An Introduction to Ecoimmunology

Laura A. Schoenle, Cynthia J. Downs, and Lynn B. Martin

"…variation itself is nature's only irreducible essence. Variation is the hard reality…" from The Median Isn't the Message by Stephen J. Gould

Immunological research has made astounding progress in describing the cellular and molecular mechanisms underlying the defenses to parasites. Researchers have developed life-saving medical procedures based on experiments conducted on genetically identical animals that have been raised in sterile, carefully controlled laboratory housing (National Research Council 2004). Yet, the reality remains that animals, including humans, are not genetically homogeneous, and both develop and live in variable environments. As a result, the ability to defend against parasites (i.e., immunity) varies among individuals, populations, and species (Schmid-Hempel 2003). Why should we care about variation in immunity? The sources and consequences of immune variation have implications for public health, wildlife management, agriculture, and conservation. Understanding the sources of variation in immunity, such as which genes influence the likelihood of developing diseases or how nutrition influences susceptibility to infection, should help identify management strategies to minimize the effects of disease (Jones et al. 2014; Bulik-Sullivan et al. 2015; Farh et al. 2015). Furthermore, integrative approaches to immunology

L. A. Schoenle (✉)
Department of Global Health, University of South Florida, Tampa, FL, USA

Department of Biology, Hamilton College, Clinton, NY, USA

C. J. Downs
Department of Biology, Hamilton College, Clinton, NY, USA

L. B. Martin
Department of Global Health, University of South Florida, Tampa, FL, USA

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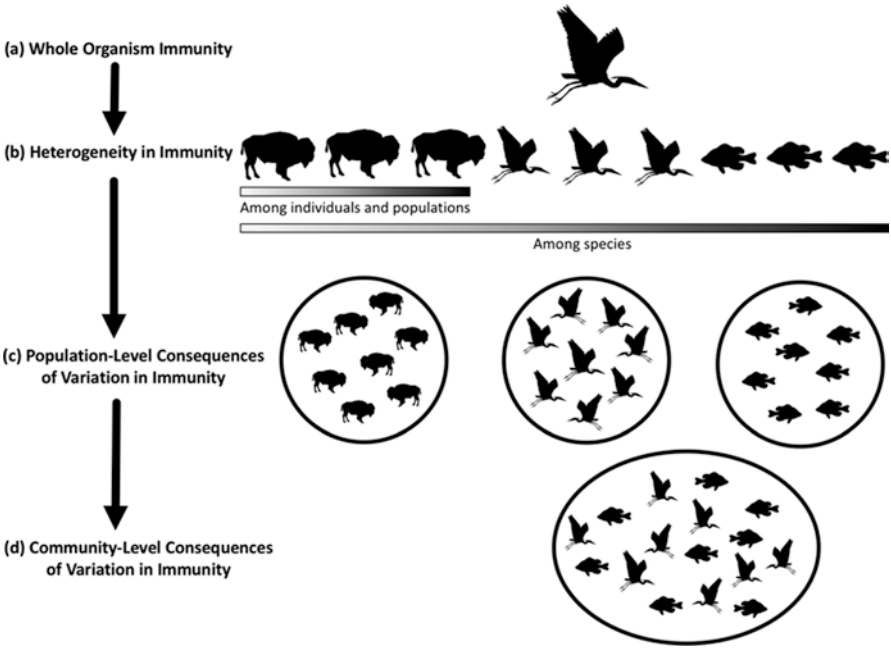

Fig. 1 The central themes in ecoimmunology integrate across levels of biological organization. (**a**) Ecoimmunologists study immunity in the context of the whole organism. Thus, immunity (as defined in the body of the paper) is a product of interacting physiological systems (e.g., nervous, endocrine, and immune systems). These interacting physiological systems underlie complex immune traits, including parasite resistance and tolerance. (**b**) Immunity varies among individual organisms because of individual-specific traits, such as developmental history and genetics, as well as across contexts due to variable environmental conditions and life history stage. Heterogeneity in immunity is also found among species. (**c**) and (**d**) Variation in immunity among individuals and species can influence host–parasite eco-evolutionary dynamics within populations and communities. Animal silhouettes CC by 4.0 to Natasha Sinegina. (Super Coloring 2017)

will enhance our ability to understand the equally intriguing consequences of that variation, such as disease dynamics and the evolution of life history traits.

Ecoimmunology is the study of the causes and consequences of variation in immunity (Brock et al. 2014; Downs et al. 2014). This field places immunology in evolutionary and ecological contexts across levels of biological organization, from the organism to community-level interactions (Fig. 1). Furthermore, ecoimmunology builds upon and complements the field of comparative immunology, the focus of this volume. In this chapter, we review the approaches and tools used by ecoimmunologists and discuss insights obtained from ecoimmunology as they relate to three central themes: (1) immunity in the context of the whole organism, (2) heterogeneity in immunity, and (3) the broad consequences of individual variation in immunity. We also provide a brief overview of the field's history in Box 1. Finally, we will reflect on the future of ecoimmunology.

Immunity in the Context of the Whole Organism

Ecoimmunologists investigate immunity as a characteristic of the whole organism rather than a series of isolated mechanisms. Although this holistic strategy has long been the goal, the approaches used to characterize immunity have evolved over time. Early efforts were relatively simplistic and focused on measuring the strength of responses to immune challenges or the magnitude of available defenses (Martin et al. 2006b). New information about the mechanisms underlying immunity and the costs of parasite defenses have led to fundamental changes in how immunity is studied (Brock et al. 2014). The complexities of immune function and the interdependent nature of physiological systems is facilitating a transition to more integrative approaches today.

Immunocompetence: The Search for a Simple Immune Measure

The quest for a measure of organismal-level immunity began with the concept of immunocompetence, or an individual's ability to prevent or eliminate a parasite infection (Demas et al. 2011). Because immunocompetence is so broad, it is logistically difficult (or even impossible) to assess. Moreover, faith in the validity of the concept led early ecoimmunologists to underestimate the complexities of parasite defenses. Early ecoimmunology studies tended to use one or two immune metrics and interpreted measured variation as an indication of overall antiparasite defense (e.g., Saino and Calza 1999; Johnsen et al. 2000; Møller and Erritzoe 2000). One such immune metric was the phytohemagglutinin (PHA) skin test, which was thought to signal the strength of T-cell-mediated immunity (Smits et al. 1999; Tella et al. 2008). For example, a study of barn swallows (*Hirundo rustica*) demonstrated that adults producing offspring with strong responses to the PHA skin test were less likely to survive until the next breeding season (Saino and Calza 1999). The authors interpreted this result as indicating that producing highly immunocompetent offspring was associated with survival costs. Although this approach pointed to interesting relationships between immunity and other traits, it began to fall out of favor after researchers raised concerns about the general concept of immunocompetence and the interpretation of this and other specific immune assays (Adamo 2004; Viney et al. 2005; Martin et al. 2006b). Whereas immunologists know well that the immune system is complex and different immune pathways are important for responding to different parasites, early ecoimmunologists hoped to be able to overcome this problem and capture something meaningful with simple assays. Now, though, the concept of immunocompetence is understood as too broad to be useful (Demas et al. 2011). This recognition arose when ecoimmunologists began interpreting results of their assays in terms of the specific immune components measured, not immunocompetence in a broad sense (Martin et al. 2006b). This epiphany was reinforced when researchers found that variation in immune measures, such as the PHA skin test or white blood cell counts, only sometimes predicted responses to an actual infection, and usually they did so weakly (Adamo 2004; Adelman et al. 2014).

What the concept of immunocompetence sought to capture, though, that there is an optimal immune response for different species or individuals, still resonates in the field today (Adamo 2004; Demas et al. 2011). But just what is an optimal immune response?

Optimal Immunity: More Isn't Always Better

The foregoing question is probably the main thing that distinguishes traditional immunology from ecoimmunology. Whereas all immunologists appreciate that more immunity is not always better (e.g., overzealousness of the immune system can cause damage to the host), ecoimmunologists have made this and other costs of immunity central to their research and resultant theories. Natural selection favors the optimal immune response, the magnitude and type of immune response that maximizes fitness (the total reproductive output within an individual's lifetime). If there are costs to immunity, the optimal immune response is not necessarily the strongest one (Schmid-Hempel 2003). For example, Soay sheep (*Ovis aries*) with higher antibody concentrations are more likely to survive the winter but also have lower reproductive success (Graham et al. 2010). Thus, mounting an antibody response is an important defense, but it carries a cost. In this and probably other systems, antibodies help control parasite burdens, which in these sheep are most problematic during winters, but they also can harm host tissue if they are autoreactive. The optimal immune response will therefore be balanced between the risk of dying from infection versus producing viable offspring (Fig. 2). Ultimately, any costs required to develop, maintain, or activate defenses will impact the expression and persistence of immune traits (Schmid-Hempel and Ebert 2003). A cornerstone of ecoimmunology is that immunity to parasites has costs at both evolutionary and individual scales (Brock et al. 2014).

The Costs of Immunity Influence Evolutionary Trade-Offs

Evolutionary costs of immunity can arise because of genetic architecture. The genes that influence immune phenotypes can regulate other traits as well or can be inherited with other genes. Similarly, transcription factors that regulate immunity may also regulate other traits (Downs et al. 2014). As a result, there are negative genetic correlations between traits that promote immunity and traits associated with other characteristics that enhance fitness (Rolff and Siva-Jothy 2003; Ardia et al. 2011). Therefore, the evolution of immunity is influenced by genetically correlated traits.

Antagonistic pleiotropy occurs when a single gene causes negative correlations between an immune trait and another trait that can enhance fitness (Rolff and Siva-Jothy 2003; Roff and Fairbairn 2007). Antagonist pleiotropy can force trade-offs that are not easily altered by selection because breaking these trade-offs requires a gene duplication event (Roff and Fairbairn 2007). Fruit fly (*Drosophila melanogaster*) defenses against parasitoid wasps present one of the most extreme examples of antagonistic pleiotropy influencing immunity. A wasp oviposits eggs inside the host fly, and if allowed to develop, the wasp's offspring kill the fly larva by consuming it

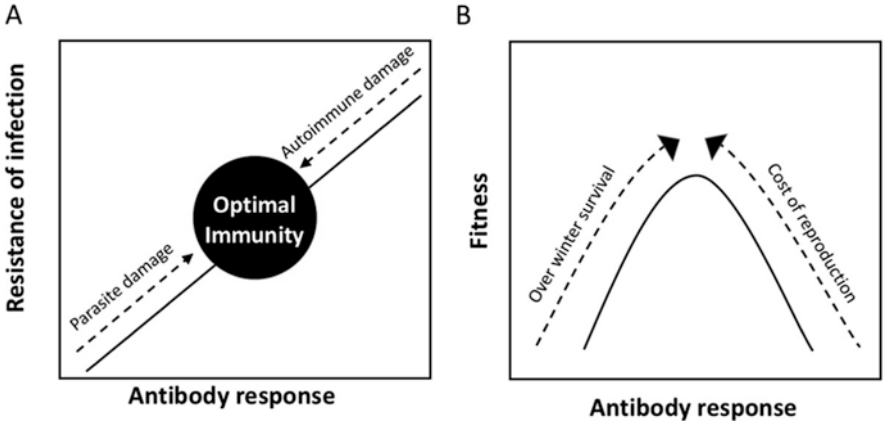

Fig. 2 The antibody response of Soay sheep provides parasite protection but also has fitness costs, and as a result, the strongest immune response does not maximize fitness (Graham et al. 2010). (**a**) Natural selection should lead to intermediate levels of immunity and resistance to parasites when there are both fitness costs and benefits to the immune response. Increasing the costs of parasite damage will favor a stronger antibody response. However, high levels of antibody production that cause autoimmune damage will favor a dampened immune response. (**b**) Individuals producing highest antibody responses had greater overwinter survival but also reduced breeding success. Individuals with the intermediate, optimal antibody response should have the highest fitness. (Adapted from Martin and Coon 2010 with permission from AAAS)

from the inside out. Some *Drosophila* genotypes can resist the wasp's attack by producing hemocytes (blood cells) that encapsulate the eggs, destroying them (Poirie et al. 2000; Kraaijeveld et al. 2001). However, this and other defenses have costs: more resistant *Drosophila* genotypes (i.e., those that can better control infections) also have slower feeding rates than more susceptible *Drosophila*. Subsequently, resistant individuals are less likely to survive in high-competition environments (Kraaijeveld and Godfray 1997; Kraaijeveld et al. 2001). Evidence suggests that a single gene might regulate the trade-off between competition and parasitoid defenses (Hodges et al. 2012). Antagonistic pleiotropy also is suspected to play a role in human aging (Franceschi et al. 2000; Goto 2008). Inflammation, an important part of the innate immune response, also contributes to cellular senescence, tissue damage, and several diseases associated with aging such as arthritis and Alzheimer's (Lambeth 2007; Freund et al. 2010). The protective advantages conferred by inflammation in younger individuals becomes costly as those individuals age, when inflammation can become chronic and more likely to cause disease (Lambeth 2007; Freund et al. 2010).

