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Immigrants in immunology: the benefits of lax borders

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The field of immunology has a long history of illuminating fundamental biological processes of critical importance to human health. From an outsider's perspective, the questions are profoundly philosophical and the experimental approaches are elegantly precise. Yet immunology can also appear impenetrable. Here we recount the experience of two graduate students from the fields of ecology and computer science, who have immigrated into immunological terrain attracted by systems-level questions. We argue that such migrations enrich the field of immunology, and that cultural and institutional changes are needed to promote more interdisciplinary explorations.

Border crossing

The past twenty years have witnessed extraordinary innovations in the quantity and complexity of information that can be collected about biological systems. Chief among these has been the revolution in high-throughput sequencing, generating astronomically large datasets that necessitate proficiency in bioinformatics and statistics to handle and analyze. The flood of genome sequences has revealed how much animals share in common, including the conservation of their immune systems. In parallel, we're coming to realize the enormous diversity and complexity of microbial life that inhabits the surfaces of all macroscopic organisms. These advances have transformed the nature of questions that can be posed about immunological systems. Rather than studying the interaction of a single immunoglobulin with a single antigen, it is now feasible to determine the entire immunoglobulin repertoire of an animal (for example for the model vertebrate, zebrafish, which has only 300 000 total B cells [1]) and enumerate its corresponding associated microbial communities [2]. In other words, we can now study the immune system from a systems biology perspective with a complete catalogue of the component parts.

We are fascinated by the reciprocal interactions between an organism's immune system and its microbiome, which we approach from the varied perspectives of a graduate student in ecology and evolution (Keaton), a graduate student in computer science (Emily), and a professor in host-microbe systems biology (Karen). Below, we share our individual thoughts on how our backgrounds shape our approaches to immunology and offer advice for lowering the barriers for entering the field of immunology.

Keaton: the immune system as a mediator of species interactions

When I think about the immune system (and exclude the fascinating phenomena of auto-immune disease, allergic reaction, and graft rejection) I think of it as a mechanism for species interaction. This is what, as someone with a background in community ecology, attracted me to studying how the host's immune system influences, and is influenced by, the microbial communities living in, on, and around the host.

When most people think about immunity, they think about fending off germs. Indeed, it's hard to argue that the primary driver behind the evolution of the immune system is anything other than as a defense against pathogens. The Red Queen Hypothesis for the evolution of sex, for example, hinges upon the ability of sexual recombination to maintain MHC diversity for combatting pathogens and parasites [3]. From a community ecology perspective, pathogen-host interactions can be modeled almost identically to predator-prey interactions. The immune system, as a whole, is a variable phenotype that can determine the strength of the effect of a pathogen on a host in the same way that thick armor or great speed can mediate the effect of a predator on prey.

Although it's easy to argue that immunity most likely evolved as defense against pathogens, it's more difficult to invoke this argument in explaining the impetus for the evolution of adaptive immunity. One can provide 'just so' stories about how vertebrates, being more complex, might have to deal with more pathogens, but the data do not provide strong support for this reasoning. Instead, as Margaret McFall-Ngai has argued [4], the vertebrate adaptive immune system may have evolved to manage the significantly more complex commensal microbial communities associated with vertebrates versus invertebrates, communities that confer extraordinary metabolic capacities to adapt to different and changing food sources. By cultivating microbial communities via the immune system, and other mechanisms, the host functions simultaneously as an active community participant as well as the 'abiotic' component of the ecosystem, creating a unique situation that is very intriguing to an ecologist.

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An obvious extension of the community ecology perspective is to view microbial pathogens as invasive species in the host-microbiota ecosystem. For example, *Salmonella enterica* Serovar Typhimurium thrives on inflammation in the intestine and actually requires it to overcome the competition of the resident microbiota [5,6]. Presumably, *S. enterica* has evolved to stimulate inflammation and withstand this harsh environment that perturbs resident commensals, much as fire-resistant grasses can invade forests by increasing the frequency of fires that remove the trees with which they compete [7]. Unlike the forests, however, a host has a vested interest in determining which microbial species win ecological competitions. From this perspective, the adaptive immune system can be viewed as playing an active and important role as an ecosystem engineer that shapes the diversity of the gut microbiota [8]. For example, IgA repertoires, in conjunction with TLR5, can pressure bacterial cells to down-regulate production of flagellin, making them less mobile and perhaps shifting the competitive landscape [9]. From my perspective, ecological concepts like community resistance, competition, invasion biology, and ecosystem engineering, have been useful for framing discussions of pathogen infection and modeling the different roles the immune system can play in the interactions between the host, its microbiota, and pathogens.

