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Lessons to be learned from studying *Vibrio cholerae* in model systems

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A response to The complete genome sequence of Vibrio cholerae: a tale of two chromosomes and of two lifestyles by Gary K Schoolnik and Fitnat H Yildiz, *Genome Biology* 2000, **1**:reviews1016.1-1016.3

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In a *Genome Biology* article [1], Schoolnik and Yildiz drew our attention to what the complete genome sequence tells us about the two lifestyles of *Vibrio cholerae*, the causative agent of the severe diarrheal disease cholera. They rightly pointed out that the genome sequence coupled with microarray technologies will enable us to learn more about how this pathogenic species adapts to the many niches it so successfully occupies. Although it is true that microarray-based technologies will identify genes that are responsible for biofilm formation and adaptation to environmental reservoirs, an important additional resource is the study of differential gene expression after host infection.

Several attempts have been made (by our own lab and that of Mekalanos) to identify the genes that are expressed *in vivo* following host infection using model systems in the mouse [2,3], the rabbit ileal loop model [4,5], and with technologies such as *in vivo* expression technology [2], signature-tagged mutagenesis [3], RNA arbitrarily-primed PCR [4] and global expression profiling using overlapping cosmid clones [5]. The two-chromosome conservation of *Vibrio cholerae* is believed to confer an evolutionary advantage in habitats that vary with climate change, and Schoolnik

and Yildiz [1] discuss the hypothesis that chromosome I genes are involved mainly in adaptation for growth in the host intestine while chromosome II genes are predominantly involved in adaptation to environmental niches. Many genes have been identified, including those involved in amino acid biosynthesis and general metabolism, motility, toxin-coregulated pilus biogenesis and peptidoglycan biosynthesis. For example, we have found homologs of *cheY* (involved in motility and chemotaxis), *pnuC* (coding for nicotinamide mononucleotide transport) and *icmF* (part of a gene cassette involved in bacterial multiplication inside host cells) to be upregulated *in vivo* in rabbit ileal loops as well as in human intestinal epithelial cell lines ([5] and our own unpublished data). In view of the fact that the genes cloned in our laboratory have been found to be present in chromosome II, we suggest that chromosome II might also be required for survival or pathogenesis of *V. cholerae* in the intestinal environment. Now that the sequence information is available, we would like to add to the predictions made by Schoolnik and Yildiz [1]: microarray-based gene expression profiling of *V. cholerae* in various animal models, in intestinal epithelial cell lines or in primary culture of strains of *V. cholerae* collected from patients, will

enable investigators to learn more about the adaptation of this human pathogen to the human gastrointestinal tract.

Moreover, Schoolnik and Yildiz [1] have drawn attention to the fact that about 54% of the *V. cholerae* open reading frames (ORFs) are not yet annotated, so functional genomic studies with mutational approaches or expression analysis might enable researchers to find more functions. It is tempting to suggest at this point that these unknown genes (ORFs that have no homology with genes present in databases) might play some useful role in *V. cholerae* physiology under conditions that have not yet been successfully mimicked in the laboratory. In conclusion, genome sequencing and annotation is important, microarray studies shed light on the adaptive strategies of *Vibrio cholerae* to its environmental niches, and further host-pathogen studies will help us identify ways in which to tame this organism.

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