Inflammation: Mechanisms, Costs, and Natural Variation

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Abstract

Inflammation is a pervasive phenomenon that operates during severe perturbations of homeostasis, such as infection, injury, and exposure to contaminants, and is triggered by innate immune receptors that recognize pathogens and damaged cells. Among vertebrates, the inflammatory cascade is a complex network of immunological, physiological, and behavioral events that are coordinated by cytokines, immune signaling molecules. Although the molecular basis of inflammation is well studied, its role in mediating the outcome of host-parasite interactions has received minimal attention by ecologists. This review provides a synopsis of vertebrate inflammation, its life-history modulation, and its effects upon host-pathogen dynamics as well as host-commensal microbiota interactions in the gut. What emerges is evidence for phenotypic plasticity of inflammatory responses despite the apparently invariant and redundant nature of the immunoregulatory networks that regulate them.

INTRODUCTION

Virulence: damage to a host arising from extraction of resources by a pathogenic infection or collateral damage produced by the host's immune response

Inflammation is a pervasive form of defense that is broadly defined as a nonspecific response to tissue malfunction and is employed by both innate and adaptive immune systems to combat pathogenic intruders. A distinctive feature of inflammatory responses in relation to other facets of antiparasite defenses is that damage to the self is unavoidable. Importantly, collateral damage from inflammation is not the same as immunopathology, which involves a specific immune-mediated attack on target tissue that is no longer recognized by the immune system as self. Autoimmune pathology reflects dysregulation of adaptive immune components, such as antibody and cell-mediated functions, and has both genetic and environmental influences (Graham et al. 2005, Råberg et al. 1998). Although inflammation-induced collateral damage can certainly contribute to immunopathology (e.g., rheumatoid arthritis, multiple sclerosis, diabetes), the damage invoked by inflammation represents a basic biological trade-off between damage control and self-maintenance and does not require the presence of self-antigens to become activated.

The emergence of the field of ecoimmunology has spurred a renewed interest in quantifying and understanding variation of immune function, which has traditionally been under the purview of cellular and molecular immunologists. However, the major difference of this relatively new field involves the assessment of immunity in nonmodel organisms in their natural environment, which has been challenging and biased toward measurement of the adaptive immune system. Ecoimmunologists are also interested in the fitness costs of immunity. A major hurdle of ecoimmunology has been integrating host immune function with host-pathogen dynamics and disease ecology (Graham et al. 2011, Hawley & Altizer 2010). In effect, studies have quantified immune function in a vacuum without assessing how these measures relate to disease resistance. Lastly, the importance of inflammation in regulating the outcome of host-pathogen interactions has received minimal attention by ecologists (Sears et al. 2011, Sorci & Faivre 2009).

This review provides an overview of inflammation and its role in mediating the ecology and evolution of host-parasite and host-commensal interactions. This review primarily focuses on inflammation in vertebrates, though we draw upon several studies among invertebrates. Although the molecular basis of inflammation is well described, we provide basic definitions of inflammation, a synopsis of inflammatory pathways, and the types of inflammatory response to provide ecologists and evolutionary biologists with proximate mechanisms that inform ultimate levels of analysis. We then present studies demonstrating life-history variation of inflammatory responses, in particular seasonal and latitudinal variation, as well as trade-offs with reproduction. Inflammation also affects both the host and pathogen, and we review the evidence that host-pathogen dynamics can be altered, such as virulence and transmission. Throughout this review, we refer to pathogen and parasite interchangeably, which we define as infectious agents that have the capability to harm hosts. The regulation of inflammation also shapes host-commensal interactions in the vertebrate gut. Such interactions benefit commensal organisms, whereas the host species neither benefits nor is harmed. The selective forces governing host-microbiota interactions in the gut is a rapidly developing field that has received minimal input from evolutionary ecologists.

WHAT IS INFLAMMATION?

Inflammation is a biological reaction to a disrupted tissue homeostasis (Medzhitov 2008). At its basic level, it is a tissue-destroying process that involves the recruitment of blood-derived products, such as plasma proteins, fluid, and leukocytes, into perturbed tissue. This migration is facilitated by alterations in the local vasculature that lead to vasodilation, increased vascular permeability, and increased blood flow.

Infection by microbial invaders is often implicated as the major culprit that promotes inflammatory responses (**Figure 1*a***). However, injury or trauma (in the absence of parasitic infection) and exposure to foreign particles/irritants/pollutants are also potent activators of inflammation (Medzhitov 2008), suggesting that this response likely evolved as a general adaptation for coping with damaged or malfunctioning tissue (Matzinger 2002). A common explanation for why infection and trauma might evoke similar inflammatory responses is that infection often follows wounding, which implies that it would be advantageous to respond to trauma as if infection occurred (Nathan 2002). The more parsimonious explanation is that both pathogens and wounding cause damage to cells and tissue and trigger similar responses (Bianchi 2007).

The primary functions of inflammation are to rapidly destroy or isolate the underlying source of the disturbance, remove damaged tissue, and then restore tissue homeostasis (Medzhitov 2008, Soehnlein & Lindbon 2010). Inflammation, when regulated properly, is putatively adaptive. This statement is supported by the increased risk of serious infections in humans with genetic deficiencies in primary components of inflammation, such as neutropenia (abnormally low level of circulating neutrophils). Defects in the genes that encode proinflammatory cytokines and effectors of inflammation using mouse knock-out studies are also characterized by increased susceptibility to infection (Martinon et al. 2009). Conversely, there are several immune-relevant genes whose disruption leads to spontaneous inflammation, suggesting that the inflammatory response is actively suppressed by regulatory gene products to maintain health when inflammatory stimuli are not present (Nathan 2002). When not regulated properly, excessive inflammation can have devastating effects, resulting in excessive collateral damage and pathology.

On an evolutionary level, inflammation is a highly conserved phenomenon and appears to be an important first line of defense for both invertebrates and vertebrates. Many of the components associated with the inflammatory cascade, such as chemotaxis and phagocytosis, are readily employed by unicellular organisms and were later co-opted as defensive mechanisms to maintain the integrity of more complex multicellular organisms (Rowley 1996). Innate immunity in the form of phagocytosis and antimicrobial peptides is present in the earliest of invertebrates, whereas the adaptive immune system evolved later and is unique to jawed vertebrates (Flajnik & Du Pasquier 2004). Adaptive immunity is hypothesized to have evolved to recognize and manage the complex communities of microbes that reside in the vertebrate digestive tract, which harbors a greater diversity of microbial fauna than the invertebrate gut (McFall-Ngai 2007).

