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GUEST EDITORIAL

Molecular Pathogenesis Lessons from the World of Infectious Diseases Research

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Infectious agents have caused epidemic and endemic diseases involved in the deaths of hundreds of millions of humans as well as significant animal morbidity and mortality throughout history. Indeed, the histories of investigative pathology and microbial pathogenesis are inexorably entwined, sharing well over a century of common ground. It is reasonable to presume that this will continue as new agents emerge (severe acute respiratory syndrome, Middle East respiratory syndrome, and other viruses), old pathogens reemerge (*Ebolavirus*), and resistance to antimicrobial agents increases in prevalence and importance.[1–4] We see no forceful counterbalances on the horizon to this ongoing "restless tide"[5] of pathogenic microbes.

In the current issue of *The American Journal of Pathology*, we present a series of reviews on four representative pathogens, including two pathogenic bacteria (brucellae and *Staphylococcus aureus*),[6,7] a virus (influenza),[8] and a parasite (*Trypanosoma cruzi*).[9] Each of these discussed microbes represents a major cause of human suffering. Contributing authors were given wide berth on which to focus on molecular pathogenic processes, broadly defined. The overarching goal was to summarize pertinent research on these pathogens, with special attention to specific molecular processes that contribute to pathogenesis and disease. Each organism illustrates different lessons about how pathogens do their dirty work. Rather than produce comprehensive reviews of all areas of pathogenesis, authors elected to highlight lessons that they believe would be of special interest to our readers.

Better Survival through Intracellular Life

One of the key themes repeatedly revealed by infectious diseases research in the past decade is that microbes are powerful agents for dissecting heretofore unknown or poorly understood cellular processes. That is, infectious agents are expert cell biologists, having evolved very clever strategies for exploiting specific molecular processes that contribute to cell integrity and organism homeostasis. This theme is highlighted in the contribution by de Figueiredo et al,[6] which focuses on the pathogenesis and immunobiology of brucellosis. *Brucella* species are a group of related Gram-negative organisms that cause very substantial economic loss in livestock such as cattle, goats, and sheep, with humans being incidental hosts. Importantly, *Brucella* species are classified by the United States Centers for Disease Control and Prevention as category B pathogens, representing potential bioterrorism agents. These organisms are largely intracellular pathogens and have thus evolved molecular strategies to substantially decrease assault by the host innate and adaptive immune processes. Thus, this review focuses on the various molecular processes used by these organisms to subvert host immunity, alter intracellular trafficking, and ensure their survival. As for virtually all other pathogens, in recent years substantial efforts have been directed toward using systems biology analyses to obtain a clearer image of the various phases of pathogenesis. These studies have revealed exciting new information about pathogen–host interaction and provided potential

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new leads for translational research, including new vaccines and therapeutics.

The Plus of Pus

Highlighting the contributions of the host and pathogen in the disease process, Kobayashi et al[7] review our understanding of *Staphylococcus aureus* abscesses. *S. aureus* is a Gram-positive coccus that is both a human commensal microbe and a pathogen. A relatively high percentage of healthy people are asymptomatically colonized with *S. aureus* in the anterior nares and other body sites. In addition, virtually all humans have antibodies directed against *S. aureus*, indicating exposure at some point during life. The high burden of *S. aureus* among humans is not without consequence. Indeed, *S. aureus* is a prominent cause of human infections globally, in health care and community settings. Antibiotic resistance is also a major problem. For example, a methicillin-resistant *S. aureus* strain known as USA300 remains the most prevalent cause of skin and soft tissue infections in the community.[10] Many of these infections manifest as abscesses, a well-known hallmark of *S. aureus*—complicated skin and soft tissue infections. In their review, Kobayashi et al[7] synthesize findings from historical and recent studies to formulate a contemporary model of the formation of *S. aureus* skin abscesses.

Influenza Virus and Bacterial Friends with Benefits

Kash and Taubenberger[8] summarize current knowledge of influenza virus pathogenesis. Influenza viruses are single-stranded RNA viruses belonging to the family Orthomyxoviridae. Influenza A virus is perhaps the most well-known of the five genera of Orthomyxoviridae, largely due to its propensity for causing human pandemics and seasonal outbreaks. For example, the influenza pandemic of 1918 was estimated to have caused 50 million deaths globally,[11] and seasonal influenza virus infections result in approximately 500,000 deaths annually.[12] Kash and Taubenberger[8] describe the factors that contribute to host susceptibility to severe influenza virus infections and death. Crucial to note, infection with influenza virus alone is seldom the cause of severe pneumonia. Rather, the majority of severe or fatal pneumonias are caused by secondary bacterial infections, with *Streptococcus pneumoniae*, *S. aureus*, and *S. pyogenes* (group A *Streptococcus*) most often linked to such infections. The high prevalence of these bacterial pathogens carried by the general population (eg, as with *S. aureus*), coupled with the pandemic nature of influenza viruses, poses a significant ongoing threat to humans. Thus, there is a clear need to move forward with research in this area as a means to promote the development of new vaccines and therapeutics for influenza virus infections. One area that remains elusive is the development of a broadly protective or universal influenza vaccine.[13]

