CELL-AUTONOMOUS IMMUNITY AND THE PATHOGEN-MEDIATED EVOLUTION OF HUMANS: OR HOW OUR PROKARYOTIC AND SINGLE-CELLED ORIGINS AFFECT THE HUMAN EVOLUTIONARY STORY

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ABSTRACT

Host immune tactics at the level of the single cell have a very large effect on disease progression and host survival. These cell-level defense mechanisms, known as cell-autonomous immunity, are among the most important determinants of human survival, yet are millions to billions of years old, inherited from our prokaryotic and single-celled ancestors. An understanding of how cell-autonomous immunity has evolved in primates is crucial to understanding the human evolutionary story, not only because multiple infectious agents thought to have strongly affected human genomic evolution are excellent manipulators of cell-autonomous immunity, but because these defenses are found in every cell in every physiological system. The ubiquity of cell-autonomous immunity highlights a biological reality not commonly addressed in human evolutionary studies—that pathogens can mediate the evolution of all body cells and, therefore, all body systems, affecting human evolution in a cell-type-specific fashion. Here we explore these very ancient tactics in light of evolutionarily important human pathogens and illustrate inter-primate differences in the potential of such defenses. Often considered an independent physiological system in human evolutionary biology, the immune system is ubiquitous, integrated into every other aspect of human physiology. It is, effectively, the entire organism. We argue, therefore, that immunity and pathogen-mediated natural selection are considerations in the examination of the evolution and function of any human physiological system or trait.

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INTRODUCTION

AS the primary boundary between a species and its environment, the immune system is under stupendous selective pressure from microorganisms (Kosiol et al. 2008; Wlasiuk and Nachman 2010a; Fumagalli et al. 2011; Karlsson et al. 2013, 2014; Brinkworth and Barreiro 2014; Casanova 2015; Quintana-Murci 2019). The impact microbial life has had on mammalian genomes is illustrated by both the overrepresentation of genes associated with immunity in lists of loci found to be under natural selection, and the broad variation in immune responses and clinical manifestations of disease between species and populations (Lambrecht 1985; Epiphanio et al. 2003; Kosiol et al. 2008; Pickrell et al. 2009; Barreiro et al. 2010; Pozzoli et al. 2010; Wong et al. 2010; Brinkworth et al. 2012; Hart and Tapping 2012; Hedrick 2012; Kobayashi et al. 2012; Karlsson et al. 2013; Raehtz et al. 2016; Okerblom et al. 2017). Although such immune responses are generated by a complex, hierarchical arrangement of immune system organs, tissues, and components, the unit of the cell has a particularly large effect on disease progression (Gaudet et al. 2016). Eukaryotic cells are great resources for many microorganisms and so individual safeguards at the cellular level, known as cell-autonomous defenses or cell-autonomous immunity, are critical factors in infection management (Randow et al. 2013). A formidable part of human immunity, they are also among the most ancient host tactics developed against infecting organisms, inherited from prokaryotic and single-celled ancestors and represented in every cell of the human body. Moreover, many of the pathogens considered the most influential in mediating the evolution of the human genome are strikingly adept at outmaneuvering cell-autonomous defenses across a range of cell types and physiological systems. The ubiquity of cell-autonomous immunity across the human body reflects a reality not often addressed in many subfields of human evolutionary biology—*the cells of every human physiological system have evolved to engage directly in pathogen defense and have been shaped by pathogens over evolutionary time* (Randow et al. 2013; Gaudet et al. 2016). Here we argue that our ancient prokaryotic and single-celled past is a crucial part of the human evolutionary story and affects human biology today. We show how human pathogens considered important in the evolution of the human genome manipulate cell-autonomous immunity, and have shaped primate evolution. We illustrate that these defenses are diverging in primate immune cells, and present evidence that they are also changing in "nonimmune" tissues. Given that cell-autonomous immune defenses are shared by all body cells, we argue that the immune system is integrated into every other aspect of human physiology and is, therefore, an important consideration for any examination of human evolutionary biology.

KEY HUMAN IMMUNE STRATEGIES ARE VERY ANCIENT, INHERITED FROM SINGLE-CELLED LIFE

Eukaryotic life emerged in a milieu of thriving bacterial, viral, and archaeal life forms (Casanova 2015). In this environment and over the eons since, infective microorganisms have exerted prodigious evolutionary pressure on all life, including humans, illustrated by the quick pace by which mammalian immune-associated genes evolve (Kosiol et al. 2008; Pickrell et al. 2009). These interactions between pathogens and multicellular hosts have driven the evolution and expansion of immune defenses intrinsic to individual cells, *cell-autonomous defenses*, into the breathtakingly expensive enterprise of molecular components, tissues, organs, and roving professional immune cells that is the canonical human immune system. For all of this expensive immune apparatus, the success of a human host's strategy against pathogenic infection remains strongly tied to cell-autonomous immune tactics. These defenses are broadly shared across all human cell types, immune cell or otherwise, conserved from archaeal, bacterial, and amoebic antimicrobial and nutrition procurement strategies that emerged in cellular life starting approximately 4.3 billion years ago (Nölling and de Vos 1992; Battistuzzi and Hedges 2009; Yutin et al. 2009; Boulais et al. 2010; Parfrey et al.

2011; Marín 2012; Yue et al. 2012; Nathan and Cunningham-Bussel 2013; Bassham and Crespo 2014; Zhang et al. 2016). They have coevolved with pathogens for billions of years, diverging by host cell type due to ever-evolving pathogen invasion strategies and the need of infecting microorganisms to negotiate passage across multiple cell types to access target resources in a multicellular host (Randow et al. 2013).

Examples of the cell-autonomous defense armory include pathogen-restricting cell organelles such as the phagosome and lysosome, restriction and mutagenic enzymes in the cytoplasm, pattern recognition receptors (PRRs) on the cell membrane and in the cell interior to detect damage and pathogens, decoy receptors throughout the cell to bind, occupy, and render ineffective pathogens and their products, and a range of associated cell activities such as phagocytosis (cell-eating), autophagy (self-eating), and release of cytotoxic (cell-killing) proteins and highly reactive oxygen and nitrogen species (Figure 1; Nölling and de Vos 1992; Kobe and Kajava 2001; Subauste 2009; Boulais et al. 2010; Marín 2012; Nathan and Cunningham-Bussel 2013; Sintsova et al. 2015; reviewed in Gaudetet al. 2016). When questions of how infectious disease has affected human evolutionary biology are framed around primate evolution, they are often addressing these immune tactics that humans share with bacteria and single-celled organisms and that have been shaped by pathogens for millions of years before the emergence of the Primate order. The ancient nature of these defenses is an important consideration in human evolutionary studies because their antiquity is both why cell-autonomous immunity exists in every cell, and the pathogens commonly considered the most pernicious and to have exerted the most stringent selective pressure on the human lineage tend to be organisms that bear microbiological innovations that manipulate these tactics (Table 1).

The Important Pathogens of Human History Tend to Readily Manipulate Cell-Autonomous Defenses

Pathogens have to traverse a host environment to complete their life cycle and are,

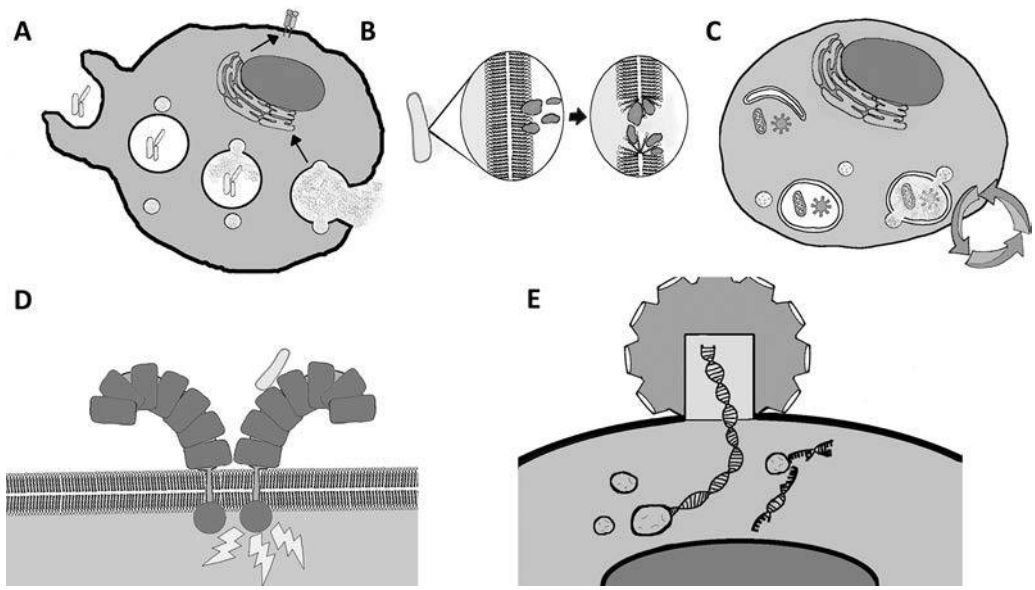


Figure 1. Example of Host Cell-Autonomous Defenses

A) phagocytosis; B) antimicrobial peptides; C) autophagy; D) pattern recognition receptor (Toll-like receptors on cell membrane are shown here); and mutagenic E) Mutagenic and restriction enzymes. Depictions are idealized. See the online edition for a color version of this figure.