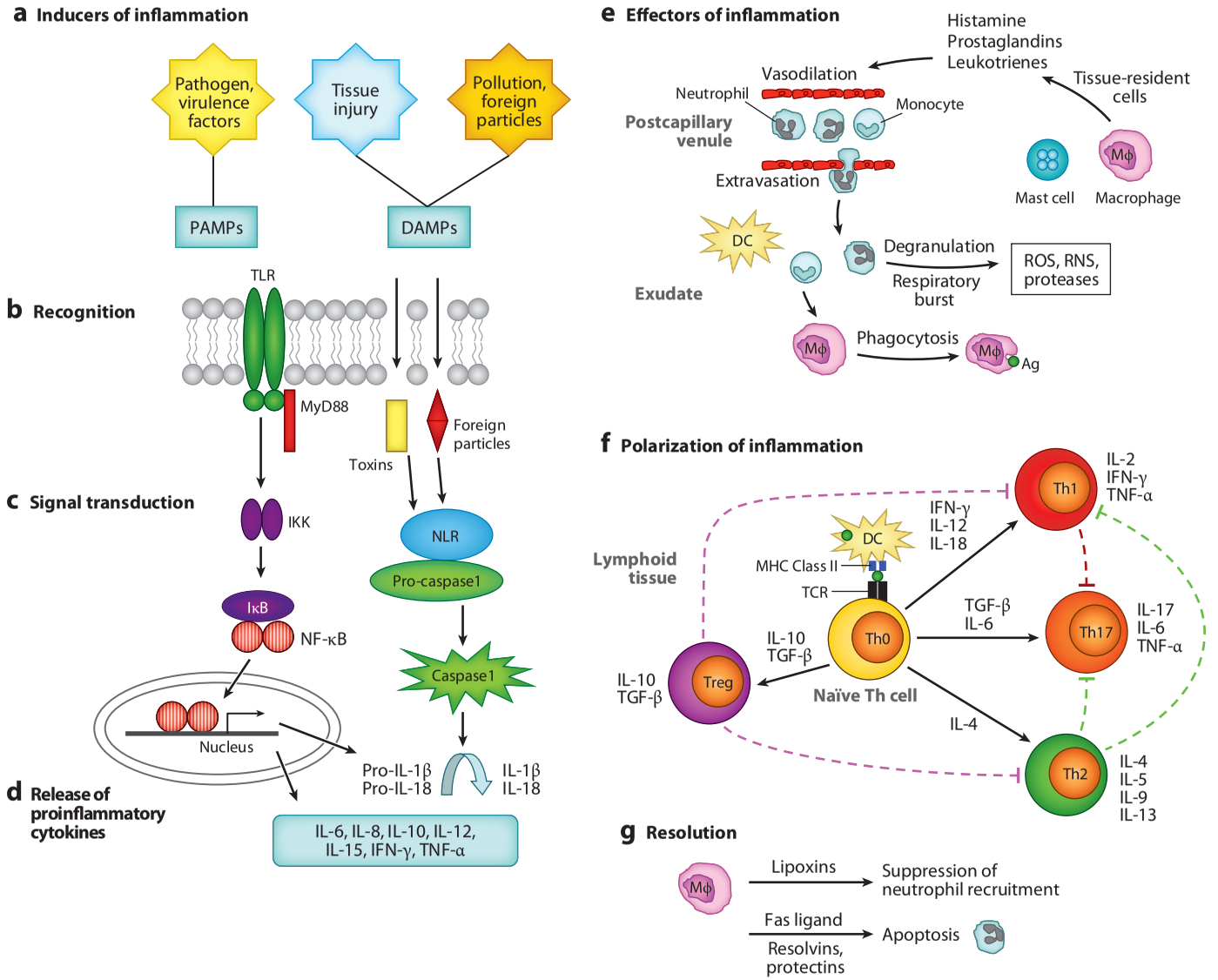
Cytokines: soluble proteins of low molecular weight that modulate the differentiation, proliferation, and function of immune cells, and coordinate inflammatory responses

DAMP: damage-associated molecular pattern

MECHANISMS OF INFLAMMATION

Inflammation consists of a tightly regulated cascade of immunological, physiological, and behavioral processes that are orchestrated by soluble immune signaling molecules called cytokines. The first step of the inflammatory cascade involves recognition of infection or damage (**Figure 1*b***). This is typically achieved by the detection of pathogen-associated molecular patterns (PAMPs), which are specifically directed toward general motifs of molecules expressed by pathogens that are essential for pathogen survival. Alarmins, or damage-associated molecular patterns (DAMPs), are endogenous molecules that signal damage or necrosis and are also recognized by the innate immune system. An advantage of detecting these signals is that inadvertent targeting of host cells and tissues is minimized. Unlike adaptive immunity, the innate immune system lacks the ability to distinguish among different strains of pathogens and whether such strains are virulent (harmful to the host) (Janeway et al. 2005).

Many damage signals are recognized by germ-line encoded receptors, such as transmembrane Toll-like receptors (TLRs) and intracellular nucleotide binding domain and leucine-rich-repeat-containing receptors (NOD-like receptors or NLRs) (Lange et al. 2001, Proell et al. 2008, Roach



et al. 2005). Once recognition of ligands occurs, TLRs activate common signaling pathways that culminate in the activation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells; **Figure 1*c***). This transcription factor is found in virtually all cell types and remains in an inactivated state bound to an inhibitor protein, IκB (Ghosh et al. 1998). Upon transduction of the signal, NF-κB is released from IκB and translocates to the nucleus, where transcription is upregulated through binding to target genes. Importantly, activation of NF-κB does not require new protein synthesis, which permits a rapid response. The NF-κB signaling system is ancient, but there is phylogenetic evidence that regulation of immune function by this pathway in vertebrates evolved independently from invertebrate immune mechanisms (Friedman & Hughes 2002). Intracellular NLRs respond to increasing numbers of DAMPs that alert the immune system to cell injury and provide a proximate pathway for sensing exposure to possible toxins or pollutants in the environment.

Transcription and translation of genes lead to the third stage of the inflammatory cascade, which is the inducible expression of proinflammatory cytokines, such as interleukin-1-beta (IL-1β), IL-6, tumor necrosis factor-alpha (TNF-α), and others (**Figure 1*d***). In conjunction with chemokines (attractants) and various costimulatory molecules, these soluble proteins facilitate the recruitment of effector cells (**Figure 1*e***), such as monocytes and neutrophils, to the site of disturbance. Neutrophils create a cytotoxic environment by releasing noxious chemicals from cytoplasmic granules (a process called degranulation). Rapid release of these chemicals requires consumption of both glucose and oxygen, known as the respiratory burst. Toxic chemicals released include highly reactive oxygen and nitrogen species (ROS and RNS, respectively) and various proteinases. These substances are destructive to both pathogens and hosts and essentially induce

Figure 1

A primer of the inflammatory cascade. (*a*) Pathogens, tissue injury, and foreign particles induce inflammation. (*b*) Transmembrane TLRs and intracellular NLRs bind to PAMPs or DAMPs, respectively. (*c*) TLRs activate a MyD88-dependent signal transduction pathway that involves the phosphorylation of the inhibitory IκB protein by IKK. NF-κB is released from IκB and translocates to the nucleus where transcription is upregulated through binding to target inflammatory genes. NLRs signal the inflammasome, which activates caspase-1 to convert cytokines into active forms (IL-1β and IL-18), which then elicit inflammation after being released from the cell. (*d*) A variety of proinflammatory cytokines and chemokines are produced and released to promote effector functions of inflammation. (*e*) Blood-borne neutrophils and monocytes migrate to the site of disturbance by chemotaxis and selectively pass through endothelial cells to reach target sites (extravasation). This influx of cells is accompanied by protein-rich fluid, known as the exudate, and promotes edema (swelling). Mast cells and tissue-resident macrophages promote this migration by releasing histamine, leukotrienes, and prostaglandins, which have rapid effects upon the vasculature, including vasodilation and increased vascular permeability. Neutrophils release toxic compounds, including ROS, RNS, and various proteases, which are nonspecific and harm both pathogen and host. Macrophages and dendritic cells participate in phagocytosis of Ag. (*f*) These cells migrate to lymphoid tissue and prime naïve T cells (Th0) to become polarized through stimulation of the TCR by antigen bound to MHC class II receptors. Th0 cells differentiate into several different types of effector and regulatory cells: Th1 cells (proinflammatory), Th2 cells (anti-inflammatory), Tregs (regulatory) and Th17 cells (proinflammatory). Depending upon the type of pathogen and other factors, the resulting Th population can be biased toward a proinflammatory, anti-inflammatory, or regulatory phenotype. Cytokines produced by polarized Th1 and Th2 are mutually inhibitory, whereas cytokines produced by Treg cells dampen both Th1 and Th2 responses. Th17 cells are highly proinflammatory and are regulated by the other Th subsets. Black arrowed and dashed lines represent stimulatory and inhibitory actions. (*g*) Resolution of inflammation occurs when neutrophils promote the switch of leukotrienes produced by macrophages and other cells to lipoxins, which initiates termination of inflammation. Fas ligand, resolvins, and protectins promote apoptosis of neutrophils. Macrophages phagocytose apoptotic neutrophils and cellular debris. Abbreviations: Ag, antigen; DC, dendritic cell; DAMP, damage-associated molecular pattern; IκB, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; IKK, inhibitor of kappa B kinase; IFN-γ, interferon-gamma; IL, interleukin; Mϕ, macrophage; MHC, major histocompatibility complex; MyD88, myeloid differentiation primary response gene (88); NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLR, nucleotide binding domain and leucine-rich-repeat-containing receptors; PAMP, pathogen-associated molecular pattern; RNS, reactive nitrogen species; ROS, reactive oxygen species; TCR, T-cell receptor; TGF-β, transforming growth factor-beta; Th, T helper cell; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T cell. Adapted from Ghosh et al. 1998, Janeway et al. 2005, Anthony et al. 2007, and Soehnlein & Lindbom 2010.