These immunological processes are fascinating to me, but as an ecologist attempting to learn immunology, I have been struck by the cultural rigidity with which subdivisions of immunology seem to be maintained—people tend to identify themselves as studying either innate or adaptive immunity, and within adaptive immunity people study either B cells or T cells. While these divisions make sense historically and are often necessary to tackle teaching the complexity of immune systems, when it comes to the burgeoning field of host-microbe interactions, it seems limiting to focus exclusively on a specific cell type in the system, rather like an ecologist only considering the effect that soil pH has on plant communities and ignoring the role of available nitrogen.

Another puzzling limitation in the field, apparent in all immunological textbooks, is the almost exclusive focus on the mouse as a model for human immunology. As an ecologist, I am accustomed to considering organismal diversity, placed within a phylogenetic framework, to understand biological processes. I first assumed that the mouse was featured in my textbooks because it served as an exemplar of all animal immune systems. However, once I started my graduate research on zebrafish immunology, I was shocked to discover how different and diverse adaptive immune systems can be between different vertebrate species, and even between different species of fish [10]. I believe that teaching immunology through the lens of phylogenetic history would better emphasize the fundamental properties of immune systems that are highly conserved and would highlight species-specific specializations to solving common immunological problems.

Emily: the immune system as a selective sampler of sequence space

As a computer scientist, I was drawn to immunology by the computational challenges of analyzing lymphocyte receptor repertoires. At first glance, libraries of B and T cell receptor genes would seem to present challenges similar to the analysis of other sequence data such as 16S ribosomal RNA genes from bacterial communities. Both data types have a skewed distribution where some sequences are very common and others are unique. However, an appreciation of the biological processes behind these skewed distributions dictates different computational approaches. Somatic recombination and hyper-mutation result in the potential for each B or T cell to have a unique receptor gene sequence. Even though this exploration of sequence space is hypothetically limitless, it is constrained by the rate of mutation from the germline sequences and the structural limitations for generating a functional receptor. Knowledge of the germline sequence can be taken into account during gene sequence clustering, and mutation rates and structure can inform us about the most likely evolutionary trajectories. In light of all this *a priori* knowledge, 'clustering' is an inadequate term to describe the analysis of receptor repertoires. In fact, the goal is not just the grouping of similar sequences, but rather the total reconstruction of the mutation process that led to the observable repertoire [11]. In my own work, I hope to compare the general structures of the B cell receptor repertoires of different vertebrates to deduce the conserved processes of repertoire generation.

I am drawn to the analysis of lymphocyte receptor repertoires not only because of the interesting computational challenges, but also because the analytical approaches I develop could have important clinical applications. Measuring the diversity of patient repertoires is now an important tool in monitoring leukemias, and will likely become a component of diagnosing infectious disease progression. Reconstructing the processes of repertoire creation can be harnessed to design better vaccines. For example, HIV researchers are searching for immunoglobins that are effective at neutralizing the virus but have not undergone extensive somatic hypermutation, reasoning that these ancestral antibodies would be easier to induce via vaccination [12].

Analysis of sequence data as complex as lymphocyte receptor repertoires requires competence in basic scripting, command line, and use of online tools. Graduate level immunologists, and biologists more generally, can fall along a spectrum from software consumers to producers, and their educational paths will differ based on their needs and inclinations. I believe that all biology graduate students should have a basic competency in Linux, writing simple scripts in a language like Python or Perl, and the use of statistical software such as MATLAB or R. These skills are essential for the informed use of existing software and to facilitate collaborations with computer scientists. This knowledge could be acquired either through specialized classes offered through biology departments or general computer science courses. Students interested in taking a more active role in software development may decide to take a longer sequence of computer science courses, just as I have chosen to take a more extensive series of biology courses.

Formal training in each other's disciplines can reduce barriers to communication, but we need to find other ways to share (Box 1). Despite the wealth of interesting immunological questions that would be of interest to bioinformaticians