Developments in Primatology: Progress and Prospects
Series Editor: Louise Barrett

Jessica F. Brinkworth
Kate Pechenkina *Editors*

Primates, Pathogens, and Evolution

Springer

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For Jordan Aria and Jeremy

Acknowledgements

First, we must thank the 30+ authors who accepted our invitation to contribute to this book. This volume unites researchers from a wide range of biological fields including Anthropology, Biochemistry, Evolutionary Biology, Genetics, Immunology, Medicine, Veterinary medicine, Virology, and Zoology. These authors provided the collection of papers that examine the molecular interactions between primates and pathogens within the context of evolution contained within, and did so while juggling many other responsibilities. The publication of an edited book is a long process. Many of the authors represented here agreed to work with us as early as 2009, when we were first recruiting speakers for a symposium at the annual meeting of the American Association of Physical Anthropologists. We thank these authors for contributing their time and effort to write interesting works and for allowing us to curate such works here. Above all, we thank them for their support and patience.

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Thanks to our editor Janet Slobodien who approached us and encouraged us to pursue this book. Melissa Higgs, editorial assistant, guided the assembly of this book, and often helped us with the fine details of assembling figures and permissions. Thanks to Lesley Poliner and Hedge Ritya, who oversaw the production and copy editing of this volume and its supporting materials. Yurii Chinenov provided critical comments on multiple chapters. Thank you Jeremy Sykes for editorial assistance and for proofing drafts.

The initial idea to develop a collection of papers that would discuss molecular host–pathogen interactions came to us while attending a number of talks and posters across scattered presentation sections at the annual meeting of the American Association of Physical Anthropologists in Columbus, Ohio, in 2008. We wanted to provide a forum for researchers interested in the evolution of primate immunity to meet, discuss findings and brainstorm. At the 2009 AAPA meetings, we began to

approach potential contributors to a symposium and edited volume that would focus on the functional outcomes of evolutionary primate–pathogen interactions. We were very fortunate to be met with great enthusiasm by our future contributors, in particular George Armelagos who immediately suggested we include the research of Graham Rook, Jenny Tung, and Kristin Harper. The original participants of the "Pathogens and evolution of human and non-human primates" symposium, held in Albuquerque, New Mexico, in April of 2010, presented some truly interesting interdisciplinary works that day. We thank those researchers for sharing their ideas and enthusiasm - George Armelagos, Nels C. Elde, Harmit Malik, Cedric Feschotte, Charlie Nunn, Kristin Harper, Jayne Raper, Jenny Tung, Susan C. Alberts, Gregory A. Wray, Felicia Gomez, Wen-Ya Ko, Sarah Tishkoff, Ajit Varki, Melanie Martin, Caleb Finch, Fabian Crespo, Rafael Fernandez-Botran, Manuael Casanova, and Christopher Tilquist. Thank you to the American Association of Physical Anthropology and the Human Biology Association who hosted this symposium at their annual meetings in Albuquerque, New Mexico, in April 2010. A very special thanks to the donors, particularly members of the law firm Labaton Sucharow, who provided funds and consideration associated with the needs of this specific symposium. A special thanks to Kelly Zieman, Leslie and Sharon Brinkworth, Cheryl and Charles Brinkworth, Deirdre O'Boy, Emerson McCallum and Michael Donnelly.

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Montreal, QC, Canada Jessica F. Brinkworth

Contents

Primates, Pathogens and Evolution: An Introduction

Jessica F. Brinkworth and Kate Pechenkina

Introduction

Primate immune systems have evolved to interact with pathogens in different ways (Mandl et al. 2008, 2011; Pandrea et al. 2007; Sawyer et al. 2004; Song et al. 2005; Soto et al. 2010). Human and nonhuman primate immune systems have diverged with some species exhibiting strong differences in immune response to certain pathogens including immunodeficiency viruses [reviewed by Pandrea and Apetrei (2010), *Toxoplasma gondii* (Epiphanio et al. 2003), herpesviruses (Estep et al. 2010; Huang et al. 1978), and trypanosomes (Thomson et al. 2009; Welburn et al. 2001)]. Why closely related primates have evolved such divergent pathogen interaction strategies is not well understood. Despite strong public interest in human/nonhuman primate evolutionary history and the importance of various primate species as biomedical models, the current picture of interspecies differences in immunity remains fairly incomplete. Our understanding of how primate immunity evolved is hindered by disconnected research on primate–pathogen molecular interaction, an uneven focus on primate coevolution with a limited number of pathogens, and the disconnect between research on primate molecular phylogeny and primate physiology. The objective of the present collection of papers is to integrate research on the evolution of primate genomes, primate immune function, primate–pathogen biochemical interaction, and infectious disease emergence to provide a knowledge base for future research on human and nonhuman primate speciation, immunity, and disease.

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The Role of Long-Term Evolutionary Processes in Shaping the Primate Immune System

Evolution of the immune system is tied to the evolutionary history of a species and intertwined with the evolution of physiological functions and developmental stages of an organism. The majority of cold-blooded vertebrates appear to experience functional shifts in their immune response depending on external temperatures, resulting, in some cases, in impaired immune responses such as the inhibition of immunoglobulin class switching (Jackson and Tinsley 2002). The importance of a graft-rejection-like immune response during tadpole to adult morphogenesis in the frog genus *Xenopus* and the failure of novel proteins associated with lactation to stimulate "nonself" immune responses in mammals, for example, both suggest that the immune system has likely evolved in parallel with the evolution of species developmental stages (Izutsu 2009; Matzinger 1994, 2002).

To interpret variation in primate immune response within and between species, the evolutionary forces that shaped the underlying molecular differences need to be examined. Of these forces, pathogen-mediated natural selection has likely been the leading factor in increasing the frequency of pathogen resistance in host populations. Factors such as an organism's environment, diet, postural behavior, and sociality led to interspecies differences in exposure to specific pathogens and the frequency with which such pathogens were encountered. Complete or partial resistance of specific human genotypes to certain pathogenic strains and the patterned distribution of these genotypes among indigenous populations around the globe is fairly well documented (Hamblin and Di Rienzo 2000; Hraber et al. 2007; Leffler et al. 2013; Marmor et al. 2001; Tishkoff et al. 2001). While the genetic variability of nonhuman primate immune factors is comparatively less well studied, specific disease resistance genotypes in some of these species have been identified. Ecological differences between savanna dwelling Guinea baboons *(Papio papio)* and chimpanzees (*Pan troglodytes*) are likely responsible for resistance on the part of the former species to the savannah-based pathogen *Trypanosoma brucei gambiensis*, and high susceptibility to fatal *T. brucei*-caused sleeping sickness in the latter. Baboons are more involved in grassland ground foraging than chimpanzees, which also exploit savannah resources but are tied to forested regions and tend to retreat to the forest for sleep (Kageruka et al. 1991). In the course of their evolution in open habitats, baboons have likely been continuously exposed to the low flying tsetse fly—the vector for *T. brucei* (Lambrecht 1985; Welburn et al. 2001). The selective pressure generated by *T. brucei* is thought to have favored fixation of two nonconservative mutations in the baboon trypanosomal lytic factor *ApoLI* that have been linked to sleeping sickness resistance and are not shared with either humans or chimpanzees (Thomson et al. 2009). In humans, two unrelated mutations in *ApoLI* that increase sleeping sickness resistance are geographically restricted to Africa and absent in European populations. Interestingly, trypanolytic variants of *ApoLI* in humans contribute to an increased risk of kidney disease, providing an example of

heterozygous advantage (Genovese et al. 2010) parallel to the classic case of the HbS variant of the HBB globin locus and other hemoglobinopathies that confer heterozygous advantage by means of increasing resistance to malaria(Allison 1956; Haldane 1949; Hedrick 2004; Kwiatkowski 2005; Lapoumeroulie et al. 1992; Oner et al. 1992).