TABLE 1
Major human pathogens—age, emergence, and cell-autonomous tactics countered

Pathogen	Disease	~Time of emergence (humans)	Context of emergence	Example host cell tactics countered	References
Human immunodeficiency virus 1 and 2 (HIV-1, HIV-2)	HIV/AIDS	>70 years ago (ya)	Bushmeat trade and consumption	AMPs (leverages) Autophagy (leverages, blocks) PRR (evades, leverages, suppresses) Enzymatic defenses (block, degrade)	Hirsch et al. (1989); Zhu et al. (1998); Gao et al. (1999); Keele et al. (2006)
Toxoplasma gondii	Toxoplasmosis	11 mya in Africa, 1.5 mya (extant strains)	Cat feces exposure, infected/ contaminated meat	Autophagy (evasion) PRR (evades)	Morrison et al. (2004); Bertranpetit et al. (2017)
Mycobacterium tuberculosis	Tuberculosis	~50–100 kya	Generalist animal-borne *Mycobacterium* bacilli (?)	Phagocytosis (leverages, disrupts phagosome maturation) PRR (blocks, suppresses)	Comas et al. (2013); Brites and Gagneux (2015)
Uropathogenic *Escherichia coli*	Urinary tract infection, sepsis	~100–300 kya	Within human host (?)	PRR (evades, leverages)	Lo et al. (2015)
Staphylococcus aureus	Staphylococcal infections, sepsis	>10 kya (?)	? Hypervirulent strains have been spread by human migration	Phagocytosis (leverages) AMPs (blocks, disassembles) PRR (evades)	Strauss et al. (2017); Richardson et al. (2018)
Vibrio cholerae	Cholera	~430 ya–10 kya	Contaminated water, facilitated by agriculture, climate variability, and trade	AMPs (blocks) Autophagy (blocks) PRR (evades)	Boucher et al. (2015); Naruszewicz-Lesiuk and Stypulkowska-Misiurewicz (2017)
Yersinia pestis	Plague	1.5–6.4 kya	Rodent flea exposure, facilitated by trade networks	Phagocytosis (uses and evades, disrupts phagosome maturation) AMPs (disassembles) Autophagy (blocks) PRR (evades, blocks, suppresses)	Cui et al. (2013)

therefore, under strong selective pressure to evade cell-autonomous immune defenses. Evasion tactics are highly varied, but can be reduced to three broad mechanisms—*blocking, escaping, and leveraging host defenses* (Figure 2). How well a pathogen can navigate these cell-autonomous immune defenses is central to its capacity to cause disease. Pathogens frequently highlighted as important in primate evolution and the human evolutionary story are particularly adept at manipulating or escaping powerful cell-autonomous defense tactics in human nonimmune and professional immune cells (see Box 1, Table 1). Here we highlight several major cell-autonomous defense tactics, illustrating their manipulation by important pathogens in human evolutionary history.

PHAGOCYTOSIS

Phagocytosis ("cell-eating") is an ancient nutritional and defense tactic that may have emerged in Archaea as early as 4.2 billion year ago (Battistuzzi and Hedges 2009; Yutin et al. 2009). Phagocytosis occurs when a cell recognizes extracellular materials through receptor binding and then internalizes those materials in intracellular compartments called phagosomes (Figure 1A). Ideally, phagosomes mature to bind with compartments inside the cell known as lysosomes, and the resulting phagolysosomes damage and break apart the microbes within them by increasing in acidity and generating antimicrobial compounds (e.g., reactive oxygen and nitrogen species). It is a complex process that requires recognition of an extraneous particle by any of a wide range of cell receptors (e.g., Fc-γ receptors, integrins, PRRs, apoptotic corpse, and scavenger receptors) and the rearrangement of the cell's cytoskeleton to engulf that threat (Yutin et al. 2009). In mammals, phagocytosis is central to immunity and required for destruction and presentation of threats to the adaptive immune system. Although phagocytosis is often discussed in the context of white blood cells

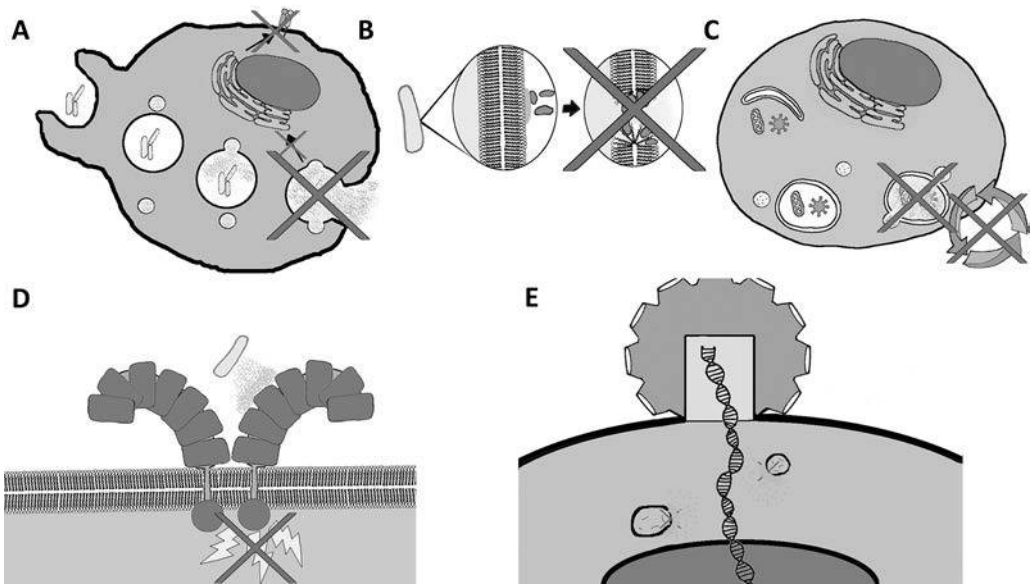


Figure 2. Examples of Pathogens Manipulating Host Cell-Autonomous Defenses

A) A common pathogen strategy is to stop the maturation of the phagosome in phagocytosis. Here a representative bacilli is blocking the fusion of lysosomes to the phagosome, preventing a breakdown of the bacteria. This action subsequently provides an intracellular space for bacterial replication and prevents presentation of the pathogen to the adaptive immune system; B) alterations to the bacterial cell wall block the actions of antimicrobial peptides; C) autophagy of a virus (xenophagy) is blocked by pathogen-halting autophagosomal maturation; D) bacilli proteins are binding to pattern recognition receptors and suppressing cell signaling; and E) virus issues factors that degrade mutagenic and restriction enzymes. Depictions are idealized. See the online edition for a color version of this figure.

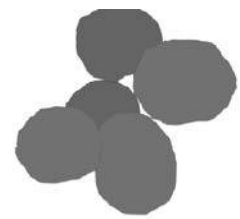
BOX 1

Major human pathogens and their putative impact on primate biology

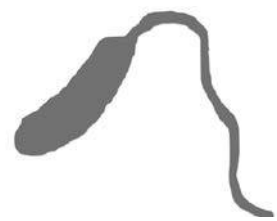
Yersinia pestis, the causative agent of plague, and one of the most deadly pathogens in the historical record, is a facultative intracellular bacteria that emerged approximately 6400 years ago in Eurasia (Cui et al. 2013). Plague manifests as a swift, severe, usually necrotizing infection that often ends in septic shock, with a 30–100% mortality rate in untreated people, depending on transmission route (i.e., flea vector, inhalation) and manifestation (bubonic approximately 30%, pneumonic and septicemic 100%; reviewed in Smiley 2008). It is an excellent immune escape "artist," usually transmitted by fleabite or inhalation (Lukaszewski et al. 2005; Peters et al. 2013). *Y. pestis* is thought to have killed approximately 30–50% of the Eurasian population during the first five years of its second pandemic (1347–1666; Gage and Kosoy 2005; Cohn 2008).

