Seeking wisdom in innate immunity

Douglas T. Fearon

Obsolescent — such was once the view of the innate immune system. That view is itself out of date. But a fresh angle of attack on the ways in which innate immunity is essential to the function of acquired immunity comes from study of the ancient defence systems of invertebrates.

The crowning accomplishment of vertebrate immunity is the acquired immune system. It produces trillions of clones of B and T lymphocytes, each expressing a unique antigen receptor, ensuring that all microorganisms will have some structure, or antigen, that can be immunologically recognized (see box). To achieve this diversity, developing lymphocytes somatically create unique antigen receptors by recombining segments of genes and randomly adding or subtracting nucleotides at sites of recombination¹. An antigen selects only those lymphocytes that have receptors of sufficient affinity for growth and differentiation.

But this genetically economical solution to producing enormous protein diversity comes with a price. It uncouples acquired immune recognition from the wisdom gained during evolution of how to cope with hostile microbes because, for the most part, the antigen receptors are not encoded in the germ line. With no information from the past, these receptors can evaluate only

antigenic structure and not its biological correlates.

Where can we find the biological wisdom that could instruct acquired immunity? In their paper on page 394 of this issue², Medzhitov, Preston-Hurlburt and Janeway propose that the search for such wisdom should be made in innate immunity, and that the clues that direct these searches can be found in ancient defence systems of invertebrates. They back up this suggestion by finding a human homologue of the *Drosophila* Toll protein, a receptor involved in innate immunity of this invertebrate, that has the potential for potentiating the T-lymphocyte response to antigen.

Acquired immunity only appeared with the evolution of vertebrates, but before then innate immune systems had been successfully defending invertebrates and plants against microbial infections for hundreds of millions of years. The germline-encoded receptors of innate systems are relatively limited in diversity and unable to make fine distinc-

tions between closely related structures. Nevertheless, they can recognize certain chemical features shared by groups of microorganisms but not by the host, such as lipopolysaccharide of Gram-negative bacterial cell walls. This capability enables innate immunity to detect the presence of an infection, if not the precise cause — a biological rather than a structural distinction.

Despite its evolutionary success, innate immunity has been treated with condescension by immunologists. It has been considered a stopgap measure, a temporary expedient for host defence, buying time until acquired immunity took over. It lacked the elegance of the genetic-recombination mechanism to generate specificity. It had no 'memory', because first and second exposures to a microbial substance elicited similar responses (curiously, this attitude neglected the evolutionary memory that allowed the rapid first response). Even worse, its overreaction to bacterial products in some circumstances caused lethal shock, suggesting that its inflammatory and cytotoxic capabilities were out of proportion to its judgement and discretion. In short, innate immunity was unsophisticated, unintelligent, indiscreet and obsolescent.

In the 1989 Cold Spring Harbor Symposium on immune recognition, Janeway acknowledged this hubris of 'acquired immunologists' when he referred to their "dirty little secret", the need to contaminate pure antigens with adjuvants to induce acquired immune responses³. Adjuvants are unpleasant concoctions of oils, salts, killed

Innate and acquired immunity

Immunity to infection is mediated by two general systems, innate (or natural) and acquired (or adaptive). Innate systems use germline-encoded proteins to identify microbial substances. For example, mammalian macrophages have mannose, lipopolysaccharide and scavenger receptors for identifying components of yeast and bacterial cell walls. Plasma proteins, such as the complement cascade, C-reactive protein, and the mannose-binding protein of the collectin family, also recognize microbial carbohydrates. These cellular and soluble proteins pre-exist, or are rapidly induced within hours of infection. They provide immediate defence against microorganisms by

directing the engulfment and breakdown of microbial cells, and the secretion of cytokines and chemokines which enhance antibacterial and antiviral cellular responses. Given that the receptors are 'hard-wired' in their ability to detect infectious organisms, innate immunity has the disadvantage of genetic inflexibility, meaning that microbes can evade surveillance through mutation.

Acquired immunity is the system of B and T lymphocytes, each of which expresses a distinct antigen receptor that has arisen, not through a process of evolution, but by somatic gene rearrangement. The generation of specificities is

without regard to targets, and leads to the creation not only of potentially microbe-specific receptors but also to self-reactivity — the self/non-self problem of acquired immunity. These undesired clones must be eliminated during their development, or perhaps hindered in their activation by self-antigen, to prevent autoimmunity.

The residual lymphocyte clones represent the pool from which those with microbial reactivity can be selected. However, on first exposure to an infectious organism, the frequency of such clones is initially too low, perhaps as few as 1 in 10,000–100,000, for a protective response. During the ensuing 1–2 weeks these

clones replicate, increasing in number by as much as 1,000 times, and mature into cells that defend the host by secreting antibodies, activating macrophages and killing virally infected cells. When the infection is cleared, many of the antigen-specific B and T lymphocytes remain as 'memory' cells which can mount a rapid response if the same microorganism is encountered again. It is this characteristic that accounts for the designation 'acquired immunity'. In effect, this system compresses evolution into two weeks, allowing the selection of specific antigen receptors to keep pace with the selection of variant microorganisms, overcoming the deficiencies of innate immunity. **D.T.F.**