liquefaction of surrounding tissue to stave off microbial metastasis (Nathan 2002). These effector mechanisms are thus major contributors to host collateral damage.

The net effect of these interactions culminates in the stereotypical cardinal signs of local inflammation: heat, swelling, redness, pain, and loss of function. The effector functions of inflammation are further regulated by the adaptive immune system (**Figure 1*f***), which is discussed below.

The last phase of inflammation is its resolution (**Figure 1*g***), which is critical for limiting collateral damage to the host (Serhan & Savill 2005). After the first few hours of inflammation, a coordinated program of resolution is set into motion by tissue-resident and recruited macrophages. During acute inflammation, these cells produce proinflammatory prostaglandins and leukotrienes, but rapidly switch to lipoxins, which block further neutrophil recruitment and instead favor enhanced infiltration of monocytes important for wound healing.

Helminth: parasitic worms that include cestodes (tapeworms), trematodes (flukes), and nematodes (roundworms)

Granuloma: fibrous tissue formed by Th2 responses to encapsulate macroparasites or foreign particles

IL: interleukin

TNF: tumor necrosis factor

POLARIZATON OF INFLAMMATION

Over the course of evolution, animals have encountered a diverse array of parasites that range from microscopic bacteria and viruses to metazoan parasites, such as helminths and arthropods. As a general rule, proinflammatory responses are more effective against smaller pathogenic microbes (bacteria, viruses) than larger parasites. This is because multicellular parasites, as well as foreign bodies and indigestible particles, are too large to be phagocytosed by individual cells. In such cases, inflammation presents a less effective option for hosts as collateral damage increases substantially in responding to a larger, uncontained pathogen (Allen & Wynn 2011). In the early stages of parasite invasion, this method of defense attempts to heal wounded tissue through the formation of granulomas (fibrous connective tissue that replaces fibrin clots) to isolate and encapsulate the invader while preventing secondary bacterial infections. It is tempting to conclude that such a repair response would provide only benefits to the host. However, excessive granuloma formation can lead to fibrosis (scarring), which impedes normal functioning of host tissue and can lead to organ failure (Wynn 2004). Taken together, optimizing both types of defense appears to be critical for mitigating fitness costs of infection.

T-helper (Th) cells, a specific population of lymphocytes of the adaptive immune system, are largely responsible for activating and orchestrating these responses. When stimulated by cells presenting antigen, naïve Th cells (Th0; never exposed to antigen) can differentiate into several different types of effector and regulatory cells: Th1 cells (proinflammatory), Th2 cells (anti-inflammatory), regulatory T-cells (Tregs), and Th17 cells (Abbas et al. 1996, Anthony et al. 2007) (**Figure 1*f***). Th1 cells regulate cellular immunity and proinflammatory responses against intracellular parasites through the release of interferon-gamma (IFN-γ), a cytokine that has potent antiviral and immunoregulatory properties and promotes further Th1 cell differentiation. Th1 cells also secrete IL-2 and TNF-α, which are important in mediating delayed type hypersensitivity responses and macrophage activation. By contrast, Th2 cells are important for humoral immunity, B-cell proliferation, regulation of allergic responses, and protection against infection from macroparasites (e.g., helminths). Th2 cells produce a different characteristic set of anti-inflammatory cytokines, such as IL-4, IL-5, IL-10, and IL-13, that stimulate further differentiation of the Th2 phenotype, promote alternative activation of macrophages, and induce B-cell antibody switching to IgE and eosinophil maturation, while downregulating the production of Th1 cytokines. In effect, Th1 and Th2 responses are mutually antagonistic and represent a balance between proinflammatory and anti-inflammatory mechanisms that may be selected upon to influence the outcome of infection (**Figure 1*f***). Ideally, an optimization of Th1/Th2 phenotypes facilitates pathogen clearance with minimum damage to host tissues (**Figure 2**), although studies

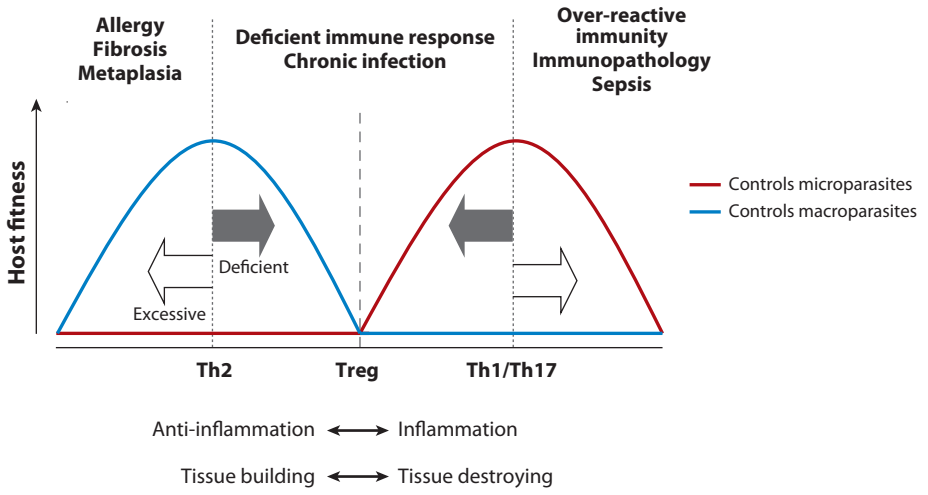


Figure 2

Host fitness is optimized relative to type of pathogen (micro- or macroparasite) and whether proinflammatory or anti-inflammatory responses are activated. A proinflammatory Th1 or Th17 response (*red line*) is more effective at controlling microparasites (viruses, bacteria, fungi, etc.), whereas an anti-inflammatory Th2 response (*blue line*) is more effective at controlling macroparasites (helminths, arthropods). To prevent excessive responses that can lead to various pathologies, these polarizing responses are tightly regulated by Treg cells. When regulation overrides effector mechanisms, chronic infection can result. Excessive and deficient responses are represented by white and gray arrows, respectively.

in captive animals demonstrate constrained ability to mount effective Th1 and Th2 responses simultaneously (Graham 2002, Mosmann & Coffman 1989).