Often it is unclear whether immune trade-offs with a genetic basis are caused by pleiotropy or linkage disequilibrium, when genes are inherited together because of their proximity on a chromosome (Saltz et al. 2017). In these scenarios, correlations between traits can be broken through genetic recombination. A meta-analysis revealed that artificial selection for rapid growth in chickens led to attenuated immune responses (van der Most et al. 2011). However, selection for various

immune traits was not always associated with reduced growth rates, and the strengths of relationships varied among lines of chickens and forms of immunity, suggesting a mechanism other than pleiotropy (van der Most et al. 2011).

The degree to which immunity is traded off with other traits depends on the relative strength of the evolutionary pressures (e.g., parasite risk, predation, conspecific competition) (Lazzaro and Little 2009). The outcome of evolutionary immune trade-offs thus vary across environments. Defenses of *Drosophila* against the parasitoid wasps vary geographically, indicating that variable selection pressures across environments lead to local optima for immunity (Kraaijeveld and Godfray 1999). For example, humidity influences the biological pathways enabling resistance to parasitoids and, thus, can alter the costs of immunity. As a result, humidity could shape the local evolution of defenses.

The Costs of Immunity Cause Trade-Offs Within Individuals

The aforementioned evolutionary costs of immunity have physiological bases. For instance, the development, activation, and even mitigation of parasite defenses can impose substantial costs on organisms (Lochmiller and Deerenberg 2000). Experimental activation of immune responses can cause increases in metabolic rate and body mass loss, indicating that immunity has energetic costs (Demas et al. 2011; Ots et al. 2001; Freitak et al. 2003; Martin et al. 2003; Eraud et al. 2005; Amat et al. 2007). Nutrient availability is also critical. For example, carotenoid availability limits the expression of immune traits in juvenile (Saino et al. 2003; Klasing et al. 2006; Tyndale et al. 2008) and adult (Blount et al. 2003; Amar et al. 2004) birds and fish. Similarly, the amino acid lysine is integral to leukocyte function and the biosynthesis of proteins associated with innate immunity (Iseri and Klasing 2014). Indeed, in chickens, the lysine required during the acute-phase response to a bacterial infection is equivalent to that in 355 feathers or 17% of an egg (Iseri and Klasing 2014). Because any resources allocated to immunity are unavailable for other activities, the resource costs of immunity can drive allocation trade-offs (Norris and Evans 2000; Lochmiller and Deerenberg 2000; Ardia et al. 2011; Downs et al. 2014). For example, energy limitation underlies a trade-off between wound healing and reproduction in the ornate tree lizard (*Uta ornatus*) (French et al. 2009). Injuries occur frequently in nature, and wound healing involves multiple components of the immune system. Experimentally wounding a lizard's skin reduced egg follicle size if the studied female was food restricted. However, when food was unlimited, there was no trade-off between wound healing and reproductive investment (French et al. 2007a, b). In addition, food restriction had no effect on wound healing in females before reproduction (French et al. 2007a). Similar allocation trade-offs between reproduction and immunity are relatively common and can be found across taxa, including insects, mammals, reptiles, and birds (Schwenke et al. 2016; Norris and Evans 2000; Hayes and Shonkwiler 2001; French et al. 2009).

Allocation trade-offs with immunity are not limited to reproduction. Other energetically costly functions, such as tissue growth or dispersal to new areas (e.g., migration), are also subject to allocation trade-offs (Soler et al. 2003; Moreno-Rueda 2010; Altizer et al. 2011). For example, some forms of immune function in

thrushes (*Catharus* spp. and *Hylocichla mustelina*) are reduced during migration when compared to breeding conspecifics (Owen and Moore 2006), and resource availability is likely to underlie these reductions (Owen and Moore 2008). At a migratory stopover site, thrushes in poor energetic condition (lower fat deposits, muscle mass, body-size-controlled condition index) had lower leukocyte and lymphocyte counts; among birds captured and brought into captivity, mass gain was associated with greater responsiveness to an immune challenge (Owen and Moore 2008). Importantly, the resource costs of immunity will only lead to trade-offs under conditions of resource limitations. If individuals can obtain sufficient resources, they can support immunity in addition to other costly activities, and there will be no allocation trade-off (van Noordwijk and de Jong 1986; Downs et al. 2014).

Immunity not only imposes energetic costs on individuals; activating immune defenses can harm hosts as well. Autoimmune disease is one form of such a cost. For example, Guillain-Barré syndrome is the result of mounting an immune response against neurons (Yuki and Hartung 2012). Lupus occurs when antibodies target multiple host organ systems (Lipsky 2001). Immune responses targeting an infection can also cause damage to hosts. During malaria infections, the loss of red blood cells is often much higher than could be achieved by the malarial parasites alone (Price et al. 2001; Evans et al. 2006). Evidence suggests that the immune response, specifically T-cell activity, damages uninfected red blood cells, increasing the severity of malarial anemia (Evans et al. 2006). In addition, immune responses to malaria and other parasites can increase concentrations of reactive oxygen metabolites (ROMs), often called free radicals (Costantini and Møller 2009). High concentrations of ROMs can damage tissue and even accelerate rates of senescence (Finkel and Holbrook 2000; Monaghan and Haussmann 2006; Haussmann and Marchetto 2010). Because individuals can harm their own tissues by activating parasite defenses, mounting overly strong immune responses could result in a loss of fitness (Råberg et al. 1998; Graham et al. 2010, 2011).

Behaviors associated with immune responses, sickness behaviors, can also be costly. When individuals mount particular types of immune responses, they exhibit specific behaviors, including lethargy, anorexia, and low libido and alertness (Adelman and Martin 2009; Adelman and Hawley 2016). Many of these behavioral changes are regulated by proinflammatory cytokine activity in the nervous system (Adelman and Martin 2009). Sickness behaviors are thought to be adaptive; they can promote energy conservation for defending against parasites (Hart 1988) or possibly support tissue repair (Medzhitov et al. 2012). However, elicitation of sickness behaviors can also reduce survival or reproductive success. For example, immune-challenged field crickets, *Gryllus campestris*, were at increased risk of predation because they slowed responses to predators and spent more time in exposed areas, possibly because of differing thermoregulation needs during infection (Otti et al. 2011). Sickness behaviors can also carry opportunity costs because they directly interfere with activities such as foraging or breeding effort. Immune-challenged house sparrows (*Passer domesticus*) reduced the rate at which they fed their offspring, had higher rates of nest abandonment, and, ultimately, fledged fewer chicks (Bonneaud et al. 2003). However, individuals appear to have evolved to

minimize the opportunity costs associated with sickness behavior. Male song sparrows (*Melospiza melodia morphna*) exhibit greater sickness behaviors in response to an immune challenge during the nonbreeding season than during the breeding season, when sickness behaviors could impair reproduction (Owen-Ashley and Wingfield 2006). This seasonal variation in sickness behaviors might be hormonally mediated; experimental increases in testosterone suppressed sickness behaviors in male Gambel's white-crowned sparrows (*Zonotrichia leucophrys gambelii*) (Ashley et al. 2009).

Complex Immune Phenotypes: Using Resistance and Tolerance to Characterize Whole-Organism Responses to Parasites

At both individual and evolutionary scales, the optimal parasite defenses will be those that maximize fitness (Schmid-Hempel 2003; Ardia et al. 2011). Studies of the costs versus benefits of immunity initiated new directions in ecoimmunology. In particular, researchers have started characterizing immunity as a complex, integrated response rather than the activity of a single physiological system operating without constraints of other life processes (Graham et al. 2011; Brock et al. 2014). Central to this new framework are resistance and tolerance (Råberg et al. 2009).

Resistance and tolerance are distinct, but not mutually exclusive, strategies for defending against parasites. Broadly speaking, parasite resistance is fighting infection and involves limiting the number of parasites infecting a host. Before a parasite successfully infects a host, resistance can include avoidance or physically blocking a parasite invasion (Best et al. 2014; Kutzer and Armitage 2016). Infected hosts can resist parasites by removing parasites or limiting their reproduction, often through actions of the host's immune system (Råberg et al. 2009). More resistant individuals will have fewer parasites or a faster rate of parasite clearance, and as a result, increased host resistance has a negative impact on parasite fitness (Råberg et al. 2007). In observational studies of free-living animals, parasite load is often used as an indicator of resistance (e.g., Coltman et al. 2001; Schoenle et al. 2017b). In experiments, resistance is often measured as the change in parasite load over time (e.g., Råberg et al. 2007, 2009). Resistance, perhaps obviously, has been the focus of traditional immunology.

In contrast, tolerance emphasizes the costs of infection rather than control of parasite burden (Råberg 2014; Kutzer and Armitage 2016). The concept of tolerance comes from the plant sciences, where researchers realized that plants could gain fitness by minimizing damage caused by herbivores, fungi, and other threats rather than avoiding, clearing, or otherwise walling off threats entirely (Caldwell et al. 1958; Schafer 1971; Strauss and Agrawal 1999). Tolerance is defined as the minimization of the costs of infection per parasite (Råberg et al. 2009). In other words, tolerance involves the regulation of damage accrued during an infection, independent of parasite load. Tolerance can be achieved by reducing the damage caused by the host's own defense mechanisms (Schneider and Ayres 2008). Consider the example of the Soay sheep mentioned earlier (Fig. 2) in which some of the

antibodies that protected from parasites and promoted overwinter survival were also associated with low fecundity (Graham et al. 2010; Nussey et al. 2014). The immune system of the Soay sheep can cause immunopathology, so preventing antibody levels from becoming too high could increase tolerance. Individuals can also increase tolerance by mitigating damage caused by parasites (Schneider and Ayres 2008). For example, the human intestinal helminth, *Schistosoma mansoni*, causes extensive tissue damage in multiple organ systems as it progresses through its life cycle (Allen and Wynn 2011). The production of Th2 cytokines promotes the repair of parasite-damaged tissues and thereby increases tolerance to the helminths (Allen and Wynn 2011). Although a relatively new area of study, ongoing research indicates that tolerance is an important trait for understanding host–parasite interactions. Tolerance is often heritable (Mazé-Guilmo et al. 2014; Parker et al. 2014), associated with host fitness (Hayward et al. 2014b), and impactful on parasite evolution (Cousineau and Alizon 2014; Cressler et al. 2015).

As forms of immunity, resistance and tolerance have great advantages relative to the concept of immunocompetence and immune variation as measured by specific assays. Because resistance and tolerance assess how individuals manage parasite loads and costs of infection for specific parasites, they are biologically relevant performance metrics. Furthermore, resistance and tolerance are integrative measures of immunity at the level of the whole organism; they incorporate the effects of multiple branches of the immune system, as well as behaviors and other physiological systems (e.g., endocrine and nervous system), on organisms' parasite loads and the costs of infection.

Integrative Ecoimmunology: Immunity as Part of a Complex, Dynamic System

Immunity is the product of interconnected physiological systems. Most people experienced this first hand through unfortunate and uncomfortable encounters with the flu. Although flu viruses do not usually enter the central nervous system, the response to the infection affects the brain, leading to fatigue, reduced alertness, reduced appetite, and poor mood (Kelley and McCusker 2014). Indeed, an infection anywhere in the body, such as the lungs or sinuses, can induce a proinflammatory cytokine response in the brain that results in many unpleasant flu symptoms (Jurgens et al. 2012). This common experience is just one example of how the immune system and parasite defenses are inextricably linked to other physiological systems. Addressing immunity in the context of the whole organism requires understanding interactions between immune defenses and other components of physiology.

An entire field, psychoneuroimmunology, is dedicated to understanding how the immune, endocrine, and nervous systems are related to behavior (Ader et al. 1995). Interest in these connections grew following the discovery of evidence suggesting that stress and depression could influence immune function (Irwin 2008). For example, early work in the field demonstrated that the death of a spouse was associated with weak responses to the PHA skin test (Bartrop et al. 1977; Schleifer et al. 1983).

Evidence also suggests that psychological stress can increase susceptibility to infectious disease (Cohen et al. 1991) and suppress the ability to heal wounds (Kiecolt-Glaser et al. 1996). Physiological links between the nervous and immune systems underlie the relationship between stress and disease. For example, the neuropeptide corticotropin-releasing hormone (CRH) is released from the hypothalamus in response to stress and is elevated in depressed humans (Irwin 2008). When high levels of CRH bind to receptors in the brain, CRH suppresses both innate and cell-mediated immune responses (Irwin et al. 1987; Strausbaugh and Irwin 1992; Irwin 2008).

