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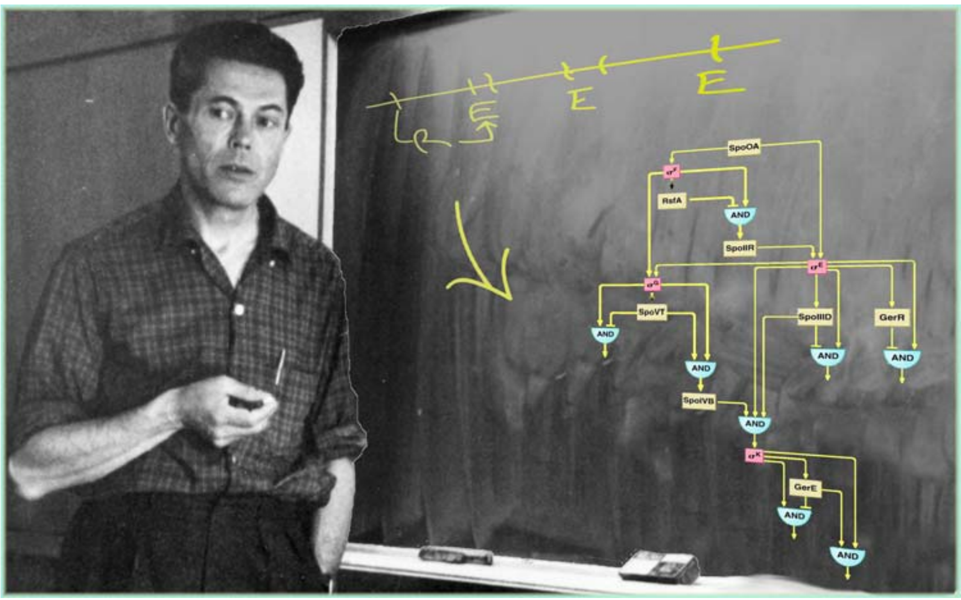

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REGULATION OF *VIBRIO CHOLERAE* VIRULENCE GENE EXPRESSION AND PATHOGENESIS IN RESPONSE TO MICROAEROPHILIC GROWTH CONDITIONS

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Vibrio cholerae, a Gram-negative bacterium causes the human diarrheal disease cholera. As a model organism, it is a genetically tractable system for understanding bacterial pathogenesis, as evidenced by the successful identification of some of its virulence factors. Yet, much remains unknown with respect to the organism's mechanisms to sense and respond to virulence activating stimuli within the host microenvironment. Anaerobic growth has been shown to increase virulence gene expression in Gram-negative enteric and non-enteric bacteria. *V. cholerae* is subjected to an oxygen-gradient during colonization of the host intestine leading to disease, suggesting a link between hypoxia and virulence gene expression. A non-redundant and arrayed transposon library was screened to identify two-component system (TCS) mutants showing significant reduction in cholera toxin (CT) production under microaerobic conditions compared to the wild-type parent. Four unique TCS that potentially sense and respond to oxygen, osmolarity or host metabolites were identified. In-frame unmarked deletion strains lacking the identified TCS sensor proteins were constructed and showed reduction in CT production only under microaerobic conditions and were significantly attenuated in an infant mouse model of Vibrio colonization in competition with the wild-type parent (P less than 0.05). Furthermore, these TCS were found to regulate CT production in response to oxygen levels in two different *V. cholerae* biotypes suggesting an important link between the host-imposed oxygen-gradient and disease outcome.