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SYMPOSIUM INTRODUCTION

Multi-Scale Drivers of Immunological Variation and Consequences for Infectious Disease Dynamics

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Synopsis The immune system is the primary barrier to parasite infection, replication, and transmission following exposure, and variation in immunity can accordingly manifest in heterogeneity in traits that govern population-level infectious disease dynamics. While much work in ecoimmunology has focused on individual-level determinants of host immune defense (e.g., reproductive status and body condition), an ongoing challenge remains to understand the broader evolutionary and ecological contexts of this variation (e.g., phylogenetic relatedness and landscape heterogeneity) and to connect these differences into epidemiological frameworks. Ultimately, such efforts could illuminate general principles about the drivers of host defense and improve predictions and control of infectious disease. Here, we highlight recent work that synthesizes the complex drivers of immunological variation across biological scales of organization and scales these within-host differences to population-level infection outcomes. Such studies note the limitations involved in making species-level comparisons of immune phenotypes, stress the importance of spatial scale for immunology research, showcase several statistical tools for translating within-host data into epidemiological parameters, and provide theoretical frameworks for linking within- and between-host scales of infection processes. Building from these studies, we highlight several promising avenues for continued work, including the application of machine learning tools and phylogenetically controlled meta-analyses to immunology data and quantifying the joint spatial and temporal dependencies in immune defense using range expansions as model systems. We also emphasize the use of organismal traits (e.g., host tolerance, competence, and resistance) as a way to interlink various scales of analysis. Such continued collaboration and disciplinary cross-talk among ecoimmunology, disease ecology, and mathematical modeling will facilitate an improved understanding of the multi-scale drivers and consequences of variation in host defense.

Introduction

The immune system plays a critical role in host–parasite interactions. From the perspective of parasites, the immune system is the primary barrier to infection, replication, and transmission following exposure (Combes 2001). More broadly, variation in host immune phenotypes can manifest in heterogeneity in traits that govern the population-level dynamics of infectious disease (Hawley and Altizer 2011; Jolles et al. 2015; Martin et al. 2016). A primary goal of the field of ecoimmunology has accordingly been to describe and explain natural variation in individual immune phenotypes (Pedersen and Babayan 2011). For example, body condition, reproductive status, and infection state can all shape an individual's immune phenotype, which can determine whether a host succumbs to infection prior to or after parasite transmission (Zuk and Stoehr 2002; French et al. 2009; Gilot-Fromont et al. 2012; MacColl et al. 2017). However, two outstanding challenges remain for considering the causes and consequences of such variation in host defense. First, how do broader evolutionary and ecological contexts (e.g., phylogenetic relatedness and landscape

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heterogeneity) shape immunological differences among hosts? Second, how can such variation in immune phenotypes be best scaled-up to inform epidemiology?

For the first question, evolutionary and ecological contexts are increasingly recognized to shape immune defense (Lee 2006; Morand et al. 2010; Schoenle et al. 2018). For example, the relationships between reproductive status and immune phenotypes may be driven by variation in life history strategies among species (Martin et al. 2007; Lee et al. 2008; Previtali et al. 2012), whereas relationships between body condition and immunity may be driven by variation in resource availability across populations (Beldomenico and Begon 2010; Gilot-Fromont et al. 2012; Downs et al. 2015; Becker et al. 2018a). The metabolic scaling of immunological traits, such as host competence, also suggests inter-specific variation in body size could influence host–parasite interactions (Han et al. 2015; Downs et al. 2019). However, unlike the macroecology of infectious disease, similarly large-scale approaches to ecoimmunology remain rare, given the challenges associated with comparing informative metrics of immune phenotypes across wild organisms (Stephens et al. 2016; Schoenle et al. 2018).