Ecoimmunologists have also devoted substantial efforts toward understanding the mechanistic links between stress and immune function. Researchers working on nonhuman vertebrates have primarily focused on glucocorticoids. Glucocorticoids increase in circulation when organisms are faced with psychological or physical challenges (Bonier et al. 2009; Boonstra 2012). They promote a suite of physiological and behavioral changes, including alterations in immune function, metabolism, and reproductive capability (Sapolsky et al. 2000). Interestingly, glucocorticoids can enhance or suppress immune function, and in some cases do both simultaneously depending on the threat or context (Sapolsky et al. 2000; Martin 2009). The relationship between glucocorticoids and immune function is highly dependent on past and current environmental conditions (French et al. 2009), host life priorities (Martin et al. 2005), and the amplitude, duration, and frequency of glucocorticoid secretion (Martin 2009; McCormick et al. 2015).

A substantial proportion of ecoimmunology studies investigating connections among physiological systems have focused on endocrine–immune interactions. Ecoimmunologists might emphasize endocrinology because many hormones can act as physiological integrators (Cohen et al. 2012), factors for which many cell types have receptors. Because so many cells carry receptors for the same hormones, the activities of disparate systems can be coordinated for the same tasks (Martin et al. 2011b). Moreover, many hormone concentrations rapidly respond to changes in the physical or social environment, further facilitating a match of the whole-organism phenotypes to current conditions (e.g., Maher et al. 2013). For example, melatonin transduces information about day length into a hormonal signal that mediates seasonal changes in immunity (Guerrero and Reiter 2002; Hardeland et al. 2011). In general, melatonin tends to enhance immune function (Martin et al. 2008; Weil et al. 2015), and by supporting a stronger immune response during winter, when days are short and risk of some infections is relatively high, melatonin might bolster immunity (Nelson 2004). Other hormonal integrators can also create links between immunity and other physiological traits. For example, in male red grouse, *Lagopus lagopus scoticus*, testosterone increased both nematode burden and comb size (Mougeot et al. 2005a, b). Grouse combs are colorful ornaments, and the form of these sexually selected traits influences female mate choice and male–male interactions (Moss et al. 1979; Rintamaki et al. 1993). Thus, the link between testosterone, comb size, and resistance to nematodes might ensure that the comb is an honest signal in this system; only high-quality males, who will have high levels of testosterone and a large comb, can cope with high parasite burdens (Folstad and Karter 1992; Mougeot et al. 2004).

Heterogeneity in Immunity

Parasites are ubiquitous. At least 50% of organisms are parasites in some way, and nearly every organism is infected with at least one parasite at some time in its life (Dobson et al. 2008). Even though all organisms face the threat of infection, extensive variation in parasite defenses endures at the individual, population, and species levels (Brock et al. 2014; Downs et al. 2014). In this section, we will address the causes of such variation, and in the following section, we will discuss the consequences (Fig. 3).

Sources of Individual Heterogeneity in Immunity

Spatiotemporal variation in infection risk as well as the value of particular sickness behaviors or other costly immune responses influence investments in immune traits. Moreover, forms of optimal immunity are apt to vary over the course of an organism's lifespan. Both the rate and extent of immune investments as well as subsequent immune development are contingent on the life history strategy of a population. In all hosts, there can be permanent, semipermanent, and reversible effects of genes and environment, ultimately altering immunity across environments (Fig. 3a).

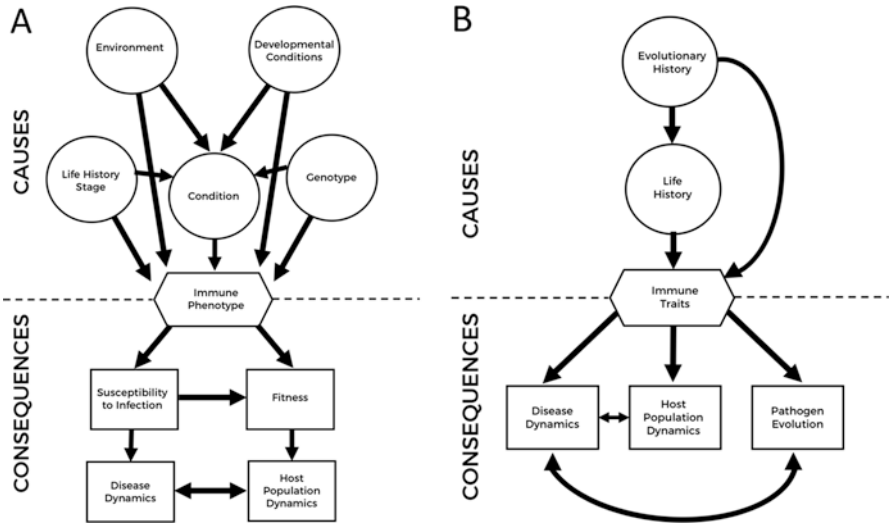

Fig. 3 The purview of ecoimmunology: (**a**) within and (**b**) among species variation in immune defenses. Circles: putative drivers of variation in immunity; squares: potential consequences of that variation; arrows: pathways by which each driver might influence immune phenotype and how variation in immune phenotype could lead to each possible consequence

Genetic Sources of Immune Heterogeneity

Hosts can express a range of immune phenotypes, and the breadth of that range is determined by genotype, developmental history, and maternal and other epigenetic effects. Genotypes vary in many immune traits, including cytokine production (de Craen et al. 2005) as well as organismal traits such as resistance and tolerance (Hayward et al. 2014a; Mazé-Guilmo et al. 2014; Parker et al. 2014). For example, nucleotide polymorphisms were associated with substantial variation in the ability to subdue bacterial infection in wild-sourced *Drosophila melanogaster* (Lazzaro et al. 2004). Furthermore, immune phenotypes are also influenced by the environment and gene-by-environment interactions. For example, *Drosophila* resistance to the ectoparasitic mite, *Macrocheles subbadius*, is also negatively genetically correlated with larval competitive ability (Luong and Polak 2008). However, the relative success of more resistant versus more competitive *Drosophila* varies with density and temperature, resulting in an environment-dependent evolutionary trade-off.

Developmental Environment and Immune Heterogeneity

Early developmental experiences can also affect the expression of immune traits, sometimes throughout life. For example, parents can transmit antibodies to their offspring that shape immunity both immediately and in the long term (Hasselquist and Nilsson 2009). In mammals, some antibody isotypes pass across the placenta and via lactation shortly after birth (Grindstaff et al. 2003; Boulinier and Staszewski 2008). Maternal antibodies can also be transferred to offspring in the egg yolks of birds, fish, and reptiles (Grindstaff et al. 2003; Boulinier and Staszewski 2008). Neonates tend to be particularly vulnerable to parasites in early life. Short-term bolstering of resistance by maternal antibodies can enhance offspring growth rates and maturation (Hasselquist and Nilsson 2009). The effects of maternal antibodies can extend beyond the neonatal phase, shaping immune function into adulthood. In laboratory animals, exposure to antibodies during development altered the immune response to antigens later in life (Wikler et al. 1980; Elliott and Kearney 1992; Lundin et al. 1999). In one study of Wistar Furth rats, the effects of neonatal antibody exposure increased the immune response to a bacterial antigen in the next generation (Lundin et al. 1999). Other components of the developmental environment, such as food availability and parental care, can also influence immune phenotype. In Gambian villages supported by subsistence farming, adult body condition and the mass of newborns were tightly linked to the growing season; body condition was significantly lower during the seasonal postharvest period when little food is available (Moore et al. 1999). People born during the postharvest period were at higher risk of death from infectious disease, suggesting long-term impacts of early-life food limitation. Other types of parental care can also affect immune traits. For example, wood ducks (*Aix sponsa*) incubated at low temperatures were less responsive to immune challenges than those incubated at average temperatures measured in the wild (Durant et al. 2012).

Environmental Conditions Influence Immune Trait Expression

Although genes and the developmental environment constrain the expression of immune traits, immunity remains responsive to fluctuations in the environment throughout organisms' lives. For example, monarch butterflies' (*Danaus plexippus*) ability to resist and tolerate the protozoan parasite *Ophryocystic elektroscirrha* depend on which species of milkweed the butterflies ate (Sternberg et al. 2012). Relationships between resource availability and immunity can be complex, however. Cuban tree frogs (*Osteopilus septentrionalis*) fed a high resource diet (i.e., more crickets) were more resistant to penetration of nematodes through the skin; if an infection was already established, though, they were also more tolerant to infection (Knutie et al. 2017). Environmental effects on immunity are not limited to resource availability. Perceived predation risk induce system-wide changes in physiology and behavior (Clinchy et al. 2013; Newman et al. 2013), including immune functions (Navarro et al. 2003; Stoks et al. 2006; Groner et al. 2013; Adamo et al. 2017). For example, house sparrows (*Passer domesticus*) exposed to predators mounted lower responses to an immune challenge (Navarro et al. 2003).

Life History Stage and Strategy

As discussed previously, parasite defenses are inextricably tied to life history strategy (Sheldon and Verhulst 1996; Ricklefs and Wikelski 2002). Life history can be defined as the patterns of investment an organism makes in growth, reproduction, and survival over its lifetime. Life history stages are periods characterized by specific patterns of investment in some processes over others (e.g., reproduction, immunity, growth, migration) (Ricklefs 1977; Stearns 1992; Roff 2002). The ability to protect against parasites varies across life history stages, including from juvenile to adult as well breeding to nonbreeding. For example, juvenile field voles (*Microtus agrestis*) were more resistant to than tolerant of macroparasites (e.g., intestinal worms, arthropods), whereas the opposite was true of adults, who tended to favor tolerance over resistance (Jackson et al. 2014). This difference could be attributed to the maturation of the immune system with age or to an adaptive strategy mediated by different risk of exposure to parasites or the greater value of growth and maturation versus finding a mate and breeding, depending on individual age. For instance, infections could be more harmful during development, favoring investment in resistance over tolerance in younger animals. Immunity also often changes from the breeding to nonbreeding season, most likely because individuals face different challenges (Zuk and Stoehr 2002; Love et al. 2008). Similarly, we observe sex differences in immunity because males and females engage in different activities during these periods (Zuk and McKean 1996; Zuk and Stoehr 2002). For example, responses to an immune challenge vary across breeding and nonbreeding life history stages in resource-limited female zebra finches (*Taeniopygia guttata*), but not in males (Love et al. 2008). Female zebra finches tend to invest more energy and effort in breeding than males, so differences in immune phenotype might reflect differences in the resources available to the immune system.

Physiology and Body Condition Influence Immune Heterogeneity

All of the sources of individual heterogeneity in immunity discussed here are also likely to influence other components of physiology, such as metabolism or the endocrine system (Ricklefs and Wikelski 2002). As a result, factors that influence immunity might not be acting directly but instead through another mechanism. Body condition is a potential mediator of immunity. For example, short day length (i.e., simulated winter photoperiod) causes a reduction in both body fat and humoral immunity in Siberian hamsters (Drazen et al. 2001). Experimental removal of fat from hamsters also causes a reduction in humoral immunity, suggesting that the presence of fat mediates the effect of day length on immunity (Demas et al. 2003). In this system, the effect of fat on immunity is driven by leptin, a hormone produced by adipose cells (Carlton and Demas 2014, 2015; Carlton et al. 2014). Poor body condition is not always associated with decreasing investment in immunity. North American elk (*Cervus elaphus*) in worse condition invested more in constitutive immune defenses than elk in better condition (Downs et al. 2015). Similarly, mallards in worse condition were less susceptible to infection with an influenza virus and had shorter periods of viral shedding (Arsnoe et al. 2011). Individuals in poor body condition might invest more in less energetically costly components of immunity, or constitutive defenses, to prevent and remove infections quickly because allowing parasites to become established could require more energetically costly specific immune responses (Downs et al. 2015).

Heterogeneity in Immunity Across Species

The fields of ecoimmunology and comparative immunity converge at the study of immune heterogeneity across species. Comparative immunology emphasizes the evolution of immunity and the extent of species-level variation in immune traits (Cooper 2003). Thus, comparative immunology enhances our understanding of how species can defend against parasites. Furthermore, ecoimmunology complements comparative immunology by evaluating why heterogeneity in immunity persists through the study of the selective forces and constraints that influence the evolution of immunity (Martin et al. 2011a; Downs et al. 2014). In this section, we discuss two potential drivers of variation in immunity across species: life history and body size.