The pathogen-directed evolutionary mechanisms that contribute to the divergence of immune systems remain hypothetical. In the simplest case, an epidemic of a highly virulent infectious disease eliminates a large number of susceptible organisms very quickly, thereby favoring the disproportional reproductive success of resistant individuals. In such a scenario pathogen-mediated selection is assumed to be strong. However, such a model of host–pathogen coevolution is pertinent in extreme cases only. Pathogens of moderate-to-low virulence can also affect host immune allele frequencies by, for example, contributing to lowered fertility in the form of physical inability to produce offspring after being infected or causing a lesser ability to acquire mates as a result of decreased mobility (Cheney et al. 1988; Levin et al. 1988). Pathogens that do not kill a host, therefore, can affect sexual selection and gene flow. Of course, the consequences of a deadly epidemic may *not* be limited to removal of the alleles that contribute to disease susceptibility, such as those of surface antigens recruited by a pathogen to penetrate the host. Such strong selective pressure may also affect alleles that contribute to increased susceptibility to coinfections or to overt immune activity that leads to the development of secondary conditions (e.g., sepsis). Pathogen pressure may also select for resistance traits and in doing so affect the frequency of linked alleles in a population through selective sweeps.

The most popularized perception of host–pathogen evolutionary interaction is the concept of a host–pathogen evolutionary arms race. This idea is derived from the application of Leigh Van Valen's 1973 Red Queen hypothesis to hosts and pathogens (Van Valen 1973). The Red Queen hypothesis proposes that closely associated organisms may coevolve so tightly that the likelihood of extinction for one or the other is constant over geological time. Changes in one species affect the tightly coevolved interface with another species, threatening either species with extinction. As stated by the Red Queen in Lewis Carroll's *Through the Looking Glass*: "Now, here, you see, it takes all the running you can do, to keep in the same place." Tightly coevolved hosts and pathogens have to "run"—that is, evolve quickly—just to maintain a balance and avoid extinction. Within this framework, it is tempting to characterize host–pathogen relationships as beneficial for the host to recognize and either tolerate or eliminate a pathogen, with a pathogen's main recourse being to evade a host's defensive mechanisms. These interactions are thought to result in head-to-head collisions between a host's immune system and a pathogen, leading to selective pressure on the immune system and the pathogen and culminating in coadaptation.

However, some pathogens actually co-opt normal mechanisms of primate immune recognition and the subsequent responses, such as cytokine release, cell trafficking, and tissue destruction, using them to their advantage. *Mycobacterium tuberculosis* (tuberculosis) infection is enhanced by the release of host anti-inflammatory cytokine IL-10 (Redford et al. 2011). Once consumed by a macrophage, *Yersinia pestis* (plague) migrates to its main point of dissemination, the

lymph nodes, while acquiring phagocytosis resistance (Oyston et al. 2000; Pujol and Bliska 2003; Zhou et al. 2006). Similarly, HIV can disseminate to the lymph nodes and other regions through antigen-presenting cells (Koppensteiner et al. 2012). Moreover, exaggerated and uncontrolled immune cell responses may result in host death—such is the case of severe sepsis and septic shock triggered by strong innate immune cell recognition of immune system insult (e.g., blood stream infections and injury) (Brown et al. 2006; Murdoch and Finn 2003; Zemans et al. 2009). Rather than acquiring permanent and costly adaptations, some pathogens can escape host immune defenses through transient amplification of a resistance gene that creates tandem arrays aptly named "genomic accordions." Poxviruses encode two factors, E3L and K3L, which inhibit the host antiviral factor protein kinase R (PKR). In viruses lacking E3L, K3L rapidly becomes amplified 10–15-fold via serial duplication, which increases viral fitness. However, the tradeoff for increased genome size is less efficient replication. Remarkably, an expanded genomic array of identical resistance genes in a pathogen increases the probability of emergence, fixation, and spreading of additional K3L mutants with improved host avoidance; these viruses subsequently lose the K3L duplicated array but retain the novel resistance mutation (Elde et al. 2012).

Two limiting factors for pathogen-driven evolution of the immune system are disadvantages rendered to the host by hyper-responsiveness, leading to autoimmune disorders, and inadvertent pressure on symbiotic and commensal organisms. An overactive immune system is responsible for the development of chronic conditions mediated by the immune system itself, such as systemic lupus erythematosus, antiphospholipid syndrome, polycystic ovary syndrome, and diabetes, among others, that negatively affect reproductive fitness and may therefore contribute to immune system evolution (Carp et al. 2012).

Consequently, immune system divergence between species is not driven by host–pathogen interaction alone but is profoundly affected by the living environment, which includes a complex network of interspecies interactions between hosts, symbionts, commensals, and pathogens (Klimovich 2002; Lee and Mazmanian 2010). A species, with its associated microorganisms, can be considered a "holobiont," an evolutionary unit encompassing the totality of organisms involved in commensalistic, symbiotic, and parasitic relations (Zilber-Rosenberg and Rosenberg 2008). Changes in the fitness of any holobiont-involved species affect the system as a whole, rather than just the fitness of the host species. Indeed, changes in the composition of intestinal microbiota may promote outgrowth or invasion by pathogenic microorganisms or induce an exaggerated host response that results in the onset of various autoimmune disorders such as inflammatory bowel disease (Maynard et al. 2012). Alternatively, dietary and environmental changes may cause a shift in species-associated microbiota that results in the appearance of new pathogens or symbionts. Establishing whether new species-specific pathogens are effectors or consequences of speciation is a daunting task.

The Role of Pathogens in Primate Speciation

Interaction with pathogens likely played an important role in primate speciation in several ways. Pathogens have contributed to primate genome divergence through direct integration of microorganismal genomes into the genomes of primate germline cells. Over millions of years, viral integration into host genomes has changed genome sequences and affected multiple biological functions (Arnaud et al. 2007; Hunter 2010). For instance, Dunlap et al. (2006) proposed that effective placenta formation in mammals is impossible without a gene coding for an envelope protein that was initially introduced by a retrovirus (HERV-W) (Dunlap et al. 2006). Once incorporated, viral genomes were inherited by offspring. Past retroviral infections of human ancestors now represent approximately 8 % of the human genome (Bannert and Kurth 2006). Due to different histories of pathogen exposure, primate genomes differ from one another in terms of the types and numbers of integrated viral sequences (Horie et al. 2010; Kim et al. 2008). As such, viral pathogens have contributed to the divergence of primate genomes and the divergent functions of primate genes (Gogvadze et al. 2009; Wang et al. 2007; Yohn et al. 2005).