Mycobacterium tuberculosis is an acid-fast obligate intracellular bacteria that has coevolved with humans for 50,000–100,000 years and uses phagocytosis as a means of host cell entry (Gutierrez et al. 2005; Gagneux 2012). The impact of its stealthy manipulation of host macrophages on human populations has been profound, with tuberculosis having killed at least 1 billion people over the past 200 years alone (Paulson 2013; Cardona 2017). Hosts typically contract the bacteria by inhalation, and in the pulmonary environment *M. tuberculosis* is almost immediately recognized and phagocytized by macrophages patrolling the alveoli (Aberdein et al. 2013).

Staphylococcus aureus is a Gram-positive bacterial opportunistic pathogen that has coevolved with humans since at least the Neolithic and is among the most common causes of infectious disease mortality in humans (e.g., causing approximately 500,000 hospitalizations and about 10,000 deaths annually in the U.S.; Lowy 1998; Klein et al. 2007; Rosenthal et al. 2010; Murdoch and Howie 2018; Richardson et al. 2018). *S. aureus* causes mild to severe infections in humans and a wide range of vertebrate hosts, having been communicated by humans to livestock through multiple cross-species transmissions since the birth of agriculture (Fitzgerald 2012; Strauss et al. 2017; Richardson et al. 2018).

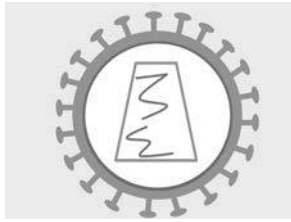


Vibrio cholerae can become a highly lethal bacteria via horizontal gene transfer. Currently causing 1.3–4 million deaths worldwide every year, it has killed millions of people over the course of at least seven cholera pandemics over approximately 430–10,000 years and has been identified as a diversifying agent on the human genome (Karlsson et al. 2013; Ali et al. 2015; Naruszewicz-Lesiuk and Stypulkowska-Misiurewicz 2017). Pathogenic *V. cholerae* attaches itself to the epithelial cells of the small intestine of hosts after oral consumption of the bacteria, where it disrupts numerous cell-autonomous defenses leading to dangerous and often lethal diarrhea (Castagnini et al. 2012).

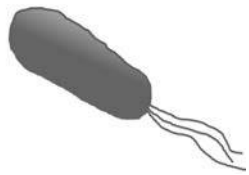


Toxoplasma gondii is a 1–2 million-year-old obligate intracellular feline-borne parasite that typically manifests as an asymptomatic lifelong infection in any healthy warm-blooded vertebrate with which it has a long evolutionary history (such as African and Asian primates; Su et al. 2003; Catão-Dias et al. 2013). The parasite tends to manifest as a severe necrotizing infection in species with comparatively limited evolutionary exposure to it, including platyrrhine and Malagasy primates (Epiphanio et al. 2003; reviewed in Dubey 2010). As such it is thought to have contributed to the diversification of primate immunity (Catão-Dias et al. 2013).

Human Immunodeficiency Virus (HIV), which typically manifests as acquired immune deficiency syndrome (AIDS) in humans, emerged after transmission of its African nonhuman primate counterparts (e.g., simian immunodeficiency virus—SIVcpz, SIVsm, SIVgor) to humans via bushmeat butchery at least 70 years ago (Hirsch et al. 1989; Zhu et al. 1998; Gao et al. 1999; Keele et al. 2006). By contrast, the 40-plus identified natural hosts of SIVs, which include several common chimpanzee subspecies, gorillas, and multiple African cercopithecoid and colobine monkeys, have coevolved with these viruses for millions of years and manifest species-specific symptoms, most rarely progressing to AIDS (reviewed in Sharp and Hahn 2011; Greenwood et al. 2013, 2015). Immunodeficiency viruses have been a diversifying factor in African primate evolution.



Uropathogenic *E. coli* (UPEC) emerged approximately 107,000–320,000 years ago, is responsible for approximately 90% of all urinary tract infections, infects 150 million people each year, and is a substantial cause of sepsis and sepsis-related mortality (Zhang et al. 2002; Levy et al. 2012; Lo et al. 2015; Terlizzi et al. 2017). UPECs maintain a robust armory of virulence factors that allow the bacteria to block or escape cell-autonomous defenses of white blood cells and epithelial cells found in the human urinary tract, and humans evolved multiple cell-autonomous strategies that appear to specifically target these strains of bacteria (reviewed in Terlizzi et al. 2017).



consuming microbes, it is also a housekeeping mechanism to clean up cellular debris and most nonimmune cells can be provoked to do it (Groves et al. 2008). It is a critical immune tactic for pathogens to evade, block, or leverage to survive. Evolutionarily important human pathogens have evolved a myriad of ways to usurp phagocytosis.

Yersinia pestis, the causative bacteria of plague, is an excellent manipulator of cell-autonomous defenses. One of the most deadly pathogens in human history, *Y. pestis* is thought to have exerted profound selective pressure on the human genome, particularly during its second pandemic. That "Black Death" outbreak started in the 14th century and killed approximately 30–50% of the Eurasian population (Moalem et al. 2002; Gage and Kosoy 2005; Cohn 2008; Laayouni et al. 2014). Arguably, the most important immune evasion strategy of *Y. pestis* is its multifaceted manipulation of phagocytosis. Upon entry to the mammalian host *Y. pestis*, a Gram-negative bacteria, immediately alters a major and highly detectable component of its cell wall—lipopolysaccharide (LPS)—replacing it with a modified, less detectable version and evading a bevy of antimicrobial tactics including phagocytosis (Montminy et al. 2006; Rebeil et al. 2006). This permits *Y. pestis* to disseminate in the host and affords it more control over which cells it will enter. The bacteria can bind to the structure that host cells reside in, the extracellular matrix (ECM), to enhance cellular invasion or trigger phagocytosis by target cells (reviewed in Ke et al. 2013). At approximately 37C in a mammalian host, and in contact with target cells (e.g., myeloid cells, epithelial cells), *Y. pestis* undertakes a plasmid (pYV/pCD1) transcriptional program that leads to a significant shift in virulence that allows the bacteria to more aggressively counter phagocytosis (Cowan et al. 2000; Lukaszewski et al. 2005; reviewed in Pha and Navarro 2016). Plasmid pYV/pCD1 arms *Y. pestis* with a bacterial mechanism called a type III secretion system (T3SS). T3SS both allows the bacteria to secrete into extracellular space and directly export into host cells newly expressed virulence factors—*Yersinia* outer proteins (Yops)—many of which specifically immobilize phagocytic activity via a multifaceted attack that degrades and halts the formation of the host cell's internal structure, the cytoskeleton (Weidow et al. 2000; Shao and Dixon 2004; Trasak et al. 2007; reviewed in Chung and Bliska 2016).

Mycobacterium tuberculosis, the 50,000–100,000-year-old obligate intracellular bacteria that manifests as human tuberculosis, also uses phagocytosis to enter its target

cell—alveolar macrophages in the human lung (Gutierrez et al. 2005; Gagneux 2012; Aberdein et al. 2013). While *M. tuberculosis* is very susceptible to reactive oxygen species generated in the phagosomes of many cells, alveolar macrophages are polarized to limit inflammation in the lungs and mount very weak oxidative responses (reviewed in Hussell and Bell 2014). Once inside an alveolar macrophage, *M. tuberculosis* uses multiple mechanisms to block its own destruction, including tearing pores into and disrupting the maturation of the phagosomes that contain it. Disruption of phagosomal maturation lets the bacteria avoid damage generated by phagolysomal acidification, while allowing it to also siphon off resources now flowing into the compartment from the cytoplasm (e.g., iron required to complete the bacterial life cycle; Sturgill-Koszycki et al. 1994; reviewed in Neyrolles et al. 2015). A permanently immature phagosome also provides *M. tuberculosis* a kind of protective cover from which to issue virulence/effector proteins into the cytoplasm without subjecting itself to the immune mechanisms lurking there (reviewed in Upadhyay et al. 2018).

