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Ruslan Medzhitov

Modern immunology in many ways is based on two major paradigms: clonal selection theory and pattern recognition theory. Both paradigms were developed initially on theoretical grounds and experimentally proven years later. The clonal selection theory provided an elegant explanation for the function of the adaptive immune system: each lymphocyte was proposed to have a distinct Ag-specific receptor made at random and selected by cognate Ags for its ability to drive activation and clonal expansion (1–3). This simple and elegant model readily explained some major puzzles of the immune system, including immune memory. The flip side of clonal selection, clonal deletion of developing lymphocytes, also addressed the problem of immune tolerance. In fact, it was thought for some time that it solved the problem altogether. In its pure form, the clonal selection theory did not require any other signals to explain immune responses and, notably, had no connection to innate immune recognition whatsoever. It was thought at the time that any Ag was immunogenic (able to elicit an immune response) so long as it was non-self. This view was supported by Peter Medawar's pioneering experiments, which defined "non-self" as being absent during development.

Interestingly, this paradigm persisted through the mid-1990s, despite multiple lines of evidence suggesting that something fundamentally important was still missing from the big picture. Indeed, the idea that lymphocytes required two signals for activation (4, 5) was already well accepted, and the early studies by Antonio Coutinho and Göran Möller (6) in the mid-1970s demonstrated distinct roles for Ag-specific and polyclonal signals (LPS) in B cell activation. Furthermore, it was clear that clonal deletion (also known as central tolerance) does not eliminate all autoreactive lymphocytes and therefore additional mechanisms of peripheral tolerance are required to prevent autoimmunity. These new findings did not fit well with the original clonal selection concept and, not surprisingly, many theories were put forward trying to fit new discoveries into a coherent general picture. However, with few possible exceptions, most of these theories attempted to explain how the immune

system functions within the framework of the clonal selection model, thus focusing on the adaptive immune system alone.

This is the context necessary to appreciate the revolutionary contribution of the article by Charles A. Janeway, Jr. (7) presented in this installment of *Pillars of Immunology*. With truly ingenious insight, Charlie outlined the concept that later became a new paradigm of immunology. He proposed that distinct forms of immune recognition, innate and adaptive, played fundamentally different roles in the immune system. He suggested that innate immune recognition is based on non-clonal, germline-encoded receptors, which he termed pattern recognition receptors (PRRs). These receptors were proposed to detect conserved components of microorganisms, or pathogen-associated molecular patterns (PAMPs), such as LPS and peptidoglycans. Their detection by PRRs signifies the presence of microbial non-self, typically a pathogen, and triggers both immediate innate immune defense and the adaptive immune response. Charlie connected innate immune sensing of pathogens with the control of inducible costimulatory signals. This, in turn, assigned distinct meaning to innate and adaptive immune recognition: the latter conferred Ag specificity, whereas the former determined the origin of the Ags. This profound insight explained the seemingly everlasting riddle of self/non-self discrimination: because PRRs are selected during evolution to detect microbial PAMPs, which are not produced by multicellular hosts, they can efficiently discriminate self from microbial non-self. By controlling expression of costimulators and other signals involved in lymphocyte activation, this ancient system of microbial sensing is coupled with the activation of the more recently evolved adaptive immune system. The pattern recognition theory thus naturally complemented the clonal selection theory: lymphocytes are indeed selected by Ags to be activated, but only when the innate immune system provides the signals that indicate the microbial origin of the Ags for which they are specific.

All of these insights now form the conceptual foundation of our understanding of innate immune recognition, innate control of the adaptive immune response, and self/non-self discrimination. They have become so fundamental that we now take them for granted. Still, it may be interesting to note that for the first 7 years following its publication, the paper featured by this commentary was almost completely ignored and had practically no citations. It now has more than a thousand citations and this number would be at least an order of magnitude higher if everyone cited the original concept rather than its re-gurgitation in one of the hundreds of review articles published on the subject in recent years.

Of course, immunology has come a long way since the time Charlie's paper was published. A more detailed discussion of its

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Abbreviations used in this article: PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor.

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implications in both historical and modern contexts has been presented previously (8). Our knowledge about all aspects of immunity is now far more advanced and sophisticated and some of the details of the article are clearly outdated. The younger generation of readers should keep in mind that we did not then know about regulatory T cells, inflammasomes, and AIRE and all the other wonderful things we have learned in the past decade or so. But what sets the classic papers apart is that their value does not erode with time. They always present a rich source of information and inspiration. They are not about details, but about thinking creatively and seeing the big picture.

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## Disclosures

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