Metagenomics and Innate Immunity – A Unique Partnership or a Battlefield?

James A. Russell John H. Boyd

Centre for Heart Lung Innovation and Division of Critical Care Medicine, St. Paul's Hospital, University of British Columbia, Vancouver, B.C., Canada

The innate immune system is the interface through which the host and micro-organisms influence human health and disease, and it is this interaction which serves as the foundation of metagenomics. We propose that metagenomics will provide novel mechanistic insight and potential therapeutics for both classic infectious disease and what we now consider to be noninfectious diseases.

Metagenomics is the evaluation of the genomics of heterogeneous organisms, most often microbes and humans. The metagenomic era started with the genomic description of the microbial community of the human host [1]. Interestingly, the majority of organisms in humans that are detected by genomics are not cultured in the laboratory [2]. The large genomic differences between organisms account for critical microbial characteristics including virulence, antibiotic resistance and host/species adaptation. In contrast to humans whose predominantly noncoding DNA remains a puzzle, about 90% of the microbial genome codes for protein and structural RNA; this is a remarkably efficient structure/function relationship [3]. Although compact genomes facilitate research, the human fecal microbial community has over 500,000 unique genes and over 3 million genes in total – some 150 times the human genome [4]! Through integrating this emerging microbial data with that of the host response, metagenomics could be used for the early accurate diagnosis of infections (a diagnostic biomarker), the discov-

ery of new pathogenic microbes [5] and the prediction of responses to therapy, even in noninfectious diseases such as atherosclerosis [6].

This issue of the *Journal of Innate Immunity* focuses on metagenomics. We have pleasure in presenting three publications specially selected for this theme issue. They focus on the skin, intestinal and lung microbiomes in diseases such as chronic mucocutaneous candidiasis, cirrhosis and pneumonia.

Smekens et al. [7] hypothesized that the STAT1/STAT3 mutations which lead to chronic mucocutaneous candidiasis would also change skin and mucosal microbiomes. Using 16S rRNA sequencing, the authors found that the skin of such patients had more Gram-negative bacteria (especially *Acinetobacter*) and less *Corynebacterium* than that of healthy controls. When they exposed leukocytes to *Acinetobacter*, the innate immune response (cytokine expression) to *Candida* was suppressed. Could this relationship be causal, or at least contributory? In other words, it appears that *Acinetobacter* tolerizes the host to the presence of *Candida*. One interpretation of these results is that alterations in the bacterial community, as a result of STAT1/STAT3, lead to more *Acinetobacter* within the dermal microbiome and thereby increase the risk of *Candida* infection. This link may shed light on the association between fungal infection and the prior use of antibiotics, an event well-known to alter bacterial communities.

Cuenca et al. [8] evaluated how alterations of the microbiome of the intestinal lymph nodes affect the immune response in an animal model of cirrhosis. Using 16S rRNA sequencing, they found that both control and cirrhotic rats had a high microbial diversity in the mesenteric lymph nodes, but that cirrhotic rats experienced decreased microbial diversity. One species (*Bifidobacterium animalis*) was positively associated with an altered IL-10 response. Thus, bacterial translocation (assessed both quantitatively using PCR and by 16S RNA sequencing) across the intestine may be more common than is conventionally understood using standard culture methods. Finally, Boyd et al. [9] review the roles of host genetics, pathogens and the acute immune response in sepsis. Better outcomes of septic shock could be achieved by (1) early accurate organism identification, paired with (2) early, accurate detection of host genomics and immunity evaluation, the essence of the metagenomic approach. Early treatment with antibiotics is fundamental in septic shock, yet clinicians do not obtain conventional culture results for 24–48 h (median 30 h in our center). Genomic approaches could rapidly and accurately identify organism(s) to drive earlier, accurate antibiotic selection. Unfortunately, current PCR-based techniques are limited in identifying unique pathogens in the blood due to the relatively low abundance of bacteria [10]. Accordingly, Boyd's group focuses on the microbiome of the sputum in community-acquired pneumonia. This technology holds great promise for the improved diagnosis of the respira-

tory pathogens in severe pneumonia. Human host genetic variation may also influence the response to an infection (e.g. the degree of immune activation and organ dysfunction) [11, 12]. There is a unique pattern of cytokines, chemokines and growth factor response in septic shock [13]. This unique innate immune response is predictive of death [14].

What is the future of medical management arising from research centered on metagenomics and innate immunity? The interaction of the microbial genome and the host could be a unique partnership in health but could also deteriorate into a battlefield of disease – discerning the difference here is critical. We foresee that the simultaneous evaluation of an individual's microbial genomes and their unique innate immune response (e.g. genomics and expression pattern) will be able to be used in many serious infections for staging patients and personalizing therapies that modulate both the pathogen load and type as well as the pace and focus of the innate immune response. In line with this, we encourage the continued submission of high-quality original research regarding the interaction of microbial genomics with innate immunity.

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