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Review

Relevance in pathogenesis research

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ABSTRACT

Research on pathogenesis of bacterial diseases involves exploration of the intricate and complex interactions among pathogen, host, and environment. Host–parasite–environment interactions that were relatively simple were the first to be understood. They include intoxications in which ingestion of a powerful bacterial toxin was sufficient to cause disease. In more complex cases bacteria occupy a variety of niches in the host and attack at an opportune time. Some bacterial pathogens have a brief encounter with the host; others are long-term guests. This variety of relationships involves a wide range of strategies for survival and transmission of bacterial pathogens. Molecular genetics, genomics and proteomics have facilitated understanding of the pathogens and hosts. Massive information often results from such studies and determining the relevance of the data is frequently a challenge. *In vitro* studies often attempt to simulate one or two critical aspects of the environment, such as temperature, pH, and iron concentration, that may provide clues as to what goes on in the host. These studies sometimes identify critical bacterial virulence factors but regulation of bacterial virulence and host response is complex and often not well understood. Pathogenesis is a process of continuous change in which timing and degree of gene expression are critical and are highly regulated by the environment. It is impossible to get the full picture without the use of natural or experimental infections, although experimental infections involve ethical and economic considerations which may act as a deterrent.

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1. Introduction

Pathogenesis research seeks to understand the intricacies of interactions among bacteria and host animals and the effects of environment on these interactions. It is also of considerable practical importance as it can lead to innovative diagnosis, treatment, prevention and eradication of disease of animals and humans. The first part of this review will address the issue of complexity at every step of pathogenesis. The subsequent parts will discuss the significance of recurring themes in pathogenesis and the importance of methodology and context for pathogenesis research.

Pathogenesis is marked by complexities at every step, making it sometimes difficult to ascribe relevance to research findings. Recurring themes are often useful guideposts, as familiar patterns and parallels in other organisms frequently help to indicate the right direction. New methodologies are a major driver in pathogenesis research and access to a variety of tools has enhanced our ability to investigate pathogenesis, especially at the cellular and molecular levels. The context in which our studies are conducted is of extreme importance and needs to be carefully considered at both the study design and interpretation stages.

Complexity in pathogenesis research is in part generated by the need to concern ourselves with not only the pathogen but also the host and the environment. Many researchers in pathogenesis research focus on the pathogen and start with identification of virulence and fitness genes, ascribing function to genes and proteins, and trying to understand regulation. Increasingly we have come to recognize the profound role of the host and the environment in regulation and function in bacterial pathogens. We have also come to recognize the added complexity associated with multifunctionality of some proteins, redundancy, co-operation, and the sequential changes that bacteria undergo on their pathogenesis journey. Pathogen, host and environment are all highly variable and all change as the process unfolds. Superimposed on this is the massive amount of genetic information which often has to be considered as advanced sequencing methodologies make it easier to generate sequence data.

We often deal with the complexities by generating big picture concepts then hiving off aspects of these and pursuing them, particularly at the cellular and molecular levels. For example, major damage to the host is often compartmentalized as occurring primarily along a bacteria-mediated pathway, through the action of bacterial toxins, or primarily through a host-response pathway, which may or may not be toxin-mediated. Furthermore, substantial host-mediated damage occurs in infections such as Gram-negative bacterial sepsis, superantigen-mediated diseases and tuberculosis – diseases that are largely the result of toxic substances released by host cells (macrophages, lymphocytes, neutrophils) in response to infection.

In Gram-negative sepsis due to the *Enterobacteriaceae*, LPS from the cell wall is bound by the pattern-recognition molecule TLR4 in conjunction with the cell-surface receptor CD14. The binding of LPS leads to recruitment of the adaptor proteins MyD88 and IRAK to the cytoplasmic domain of TLR4. This complex initiates a signaling cascade of phosphorylation events ending with the release of NF-κB, which migrates to the nucleus where it activates the transcription of proinflammatory genes. Similar signal transduction pathways are activated by Gram-positive cell wall constituents such as peptidoglycan and lipoteichoic acid via TLR2 or TLR6. Interestingly, a number of oral Gram-negative bacteria, including *Prevotella oris* and *Porphyromonas gingivalis* interact with host cells through TLR-2, although some reports indicate that *P. gingivalis* can activate host cell pathways through both TLR-2 and TLR-4 (Bainbridge and Darveau, 2001; Nemoto et al., 2006; Konopka et al., 2010). The role of LPS in Gram-negative sepsis is clear; LPS also contributes to pathogenesis in other disease syndromes in ways that are more subtle and a potential role for LPS needs to be considered in pathogenesis of a wide variety of Gram-negative pathogens.

A bacterial function may benefit both the pathogen and the host. One researcher mused as to whether granuloma formation represented confinement in the penitentiary or living in the penthouse condo (Paige and Bishai, 2010). It may well be that it is a bit of both. This is illustrated by studies with Rv0386, a *Mycobacterium tuberculosis* adenylate cyclase that subverts host-cell signal transduction, leading to a progranulomatous response with excess TNF-alpha secretion. Loss of adenylate cyclase is associated with reduced TNF-alpha levels in mouse lungs and poorer bacterial survival (Agarwal et al., 2009). TNF-alpha is considered to be required for host containment of tuberculosis, but this study indicates that eliciting an excessive TNF-alpha response may be part of the bacterial virulence strategy. These observations suggest that the granuloma response may be advantageous to the pathogen; supporting this is data that bacterial mutants that lack granuloma promoting genes have reduced survival. This response is also beneficial to the host as it contains the pathogen, although allowing for the possibility of activation at a later time.

Bacterial superantigens, potent lethal toxins associated primarily with *Staphylococcus aureus* and *Streptococcus pyogenes*, are examples of bacterial products that induce damage by the host reaction (Lappin and Ferguson, 2009; Stow et al., 2010). Superantigens trigger an excessive cellular immune response that can lead to lethal toxic shock. Bypassing the restricted presentation of conventional