Staphylococcus aureus, an opportunistic bacterial pathogen that has coevolved with humans since at least the Neolithic, infects a range of tissues and organs and is among the most common causes of infection mortality worldwide (Lowy 1998; Rosenthal et al. 2010; Murdoch and Howie 2018). It also readily controls host cell phagocytosis. *S. aureus* both uses and blocks phagocytosis as part of its exploitation of the host, co-opting host macrophage phagocytosis to form long-term bacterial reservoirs in host tissues (Lowy 1998; Agerer et al. 2005; Clement et al. 2005; Rosenthal et al. 2010). This process is enhanced by adhesive staphylococcal proteins called adhesins, which bind to a host protein prominent in the ECM known as fibronectin (Agerer et al. 2005). These adhesins also attract and bind to host immune cell receptors (i.e., $\alpha5\beta6$ integrins), which leads to the formation of a "fibronectin bridge" between the bacteria and the cell receptors, and triggers the host cell to consume the bacterium (Agerer et al. 2005). Unlike *Y. pestis* and *M. tuberculosis*, *S. aureus* does not always immediately obviously manipulate immune cell phagosome integrity or maturation (reviewed in Horn et al. 2018). All known *S. aureus* strains, however, very aggressively counter reactive oxygen and nitrogen species generated in phagosomes, each strain having multiple enzymes that specifically target and disassemble this antimicrobial process (reviewed in Gauppet al. 2012). The bacteria readily adapts to phagocytic killing tactics and if phagosomal conditions become intolerable, some highly virulent *S. aureus* strains can escape the phagosome of host cells (usually nonimmune cells) and take up residence in the cytoplasm (Strobel et al. 2016; Guerra et al. 2017). *S. aureus* has also evolved extraordinary tolerance to phagosomal killing by macrophages specifically, seeming to persist and wear out the phagosomal killing ability of individual cells over the course of infection (Jubrail et al. 2016). In this manipulation of phagocytosis, replicated bacteria escape "worn out" cells when they die and are taken up by new macrophages, allowing for continuous viable *S. aureus* infection and dissemination into new tissues (Lehar et al. 2015).

ANTIMICROBIAL PEPTIDES

Antimicrobial peptides (AMPs) are powerful host molecules that bore pores into and disintegrate bacterial membranes, disrupt microbial metabolism, and modulate the activities of immune cells (Figure 1B; reviewed in Cole and Nizet 2016). AMPs emerged with Archaea approximately 4.3 billion years ago and the cells of vertebrate species have evolved to express different types of these peptides in a species-specific manner (Maxwell et al. 2003; Semple et al. 2003; Das et al. 2010; Parfrey et al. 2011; Notomista et al. 2015; Blodkamp et al. 2016; Peel et al. 2016, 2017). AMPs are small, 10–50 amino acids long, issued within and outside host cells and bind mainly to bacterial lipids via electrostatic charge (Cole and Nizet 2016). Their functions are very diverse, with some of the better characterized AMPs known to complete actions as varied as directly disintegrating bacterial membranes, cell trafficking, controlling cell death, and regulating the differentiation and polarization of host immune cells (Davidson et al. 2004; reviewed in Choi et al. 2012). In vertebrates there are

two large groups of AMPs defined by structure—defensins and cathelicidins. While the functions of these AMPs broadly overlap, the peptides differ in their number and expression by species and cell type (Cole and Nizet 2016). Defensins can be separated by structure and cell location into three categories: β-defensins, found in epithelial cells of all vertebrates; α-defensins found in a white blood cell called a neutrophil and Paneth cells (found in crypts of the small intestine) of mammals; and θ-defensins found in the neutrophils of some nonhuman primates (Tang et al. 1999; Maxwell et al. 2003; Nguyen et al. 2003; Das et al. 2010; Avila 2017). Cathelicidins disintegrate proteins (they are "proteolytic") and are expressed in a range of white blood cells and epithelial cells (reviewed in Niyonsaba et al. 2010). The antiquity of AMPs has provided ample time for coevolution with pathogens. A pathogen that encounters a host immune cell must be able to evade or leverage the potent actions of AMPs to survive. Multiple pathogens important to the human evolutionary story do precisely that.

S. aureus has long coevolved with neutrophils and is resistant to multiple cell-autonomous defenses issued by these cells, including degradation by several human α- and β-defensins (Chertov et al. 1996; reviewed in Spaan et al. 2013). For example, the bacteria can alter the electrostatic charge of its cell envelope and lessen AMP binding to it, via expression of staphylococcal genes *mprF* and *dltABCD* (Peschel et al. 2001; Weidenmaier et al. 2005). Some strains produce enzymes, including staphylokinase and aureolysin, that degrade α-defensin and cathelicidin, respectively (Jin et al. 2004; Sieprawska-Lupa et al. 2004). Similarly, *Y. pestis* is known to inhibit cathelicidin activity, likely through cleavage via plasminogen activator outer membrane protein (Pla; Galván et al. 2008).

Anti-AMP strategies can also be very complex. Several bacterial pathogens express toxins, the toxicity of which stem from toxin-mediated modifications to host proteins via a process known as ADP-ribosylation. Examples include cholera toxin, which mediates the pathogenicity of ***Vibrio cholerae***, the causative bacteria of cholera and a diversifying agent on the human genome for approximately 430–10,000 years (Karlsson et al. 2013; Naruszewicz-Lesiuk and Stypulkowska-Misiurewicz 2017). Pathogenic *V. cholerae* attaches itself to the epithelial cells of the small intestine of hosts after oral consumption of the bacteria, secreting cholera toxin as it colonizes the gut. Cholera toxin is transported to the host cell cytosol where, via ADP-ribosylation it modifies and halts the actions of human α-defensins (Castagnini et al. 2012). *V. cholerae* infection also lowers cathelicidin expression in intestinal epithelial cells through an unknown mechanism (Chakraborty et al. 2008).

AUTOPHAGY

Autophagy is a cellular housekeeping and antimicrobial process by which cells remove unrequired and/or degrading intracellular material in the cytoplasm and recycle its components (Figure 1C). It emerged in yeast approximately 1 billion years ago (Glick et al. 2010; Gaya et al. 2015). Shared across all cell types, autophagy is regulated by complex genetic pathways that overlap substantially with immune pathways controlling programmed cell death, pathogen recognition, and AMP function (Subauste 2009; Deretic 2011; Rekha et al. 2015). The autophagic process begins with the formation of a compartment inside the host cell (autophagosome) around material to be destroyed (e.g., pathogens), the fusing of that compartment to acid- and enzyme-containing lysosomes (autolysosome), possible recruitment of AMPs, and the subsequent destruction of the compartments' contents (Alonso et al. 2007; reviewed in Lamb et al. 2013). The process can be selective, with particular intracellular components targeted and tagged with molecules (e.g., cargo receptors, polyubiquitin chains) in advance of autophagosome formation (Khaminets et al. 2016). Although autophagy can be antimicrobial in response to pathogen detection, it also appears to be necessary for the delivery of some pathogens to intracellular immune receptors—immune detection of Sendai virus (SeV), and vesicular stomatitus virus (VSV) in certain mouse white blood cells (dendritic cells), for example, occurs this way (Lee et al. 2007). Should a pathogen find itself inside any host cell, autophagy is a tactic that it must outcompete. Many of the

pathogens that have exerted great selective pressure on the primate genome do just that.

Toxoplasma gondii, is a 1–2 million-year-old obligate intracellular feline-borne parasite that typically manifests as an asymptomatic lifelong infection in any healthy warm-blooded vertebrate with which it has a long evolutionary history (i.e., African and Asian primates), but a severe necrotizing infection in animals with comparatively limited evolutionary exposure to it (South American monkeys and Malagasy primates; Epiphanio et al. 2003; Catão-Dias et al. 2013; reviewed in Dubey 2010). *T. gondii* outmaneuvers autophagy readily. The parasite first evades the antimicrobial consequences of phagocytosis by quickly invading cells and shielding itself with a self-made parasitophorous vacuole as it enters (Dubey 2007). This is a short respite for *T. gondii*, as within minutes of infection, host autophagocytic markers bind to the parasitophorous vacuole, targeting it for destruction (Choi et al. 2012; Selleck et al. 2015). *T. gondii* in these identified vacuoles counters the autophagocytic process by releasing proteins (MIC1, MIC3, MIC6) that bind host receptors and leads to the activation a host immune pathway (mTORC1) that suppresses autophagy (Meissner et al. 2002; Kim et al. 2011).