For the second issue, integrating immunological heterogeneity into classic epidemiological models (e.g., susceptible–infected–recovered frameworks) could provide novel insights into host–parasite dynamics and improve infectious disease control, as defense traits such as host resistance and tolerance can directly translate into parameters governing the likelihood of parasite invasion (i.e., the basic reproductive number, R_0; Anderson and May 1991; Hawley and Altizer 2011; Jolles et al. 2015). For example, models of bat rabies that incorporated immunological variation within colonies have provided plausible explanations for field data (Dimitrov et al. 2007). Variable immunity is often integrated phenomenologically, such as by adjusting parameters governing host susceptibility (e.g., Becker and Hall 2014) or including skewed distributions of infectiousness (e.g., superspreading dynamics; Lloyd-Smith et al. 2005). However, models that mechanistically link within-host interactions to between-host parameters can generate distinct predictions about population-level infection dynamics (Mideo et al. 2008; Hite and Cressler 2018). Predictions from such nested frameworks can have different and important implications for disease control (Civitello et al. 2018); however, more exploration of how to integrate these two scales is needed to outline best practices and improve inference.

The goal of our symposium, "The Scale of Sickness: How Immune Variation Across Space and Species Affects Infectious Disease Dynamics," at the 2019 annual meeting of the Society for Integrative and Comparative Biology was to integrate perspectives from ecoimmunology, disease ecology, and mathematical modeling. We hoped to synthesize the complex drivers of immunological variation across biological scales of organization and to incorporate within-host differences into epidemiological frameworks. We aimed to challenge participants and attendees to consider approaches that connect individual-, landscape-, or species-level variation in immunity to their ecological, evolutionary, or epidemiological outcomes. Ultimately, such efforts could illuminate general principles about the drivers of host defense and improve infectious disease predictions and control. Below, we synthesize key insights from the symposium and outline several critical areas for future research to understand the multi-scale drivers and consequences of variation in defense.

Inter-specific and inter-population variation

Variation in host immune defenses at the scale of species and populations could have profound implications for disease dynamics through effects on the numbers and immunological state of susceptible, infected, and recovered individuals in a (meta)community. For example, inter-specific variation in host competence (the ability to infect new hosts and vectors), which is partly driven by immunological differences among species, shapes human risk of vector-borne exposure to *Borrelia burgdorferi*, the causative agent of Lyme disease (LoGiudice et al. 2003; Previtali et al. 2012; Ostfeld et al. 2014). Quantifying inter-specific variation in immune defense can be facilitated by classic tools from ecoimmunology. Although white blood cell counts, bacterial killing ability (BKA), spleen size, and response to phytohemagglutinin (PHA), among other host outcomes, have revealed immune variation among broad taxa (Martin et al. 2007; Lee et al. 2008; Previtali et al. 2012; Schneeberger et al. 2013; Heinrich et al. 2016), an ongoing challenge remains to connect such variation to differences in protection from infection and to life history (Demas et al. 2011). Tissue regeneration is a specific trait rare among mammals, with African spiny mice (*Acomys* spp.) being one of the few mammalian taxa that can regenerate complex structures in response to injury. Although cellular mechanisms responsible for this

trait remain mostly unknown, inflammatory responses may differ between regenerating and non-regenerating rodent species (Simkin et al. 2017). Cyr et al. (2019) compared neutrophil traits (e.g., abundance, migratory ability, phagocytosis ability, and BKA) between tissue-regenerating *Acomys* and regeneration-incompetent *Mus musculus*. Tissue-regenerating *Acomys* had fewer neutrophils in blood and more band neutrophils in bone marrow than *Mus*, although bone marrow neutrophils from *Acomys* did not differ from *Mus* neutrophils in migratory ability. However, *Acomys* bone marrow neutrophils displayed more phagocytic activity than those from *Mus*. Furthermore, *Acomys* blood killed more *Escherichia coli* than blood from *Mus*; the former was driven by sera, whereas the latter was driven by inflammatory cells. Such results suggest subtle constitutive differences in neutrophil development, mobilization, and phagocytic function in *Acomys* that may help these species maintain balance between the tissue damage and regenerative roles of inflammation. Differences were also consistent between captive and wild populations of *Acomys* and *Mus*, suggesting that intra-specific comparisons can help reinforce and strengthen broader comparisons of host defense between species and genera.

