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Landes Highlights

Phage-bacterial interactions in the evolution of *Vibrio cholerae*

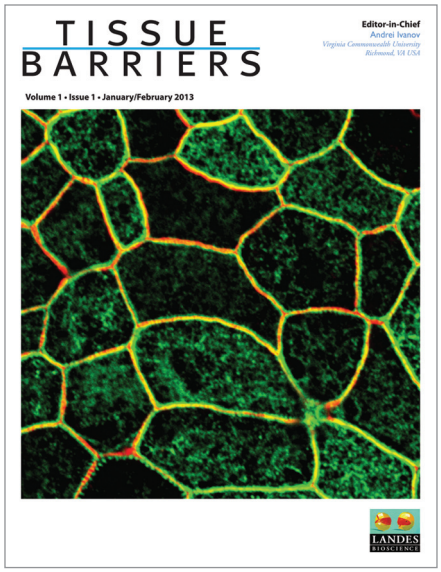
Interaction with their bacteriophages is believed to be one of the drivers of bacterial evolution. Phages contribute to the evolution of bacteria by mediating horizontal transfer of clusters of genes and genomic rearrangements, as well as by bactericidal selection. In a recent review Drs Shah Faruque and John Mekalanos have summarized available information on the interactions of phage and *Vibrio cholerae* and the effect of these interactions on the genetics, epidemiology and evolution of the pathogen. *V. cholerae* the causative agent of cholera epidemics evolved from environmental non-pathogenic strains by acquisition of virulence genes. The major virulence factors of *V. cholerae*, cholera toxin (CT) and toxin coregulated pilus (TCP) are encoded by a lysogenic bacteriophage (CTXφ) and a pathogenicity island, respectively. Additional phages which cooperate with the CTXφ in horizontal transfer of genes in *V. cholerae* have been characterized, and the potential exists for discovering yet new phages or genetic elements which support the transfer of genes for environmental fitness and virulence leading to the emergence of new epidemic strains. Phages have also been shown to play a crucial role in modulating seasonal cholera epidemics.

Reference

Faruque SM, Mekalanos JJ. Phage-bacterial interactions in the evolution of toxigenic Vibrio cholerae. Virulence 2012; 3:556-65; PMID:23076327; http://dx.doi.org/10.4161/viru.22351

EPEC protein induces multinucleation and cell hypertrophy in intestinal cells

Multinucleation and cell enlargement (hypertrophy) are important cellular processes that generally arise from the fusion of mononucleated cells, giving rise to an enlarged multinucleated cell called a syncytium. Although syncytia play important roles in normal physiology and disease, the molecular mechanisms that lead to multinucleation and hypertrophy remain poorly understood. In a recent study, Drs Paul Dean and Brendan Kenny showed that a single bacterial virulence protein, EspF, from the human pathogen enteropathogenic *Escherichia coli* (EPEC) induces extreme multinucleation in small intestinal epithelial cells. EspF is a relatively small but well-studied EPEC effector that displays a broad range of biological activities including the targeting of host mitochondria and nucleoli leading to their dysfunction. Ectopic expression of EspF induced cell-cell internalization events, presumably responsible for the enlarged multinucleated cells. These extreme phenotypes were dependent on a C-terminal polyproline-rich domain in EspF and not linked to the targeting of mitochondria or the nucleolus. In summary, the study identifies a single bacterial protein that induces extreme alterations in epithelial cell behavior leading to the induction of a multinucleated syncytium-like intestinal cell. The subversive functions of EspF may provide valuable insight into the molecular mechanisms that mediate cell fusion, multinucleation and cell hypertrophy.



Reference

Dean P, Kenny B. A bacterial encoded protein induces extreme multinucleation and cell-cell internalization in intestinal cells. Tissue Barriers 2013; 1: In press.