Pathogens can also block the autophagocytic process or use it to their benefit. While colonizing the host's small intestine, *V. cholerae* expresses multifunctional-autoprocessing repeat-in-toxin (MARTX) toxins, a component of which (alpha-beta hydrolase), blocks the autophagy pathway of host epithelial cells lining the gut (Agarwal et al. 2015a,b). *Y. pestis* is also known to survive in macrophage autophagosomes by blocking acidification of the compartment (Pujol et al. 2009). Some *S. aureus* strains survive and proliferate in autophagosomes, benefitting from triggering autophagy by blocking acidification and replicating protected inside the compartment (Schnaith et al. 2007; Mestre et al. 2010; Wang et al. 2019).

At least 70 years ago ***human immunodeficiency virus 1 (HIV-1)***, the causative agent of acquired immune deficiency syndrome (AIDS), newly descended from an expansive group of simian immunodeficiency viruses (SIVs) that have coevolved with and likely altered the immune systems of over 40 African nonhuman primate species for millions of years (Hirsch et al. 1989; Zhu et al. 1998; Gao et al. 1999; Keele et al. 2006; reviewed in Sharp and Hahn 2011). HIV-1 is a stealthy manipulator of human immunity with a famous decade-long latency period of minimal symptoms, due, in part, to the virus' multiprong control of autophagy. The virus co-opts autophagy machinery to assemble virions, with the viral protein Gag (group-specific antigen), responsible for viral matrix and capsid production, associating with the autophagosome very early in this process (Kyei et al. 2009). The virus also severely restricts the antimicrobial function of autophagy after cellular infection. Once inside a host cell, HIV-1 issues the viral protein Nef (negative regulatory factor), blocking maturation of the autophagosome by stopping specific transcription factors from translating key genes in the autophagy pathways (Campbell et al. 2015). It also expresses viral protein Vif (viral infectivity factor), which interferes with autophagy by binding to and occupying a protein (microtubule-associated proteins 1A/1B light chain 3A: L3) that is required for development and maturation of autophagosomes (Cherra et al. 2010; Borel et al. 2015).

PATTERN RECOGNITION RECEPTORS

All host cells have evolved sophisticated harm detection systems that involve cell receptors binding to molecular motifs broadly shared across pathogens (pathogen-associated molecular patterns—PAMPS, e.g., LPS from Gram-negative bacteria, glycosylphosphatidylinositol (GPI) anchors from the cell membrane of some protozoan parasites) or indicative of host damage (damage-associated molecular patterns—DAMPS, e.g., heat shock proteins; Figure 1D). These pattern-recognition receptors are critical first line of defense proteins, detecting nonself or danger (e.g., pathogens), including altered-self (e.g., cancer) and damage (e.g., heat shock proteins leaking from damaged cells; Janeway 1989; Matzinger 1994, 2002). PRRs are selective in what molecular motifs they recognize, with different receptors detecting particular PAMPS or DAMPS (e.g., TLR4-LY96: penta- and hexa-acylated LPS from Gram-negative bacteria, TLR2: peptidoglycan from Gram-positive bacteria). Major

PRR families in primates include Toll-like receptors (TLRs 1-10), NOD-like receptors—22 in humans; e.g., nucleotide-binding oligomerization domain-containing protein 1 (NOD1), NOD-like receptor protein 3 (NLRP3)—and RIG-I-like receptors—e.g., retinoic acid-induced gene I (RIG-I), cyclic GMP-AMP synthase (cGAS)—among others, that variably detect approaching or internalized/vacuolized pathogens and molecules indicative of "danger" to the host, activating immune pathways in cells in response (Chamaillard et al. 2003; Kanneganti et al. 2006; Cheng et al. 2007; Choi et al. 2009). With cell activation, immune-associated transcription factors (e.g., IRF3, IRF7, and NF-κB) translocate to the nucleus and mediate the release of a barrage of antimicrobial weaponry, including signaling proteins that are antiviral or pro/anti-inflammatory (cytokines), AMPs, chemokine proteins to trigger the migration of other immune cells to the location, programmed cell death (apoptosis), autophagy, and phagocytosis (Kell and Gale 2015; Dolasia et al. 2018). Common to these receptors is an amino acid motif central to innate immune sensing known as a leucine-rich repeat (LRR), a structure for protein recognition that predates the prokaryote-eukaryote divergence approximately 4.3 billion years ago (Kobe and Kajava 2001; Battistuzzi and Hedges 2009; Marín 2012; Yue et al. 2012). PRRs replete with LRRs and structurally related to those found in animals are known in plants, which suggests that PRRs emerged prior to the divergence of plant and metazoan life approximately 1.5 billion years ago (Wang et al. 1999; Parfrey et al. 2011; reviewed in Zipfel 2014; Meunier and Broz 2017). PRRs are sensitive sentinels that trigger immediate, powerful cell responses to pathogens and help modulate subsequent responses. Multiple pathogens credited with having strongly influenced primate evolution have evolved means to manipulate these detection systems. Here we highlight how several pathogens thought important to the human evolutionary story contend with particular PRRs.

Y. pestis (plague) uses PRRs to issue its virulence factors directly into host cells, binding to a host PRR (complement receptor 3—CR3) to inject Yops into neutrophils and halt the antibacterial activities of those cells (Merritt et al. 2015). The bacteria also disrupts PRR recognition of itself by injecting into host cells a Yop (YopJ) that interferes with a central protein in the signaling cascade (tumor necrosis factor receptor-associated factor—TRAF) of two major PRR pathways involved in the detection of *Y. pestis*—Toll-like receptor 2 (TLR2) and TLR4 pathways (Sweet et al. 2007). *Y. pestis* appears to be able to further suppress antibacterial responses via binding of bacterial protein LcrV (low-calcium response V antigen) to TLR2 and a receptor known as cluster of differentiation 14 (CD14) in a transfected cell model (human embryonic kidney 293—HEK 293), which suggests it may be able to manipulate TLR2+ CD14+ positive cells such as monocytes, macrophages, and dendritic cells in a similar way in a host (Sing et al. 2002). As highlighted above, the opening host infection strategy of *Y. pestis* is evasion of PRR detection, which allows the bacteria to escape phagocytosis. In a flea vector, the bacteria produces a LPS with six acyl chains that contributes to a strong outer membrane but is highly detectable to mammalian PRR TLR4 (and coreceptor LY96/MD2; Montminy et al. 2006; Rebeil et al. 2006; Li et al. 2013). Once the bacteria enters the approximate 37C environment of a mammalian host, it begins to replace the LPS in its cell wall with LPS that has fewer acyl chains and is less detectable to TLR4-LY96, allowing the bacteria to avoid triggering vigorous early immune responses (Montminy et al. 2006; Rebeil et al. 2006). *Y. pestis* can also squelch early proinflammatory responses via manipulation of PRRs. For example, LPS that can be detected by TLR4-LY96/MD2 and chaperone CD14 on dendritic cells has been found to trigger the production of the cytokine IL-12 (interleukin 12), which in turn stimulates the production of anti-inflammatory cytokine IL-10 in natural killer cells, a reaction that contributes to the inhibition of a sterilizing inflammation response to *Y. pestis* (Perona-Wright et al. 2009).

Many bacterial species alter cell walls to evade detection by PRRs. *Y. pestis, S. aureus, V. cholerae*, and *Escherichia coli*, for example, encapsulate their cell walls in polysaccharides in a variety of challenging host and external

environments, and these capsules limit detection and elimination of the bacteria by immune cells (Peterson et al. 1978; Du et al. 2002; Chen et al. 2007; Whitfield 2009). Pathogens can also grossly change their morphology to escape host immunity. Uropathogenic *E. coli* (UPEC), a bacteria that has coevolved with humans for at least 100,000 years and a major bacterial cause of human infectious disease mortality, undergoes large-scale physical alterations and *uses PRR detection* to do so. The bacteria is detected by PRRs TLR4 and TLR5 on the host cell membranes of a range of innate immune cells, and this detection triggers the production of sterilizing inflammation by the host (Hedges et al. 1991; Samuelsson et al. 2004; Smith et al. 2011). It also triggers a major shift in bacterial form and virulence. *E. coli* that have escaped this inflammation by entering bladder cells become filamentous in a TLR4-activation dependent manner and, thereafter, are able to resist phagocytosis by neutrophils (Justice et al. 2004, 2006; Song et al. 2007).