Merrill et al. (2019) expanded upon these between-species comparisons and include within-specie comparisons by asking how local environmental conditions affect the immune phenotypes of five shrubland bird species. Using assays common in ecoimmunology (i.e., leukocyte profiles and BKA), the authors found that the relationship between local environment and immunity varied on the basis of intra-specific (i.e., age) and inter-specific (i.e., species identity) factors. In particular, whereas local land cover did not predict immune phenotypes for adult birds, BKA and the proportions of heterophils and basophils were inversely related to the relative abundance of local grassland and shrub cover for nestlings in most species. Yet heterophil counts for American robins (*Turdus migratorius*) and northern cardinals (*Cardinalis cardinalis*) were inversely related to this land cover type. Age also more generally predicted immunity, with lower BKA, more heterophils, and more eosinophils in nestlings, especially for robins and gray catbirds (*Dumetella carolinensis*).

The importance of environmental conditions for shaping immune phenotypes was further emphasized by two other spatial analyses (Albery et al. 2019; Becker et al. 2019c). Albery et al. illustrated the strength of spatially explicit statistical modeling approaches, such as the Integrated Nested Laplace Approximation (INLA), in assessing how host defenses vary across fine scales (Blangiardo et al. 2013; Albery et al. 2019). Using a well-studied population of red deer (*Cervus elaphus*) on the Isle of Rum, the authors highlighted high spatial heterogeneity in general and helminth-specific antibody concentrations. Fine-scale spatial patterns in immunity did not align with spatial patterns in parasite intensity, suggesting that fine-scale environmental factors acting on host exposure may be more important than susceptibility in driving observed spatial patterns of infection in this system. Importantly, this analysis highlights the importance of controlling for spatial dependence in analyses of inter-population variation, even at fine scales.

As the above studies attest, local environmental conditions can influence host immune variation. However, larger-scale processes can also be impactful, as can interactions between factors operating at local and larger scales. For instance, parasite diversity, abiotic conditions, food availability, and predator abundance can vary from forest plot to landscape levels and also shape immunity (Hasselquist 2007; Morand et al. 2010). Differentiating between the influence of local- and large-scale environmental predictors and quantifying their relative importance is only possible via comparisons of populations of broadly distributed species. Becker et al. (2019c) used leukocyte profiles from colonies of common vampire bats (*Desmodus rotundus*) sampled across their geographic range spanning Mexico to Argentina to identify strong spatial autocorrelation at both small and very large scales (~6000–8000 km). Generalized additive models (GAMs) revealed that these spatial patterns were driven by proximity of colonies to geographic range limits and localized abundance of livestock prey. This analysis highlights the importance of assessing immunological variation at multiple spatial scales with high spatial replication.

These scale-sensitive assessments of inter- and intra-specific variation provide several important insights for ecoimmunology. Cyr et al. (2019) highlight how accounting for within-species variation can facilitate inference of between-genera differences and the need to quantify differences in functional immune traits. Lastly, between-population comparisons facilitate understanding of the forces that exist to affect immune variation across spatial scales (e.g., Becker et al. 2019c; Merrill et al. 2019). Furthermore, while comparative approaches to ecoimmunology increasingly have considered phylogenetic dependence (Brace et al. 2017), these analyses also emphasize the need to control for space and

highlight statistical tools to account for this dependence (Albery et al. 2019; Becker et al. 2019c).

