

Chapter 39

Connecting Microbial Population Genetics with Microbial Pathogenesis: Engineering Microfluidic Cell Arrays for High-Throughput Interrogation of Host-Pathogen Interaction

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ABSTRACT

A bacterial species typically includes heterogeneous collections of genetically diverse isolates. How genetic diversity within bacterial populations influences the clinical outcome of infection remains mostly indeterminate. In part, this is due to a lack of technologies that can enable contemporaneous systems-level interrogation of host-pathogen interaction using multiple, genetically diverse bacterial strains. This chapter presents a prototype microfluidic cell array (MCA) that allows simultaneous elucidation of molecular events during infection of human cells in a semi-automated fashion. It shows that infection of human cells with up to sixteen genetically diverse bacterial isolates can be studied simultaneously. The versatility of MCAs is enhanced by incorporation of a gradient generator that allows interrogation of host-pathogen interaction under four different concentrations of any given environmental variable at the same time. Availability of high throughput MCAs should foster studies that can determine how differences in bacterial gene pools and concentration-dependent environmental variables affect the outcome of host-pathogen interaction.

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INTRODUCTION

...organisms of the most different sorts are constructed from the very same battery of genes. The diversity of life forms results from small changes in the regulatory systems that govern expression of these genes. ~ Francois Jacob, Of Flies, Mice and Men

Decades of population-based molecular epidemiological studies have revealed three general aspects of bacterial pathogenesis: (1) there is extensive genetic diversity within most bacterial species; (2) sibling bacterial species, and even strains within species, differ in their virulence potential; and (3) that normally harmless bacteria can be pathogenic in an injured or immuno-compromised host (Dykhuizen & Kalia, 2008). Thus, for several decades, studies aimed at understanding the mechanisms of bacterial pathogenesis have focused on addressing two major questions: (1) what are the molecular and evolutionary mechanisms that generate and maintain genetic diversity among natural bacterial populations? And (2) what are the mechanisms employed (or exploited) by bacterial pathogens to cause human disease? While several strides have been made in our understanding of both aspects, we have only just begun to comprehend the impressive complexity in the molecular nature of host-pathogen interactions, and the resulting clinical outcomes. Even infection with genetically related bacterial isolates can result in multiple clinical outcomes that range from asymptomatic and benign carriage to development of severe and fatal disease in the human host. These complex interactions are perhaps best illustrated by the two bacterial pathogens: *Helicobacter pylori* and *Streptococcus pyogenes*. Both these bacterial species are considered obligate human-specific pathogens and are responsible for a wide-variety of clinical disorders (Atherton & Blaser, 2009; Carapetis JR, Steer AC, Mulholland EK, & M., 1995). For example, *H. pylori* can cause gastric cancer, peptic

ulcers, duodenal ulcers, atrophic gastritis, and *S. pyogenes* can cause a spectrum of diseases that range from mild (strep throat) to severe invasive diseases (e.g. TSLs) and autoimmune syndromes such rheumatic fever. Paradoxically, both *H. pylori* and *S. pyogenes* can also establish long-term colonization in their human host without causing any significant disease. Disconcertingly, there are no reliable markers that can predict the likelihood of a particular clinical outcome following infection by either *H. pylori* or *S. pyogenes*. Thus, understanding the molecular basis for such clearly distinct clinical outcomes of infections with genetically related bacterial isolates is a fundamental problem in pathogenesis and, which is necessary to address in order to develop predictive models for infectious disease risks.

Systems approaches to develop predictive network models of disease are based on the notion that disease-perturbed gene and protein regulatory networks differ from their normal counterparts. Host cellular response to an infectious agent likely involves interactions at multiple gene loci and environmental cues in particular, contact with bacterial cell and/or its secreted products. The response might include fluxes in gene regulatory networks that integrate dynamically changing signals and activate batteries of genes mediating physiological responses via proteins that may function alone, in complexes, or in networks that arise from protein interactions (Nicholson, Holmes, Lindon, & Wilson, 2004). Any host response invokes an equivalent “negotiating response” from the bacterium (Figure 1). This dynamical interaction of cellular entities is representative of the heterogeneity that characterizes biology - from the differences in how individual cells respond to bacterial stimulus, to the diversity of cell types and environments within real tissues and their associated microbiomes.

In addition, many infectious diseases, in particular those that result from chronic infections, have a multifactorial etiology (Ewald, 2004); however, majority of studies aimed at character-

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