BACTERIAL PATHOGENESIS

Phages and the timing of cholera

It has been 150 years since the epidemiologist John Snow traced the source of an epidemic of cholera to the Broad Street pump in London. Yet, despite Snow's acuity, certain parts of the world are still blighted by cholera epidemics that occur with an as-yet-unexplained seasonal regularity.

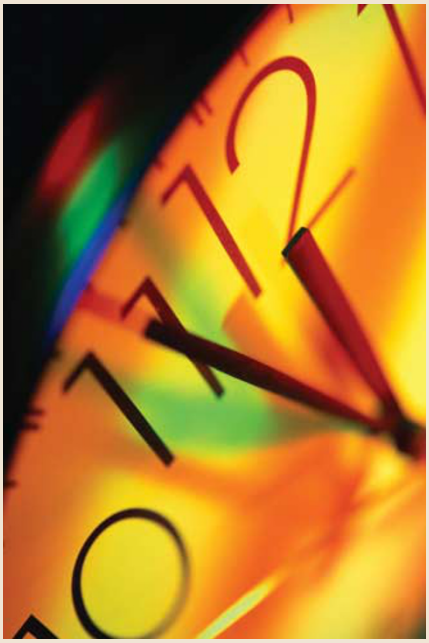
Now, the combined efforts of scientists from Bangladesh, India and the United States have revealed that epidemics of cholera are inversely correlated with the prevalence of cholera phages in contaminated water, and these findings are reported in *Proceedings of the National Academy of Sciences USA*.

John Mekalanos and co-workers analysed samples from water sources in Dhaka, Bangladesh — a city where cholera epidemics occur during certain months every year. The researchers found a statistically significant inverse correlation between the level of virulent cholera phages and that of phage-susceptible epidemic *Vibrio cholerae* strains O1 and O139 in sampled water. Importantly, when the time of onset of cholera epidemics was compared with the concentration of cholera phages in these samples, a striking pattern was observed — cholera epidemics that were caused by either the O1 or O139 serogroup strains usually commenced when low levels of O1 or O139-specific cholera phages were recovered. By contrast, a decline in the number of clinical cholera cases was associated with a marked increase in the prevalence of phages that were specific for the epidemic cholera strain.

Interestingly, during the study period, several environmental (non-pathogenic) *V. cholerae* strains were found to carry serotype-specific temperate phages, and the authors propose that the release of these phages by environmental strains might control cholera during the period between epidemics.

Finally, Mekalanos and his team propose a model in which cycles of phage amplification and predation might explain the seasonality of this disease.

Shannon Amoils



References and links

ORIGINAL RESEARCH PAPER Faruque, S. M. *et al.* Seasonal epidemics of cholera inversely correlate with the prevalence of environmental cholera phages. *Proc. Natl Acad. Sci. USA* 14 Jan 2005 (doi:10.1073/pnas.0408992102)

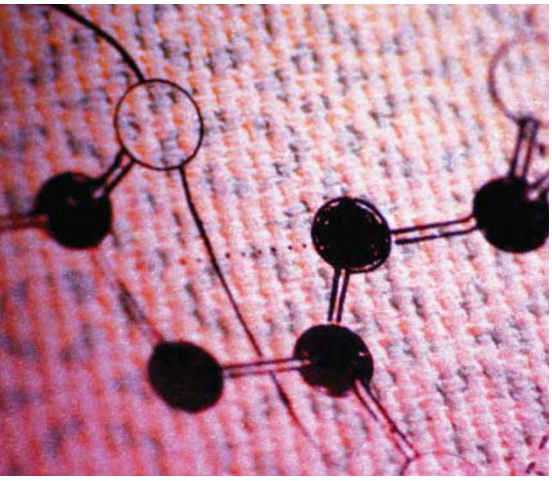
WEB SITE

International Centre for Diarrhoeal Disease Research, Bangladesh: http://www.icddrb.org/

VIROLOGY

The missing link…

A long-standing dilemma that has puzzled researchers of varicella zoster virus (VZV), the causative agent of chickenpox (varicella) and shingles (zoster), is how airborne virions that emerge from skin lesions are able to readily transmit to new hosts, yet when grown *in vitro*, the virus is highly cell-associated and very few infectious virions are released. A new study published in *Cell* resolves this issue and implicates a host protein — the mannose 6-phosphate receptor (MPR) — as being a key molecule in both processes.



Cell association of VZV has been attributed to the diversion of newly assembled virions to late endosomes where they are degraded prior to exocytosis. As previous work has shown that VZV is able to interact with cation-independent MPRs via its envelope glycoproteins, Michael Gershon and colleagues speculated that the presence of MPRs in the membrane of vesicles used to transport the newly enveloped virions could be responsible for their re-routing to late endosomes. Furthermore, previous research also demonstrated that mannose 6-phosphate, the ligand of MPRs, inhibits the infection of host cells by free VZV particles, indicating that MPRs have a role in the infection of new cells. The goal of this study was to test the hypothesis that the intracellular trafficking of newly assembled VZV and the infection of target cells by free virions are MPR-dependent.

To this end, the authors generated five human cell lines deficient in MPRs using antisense cDNA technology. Analysis of these cell lines revealed that all were resistant to infection by cell-free VZV, although the cells could be infected by cell-associated VZV. Once infected, the authors were able to demonstrate that the mutant cell lines could secrete infectious virions, thus supporting the hypothesis that both infection of naive cells by the free virus and diversion of newly assembled VZV to late endosomes require the participation of MPRs.

Further investigation of VZV infection in human epidermis revealed that the intracellular pathway of virus in superficial epidermal cells resembled that observed with the MPR-deficient cell lines. These results support the contention that, as MPR expression is lost in maturing superficial epidermal cells of the skin and VZV is not diverted to late endosomes, the virus can be secreted in a form able to propagate infection to new hosts in a controlled manner.

David O'Connell

References and links

ORIGINAL RESEARCH PAPER Chen, J. J. *et al.* Mannose 6-phosphate receptor dependence of varicella zoster virus infection *in vitro* and in the epidermis during varicella and zoster. *Cell* **119**, 915–926 (2004)