Variation in Species' Life History Underlies Heterogeneity in Immunity

Species-level immune variation is the product of evolutionary history, including historic selective pressures and inherited genetic and physiological constraints (Fig. 3b). One way to understand this variation is to consider parasite defenses in the context of life history traits. Life history traits covary along a continuum called the pace-of-life axis (Hille and Cooper 2015). Species with a fast pace of life tend to grow quickly, reproduce early and in high numbers, and have short lifespans. Species with a slow pace of life express the opposite traits: slow maturation, late reproduction, few offspring per reproductive bout, long lifespans, and large body sizes. Thus, evaluating how immunity maps onto the pace-of-life axis will provide

insights into species-level immunity variation (Sheldon and Verhulst 1996; Zuk and Stoehr 2002). The most basic prediction is that individuals with a slower pace of life should exhibit greater immunity because investing in parasite defenses should enhance survival because long-lived organisms should encounter more parasites during their lifetimes (Williams 1966; Ricklefs 1998).

Multiple researchers have hypothesized that fast paces of life are associated with constitutive innate immunity and inflammatory responses, whereas slow paces of life are linked to acquired immunity and anti-inflammatory responses (Lee 2006; Sears et al. 2011). Evidence supporting this hypothesis exists both within and across species (Tieleman et al. 2005; Martin et al. 2006a, 2007; Previtali et al. 2012; Downs et al. 2013; Pap et al. 2015). For example, house sparrows with a slower pace of life exhibit stronger acquired immune responses and lower inflammatory response than fast-living house sparrows (Martin et al. 2006a). Similarly, rodent species with slower paces of life had the lowest innate and strongest acquired immune responses (Martin et al. 2007; Previtali et al. 2012). Multiple cross-species analyses of birds have found that higher mass-adjusted basal metabolic rate, which is associated with a fast pace of life, correlates with lower innate immune responses (Tieleman et al. 2005; Pap et al. 2015; but see Versteegh et al. 2012). There is also evidence that selection for maximal metabolic rate, a trait associated with a fast pace of life, enhanced innate immunity and decreased adaptive immunity in mice (Downs et al. 2013).

Studies have also evaluated the relationship of resistance and tolerance with life history strategy. Because inflammation can cause substantial damage to host tissue as well as to parasites, tolerance is predicted to be associated with anti-inflammatory responses, acquired immunity, and a slower pace of life (Sears et al. 2011). Greater resistance to parasites is predicted to be associated with fast-paced living and stronger innate and proinflammatory immune responses. A comparative study of 13 amphibian species found support for these predictions (Johnson et al. 2012). Fast-living species suffered more severe limb malformations and more pathology during trematode infection than slow-living ones. Counter to predictions for resistance, though, faster-pace-of-life species had greater parasite burdens than slower-pace-of-life species. In another study (Sears et al. 2015), tadpoles with a faster pace of life were more resistant, but slower-pace-of-life species were more tolerant of the same type of trematode infection.

Species-Level Variation in Immunity Can Scale with Body Mass

Body size, as a trait in itself, might affect inter- and intraspecific variation in immunity (Langman and Cohn 1987; Wiegel and Perelson 2004; Perelson et al. 2006; Han et al. 2015). Numerous traits of animals change in a predictable manner, or scale, with body size (Schmidt-Nielson 1984; Calder 1996). We can predict with remarkable accuracy the lifespan, heart rate, sleeping patterns, metabolism, and many other characteristics of organisms from body size alone. Several theoretical models of the immune system suggest that the relationship between body size and immunity is the result of physiological structure (e.g., vasculature, tissue organization) or metabolic rate, which could drive immune cell generation and transport throughout the body (Langman and Cohn 1987; Wiegel and Perelson 2004; Perelson

et al. 2006). Scaling of immune function might also be related to the role that immune function plays in regulating life history traits. Immune function supports survival, so longer-lived individuals are predicted to invest more in immunity. In addition, lifespan increases with body mass and immunity might scale in the same way because the immune system is required to function for a longer time (Wiegel and Perelson 2004).

Some empirical evidence suggests that some aspects of immunity, such as white blood cell numbers (Nunn 2002; Nunn et al. 2003; Tian et al. 2015) and the costs of immune responses (Brace et al. 2017), are related to body size. Presently, all conclusions about body mass and immunity are premature. We do not yet know how size affects defenses against parasites. However, it is important to generate such information because it has important implications for public health. For instance, the effectiveness and toxicity of most pharmaceuticals are assessed initially in small mammals such as rodents. Drug effects do not scale directly with size, though, but we rarely take this into account when developing human treatment plans (Blanchard and Smoliga 2008; Mahmood et al. 2016; Smoliga and Blanchard 2017). Similarly, the most dangerous novel infectious diseases (e.g., Ebola, Nipah, SARS, Hendra viruses, among others) have spread recently from animals to people. Information on immune scaling could help us predict which species are most likely to dilute and amplify infection risk for other species, including humans (Han et al. 2015).

Broad Consequences of Individual Variation in Immunity

Variation in immunity is important ecologically. Heterogeneity in immunity can influence disease transmission through populations and communities, which can alter rates of survival and reproduction of resident organisms (Fig. 4a, b) (Ezenwa and Jolles 2011; Hawley and Altizer 2011; Adelman 2014). Many mechanisms can mediate these outcomes, but one of the most conspicuous is host competence. Host competence represents the ability to transmit parasites to another host or a vector (Hawley and Altizer 2011; Gervasi et al. 2015; Martin et al. 2016; VanderWaal and Ezenwa 2016). Immunity is a, but not the only, key part of host competence. Individuals' immune responses obviously influence their susceptibility to infection (e.g., Savage and Zamudio 2011) and subsequent parasite loads (e.g., Bichet et al. 2012), both of which are important to the ability to transmit infection (Gervasi et al. 2015). However, individuals that are more tolerant or maintain rather than eliminate an infection (e.g., Graham et al. 2010; Jackson et al. 2014) also have more opportunities to transmit parasites (Hawley and Altizer 2011; Martin et al. 2016). Further, immune responses are also linked to sickness behaviors that could influence contact rates between infected individuals and susceptible hosts or vectors (Barron et al. 2015).

Competence is therefore an organismal trait comprised of processes that operate at multiple levels of organization (VanderWaal and Ezenwa 2016). Moreover, it seems so plastic that in some cases individuals within species could be as distinct as groups of species (Gervasi et al. 2015). Depending on where an organism (genotype) finds itself, its role in a disease epidemic can be quite different. For instance, differences in diet quality among laboratory mice (*Mus musculus*) influence eosinophil levels, and

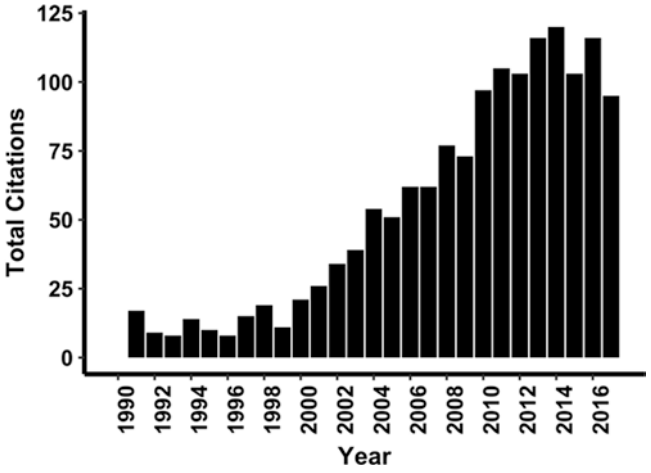

Fig. 4 Annual citations in ecoimmunology from 1990 through October 2017. Citations were identified in the ISI Web of Science database using the search terms ecol (ecology and ecological) and immunol (immunology and immunological)

variation in eosinophils predicts the amount of helminth eggs shed by mice (Budischak et al. 2015). In Grant's gazelles (*Nanger granti*), nematode shedding rates are higher in territorial males than in nonterritorial males and females (Ezenwa 2004). This particular difference in competence among classes of gazelle could be attributed to differences in testosterone, which is associated with immune phenotype as well as the likelihood of defending a territory and parasitism (Ezenwa et al. 2012). Species differences in immunity and competence also underlie spatial variation in Lyme disease risk (LoGiudice et al. 2003; Keesing et al. 2010). Highly disturbed forest sites in the Northeastern United States tend to have less species diversity overall and higher densities of the white-footed mouse (*Peromyscus leucopus*). The white-footed mouse is a highly competent host for Lyme, at least in part due to its immune profile (Donahue et al. 1987; Martin et al. 2007; Previtali et al. 2012; Ostfeld et al. 2014). When there are both a low diversity of hosts available for the vector of Lyme disease, the tick *Ixodes scapularis*, and high densities of the white-footed mouse, then a higher proportion of ticks carry the Lyme-causing bacterium, increasing the risk of disease for all hosts in the community (LoGiudice et al. 2003).

Variation in immunity has the potential to influence population dynamics independent of disease (Lochmiller 1996). Individuals require resources to both develop their immune system and maintain its ability to respond to threats (Demas et al. 2011; Klasing 1988; Ots et al. 2001; Klasing et al. 2006). These costs of immunity can influence individuals' ability to invest in reproduction or other traits important to survival, thereby influencing birth and death rates of populations (Downs and Stewart 2014). For example, environmental conditions, such as precipitation or human disturbance, can shift trade-offs between investment in immunity and reproduction in multiple species of reptiles (Smith and French 2017). Immunity also contributes to survival and population dynamics through influences on recruitment and longevity, which in turn affect lifetime reproductive success. For example,

cell-mediated immunity was a better predictor of recruitment nesting into a breeding population of pied flycatchers (*Ficedula hypoleuca*) after 2 years than mass or hatch date, more traditionally used predictors of recruitment (Moreno et al. 2005).

Few empirical data sets link variation in host immunity to host population dynamics directly, an application of comparative immunology that remains relatively unexplored. However, immunity is linked to both disease transmission and infection outcomes, and parasite effects on host fitness can influence population dynamics. Parasites influence host fitness both by directly killing hosts and through sublethal effects that indirectly reduce survival rates or alter reproductive output (Hatcher et al. 2006). For example, avian malaria (*Plasmodium* spp.) can cause rapid mortality, particularly in areas where the parasites were recently introduced (Atkinson and Van Riper III 1991; Atkinson et al. 1995; LaPointe et al. 2012). Avian malaria is particularly deadly for many Hawaiian birds, and mathematical models indicate that the parasites are a major factor causing population declines and blocking the recovery of at-risk species (Samuel et al. 2011). In addition, climate warming is extending the reach of the parasites and their vectors in Hawaii, further restricting the host-population distributions. Over most of its range, avian malaria infections tend to be chronic, but infection has sublethal effects that can reduce fitness (Bennett et al. 1993; Merino et al. 2000; Valkiūnas 2005; Marzal et al. 2005; Asghar et al. 2015; Schoenle et al. 2017a). Even sublethal effects of parasites can alter population dynamics, though. For example, intestinal nematodes reduced reproductive success by 2–13% in the Svalbard reindeer (*Rangifer tarandus*) (Albon et. al 2002). This reduction in fecundity was sufficient to limit reindeer population growth, even without any measurable effects of nematodes on reindeer survival. In some cases, it is the interaction between the effects of parasites and other environmental challenges that underlie population-level patterns. A study of white-footed and deer mice (*Peromyscus maniculatus*) demonstrated that population crashes were caused by the combination of nematode infections and decreases in resource availability (Pedersen and Grieves 2008). Experiments manipulating both food availability and parasite infection indicated that while each stressor was involved in population regulation, both were required to replicate population crashes.

Conclusions and Future Directions

The field of ecoimmunology has begun to explain why we observe substantial variation in immune defenses and provide some understanding of the implications of that variation. Perhaps the greatest contribution of the field has been to establish that immunity has costs, and those costs can lead to trade-offs within individuals and at an evolutionary scale (Lochmiller and Deerenberg 2000; Schmid-Hempel 2003; Brock et al. 2014). Identifying the costs of parasite defenses led the field in new directions. One of the most influential developments has been the concept of tolerance, which incorporates the costs of infection into measures of immunity. The study of tolerance has expanded beyond ecoimmunology, reaching into human biomedicine, wildlife ecology, and public health. For example, public concern has been growing around an “antibiotic crisis” caused by the rise of drug-resistant microbes

and a decline in the discovery of effective antibiotics (Martens and Demain 2017). Shifting the focus of treatments from resistance to tolerance presents a potential solution: the development of drugs that reduce the virulence of infections rather than parasite elimination (Vale et al. 2014, 2017; Totsika 2017). Furthermore, ecoimmunology has begun to evaluate the constraints that shape immunity and, by combining forces with disease ecology, to use information about immunity to predict the spread of infectious disease (Hawley and Altizer 2011; VanderWaal and Ezenwa 2016).