The notion of a simplified bimodal response to infection that activates either the Th1 or Th2 phenotype has been eclipsed by recent discoveries of cross-regulation by additional T cells. Treg cells are important for suppressing the activation, proliferation, and effector functions of various immune cells that include T cells, NK cells, B cells, and antigen-presenting cells (Sakaguchi et al. 2010). Although the role of Treg cells in regulating homeostasis of the immune system is still being elucidated, there is evidence that these immune cells dampen both Th1 and Th2 responses by secreting IL-10 and TGF-β. These immunosuppressive cytokines inhibit the proliferation of both Th1 and Th2 responses to presumably minimize tissue damage (**Figure 2**). Treg cells also appear to play a role in mediating the outcome of chronic infection while preventing inflammation in immune-privileged organs. For example, removal of Treg cells during chronic infection with *Schistosoma mansoni* leads to increased liver damage in mice (Suvas et al. 2004). If Treg cells are inhibited, then tissue-damaging immunopathology results. However, an increased reliance upon Treg cells could lead to enhanced pathogen survival and, in some instances, long-term chronic infection (Belkaid & Tarbell 2009). Thus, a fine balance between regulatory and effector functions is established for hosts to effectively cope with pathogenic challenges (**Figure 2**). Th17 cells, a third subset of effector Th cells that was discovered in 2007, are largely involved in clearing extracellular microparasites that require a massive amount of inflammation and are not adequately handled by Th1 or Th2 responses (Korn et al. 2009).

Few coinfection studies have examined host Th1/Th2 polarization in free-living populations. One notable exception is in African buffalo (*Syncerus caffer*), where IFN-γ production and eosinophil counts in the blood were used to quantify Th1 (inflammatory) and Th2 (anti-inflammatory) phenotypes, respectively. African buffalo are one of the primary hosts of bovine

Treg cell: regulatory T cell

Th cell: T helper cell

tuberculosis (TB; caused by *Mycobacterium bovis*) and are also parasitized by a diverse assemblage of gastrointestinal nematodes. At the herd level and across the entire population, a negative correlation between TB prevalence and worm infection prevalence was documented (Jolles et al. 2008). These observed infection patterns were attributed to a combination of factors. First, coinfected buffalo suffered accelerated mortality compared to animals infected with either TB or worms. Second, trade-offs between the Th1 and Th2 responses affected TB transmission patterns. Buffalo that were worm-free had strong Th2 responses, and there was a significant negative correlation between Th1 and Th2 responses in TB-negative buffalo during the dry season (but not the wet season) (Jolles et al. 2008). These data suggest that animals whose immune systems were effective at fighting off worms were less able to simultaneously mount a strong Th1 response toward TB. This apparent cross-regulation of Th1 and Th2 responses is also more pronounced under conditions of seasonal resource limitation. Cross-regulation of Th1/Th2 responses is upheld in other naturally occurring populations (Jackson et al. 2011, Robinson et al. 2011), suggesting functional constraints.

Sickness behavior: behavioral symptoms triggered by the acute phase response, including reduced food and water intake, somnolence, reduced activity, anhedonia, and reduced libido

Acute phase response: systemic response to infection, triggered by proinflammatory cytokines, that includes fever, sickness behavior, and release of acute phase proteins from the liver

Another example of the costs of polarizing inflammation comes from humans. The increased prevalence of allergic disease (asthma, rhinoconjuctivitis, and eczema) in developing countries over the past several decades has been attributed to a decline in childhood infections as a result of improved hygiene, vaccination, and use of antibiotics (Strachan 1989). Coined the hygiene hypothesis, this theory has an immunological explanation. If reduction in early-life microbial burden leads to insufficient stimulation of Th1 (proinflammatory) responses, then this effect could upset the Th1/Th2 balance, leading to expansion of Th2 (anti-inflammatory) cells. Excessive Th2 responses are characterized by increased IgE production to allergens, mastocytosis, and eosinophilia. This hypothesis is supported by the lack of allergic disease reported in developing countries where early-life infections are more common. However, this hypothesis fails to explain why there is a corresponding increase in Th1-autoimmune diseases, such as Type I diabetes, or why Th2-mediated helminth infections do not cause allergy. Instead, it has been hypothesized that persistent immune challenge in developing countries, with recurrent cycles of infection and inflammation, has resulted in a robust anti-inflammatory network that controls allergic disease (Yazdanbakhsh et al. 2002). This network would be weakly formed in children of industrialized countries, possibly leading to inappropriate allergic responses. Together, these studies support the concept that the apparent dichotomy between proinflammatory (Th1/Th17) and anti-inflammatory (Th2) defenses can significantly alter the course of infectious disease in vertebrate hosts. Thus, there is a pressing need to incorporate measures of Th1/Th2/Th17/Treg immunity (e.g., measurement of cytokines) into ecoimmunology studies to assess relationships with pathogen load and fitness parameters of the host (Graham et al. 2011).

TYPES OF INFLAMMATION DRIVE THEIR COSTS

Location

Distinguishing among different types of inflammation (**Table 1**, **Figure 3**) is critical for understanding relative fitness costs to the host. Importantly, inflammation and its sequelae vary both spatially and temporally (Medzhitov et al. 2012). Inflammation normally begins in a localized area, but depending upon the severity of the infection/wound, it can spread rapidly to the periphery. This systemic response is triggered by proinflammatory cytokines, particularly IL-1, IL-6, and TNF-α, which are released in the circulation and activate fever and sickness behaviors in the brain as well as acute phase protein secretion from the liver. Inflammation in this peripheral acute phase response is costlier to produce and maintain than local inflammation. In the absence of

Table 1 Types of inflammatory responses are categorized by intensity (low-grade versus high-grade) and duration (acute versus chronic)

Intensity	Duration	
	Acute	Chronic
Low-grade	Para-inflammation Metaplasia	Inflammatory diseases (diabetes mellitus, atherosclerosis) Autoimmune disorders Neurodegenerative diseases Tumor growth Tissue damage (fibrosis)
High-grade	Acute phase response Release of cytokines Neutrophil migration Recruitment of effector cells (neutrophils, macrophages) Localized tissue damage	Sepsis Cytokine storm Tissue destruction

infection, increased inflammation is clearly maladaptive and can lead to inappropriate pathologies, such as inflammatory diseases and autoimmunity (**Figure 3*a***). However, the inflammatory response benefits hosts during a pathogenic challenge (**Figure 3*b***). If the infection is cleared by inflammatory processes, then resolution of inflammation can occur (**Figure 3*b***). Another scenario involves pathogen manipulation of the inflammatory response. Several different types of pathogens are known to trigger inflammatory defenses rather than evade them (reviewed by Sorci & Faivre 2009). For example, some intracellular pathogens have evolved to replicate within immune cells. During an inflammatory response, immune cells are recruited to the site of infection, which inadvertently increases transmission and spread of the pathogen (Sorci & Faivre 2009). For these

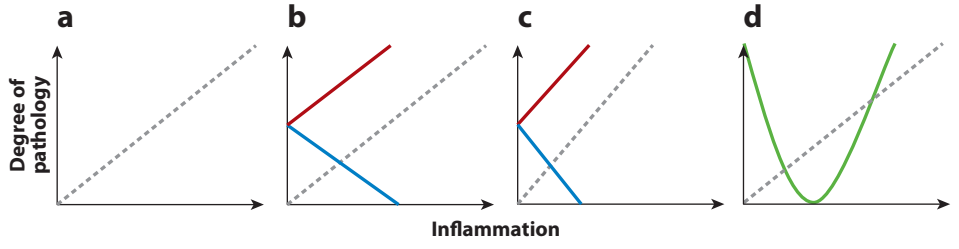


Figure 3

Relationship between inflammatory response and degree of pathology (morbidity). (*a*) In the absence of infection, inflammation increases pathology, as is the case for many autoinflammatory and autoimmune disorders. (*b*) During a pathogenic infection, the effectiveness of peripheral inflammation in clearing the pathogen is an important factor influencing host morbidity. If inflammation decreases pathogen load, then clearance of the pathogen will result when the morbidity costs of parasitism (*blue line*) equal the costs of the host inflammatory response in the absence of pathogen (*gray dashed line*). Once clearance occurs, inflammation resolves. However, if the pathogen evades or manipulates the host inflammatory response, then the combination of host inflammatory collateral damage and direct damage from the pathogen increases pathology (*red line*). (*c*) In the brain, the survival costs of exhibiting inflammation are greater than in the periphery, as represented by an increased slope relating morbidity to host inflammation (*gray dashed line*). Red and blue lines represent relationships as described above. (*d*) The diverse microbiota in the gut requires mild inflammation (*green line*) to control opportunistic pathogens while minimizing damage to the self and commensal flora.

special cases, the costs of pathology should increase owing to damage incurred from both host inflammation and pathogen exploitation (*red line*, **Figure 3*b***).

