PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Quorum sensing in *Vibrio cholerae*?

ArticleInfo		
ArticleID	:	4345
ArticleDOI	:	10.1186/gb-2002-3-6-reports0032
ArticleCitationID	:	reports0032
ArticleSequenceNumber	:	24
ArticleCategory	:	Paper report
ArticleFirstPage	:	1
ArticleLastPage	:	4
ArticleHistory	:	RegistrationDate : 2002–4–1 Received : 2002–4–1 OnlineDate : 2002–5–24
ArticleCopyright	:	BioMed Central Ltd2002
ArticleGrants	:	

ArticleContext	:	130593366

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Abstract

An investigation of the effects of *Vibrio cholerae* cell density on virulence

Significance and context

Vibrio cholerae is a human pathogen that causes cholera, a severe diarrheal disease in humans. Although virulence is due to the production of a cholera enterotoxin (CT) and a toxin-co-regulated pilus (TCP), required for colonization, there are several environmental factors, whose mode of action are not well understood, that are also important in regulating virulence. It has been proposed that the sensor proteins ToxR and TcpPsense environmental factors that activate a signal transduction pathway, leading to the expression of genes required for CT and TCP production. It has also recently been shown that bacteria monitor their cell densities through the exchange of chemical compounds - auto-inducers - in a process called quorum sensing. The marine bacterium *V. harveyi*, for instance, has a quorum-sensing system and produces two auto-inducers, AI-1 and AI-2. Analysis of the *V. cholerae* genome sequence shows that it also carries the genes required for the synthesis of AI-2. Zhu *et al*. now show that *V. cholerae* has a *V. harveyi*-like quorum-sensing system, which is involved in virulence. This study provides useful information about how *V. cholerae* behaves during its initial infection of humans.

Key results

The *luxCDABE* operon of *V. harveyi*, responsible for the quorum-sensing-dependent bioluminescence phenotype, was introduced into wild-type *V. cholerae*, and into strains that contain a mutation in the *luxO* or *hapR* genes. These encode negative and positive regulators of the operon, respectively. The results showed that a quorum-sensing circuit is present in *V. cholerae*. In contrast to *V. cholerae hapR* mutants, *luxO* mutants were unable to colonize host tissues - no *luxO* mutant bacteria could be recovered from the small intestines of treated mice - suggesting a requirement for the quorum-sensing circuit for *V. cholerae* pathogenicity. Furthermore, many genes were found to be either up- or down-regulated in a *luxO* mutant as compared to the wild-type strain. This latter group of genes includes the entire ToxR regulon, which is involved in the synthesis of CT and TCP. The LuxO-dependent down-regulation of the virulence regulon was mediated through a down-regulation of the TcpP protein, encoded by *tcpP*, whose expression required LuxO. LuxO does not, however, regulate *tcpP* directly, but via the HapR protein. The expression of *hapR* increases significantly in a *luxO* mutant, and HapR represses *tcpP* expression,

resulting in downregulation of the ToxR regulon. Interestingly, *hapR* is expressed at low cell densities in *luxO* mutants but not in wild-type bacteria, suggesting that HapR acts at an early stage of growth to affect virulence. As well as being involved in the repression of the ToxR regulon, HapR is also required for the production of the HA protease (encoded by *hapA*) at high cell densities; this protein is considered to be a 'detachase' during colonization, thereby promoting the induction of new infection centers. HA protease production by a *luxO* mutant started earlier during growth and was increased compared to the wild-type strain, but was severely inhibited in a *hapA* or a *hapR* mutant. A motility study showed, in addition, that a *luxO* mutant was less motile than wild-type bacteria, in agreement with there being altered expression of genes involved in chemotaxis in a *luxO* mutant.

Links

The Institute of Genomic Research website provides links to the *V. cholerae* genome database.

Conclusions

Zhu *et al*. demonstrated that a quorum-sensing system of *V. cholerae* is involved in the negative regulation of virulence, via cessation of the inhibition of HapR. HapR negatively regulates expression of the ToxR regulon, but stimulates the production of a protease at higher cell densities that is involved in the detachment of *V. cholerae* cells, thereby promoting the induction of new infection centers.

Reporter's comments

This study contributes significantly to our understanding of the molecular mechanisms that occur during initial infection by *V. cholerae*. Identification of the auto-inducers, and finding out how they are synthesized and secreted, might be useful in the search for therapeutics that could block the spread of *V. cholerae* at the beginning of infection.

Table of links

Proceedings of the National Academy of Sciences of the United States of America

The Institute of Genomic Research

References

1. Zhu J, Miller MB, Vance RE, Dziejman M, Bassler BL, Mekalanos JJ: Quorum-sensing regulators control virulence gene expression in *Vibrio cholerae*. Proc Natl Acad Sci USA. 2002, 99: 3129-3134. 0027-8424