From individual immunity to epidemiology

Individual, population, and species determinants of immunological variation can each have consequences for infectious disease dynamics. However, scaling immunological variation from individual- to population-level outcomes (e.g., epidemics, evolution of tolerance, and extended infection seasons) first requires robust modeling of within-host interactions. Rynkiewicz et al. (2019) highlighted the complexities of representing within-individual variation in defense. In their study of wood mice (*Apodemus sylvaticus*) treated with antihelminthics, the authors showed that TNF-α production differs between the systemic (spleen cells) and local (mesenteric lymph node cells) scales within a host. This suggests that careful consideration must be taken when using immune measures derived at a single scale (e.g., circulating blood) to represent within-host dynamics. Acknowledging this within-host complexity of immunological variation, Stewart Merrill et al. (2019) evaluated four within-host factors that could influence susceptibility to infection. Using the tractability of *Daphnia dentifera* (Stewart Merrill and Cáceres 2018), the authors tested how parasite exposure, physical barriers to infection (i.e., gut epithelium), internal defenses (i.e., hemocyte responses), and body size differentially predicted the probability of realized infection (Combes 2001). Physical barriers and internal defenses best determined host susceptibility, revealing within-host metrics that could be translated into parameter values for epidemiological models. Similarly, Henschen and Adelman (2019) discussed various ways of conceptualizing and measuring tolerance. Whereas ecoimmunology has traditionally focused on host resistance mechanisms that control parasite burden, tolerance has gained attention as an effective and common mechanism by which individuals mitigate the effects of an infection (Knutie et al. 2016; Budischak and Cressler 2018; Burgan et al. 2019; Martin et al. 2019). Henschen and Adelman (2019) highlighted how the effects of tolerance on parasite transmission should vary with the specific mechanisms involved. Specially, they argued that tissue-specific tolerance driven by damage-avoidance will decrease overall transmission, whereas tissue-specific tolerance driven by damage-repair will increase overall transmission.

To scale within-host variation in the aforementioned defenses to population-level infection dynamics, novel modeling methods are also necessary. Whereas mathematical models have often addressed spatial complexity (Plowright et al. 2011; Becker et al. 2018b), explicit models of within-host infection dynamics are rare and challenging (Mideo et al. 2008; Handel and Rohani 2015; Restif and Graham 2015). One important barrier to linking within- and between-host scales is how to use data on within-host variation to generate parameter estimates for epidemiological models. Recent statistical developments have enabled the estimation of population-level parameters using individual-level antibody titers (Borremans et al. 2016; Pepin et al. 2017). Specifically, longitudinal experimental data on antibody kinetics within a host can be used to estimate force of infection (λ), the rate at which susceptible individuals become infected. Pepin et al. (2019) integrated this quantitative framework with a survival analysis; through a case study of avian influenza virus in wild pigs, the authors showed that this expanded method reduces the statistical bias that can be present for opportunistically collected serological data. More broadly, this method provides a promising avenue for harnessing immunological variation within and among hosts to improve epidemiological inference.

An additional challenge to linking within- and between-host dynamics is in defining the degree of model complexity needed to represent both scales. Increasing evidence suggests that mechanistically linking within-host processes to between-host interactions can generate distinct predictions about infectious disease. For example, past modeling efforts nested a within-host model, where host resource intake was split among maintenance, immune defense, and energy stolen by the parasite for replication, to a classic population-level transmission model (Hite and Cressler 2018). This approach showed that resource intake and virulence evolution could create emergent transmission dynamics not predicted by a population-level model alone. Similarly, an explicit within-host model of *Schistosoma mansoni* infection in intermediate hosts (i.e., snails) provided an accurate fit to individual-level infection burden data and yet counterintuitively suggested unimodal relationships between snail density and human risk (Civitello et al. 2018). Malishev and Civitello (2019) provided a framework using dynamic energy budget (DEB) theory to translate individual-level processes into population-level infection outcomes. DEB models predict changes in life history of individuals by tracking resource uptake and use for growth, maturity, reproduction, and survival (Kooijman and Kooijman 2010). The authors again

focused on *S. mansoni* in snails to scale growth, reproduction, parasite production, and mortality to parasite transmission across a gradient of food resources, capturing not only individual but also environmental variation in within-host processes. Their model showed that infected hosts produce fewer parasites at lower resources as competition increases, which produces brief epidemics in the host growth season when resources are abundant and infected hosts are few.