An important goal of future research is to understand the fitness consequences of different immune phenotypes and the resulting consequences for infectious disease dynamics. Individuals' ability to resist or tolerate infection can change with environmental conditions and life history stage or strategy (Blanchet et al. 2010; Jackson et al. 2014; Sears et al. 2015; Knutie et al. 2017). However, very few studies compare the fitness benefits of a more tolerant to a more resistant phenotype. Studies of Soay sheep defenses against intestinal nematodes find that resistance to nematodes is associated with lower reproductive success (Hayward et al. 2014a), whereas tolerance is associated with greater reproductive success (Hayward et al. 2014b). Furthermore, resistance is independent of tolerance in this system, indicating that individuals are not forced to trade off investment in these strategies (Hayward et al. 2014a). Thus, to understand how defense strategies affect disease dynamics, it might be important to address how resistance and tolerance influence fitness independently. To our knowledge, no studies have assessed the fitness benefits of resistance and tolerance across contexts. Like other components of immunity, resistance and tolerance could vary adaptively across environments or life history stages. Because resistance and tolerance influence hosts' parasite load and the duration of infection, these strategies can have important implications for infectious disease transmission, parasite prevalence, and even the evolution of virulence (Restif and Koella 2004; Miller et al. 2006; Adelman 2014; Gopinath et al. 2014). Determining how investment in resistance and tolerance within populations scales to disease dynamics within populations is an important future direction.

Another important frontier in ecoimmunology is to understand how environmental change influences disease dynamics. Chemical pollutants from industry and agriculture can alter immune function and have been associated with multiple disease outbreaks in wildlife (Grasman 2002). For example, the industrial contaminants polychlorinated biphenyls have been linked to infectious disease deaths in numerous marine mammal species, including harbor porpoises (*Phocoena phocoena*) and striped dolphins (*Stenella coeruleolba*) (Ross 2002). Urbanization is linked to changes in disease dynamics (Bradley and Altizer 2006), and traits of the urban environment, such as light pollution, alter immune function (Bedrosian et al. 2011). Climate change can also alter immunity (Hernroth et al. 2012), which could amplify the risks of infectious disease outbreaks as the ranges of parasites and vectors change in response to a warming climate (Greer et al. 2008). The frameworks are already in place to understand the relationships between environmental factors and immunity as well as immunity and disease dynamics. By improving our understanding of the causes and consequences of immune variation in the context of anthropogenic change, ecoimmunology could provide insights that have implications for public health and conservation.

Finally, building on the connections between the fields of ecoimmunology and comparative immunology will continue to advance our understanding of diversity in immune function. Both fields have made substantial progress through research on both model and nonmodel organisms and by addressing how multiple physiological systems interact to produce immune defenses (Cooper 1984, 2002, 2006; Martin et al. 2006b). In this chapter we discussed two areas of research that link ecoimmunology and comparative physiology: (1) the selective forces and constraints that influence heterogeneity in immunity and (2) how variation in immunity can influence disease dynamics. Characteristics inherent in species, such as body size or life history, can constrain or influence selection on immune traits and, thus, help explain patterns of immunity and disease spread across species that are not explained by phylogenetic relationships (Calder 1996; Han et al. 2015; Brace et al. 2017). Investigating comparative immunology in the context of community ecology is changing how we evaluate infectious disease risk. Because multiple species within a community can be at risk for the same parasitic infections, evaluating heterogeneity in host immunity can help parameterize models predicting infectious disease spread (Adelman 2014; VanderWaal and Ezenwa 2016). Incorporation of ecological factors and organismal traits into comparative studies of immunity can provide insights into both the evolution of immune defenses and community-level consequences of cross-species variation in immunity.

Box 1 The Origins and Central Tenets of Ecoimmunology: A Brief History

Ecoimmunology emerged when researchers began formally considering immunology in an ecological and evolutionary context. One of the first papers to link immunology to ecology was published in 1973 and addressed age-related variation in the prevalence and intensity of schistosome infections in humans (Martin et al. 2011a). It suggested that the lower infection prevalence and intensity observed in older humans could be driven by ecological factors (e.g., parasite exposure, death of hosts with high-intensity infection) in addition to or instead of acquired immunity (Warren 1973). More recent work has confirmed these claims: patterns of human contact with water, management of waterways, and antibody levels are all important in predicting the risk of schistosome infection (Brooker 2007; Moira et al. 2010). Although it was not established as a field until the 1990s, other early studies addressed ideas that remain at the core of ecoimmunology, including trade-offs between physiological functions (Williams 1966), mechanistic links between the immune system and other aspects of physiology (Grossman 1985), the costs and benefits of controlling parasite loads (Behnke et al. 1992), and the effects of resource availability on immunity (Klasing 1988).

Advances in behavioral ecology and endocrinology associated with sexual selection theory were key to the formalization of the field of ecoimmunology. The Hamilton and Zuk hypothesis proposed a role for parasite defenses in influencing the evolution of sexually selected traits, which enable the opposite sex to assess the quality of potential mates (e.g., colorful feathers in birds,

"push-up" display in some lizards) (Hamilton and Zuk 1982). Hamilton and Zuk postulated that sexually selected traits could serve as honest signals of resistance to parasites. The later publication of the immunocompetence handicap hypothesis (ICHH) in 1992 promoted interest in immune mechanisms that could mediate honesty in sexual traits (Folstad and Karter 1992). The ICHH posited that androgens (e.g., testosterone) support both the expression of male secondary sexual traits and suppress immune function, and as a result, sexual trait expression depends on parasite exposure. A meta-analysis revealed weak support for the hypothesis, probably because the ICHH is too simple to capture the complexities of how endocrine–immune interactions influence phenotype (Roberts et al. 2004). Nevertheless, the ICHH was significant to the development of ecoimmunology because it was one of the first widely tested theories linking immunological mechanisms to larger-scale biological processes.

In 1996, Sheldon and Verhulst published an influential paper coining the phrase "ecological immunology," which is arguably the beginning of ecoimmunology as a field. In this paper, Sheldon and Verhulst discussed the costs of immune responses and suggested that immunity is subject to trade-offs. Furthermore, they highlighted that trade-offs can take both physiological and evolutionary forms (Sheldon and Verhulst 1996). Early in the development of ecoimmunology, research on physiological trade-offs primarily involved allocation trade-offs: how organisms distribute limited resources across various functions (Sheldon and Verhulst 1996; Lochmiller and Deerenberg 2000; Schmid-Hempel 2003). As the field grew, research expanded to include other costs individuals pay to develop, maintain, and activate parasite defenses (Adelman and Martin 2009; Graham et al. 2010). Around the same time, evolutionary trade-offs attracted attention and were found to occur when selection favored the investment in one trait to the detriment of another (Schmid-Hempel 2003). This form of trade-off is represented by negative genetic correlations often seen among traits (Schmid-Hempel 2003; Ardia et al. 2011). Today, research addresses the consequences of costs and trade-offs for host–parasite coevolution as well as host population cycling and disease dynamics (e.g., Cousineau and Alizon 2014; VanderWaal and Ezenwa 2016).

Ecoimmunology has continued to grow since its inception in 1996, and the integrative nature of the field endures. The number of ecoimmunology publications produced annually (identified using the search terms ecol* and immunol* in the ISI Web of Science database) has increased more than tenfold since the establishment of the field in 1996 (Fig. 4). Ecoimmunology research incorporates techniques and theories from diverse fields, including ecology, evolutionary biology, epidemiology, comparative physiology, animal behavior, neurobiology, genomics, and proteomics. In 2009, the National Science Foundation funded a Research Coordination Network in Ecological Immunology, and in 2014, the Society for Integrative and Comparative Biology introduced a Division of Ecoimmunology and Disease Ecology (Martin et al. 2014). Going forward, we anticipate that ecoimmunology will continue to make valuable contributions to our understanding of host–parasite interactions.

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References

Adamo SA (2004) How should behavioural ecologists interpret measurements of immunity? Anim Behav 68:1443–1449

Adamo SA, Easy RH, Kovalko I, Macdonald J, Mckeen A, Swanburg T, Turnbull KF, Reeve C (2017) Predator exposure-induced immunosuppression: trade-off, immune redistribution or immune reconfiguration? J Exp Biol 220:868–875

Adelman JS (2014) Immune systems: linking organisms, populations, and evolution through disease. In: Martin LB, Ghalambor CK, Woods HA (eds) Integrative organismal biology. Wiley, Hoboken, pp 169–185

Adelman JS, Hawley DM (2016) Tolerance of infection: a role for animal behavior, potential immune mechanisms, and consequences for parasite transmission. Horm Behav 88:79–86

Adelman JS, Martin LB (2009) Vertebrate sickness behaviors: adaptive and integrated neuroendocrine immune responses. Integr Comp Biol 49:202–214

Adelman JS, Ardia DR, Schat KA (2014) Ecoimmunology. In: Schat KA, Kaspers B, Kaiser P (eds) Avian immunology, 2nd edn. Academic Press, San Diego, pp 391–411

Ader R, Cohen N, Felten D (1995) Psychoneuroimmunology: interactions system and the immune system. Lancet 345:99–103

Albon SD, Stien A, Irvine RJ, Langvatn R, Ropstad E, Halvorsen O (2002) The role of parasites in the dynamics of a reindeer population. Proc R Soc B: Biol Sci 269(1500):1625–1632

Allen JE, Wynn TA (2011) Evolution of Th2 immunity: a rapid repair response to tissue destructive pathogens. PLoS Pathog 7:e1002003

Altizer S, Bartel R, Han BA (2011) Animal migration and infectious disease risk. Science 331:296–303

Amar EC, Kiron V, Satoh S, Watanabe T (2004) Enhancement of innate immunity in rainbow trout (Oncorhynchus mykiss Walbaum) associated with dietary intake of carotenoids from natural products. Fish Shellfish Immunol 16:527–537

Amat JA, Aguilera E, Visser GH (2007) Energetic and developmental costs of mounting an immune response in male greenfinches (Carduelis chloris). Ecol Res 22:282–287

Ardia DR, Parmentier HK, Vogel LA (2011) The role of constraints and limitation in driving individual variation in immune response. Funct Ecol 25:61–73

Arsnoe DM, Ip HS, Owen JC (2011) Influence of body condition on influenza A virus infection in mallard fucks: experimental infection data. PLoS One 6:e22633

Asghar M, Hasselquist D, Zehtindjiev P, Westerdahl H, Bensch S (2015) Hidden costs of infection: chronic malaria accelerates telomere degradation and senescence in wild birds. Science 347:436–438

Ashley NT, Hays QR, Bentley GE, Wingfield JC (2009) Testosterone treatment diminishes sickness behavior in male songbirds. Horm Behav 56:169–176

Atkinson CT, Van Riper C III (1991) Pathogenicity and epizootiology of avian haematozoa: Plasmodium, Leucocytozoon, and Haemoproteus. In: Loye JE, Zuk M (eds) Bird-parasite interactions: ecology, evolution, behavior. Oxford University Press, Oxford, pp 19–48

Atkinson CT, Woods KL, Dusek RJ, Sileo LS, Iko WM (1995) Wildlife disease and conservation in Hawaii: pathogenicity of avian malaria (Plasmodium relictum) in experimentally infected Iiwi (Vestiaria coccinea). Parasitology 111:S59–S69

Barron DG, Gervasi SS, Pruitt JN, Martin LB (2015) Behavioral competence: how host behaviors can interact to influence parasite transmission risk. Curr Opin Behav Sci 6:35–40

Bartrop RW, Lazarus L, Luckhurst E, Kiloh LG, Penny R (1977) Depressed lymphocyte function after bereavement. Lancet 309:834–836