While portions of primate genomes have diverged because of species-specific viral integration, some loci appear to have evolved under pathogen-driven selection. Multiple pathogens have been identified as having exerted selective pressure on primate immune factors for millions of years [i.e., retroviruses and apolipoprotein B-editing catalytic polypeptide 3G (APOBEC3G) (Sawyer et al. 2004), retroviruses and Tripartite Motif 5 alpha (TRIM5α) (Sawyer et al. 2005; Song et al. 2005), *Plasmodium falciparum* and glycophorin C (Maier et al. 2003), and *Mycobacterium tuberculosis* an granulysin (Stenger et al. 1998)]. Primate immune genes, proteins, and cells have structurally and functionally diverged. Primate immune factors show evidence of selection [CC-motif receptor 5 (Wooding et al. 2005), Toll-like Receptors 1 and 4 (Nakajima et al. 2008; Wlasiuk and Nachman 2010), TRIM5α (Sawyer et al. 2005), Cluster of Differentiation-45 (Filip and Mundy 2004), and Protein kinase R (Elde et al. 2009)] or interspecies divergence in function [Major-histocompatibility Complexes, Killer cell Immunoglobulin-like Receptors (Abi-Rached et al. 2010; Moesta et al. 2009), Toll-like Receptor 7 (Mandl et al. 2008, 2011), and ApoLI (Thomson et al. 2009)]. Reconstructions of primate evolutionary relationships based on the regulatory and coding sections of immune system genes deviate significantly from generally accepted primate phylogenies [Toll-like receptor 2 (Yim et al. 2006), CXC-motif receptor 4 (Puissant et al. 2003), and Major Histocompatability-DQA1 (Loisel et al. 2006)]. Although it appears that pathogens have directly contributed to the evolution of individual loci, we primarily understand these changes in the context of the primary structures of individual genes or proteins and not in the context of immune function. Until the functional effects of these changes are considered, it is impossible to appreciate how they contributed to speciation or disease susceptibility and progression. A goal of this volume is to integrate available information on structural and functional differences in primate immunity with data on the evolutionary analysis of gene sequences, pathogen life cycles, and evolutionary history.

Clinical Implications of Primate–Pathogen Coevolution

As a consequence of primate–pathogen evolutionary interactions, primates exhibit strong interspecies and interpopulation differences in immune response to a broad range of pathogens, some of which are major agents of human disease. Many lineages of African nonhuman primates have hosted immunodeficiency viruses (IV) over millions of years and their extant descendents do not develop the overt immune activation and white blood cell loss that typifies late stage IV infection (AIDS) in comparatively new hosts such as humans or Asian monkeys [reviewed in Pandrea and Apetrei 2010; see also Greenwood et al. 2013]. Nonhuman primate Herpes simian B virus infections in their natural hosts are fairly asymptomatic or manifest mildly, in a manner similar to human herpes simplex mucosal blisters. When transmitted to naïve primate hosts, including humans, these herpes infections can progress to encephalopathy (Artenstein et al. 1991; Chellman et al. 1992; Estep et al. 2010; Vizoso 1975). Unless severely immunocompromised, humans infected with the brain and muscle parasite *Toxoplasma gondii* are asymptomatic or develop a self-limited disease characterized by fever and enlarged lymph nodes (Jones et al. 2007). By contrast, *T. gondii* infections in New World monkeys are characterized by loss of strength, respiratory difficulty, and high mortality (Epiphanio et al. 2003; Catão-Dias et al. 2013). Research on the molecular mechanisms responsible for such variation in disease manifestation among different primate species involves multiple, often disparate areas of study, which contributes to gulfs between research on immune function, research on primate–pathogen evolution, and the clinical application of the resultant findings.

Arguably, the molecular mechanisms of immunodeficiency virus infection in primates are the best understood primate–pathogen interactions. The severity of the HIV pandemic and a strong interest in developing viable therapies have encouraged the examination of disease susceptibility and progression in primates, but mainly in a limited selection of catarrhine species. Primate-IV studies often use a comparative evolutionary approach as a starting point for the analysis of primate immunity and disease progression. An important advance in HIV therapy research has been the finding that IVs have emerged multiple times in the course of primate evolution and have closely coevolved with their hosts over millions of years (Pandrea and Apetrei 2010; Santiago et al. 2002; Switzer et al. 2005; Van Heuverswyn et al. 2006; Zhu et al. 1998). Comparative studies of primate-IV interactions have led to the identification of several immune factors thought to be under selective pressure from IVs and might serve as therapeutic targets including TRIM5α (Ortiz et al. 2006), APOBEC3G (Sawyer et al. 2004, 2005), Tetherin/BST2 (Jia et al. 2009), IL-4 (Koyanagi et al. 2010; Rockman et al. 2003), TLR7 (Mandl et al. 2008), TRAIL (Kim et al. 2007), CCR5 (Wooding et al. 2005), and MHC I (de Groot et al. 2002). A limited number of broader interspecies differences in the proportion of immune cell types, activation of immune cells, expression of immune genes, and stimulation of cell death that may affect disease progression have also been noted (Kim et al. 2007; Mandl et al. 2008; Soto et al. 2010). While primates serve as models for the

study of other diseases and have been examined as xenotransplantation subjects, what we currently know about interspecies differences in primate immune function is largely derived from comparative IV-primate research.

Although the genetic and functional differences identified through IV research may also contribute to a clearer picture of general immune responses to pathogens, we do not know how many of these immune factors are activated across primate species or whether this activation is stimulated in a similar way by other pathogens. This gap points to fundamental problems in our understanding of primate–pathogen interactions. First, current research is biased toward a limited number of species such as rhesus macaques (*Macaca mulatta*), humans, and sooty mangabeys (*Cercocebus atys*). Second, these studies typically use a challenge model. As such, cross-species examinations of resting/baseline primate immunity are extremely limited. How the activation and coordination of multiple immune factors coevolved with pathogens has yet, therefore, to be thoroughly investigated. To develop a better understanding of how pathogens affect primate speciation, conservation, and health, considerable additional information is needed on the differences in resting/baseline immune function and non-IV pathogen–host interactions across a greater number of primate species. Given the expense and special care considerations inherent in acquiring experimental data from primate species, it is particularly important that these efforts are comprehensive and that the resulting reports are made readily accessible.

The Effects of Increasing Human and Wild Nonhuman Primate Contact on Primate–Pathogen Interaction

In areas where human settlements and nonhuman primate habitats overlap, the potential for interspecies disease transmission increases dramatically (Chapman et al. 2005; Daszak et al. 2000; Duval and Ariey 2012; Reynolds et al. 2012; Stothard et al. 2012; Wheatley and Harya Putra 1994). Such transmission events can decimate wild primate populations, as new infectious diseases may profoundly affect animal survival, sociality, and reproduction (Berdoy et al. 2000; Nunn et al. 2008; Nunn 2012). Increased ecotourism and residential/agricultural contact has led to heightened transmission of anthroponotic pathogens to wild primates and subsequently to increased mortality in primate populations [e.g., chimpanzees and Polio virus (Wallis and Lee 1999), gorillas and respiratory disease (Palacios et al. 2011), baboons and *Schistosoma mansoni* (Farah et al. 2003; Murray et al. 2000), chimpanzees and paramyxoviruses (Kondgen et al. 2008), chimpanzees and *Schistosoma mansoni* (Stothard et al. 2012), and baboons and *Mycobacterium* (Keet et al. 2000)]. *Plasmodium falciparum* may have been introduced anthropolonotically to the neotropical primates during the colonial era, possibly through the forced migration of African slaves during the slave trade. Neotropical primate *P. simium* has been proposed to have emerged from Asian *P. vivax* during the nineteenth century, and perhaps introduced to South America by laborers from East Asia (reviewed in Cormier 2010).

