

## Editorial

One hundred and fifty years ago, there was no clear understanding as to what infections actually were. Many viewed them as the will of God. Gradually it was accepted that in all their nefarious complexity, infections represent host infestation by microbes. Only when this realization became engrained did it occur to immunologists to ask how we recognize microbes and defeat them. In due course it was observed that two rather different forms of immunity exist: one adaptive and one innate. A fascinating contemporary account of the nascent concept was offered by Professor the Count K.A.H. Mörner, Rector of the Royal Caroline Institute, on December 10, 1908, when he introduced the Nobel Prize in Medicine or Physiology, that year awarded to Ehrlich and Metchnikoff<sup>1</sup>:

It has been shown that protection against disease can be of two kinds. It can consist in the ability to destroy microbes or to inhibit their further development. This is a bacteria-destroying immunity. But there is also a protection of another kind, one which acts against the bacteria products.

Mörner described the phagocytic cells of Metchnikoff and the antitoxins of Ehrlich and told how they worked cooperatively to protect the host. But as each question begets another, it was wondered even then how the initial recognition of microbes was accomplished. The question is often couched in terms of 'self/non-self discrimina-

tion', and it came to be the central mystery of immunology. What ignites the immune response? How are microbes recognized as foreign, while host cells are not? Unless one reverts to a concept of divine guidance, one must suppose that specific receptors distinguish between host and microbe, and do so with great specificity and reliability.

Where adaptive immunity is concerned, the production of antibodies and the development of T cell receptors against foreign molecules were both found to depend upon a remarkable recombinatorial process that evolved only in vertebrates, so far as we know. Tolerance to self is enforced at several levels, perhaps foremost by negative selective processes. But for nearly half a century, it has been clear that innate responses help to drive adaptive responses. Therefore, the question of innate immune self/non-self discrimination assumed primacy. And the question remained a stubborn one. Only 15 years ago, there was still no clear understanding as to how the host becomes aware of microbes to which it has not previously been exposed.

Not all was darkness. Many of the key molecular cues furnished by microbes (e.g., lipopolysaccharides, lipopeptides, nucleic acids) were defined early on, and the existence of receptors for these molecules was widely assumed. But the identity of the receptors remained an open question. A few startling discoveries changed the situation, revealing the identities of the proteins that initiate most of the complex biological changes that follow inoculation of microbes. Today we know of the Toll-like receptors, which recognize most types of microbes based

<sup>1</sup> Ehrlich P, Metchnikoff E: Nobel Lectures, Physiology or Medicine 1901–1921. Amsterdam, Elsevier Publishing Company, 1967.

on a handful of signature molecules including those just named; the ‘inflammasome’, which contains proteins of the NOD/NALP family, and leads to the generation of IL-1, and the RIG-I-like helicases, which detect cytoplasmic nucleic acids of viral origin. We know of certain cells that are specialized executors of innate immunity (neutrophils, natural killer cells and macrophages, for example), and we recognize that almost all cells show some measure of autonomous immunity.

Although more and more elements are added, the picture that we see today remains amazing in its simplicity in at least one respect. There are not thousands of receptors, nor even hundreds, but at present, perhaps only two or three dozen that are ‘known’ to have a non-redundant function in sensing microbes. These receptors detect neither nebulous ‘patterns’ nor ‘danger’ per se, but definable molecules, through interactions that have, in some cases, been resolved crystallographically. Nor do receptors in the classical sense need to mediate the first interactions that trigger awareness of infection. In *Drosophila*, for example, sensing can be initiated by microbial proteases, which activate host proteolytic cascades, ultimately leading to a response.

Where do we go from here? The same biochemical pathways that evolved to protect us from infection clear-

ly harm us when improperly regulated. Autoinflammatory and autoimmune diseases depend upon them. Endogenous ligands for Toll-like receptors and the other sensors sometimes drive such diseases. We can foresee a time when therapies will directly target the aberrant process that is causal. We can also imagine that adaptive responses might be activated more reliably (and with fewer side effects) once a deep understanding of adjuvant biochemistry is at hand.

But practical implementation aside, there is profound beauty in the innate immune system, and we offer a few points to consider in closing. Innate immunity is not ‘primitive immunity’ as some have described it. Conversely, it has evolved longer than adaptive immunity and has become extremely refined. It is, by some measures, the most important type of immunity we have. A great deal of evolutionary perspective can be achieved by comparing the defensive strategies that apply in highly divergent organisms (e.g., the mouse vs. the fruit fly vs. worms vs. plants). These model organisms have led the way to our present understanding. We expect them to guide us far into the future and to read about work with them in the pages of this journal.

*Bruce Beutler, La Jolla, Calif.*  
*Jules Hoffmann, Strasbourg*