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Why study the evolution of immunity?

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Abstract

Investigations of immune recognition in nonmammalian species provide new insights into the evolution of immunity and the inner workings of the mammalian immune system. Very diverse mechanisms are used by different multicellular organisms to recognize and cope with the rapidly evolving microbial world.

The beginning of life on Earth with single-cell organisms more than 3.5 billion years ago and the much later development of multicellular organisms ensured continuous interaction between the diverse species, both cooperative and fiercely competitive in nature. The need for self-defense in the ongoing struggle for survival inevitably led to the evolutionary refinement of intricate immune systems, including the adaptive immune system. At a time when much-needed knowledge about the molecular and cellular basis for immune defense is being gained from studies of humans and mouse models, should effort and resources be devoted to comparative approaches to understanding immunity as an integrated evolutionary process?

Historic precedent may not be the most compelling reason for pursuing any line of scientific inquiry, but it is worth recalling that discoveries made in comparative immunology have greatly influenced the field of immunology. The observations of phagocytosis by mesenchymal cells in echinoderms, such as starfish and sea urchins, led to the original conceptualization of self versus nonself recognition¹. Almost a century later, studies of birds attributed cellular and humoral immune function to the separate T and B lineages of lymphocytes, well before the genetics of their specific receptors and otherwise distinctive phenotypes could be understood². Decades later, the avian model brought gene conversion under scrutiny as a chief alternative strategy in the diversification of antibodies³. More recently, the conceptualization of Toll receptors as crucial mediators of innate immunity has benefited greatly from the analysis of insect responses to pathogens⁴.

Several important themes about the evolution of immunity are now recognized (Fig. 1). Innate immunity preceded adaptive immunity in the evolution of immune recognition and it provides the common thread that ties together immune recognition in invertebrates and vertebrates^{5,6}. Clonally diverse lymphocytes seem to be a vertebrate 'invention', although their antigen-specific receptors have diverged along two main lines in vertebrates. Those in all jawed vertebrates, sharks to humans, are based on the rearrangement of segmental

elements encoding the immunoglobulin domains in T and B cell receptors and are mediated by recombinase-activating proteins RAG-1 and RAG-2 (ref. 7). In contrast, the random assembly of diverse leucine-rich repeat modules generates the lymphocyte receptor repertoire in jawless vertebrates, lamprey and hagfish in a RAG-independent way⁸. Mounting evidence indicates that invertebrate immune-type receptors may undergo somatic diversification or elaborate RNA processing mechanisms^{9,10}. Even without lymphocytes, invertebrates can achieve adaptive protective immunity, if not true immunological memory¹¹. Finally, polymorphic diversification of cellular receptors and their ligands may ensure self-nonself recognition in marine invertebrates to prevent interspecies fusion and foreign stem cell invasion¹². Such discoveries, although unanticipated, were not a complete surprise given the relentless microbial challenges and widespread commensal relationships faced by invertebrates and vertebrates^{13,14}.

Comparative immunology poses formidable technical hurdles for the experimentalist. Although decades of technological development in mammalian immunology have yielded an impressive array of resources in the form of cell lines, monoclonal reagents and gene-modification strategies, few comparative models offer the investigative tools available to immunologists studying humans or mice. Even sustainable cell culture is not yet possible for some of the most interesting nontraditional animal models, although genome science can be a 'great equalizer' that becomes more powerful as more genomes are annotated. Comparative genomics approaches have already shown that the basic mechanistic components that diversify immunoglobulin and T cell antigen receptors, including RAG-1 and RAG-2 homologs, essential ligases, polymerases and DNA-repair factors, exist on both 'sides' of the deuterostome split^{15,16}; one branch includes echinoderms such as sea urchins and the other includes chordates such as fish and humans. Nevertheless, the steps through which gene regulatory networks evolved to connect and integrate DNA damage and repair mechanism and the other cellular functions required for the somatic diversification of vertebrate immune receptors remain unknown.

Comparative analysis of regulatory genes can facilitate the elucidation of layered, interwoven developmental processes that have become obscured over the passage of time¹⁷. In addition to their inherent value as important genome resources, alternative animal model systems may also offer unique experimental advantages. The zebrafish, for example, provides a robust developmental model in which the T and B lymphocyte compartments, as well as other immune mediators, resemble their mammalian counterparts. Fluorochrome-marked cell lineages in the transparent embryos of transgenic zebrafish are easily visualized in real time. High-throughput mutagenesis screenings can delineate key developmental pathways as well as create informative disease models, and efficient small-molecule screens can identify potential therapeutic agents that modulate immune functions¹⁸. Similarly, the development of immunocytes in the simple sea urchin larva can be efficiently modified by transgenesis and by inhibition of specific mRNA molecules by morpholinos to delineate gene-regulatory networks affecting immunity. To appreciate the potential of comparative genetics in elucidating essential pathways in innate immunity, one need look no further than the insight gained from the delineation of the Toll and Imd pathways in *Drosophila*⁴.

What emerges from the comparative viewpoint is a deeper appreciation of the acquisition of complexity in the evolution of immunity and glimpses of unforeseen alternatives in immune receptor diversification. Still, all of the knowledge gained so far through comparative immunology is based on only a few more than 30 extant animal phyla. Expansion of the extent of the available genome resources, along with better understanding of transcription at both the transcriptosome and spliceosome levels, may demonstrate conserved features of the coding and noncoding portions of DNA that sustain genetic stability or promote change at the mitotic and meiotic levels. Moreover, the use of comparative approaches will provide

information about the ways that innate and adaptive immunity are interwoven and affect the constantly evolving relationships among humans, commensal organisms and microbial pathogens. Given the lessons learned thus far from tracing the evolution of immunity, it can be safely anticipated that future studies of ‘new’ biological forms and functions in the evolutionary succession will yield invaluable insight into host-parasite interactions. Who can predict the practical applications that may come from exploring immune system diversity driven by evolutionary challenges?

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Figure 1.

Present ideas of immune diversity in alternative model systems. Left to right: fly (*drosophila*), snail (*biomphalaria*), sea urchin (*strongylocentrotus*), amphioxus (*branchiostoma*), lamprey (*petromyzon*), shark (*heterodontus*), chicken (*gallus*) and mouse-human (*mus-homo*). Molecules such as RAG-1 and RAG-2 have been identified in sea urchin¹⁵, but only a gene like *RAG1* has been characterized thus far in amphioxus. Amphioxus VCBPs (variable (V) region–containing chitin-binding proteins) have a ‘head-to-tail’ organization, which defines a unique potential binding surface, and have a considerable genetic polymorphism. Hypermutation has been noted in genes encoding snail fibrinogen-related proteins (FREPs). Three independent phyletic lineages are presented in red and yellow (protostomes) and in blue (deuterostomes); phylogenetic relationships are not drawn to evolutionary time scale. This diagram emphasizes some of the findings that have influenced the understanding of immune function and/or suggest alternative mechanisms of immune recognition. They are not intended to be inclusive for any given system or to include all systems in which notable findings relevant to the subject of this commentary have been made. Findings not in the text are in refs. 4,7,16. Dscam, Down's syndrome cell adhesion molecule; CDR3, complementarity-determining region 3; FR2, framework region 2; XRCC4, DNA-repair protein; Ku70 and Ku80, DNA-binding proteins; DNA-PK, DNA-dependent protein kinase; TCR, T cell antigen receptor; Ig, immunoglobulin; Ψ, pseudo.