The transmission of pathogens from nonhuman primates to humans has also had a profound effect on human health. The current HIV-1/AIDS pandemic likely originated with human consumption of SIV-contaminated nonhuman primate bushmeat (Gao et al. 1999). The emergence of other diseases in humans has likewise been attributed to human and nonhuman primate contact [i.e., Human T-Lymphotropic virus 1 (Vandamme et al. 1998), Monkeypox (Mutombo et al. 1983; Reynolds et al. 2012), and Malaria (Liu et al. 2010)]. As humans encroach even farther onto nonhuman primate ranges, the need for veterinary and medical intervention will increase. To be able to develop appropriate modes of intervention, it is very important to have good information on the broad differences and similarities of primate immune systems as well as the biochemical mechanics of specific primate–pathogen interactions.

Research on Primate–Pathogen Interaction Remains Scattered and Incomplete

Despite the importance of pathogen-primate interactions over the course of primate evolution, research on the functional outcomes of pathogen-mediated primate evolution is incomplete and scattered across many disciplines. A unified approach to the evolution of primate immunity will help better define the mechanisms of disease emergence, immune function, resistance, and ecology.

To better understand the differences in human and nonhuman primate immunity and help guide future research, it is important to integrate information from researchers who study the effects of pathogens on the evolution of primate genome diversity, cell function, immune response, and gene expression. This volume is one attempt at such a synthesis, incorporating contributions from a multidisciplinary group of authors who:

1. Provide a compilation of current baseline information about primate–pathogen interaction and comparative primate immunity.
2. Describe and analyze infectious disease emergence and pathogen escape of host defense mechanisms in the context of primate–pathogen coevolution.
3. Explore divergent primate immune functions and the pathogen-mediated molecular evolution of primates.
4. Discuss the human health implications of primate–pathogen evolutionary interaction.

Overview

The first section, *Immunity and Primate Evolution,* includes chapters that discuss major elements of the primate immune system (Brinkworth and Thorn; Brinkworth and Sterner), the use of primates as models of immune system evolution (Loisel and Tung)

and the pathogen-mediated evolution of primates (Gomez et al. and Allen et al.). The second section, *Emergence and Divergent Disease Manifestation,* provides data on the emergence, biochemical mechanics, and interspecies differences in immune response to immunodeficiency viruses, as well as a range of clinically important, but otherwise neglected pathogens. Attention is focused on how some primate pathogens have emerged (Harper and Knauf; Greenwood et al.), coevolved with and escaped the defenses of their hosts (Wong et al.), and triggered divergent responses in different primate species (Catao-Dias et al. and Greenwood et al.). The third and final section, *Primates, Pathogens, and Health*, focuses on how primate–pathogen coevolution affects the health of modern primates. Three papers on the health and evolutionary impact of disruptions to human and microorganism association (Rook, Martin and Blackwell, and Harper et al.) review and test the hygiene hypothesis. The volume closes with an analysis of major human and nonhuman primate cross-species pathogen transmission events, the social and biological factors that contributed to those events, and what the evolutionary, public health, and conservation consequences of these events might be (Harper et al.). We thought it a wonderful chapter with which to close.

Conclusion

Primate immune systems have been formed through complex evolutionary processes, within which pathogens have played an important role. The evolution of primate immunity has likely been more nuanced than natural selection driven by coevolutionary arms races with pathogens or large pathogen-mediated selective sweeps of hosts. Rather, the evolution of the primate immune system has likely been considerably shaped by, amongst other possibilities, moderately virulent pathogens, pathogen strategies that co-opt normal immunity, viruses integrated into the primate genome, commensal microorganism maintenance, autoreactivity, and overt immune responses, as well as the evolution of primate developmental stages. As close relatives, animals within the order Primates can be comparatively studied to not only clarify how primate immune systems have functionally diverged and highlight therapeutic targets for disease, but also to help define how such divergence contributes to disease emergence and interspecies disease transmission. As such, mapping the evolution of the primate immune system can improve our understanding of primate speciation, primate conservation, and human health. This volume is one effort to unite information on the evolutionary interactions between primate immune systems and pathogens. The chapters in this volume represent research from a broad range of disciplines involved in the study of primate–pathogen molecular interaction, primate immune function, and primate–pathogen coevolution. The work presented here discusses primate interactions with both major and neglected pathogens, attempts to bridge research on molecular evolution and primate immune function, and illustrates the impact of primate–pathogen evolutionary interactions on human and nonhuman primate health. With this effort we aim to provide a sound base of knowledge for future investigation of human and nonhuman primate evolution, immunity, and disease.

References

Abi-Rached L, Moesta AK, Rajalingam R, Guethlein LA, Parham P (2010) Human-specific evolution and adaptation led to major qualitative differences in the variable receptors of human and chimpanzee natural killer cells. PLoS Genet 6(11):e1001192

Allison AC (1956) The sickle-cell and haemoglobin C genes in some African populations. Ann Hum Genet 21(1):67–89

Arnaud F, Caporale M, Varela M, Biek R, Chessa B, Alberti A, Golder M, Mura M, Zhang YP, Yu L et al (2007) A paradigm for virus–host coevolution: sequential counter-adaptations between endogenous and exogenous retroviruses. PLoS Pathog 3(11):e170

Artenstein AW, Hicks CB, Goodwin BS Jr, Hilliard JK (1991) Human infection with B virus following a needlestick injury. Rev Infect Dis 13(2):288–291

Bannert N, Kurth R (2006) The evolutionary dynamics of human endogenous retroviral families. Annu Rev Genomics Hum Genet 7:149–173

Berdoy M, Webster JP, Macdonald DW (2000) Fatal attraction in rats infected with *Toxoplasma gondii*. Proc Biol Sci 267(1452):1591–1594

Brown KA, Brain SD, Pearson JD, Edgeworth JD, Lewis SM, Treacher DF (2006) Neutrophils in development of multiple organ failure in sepsis. Lancet 368(9530):157–169

Carp HJ, Selmi C, Shoenfeld Y (2012) The autoimmune bases of infertility and pregnancy loss. J Autoimmun 38(2–3):J266–J274

Catão-Dias JL, Epiphanio S, Martins Kierulff MC (2013) Neotropical primates and their susceptibility to *Toxoplasma gondii*: new insights for an old problem. In: Brinkworth JF, Pechenkina E (eds) Primates, pathogens, and evolution. Springer, Heidelberg

Chapman CA, Gillespie TR, Goldberg TL (2005) Primates and the ecology of their infectious diseases: How will anthropogenic change affect host-parasite interactions? Evolut Anthropol 14:134–144

Chellman GJ, Lukas VS, Eugui EM, Altera KP, Almquist SJ, Hilliard JK (1992) Activation of B virus (Herpesvirus simiae) in chronically immunosuppressed cynomolgus monkeys. Lab Anim Sci 42(2):146–151

Cheney DL, Seyfarth RM, Andelman SJ, Lee PC (1988) Reproductive success in vervet monkeys. In: Clutton-Brock TH (ed) Reproductive success. Chicago University Press, Chicago, IL, pp 384–402