Multiple PRRs recognize *HIV-1* and initiate antiviral responses in the cell, and the virus has evolved multiple means of disrupting and escaping this detection at various stages of its life cycle. For example, TLR7 and TLR8, which are particularly strongly expressed inside intracellular compartments known as endosomes in white blood cells called dendritic cells (plasmacytoid), recognize the single-stranded RNA genome of infecting HIV (Diebold et al. 2004; Heil et al. 2004). One means of avoiding detection of TLR7 and TLR8 is to not enter dendritic cells or endosomes. Indeed, immunodeficiency viruses bypass some of this detection by preferentially infecting T cells and macrophages, which have lower TLR7 and TLR8 expression, or quickly entering the cytosol, which does not maintain TLR7 and TLR8 (Diebold et al. 2004; Heil et al. 2004; Yan and Lieberman 2011). There are, however, moments in the virus life cycle when it is particularly vulnerable to PRR detection and HIV has evolved multiple means of escape. To replicate, HIV must incorporate its viral genome into a host cell genome, a process that requires the production of DNA from the virus' single-stranded RNA genome and leaves the virus vulnerable to PRR detection. DNA-sensing PRRs, cytosolic GMP-AMP synthase (cGAS), and gamma interferon inducible protein 16 (IFI16) can detect HIV DNA as it is being incorporated into the host genome. HIV has evolved to partially evade this detection by two mechanisms: physically shielding the assembling DNA from detection with the virus' capsid; and keeping the genomic incorporation process tidy of extra PAMPs by triggering host cell machinery to remove excess DNA produced during this process (Unterholzner et al. 2010; Gao et al. 2013; Laguette et al. 2014). Immunodeficiency viruses have also evolved to simply destroy PRRs and downstream products of detection, and express an enzyme (e.g., HIV protease) that can cleave a PRR in cell cytoplasm that detects single-stranded RNA (RIG-I), and viral protein U (Vpu) that degrades important responding host transcription factors that modulate cell responses to infection (NF-κB and IRF3; Solis et al. 2011; Park et al. 2014; Manganaro et al. 2015).

ENZYMATIC DEFENSES AGAINST NUCLEIC ACIDS

There are hundreds of enzymatic defense mechanisms in vertebrate cells, with mutagenic and restriction enzymes being the most intensely studied in primates (Figure 1E). Enzyme modification and restriction/digestion of nucleic acids of microorganisms are among the most ancient of host cell-autonomous defense mechanisms, conserved as a tactic for over 4 billion years (Koonin et al. 2017). Shaped under continual selective pressure from viruses, genes responsible for enzymatic restriction and modification are among the most quickly evolving genes in vertebrate genomes (Randow et al. 2013; Koonin et al. 2017). Of these many enzymatic defenses, the most intensely studied comparatively in primates are APOBEC3s (apolipoprotein B mRNA editing enzyme catalytic subunit 3) and TRIMs (tripartite motif-containing proteins; Sawyer et al. 2004; Zhang and Webb 2004; Wu et al. 2013; McCarthy et al. 2015). APOBECs emerged with vertebrates approximately 630 million years ago and introduce clusters of mutations to host and viral genomes by deaminating the nucleoside cytidine

to uridine in RNA or cytosine to uracil in DNA (Caval et al. 2014; dos Reis et al. 2015; Gold et al. 2015; reviewed in Chiu and Greene 2008; Jaszczur et al. 2013). In primates these genes have rapidly expanded in number and specialization, appearing to have coevolved with a wide range of mammalian viruses (Sawyer et al. 2004; Chen and MacCarthy 2017; reviewed in Harris and Dudley 2015). By contrast, the emergence of TRIMs precedes the emergence of metazoans approximately 1.5 billion years ago (Han et al. 2011; Parfrey et al. 2011; Marín 2012; Gaya et al. 2015). The gene family has undergone considerable gene expansion in vertebrate life, with humans maintaining almost 100 *TRIM* genes that control many aspects of cell-autonomous immunity, including pattern recognition receptors, cell signaling, and autophagy, by adding the regulatory protein ubiquitin to host or viral proteins (a process known as ubiquitination; Han et al. 2011; Marín 2012; reviewed in Hatakeyama 2017). Ubiquitination by TRIMs is known to limit viruses by degrading viral capsids, turning on antiviral pathways in the host cell, mediating host cell autophagy, and modulating epigenetic silencing (reviewed in Fletcher and Towers 2013). For a pathogen entering host cell cytoplasm, enzymatic defenses are to be countered or evaded to survive. APOBECs and TRIMs are most intensely studied in the context of immunodeficiency virus infection in primates as both important limiting factors of cellular infection and as defenses readily escaped by these viruses in naïve HIV/SIV hosts.

For *immunodeficiency viruses HIV and SIV* to complete their life cycle, they must incorporate their genomes into host cell genomes via a reverse transcriptase-mediated multistage process in the host cell nucleus. HIV/SIV reverse transcriptase is vulnerable to being bound by host APOBEC proteins 3G (APOBEC3G) and 3F (APOPBEC3F) during this process, and these host proteins may then be packaged into HIV/SIV virions (Sheehy et al. 2002; Holmes et al. 2007). Within HIV virions, APOBEC3G and 3F can hypermutate the viral genome and inhibit the virus' reverse transcriptase, limiting viral replication (Bishop et al. 2008). HIV/SIVs in most hosts block these APOBECs by issuing the Vif protein, which binds the enzymes and recruits them to another enzyme complex where they are degraded (Marin et al. 2003; Stopak et al. 2003; Yu et al. 2003; Sawyer et al. 2004). Vif and APOBECs have tightly coevolved, and the ability of Vif to counter APOBEC3G, in particular, is species-specific in primates depending on their evolutionary history with immunodeficiency viruses. Vifs are best able to efficiently bind and counter APOBECs from immunodeficiency virus (IV) naïve species and usually their own host species (Bogerd et al. 2004; Compton and Emerman 2013; Etienne et al. 2015). Sooty mangabeys are natural IV hosts that are an exception to this finding, with a multiamino acid insertion in APOBEC3G conferring the ability to fully block Vif activity (Compton and Emerman 2013).

Several TRIM proteins also appear to be coevolving with a range of viruses in mammals, including TRIM25 (*influenza A*), TRIM23 (*yellow fever virus, human cytomegalovirus*), and TRIM19 (multiple viruses; Laurent-Rolle et al. 2014; reviewed in Rajsbaum and García-Sastre 2013). Primate TRIM5α has attracted attention for being in an apparent evolutionary arms race with retroviruses, including *immunodeficiency viruses* (Sayah et al. 2004; Stremlau et al. 2004). The enzyme undertakes two antiviral activities that make it a potential target for pathogen manipulation. It can activate a host cell's NF-κB pathway, triggering a range of antimicrobial responses, and its B30.2 domain can bind to the viral capsid of *HIV-1* in the cell cytoplasm and destroy its viral core (Stremlau et al. 2004; reviewed in Grütter and Luban 2012). The ability of TRIM5α to bind to a given retrovirus such as HIV-1, however, grossly differs across primate species, and hosts tend to not mount effective TRIM5α defenses against their own retroviruses. For example, human TRIM5α, although effective against various mouse and horse viruses, only weakly recognizes laboratory strains of HIV-1 that have been reared in human cells (Hatzioannou et al. 2004; Sayah et al. 2004; Stremlau et al. 2004). Owl monkeys and rhesus macaque TRIM5α strongly recognize and limit HIV-1 specifically, suggesting that TRIM5α partially determines the success of cross-species transmissions of retroviruses (Sayah et al. 2004;

Stremlau et al. 2004; Kirmaier et al. 2010; Yeh et al. 2011).

