the usual 'habitats' for *Vibrionaceae*, the family of bacteria invading human intestine and causing severe diarrhea and dehydration. Among all highly relative members, *Vibrio cholerae*, the causative element of *cholera*, is the most studied since its genome was deciphered in 2000. The sequencing project confirmed that bacterial pathogens can have divided genomes as eukaryotes.

V. cholerae possesses two chromosomes that differ in size and genetic features. The bigger chromosome I (ChrI, 3 Mbp) resembles chromosomes of *Escherichia coli* and *Bacillus subtilis*, whereas the smaller chromosome II (ChrII, 1 Mbp) is similar to many plasmids found in gram-negative bacteria. However, both chromosomes carry essential genes and are indispensible for viability of the bacterium. Studies on replication and segregation control of the chromosomes in *V. cholerae* revealed unique features and orchestration that might be of particular interest in the search for novel drugs against *cholera*. To date, no antibiotic or vaccine has been found to be effective or specific enough to combat the disease.

The groups of Matt Waldor at Brigham and Women's Hospital (Harvard, Massachusetts, USA) and Dhruba Chattoraj at National Cancer Institute in National Institutes of Health (Bethesda, Maryland, USA) in particular, described in depth ChrII genetic elements and the mechanisms of replication and segregation, reporting for first time that: transcription regulates binding of a protein to a regulatory site [1]; two different regulatory sites interact via the bound ChrII-specific replication initiator protein RctB to regulate replication in a cell-cycle-dependent manner [2]; replication and segregation proteins, RctB and ParB2 respectively, compete for binding to same site to control replication frequency [3]; RctB binds to DNA in two forms [4] and binds to a novel site in ChrI, to coordinate replication of the two chromosomes in the cell cycle [5, 6]. The latter work revealed a new check-point control mechanism to maintain chromosomes in bacteria.

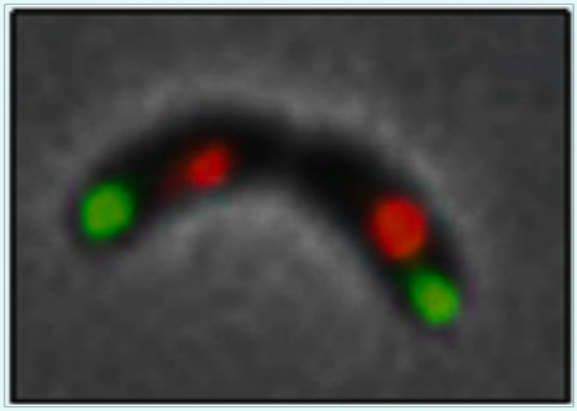

Figure 1: Vibrio cholerae cells with Chromosome I (green) and Chromosome II (red) visualized under fluorescent microscope.

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Taking all the above into account, RctB appears to be the central regulator of replication and an essential protein, and therefore would be a target for developing anti-*cholera* drugs. Moreover, the protein is not found outside of the *Vibrionaceae* family and could serve as a *Vibrio*-specific drug target. Solving the crystal structure of the protein and search for small peptides to inactivate RctB are undergoing [7].

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