Cormier LA (2010) The historical ecology of human and wild primate malarias in the new world. Diversity 2(2):256–280

Daszak P, Cunningham AA, Hyatt AD (2000) Emerging infectious diseases of wildlife–threats to biodiversity and human health. Science 287(5452):443–449

de Groot NG, Otting N, Doxiadis GG, Balla-Jhagjhoorsingh SS, Heeney JL, van Rood JJ, Gagneux P, Bontrop RE (2002) Evidence for an ancient selective sweep in the MHC class I gene repertoire of chimpanzees. Proc Natl Acad Sci USA 99(18):11748–11753

Dunlap KA, Palmarini M, Varela M, Burghardt RC, Hayashi K, Farmer JL, Spencer TE (2006) Endogenous retroviruses regulate periimplantation placental growth and differentiation. Proc Natl Acad Sci USA 103(39):14390–14395

Duval L, Ariey F (2012) Ape *Plasmodium* parasites as a source of human outbreaks. Clin Microbiol Infect 18(6):528–532

Elde NC, Child SJ, Geballe AP, Malik HS (2009) Protein kinase R reveals an evolutionary model for defeating viral mimicry. Nature 457(7228):485–489

Elde NC, Child SJ, Eickbush MT, Kitzman JO, Rogers KS, Shendure J, Geballe AP, Malik HS (2012) Poxviruses deploy genomic accordions to adapt rapidly against host antiviral defenses. Cell 150(4):831–841

Epiphanio S, Sinhorini IL, Catao-Dias JL (2003) Pathology of toxoplasmosis in captive new world primates. J Comp Pathol 129(2–3):196–204

Estep RD, Messaoudi I, Wong SW (2010) Simian herpesviruses and their risk to humans. Vaccine 28(Suppl 2):B78–B84

Farah I, Borjesson A, Kariuki T, Yole D, Suleman M, Hau J, Carlsson HE (2003) Morbidity and immune response to natural schistosomiasis in baboons (Papio anubis). Parasitol Res 91(4):344–348

Filip LC, Mundy NI (2004) Rapid evolution by positive Darwinian selection in the extracellular domain of the abundant lymphocyte protein CD45 in primates. Mol Biol Evol 21(8): 1504–1511

Gao, F, Bailes E, Robertson DL, Chen Y, Rodenburg CM, Michael SF, Cummins LB, Arthur LO, Peeters M, Shaw GM, Sharp PM, Hahn, BH (1999) Origin of HIV-1 in the chimpanzee Pan troglodytes troglodytes. Nature 397:436–441

Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, Bowden DW, Langefeld CD, Oleksyk TK, Uscinski Knob AL et al (2010) Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science 329(5993):841–845

Gogvadze E, Stukacheva E, Buzdin A, Sverdlov E (2009) Human-specific modulation of transcriptional activity provided by endogenous retroviral insertions. J Virol 83(12):6098–6105

Greenwood EJD, Schmidt F, Heeney JL (2013) The evolution of SIV in primates and the emergence of the pathogen of AIDS. In: Brinkworth JF, Pechenkina E (eds) Primates, pathogens, and evolution. Springer, Heidelberg

Haldane JBS (1949) The rate of mutation of human genes. Heredita 35(suppl):267–273

Hamblin MT, Di Rienzo A (2000) Detection of the signature of natural selection in humans: evidence from the Duffy blood group locus. Am J Hum Genet 66(5):1669–1679

Hedrick P (2004) Estimation of relative fitnesses from relative risk data and the predicted future of haemoglobin alleles S and C. J Evol Biol 17(1):221–224

Horie M, Honda T, Suzuki Y, Kobayashi Y, Daito T, Oshida T, Ikuta K, Jern P, Gojobori T, Coffin JM et al (2010) Endogenous non-retroviral RNA virus elements in mammalian genomes. Nature 463(7277):84–87

Hraber P, Kuiken C, Yusim K (2007) Evidence for human leukocyte antigen heterozygote advantage against hepatitis C virus infection. Hepatology 46(6):1713–1721

Huang ES, Kilpatrick B, Lakeman A, Alford CA (1978) Genetic analysis of a cytomegalovirus-like agent isolated from human brain. J Virol 26(3):718–723

Hunter P (2010) The missing link. Viruses revise evolutionary theory. EMBO Rep 11(1):28–31

Izutsu Y (2009) The immune system is involved in Xenopus metamorphosis. Front Biosci 14:141–149

Jackson JA, Tinsley RC (2002) Effects of environmental temperature on the susceptibility of *Xenopus laevis* and *X. wittei* (Anura) to *Protopolystoma xenopodis*(Monogenea). Parasitol Res 88(7):632–638

Jia B, Serra-Moreno R, Neidermyer W, Rahmberg A, Mackey J, Fofana IB, Johnson WE, Westmoreland S, Evans DT (2009) Species-specific activity of SIV Nef and HIV-1 Vpu in overcoming restriction by tetherin/BST2. PLoS Pathog 5(5):e1000429

Jones JL, Kruszon-Moran D, Sanders-Lewis K, Wilson M (2007) *Toxoplasma gondii* infection in the United States, 1999 2004, decline from the prior decade. Am J Trop Med Hyg 77(3):405–410

Kageruka P, Mangus E, Bajyana Songa E, Nantulya V, Jochems M, Hamers R, Mortelmans J (1991) Infectivity of *Trypanosoma* (Trypanozoon) *brucei gambiense* for baboons (Papio hamadryas, Papio papio). Ann Soc Belg Med Trop 71(1):39–46

Keet DF, Kriek NP, Bengis RG, Grobler DG, Michel A (2000) The rise and fall of tuberculosis in a free-ranging chacma baboon troop in the Kruger National Park. Onderstepoort J Vet Res 67(2):115–122

Kim N, Dabrowska A, Jenner RG, Aldovini A (2007) Human and simian immunodeficiency virus-mediated upregulation of the apoptotic factor TRAIL occurs in antigen-presenting cells from AIDS-susceptible but not from AIDS-resistant species. J Virol 81(14):7584–7597

Kim HS, Kim DS, Huh JW, Ahn K, Yi JM, Lee JR, Hirai H (2008) Molecular characterization of the HERV-W env gene in humans and primates: expression, FISH, phylogeny, and evolution. Mol Cells 26(1):53–60

Klimovich VB (2002) Actual problems of evolutional immunology. Zh Evol Biokhim Fiziol 38(5):442–451

Kondgen S, Kuhl H, N'Goran PK, Walsh PD, Schenk S, Ernst N, Biek R, Formenty P, Matz-Rensing K, Schweiger B et al (2008) Pandemic human viruses cause decline of endangered great apes. Curr Biol 18(4):260–264

Koppensteiner H, Brack-Werner R, Schindler M (2012) Macrophages and their relevance in human immunodeficiency virus type I infection. Retrovirology 9:82

Koyanagi M, Kerns JA, Chung L, Zhang Y, Brown S, Moldoveanu T, Malik HS, Bix M (2010) Diversifying selection and functional analysis of interleukin-4 suggests antagonism-driven evolution at receptor-binding interfaces. BMC Evol Biol 10:223

Kwiatkowski DP (2005) How malaria has affected the human genome and what human genetics can teach us about malaria. Am J Hum Genet 77(2):171–192