Immunological privilege: lack of a response (tolerance) against an introduced antigen to protect against inflammatory damage exhibited by certain tissues, such as brain, eye, placenta, and testis

Even more costly is the activation of inflammatory responses within tissues or organs that exhibit immunological privilege, a tissue-specific phenomenon that involves a lack of a response, or tolerance, to foreign antigens. In these organs, immunological tolerance of antigens appears to be favored over activation of the inflammatory response. It is hypothesized that immunological privilege is an adaptation to protect essential structures from the damaging effects of inflammation (Kaplan & Niederkorn 2007). When inflammation does occur, the resulting tissue damage can lead to permanent loss of function, morbidity, and mortality. For example, inflammation in the brain can have rapid and deleterious consequences for the host that are far greater than the costs of peripheral inflammation, as depicted by a steep morbidity curve in **Figure 3*c***. Most of the neuronal damage from bacterial meningitis and cerebral malaria is attributed to over-reactive inflammatory responses. Also, a significant proportion of damage that occurs from traumatic brain injury is from inflammatory processes rather than from direct mechanical damage. This suggests that inflammation in the brain after trauma is maladaptive rather than beneficial, as many traumatic injuries to the central nervous system are fatal in humans (and presumably other species) without modern medical intervention (reviewed by Weil et al. 2008). Furthermore, unlike peripheral tissues, damage to the central nervous system can cause irreparable harm because regeneration potential is limited (Weil et al. 2008). A unique case of selection for mild, yet persistent, inflammation (rather than no inflammation) in the vertebrate gut is discussed in a later section.

Timing

Another important consideration is the time course of inflammation. Acute inflammation encompasses the immediate and early responses to an injurious agent and is quickly resolved. Once the disturbance is removed, there is strong selective pressure for the inflammatory response to end so that tissue repair can restore functionality. Chronic inflammation results when the disturbance persists. The beginning of chronic inflammation is often characterized by the replacement of neutrophils with macrophages and other immune cells, such as T cells (Medzhitov 2008). During a chronic inflammatory state, granulomas are typically formed in a final attempt to wall off the host from pathogens. Persistent inflammation leads to increased cellular turnover and provides selection pressure that results in the emergence of cells that are at high risk for cancer. Chronic inflammation is also associated with a variety of cardiovascular, metabolic, and neurodegenerative diseases (**Table 1**), as well as stroke and myocardial infarction (reviewed by Hotamisligil 2006). Many of these diseases are often tied to aging, suggesting that the costs of chronic inflammation are not realized until later in life. For example, it has been proposed that the historical increase in human life span is a result of reduced life-time exposure to inflammatory insults from infectious disease (Finch & Crimmins 2004). Age-related inflammatory disease, from the progressive buildup of oxidative damage from chronic inflammation, could be the cost paid for having a robust immune system during early life. Although there is a general lack of empirical evidence to support this hypothesis, a recent study in mealworm beetles (*Tenebrio molitor*) demonstrated that increased inflammatory response early in life accelerates aging (Pursall & Rolff 2011).

Magnitude

The magnitude of the inflammatory response is also important when assessing costs. A low response could result in an underreactive and deficient immune response, whereas excessive

inflammation leads to costly collateral damage that, if unchecked, causes serious pathology. Thus, there is balancing selection for an intermediate level of inflammation to occur in most cases (**Figure 2**). Even moderate tissue stress, known as low-grade or para-inflammation, can trigger the inflammatory cascade. This response is graded and intermediate between baseline homeostasis and a classic inflammatory response (Medzhitov 2008). Para-inflammation is hypothesized to play a large role in the development of chronic inflammatory conditions and the eventual pathogenesis of several modern human diseases, as previously discussed.

When location, timing, and magnitude of inflammation are considered together, a hierarchy of costs is established. Chronic and high-grade inflammatory responses in immune-privileged organs lead to high fitness costs that include extensive damage, whereas acute, low-grade inflammation in localized tissue is the least expensive option. Thus, we predict that hosts should attempt to minimize these costs through the efficient delivery of immune cells to focal sites, the use of regulatory networks that quickly resolve inflammation, and the minimization of inflammation spreading into the periphery (such as the blood, which triggers cytokine storm and sepsis) or organs sensitive to inflammatory damage (brain, eye, testes, etc.).

NATURAL VARIATION OF INFLAMMATION

Hosts vary substantially in immune function and their ability to resist or tolerate infection (Medzhitov et al. 2012, Råberg et al. 2007). Ecoimmunology studies have demonstrated that activation of the immune system typically generates measurable costs through trade-offs with other life-history parameters (e.g., reproduction, growth, age) (Sadd & Schmid-Hempel 2009, Schmid-Hempel & Ebert 2003, Sheldon & Verhulst 1996). Some of these trade-offs are not apparent unless the host is exposed to stressful conditions (Hanssen et al. 2004, Moret & Schmid-Hempel 2000, Råberg et al. 1998). In contrast, the costs of inflammatory responses are normally overt. First, substantial energetic costs are involved. Mounting a febrile response involves a rise in the thermoregulatory set point that results in a 10–15% increase in metabolic rate for every 1°C increase in body temperature (Roe & Kinney 1965). Glucose use can also increase up to 68% during an acute phase response (Klasing 1998). Perhaps the most striking example involves sepsis, which is a whole-body inflammatory state that involves a 30–60% increase in metabolic rate (Lochmiller & Deerenberg 2000). Second, inflammation-induced collateral damage that is reparable requires time and energy to restore through tissue remodeling. Life-history costs of repair are largely ignored by ecoimmunology studies, but they could play a critical role during host recovery. Host damage that is irreparable obviously has deleterious effects upon normal physiological functioning and, ultimately, host fitness. Third, activation of sickness behavior involves a temporal cost to hosts. Most animals generally forego normal functions during behavioral symptoms of infections perhaps as an adaptation to conserve energy and minimize the risk of predation (Hart 1988). These symptoms of infection are regulated by inflammatory mediators, as blocking the effects of proinflammatory cytokines in the brain using receptor antagonists can diminish sickness behaviors (Dantzer 2001). Modification of host behavior can also affect disease dynamics, such as contact rates (Hawley & Altizer 2010).