In a complementary approach, Hall (2019) used differential equation models to explicitly link within-host dynamics to population-level parasite transmission. A within-host model of microparasite interactions with the immune system was used to generate variation in infectious periods at the population level. Because food availability can modify within-host dynamics by altering immune performance (Strandin et al. 2018), the host immune response was linked to resource intake, the distribution of which is given in relation to variation in resource abundance in the environment (e.g., food scarcity and food subsidization; Becker et al. 2015). When host immune performance was coupled to resource intake, the models showed that resource scarcity can result in large epidemics by creating supershedding individuals, whereas resource subsidization can reduce or prevent parasite transmission by homogenizing resource allocation to host defense. Importantly, a non-coupled model (i.e., homogeneity in infectious periods) greatly underestimated epidemic outbreak size, suggesting that the explicit modeling of within-host dynamics is critical to developing accurate disease predictions at the population scale. Hite and Cressler (2019) presented an alternative modeling framework for assessing how reduced resource intake driven by infection (i.e., parasite-mediated anorexia) affects disease dynamics over evolutionary time. The authors used differential equation models to account for the resource-dependent feedbacks between multiple host and parasite traits, including those between resources and virulence and between resources and recovery. Using an adaptive dynamics framework and evolutionary invasion analysis (Diekmann et al. 2009), their model suggested that interventions that alter host diet and nutritional intake could either reduce infectious disease severity or inadvertently select for more harmful parasite strains and drive larger epidemics.

Although many opportunities for linking within- and between-host dynamics remain (Mideo et al. 2008; Handel and Rohani 2015), the above efforts provide several important insights. Notably, experimental studies can help identify the within-host scales most critical to host–parasite interactions (e.g., Rynkiewicz et al. 2019; Stewart Merrill et al. 2019). Statistical developments can also leverage such within-host variation (e.g., antibody kinetics) to guide parameterization of epidemiological models, even in the face of opportunistic sampling of wildlife (Pepin et al. 2019). In terms of model structure, Malishev and Civitello (2019) and Hall (2019) demonstrate that explicit consideration of within-host dynamics, either by modeling host energetics and physiology (e.g., DEB) or linking within-host processes to food intake and resource availability, can generate distinct predictions about the timing and magnitude of epidemics in a population. Furthermore, Hite and Cressler (2019) highlight that the feedbacks between resources, host immunological traits, and infection can have vastly different outcomes across evolutionary time for the evolution of virulence. These studies more broadly showcase a range of analytic tools for successfully linking the within- and between-host scales.

Novel approaches and future directions

What factors best determine immunological differences between hosts, and how can such variation be best scaled up to inform population-level epidemiology? We assert that answering such broad questions depends upon continued collaboration and disciplinary cross-talk between ecoimmunology, disease ecology, and mathematical modeling. In addition to the work highlighted here on the determinants and epidemiological consequences of immunological variation, we highlight several promising avenues for continued work on this topic.

Statistical tools

Our symposium highlighted a range of statistical tools for comparing immune phenotypes across species and population and for converting this variation into parameter estimates for epidemiological models. Given recognized limits and caveats of comparative immunology (Downs et al. 2014; Fassbinder-Orth 2014), future large-scale approaches to ecoimmunology would benefit from the statistical tools used for macroecological approaches to parasite and endocrinology datasets (Stephens et al. 2016; Martin et al. 2018). Similarly, use of statistical approaches that partition immunological variation among varying levels of biological organization can illuminate the appropriate relationships to include when modeling infection dynamics across scales (Downs and Dochtermann 2014). In addition to refinement of methods that account for phylogenetic dependence,

machine learning algorithms also hold promise given their ability to accommodate heterogeneous datasets and the high degree of collinearity that can characterize macroecology (Hochachka et al. 2007; Kelling et al. 2009). For example, algorithms such as phylogenetic factorization and boosted regression trees have leveraged phylogenies and trait data to understand patterns in which viruses are most prone to be zoonotic and which bat species are likely henipavirus reservoirs (Washburne et al. 2018; Plowright et al. 2019). Use of such tools could identify new patterns in ecoimmunology datasets and generate new hypotheses for why certain clades or trait profiles of species invest more in particular immune phenotypes.