Lambrecht FL (1985) Trypanosomes and Hominid evolution. Bioscience 35(10):640–646

Lapoumeroulie C, Dunda O, Ducrocq R, Trabuchet G, Mony-Lobe M, Bodo JM, Carnevale P, Labie D, Elion J, Krishnamoorthy R (1992) A novel sickle cell mutation of yet another origin in Africa: the Cameroon type. Hum Genet 89(3):333–337

Lee YK, Mazmanian SK (2010) Has the microbiota played a critical role in the evolution of the adaptive immune system? Science 330(6012):1768–1773

Leffler EM, Gao Z, Pfeifer S, Segurel L, Auton A, Venn O, Bowden R, Bontrop R, Wall JD, Sella G et al (2013) Multiple instances of ancient balancing selection shared between humans and chimpanzees. Science 339(6127):1578–1582

Levin JL, Hilliard JK, Lipper SL, Butler TM, Goodwin WJ (1988) A naturally occurring epizootic of simian agent 8 in the baboon. Lab Anim Sci 38(4):394–397

Liu W, Li Y, Learn GH, Rudicell RS, Robertson JD, Keele BF, Ndjango JB, Sanz CM, Morgan DB, Locatelli S et al (2010) Origin of the human malaria parasite *Plasmodium falciparum* in gorillas. Nature 467(7314):420–425

Loisel DA, Rockman MV, Wray GA, Altmann J, Alberts SC (2006) Ancient polymorphism and functional variation in the primate MHC-DQA1 5′ cis-regulatory region. Proc Natl Acad Sci USA 103(44):16331–16336

Maier AG, Duraisingh MT, Reeder JC, Patel SS, Kazura JW, Zimmerman PA, Cowman AF (2003) *Plasmodium falciparum* erythrocyte invasion through glycophorin C and selection for Gerbich negativity in human populations. Nat Med 9(1):87–92

Mandl JN, Barry AP, Vanderford TH, Kozyr N, Chavan R, Klucking S, Barrat FJ, Coffman RL, Staprans SI, Feinberg MB (2008) Divergent TLR7 and TLR9 signaling and type I interferon production distinguish pathogenic and nonpathogenic AIDS virus infections. Nat Med 14(10):1077–1087

Mandl JN, Akondy R, Lawson B, Kozyr N, Staprans SI, Ahmed R, Feinberg MB (2011) Distinctive TLR7 signaling, type I IFN production, and attenuated innate and adaptive immune responses to yellow fever virus in a primate reservoir host. J Immunol 186(11):6406–6416

Marmor M, Sheppard HW, Donnell D, Bozeman S, Celum C, Buchbinder S, Koblin B, Seage GR 3rd (2001) Homozygous and heterozygous CCR5-Delta32 genotypes are associated with resistance to HIV infection. J Acquir Immune Defic Syndr 27(5):472–481

Matzinger P (1994) Tolerance, danger, and the extended family. Annu Rev Immunol 12: 991–1045

Matzinger P (2002) The danger model: a renewed sense of self. Science 296(5566):301–305

Maynard CL, Elson CO, Hatton RD, Weaver CT (2012) Reciprocal interactions of the intestinal microbiota and immune system. Nature 489(7415):231–241

Moesta AK, Abi-Rached L, Norman PJ, Parham P (2009) Chimpanzees use more varied receptors and ligands than humans for inhibitory killer cell Ig-like receptor recognition of the MHC-C1 and MHC-C2 epitopes. J Immunol 182(6):3628–3637

Murdoch C, Finn A (2003) The role of chemokines in sepsis and septic shock. Contrib Microbiol 10:38–57

Murray S, Stem C, Boudreau B, Goodall J (2000) Intestinal parasites of baboons (Papio cynocephalus anubis) and chimpanzees (Pan troglodytes) in Gombe National Park. J Zoo Wildl Med 31(2):176–178

Mutombo M, Arita I, Jezek Z (1983) Human monkeypox transmitted by a chimpanzee in a tropical rain-forest area of Zaire. Lancet 1(8327):735–737
Nakajima T, Ohtani H, Satta Y, Uno Y, Akari H, Ishida T, Kimura A (2008) Natural selection in the TLR-related genes in the course of primate evolution. Immunogenetics 60(12):727–735
Nunn CL (2012) Primate disease ecology in comparative and theoretical perspective. Am J Primatol 74(6):497–509
Nunn C, Thrall P, Stewart K, Harcourt A (2008) Emerging infectious diseases and animal social systems. Evolut Ecol 22(4):519–543
Oner C, Dimovski AJ, Olivieri NF, Schiliro G, Codrington JF, Fattoum S, Adekile AD, Oner R, Yuregir GT, Altay C et al (1992) Beta S haplotypes in various world populations. Hum Genet 89(1):99–104
Ortiz M, Bleiber G, Martinez R, Kaessmann H, Telenti A (2006) Patterns of evolution of host proteins involved in retroviral pathogenesis. Retrovirology 3:11
Oyston PC, Dorrell N, Williams K, Li SR, Green M, Titball RW, Wren BW (2000) The response regulator PhoP is important for survival under conditions of macrophage-induced stress and virulence in Yersinia pestis. Infect Immun 68(6):3419–3425
Palacios G, Lowenstine LJ, Cranfield MR, Gilardi KV, Spelman L, Lukasik-Braum M, Kinani JF, Mudakikwa A, Nyirakaragire E, Bussetti AV et al (2011) Human metapneumovirus infection in wild mountain gorillas, Rwanda. Emerg Infect Dis 17(4):711–713
Pandrea I, Apetrei C (2010) Where the wild things are: pathogenesis of SIV infection in African nonhuman primate hosts. Curr HIV/AIDS Rep 7(1):28–36
Pandrea I, Apetrei C, Gordon S, Barbercheck J, Dufour J, Bohm R, Sumpter B, Roques P, Marx PA, Hirsch VM et al (2007) Paucity of CD4+CCR5+ T cells is a typical feature of natural SIV hosts. Blood 109(3):1069–1076
Puissant B, Abbal M, Blancher A (2003) Polymorphism of human and primate RANTES, CX3CR1, CCR2 and CXCR4 genes with regard to HIV/SIV infection. Immunogenetics 55(5):275–283
Pujol C, Bliska JB (2003) The ability to replicate in macrophages is conserved between Yersinia pestis and Yersinia pseudotuberculosis. Infect Immun 71(10):5892–5899
Redford PS, Murray PJ, O'Garra A (2011) The role of IL-10 in immune regulation during M. tuberculosis infection. Mucosal Immunol 4(3):261–270
Reynolds MG, Carroll DS, Karem KL (2012) Factors affecting the likelihood of monkeypox's emergence and spread in the post-smallpox era. Curr Opin Virol 2(3):335–343
Rockman MV, Hahn MW, Soranzo N, Goldstein DB, Wray GA (2003) Positive selection on a human-specific transcription factor binding site regulating IL4 expression. Curr Biol 13(23):2118–2123
Santiago ML, Rodenburg CM, Kamenya S, Bibollet-Ruche F, Gao F, Bailes E, Meleth S, Soong SJ, Kilby JM, Moldoveanu Z et al (2002) SIVcpz in wild chimpanzees. Science 295(5554):465
Sawyer SL, Emerman M, Malik HS (2004) Ancient adaptive evolution of the primate antiviral DNA-editing enzyme APOBEC3G. PLoS Biol 2(9):E275
Sawyer SL, Wu LI, Emerman M, Malik HS (2005) Positive selection of primate TRIM5alpha identifies a critical species-specific retroviral restriction domain. Proc Natl Acad Sci USA 102(8):2832–2837
Song B, Javanbakht H, Perron M, Park DH, Stremlau M, Sodroski J (2005) Retrovirus restriction by TRIM5alpha variants from old world and new world primates. J Virol 79(7):3930–3937
Soto PC, Stein LL, Hurtado-Ziola N, Hedrick SM, Varki A (2010) Relative over-reactivity of human versus chimpanzee lymphocytes: implications for the human diseases associated with immune activation. J Immunol 184(8):4185–4195
Stenger S, Hanson DA, Teitelbaum R, Dewan P, Niazi KR, Froelich CJ, Ganz T, Thoma-Uszynski S, Melián A, Bogdan C et al (1998) An antimicrobial activity of cytolytic T cells mediated by granulysin. Science (New York, NY) 282(5386):121–125
Stothard JR, Mugisha L, Standley CJ (2012) Stopping schistosomes from "monkeying-around" in chimpanzees. Trends Parasitol 28(8):320–326
Switzer WM, Parekh B, Shanmugam V, Bhullar V, Phillips S, Ely JJ, Heneine W (2005) The epidemiology of simian immunodeficiency virus infection in a large number of wild- and captive-born