Increasingly, experimental studies have identified life-history trade-offs where activation of the immune system leads to a corresponding decline in reproductive success or somatic growth (reviewed by Schmid-Hempel & Ebert 2003). Conversely, experimentally increasing reproductive effort (e.g., increasing brood size) can lead to a corresponding decrease in a host's immune response. There are significant well-described effects upon normal life-history functions during an inflammatory response. Local tissue inflammation leads to increased pain, which can deter animals from participating in normal activities. If inflammation spreads peripherally or centrally, then

Table 2 Examples of studies demonstrating life-history variation of lipopolysaccharide (LPS)-induced inflammation

Type of variation	Species	Study	Result
Age	House Mouse (*Mus musculus*)	Godbout et al. 2005	Neuroinflammation and sickness behavior increase in aged mice
	Norway Rat (*Rattus norvegicus*)	Foster et al. 1992	Increased duration of fever and elevated IL-6 and TNF in aged rats
	Tree Swallow (*Tachycineta bicolor*)	Palacios et al. 2011	Stronger anorexic responses and less parental care in older females[a]
Latitudinal	Song Sparrow (*Melospiza melodia*)	Adelman et al. 2010b	Fever diminished at higher latitude
	White-crowned Sparrow (*Zonotrichia leucophrys*)	Owen-Ashley et al. 2008	Anorexic responses vary by latitude, but are affected by body condition
Seasonal	Siberian Hamster (*Phodopus sungorus*)	Bilbo et al. 2002	Short day lengths attenuate fever and IL-1, IL-6
	White-crowned Sparrow (*Zonotrichia leucophrys*)	Owen-Ashley et al. 2006	Short day lengths diminish anorexic response
	Song Sparrow (*Melospiza melodia*)	Owen-Ashley & Wingfield 2006	Long days diminish sickness behavior in breeding males
Trade-offs with reproduction	House Sparrow (*Passer domesticus*)	Bonneaud et al. 2003	Increasing clutch size ameliorates feeding of nestlings in breeding females
	House Mouse (*Mus musculus*)	Aubert et al. 1997, Weil et al. 2006a	Parental care is resumed if survival of offspring is threatened; maternal aggression is unaffected
	Siberian Hamster (*Phodopus sungorus*)	Weil et al. 2006b	Short-day regression of gonads is delayed

[a]Effect observed only during the first year of the study.

proinflammatory cytokines can have direct inhibitory effects upon the hypothalamo-pituitary-gonadal axis that governs the release of sex steroids important for male and female reproduction. Behaviors associated with reproduction, such as sexual behavior, mating, aggression, and parental care, are typically suppressed in favor of sickness behaviors, which involve somnolence (sleepiness), reduced food and water intake, and depressive-like behaviors (reviewed by Ashley & Wingfield 2012). Although debated, such behaviors are thought to impart a selective advantage to hosts during an infection to conserve energy while reducing the intake of micronutrients that are important for pathogen growth (Hart 1988).

If inflammation carries substantial costs, then its activation should vary in relation to other life-history processes that have lower fitness costs. Accumulating evidence from both captive and field studies suggests that inflammatory responses are not fixed but display phenotypic plasticity (**Table 2**). To trigger inflammation, many studies have relied upon challenging animals with lipopolysaccharide (LPS; an immunogenic compound isolated from the cell wall of bacteria that mimics the onset of an infection in a dose-dependent fashion and is readily recognized by TLR4 on vertebrate immune cells), and then measuring physiological (cytokines, fever) or behavioral (anorexia, reductions in parental care or territorial aggression) responses.

LPS: lipopolysaccharide

Several studies have demonstrated seasonal modulation of inflammation (**Table 2**). Resources fluctuate dramatically and predictably in seasonal environments, especially in temperate and boreal regions, where low ambient temperatures and reduced food supply characterize winter. Seasonal

environments can dramatically alter disease dynamics (Altizer et al. 2006), as well as the allocation of resources that hosts dedicate toward immunological defenses (Martin et al. 2008, Nelson 2004, Nelson & Demas 1996). Many seasonally breeding rodents prepare for the arrival of winter by enhancing various components of immune function, and this upregulation can be triggered experimentally by exposing captive rodents to short day lengths, a reliable environmental cue that forecasts winter (Nelson & Demas 1996). For example, in field voles (*Microtus agrestis*), both proinflammatory and anti-inflammatory cytokine mRNAs were generally upregulated during winter, and lowest during the breeding season (Jackson et al. 2011). Alternatively, seasonal changes in immune function could also be driven by intraseasonal trade-offs where immune system demands compete directly with reproduction or other costly life-history activities, such as migration and molting (Martin et al. 2008). In Siberian hamsters (*Phodopus sungorus*), exposure to short days increased several parameters of innate immunity (Martin et al. 2008), but attenuated LPS-induced fever and sickness behavior (Bilbo et al. 2002). It is hypothesized that prolonged inflammatory responses are selected against to presumably optimize energy expenditure with survival outcome when energy availability is low (Nelson 2004). A similar seasonal pattern has been observed in seasonally breeding songbirds (Owen-Ashley et al. 2006). Whether inflammation is suppressed during breeding or nonbreeding is highly contingent upon seasonal fluctuations in energy stores, with poor body condition and elevated glucocorticosteroids associated with diminished inflammation (Owen-Ashley & Wingfield 2007). It is unknown whether host inflammation is modulated according to seasonal parasite dynamics (e.g., prevalence, transmission); this requires further carefully designed experiments.

As latitude increases, seasonal fluctuations in energy availability become more pronounced. The summer breeding season is truncated at higher latitudes, and any disruption can delay reproduction until the following year. Coupled with decreased pathogen risk at higher latitudes (Piersma 1997), it is hypothesized that selection should minimize inflammatory responses that would otherwise interfere with limited reproductive opportunities. In support of this hypothesis, free-ranging song sparrows (*Melospiza melodia*) breeding in Washington State reduced febrile responses to LPS compared to conspecifics breeding in California, and these differences persisted in captivity, suggesting a role for genetic (or maternal) effects (Adelman et al. 2010a,b).

Reproduction is also costly and can potentially trade-off with the ability to mount inflammatory responses. LPS treatment reduces the nestling feeding rate of female house sparrows (*Passer domesticus*). However, when brood size is increased, feeding rates are ameliorated (Bonneaud et al. 2003). Female mice are less sensitive to LPS challenge when survival of pups is threatened (Aubert et al. 1997, Weil et al. 2006a), and LPS treatment delays gonadal regression upon exposure to short day lengths in Siberian hamsters (Weil et al. 2006b). These studies support the terminal investment hypothesis, which predicts that organisms should invest in current reproduction if the probability of the next reproductive event is low. The physiological mechanisms underlying terminal investment remain largely unexplored.

Other studies have reported increased proinflammatory responses with age (**Table 2**), which is consistent with human studies (Licastro et al. 2005). Genes regulating inflammation might provide a benefit to hosts early in life by controlling infection, but later become deleterious, as proposed by the antagonistic pleiotropy model (Williams 1957). Alternatively, the disposable soma hypothesis states that there is little incentive to invest in mechanisms of self-maintenance, such as Th2-type tissue repair from proinflammatory damage, because the payoff is minimal relative to the expected longevity of the individual (Kirkwood 1977). Differentiating between these two hypotheses represents a major challenge for evolutionary ecologists.

INFLAMMATION AND HOST-PARASITE INTERACTIONS

Effects Upon Host Fitness

At the individual level, there is ample evidence that inflammation is beneficial in the short term, but detrimental at chronic levels. For example, disabling inflammation through the use of antagonists or selective gene knock-outs can increase susceptibility to infection (Nathan 2002). These studies suggest that inflammation improves host resistance in the short term. There is also evidence that the inflammatory cascade is important for resistance against multicellular pathogens. For example, knock-out mice deficient in IL-1 were more susceptible to infection by a gastrointestinal nematode, *Trichuris muris*, than wild-type mice (Helmby & Grencis 2004). When scaling up to population-level effects, there is a lack of studies that have examined inflammatory markers in relation to host population dynamics.