Bedrosian TA, Fonken LK, Walton JC, Nelson RJ (2011) Chronic exposure to dim light at night suppresses immune responses in Siberian hamsters. Biol Lett 7:468–471
Behnke JM, Barnard CJ, Wakelin D (1992) Understanding chronic nematode infections: evolutionary considerations, current hypotheses and the way forward. Int J Parasitol 22:861–907
Bennett GF, Peirce MA, Ashford RW (1993) Avian haematozoa: mortality and pathogenicity. J Nat Hist 27:993–1001
Best A, White A, Boots M (2014) The coevolutionary implications of host tolerance. Evolution 68:1426–1435
Bichet C, Cornet S, Larcombe S, Sorci G (2012) Experimental inhibition of nitric oxide increases Plasmodium relictum (lineage SGS1) parasitaemia. Exp Parasitol 132:417–423
Blanchard OL, Smoliga JM (2008) Translating dosages from animal models to human clinical trials — revisiting body surface area scaling. J Fed Am Soc Exp Biol 29:1629–1634
Blanchet S, Rey O, Loot G (2010) Evidence for host variation in parasite tolerance in a wild fish population. Evol Ecol 24:1129–1139
Blount JD, Metcalfe NB, Birkhead TR, Surai PF (2003) Carotenoid modulation of immune function and sexual attractiveness in zebra finches. Science 300:125–128
Bonier F, Martin PR, Moore IT, Wingfield JC (2009) Do baseline glucocorticoids predict fitness? Trends Ecol Evol 24:634–642
Bonneaud C, Mazuc J, Gonzalez G, Haussy C, Chastel O, Faivre B, Sorci G (2003) Assessing the cost of mounting an immune response. Am Nat 161:367–379
Boonstra R (2012) Reality as the leading cause of stress: rethinking the impact of chronic stress in nature (Fox C (ed)). Funct Ecol 27(1):11–23
Boulinier T, Staszewski V (2008) Maternal transfer of antibodies: raising immuno-ecology issues. Trends Ecol Evol 23:282–288
Brace AJ, Adelman JS, Grindstaff JL, Lajeunesse MJ, Ardia DR, Hawley DM, Buchanan KL, Matson KD, Fair JM, Martin LB (2017) Costs of immune responses are related to host body size and lifespan. J Exp Zool A Ecol Integr Physiol 327(5):1–8
Bradley CA, Altizer S (2006) Urbanization and the ecology of wildlife diseases. Trends Ecol Evol 22:95–102
Brock PM, Murdock CC, Martin LB (2014) The history of ecoimmunology and its integration with disease ecology. Integr Comp Biol 54:353–362
Brooker S (2007) Spatial epidemiology of human schistosomiasis in Africa: risk models, transmission dynamics and control. Trans R Soc Trop Med Hyg 101:1–8
Budischak SA, Sakamoto K, Megow LC, Cummings KR, Urban JF, Ezenwa VO (2015) Resource limitation alters the consequences of co-infection for both hosts and parasites. Int J Parasitol 45:455–463
Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Consortium, R, Consortium, P.G, Anorexia, G.C. for A.N. of the W.T.C.C.C, Duncan L, Perry JRB, Patterson N, Robinson EB, Daly MJ, Price AL, Neale BM (2015) An atlas of genetic correlations across human diseases and traits. Nat Genet 47:1236–1241
Calder WA (1996) Size, function, and life history. Dover Publications, Inc., Mineola
Caldwell R, Schafer J, Compton L, Patterson F (1958) Tolerance to cereal leaf rusts. Science 128:714–715
Carlton ED, Demas GE (2014) Leptin mediates seasonal variation in some but not all symptoms of sickness in Siberian hamsters. Horm Behav 66:802–811
Carlton ED, Demas GE (2015) Body mass affects seasonal variation in sickness intensity in a seasonally breeding rodent. J Exp Biol 218:1667–1676
Carlton ED, Cooper CL, Demas GE (2014) Metabolic stressors and signals differentially affect energy allocation between reproduction and immune function. Gen Comp Endocrinol 208:21–29
Clinchy M, Sheriff MJ, Zanette LY (2013) Predator-induced stress and the ecology of fear. Funct Ecol 27:56–65
Cohen S, Tyrrell DAJ, Smith AP (1991) Psychological stress and susceptibility to the common cold. N Engl J Med 325:606–612

Cohen AA, Martin LB, Wingfield JC, McWilliams SR, Dunne JA (2012) Physiological regulatory networks: ecological roles and evolutionary constraints. Trends Ecol Evol 27:428–435
Coltman ADW, Pilkington J, Kruuk LEB, Wilson K, Pemberton JM (2001) Positive genetic correlation between parasite resistance and body size in a free-living ungulate population. Evolution 55:2116–2125
Cooper EL (ed) (1984) Stress, immunity, and aging. Marcel Dekker, Inc., New York
Cooper EL (2002) Comparative immunology. Curr Pharm Des 8:99–110
Cooper EL (2003) Comparative immunology. Integr Comp Biol 43:278–280
Cooper EL (2006) Comparative immunology. Integrative Zool 1:32–43
Costantini D, Møller AP (2009) Does immune response cause oxidative stress in birds? A meta-analysis. Comp Biochem Physiol A Mol Integr Physiol 153:339–344
Cousineau SV, Alizon S (2014) Parasite evolution in response to sex-based host heterogeneity in resistance and tolerance. J Evol Biol 27:2753–2766
de Craen AJM, Posthuma D, Remarque EJ, van den Biggelaar AHJ, Westendorp RGJ, Boomsma DI (2005) Heritability estimates of innate immunity : an extended twin study. Genes Immun 6:167–170
Cressler CE, Graham AL, Day T (2015) Evolution of hosts paying manifold costs of defence. Proc R Soc B 282:20150065
De Moira AP, Fulford AJC, Kabatereine NB, Ouma JH, Booth M, Dunne DW (2010) Analysis of complex patterns of human exposure and immunity to Schistosomiasis mansoni: the influence of age, sex, ethnicity and IgE. PLoS Negl Trop Dis 4:e820
Demas GE, Drazen DL, Nelson RJ (2003) Reductions in total body fat decrease humoral immunity. Proc R Soc B 270:905–911
Demas GE, Zysling DA, Beechler BR, Muehlenbein MP, French SS (2011) Beyond phytohaemagglutinin: assessing vertebrate immune function across ecological contexts. J Anim Ecol 80:710–730
Dobson A, Lafferty KD, Kuris AM, Hechinger RF, Jetz W (2008) Homage to Linnaeus: how many parasites? How many hosts? Proc Natl Acad Sci 105:11482–11489
Donahue JG, Piesman J, Speilman A (1987) Reservoir competence of white-footed mice for Lyme disease spirochetes. Am J Trop Med Hyg 36:92–96
Downs CJ, Stewart KM (2014) A primer in ecoimmunology and immunology for wildlife research and management. Calif Fish Game 100:371–395
Downs CJ, Brown JL, Wone B, Donovan ER, Hunter K, Hayes JP (2013) Selection for increased mass-independent maximal metabolic rate suppresses innate but not adaptive immune function. Proc R Soc B 280:20122636
Downs CJ, Adelman JS, Demas GE (2014) Mechanisms and methods in ecoimmunology: integrating within-organism and between-organism processes. Integr Comp Biol 54:340–352
Downs CJ, Stewart KM, Dick BL (2015) Investment in constitutive immune function by North American elk experimentally maintained at two different population densities. PLoS One 10:125586
Drazen DL, Demas GE, Nelson RJ (2001) Leptin effects on immune function and energy balance are photoperiod dependent in Siberian hamsters (Phodopus sungorus). Endocrinology 142:2768–2775
Durant SE, Hopkins WA, Hawley DM, Hepp GR (2012) Incubation temperature affects multiple measures of immunocompetence in young wood ducks (Aix Sponsa). Biol Lett 8:108–111
Elliott M, Kearney JF (1992) Idiotypic regulation of development of the B-cell repertoire. Ann N Y Acad Sci 651:336–345
Eraud C, Duriez O, Chastel O, Faivre B (2005) The energetic cost of humoral immunity in the Collared Dove, Streptopelia decaocto: is the magnitude sufficient to force energy-based trade-offs? Funct Ecol 19:110–118
Evans KJ, Hansen DS, Van Rooijen N, Buckingham LA, Schofield L (2006) Severe malarial anemia of low parasite burden in rodent models results from accelerated clearance of uninfected erythrocytes. Blood 107:1192–1199

Ezenwa VO (2004) Host social behavioår and parasitic infection: a multifactorial approach. Behav Ecol 15:446–454
Ezenwa VO, Jolles AE (2011) From host immunity to pathogen invasion: the effects of helminth coinfection on the dynamics of microparasites. Integr Comp Biol 51:540–551
Ezenwa VO, Stefan Ekernas L, Creel S (2012) Unravelling complex associations between testosterone and parasite infection in the wild. Funct Ecol 26:123–133
Farh KK, Marson A, Zhu J, Kleinewietfeld M, Housley WJ, Beik S, Shoresh N, Whitton H, Russell JH, Shishkin AA, Hatan M, Carrasco-alfonso MJ, Luckey CJ, Patsopoulos NA, De Jager PL (2015) Genetic and epigenetic fine-mapping of causal autoimmune disease variants. Nature 518:337–343
Finkel T, Holbrook NJ (2000) Oxidants, oxidative stress and the biology of ageing. Nature 408:239–247
Folstad I, Karter A (1992) Parasites, bright males, and the immunocompetence handicap. Am Nat 139:603–622
Franceschi C, Bonafè M, Valensin S, Benedictis GDE (2000) An evolutionary perspective on immunosenescence. Ann NY Acad Sci 908:244–254
Freitak D, Ots I, Vanatoa A (2003) Immune response is energetically costly in white cabbage butterfly pupae. Biol Lett 270:S220–S222
French SS, Denardo DF, Moore MC (2007a) Trade-offs between the reproductive and immune systems: facultative responses to resources or obligate responses to reproduction? Am Nat 170:79–89
French SS, Johnston GIH, Moore MC (2007b) Immune activity suppresses reproduction in food-limited female tree lizards Urosaurus ornatus. Funct Ecol 21:1115–1122
French SS, Moore MC, Demas GE (2009) Ecological immunology: the organism in context. Integr Comp Biol 49:246–253
Freund A, Orjalo AV, Desprez P, Campisi J (2010) Inflammatory networks during cellular senescence: causes and consequences. Trends Mol Med 16:238–246
Gervasi SS, Civitello DJ, Kilvitis HJ, Martin LB (2015) The context of host competence: a role for plasticity in host – parasite dynamics. Trends Parasitol 31:419–425
Gopinath S, Lichtman JS, Bouley DM, Elias JE, Monack DM (2014) Role of disease-associated tolerance in infectious superspreaders. Proc Natl Acad Sci 111:15780–15785
Goto M (2008) Inflammaging (inflammation + aging): a driving force for human aging based on an evolutionarily antagonistic pleiotropy theory? Biosci Trends 2:218–230
Graham AL, Hayward AD, Watt K a, Pilkington JG, Pemberton JM, Nussey DH (2010) Fitness correlates of heritable variation in antibody responsiveness in a wild mammal. Science 330:662–665
Graham AL, Shuker DM, Pollitt LC, Auld SKJR, Wilson AJ, Little TJ (2011) Fitness consequences of immune responses: strengthening the empirical framework for ecoimmunology. Funct Ecol 25:5–17
Grasman KA (2002) Assessing immunological function in toxicological studies of avian wildlife. Integr Comp Biol 42:34–42
Greer A, Ng V, Fisman D (2008) Climate change and infectious diseases in North America: the road ahead. Can Med Assoc J 178:715–722
Grindstaff JL, Brodie ED, Ketterson ED (2003) Immune function across generations: integrating mechanism and evolutionary process in maternal antibody transmission. Proc R Soc B 270:2309–2319
Groner ML, Buck JC, Gervasi SS, Blaustein AR, Reinert LK, Rollins-Smith LA, Bier ME, Hempel J, Relyea RA, Elyea RICKAR (2013) Larval exposure to predator cues alters immune function and response to a fungal pathogen in post-metamorphic wood frogs. Ecol Appl 23:1443–1454
Grossman CJ (1985) Interactions between the gonadal steroids and the immune system. Science 227:257–261
Guerrero JM, Reiter RJ (2002) Melatonin-immune system relationships. Curr Top Med Chem 2:167–179