chimpanzees: evidence for a recent introduction following chimpanzee divergence. AIDS Res Hum Retroviruses 21(5):335–342

Thomson R, Molina-Portela P, Mott H, Carrington M, Raper J (2009) Hydrodynamic gene delivery of baboon trypanosome lytic factor eliminates both animal and human-infective African trypanosomes. Proc Natl Acad Sci USA 106(46):19509–19514

Tishkoff SA, Varkonyi R, Cahinhinan N, Abbes S, Argyropoulos G, Destro-Bisol G, Drousiotou A, Dangerfield B, Lefranc G, Loiselet J et al (2001) Haplotype diversity and linkage disequilibrium at human G6PD: recent origin of alleles that confer malarial resistance. Science 293(5529):455–462

Van Heuverswyn F, Li Y, Neel C, Bailes E, Keele BF, Liu W, Loul S, Butel C, Liegeois F, Bienvenue Y et al (2006) Human immunodeficiency viruses: SIV infection in wild gorillas. Nature 444(7116):164

Van Valen L (1973) A new evolutionary law. Evolut Theor 1:1–30

Vandamme AM, Salemi M, Desmyter J (1998) The simian origins of the pathogenic human T-cell lymphotropic virus type I. Trends Microbiol 6(12):477–483

Vizoso AD (1975) Recovery of herpes simiae (B virus) from both primary and latent infections in rhesus monkeys. Br J Exp Pathol 56(6):485–488

Wallis J, Lee DR (1999) Primate conservation: the prevention of disease transmission. Int J Primatol 20(6):803–826

Wang T, Zeng J, Lowe CB, Sellers RG, Salama SR, Yang M, Burgess SM, Brachmann RK, Haussler D (2007) Species-specific endogenous retroviruses shape the transcriptional network of the human tumor suppressor protein p53. Proc Natl Acad Sci USA 104(47):18613–18618

Welburn SC, Fevre EM, Coleman PG, Odiit M, Maudlin I (2001) Sleeping sickness: a tale of two diseases. Trends Parasitol 17(1):19–24

Wheatley B, Harya Putra DK (1994) Biting the hand that feeds you: Monkeys and tourists in Balinese monkey forests. Trop Biodivers 2:317–327

Wlasiuk G, Nachman MW (2010) Adaptation and constraint at Toll-like receptors in primates. Mol Biol Evol 27(9):2172–2186

Wooding S, Stone AC, Dunn DM, Mummidi S, Jorde LB, Weiss RK, Ahuja S, Bamshad MJ (2005) Contrasting effects of natural selection on human and chimpanzee CC chemokine receptor 5. Am J Hum Genet 76(2):291–301

Yim JJ, Adams AA, Kim JH, Holland SM (2006) Evolution of an intronic microsatellite polymorphism in Toll-like receptor 2 among primates. Immunogenetics 58(9):740–745

Yohn CT, Jiang Z, McGrath SD, Hayden KE, Khaitovich P, Johnson ME, Eichler MY, McPherson JD, Zhao S, Paabo S et al (2005) Lineage-specific expansions of retroviral insertions within the genomes of African great apes but not humans and orangutans. PLoS Biol 3(4):e110

Zemans RL, Colgan SP, Downey GP (2009) Transepithelial migration of neutrophils: mechanisms and implications for acute lung injury. Am J Respir Cell Mol Biol 40(5):519–535

Zhou D, Han Y, Yang R (2006) Molecular and physiological insights into plague transmission, virulence and etiology. Microbes Infect 8(1):273–284

Zhu T, Korber BT, Nahmias AJ, Hooper E, Sharp PM, Ho DD (1998) An African HIV-1 sequence from 1959 and implications for the origin of the epidemic. Nature 391(6667):594–597

Zilber-Rosenberg I, Rosenberg E (2008) Role of microorganisms in the evolution of animals and plants: the hologenome theory of evolution. FEMS Microbiol Rev 32(5):723–735

Part I
Immunity and Primate Evolution

Vertebrate Immune System Evolution and Comparative Primate Immunity

Jessica F. Brinkworth and Mitchell Thorn

Introduction

Molecular and cellular responses as diverse as RNA interference against viral infections in plants, antimicrobial peptides production in insects, and macrophage phagocytosis of *Listeria monocytogenes* bacterium in mammals are all manifestations of the immune system—an array of defense mechanisms against pathogens, cellular debris, and cancerous and dying cells that can secure the survival of host. It is an exquisitely organized and regulated system of defenses that has diversified over hundreds of millions years and, yet, is suitably conserved such that multiple organisms (e.g., insects, lamprey, dogs, rodents, and primates) can serve as immunological models of human health.

The practice of studying the immune system within the context of evolution, or "comparative immunology", emerged in the late nineteenth century. The most famous early example of a comparative immunological approach is Elie Metchnikoff's 1882 discovery of leukocyte phagocytosis. When Metchnikoff inserted rose thorns into starfish larvae to determine if the "wandering" cells (leukocytes) of starfish responded to bodily invasion by foreign matter (Metchnikoff 1893), he found the cells aggregated around the thorns. He then reiterated his experiment through the application of microorganisms to increasingly derived species (e.g., flies, rabbits) known to maintain leukocytes to find that, universally, a subset of these cells ingested microbes and offered host protection (Metchnikoff 1887).

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Thus, the innate immune strategy of phagocytosis was discovered. The comparative immunological approach Metchnikoff employed goes a step beyond simply applying a representative animal model to a question of immunity. Comparative immunology involves comparing differences and similarities in organisms' immune responses to draw broader conclusions about immune system function and its evolution. This approach can be useful for the identification of immune system components responsible for particular disease phenotypes, as well as the discovery of novel immune mechanisms. The use of other vertebrate animals such as jawless vertebrates, amphibians, and rodents as biomedical models can shed light on overriding principles of immunity. Comparisons of primate immunity in the context of vertebrate immune system evolution can be useful for the understanding of biomedical model use, primate evolution, and human health.

