On the road to systems biology of host–pathogen interactions

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“...scientists in the area of microbial pathobiology will soon regard the integrated ‘omics’ approach as the fundamental tool of their discipline.”

This issue of *Future Microbiology* describes progress that has been made “on the road to systems biology of host–pathogen interactions”. The interplay between a given viral, bacterial or parasitic pathogen with their respective host organisms can be viewed as the battle of two genomes, each with its own selfish need to perpetuate itself, even if that means manipulating, or even eliminating, the other organism. On the other hand, the opposing organisms may undergo a détente in which their mutual existence is beneficial or synergistic. For example, a human being contains at least ten-times more bacterial cells than host cells and, in many ways, humans can also be viewed as a human/microbe hybrid with eukaryotic and prokaryotic cells being intrinsically interdependent. Host–pathogen relationships are highly complex and mutual interactions occur at every conceivable level: at the cellular level pathogen proteins interact with and modulate their host cell environment; at the tissue level pathogens can alter the cytokine balance needed for tissue homeostasis; at the organismal level pathogens evade and manipulate the host’s immune system; and, finally, at the population level pathogens and host species influence each other’s evolution. A complete understanding of these interactions at every level is the ultimate goal of ‘systems microbiology’.

Achieving this goal requires us to:

- Be able to measure host–pathogen parameters at a global level, and measure how these parameters change kinetically as the relationship between host and pathogen progresses;
- Integrate different types of global measurements into a consolidated picture of their dynamic relationship;
- Develop testable models of these interactions; for example, by developing computational methods with genuine predictive powers.

The reviews and editorials presented in this issue discuss recent developments towards eventually achieving each of these approaches. The editorial by Didier Raoult is particularly provocative and argues that the global, functional genomics-type experiments that do not necessarily have an underlying hypothesis will be the future of microbiology, as such experiments will inevitably result in novel, unexpected revelations about host–pathogen systems [1]. The readers can decide for themselves if they agree with his prediction that classic hypothesis-driven research will be eventually replaced by hypothesis-null ‘discovery’ research in the future. Tisoncik and Katze make a strong case for mathematical modeling and iterative validation experiments being at the core of any experimental inquiry that can be called ‘systems biology’ [2]. However, as discussed in the review by Watterson and Ghazal, mathematical modeling of complex biological systems is still exceedingly challenging, as they propose a logical, binary approach to simplify modeling of signal transduction cascades [3]. The challenges in mathematical modeling, together with the fact that there are still huge challenges in our ability to measure all parameters of a given host–pathogen system, are the major reason why, so far, very few host–pathogen interactions have been studied by true systems biology approaches. However, the global determination of factors that control host–pathogen interaction has made great progress in recent years and this progress is the main focus of this issue.

One revolution that has taken place recently is the acceleration of pathogen discovery and identification of new microbial families for which the hosts have not yet been defined. As discussed in the review by Tang and Chiu for viruses [4] and by Leski *et al.* for bacteria [5], pathogen-specific DNA microarrays, comparative genome

hybridization and next-generation deep sequencing has revolutionized our ability to detect novel microbial entities or to establish novel disease etiologies of known pathogens. The same metagenomics techniques also allow investigators to study changes in pathogen populations within a host organism or host population. These techniques not only generate novel insights into host–pathogen interactions, but they will also be extremely valuable in developing future advances in diagnostics and epidemiology.

DNA microarrays are, by far, the most robust current functional genomics tool for measuring global responses of both pathogens and their host organisms. As discussed by Sturdevant *et al.*, DNA microarrays have been used to study both pathogen responses to the host as well as the host responses to the pathogen [6]. In many instances, these studies are now integrated with other ‘omics’ techniques, such as proteomics. One example of such data integration is the meta-analysis of poxviral T cell and antibody epitope data, described by Alex Sette and colleagues, where virus-specific DNA microarray data revealed an unexpectedly skewed preference of CD8⁺ T cells to recognize early gene products and CD4⁺ T cells to recognize late gene products, and also that a close linkage exists between antibody epitopes with CD4-restricted T-cell epitopes [7]. Another example of this kind of data integration is the combination of proteomics with DNA array technology to measure antibody responses to known and novel pathogens, as discussed by Felgner *et al.* [8].

DNA microarrays are often used to make predictions about protein expression and abundance, that is, they are actually used as a proteomics tool by inference from transcriptomics measurements. While it is easier to measure mRNA abundance than protein abundance for a number of reasons, these two measurements often do not correlate, as highlighted in the chapter by Sette *et al.* [7]. Fortunately, proteomics has made great strides in recent years and many host–pathogen interaction studies now directly monitor global protein levels, as reviewed by Bhavsar *et al.* [9]. Progress has also been made in global methods that monitor post-translational modifications, although many challenges remain, as exemplified in the review by Reid *et al.* on glycomics, the global measurement of glycoproteins and glycolipids [10]. Such glycosylated proteins and lipids play a particularly decisive role in bacterial

pathogenesis, and this clearly represents an area where further technological advances are needed.

Another emerging field is metabolomics: the study of host and pathogen metabolites on a global scale. As reviewed by Borchers *et al.*, the metabolic phenotypes (metatypes) of the human/microbe hybrid (or superorganism) can be correlated with disease phenotypes, as they are derived from, or in response to, specific microbes present [11].

Similarly, virus-infected cells can be viewed as a hybrid between two organisms, with both partners contributing to the outcome of infection. Thus, viruses and their global dynamics can only be understood in the context of their respective host cells and tissues. To better understand their mutual interactions, large-scale protein interactomics studies have been initiated, as reviewed by Mendez-Rios and Uetz, with the goal of identifying all interactions between viral proteins and host cell proteins [12]. For complex viruses, such as poxviruses and herpesviruses, similar studies have also monitored the protein–protein interactions within the viral proteome. These studies already revealed that many viral proteins have preferentially target highly connected host proteins. As discussed by Hirsch, one way to examine the relevance of such interactions is to selectively knockdown host-cell target proteins using siRNA [13]. The availability of large siRNA libraries now enables investigators to examine which host cell proteins are supportive, inhibitory or neutral towards an ongoing viral infection. One of the troubling aspects of these global siRNA knockdown screenings is the frequent disparity of the datasets generated by competing labs, suggesting that either the technology itself needs further refinements or else the inherent variability between virus–cell pairings chosen is much greater than currently appreciated.

While many of these ‘omics’ studies are highly interesting in their own right, comparing multiple cross-disciplinary studies by meta-analysis often reveals trends that are overlooked in the individual studies. For instance, a comparison of several siRNA screens shows that certain host-cell protein complexes, or their activation states, are essential for the optimal replication of many viruses from different classes. In addition, the statistical significance of individual ‘omics’ results can be strongly enhanced when different ‘omics’ experiments are combined and their results integrated. Such

data integration across ‘omics’ platforms is discussed in the review by Kint *et al.*, who state that “integration of data in a reliable way is still very challenging and, until now, the number of studies actually combining several strategies is limited” [14].

It is our intention to use this review compendium as a vehicle to foster further development of systems biology approaches to the study of host–pathogen interactions. In 2010, this field is still in its infancy and many of the current approaches have been sometimes described as global ‘fishing expeditions’, but it is our contention that the next generation of scientists in

the area of microbial pathobiology will soon regard the integrated ‘omics’ approach as the fundamental tool of their discipline.

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