Cell Autonomous Defenses Are Quickly Diverging in Primates

As primate geographic distribution and pathogen exposure differ across species, such cell-autonomous defenses have been in evolutionary conflict with different pathogens and under differing types and degrees of selective pressure (Lambrecht 1985; Martin 2003; Nunn et al. 2004; Pandrea et al. 2007; Pozzoli et al. 2010; Wlasiuk and Nachman 2010a,b; Catão-Dias et al. 2013; Karlsson et al. 2013; Raehtz et al. 2016). As a result, primate cell-autonomous defenses have functionally diverged over evolutionary time in ways that impact the interactions of immune cells and major human pathogens, as well as the coordination of host cell responses (see Table 2). For example, there is emerging evidence that the regulation of *phagocytosis* is diverging in primates. Sialic acids, glycoproteins on the surface of every cell in the body, assist in regulating phagocytosis and are expressed differently on human and chimpanzee macrophages in a manner (Neu5Gc- versus Neu5Gc+) that appears to affect the rate of phagocytosis and phagosomal killing of bacteria in these species (Meesmann et al. 2010; Okerblom et al. 2017). Phagocytosis is also regulated by a multitude of cell receptors, several of which are known to be undergoing evolutionary alterations in primates. CEACAM3 (carcinoembryonic antigen-related cell adhesion molecule 3), a phagocytic receptor on granulocyte white blood cells (e.g., neutrophils, eosinophils, basophils) is a decoy receptor for pathogenic bacteria that is very quickly diverging between humans and gorillas at amino acid sites important for binding bacteria ahead of phagocytosis (Schmitter et al. 2004; Adrian et al. 2019). Multiple *pattern recognition receptors* can also trigger the phagocytic process. The genes of several TLRs that can act as phagocytic receptors (*TLR1*, *TLR4*, and *TLR6*) have been found to be under positive selection in primates, as well as human populations (*TLR1, TLR6*, and *TLR10*) suggesting functional change in microbial sensing capabilities, which also determine initiation of phagocytosis (Nakajima et al. 2008; Barreiro et al. 2009; Wlasiuk and Nachman 2010a; Quach et al. 2013; Laayouni et al. 2014). At least one study has connected these alterations in TLR1, TLR6, and TLR10 sequence in humans to differences in peripheral blood mononuclear cell gene and cytokine expression to bacterial exposure (heat-killed *Y. pestis*; Laayouni et al. 2014).

PRRs have been intensely studied for functional differences across primates. The receptors have even been examined for evidence of ancient hominin interbreeding. Neanderthal and Denisovan haplotypes of the *TLR-6-1-10* thought to reduce *Helicobacter pylori* bacterial infection susceptibility have been found in the 22 non-African populations representing peoples from various locations in Central America, Europe, and Asia (Dannemann et al. 2016). Similarly RIG-I-like receptors RIG-I and IFIH1 (interferon-induced helicase C domain-containing protein 1), intracellular PRRs that detect viral RNA, have multiple codons under positive selection in mammals as do the cytoplasm resident NOD-like receptors (NLRs) that recognize bacteria, viruses, and fungi (Kong et al. 2011; Lemos de Matos et al. 2013; Cagliani et al. 2014; Fitzgerald et al. 2014). Multiple functional studies have also highlighted strong differences in early cytokine and genomic responses to TLR-detected bacterial and viral molecules (i.e., LPS, lipomannan from *Mycobacterium smegmatis*, single-stranded RNA mimetics) between primate species such that they may affect disease susceptibility (Mandl et al. 2008; Barreiro et al. 2010; Brinkworth et al. 2012). In humans, genetic variants of TLRs and NLRs (*TLR1*, *TLR9*, and *NOD2*) have been associated with differing susceptibility to mycobacterial infection (tuberculosis, leprosy; Austin et al. 2008; Berrington et al. 2010; Wong et al. 2010; Hart and Tapping 2012; Kobayashi et al. 2012; Pan et al. 2012).

Sometimes stimulated by PRR recognition, *autophagy* is functionally diverging in mammals and primates as well (Capela et al. 2016). The process has coevolved with life span, and is more strongly induced in longer-lived mammals and humans (centenarians; Pride et al. 2015; Triplett et al. 2015; Dammann 2017; Xiao et al. 2018). Variation in autophagy induction is a factor in infectious disease resistance, with sequence variations in autophagy-related genes

(*NOD2, PARK2,* and *ATG16L1*) associated with increased risk of particular *Mycobacterium* infections in humans, for example (Capela et al. 2016). Enzymes TRIM5α and TRIM23 act as autophagy receptors, assisting in autophagosomal degradation of retroviruses and DNA viruses (e.g., herpes simplex virus), and are rapidly evolving in primates (Sawyer et al. 2005; Ortiz et al. 2009; Poole et al. 2009; Han et al. 2011; Marín 2012; Laurent-Rolle et al. 2014; Mandell et al. 2014; Sparrer et al. 2017). Overall, as a group of *enzymatic defenses*, *TRIM* genes are rapidly diversifying in primates. Of the approximate 100 *TRIM* genes identified, seven have emerged with humans, 11 are specific to humans and African apes, and copy numbers of these genes are variable in human populations (Han et al. 2011). There appear to be functional ramifications to these genetic changes. For example, TRIM5α also exhibits species-specific ability to recognize and degrade viral capsids, while alterations in transcription factor-binding sites associated with TRIM23 in humans suggests this gene modulates antiviral signaling differently in our species than in other primates (Sawyer et al. 2005; Ortiz et al. 2009; Nakayama and Shioda 2012; He et al. 2016). Such rapid evolution has been traditionally credited to conflict with ancient viruses, and has been noted in APOBEC genes as well. *APOBEC3* genes have expanded considerably in primates, and all seven paralogs appear to be are under positive selection (Sawyer et al. 2004; reviewed in Harris and Dudley 2015). Both *APOBEC3G* and *APOBEC3H*, for instance, have been found to be under intense positive selection in primates at amino acid sites that directly interact with HIV/SIV Vif protein (Sawyer et al. 2004; Ortiz et al. 2006, 2009).

Antimicrobial peptides are also rapidly diversifying in primates and mammals, generally, with species showing great diversity in cathelicidin and defensin genetic sequence, gene number, and copy number (Maxwell et al. 2003; Patil et al. 2004; Das et al. 2010). Humans and other catarrhine primates maintain a single cathelicidin, however, human-specific divergence in the function of that peptide is suggested by the high levels our species must express compared to animals that have larger cathelicidin repertoires to achieve the same direct antimicrobial effects (Zelezetsky et al. 2006; Blodkamp et al. 2016). Similarly, defensins are also quickly diversifying in primates, with α-defensins undergoing birth and death evolution, and β-defensins expanding in number prior to the divergence of platyrrhine and catarrhine primates (Maxwell et al. 2003; Semple et al. 2003; Das et al. 2010). Although θ-defensins in model catarrhine monkeys, such as rhesus macaques, appear to be engaged in staunch antiviral and antibacterial activity, the function of these peptides halts in the hominoid lineage (Tang et al. 1999; Seidel et al. 2010). There is a stark abruption in θ-defensin expression in primates after the divergence of the human and orangutan lineages, with the former lineage having acquired a premature stop codon in the gene (Nguyen et al. 2003). Attempts to synthetically generate the human version of θ-defensin or suppress the human early stop codon have shown that an expressed protein very effectively inhibits HIV-1 cellular infection, suggesting that divergence of AMPs in primates may help explain interspecies differences in disease manifestation (Munk et al. 2003; Venkataraman et al. 2009).

The Ubiquity of Cell-Autonomous Defenses Means Nonimmune Cells Have Immune Traits

Cell-autonomous defenses have been maintained in multicellular life for millennia because all cells are potential microbial targets and conduits for infections that limit reproductive fitness (Randow et al. 2013; Gaudet et al. 2016). Under ubiquitous pathogen pressure, cell-autonomous immune tactics have remained "hardwired" and varied in all cell types, making immunity and pathogen manipulations of it important considerations in the assessment of evolution and variation of all human physiological systems. The pathogens typically considered historically important in shaping the human genome manipulate the cell-autonomous defenses of both professional immune cells and nonimmune cells. There is increasing evidence that cells in physiological systems that are central to classic questions in human evolutionary biology (e.g., evolution of the human brain, human locomotion, human skeletal biology, skin color variation) have