Clostridium difficile vaccine development

The anaerobic Gram-positive bacillus *Clostridium difficile* has the ability to form spores resistant to many commonly used hospital disinfectants and can survive on medical devices, floors and on the hands of medical staff for several months. Diarrhea caused by *C. difficile* is one of the most significant emerging hospital aquired infections in Western countries, and its prevalence has increased alarmingly over the past two decades. *C. difficile* produces two key virulence determinants, toxin A (TcdA) and toxin B (TcdB). Recently, Dr Shan Lu and colleagues used a DNA vaccination approach to screen for the immunogenicity of different fragments of toxin A and toxin B from *C. difficile*. With this approach, protein antigens do not need to be produced in vitro and the immunogenicity of candidate *C. difficile* antigens can be identified directly in animals. The researchers individually cloned codon optimized toxin gene fragments into the DNA vaccine vector and tested them in mice and rabbits for their ability to elicit *C. difficile* toxin-specific antibody responses. Only a subset of the *C. difficile* toxin fragments, including the C-terminal receptor binding domain of toxin A and a novel N-terminal enzymatic domain of toxin B, were able to elicit protective antibody responses as determined by protection of target cells in a cytotoxicity assay or by preventing death of mice in a passive antibody protection study. Significantly, antibodies elicited by the novel N-terminus of the toxin B DNA vaccine were able to increase the level of protection when used in combination with anti-toxin A antibodies in a toxin challenge model in mice. The findings from this study point to the potential of the N-terminus of toxin B as a candidate for the development of vaccines or antibody-based therapeutics against *C. difficile*.

Reference

Jin K, Wang S, Zhang C, Xiao Y, Lu S, Huang Z. Protective antibody responses against *Clostridium difficile* elicited by a DNA vaccine expressing the enzymatic domain of toxin B. Hum Vaccin Immunother 2012; 9; PMID:23143772

Antimicrobial stewardship

The increasing emergence of antimicrobial resistance presents a serious public health problem. Because the pharmaceutical industry pipeline for new antibiotics has been curtailed in recent years, the sensible and responsible use of currently available antibiotics is essential. Antimicrobial stewardship is one component of a multifaceted approach to preventing emergence of antimicrobial resistance. Good antimicrobial stewardship involves selecting an appropriate drug and optimizing its dose and duration to cure an infection while minimizing toxicity and conditions for selection of resistant bacterial strains. A series of Special Focus reviews in the journal Viurlence covers the most important aspects of antimicrobial stewardship, including prospective audit and feed back systems and objective evaluation of outcomes,[1] formulary restriction with prior authorization,[2] new antibiotics in the pipeline,[3] patient isolation to prevent spread of multidrug-resistant pathogens,[4] early diagnosis of resistant pathogens[5] and education of prescribers in antimicrobial stewardship practices.[6] The most important trends and figures are summarized in an infographic.[7]

Reference

1. Chung GW, Wu JE, Yeo CL, Chan D, Hsu LY. Antimicrobial stewardship: A review of prospective audit and feedback systems and an objective evaluation of outcomes. Virulence 2013; 4:151-7; PMID:23302793; http://dx.doi.org/10.4161/viru.21626

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3. Gould IM, Bal AM. New antibiotic agents in the pipeline and how they can help overcome microbial resistance. Virulence 2013; 4:185-91; PMID:23302792; http://dx.doi.org/10.4161/viru.22507

4. Landelle C, Pagani L, Harbarth S. Is patient isolation the single most important measure to prevent the spread of multidrug-resistant pathogens? Virulence 2013; 4:163-71; PMID:23302791; http://dx.doi.org/10.4161/viru.22641

5. Bhattacharya S. Early diagnosis of resistant pathogens: How can it improve antimicrobial treatment? Virulence 2013; 4:172-84; PMID:23302786; http://dx.doi.org/10.4161/viru.23326

6. Pulcini C, Gyssens IC. How to educate prescribers in antimicrobial stewardship practices. Virulence 2013; 4:192-202; PMID:23361336; http://dx.doi.org/10.4161/viru.23706

7. Nemchenko A. Infographic: Antimicrobial Stewardship. Virulence 2013; 4:150; PMID:23324540; http://dx.doi.org/10.4161/viru.23630