Figure 1 Integration of innate and acquired immune recognition. In a primary immune response, antigen is first subjected to biological evaluation by innate immunity for its possible microbial origin. If considered as such, antigen is presented in a more immunogenic form to the acquired immune system, causing the clonal expansion of lymphocytes that recognize antigen with a high degree of structural specificity. B lymphocytes then produce antibodies to eliminate the antigen-carrying invader, such as a bacterium. Or different types of T lymphocyte activate macrophages to destroy intracellular microbes, or themselves kill cells infected, for instance, by a virus.

bacteria, bacterial products and so on, none of which has anything to do with the interaction of antigen and antigen receptors on lymphocytes, but all of which magnify the acquired immune response. He suggested that adjuvants had this effect because innate immunity recognized them as microbial, and the admixed antigen became guilty by association. This judgement was transmitted to the acquired immune system to induce a vigorous response to the antigen.

We now know of several means by which innate immunity communicates its biological evaluation of an antigen to acquired immunity: the secretion of cytokines by macrophages and natural killer cells⁴; the attachment of a complement protein to antigen⁵; the preferential uptake of microbial antigen by lectin receptors on cells that specialize in presenting antigen to lymphocytes⁶; the maintenance of antigen-reactive T lymphocytes⁷; and the expression of the membrane proteins B7.1 and B7.2 on the antigen-presenting cells⁸. The B7.1 and B7.2 proteins, which can be induced by lipopolysaccharide, interact with receptors on T lymphocytes to deliver a 'second signal', the first being that of the antigen receptor. Because two signals are required for lymphocyte activation, Medzhitov and colleagues' finding² that the human homologue of Toll induces B7.1 on macrophages places it in the communication network between innate and acquired immunity.

Interpreting the 'second signal' as a link connecting innate and acquired immunity heralds a fundamental shift in emphasis in immunology. This signal was originally proposed as a solution to the problem of self/non-self discrimination. With the second signal now being related to the biased recognition of microbial antigens, immunology moves away from self/non-self as a unifying concept towards the new dichotomous classifications, infectious/non-infectious^{3,9} and dangerous/not dangerous¹⁰. These distinctions necessarily depend on the capabilities of innate immunity, and seem to be closer to the essence of the immune

response, which is protection from infection.

If we accept the principle that the biological wisdom of innate immunity must be integrated with the structural specificity of acquired immunity (Fig. 1), how do we identify proteins that mediate this process? Medzhitov *et al.*² provide an approach that should be generally applicable: search the ever more complete library of the human genome for mammalian homologues of immune proteins in invertebrates. Their choice of the search term, *Drosophila* Toll, was especially apt because it activates Dorsal,

a gene transcription factor with homologues in the mammalian NF- κ B system which is involved in so many innate and acquired immune reactions¹¹.

Finally, what will we do with these newly identified proteins? We will understand better what makes an antigen immunogenic, both self and foreign. This will lead to more effective therapies for autoimmunity and vaccines for infectious diseases and tumours. By then, even the most sceptical among us will be convinced of the wisdom of innate immunity. □

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Solar physics

Gravity waves with a new spin

Douglas Gough

The Sun loses angular momentum to the solar wind via its magnetic field, slowing down the rotation of the outer, convective layers. The core was once thought to be weakly coupled to the outer layers, rotating up to ten or more times faster than the convection zone, but helioseismology has shown that much of the radiative interior rotates at a similar rate to the surface. What couples the two regions so strongly? In two recent papers^{1,2} wave transport is invoked: gravity waves (similar to internal ocean waves, whose restoring force is buoyancy), generated near the interface between the convective and radiative regions, transport retrograde angular momentum into the interior, thereby spinning it down. Previous estimates³ had cast doubt on the efficacy with which the transport can take place. So what has changed?

The Sun can be divided into two zones, the upper layer where heat transport is by convection, and a lower, stable layer where it is radiative. The angular velocity of the surface decreases with latitude⁴, the value at the poles being about 70 per cent of that at the equator. Helioseismology — the study of small oscillations in the shape of the Sun — can probe conditions below the surface, and has shown that variation persists down to the base of the

convection zone⁵. Most of the radiative interior rotates almost uniformly at an intermediate rate. The radiative zone is separated from the convection zone by a thin shear layer, called the tachocline⁶, whose thickness is about 5 per cent of the Sun's radius⁷.

Turbulence can redistribute angular momentum within the convective zone in less than a year, so we can assume that this zone adjusts itself to its own will, and then ask why the interior rotates as it does. There are two main questions. Why does the interior rotate almost rigidly? And why does it rotate at the rate it does?

A natural agent for stiffening the interior is a magnetic field. Just 10 μ G (10^{-9} T), a value comparable to the interstellar field, can redistribute enough angular momentum over the lifetime of the Sun for the core to rotate rigidly. But popular opinion is that such a field should penetrate into the convection zone, and thereby transmit the differential rotation of the outer envelope into the core. (Indeed, a modicum of penetration at high latitudes might cause the apparently slow rotation of the innermost core⁸.) Alternatively, as a consequence of the circulation in the tachocline (see Fig. 1), the global field could be almost wholly contained in the