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INSIDE LAB INVEST

FILOVIRUS VICTIMS: TARGETS OR BYSTANDERS, MURDER OR SUICIDE? Outbreaks of hemorrhagic fevers induced by filoviruses such as the Ebola virus have captured popular attention because of the ferocity of the symptoms and the high mortality rate. Nonetheless, the processes underlying tissue injury are poorly understood. In this issue (Lab Invest 2000;80:171–186) **Geisbert and colleagues** seeks to understand the lymphopenia that is one of the hallmarks of the disease. Cells of the mononuclear phagocyte system are known to be primary targets of infection. Because lymphocytes are refractory to filovirus infection in vitro, the authors hypothesize that cytokines or other mediators cause lymphoid destruction in vivo. In support of this hypothesis, the authors report that infection of monkeys with filoviruses increases the frequency of apoptotic lymphocytes, which are themselves uninfected. Infection evidently induces lymphocyte apoptosis indirectly. Interestingly and paradoxically, infected cells do not usually undergo apoptosis. The authors speculate that filoviruses, like several other viruses, encode anti-apoptotic proteins to protect infected cells from the same mechanisms that kill uninfected neighbors. Because filovirus infection causes extraordinary hemorrhagia, it had been reasonable to suspect a direct effect of infection on endothelial cells. However, the authors failed to observe apoptotic endothelial cells. They hypothesize that the extreme vascular changes, like lymphocytic apoptosis, are induced by mediators released from infected cells. The next steps are to identify these putative mediators of lymphocyte and endothelial responses, which could be host-derived cytokines or virally encoded effector proteins or both. Outbreaks of infection with Ebola or Marburg viruses may become more common as geographical barriers between humans and animal reservoirs continue to dwindle, and the clinical tools available for managing the disease are meager. The work of Geisbert and colleagues, which defines key elements of filovirus pathogenesis, raises the hope that it will become possible to manage the disease through judicious use of cytokine antagonists, anti-apoptotic agents, and other immuno-modulators.

P. AERUGINOSA *VIRULENCE FACTORS IMPEDE EPITHELIAL REPAIR:* *Pseudomonas aeruginosa* is an opportunistic pathogen afflicting patients with a variety of chronic respiratory conditions, including cystic fibrosis, bronchiectasis, and emphysema. Others at increased risk include those immunocompromised by medication or AIDS. Contact lens wearers may also suffer, because *P. aeruginosa* is the most frequent infection of the cornea. Once established, *P. aeruginosa* infections are difficult to eradicate, and chronicity is common. Thus, understanding the factors that impair host clearance of this pathogen is an important challenge, but one that has proved daunting. Typically, such infections are suppurative and slow to heal. Beyond the usual tissue damaging suspects, such as peroxides and proteases released by infiltrating neutrophils, additional factors specific for this bacterium appear to be at play. Collectively, these bacterium-specific virulence factors are thought to directly impair epithelial wound closure, enhance the level of tissue destruction, and thereby perpetuate conditions conducive to the survival of the pathogen. Some of these virulence factors are now well appreciated, such as the ability of pathogenic strains of *P. aeruginosa* to selectively enter respiratory epithelial cells. However, sorting out the direct effects of the pathogen from effects arising from the host response or from soluble mediators released by the organism has remained one of the most difficult challenges. In this issue, **de Bentzmann and colleagues** offer several new and provocative insights into the process (Lab Invest 2000;80:209–220). To gain clarity, they first ask if there are direct effects of soluble mediators released by pathogenic *P. aeruginosa* on the motility of human respiratory epithelial cells in culture. Cell motility is required in vivo for wound closure; as such, it is a good in vitro surrogate of this process. By studying cells in culture, they are able to cleanly isolate the effects of soluble bacterial factors from host inflammation and the direct actions of the bacterium. Their results are clear: bacterial supernatants directly impair epithelial cell motility, cytoskeletal organization, and epithelial integrity. Next, they compare the virulence of an elastase deficient strain of *P. aeruginosa*; this strain is without effect, suggesting that elastase plays a central role in pathogenicity. Finally, they demonstrate that one consequence of the putative elastase activity released by the wild-type organism is the inappropriate activation of the gelatinolytic enzymes MMP-2 and MMP-9. These enzymes are produced in their zymogen form by the epithelial cells; however, their

activity is normally titrated to carefully effect the removal of damaged tissue prior to wound closure. In the presence of bacterial supernatants, this balance is distorted in a way that accentuates the destructive process. Although it is certain that many additional virulence factors are at play, the present results reveal with unusual clarity one pathway of virulence and offer a rationale for considering potentially novel therapeutic approaches to these chronic disorders.

MODELS FOR DISCOVERY-DRIVEN EXPERIMENTS: The development of technology (genomics, proteomics, tissue arrays) is giving us the capacity to look at complex events in biology in a comprehensive fashion. Thousands of data points can be obtained in a single experiment, and bio-informatics enables us to process, display, and organize the data sets to create new groupings that had not been intuitively obvious. The picture that emerges from such experiments is not constraint by a priori hypotheses and often produces unpredictable findings. It seems safe to forecast that in the post-genomic era, the study of patients with advanced technologies will continue to yield insight into normal function and will point to efficient and rational ways to prevent and treat disease. Experimental models for human disease, when studied with the same tools, promise to yield laws and principles that will generate new theoretical models and in turn serve as the basis for practical applications. The relevance of the experimental models becomes crucial if the subtle choreography of gene expression programs in diseased tissues is to advance the understanding of health and disease in the human. Studies of developmental programs in yeast using expression arrays point to the importance of morphology to guide the process of gene discovery. The use of morphological landmarks is likely to be even more important to unravel the expression programs deployed during carcinogenesis. In this issue (Lab Invest 2000;80:221–232) **Singh et al** present a thorough analysis of the similarities and differences between human and experimentally induced mammary tumors in the rat. Thorough descriptive comparative studies are needed to bring the proper context and perspective to the findings that will emerge from watching genomes in action. Comparative pathology is likely to provide a useful framework to annotate the data that will be forthcoming as human preneoplastic and tumoral tissues are examined with the tools of our brave new world.

PROLACTIN AND AUTOIMMUNITY: Prolactin was originally described as a regulator of lactation, but has since been found to have immune regulatory properties as well. Specifically, prolactin stimulates T and B lymphocytes and has been found to be elevated in the serum of patients with systemic autoimmunity, especially in systemic lupus erythematosis (SLE). The source of prolactin in these settings is unknown. In the current issue of the journal (Lab Invest 2000;80:239–248), **Steinfeld and colleagues** examine the labial minor salivary glands of patients with Sjögren's Syndrome (including those with and without systemic manifestations) and of healthy volunteer controls. Prolactin mRNA and protein was found in the acinar cells of the glands in patients, but not controls. The expression of prolactin was more elevated in those patients with clinical extraglandular disease and these levels are positively correlated with production of autoantibodies to Ro and La nuclear proteins. Surprisingly, the receptor appeared elevated on ductal epithelial cells but not on infiltrating mononuclear cells. Thus the current study implicates prolactin as a participant in organ-based autoimmunity, but does not identify a cause for its overexpression by a target tissue and does not establish its mechanism of action. Further investigation of Sjögren's patients and others with organ-specific autoimmune diseases (eg, Type I diabetes or autoimmune thyroiditis) are clearly needed to sort out the roles of prolactin in these types of disorders.