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Animal models for host–pathogen interactions

Editorial overview

Bruno Lemaitre and Frederick M Ausubel

Current Opinion in Microbiology 2008, 11:249–250

Available online 5th June 2008

1369-5274/\$ – see front matter

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DOI 10.1016/j.mib.2008.05.002

Bruno Lemaitre

Global Health Institute, EPFL, Station 15,
Lausanne, CH-1015, Switzerland
e-mail: bruno.lemaitre@epfl.ch

Bruno Lemaitre is a professor of the Global Health Institute (Ecole Polytechnique Fédérale de Lausanne, Switzerland). His research group pursues an integrated approach to host–pathogen interactions in *Drosophila*, analyzing the basis of microbial infection and the corresponding host defense responses.

Frederick M Ausubel

Department of Molecular Biology,
Massachusetts General Hospital, Richard B.
Simches Research Building, 185 Cambridge
Street, Boston, MA 02114, USA
e-mail: ausubel@molbio.mgh.harvard.edu

Fred Ausubel is a professor of Genetics at Harvard Medical School. His laboratory is located in the Department of Molecular Biology at Massachusetts General Hospital. His group studies innate immune response pathways in the nematode *Caenorhabditis elegans* and the plant *Arabidopsis thaliana* and virulence mechanisms in the broad host range opportunistic bacterial pathogen *Pseudomonas aeruginosa*.

Microbial infections are characterized by a continual dramatic interplay between pathogen and host: pathogens exploit an array of host cell functions during infection and their hosts respond with appropriate immune responses. Host–pathogen interactions are complex and dynamic by nature and are generally analyzed with a reductionist approach focusing on one facet of the interaction. This is especially true for infections impacting human health, for which experimental studies at the organism level are difficult, expensive, or ethically questionable. To overcome the limitations associated with using mammalian models of infection, many laboratories have turned to analyzing host–pathogen interactions in laboratory models. Thus, model hosts such as the nematode *Caenorhabditis elegans*, the social amoeba *Dictyostelium discoideum*, the fruit fly *Drosophila melanogaster*, and the zebrafish *Danio rerio* have been employed for host–pathogen interaction studies because of their short generation times, affordability, and amenability to forward and/or reverse genetic analysis. In addition, host–pathogen studies on these model hosts benefit from genetic and genomic tools and resources that have been generated over the years by the relatively large scientific communities using each of these models. Because the study of host–pathogen interactions using model hosts is perceived as a relatively new and cutting edge field, it has attracted scientists with formal training in other fields such as development or evolutionary biology, producing a stimulating exchange of ideas.

Importantly, host–pathogen studies employing model hosts have revealed the existence of similarities in host defense mechanisms as well as conservation of microbial strategies used to subvert these defenses. Thus, *C. elegans*, *Drosophila*, and *Dictyostelium* are now used routinely in simple, relatively high throughput screens to identify pathogen virulence factors, or in drug discovery screening to identify antimicrobial compounds that target pathogen virulence or host defense rather than the viability of the pathogen *in vitro*. In addition to inter-phylo similarities, each model host offers a unique perspective on host/microbe relationships, allowing interesting comparisons between host defense mechanisms and pathogen strategies in phylogenetically distant metazoans. This in turn has spurred an interest in identifying diverse natural pathogens of the model hosts in order to investigate the intricacies of highly evolved interactions, with the hope of uncovering new general principles of how hosts perceive and resist pathogens and how pathogens overcome this resistance. These studies are likely to yield important new insights concerning the evolutionary arms race between pathogens and their hosts.

In this issue of *Current Opinion in Microbiology*, we present seven fascinating reviews addressing various facets of host–pathogen interactions in different animal models.

Shivers *et al.* discuss the *C. elegans* transcriptional response to microbial infection in the light of forward and reverse genetic analysis coupled with microarray-based transcriptional profiling studies. These studies suggest the existence of distinct pathogen-specific responses in the relatively primitive nematode worm, revealing a higher degree of complexity than expected. In addition to the activation of immune defense pathways in the face of direct pathogen challenge, Zhang and Yun describe how *C. elegans* sense different bacteria in their environment and learn to discriminate between innocuous and pathogenic microbes. This remarkably sophisticated pathogen avoidance behavior appears to be an efficient strategy to limit infectious disease for an organism that lives in the soil and feeds on microorganisms. In particular, Zhang and Yun describe a series of molecular cellular, genetic, and behavioral analyses on the interactions of *C. elegans* with presumptive natural pathogens, which have provided novel insights into how ecologically relevant behaviors are regulated by the function of the nervous system.

The development of large scale genomic RNAi screening methods in cultured cells has been a major enabling technology breakthrough in the past few years that has been applied to the study of host–pathogen interactions as an efficient way to identify host factors targeted by pathogens. S Cherry highlights the application of RNAi screening to pathogen–host interactions in *Drosophila* S2 cells as well as the lessons learned from this approach. Because S2 cells are phagocytotic, express immune receptors, and can be infected with viruses, RNAi screens have been particularly effective in identifying MAMP (microbe-associated molecular pattern) receptors, phagocytic receptors, and factors important for viral replication.

Phagocytosis is a key mechanism for defense in most metazoans (although apparently not in *C. elegans*), and in protozoa it is also a feeding mechanism. *Dictyostelium discoideum*, the well-studied social amoeba, is proving useful in the analysis of phagocytosis and intracellular killing of bacteria as illustrated in the review by Cosson and Soldati. Studies with *Dictyostelium* also shed light on the evolutionary origins of phagocytosis and suggest that the virulence mechanisms of many well-armed pathogens, including human pathogens, may have originally evolved in environmental bacteria as a way to resist protozoan phagocytosis. More generally, it may be

possible to trace the origins of many virulence factors to the selective pressure to counteract predation by microherbivores, including nematodes as well as protozoans.

Mycobacterium tuberculosis causes severe respiratory infections in humans, but it is difficult to work with established models of mycobacterial infection. *M. marinum* is a useful mycobacterial model because it is closely related to *M. tuberculosis* and displays pathogenic properties in its natural hosts (fish and frogs) similar to those of *M. tuberculosis* in humans. Lesley and Ramakrishnan delineate the steps of *M. marinum* infection in a whole animal zebrafish model. Zebrafish (*D. rerio*) is a powerful model that has been primarily used to study vertebrate development, but is now being used to study host–pathogen interactions as well. In the case of *M. marinum* infection, although innate macrophages restrict initial bacterial growth, they also convey infecting bacteria into the granuloma, which serves as a site of bacterial growth and facilitates bacterial spreading, revealing striking similarities with *M. tuberculosis* pathogenesis in humans.

Finally, two reviews analyze host–pathogen interactions from an evolutionary point of view. Large scale sequencing of 12 *Drosophila* species has enabled a comparison of different components of the immune system with respect to their evolutionary dynamics, providing a textbook case that reflects the arms race between hosts and pathogens. B Lazzaro reviews the state of our knowledge on the evolution of antimicrobial immune genes in *Drosophila* and other insects, with the goal of providing a logical framework for understanding the evolution of immune factors in the context of their function in the immune response. Experimental analysis of the co-evolution of pathogens with their host is generally challenging. *Daphnia* and its parasites have become recognized as an excellent model system for studying the ecological, epidemiological, and evolutionary interactions between hosts and parasites. D Ebert describes the advantages of this system for the study of infectious disease biology and summarizes our current understanding of *Daphnia*–parasite co-evolution.

These diverse reviews reflect the rapid development of research on animal models in the field of infectious disease.