Infection can negatively impact hosts through damage from the parasite and through tissue damage caused by inflammatory responses to the pathogen. **Table 3** provides examples of human pathologies from various infections where a proportion of the damage to the host is caused by inflammation. Such damage includes oxidative stress from ROS and RNS as well as degradation of proteins by proteases. Hosts can mitigate some of this damage and increase tolerance by producing antioxidants (Finkel & Holbrook 2000) or switching to a Th2 (anti-inflammatory) phenotype. There are very few examples where virulence is determined solely by direct damage delivered by the pathogen and its virulence factors (e.g., dental caries, paralysis from neurotoxins) (Margolis & Levin 2008). Instead, host inflammation significantly contributes to disease pathology, and in some cases, the damage from self-harm is greater than the damage caused by the pathogen itself (Graham et al. 2005).

In principle, any mechanism that involves self-damage should be selected against, yet inflammation is one of the most highly conserved biological processes and is routinely involved in the pathogenesis of many diseases. Why is this the case? The evolution of inflammatory collateral damage may depend upon two limitations of host defense: delayed activation of adaptive immunity and weak specificity of innate immunity (Sorci & Faivre 2009). First, whereas adaptive immunity requires days or weeks to fully develop, inflammatory responses are activated within minutes. Pathogens have much shorter generation times than their hosts and rapidly proliferate unless appropriate host defenses are in place. The onset of pathogenic infection represents a vulnerable period for the hosts because adaptive immune function is not fully developed. Hosts may only be left with the option of activating highly costly and damaging defenses to minimize pathogen load until more effective defenses can take over. As long as the benefit of mitigating or clearing infection is greater than the deleterious costs of collateral tissue damage, this response should prevail in the short term. Second, inflammation entails a nonspecific response to infection. Although pathogens are readily distinguished from the self to trigger inflammation, further refinement of immunity to specific injurious agents is constrained by nonspecific immune responses. It should be noted that collateral immunological damage is not unique to vertebrates, as self-damage from inflammation occurs in invertebrates as well (Sadd & Siva-Jothy 2006). Thus, the evolution of highly cytotoxic defenses likely represents a significant yet costly response for the host.

Effects Upon Parasite Fitness

The study of pathogen virulence has attempted to understand the morbidity and mortality of hosts caused by parasites and pathogens. Most models of virulence have arisen from the classic virulence-transmission trade-off model formulated by Anderson & May (1982) and

Table 3 Examples of inflammation contributing to pathogenesis in humans[a]

Pathology	Pathogen	Site of damage	Type of damage	Mechanism
Flu	1918 Spanish Influenza (reconstructed)	Lung	Alveolar damage Edema Hemorrhagic exudate	Alteration of host IFN-mediated antiviral response (Kobasa et al. 2007)
Duodenal Ulcer	*Helicobacter pylori*	Gastric and duodenal mucosa	Mucosal atrophy	Chronic inflammation
Toxic Shock Syndrome/Scarlet Fever	*Staphylococcus* *Streptococcus*	Circulatory system Systemic	Septic shock	Extreme inflammation Cytokine storm Oxidative damage
Pneumonia	Various species, e.g., *Streptococcus pneumoniae*, *Neisseria meningitides*	Lung	Alveolar damage Edema	Induction of proinflammatory cytokines Edema Fibrin deposition
Cerebral Malaria	*Plasmodium* spp.	Brain	Vascular leakage Brain hemorrhage	Release of proinflammatory cytokines
Cutaneous Anthrax	*Bacillus anthracis*	Skin	Tissue necrosis	Release of proinflammatory cytokines
Tuberculosis	*Mycobacterium tuberculosis*	Lung	Recruitment of fluid and cells into the air spaces of the lungs Necrosis	Release of proinflammatory cytokines, namely TNF-α
Meningitis	*S. pneumoniae* *N. meningitides*	Brain Spinal cord	Brain damage Increased blood-brain permeability Increased intracranial pressure	Release of proinflammatory cytokines

[a]Modified from Margolis & Levin (2008).

Ewald (1983):

$$R_0 = \frac{\beta S}{\mu + \alpha + \gamma}.$$

In this equation, R_0 is the basic reproductive number and is defined as the average number of secondary infections arising from one infected individual from a wholly susceptible host population. Pathogens can increase R_0 by enhancing transmission (β) or by decreasing the rate of parasite-induced mortality or virulence (α) or recovery rate of hosts (γ). α is influenced by the rate at which the parasite is cleared, which is a function of host resistance. S is the density of susceptible hosts in the population and μ is the natural mortality rate of the host, which can also affect pathogen fitness. If the host dies before transmission can occur, then the fitness of the pathogen effectively drops to zero (Anderson & May 1982, Frank 1996). Following this model, a fundamental trade-off between transmission and virulence is formed. Increased virulence should favor the

production of more transmission forms per unit time (benefit) but limits the infectious period by host death (cost). Natural selection favors those pathogen strains that optimally balance these costs and benefits, leading to an intermediate level of virulence in most cases (reviewed in Alizon et al. 2008).

The trade-off model assumes that infection-induced mortality is solely a consequence of pathogen exploitation. However, a wealth of evidence suggests that host mortality from infection is often dependent upon the amount of collateral damage caused by host inflammation (Graham et al. 2005, Margolis & Levin 2008). Several testable predictions can be made when extending the trade-off model to incorporate inflammatory responses. First, it is predicted that inflammation directly enhances clearance of intracellular pathogens, albeit in a biased manner. Although inflammation is broadly effective at clearing infection, mathematical models predict that avirulent (or slow-growing) strains would be cleared faster than virulent (fast-growing) strains, selecting for more virulent strains to proliferate (Antia et al. 1994). This assumption, however, is entirely dependent upon the effectiveness of the inflammatory defense (magnitude, duration) in clearing the particular pathogen. Second, inflammatory responses cause damage to both host and pathogen and should thus directly contribute to increased virulence. Based upon these relationships, it is tempting to presume that inflammation leads to an obligatory increase in virulence and should, therefore, be selected against. However, before arriving at such a conclusion, it is necessary to investigate whether increased virulence from inflammation leads to a corresponding increase in parasite transmission. There are certainly cases where increased inflammation enhances the transmission of pathogens (e.g., diarrhea). However, if host inflammatory responses increase virulence without increasing transmission, then there would be selection for the opposite effect, which is decreased virulence (Graham et al. 2005). This is because any increase in self-damage would not provide an incremental advantage to the pathogen. In addition, whether or not damage from the parasite is dependent upon collateral damage is also important. If collateral damage is independent from pathogen-induced damage, then a high level of infection-induced mortality is expected because self-harm undermines the restrained exploitation of the parasite (Day et al. 2007). Conversely, reduced host mortality is predicted if a rise in collateral damage is accompanied by increased pathogen exploitation. In this case, natural selection would favor parasite strains that minimize collateral damage (Day et al. 2007). Thus, inflammatory responses have the potential to influence the outcome of host-parasite interactions, although empirical studies that manipulate levels of collateral host damage (without affecting pathogen-mediated virulence) are needed (Long & Boots 2011).

