TOLL-LIKE RECEPTORS AND THEIR PLACE IN IMMUNOLOGY

Where does the immune response to infection begin?

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And for that matter, where does all immunity begin, including autoimmunity? Is there a 'first cause' of such complex phenomena? A molecular spark that lights the fire? The answer is much simpler than many might have thought even a short time ago.

For more than a century, we have known of the existence of two basic types of immunity in mammals. There is adaptive immunity (known as specific immunity), so named because it reacts specifically to the situation, gathering strength once a particular micro-organism attacks the host. And there is innate immunity (known as natural immunity or innate resistance), so named because we are born with it, and it defends us against microbes we have never seen before. Both of these immune systems (in fact, any immune system imaginable) must have a means of sensing infection, discriminating self from non-self, and controlling or eradicating infection.

Although effector mechanisms were defined for both systems decades ago, the key molecular sensors used by the mammalian innate immune system to detect microorganisms were identified only in the late 1990s. Their discovery was presaged by work in *Drosophila* (discussed in this special issue by Bruno Lemaitre), which led to the realization that a cell-surface protein known as Toll — previously better known for its role in development — is a key component of a biochemical pathway that alerts flies to infection, prompting the production of antimicrobial peptides. This discovery coincided with steady advances in genetic technology that allowed others to show that mammals use 'Toll-like receptors' (TLRs) as direct sensors of microbial infection.

The discovery of TLR function was a triumph of reductionism and filled a great void in immunology. Immune responses are tremendously complex when fully developed, yet it now appears they are ignited by only a few molecules. Mammalian responses to virtually all microorganisms depend upon TLRs *ab initio*. The TLRs are the key site of direct and consequential contact between the cellular immune system and its microbial quarry. If the TLRs, their adaptors, or the kinases to which these adapters are linked are lacking, the host is severely immunocompromised. Macrophages do not make the requisite cytokines to initiate the full repertoire of innate immune responses. They do not summon neutrophils to aid in the destruction of microorganisms. Neither do neutrophils respond directly to microorganisms in the way that they should. And without the innate immune response that precedes it, the adaptive immune response is feeble. The TLRs are clearly at the top of the immune-system pyramid.

This level of understanding is new, and the field has developed quickly. Both random and targeted germline mutagenesis have helped to resolve the complexity of the TLRs and their signalling pathways, and we are beginning to elucidate a conceptual framework or 'roadmap' that will be essential to understanding just how the TLRs work and what they do. Here, Shizuo Akira reviews recent advances in signalling, taken from strong genetic data. Luke O'Neill has organized what is known about TLR signalling into poster format, so that we might immediately understand how mammalian innate immune sensing and signalling operate. These presentations provide a foundation on which anyone might build.

Although any scientific advance is a fine thing in its own right, most of us would like to know how we might best put it to use. Here, Richard Ulevitch considers how the TLRs might be targeted therapeutically. We have imagined (and hoped) that sterile inflammation, as it occurs in autoimmune diseases, for example, could depend on activation of the same biochemical pathways as those triggered by microorganisms, by yet-to-be-identified endogenous stimuli. With this in mind, quasi-infectious stimuli, such as lipopolysaccharide, have long been used to induce, model and study inflammation. We have also known that, where infection is concerned, terrible consequences sometimes arise from the host's earnest attempt to defend itself. The TLRs offer a clear entry point into these problems. Although we cannot yet know where our new knowledge will lead, we know where the trail begins.