EDITORIAL

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Toll Bridges

This month's issue of *Nature Immunology* presents a focus on Bridging Innate and Adaptive immunity. A series of commissioned articles explore this important interface. Our focus website (http://www.nature.com/ni/focus/bridging_immunity/), free during October, also includes regularly updated highlights of recent research, an annotated list of classic papers and links to selected Nature Publishing Group papers relevant to this topic. Classics papers linking innate and adaptive immune responses herald back to the early twentieth century, when bacterial components were found to promote immune responses. However, the dichotomy of the innate and adaptive immune response was not fully established at this time and not until the last decades of the twentieth century did the link between the two systems become truly obvious.

Immunologists at the turn of the twentieth century were divided into two camps. The humoralists believed that soluble (so-called 'humoral') substances were responsible for adaptive immunity, like that demonstrated by antitoxins and humoral bactericidal effects. The cellularists, however, believed immunity was innate and mainly phagocytic and was therefore mediated by cells. Complement, being soluble, was known to be important for humoral responses, but unbeknownst to practitioners at the time, it is a component of the innate immune system. In 1904 Almoth Wright described the efficient process of opsonization and with it tried to link cellular phagocytic immune responses to the adaptive humoral response. But humoral and therefore acquired immunity dominated immunology until Gowans brought back the cells — and this time they were lymphocytes. But even then, it was difficult to integrate the two systems.

Although research into the innate immune response continued throughout the twentieth century, its luster dimmed in the glare of the more exotic adaptive immune response. A series of key findings, starting with the identification of lymphocytes as mediators of immune responses during the Second World War and culminating in the discovery of how antibody and T cell receptor diversity were generated, seemed to blind immunologists to the innate immune response. 'Mainstream' immunologists described innate defenses as a primitive stopgap measure to hold the fort before the arrival of sophisticated adaptive immune responses. Somehow, immunologists continued to overlook the evolutionary success of the innate immune response. The shadows began to recede with the discovery of Toll-like receptors (TLRs) and, with it, the realization that the innate immune response not only provides a first line of defense but also is critical for prodding the adaptive immune response into action. Finally, a framework for reconciliation was emerging.

In 1989, Charles A. Janeway Jr. suggested in his celebrated Cold Spring Harbor lecture that the innate immune response initiates the adaptive immune response through pattern-recognition receptors that recognize microbial products, now called pathogen-associated molecular patterns (PAMPs). In 1996, Jules Hoffmann's group showed the Toll receptor functioned as a pattern-recognition receptor in drosophila, and a year later a human Toll homolog (now called Toll-like receptor 4) was identified that could trigger the adaptive immune response. By the late 1990's, support for Janeway's hypothesis was sealed when mouse TLR4 was genetically determined to recognize lipopolysaccharide. Immunologists have since identified other mammalian TLRs, each recognizing distinct PAMPs. In this focus issue, Iwasaki and Medzhitov review the essential function of these TLRs in coordinating the adaptive immune response. Recent evidence has linked TLR pathways to human diseases; Schwartz and colleagues provide their perspective on the importance of these receptors in human health.

TLR research established the link between innate and adaptive immunity but, as pointed out by Beutler in his overview, other components of the innate immune system also heavily influence adaptive immunity. The complement system represents one key example. The first evidence that complement could regulate the adaptive immune response was suggested by the observations that a fragment of the C3 complement protein binds to circulating lymphocytes and follicular dendritic cells in lymphoid follicles and that transient C3 depletion abrogates antibody responses. It is now clear that C3 regulates B cell responses through complement receptors CD21 and CD35 expressed by B cells and follicular dendritic cells. T cells, as reviewed by Carroll in this focus, also have a 'complement component' to their function. Exactly how complement enhances T cell priming, however, is still a mystery.

Natural killer (NK) cells are another component of the innate immune system that can influence adaptive immunity. Raulet reviews the interactions of NK cells with immature dendritic cells that induce dendritic cells to mature. And just like TLR-mediated dendritic cell maturation, NK cells can induce upregulation of major histocompatibility complexes and costimulatory molecules for the productive stimulation of antigen-specific T cells. NK cells also lyse dendritic cells, which interferes with adaptive immunity. More studies are needed to determine how important the crosstalk between NK cells and dendritic cells is *in vivo*.

A plethora of other innate pattern-recognition receptors, such as the intracellular receptor NOD2, have been identified since the discovery of TLRs. The contribution of these receptors to the bridging of innate and adaptive immunity must still be clarified, but these receptors may be part of an overlapping network that ensures innate recognition of microbes and activation of the adaptive immune response. An important area that we still know little about is the extent to which adaptive immune responses acts back on the innate immune system (see Research Highlights). Continued research in this area will illuminate the secrets of this two-way bridge and perhaps lead to development of new therapies. One thing is certain: the road to and from innate immunity will continue to be well traveled for the foreseeable future. But for now, we invite you to read the focus and enjoy the progress that has already been made.