Advances in meta-analysis relevant to ecology and evolution (Lajeunesse 2009; Nakagawa and Santos 2012) could also help reveal new relationships between phylogeny, life history, environmental conditions, and immunity, especially in lieu of empirical studies that compare immune phenotypes across standardized conditions. For example, a phylogenetic meta-analysis of the effect size for immune response between control and treatment hosts (e.g., PHA challenge, vaccination) showed that immune activation is generally costly for hosts, but that host body size and life history orientation impinge on the magnitude of such costs (Brace et al. 2017). Similarly, a phylogenetic meta-analysis of the effect size between acute handling stress or storage time of plasma and BKA showed that whereas BKA in birds was strongly diminished by both stressors, bat BKA measures were generally robust, potentially implicating immunological distinctiveness between host classes (Becker et al. 2019a). Application of future meta-analyses could address several long-considered questions in ecoimmunology, such as testing support for latitudinal gradients in immunity (Hasselquist 2007; Morand et al. 2010) and asking if and how anthropogenic changes such as deforestation and urbanization have predictable and consistent effects on host defense (Martin et al. 2010; Messina et al. 2018).

Application of these statistical tools would especially benefit from more widespread adoption of reproducible research practices in ecoimmunology, including the need to register and deposit sample collection and analysis plans prior to publication and to make raw data and analysis scripts publicly available in online repositories. Pre-registration can distinguish confirmatory (hypothesis-testing) from exploratory analyses (hypothesis-generating) and help minimize questionable research practices, such as cherry picking statistically significant results (Fraser et al. 2018; Nosek et al. 2018). Greater transparency and data accessibility could also facilitate the above comparative analyses by limiting publication bias (e.g., effect sizes can be derived even if not reported) and better enabling data syntheses (Nakagawa and Santos 2012).

(Spatio)temporal variation

Studies highlighted here also emphasize the importance of considering not only spatial but also temporal variation in immune phenotypes. For example, Rynkiewicz et al. (2019) and Pepin et al. (2019) highlight the power of longitudinal studies in strengthening inference from experimental studies of within-host dynamics. Similarly, Albery et al. (2019) show that spatial patterns in antibody concentrations also differ between seasons and illustrate the use of INLA to capture both spatial and temporal patterns simultaneously. While seasonality has long been influential to host immunity (Nelson 2002; Altizer et al. 2006), future studies would be valuable to identify the joint spatial and temporal dependencies in host defense. Range expansions, such as those of house sparrows (*Passer domesticus*) and black rats (*Rattus rattus*) in Senegal (Diagne et al. 2017; Martin et al. 2017), are particularly tractable for such efforts, as the invasion represents an explicitly spatiotemporal process. Spatiotemporal sampling designs can also minimize unwanted noise or artifacts introduced into comparative analyses (Becker et al. 2019b), such as by those caused by sampling populations across a landscape in different seasons or years.

Quantifying immune variation

Lastly, a consistent theme throughout the studies highlighted here focuses on how to describe variation in immunity at the scale of individuals in ways that best translate into epidemiology (e.g., Henschen and Adelman 2019; Pepin et al. 2019; Stewart Merrill et al. 2019). Recent work suggests focusing on host tolerance, competence, and resistance as defensive traits rather than on the outcomes of specific immunological assays. Arguably, these organismal traits have the capacity to bring us closest to the phenomena most relevant to disease dynamics at super-individual scales (Gervasi et al. 2015; Martin et al. 2016, 2019; Burgan et al. 2019; Downs et al. 2019). Although understanding the cellular- or molecular-level drivers of immunological variation is clearly important, we appeal that including organismal-level traits in studies of host defense and will become particularly important to interlinking various scales of analysis.

Concluding thoughts

Perspectives and data from ecoimmunology are being increasingly integrated with those from disease ecology and epidemiology (Hawley and Altizer 2011; Brock et al. 2014; Handel and Rohani 2015). The papers arising from our symposium "The Scale of Sickness: How Immune Variation Across Space and Species Affects Infectious Disease Dynamics" highlight the advances toward this goal as well as illuminate knowledge gaps and areas that are technically difficult to bridge between fields and approaches. As we collect more data on intra- and interspecific differences in host competence and underlying immune traits, as more researchers engage in studies of wildlife immunology across different spatiotemporal scales and link variation across levels of biological organization, and as studies continue to integrate knowledge of individual-level variation and mechanisms into ecological and evolutionary models, we will begin to see patterns that will better help us predict responses to and dynamics of infectious disease.

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