Because inflammation is nonspecific, there is ample evidence from the literature demonstrating the ability of microbes to manipulate or undermine the inflammatory cascade of hosts for their own benefit, thereby generating conditions that ensure their survival for a protracted period of time (reviewed in Sorci & Faivre 2009). A common mechanism employed is the induction of host anti-inflammatory cytokines, such as IL-10 and TGF-β, to temper the inflammatory cascade (Redpath et al. 2001). This can be achieved through the production of molecules that are similar to IL-10, such as viral IL-10, or through the direct induction of host immunosuppressive cytokines. Other mechanisms of evasion include interference with ROS and RNS production and resistance to phagocytic digestion (reviewed in Sorci & Faivre 2009). Although pathogens regularly employ antigenic variation to evade recognition by antigen-specific defenses, there are constraints in the ability of pathogens to modify PAMPs, which are molecules essential for pathogen survival and consequently recognized by the innate immune system. In other scenarios, within-host selection might favor pathogens triggering inflammation to exclude within-host competitors. A strategy of proactive invasion can allow a rare pathogen with enhanced immune resistance to invade and supplant competitors by promoting inflammation (Brown et al. 2008).

GUT INFLAMMATION AND HOST-COMMENSAL INTERACTIONS

The vertebrate gut is home to one of the most dense microbial populations on Earth, with up to 100 trillion (10^{14}) microbes inhabiting the human intestinal tract (Ley et al. 2006). Within this ecosystem, bacteria species dominate, especially the Firmicutes and the Bacteroidetes. Equally impressive is the ability of the intestinal epithelium (composed of a single layer of cells) to function as a selective barrier that must repel pathogens, tolerate commensals and food antigens, and rapidly incorporate nutrients essential for survival (MacDonald & Monteleone 2005). Besides producing microbial peptides, proinflammatory cytokines are also secreted by these cells in response to microbes. Gut-associated lymphoid tissue (GALT) is a collective term for lymphoid tissues located in the intestine that include Peyer's patches and isolated lymphoid follicles. These tissues play a large role in activating immune function that is restricted to the gut environment.

Gut inflammation can be triggered a number of different ways that include increasing exposure to pathogenic organisms, breaching the intestinal lumen, being exposed to irritants, or disabling the immunoregulatory network (Izcue et al. 2009). Intestinal homeostasis of immunity is achieved through the coordination of various regulatory mechanisms, including regulatory T cells (Tregs). These cells have been shown to significantly control gut inflammation by secreting immunosuppressive cytokines, such as IL-10 and TGF-β.

Under normal conditions, regulatory mechanisms override inflammatory signals reacting to stimuli produced by intestinal flora. The goal is to prevent immunological defenses from responding to harmless antigens found in the intestine while keeping opportunistic flora at bay, which requires low-grade, chronic inflammation. This statement is evidenced by studies in germ-free animals that demonstrate a mild state of inflammation when colonized by commensal flora (**Figure 2*d***). The absence of flora results in underdeveloped immune organs, such as the spleen, and in GALT. These differences are no longer apparent once hosts are colonized with intestinal flora (Rakoff-Nahoum et al. 2004). If regulatory mechanisms are removed due to dysregulation, then the balance is tipped toward a heightened immune response, which leads to chronic inflammation and the development of inflammatory bowel disease. Disruption of the intestinal barrier also leads to chronic inflammation because the immune system is exposed to a greater amount of proinflammatory stimuli. A reduction in basal inflammation would presumably fail to control opportunistic pathogens, which would result in the accumulation of proinflammatory stimuli and trigger chronic inflammation despite an initial reduced inflammatory state (Izcue et al. 2009). Thus, the balance between host and flora is precarious, requiring finely tuned regulatory and effector mechanisms.

Does gut inflammation in turn alter the evolutionary dynamics of commensal microflora? Recent evidence suggests that acute inflammation can enhance the rate of horizontal gene transfer between pathogenic and commensal flora in the gut, which fosters the spread of virulence and antibiotic-resistant genes (Stecher et al. 2012). These findings suggest that inflammation can promote the coevolution of pathogenic microbes and commensal organisms in the gut, which paves the way for rapid evolution of emerging infectious diseases with novel phenotypes.

CONCLUSIONS

This review provides a framework for linking proximate mechanisms of inflammation with ecological and evolutionary perspectives to better understand the selective forces shaping natural variation of inflammation in vertebrates. Inflammation is a costly host defense mechanism that exhibits phenotypic plasticity despite the seemingly rigid and redundant immunoregulatory networks that govern it. However, these networks can be altered or dysregulated over the life span

of the individual, as evidenced by an increase in chronic inflammation with age (Licastro et al. 2005). Furthermore, a bias in inflammatory status during early life can potentially reinforce the strength of the regulatory network during adulthood (Yazdanbakhsh et al. 2002). Whether such relationships apply to wild populations is untested. Examination of the potential organizational effects that alter immunoregulation of inflammation is a promising area of research to understand the trade-offs underlying inflammation.

Despite the tremendous progress that has been made toward understanding the proximate mechanisms of acute and chronic inflammation, very little is known about the role inflammation plays in regulating host population dynamics in the wild. Understanding some of the proximate mechanisms, such as signaling transduction and T-cell polarization, allows us to make predictions regarding how hosts respond to and control helminth parasites versus viral infections, for example. It is tempting to assume that chronic inflammation is rare in populations because individuals exhibiting such a state would presumably experience high fitness costs in the form of reduced fecundity and increased extrinsic mortality from predation or disease. However, we would also predict that chronic inflammation should increase in populations that have been exposed to rapidly emerging threats of the twenty-first century that include increased chemical and light pollution and the emergence of novel pathogens, which can trigger inflammatory states.

These possibilities raise several intriguing questions that could be experimentally tested: Are inflammatory states present in natural populations? If so, do individuals with high inflammation have the highest or lowest pathogen loads? Does this proportion vary in relation to sex, age, or season? Does inflammation resolve for some individuals, but not others? Does the activation and maintenance of host inflammation affect vital rates, such as fecundity and mortality? To begin answering these types of questions, immunological methods to accurately measure inflammatory states are required. Although there are several classic markers of inflammation, such as acute phase proteins (e.g., C-reactive protein, haptoglobin), cytokine levels measured in blood or other tissues using enzyme-linked immunosorbent assay (ELISA) or quantification of cytokine mRNA using rtPCR represent attractive options for assessing inflammatory states in wild populations. A panel of inflammatory (IL-1, IL-6, TNF, IFN, IL-17), anti-inflammatory (IL-4, IL-5), and regulatory (IL-10) cytokine activity could be ascertained in a single sample (Graham et al. 2007). A major challenge is developing such assays for nonmodel species because cytokine structure is highly variable between species, and antibody reagents used for measuring cytokines in murine and human studies do not necessarily cross-react with nonmodel species. However, the availability of high-throughput sequencing technologies and entire genome sequences makes it entirely possible to measure cytokine mRNA (Jackson et al. 2011). Coupling these measures with assessment of pathogen load and host vital rates would represent a powerful combination for assessing the role of inflammation in regulating host population dynamics. Lastly, monitoring the inflammatory state of populations could provide valuable insight for evaluating how animal populations respond to and cope with increasing environmental threats from pollution as well as emerging infectious disease from global climate change.

FUTURE ISSUES

1. Increasingly sophisticated molecular techniques need to be developed to explore inflammatory markers to elucidate the extent and natural variation of inflammation in free-living populations.

2. Although there are a number of studies demonstrating modulation of inflammation in a variety of life-history contexts, future studies should address how this modulation leads to alterations in life span, fecundity, survival, and resistance to disease.
3. Understanding the linkages between inflammation-induced collateral damage, tolerance to infection, and host recovery/repair will help address methods that measure the capacity of a host to cope with infection.
4. More examples that document polarized inflammatory states in hosts that are infected with an assemblage of different parasite species are needed.
5. Further insights in the role that inflammation plays in shaping the interactions between commensal and pathogenic bacteria in the vertebrate gut will increase our understanding of within-host competition, evolution of virulence, and emergence of novel pathogens.

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Errata

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