The Case for Immuno-Informatics

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Charles G. Orosz, PhD
Department of Surgery/Transplant
The Ohio State University
353 Means Hall
1654 Upham Drive
Columbus, OH 43210, USA
Tel.: 614-293-3212
Fax: 614-293-4541
e-mail: orosz-1@medctr.osu.edu
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Introduction

In previous communications,[1] we have presented a view of the immune system that differs significantly from conventional conceptualizations. We have maintained that the immune system is a functional network, indeed a network of networks, designed to help maintain homeostasis within the broad physiologic system that constitutes the organism. Although immunologists have long appreciated the networked nature of the immune system, it is commonly ignored by most of them. This allows immunologists to minimize the complexity of their experimental systems and to simplify their resulting conceptualizations. Nevertheless, there are few features of immunity as formative as its networked nature, and a true understanding of the immune system will not be developed until its networked nature has been accommodated.

We believe that the immune system, like all complex, adaptive systems, is a highly dynamic structure that is inherently capable of maintaining coherence under stress, of adapting to change, and of learning. The previous communications have focused primarily on the features of the immune network that contribute to its dynamic nature and its ability to maintain coherence in the face of change. We have referred to this topic as immuno-ecology, the study of the principles by which complex immune responses self-organize and operate.[2] In general, the principles of immuno-ecology permit the immune system to cope with, and even benefit from, its own complexity. We now turn to the related topic that involves the immune system's capacity for adaptation and learning. We have referred to this topic as immuno-informatics, the study of the principles by which the immune system generates, posts, processes, and stores information.[2] In general, the principles of immuno-informatics allow the immune system to evaluate and respond to new or changing conditions. The distinction between immuno-ecology and immuno-informatics is highly artificial, since each is completely dependent on the other. The immune system could not appropriately exercise its response options without information, and immune information is generated by the choices made in a complex, adaptive system. However, to appreciate their individual contributions, it is useful to consider immuno-ecology as the vehicle of immunologic function, which is fueled by immuno-informatics.

Why Immuno-Informatics?

The immune system can be characterized as a complex, adaptive system. Complexity provides a reservoir of options to the immune system, and conditional use of these options permits adaptation to change. This raises the question of how the immune system chooses appropriately from among its options. This appears to involve trial and error fine tuned by 2 avenues of information: memory and feedback. Immunologic memory provides information on successful prior strategies, whereas feedback provides information on the success of current strategies. Together, these 2 avenues of information guide and stabilize the adaptive flexibility of the immune system, providing it with a strong competitive advantage over the inflexible operations of replicating invaders and other immune challenges.

The View from the Population Level

To appreciate this process, it is useful to consider the fundamental nature of the immune system. When viewed at the population level, an immune response involves the mobilization of heterogeneous masses of leukocytes to sites of damage or invasion. Biologists refer to this process as tissue inflammation. In fact, inflammation represents a leukocyte swarm,[3] a process whereby large numbers

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of various leukocyte subtypes, each with a different series of genetically programmed response options, move to a new site in the body. The development of an effective immune response requires a complex, coordinated series of events, including (1) the mobilization of the swarm to the challenge site, (2) the recognition of the challenge agents, (3) the selection and implementation of an appropriate response option, and (4) the disassembly of the response when the challenge has been effectively addressed. Often, selected cell types within the leukocyte swarm can recognize the challenge agent directly, by its displayed elements, or indirectly, by its pathogenic footprint in challenged tissues. We refer to this fundamental recognition process as innate immunity. As a backup, mammalian immune systems can transport elements of the challenge site back to the leukocyte hive (lymph node/spleen) for review by the adaptive immune system (T cells and B cells). Among other things, the adaptive system provides a memory component to the immune system. When engaged, selected elements of the adaptive system are mobilized to the challenge site to reinforce the local response and to provide additional response options. Because the immune system cannot know in advance the nature of the immune challenge, the initial responses appear to be preprogrammed in nature and to involve a wide range of sensory agents, in effect, an all-purpose leukocyte swarm. As the immune response evolves, information is gathered about the challenge agent that facilitates the selection of appropriate response options. The response shifts from an all-purpose survey to a focused endeavor involving selected immune components. At some point, the leukocyte swarm completes its tasks and enters the final phase of the response, the disassembly of the swarm in preparation for the return to tissue homeostasis.

During an immune response, many immune agents within the challenge site and within the immune hives (peripheral lymphoid organs) cooperate to mobilize and modify the immune swarm, but this process merely sets the stage for the immune response. The core element of the immune response is the process by which the immune system evaluates and deals with an immune challenge at a specific site in the body. Each response is built de novo by the immune components that swarm into the site. The challenge agents provide important information to the immune system, but they are not the only source of information at the challenge site. Equally important is the nature of the challenge site itself. For example, some sites, such as the eye, are nonpermissive for virtually all immune responses. Other sites may be nonpermissive for selected types of immune responses. Presumably, this reflects the degree of compatibility between a particular immune response option and local tissue function. In general, the choice of local immune response options reflects a compromise between the agenda of the immune system and the physiologic agenda of the tissues at the challenge site. The immune system does not necessarily build the optimal immune response. It builds the best response that it can under the conditions present at the specific location. Thus, 2 different tissues could simultaneously develop very dissimilar immune responses to the same challenge agent. In this way, the information available at the local level of the immune response is critical. Together, the challenge agents and the local site conditions provide a unique set of information to the swarm participants, which, in turn, use this information to select from among their available response options to build an immune response. The selection of a specific option provides more local information to the swarm participants, and this iterative process of information generation and transmission permits the evolution of the local immune response. This process of information flow is pure immuno-informatics.