Hamilton WD, Zuk M (1982) Heritable true fitness and bright birds: a role for parasites? Science 218:384–387
Han BA, Park AW, Jolles AE, Altizer S (2015) Infectious disease transmission and behavioural allometry in wild mammals. J Anim Ecol 84:637–646
Hardeland R, Cardinali DP, Srinivasan V, Spence DW, Brown GM, Pandi-Perumal SR (2011) Melatonin — a pleiotropic, orchestrating regulator molecule. Prog Neurobiol 93:350–384
Hart B (1988) Biological basis of the behavior of sick animals. Neurosci Biobehav Rev 12:123–137
Hasselquist D, Nilsson J-Å (2009) Maternal transfer of antibodies in vertebrates: trans-generational effects on offspring immunity. Philos Trans R Soc B 364:51–60
Hatcher MJ, Dick JTA, Dunn AM (2006) How parasites affect interactions between competitors and predators. Ecol Lett 9:1253–1271
Haussmann MF, Marchetto NM (2010) Telomeres: linking stress and survival, ecology and evolution. Curr Zool 56:714–728
Hawley DM, Altizer SM (2011) Disease ecology meets ecological immunology: understanding the links between organismal immunity and infection dynamics in natural populations. Funct Ecol 25:48–60
Hayes JP, Shonkwiler JS (2001) Morphometric indicators of body condition: worthwhile or wishful thinking. In: Speakman JR (ed) Body composition analysis of animals: a handbook of non-destructive methods. Cambridge University Press, New York, pp 8–38
Hayward AD, Garnier R, Watt K a, Pilkington JG, Grenfell BT, Matthews JB, Pemberton JM, Nussey DH, Graham AL (2014a) Heritable, heterogeneous, and costly resistance of sheep against nematodes and potential feedbacks to epidemiological dynamics. Am Nat 184:S58–S76
Hayward AD, Nussey DH, Wilson AJ, Berenos C, Pilkington JG, Watt KA, Pemberton JM, Graham AL (2014b) Natural selection on individual variation in tolerance of gastrointestinal nematode infection. PLoS Biol 12:e1001917
Hernroth B, Nilsson Skold H, Wiklander K, Jutfelt F, Baden S (2012) Simulated climate change causes immune suppression and protein damage in the crustacean Nephrops norvegicus. Fish Shellfish Immunol 33:1095–1101
Hille SM, Cooper CB (2015) Elevational trends in life histories: revising the pace-of-life framework. Biol Rev 90:204–213
Hodges TK, Laskowski KL, Squadrito GL, De Luca M, Leips J (2012) Defense traits of larval Drosophila melanogaster exhibit genetically based trade-offs against different species of parasitoids. Evolution 67:749–760
Irwin MR (2008) Human psychoneuroimmunology: 20 years of discovery. Brain Behav Immun 22:129–139
Irwin MR, Vale W, Britton KT (1987) Central corticotropin-releasing factor suppresses natural killer cytotoxicity. Brain Behav Immun 1:81–87
Iseri VJ, Klasing KC (2014) Changes in the amount of lysine in protective proteins and immune cells after a systemic response to dead Escherichia coli: implications for the nutritional costs of immunity. Integr Comp Biol 54:922–930
Jackson JA, Hall AJ, Friberg IM, Ralli C, Lowe A, Zawadzka M, Turner AK, Stewart A, Birtles RJ, Paterson S, Bradley JE, Begon M (2014) An immunological marker of tolerance to infection in wild rodents. PLoS Biol 12:1–13
Johnsen A, Anderson V, Sunding C, Lifjeld JT (2000) Female bluethroats enhance offspring immunocompetence through extra-pair copulations. Nature 406:296–300
Johnson PTJ, Rohr JR, Hoverman JT, Kellermanns E, Bowerman J, Lunde KB (2012) Living fast and dying of infection: host life history drives interspecific variation in infection and disease risk. Ecol Lett 15:235–242
Jones KD, Thitiri J, Ngari M, Berkley JA (2014) Childhood malnutrition: toward an understanding of infections, inflammation, and antimicrobials. Food Nutr Bull 35:64–70
Jurgens HA, Amancherla K, Johnson RW (2012) Influenza infection induces neuroinflammation, alters hippocampal neuron morphology, and impairs cognition in adult mice. J Neurosci 32:3958–3968

Keesing F, Belden LK, Daszak P, Dobson A, Harvell CD, Holt RD, Hudson P, Jolles A, Jones KE, Mitchell CE, Myers SS, Bogich T, Ostfeld RS (2010) Impacts of biodiversity on the emergence and transmission of infectious diseases. Nature 468:647–652
Kelley KW, McCusker RH (2014) Getting nervous about immunity. Semin Immunol 26:389–393
Kiecolt-Glaser JK, Glasertt R, Gravensteint S, Malarkeyt WB (1996) Chronic stress alters the immune response to influenza virus vaccine in older adults. Proc Natl Acad Sci 93:3043–3047
Klasing KC (1988) Influence of acute feed deprivation or excess feed intake on immunocompetence of broiler chicks. Poult Sci 67:626–634
Klasing KC, Koutsos EA, Garcı JC (2006) Nutritional immunology carotenoids from In Ovo or Dietary Sources Blunt Systemic Indices of the Inflammatory Response in Growing Chicks (Gallus gallus domesticus). J Nutr 1(2):1027–1031
Knutie SA, Wilkinson CL, Wu QC, Ortega CN, Rohr JR (2017) Host resistance and tolerance of parasitic gut worms depend on resource availability. Oecologia 183:1031–1040
Kraaijeveld AR, Godfray CJ (1997) Trade-off between parasitoid resistance and larval competitive ability in Drosophila melanogaster. Nature 389:278–281
Kraaijeveld AR, Godfray HCJ (1999) Geographic patterns in the evolution of resistance and virulence in Drosophila and its parasitoids. Am Nat 153:S61–S74
Kraaijeveld AR, Limentani EC, Godfray HCJ (2001) Basis of the trade-off between parasitoid resistance and larval competitive ability in Drosophila melanogaster. Proc R Soc B 268:259–261
Kutzer MAM, Armitage SAO (2016) Maximising fitness in the face of parasites: a review of host tolerance. Zoology 119:281–289
Lambeth JD (2007) Nox enzymes, ROS, and chronic disease: an example of antagonistic pleiotropy. Free Radic Biol Med 43:332–347
Langman RW, Cohn M (1987) The E-T (elephant-tadpole) paradox necessitates the concept of a unit of B-cell function: the protecton. Mol Immunol 24:675–691
LaPointe DA, Atkinson CT, Samuel MD (2012) Ecology and conservation biology of avian malaria. Ann NY Acad Sci 1249:211–226
Lazzaro BP, Little TJ (2009) Immunity in a variable world. Philos Trans R Soc B 364:15–26
Lazzaro BP, Sceurman BK, Clark AG (2004) Genetic basis of natural variation in D. melanogaster antibacterial immunity. Science 303:1873–1877
Lee KA (2006) Linking immune defenses and life history at the levels of the individual and the species. Integr Comp Biol 46:1000–1015
Lipsky PE (2001) Systemic lupus erythematosus: an autoimmune disease of B cell hyperactivity. Nat Immunol 2:764–766
Lochmiller RL (1996) Immunocompetence and animal population regulation. Oikos 76:594–602
Lochmiller RL, Deerenberg C (2000) Trade-offs in evolutionary immunology: just what is the cost of immunity? Oikos 88:87–98
LoGiudice K, Ostfeld RS, Schmidt KA, Keesing F (2003) The ecology of infectious disease: effects of host diversity and community composition on Lyme disease risk. Proc Natl Acad Sci 100:567–571
Love OP, Salvante KG, Dale J, Williams TD (2008) Sex-specific variability in the immune system across life-history stages. Am Nat 172:E99–E112
Lundin BS, Dahlman-Hoglund A, Pettersson I, Dahlgren UIH, Hanson LA, Telemo E (1999) Antibodies given orally in the neonatal period can affect the immune response for two generations: evidence for active maternal influence on the newborn's immune system. Scand J Immunol 50:651–656
Luong LT, Polak M (2008) Environment-dependent trade-offs between ectoparasite resistance and larval competitive ability in the Drosophila – Macrocheles system. Heredity 99:632–640
Maher JM, Werner EE, Denver RJ (2013) Stress hormones mediate predator-induced phenotypic plasticity in amphibian tadpoles. Proc R Soc B 280:20123075
Mahmood I, Cheng A, Brauer E, Humeniuk R (2016) Prediction of antimalarial drug clearance in children: a comparison of three different interspecies scaling methods. Eur J Drug Metab Pharmacokinet 41:767–775

Martens E, Demain AL (2017) The antibiotic resistance crisis, with a focus on the United States. J Antibiot 70:520–526
Martin LB (2009) Stress and immunity in wild vertebrates: timing is everything. Gen Comp Endocrinol 163:70–76
Martin LB, Coon CC (2010) Infection protection and natural selection. Science 330:602–603
Martin LB, Scheuerlein A, Wikelski M (2003) Immune activity elevates energy expenditure of house sparrows: a link between direct and indirect costs? Proc R Soc B 270:153–158
Martin LB, Gilliam J, Han P, Lee K, Wikelski M (2005) Corticosterone suppresses cutaneous immune function in temperate but not tropical house sparrows, Passer domesticus. Gen Comp Endocrinol 140:126–135
Martin LB, Hasselquist D, Wikelski M (2006a) Investment in immune defense is linked to pace of life in house sparrows. Oecologia 147:565–575
Martin LB, Weil ZM, Nelson RJ (2006b) Refining approaches and diversifying directions in ecoimmunology. Integr Comp Biol 46:1030–1039
Martin LB, Weil ZM, Nelson RJ (2007) Immune defense and reproductive pace of life in Peromyscus mice. Ecology 88:2516–2528
Martin LB, Weil ZM, Nelson RJ (2008) Seasonal changes in vertebrate immune activity: mediation by physiological trade-offs. Philos Trans R Soc B 363:321–339
Martin LB, Hawley DM, Ardia DR (2011a) An introduction to ecological immunology. Funct Ecol 25:1–4
Martin LB, Liebl AL, Trotter JH, Richards CL, Mccoy K, Mccoy MW (2011b) Integrator networks: illuminating the black box linking genotype and phenotype. Integr Comp Biol 51:514–527
Martin LB, Boughton RK, Ardia DR (2014) A new division of ecoimmunology and disease ecology. Integr Comp Biol 54:338–339
Martin LB, Burgan SC, Adelman JS, Gervasi SS (2016) Host competence: an organismal trait to integrate immunology and epidemiology. Integr Comp Biol 56:1225–1237
Marzal A, de Lope F, Navarro C, Møller AP (2005) Malarial parasites decrease reproductive success: an experimental study in a passerine bird. Oecologia 142:541–545
Mazé-Guilmo E, Loot G, Páez DJ, Lefèvre T, Blanchet S (2014) Heritable variation in host tolerance and resistance inferred from a wild host – parasite system. Proc R Soc B 281:20132567
McCormick GL, Shea K, Langkilde T (2015) How do duration, frequency, and intensity of exogenous CORT elevation affect immune outcomes of stress? Gen Comp Endocrinol 222:81–87
Medzhitov R, Schneider DS, Soares MP (2012) Disease tolerance as a defense strategy. Science 335:936–941
Merino S, Moreno J, Sanz JJ, Arriero E (2000) Are avian blood parasites pathogenic in the wild? A medication experiment in blue tits (Parus caeruleus). Proc R Soc B Biol Sci 267:2507–2510
Miller MR, White A, Boots M (2006) The evolution of parasites in response to tolerance in their hosts: the good, the bad, and apparent commensalism. Evolution 60:945–956
Møller AP, Erritzoe J (2000) Predation against birds with low immunocompetence. Oecologia 122:500–504
Monaghan P, Haussmann MF (2006) Do telomere dynamics link lifestyle and lifespan? Trends Ecol Evol 21:47–53
Moore SE, Cole TJ, Collinson AC, Poskitt EME, Mcgregor IA, Prentice AM (1999) Prenatal or early postnatal events predict infectious deaths in young adulthood in rural Africa. Int J Epidemiol 28:1088–1095
Moreno J, Merino S, Sanz JJ, Arriero E, Morales J, Moreno J, Merino S, Sanz JJ, Arriero E, Morales J, Tomas G (2005) Nestling cell-mediated immune response, body mass and hatching date as predictors of local recruitment in the pied flycatcher Ficedula hypoleuca. Oikos 36:251–260
Moreno-Rueda G (2010) Experimental test of a trade-off between moult and immune response in house sparrows Passer domesticus. J Evol Biol 23:2229–2237
Moss R, Kolb HH, Marquiss M, Watson A, Treca B, Watt D, Glennie W (1979) Agressiveness and dominance in captive cock red grouse. Aggress Behav 5:59–84

