Editorial

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Systems Biology and Innate Immunity

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The innate immune system is the first line of host defense against invading microorganisms and is essential for maintenance of host health. The innate immune response is largely mediated by soluble host factors – such as complement – and phagocytic leukocytes. Cells of the innate immune system are equipped to recognize a diversity of pathogens through pattern recognition receptors present on the cell surface. In addition, deposition of complement and antibody on the microbial surface enhance the phagocytic process. The ability of phagocytes to ingest and kill pathogenic microorganisms is immediate, nonspecific and not dependent on previous exposure to microbes. The innate immune response plays a pivotal role in initiating inflammation, and regulation of this critical process is highly complex. Over the past decade, our understanding of complex biological processes – including the molecular mechanisms of innate host defense – has increased dramatically through the application of systems biology-level approaches. For example, genome-wide transcript analyses and proteomics studies have been instrumental in dissecting complex signal transduction pathways involved in recognition and killing of bacterial and fungal pathogens by cells of the innate immune system. In addition, similar strategies have been used to elucidate a diversity of host pathways involved in defense against viral pathogens. A thematic focus section in this issue of *Journal of Innate Immunity* highlights the use of systems biology approaches to better understand innate immunity.

Inflammatory disorders or syndromes are readily amenable to investigation by systems biology approaches, largely because an extensive repertoire of antibodies, reagents and assays exists for the evaluation of inflammatory cells and molecules. Moreover, inflammatory disorders often have systemic sequelae such as changes in acute inflammatory molecules, which can be measured quantitatively in blood, plasma or serum. Rheumatoid arthritis is a chronic inflammatory disease associated with damage to joint cartilage and bone, as reviewed by Scott et al. [1]. Tumor necrosis factor and cytokines such as interleukin 6 are known contributors to inflammation in rheumatoid arthritis [1]. In the first article of this thematic focus section, Masi et al. [2] utilize serum samples from a relatively large human cohort to identify host inflammatory molecules that might be predictive for rheumatoid arthritis. Analysis of the data from the study cohort using statistical modeling permitted construction of an integrative model of serum inflammatory molecules. The model is a step toward a comprehensive understanding of immune networks and patterns of inflammatory molecule expression that precede or predict the onset of rheumatoid arthritis.

The complement system is one of the first components of the host innate immune system to respond to invading

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microorganisms. There are numerous functions of complement proteins, including the opsonization of microbes for host recognition and activation of the inflammatory response [3]. Complement activation produces protein fragments known as anaphylatoxins – e.g. C5a – which are known regulators of inflammation [3]. C5a receptors are present on many cell types, including neutrophils, and C5a is a known neutrophil chemoattractant and has been reported to either directly activate these leukocytes or prime them for enhanced function [3, 4]. Notably, previous studies in mice have demonstrated that the C5a receptor is important for innate host defense against infection [5]. The ability of complement components such as C5a to diffuse to-and-from bacteria, especially those in biofilm matrices, is likely critical for the function of these molecules in the context of host defense. However, there is limited knowledge of this process. To that end, Conrad et al. [6] used a mathematical modeling approach to predict how bacterial biofilm matrices influence production and diffusion of C5a.

Neutrophils are critical in the defense against bacterial infections. These host cells are the most abundant leukocytes in humans and are recruited rapidly to sites of infection. Most bacteria are ingested and killed readily by neutrophils and this process ultimately leads to neutrophil apoptosis or phagocytosis-induced cell death, a process important for the resolution of the inflammatory response. However, some bacteria have evolved means to circumvent killing by neutrophils and thereby cause infections. The ability of bacteria to delay neutrophil apoptosis and turnover or cause some other form of cell death (e.g. cytolysis) is an important component of pathogenesis [7]. Inasmuch as neutrophils have a relatively short lifespan (9–10 days, with ~1 day in circulation), they are not especially well suited as hosts for intracellular pathogens. Indeed, macrophages, which are long-lived phagocytes, are targeted as appropriate host cells by many bacterial pathogens. That said, there are a few bacterial pathogens that survive and replicate within neutrophils, including *Anaplasma phagocytophilium* [8] and *Francisella tularensis* [9]. Although progress has been made, our understanding of the molecular mechanisms that permit these pathogens to prolong neutrophil survival remains incompletely characterized. In this special focus section, Schwartz et al. [10] use a microarray-based approach to gain a better understanding of the mechanisms used by *F. tularensis* to delay neutrophil apoptosis. The authors demonstrate that the pathogen triggers specific antiapoptotic and prosurvival mechanisms to survive within neutrophils.

A comprehensive understanding of the interaction of host and pathogen molecules during infection can provide a potentially important view of the disease process. For example, previous work by Shea et al. [11] determined concurrent host and pathogen transcriptomes – known collectively as an interactome – during infection of non-human primates with *Streptococcus pyogenes*. Such interactome studies can identify biological processes important for both host and pathogen during infection. Using an interactome approach combined with previous protein-protein interaction data and mathematical modeling, Kuo et al. [12] investigated the host and pathogen molecules involved in the infection of zebrafish with *Candida albicans*. Zebrafish are genetically tractable and have become widely used as a host model for infectious disease research. *C. albicans* is an opportunistic fungal pathogen of humans that grows as either a budding yeast or filamentous hyphae, and the ability of the yeast to form hyphae is important for virulence [13, 14]. The studies by Kuo et al. [12] identified a protein-protein interaction network that provides new insight into development of hyphae during *C. albicans* infection. The findings can be used as a springboard for more targeted studies of the specific pathways and molecules involved in the fungal invasion process.

It is well established that circadian rhythms regulate key daily functions and behaviors, such as metabolism and sleep-wake cycles [15–17]. Indeed, much research focus has been placed on understanding the influence of circadian rhythms on metabolism and dietary health. There is also compelling evidence that circadian rhythms influence or regulate immune system function. For example, a circadian clock in macrophages regulates changes in expression of genes important for pathogen recognition and the innate immune response [18], and phagocytosis is circadian-regulated in *Drosophila* [19]. Plant innate defenses against bacterial pathogens are optimal in daytime [20], a phenomenon related at least in part to circadian control of the recognition of pattern-associated molecular patterns [21]. In mammals, REV-ERBα (a nuclear receptor and transcriptional repressor) and cryptochrome and CLOCK (core clock proteins), have been identified recently as important links between circadian rhythm and immune function [22–24]. Given the importance of circadian rhythms in innate immunity, it is not surprising that disruption of the circadian cycle is associated with inflammatory syndromes [25]. The confluence of innate immunity and circadian cycle is highly complex, and it is within this context that Mavroudis et al. [26] review the use of systems biology-level approaches as a

means to gain an enhanced understanding of the role of circadian rhythms in innate immunity. These authors underscore the use of mathematical models to predict function and mechanisms of clock networks.

Systems biology and system biology approaches are changing rapidly as technology moves forward. As a result, many areas of basic and applied research, including the field of innate immunity, are now poised to undergo – or have undergone – major scientific breakthroughs. The articles presented in this thematic focus section provide examples of the diverse nature of systems biology approaches in innate immunity.

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