Primates are a recent addition to the comparative exploration of animal immune responses. Direct interspecies comparisons of primate immune system function emerged in the 1920s but did not become common until decades later. The understanding of comparative primate immunity mainly developed through nonhuman primate/human xenotransplantation studies in the 1960s, as well as immunodeficiency virus research from the late 1980s onwards (Benveniste et al. 1986; Daniel et al. 1984; Hardy et al. 1964; Hitchcock et al. 1964; Murphey-Corb et al. 1986; Reemtsma et al. 1964a, b; Starzl et al. 1964). Until the adoption of catarrhine (Old World monkey, apes, and humans) species for HIV research, few immunological studies using different primate species compared interspecies differences. It is now well established that primates exhibit within-order variation and, sometimes, biologically unique manifestations of infectious diseases (Epiphanio et al. 2003; Ngampasutadol et al. 2008; Pandrea and Apetrei 2010; Thomson et al. 2009; Walker 1997). Still, monkey and ape species are commonly used in immunological research as corollaries for human disease progression due to their biochemical, physiological, and genetic similarity to humans. Because there are so many immune system similarities between primate species, there is a tendency in non-HIV literature to make the assumption that what is represented in one primate species is represented in other primate species and, possibly, other nonprimate models. By making this assumption a researcher risks overlooking aspects of primate immune systems that are unique and using primates unnecessarily to explore immunological traits that they share with many other model organisms. Comparative information on baseline primate immunity, particularly the anatomy and function of major immune organs and cell types, is rare and scattered across many fields. In certain cases it is entirely unexplored. The goal of this chapter is to illustrate the place of primates in immune system evolution by (1) putting the emergence of major primate immune system components in the context of the evolution of vertebrate immunity as a whole and (2) illustrating how baseline primate immunity has diversified by uniting and highlighting the available information on interspecies functional differences in baseline primate immune system structures and components.

Overview of the Mammalian Immune System

As jawed vertebrates, mammals maintain an immune system that can be broken into two major arms based on function. The innate immune response is the more ancient of these two arms, having invertebrate origins (Leulier et al. 2003; Yoshida et al. 1986). Innate immune defenses are inherited, germline encoded, nonspecific, and typified by barriers (e.g., mucosa, skin), antimicrobial peptides, phagocytosis (initiated by cells such as macrophages and neutrophils), and inflammation (Janeway and Medzhitov 2002; Kumar et al. 2009). This kind of immunity limits initial infections by recognizing "nonself", and damage through a variety of sophisticated but generalized mechanisms, including inherited pattern recognition receptors (e.g., Toll-like receptors, NOD-like receptors) that detect foreign material through molecular patterns associated with pathogens or cellular damage. These patterns can be shared broadly by microorganisms or may signal tissue damage. They are conventionally and somewhat imprecisely referred to as pathogen- or danger- associated molecular patterns (PAMPS or DAMPS) (Seong and Matzinger, 2004).

By contrast, adaptive immunity is highly specific, not immediate, key to immunological memory, modulated by innate immunity, and acquired over a lifetime. While phagocytosis is an important tool in innate immune defenses, the targeting of matter bearing specific epitopes by lymphocytes (e.g., T and B cells) and the retention of some of these target-specific lymphocytes is key to adaptive immunity. Lymphocytes express membrane receptors (T-cell receptors for T cells and B-cell receptors for B cells) that recognize antigens. Unlike innate immunity, which makes use of germline encoded receptors, adaptive immunity has been traditionally viewed as reliant on receptors and immunoglobulins that are made highly variable through recombination activating gene (RAG)-mediated gene rearrangement/somatic recombination that occurs during lymphocyte development. From a limited number of receptor genes is borne a broad repertoire of specific receptors. As a result, rather than recognizing pathogens through PAMPS, the lymphocytes and immunoglobulins of the adaptive system recognize and "remember" distinct epitopes [reviewed in (Hardy 2003)].

The simplified view of the vertebrate immune system function is one of immediate recognition of invading pathogens by the innate immune system and subsequent initiation of a specific adaptive immune response. In mammals, for example, when innate immune cells recognize foreign antigens, they initiate the release of reactive signaling proteins known as cytokines. Cytokines degrade pathogens nonspecifically and initiate activation of an epitope/pathogen-specific T and B cell-mediated adaptive immune response. T and B cells can become activated when receptors they bear belonging to the immunoglobulin receptor superfamily, T- and B-cell receptors (TCRs and BCRs), recognize specific epitopes that are presented to them via major histocompatibility complexes (MHC) on phagocytic cells (e.g., macrophages and dendritic cells). B cells can also become activated through direct encounters with pathogens bearing these epitopes. Activated T and B cells then clonally replicate in

secondary lymphoid tissues, to be released as cytotoxic, phagocytic, or antibody producing cells that recognize and attempt to eliminate a specific epitope target. Engagement of the adaptive immune response typically occurs after the 4th hour of infection. The first clonal adaptive immune cells are released ~96 hours from the point of initial T- or B-cell activation. The first minutes and days of infection, therefore, are mainly mediated by innate immunity. As an infection is cleared over successive hours, most clonal T and B cells die off. A small percentage, however, remain in circulation as memory T and B cells. Memory cells speed the adaptive response to reencountered foreign epitopes and are the basis for immunological memory of past infections (Davis and Chien 2003; Jenkins 2003; Paul 2003).

Even this simplified description of mammalian immune system function only partially represents the immune system of other vertebrate classes as certain key components (e.g., lymph nodes, spleen components, and particular immunoglobulins/BCRs) did not appear until the emergence of recent vertebrate classes such as birds and mammals. The traditional paradigm of adaptive immunity is that it emerged in the last common ancestor of jawed vertebrates (gnathostomata) approximately 625 million years ago (mya). All lower vertebrates were thought to survive microbial assault only by initiating a generalized innate immune response. However, in the last decade it has become apparent that some components we associate with adaptive immunity emerged much earlier than previously assumed. The first evidence of lymphocyte-derived cytokines and receptors with immunoglobulin (Ig)-like domains, for example, can be found in sponges (Blumbach et al. 1999). In 2007, first evidence of somatic diversification of antigen receptors in lamprey came to light, supporting the existence of an "adaptive" immune system in jawless vertebrates (agnatha) (Guo et al. 2009; Rogozin et al. 2007). While these receptors, known as variable lymphocyte receptors (VLRs, discussed further below), are not related to the immunoglobulin receptor superfamily and are therefore not precursors to TCRs and BCRS, they appear to serve a similar function as antigen receptors (reviewed in Boehm et al. 2012b). Since the discovery of VLRs, it now seems possible that adaptive immune systems based on antigen receptor diversity mediated by gene rearrangement/somatic recombination may have evolved more than once in Metazoan history (Boehm et al. 2012b). The possibility that such sophisticated immune strategies in diverse vertebrate clades may be the outcome of convergent evolution attests to the immense evolutionary pressures that have shaped the vertebrate immune system.

The Evolution of Vertebrate Immunity: Major Lymphoid Tissues and Organs

Lymphoid tissues function as the sites of lymphoid cell development, selection of antigen–receptor repertoires, and effector cell coordination. These structures can be divided into primary or secondary lymphoid tissues based on their main function. Primary lymphoid tissues are sites of lymphocyte effector cell poiesis and