Mougeot F, Irvine JR, Seivwright L, Redpath SM, Piertney S (2004) Testosterone, immunocompetence, and honest sexual signaling in male red grouse. Behav Ecol 15:930–937
Mougeot F, Redpath SM, Piertney SB (2005a) Elevated spring testosterone increases parasite intensity in male red grouse. Behav Ecol 17:117–125
Mougeot F, Redpath SM, Piertney SB, Hudson PJ, The S, Naturalist A, August N (2005b) Separating behavioral and physiological mechanisms in testosterone-mediated trade-offs. Am Nat 166:158–168
National Research Council (2004) Science, medicine, and animals. National Academies Press, Washington (DC)
Navarro C, de Lope F, Marzal A, Møller AP (2003) Predation risk, host immune response, and parasitism. Behav Ecol 15:629–635
Nelson RJ (2004) Seasonal immune function and sickness responses. Trends Immunol 25:187–192
Newman AEM, Zanette LY, Clinchy M, Goodenough N, Soma KK (2013) Stress in the wild: chronic predator pressure and acute restraint affect plasma DHEA and corticosterone levels in a songbird. Stress 16:363–367
van Noordwijk AJ, de Jong G (1986) Acquisition and allocation of resources: their influence on variation in life history tactics. Am Nat 128:137–142
Norris K, Evans MR (2000) Ecological immunology: life history trade-offs and immune defense in birds. Behav Ecol 11:19–26
Nunn CL (2002) A comparative study of leukocyte counts and disease risk in primates. Evolution 56:177–190
Nunn CL, Gittleman JL, Antonovics J (2003) A comparative study of white blood cell counts and disease risk in carnivores. Proc R Soc B 270:347–356
Nussey DH, Watt KA, Clark A, Pilkington JG, Pemberton JM, Graham AL, Mcneilly TN (2014) Multivariate immune defences and fitness in the wild: complex but ecologically important associations among plasma antibodies, health and survival. Proc R Soc B 281:20132931
Ostfeld RS, Levi T, Jolles AE, Martin LB, Hosseini PR, Keesing F (2014) Life history and demographic drivers of reservoir competence for three tick-borne zoonotic pathogens. PLoS One 9:e107387
Ots I, Kerimov AB, Ivankina EV, Ilyina TA (2001) Immune challenge affects basal metabolic activity in wintering great tits. Proc R Soc B 268:1175–1181
Otti O, Gantenbein-Ritter I, Jacot A, Brinkhof MWG (2011) Immune response increases predation risk. Evolution 66:732–739
Owen JC, Moore FR (2006) Seasonal differences in immunological condition of three species of thrushes. Condor 108:389–398
Owen JC, Moore FR (2008) Relationship between energetic condition and indicators of immune function in thrushes during spring migration. Can J Zool 647:638–647
Owen-Ashley NT, Wingfield JC (2006) Seasonal modulation of sickness behavior in free-living northwestern song sparrows (Melospiza melodia morphna). J Exp Biol 209:3062–3070
Pap PL, Vágási IC, Vincze O, Osvath G, Veres-Szaszka J, Czirják GÁ (2015) Physiological pace of life: the link between constitutive immunity, developmental period, and metabolic rate in European birds. Oecologia 177:147–158
Parker BJ, Garcia JR, Gerardo NM (2014) Genetic variation in resistance and fecundity tolerance in a natural host-pathogen interaction. Evolution 68:2421–2429
Pedersen AB, Greives TJ (2008) The interaction of parasites and resources cause crashes in a wild mouse population. J Anim Ecol 77(2):370–377
Perelson AS, Bragg JG, Wiegel FW (2006) The complexity of the immune system: scaling laws. In: Deisboeck TS, Kresh JY (eds) Complex systems science in biomedicine. Springer, New York, pp 451–459
Poirie AM, Frey F, Hita M, Huguet E, Lemeunier F, Periquet G, Carton Y, Poiriel M, Frey F, Hital M, Huguet E, Lemeunier F, Periq G (2000) Drosophila resistance genes to parasitoids: chromosomal location and linkage analysis. Proc R Soc B 267:1417–1421
Previtali MA, Ostfeld RS, Keesing F, Jolles AE, Hanselmann R, Martin LB (2012) Relationship between pace of life and immune responses in wild rodents. Oikos 121:1483–1492

Price RN, Simpson JA, Nosten F, Luxemburger C, Hkirjaroen L, ter Kuile F, Chongsuphajaisiddhi T, White NJ (2001) Factors contributing to anemia after uncomplicated falciparum malaria. Am J Trop Med Hyg 65:614–622
Råberg L (2014) How to live with the enemy: understanding tolerance to parasites. PLoS Biol 12:e1001989
Råberg L, Graham AL, Hasselquist D, Svensson E (1998) On the adaptive significance of stress-induced immunosuppression. Proc R Soc B 265:1637–1641
Råberg L, Sim D, Read AF (2007) Disentangling genetic variation for resistance and tolerance to infectious diseases in animals. Science 318:812–814
Råberg L, Graham AL, Read AF (2009) Decomposing health: tolerance and resistance to parasites in animals. Proc R Soc B 364:37–49
Restif O, Koella JC (2004) Concurrent evolution of resistance and tolerance to pathogens. Am Nat 164:E90–E102
Ricklefs RE (1977) On the evolution of reproductive strategies in birds. Am Nat 111:453–478
Ricklefs RE (1998) Evolutionary theories of aging: confirmation of a fundamental prediction, with implications for the genetic basis and evolution of life span. Am Nat 152:24–44
Ricklefs RE, Wikelski M (2002) The physiology/life-history nexus. Trends Ecol Evol 17:462–468
Rintamaki PT, Hoglund J, Karvonen E, Alatalo RV, Bjorklund N, Lundberg A, Ratti O, Vouti J (1993) Combs and sexual selection in black grouse (Tetrao tetrix). Behav Ecol 11:465–471
Roberts ML, Buchanan KL, Evans MR (2004) Testing the immunocompetence handicap hypothesis: a review of the evidence. Anim Behav 68:227–239
Roff DA (2002) Life history evolution. Sinauer Associates, Sunderland
Roff DA, Fairbairn DJ (2007) The evolution of trade-offs: where are we? J Evol Biol 20:433–447
Rolff J, Siva-Jothy MT (2003) Invertebrate ecological immunology. Science 301:472–476
Ross PS (2002) The role of immunotoxic environmental contaminants in facilitating the emergence of infectious diseases in marine mammals. Hum Ecol Risk Assess Int J 8:277–292
Saino N, Calza S (1999) Barn swallows trade survival against offspring condition and immunocompetence. J Anim Ecol 68:999–1009
Saino N, Ferrari R, Romano M, Martinelli R, Møller AP (2003) Experimental manipulation of egg carotenoids affects immunity of barn swallow nestlings. Proc Biol Sci 270(1532):2485–2489
Saltz JB, Hessel FC, Kelly MW (2017) Trait correlations in the genomics era. Trends Ecol Evol 32:279–290
Samuel MD, Hobbelen PHF, DeCastro F, Ahumada JA, Lapointe DA, Atkinson CT, Woodworth BL, Hart PJ, Duffy DC (2011) The dynamics, transmission, and population impacts of avian malaria in native Hawaiian birds: a modeling approach. Ecol Appl 21:2960–2973
Sapolsky RM, Romero LM, Munck AU (2000) How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev 21:55–89
Savage AE, Zamudio KR (2011) MHC genotypes associate with resistance to a frog-killing fungus. Proc R Soc B 108:16705–16710
Schafer JF (1971) Tolerance to plant disease. Annu Rev Phytopathol 9:235–252
Schleifer SJ, Keller SE, Camerino M, Thorton JC, Stein M (1983) Suppression of lymphocyte stimulation following bereavement. J Am Med Assoc 250:374–377
Schmid-Hempel P (2003) Variation in immune defence as a question of evolutionary ecology. Proc R Soc B 270:357–366
Schmid-Hempel P, Ebert D (2003) On the evolutionary ecology of specific immune defence. Trends Ecol Evol 18:27–32
Schmidt-Nielson K (1984) Scaling: why is animal size so important. Cambridge University Press, New York
Schneider DS, Ayres JS (2008) Two ways to survive infection: what resistance and tolerance can teach us about treating infectious diseases. Nat Rev Immunol 8:889–895
Schoenle LA, Kernbach M, Haussmann MF, Bonier F, Moore IT (2017a) An experimental test of the physiological consequences of avian malaria infection. J Anim Ecol 86(6):1483–1496

Schoenle LA, Schoepf I, Weinstein NM, Moore IT, Bonier F (2017b) Higher plasma corticosterone is associated with reduced costs of infection in red-winged blackbirds. Gen Comp Endocrinol 256:89–98
Schwenke RA, Lazzaro BP, Wolfner MF (2016) Reproduction – immunity trade-offs in insects. Annu Rev Entomol 61:239–256
Sears BF, Rohr JR, Allen JE, Martin LB (2011) The economy of inflammation: when is less more? Trends Parasitol 27:382–387
Sears BF, Snyder PW, Rohr JR (2015) Host life-history and host-parasite syntopy predict behavioral resistance and tolerance of parasites. J Anim Ecol 84:625–636
Sheldon BC, Verhulst S (1996) Ecological immunology: costly parasite defences and trade-offs in evolutionary ecology. Trends Ecol Evol 11:317–321
Smith GD, French SS (2017) Physiological trade-offs in lizards: costs for individuals and populations. Integr Comp Biol 57(2):1–8
Smits JE, Bortolotti GR, Tella JL (1999) Simplifying the phytohaemagglutinin skin-testing technique in studies of avian immunocompetence. Funct Ecol 13:567–572
Smoliga JM, Blanchard OL (2017) Allometric scaling models: history, use, and misuse in translating resveratrol from basic science to human clinical applications. Funct Foods Health Dis 7:338–352
Soler JJ, De Neve L, Perez-Contreras T, Soler M, Sorci G (2003) Trade-off between immunocompetence and growth in magpies: an experimental study. Proc R Soc B 270:241–248
Stearns SC (1992) The evolution of life histories. Oxford University Press, New York
Sternberg ED, Lefèvre T, Li J, de Castillejo CLF, Li H, Hunter MD, De Roode JC (2012) Food plant-derived disease tolerance and resistance in a natural butterfly-plant-parasite interactions. Evolution 66:3367–3377
Stoks R, De Block M, Slos S, Van Doorslaer W, Rolff J (2006) Time constraints mediate predator-induced plasticity in immune function, condition, and life history. Ecology 87:809–815
Strausbaugh H, Irwin MR (1992) Central corticotropin-releasing hormone reduces cellular immunity. Brain Behav Immun 6:11–17
Strauss S, Agrawal A (1999) The ecology and evolution of plant tolerance to herbivory. Trends Ecol Evol 14:179–185
Super Coloring (2017) URL supercoloring.com. Accessed 5 Oct 2017
Tella JL, Lemus J a, Carrete M, Blanco G (2008) The PHA test reflects acquired T-cell mediated immunocompetence in birds. PLoS One 3:e3295
Tian J, Courtiol A, Schneeberger K, Greenwood AD, Czirják GÁ (2015) Circulating white blood cell counts in captive and wild rodents are influenced by body mass rather than testes mass, a correlate of mating promiscuity. Funct Ecol 29:823–829
Tieleman BI, Williams JB, Ricklefs RE, Klasing KC (2005) Constitutive innate immunity is a component of the pace-of-life syndrome in tropical birds. Proc R Soc B 272:1715–1720
Totsika M (2017) Disarming pathogens: benefits and challenges of antimicrobials that target bacterial virulence instead of growth and viability. Future Med Chem 9:267–269
Tyndale ST, Letcher RJ, Health JW, Heath D (2008) Why are salmon eggs red? Egg carotenoids and early life survival of Chinook salmon (Oncorhynchus tshawytscha). Evol Ecol Res 10:1187–1199
Vale PF, Fenton A, Brown SP (2014) Limiting damage during infection: lessons from infection tolerance for novel therapeutics. PLoS Biol 12:e1001769
Vale PF, Mcnally L, Doeschl-Wilson A, King KC, Popat R, Domingo-Sananes MR, Allen JE, Soares MP, Kummerli R (2017) Beyond killing: can we find new ways to manage infection. Evol Med Public Health 2016(1):148–157
Valkiūnas G (2005) Avian malaria parasites and other Haemosporidia. CRC Press, Boca Raton
Van der Most PJ, De Jong B, Parmentier HK, Verhulst S (2011) Trade-off between growth and immune function: a meta-analysis of selection experiments. Funct Ecol 25:74–80
VanderWaal KL, Ezenwa VO (2016) Heterogeneity in pathogen transmission: mechanisms and methodology. Funct Ecol 30:1606–1622

Versteegh MA, Schwabl I, Jaquier S, Tieleman BI (2012) Do immunological, endocrine and metabolic traits fall on a single pace-of-life axis? Covariation and constraints among physiological systems. J Evol Biol 25:1864–1876
Viney ME, Riley EM, Buchanan KL (2005) Optimal immune responses: Immunocompetence revisited. Trends Ecol Evol 20:665–669
Warren KS (1973) Regulation of the prevalence and intensity of schistosomiasis in man: immunology or ecology? J Infect Dis 127:595–609
Weil ZM, Borniger JC, Cisse YM, Salloum BAA, Nelson RJ (2015) Neuroendocrine control of photoperiodic changes in immune function. Front Neuroendocrinol 37:108–118
Wiegel FW, Perelson AS (2004) Some scaling principles for the immune system. Immunol Cell Biol 82:127–131
Wikler BYM, Demeur C, Dewasme G, Urbain J (1980) Immunoregulatory role of maternal idiotypes. J Exp Med 152:1024–1035
Williams GC (1966) Adaptation and natural selection. Princeton University Press, Princeton
Yuki N, Hartung H-P (2012) Guillain–Barré Syndrome. N Engl J Med 366:2294–2304
Zuk M, McKean KA (1996) Sex differences in parasite infections: patterns and processes. Int J Parasitol 26:1009–1024
Zuk M, Stoehr AM (2002) Immune defense and host life history. Am Nat 160:S9–S22