Chagas Heart Disease and Parasite-Stimulated Self-Inflicted Harm

Bonney and Engman[9] focus on Chagas heart disease, with special attention to the history and current understanding of the devastating autoinflammatory cardiomyopathy that unfortunately is so characteristic of this disease. Chagas disease, caused by the parasite *Trypanosoma cruzi*, detrimentally affects 10 million people globally. It represents one member of the group of infections classified as neglected tropical diseases. Despite more than 100 years of study, we still lack a precise understanding of the molecular events involved in this cardiomyopathy. Bonney and Engman[9] very nicely summarize the proposed contributory mechanisms, including the two best studied: parasite persistence and autoimmunity. Their review includes a scholarly and balanced treatment of the history of autoimmunity research in Chagas heart disease. They also discuss the research challenges imposed by the exceptionally variable clinical outcome.

Summary and Future Perspective

This review series summarizes findings from crucial research areas in four pathogens of global interest. However, additional work in investigative pathology is needed in all areas of basic and translational infectious diseases research. We hope this review series illustrates the opportunities for the field of investigative pathology in studying the molecular basis of pathogen—host interactions.

References

1. Morens DM, Fauci AS: Emerging infectious diseases: threats to human health and global stability. PLoS Pathog 2013, 9:e1003467
2. Berry M, Gamieldien J, Fielding BC: Identification of new respiratory viruses in the new millennium. Viruses 2015, 7: 996—1019
3. Gire SK, Goba A, Andersen KG, Sealfon RS, Park DJ, Kanneh L, et al: Genomic surveillance elucidates Ebola virus origin and transmission during the 2014 outbreak. Science 2014, 345: 1369—1372
4. Report to the President on combating antibiotic resistance. Executive Office of the President. President's Council of Advisors on Science and Technology. 2014
5. Krause RM: The Restless Tide: The Persistent Challenge of the Microbial World. Washington, D.C., National Foundation for Infectious Diseases, 1981
6. de Figueiredo P, Ficht TA, Rice-Ficht A, Rossetti CA, Adams LG: Pathogenesis and immunobiology of brucellosis: review of Brucella-host interactions. Am J Pathol 2015, 185:1505—1517

7. Kobayashi SD, Malachowa N, DeLeo FR: Pathogenesis of Staphylococcus aureus abscesses. Am J Pathol 2015, 185:1518−1527
8. Kash JC, Taubenberger JK: The role of viral, host, and secondary bacterial factors in influenza pathogenesis. Am J Pathol 2015, 185: 1528−1536
9. Bonney KM, Engman DM: Autoimmune pathogenesis of Chagas heart disease: looking back, looking ahead. Am J Pathol 2015, 185:1537−1547
10. Talan DA, Krishnadasan A, Gorwitz RJ, Fosheim GE, Limbago B, Albrecht V, Moran GJ; EMERGEncy ID Net Study Group: Comparison of Staphylococcus aureus from skin and soft-tissue infections in US emergency department patients, 2004 and 2008. Clin Infect Dis 2011, 53:144−149
11. Taubenberger JK, Morens DM: The pathology of influenza virus infections. Annu Rev Pathol 2008, 3:499−522
12. Russell CA, Jones TC, Barr IG, Cox NJ, Garten RJ, Gregory V, Gust ID, Hampson AW, Hay AJ, Hurt AC, de Jong JC, Kelso A, Klimov AI, Kageyama T, Komadina N, Lapedes AS, Lin YP, Mosterin A, Obuchi M, Odagiri T, Osterhaus AD, Rimmelzwaan GF, Shaw MW, Skepner E, Stohr K, Tashiro M, Fouchier RA, Smith DJ: The global circulation of seasonal influenza A (H3N2) viruses. Science 2008, 320:340−346
13. Lu Y, Welsh JP, Swartz JR: Production and stabilization of the trimeric influenza hemagglutinin stem domain for potentially broadly protective influenza vaccines. Proc Natl Acad Sci U S A 2014, 111: 125−130