Information transfer occurs via cell-to-cell communication during every phase of the immune responses. Communication can occur via a wide range of direct (cell-cell contact) or indirect (cell contact with secreted mediators) mechanisms. Ultimately, this information helps the leukocyte swarm to (1) localize to the appropriate site in the body, (2) recognize formative features of the local situation, (3) develop appropriate immune effector mechanisms, and (4) disassemble when its goals have been met.

It should be noted that response options can range from eradication of the challenge agent to its acceptance and incorporation into the organism. Thus, the immune response must involve a decision-making process that determines how best to deal with the challenge agent with regard to the broader interests of the body. Furthermore, feedback information must be generated as the immune response develops that allows the immune system to determine whether it is making progress toward the implementation of its decision. Immune decision making, strategy development, and strategy appraisal are all important aspects of immuno-informatics.

Clearly, vast amounts of information are generated and traded among members of leukocyte swarms and leukocyte hives during immune responses. Swarm members also trade information with resident cells of the challenged tissues. Indeed, the amount of information traded concurrently during an immune response is daunting. This fact raises problems, both for the immune system and for its investigators. Virtually all immunologists appreciate that leukocytes communicate through cytokines, chemokines, and costimulators, but most study these communications as infobytes rather than as an integrative, information-sharing conversation among leukocyte swarm members and the tissues that they visit. Indeed, the linguistics of the immune system remain obscure and are worthy of study in their own right. Furthermore, it is unclear how the multiple, simultaneous conversations that occur at a challenge site remain coherent and do not degenerate into chaos-generating babble. This is an immuno-ecologic issue. One principle that apparently governs this aspect of immune function is conditional reception, the selective expression receptors in various situations. This effectively allows cells to "listen" to one conversation at a time. The operation and value of this working principle has been discussed elsewhere.[3]

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The View from the Individual Leukocyte Level

Of course, leukocyte swarms are composed of hordes of individual leukocytes, each generating and responding to selected sets of information. How each one obtains, processes, and responds to this information has been the primary focus of conventional immunologic investigation. It is only when investigators consider the behavior of large numbers of heterogeneous, interactive leukocytes that understanding is quickly lost. Leukocyte population behavior within tissues is the frontier of modern immunology.

The behavior of individual leukocytes is similar to that of colonial insects. Like ants and bees, individual leukocytes are endowed with a set of genetically defined behavior patterns, each of which they deploy conditionally when the correct environmental stimuli are encountered. Their responses are thoughtless, reflexive, choreographed, and performed without hesitation. The immediate microenvironment provides the selective stimuli (information) needed to alter the behavior of each leukocyte. In the absence of such stimuli, leukocytes simply continue their current behavior. Thus, individual leukocytes are slaves to the information presented by the immediate environment. Given the list of cues and responses, the behavior of individual leukocytes is totally predictable. Leukocytes do not consider options or ponder consequences. They act unhesitatingly without concern for their own well-being or the well-being of others. Each operates as an expendable, mindless automaton with no personal worth, no personal agenda, and no personal understanding of the overall situation.

What makes this system work is the virtually unlimited number of leukocytes available to it, and the huge numbers of leukocytes that are recruited into each swarm process. The loss or malfunction of an individual is relatively inconsequential because others readily compensate it. Although each individual may perform only a small part of a task, hordes of individuals operating together can perform big jobs. They may be inefficient, but they are reliable. Of interest is the fact that they do so with no leaders and with no blueprints. Under these conditions, leadership and plans are unnecessary. Thus, information related to these categories is unnecessary. Furthermore, complex tasks can evolve in a coordinated fashion when the workers add new stimuli (information) to the environment through completion of their initial tasks. This process induces new behaviors that build on previous behaviors. Highly complex tasks can be accomplished in this manner. However, the progression of these tasks depends completely on the availability of components and operational information within the local environment. These influence the choices made at each step in the process and, thus, guide the direction in which the task evolves. A missing component is rarely a problem, since the networked nature of the system provides alternative options for missing components. Operational information permits the effective substitution of alternative components so that the task is eventually performed, despite changes in the route to the end.

This element of conditional evolution makes leukocyte swarm functions somewhat unpredictable, unlike the functions of individual swarm members. This provides a serious problem to investigators, whose current approach involves the ever more detailed analysis of individual swarm components. Such investigations cannot reveal the progression of swarm functions because they ignore the element of conditional evolution. Thus, investigators struggle to understand immune responses, despite their considerable understanding of how individual leukocytes operate. What they fail to appreciate is the importance of local immune response conditions, which control the availability of formative response elements and the availability of operational information. Understanding the former is the goal of immuno-ecology, whereas understanding the latter is the goal of immuno-informatics.

Summary

The networked nature of the immune system endows it with options, but little is known about how these options are exercised in the event of new or changing conditions. Option selection in a leaderless swarm system requires 2 things: the generalized provision of information to the individual swarm members and rules by which each of the various swarm members respond to that information. Currently, little is known about the informational aspects of immune function. What constitutes immune information? How is this information generated? How is it distributed, received, and processed? These are questions that constitute the area that we have termed immuno-informatics. This communication is the first in a series of articles on the topic of immuno-informatics. In it, we describe why the immune system needs an information system and how an information system contributes to an immune response. A subsequent communication will address what constitutes information within the immune system and how such immune information is generated. A third will address how immune information is received, processed, and stored by components of the immune system. Understanding information flow within the immune system is a daunting challenge. However, it is a necessary endeavor if we are ever to truly understand the function of the immune system.

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