TABLE 2
Examples of cell-autonomous defenses that are diverging in primates

Defense tactic	Mechanism	Function	Species	Difference	Time since divergence (mya)	References
Phagocytosis	Sialic acid Neu5Gc	Modulates phagocytosis/ phagosomal killing	Humans versus chimpanzees	Absence in humans enhances phagocytosis/phagosomal killing	~2–6 mya	Meesmann et al. (2010); Schrago and Voloch (2013); Okerblom et al. (2017)
	CEACAM3 (receptor)	Triggers phagocytosis, white blood cell decoy receptor for bacteria	Humans and chimpanzees versus gorillas, rhesus macaques	Site substitutions in humans/ chimps allow binding to important bacterial pathogens	~9 mya	Schmitter et al. (2004); Roth et al. (2013); Schrago and Voloch (2013); Adrian et al. (2019)
	TLR1, TLR4, TLR6	Triggers phagocytosis	Across major primate clades, within humans	Under positive selection	~	Barreiro et al. (2009); Wlasiuk and Nachman (2010a); Quach et al. (2013)
PRRs	TLR1, TLR6, TLR10	Detection of microbial threats	Human Eurasian populations	Ancient hominin sequences in Eurasian genomes, possible alteration bacterial detection	~0.05 mya	Sankararaman et al. (2012); Dannemann et al. (2016)
	TLR7, TLR9	Detection of immunodeficiency viruses (IV)	IV natural host sooty mangabey versus naïve host rhesus macaque	Lowered IFN responses/less overt responses to IV infection in sooty mangabeys	13.8 mya	Mandl et al. (2008); Schrago and Voloch (2013)
	TLR4	Detection of Gram-negative bacterial molecules (LPS)	Human and rhesus macaque versus chimp	Strong differences in monocyte antibacterial and antiviral gene pathway responses	6 mya	Barreiro et al. (2010); Schrago and Voloch (2013)
	TLR4	Detection of Gram-negative bacterial molecules (LPS)	Human and chimp versus olive baboon	Strong differences in total blood leukocyte cytokine responses	~29 mya	Brinkworth et al. (2012); Schrago and Voloch (2013)
	RIG-I and IFIH1	Viral RNA detection	Mammals	Diverging under positive selection	-	Lemos de Matos et al. (2013); Cagliani et al. (2014); Fitzgerald et al. (2014)
	Multiple NOD-like receptors (NLRs)	Bacteria, viruses, and fungi detection in cytoplasm, modulation of inflammation	Mammals, human populations	Diverging under positive selection. Associated with differing *Mycobacterium* susceptibility in humans	-	Austin et al. (2008); Berrington et al. (2010); Kong et al. (2011); Pan et al. (2012); Vasseur et al. (2012)

Autophagy	NOD2, PARK2, ATG16L1	Autophagic pathway regulation	Human populations	Variants associated with differing *Mycobacterium* susceptibility in humans	-	Capela et al. (2016)
	TRIM5α, TRIM23	Autophagosomal receptor, assists in viral degradation	Primates and mammals	Rapid recurrent positive selection at binding sites, particularly strong in humans (*TRIM5α*)	~2–6 mya (*TRIM5α*, human lineage)	Sawyer et al. (2005); Ortiz et al. (2009); Han et al. (2011); Marín (2012); Schrago and Voloch (2013); Mandell et al. (2014)
Enzymatic defenses	TRIMs	Antimicrobial enzymes	Primates	Rapid diversification: 11/~100 genes emerged in African apes, 7/~100 in humans alone	~2–~9 mya	Han et al. (2011); Schrago and Voloch (2013)
	TRIM5α	Antimicrobial enzyme that degrades viral capsids	Primates	Rapid diversification, species-specific recognition and degradation of viral capsids	-	Sawyer et al. (2005); Ortiz et al. (2009); Nakayama and Shioda (2012)
	TRIM23	Antimicrobial enzyme that degrades viruses by modulating antiviral cascades	Humans versus other primates	Rapid evolution of transcription factor-binding sites around DNase I hypersensitive sites associated with TRIM23 regulation	~ 6 mya?	Schrago and Voloch (2013); He et al. (2016)
	APOBEC3 (G and F) genes	Hypermutate the viral genome and inhibit the virus' reverse transcriptase	Primates	Diversifying rapid evolution at amino acid sites that interact with HIV/SIV Vif protein	-	Sawyer et al. (2004); Ortiz et al. (2006, 2009)
AMPs	Cathelicidin	Proteolytic against bacterial membranes	Human/catarrhine primates versus other primates	Alterations in expression that correspond with comparatively low number of genes in humans/catarrhines	~29 mya	Zelezetsky et al. (2006); Schrago and Voloch (2013); Blodkamp et al. (2016)
	α-defensin β-defensin	Disintregrating bacterial membranes, cell trafficking, controlling cell death, and regulating host immune cells	Haplorrhine primates	Expansion	~60 mya	Maxwell et al. (2003); Semple et al. (2003); Das et al. (2010); Schrago and Voloch (2013)
	θ-defensins	Antiviral and antibacterial activity	Human versus other catarrhines	Not expressed in humans	~29 mya	Nguyen et al. (2003); Schrago and Voloch (2013)

Mya = millions of years.

likely been directly shaped by pathogens. For example, the cells at the center of human cognition—neurons and astrocytes—transmit and regulate electrical impulses in the nervous system. They use tactics such as autophagy to control viral infections (xenophagy), maintain many receptors for pathogen recognition (pattern recognition receptors) that detect pathogens and host damage, are capable of phagocytosis (astrocytes) and express Fc receptors regulating the process, and issue neuropeptides with antimicrobial properties (Cameron et al. 2007; Liu et al. 2010; Okun et al. 2010; Orvedahl et al. 2010; Augustyniak et al. 2012; Yordy et al. 2012; Chiu et al. 2013; Chung et al. 2013). Pathogen and environmental interactions with such immune tactics are known to affect human behavior and vice versa (Dantzer and Kelley 1989; Chiu et al. 2013; Liu et al. 2014; Stock et al. 2017). Similarly, cells important to understanding bone structure and metabolism, osteocytes, and their progenitor osteoblasts maintain pattern recognition receptors, antimicrobial peptides, and the ability to phagocytize bacteria (Hudson et al. 1995; Varoga et al. 2009; Josse et al. 2015; Alonso-Pérez et al. 2018). *These kinds of immune traits appear again and again across body systems* that are either of heavy focus in human evolutionary biology (e.g., skin color variation, reproductive organ variation, differential metabolism) or may shape data collection in comparative human studies (e.g., desalination and cytokines in urine; Monks et al. 2005; Ichimura et al. 2008; Murase et al. 2013; Guerriero et al. 2014; Kiziltas 2016; Zhou et al. 2016; Penberthy et al. 2018). Understanding how cell-autonomous defense tactics have coevolved with pathogens can be very important to understanding grander questions of human evolutionary biology.

. . .and the Immune Traits of Cells in "Nonimmune" Body Systems Are Also Diverging in Primates

To illustrate that these tactics have diverged in primate "nonimmune" body systems we offer here a very basic pairwise contrast of two tissues generally considered to not be professional immune tissues in primates, the brain and liver, from humans and rhesus macaque. Briefly, we contrasted the whole genome gene expression of brain and liver tissue samples isolated from humans and rhesus macaques at a physiological baseline using transcriptomes from a single study published on the Genome Omnibus Expression database (GSE50782). Orthologous genes (14,369) filtered to remove lowly expressed genes from the tissues were contrasted by type between species, with 8257 (liver) and 10,202 (brain) genes found to be differentially expressed (DE; fold change >20% and Benjamini-Hochberg fdr<0.05; Supplemental Table 1, available at https://doi.org/10.1086/710389). Interspecies DE genes were analyzed for genetic pathway enrichment (overrepresentation analysis, Enrichr; Kuleshov et al. 2016; Figure 3; Supplemental Table 2, available at https://doi.org/10.1086/710389). Of the top 25 most significantly enriched genetic pathways—Kyoto Encyclopedia of Genes and Genomes (KEGG) 2019 human database—in the human liver-macaque liver, and human brain-macaque brain DE gene lists, approximately 28% were cell-autonomous defenses or defense related, including pathways associated with phagocytosis and autophagy (Fc-γ R-mediated phagocytosis, autophagy, endocytosis, lysosome, mitophagy, regulation of actin cytoskeleton, focal adhesion), reactive oxygen species (peroxisome), and enzyme restriction (ubiquitin-mediated proteolysis; fdr <0.05). Phagocytosis-related pathways feature prominently in the top 5 overrepresented pathways of each tissue contrast (40% liver top 5, 60% brain top 5; Supplemental Table 2). This snapshot analysis highlights the potential of the evolution of cell-autonomous defenses to influence the operation of physiological systems outside of immunity and suggests that pathogen-mediated selection could be a consideration of the evolutionary biology of "nonimmune" systems.

Cell-Autonomous Immunity Provides New Ways of Thinking About the Human Evolutionary Story

Cell-autonomous defenses are extremely important to host survival. They have been maintained over millions and billions of years, rapidly coevolving with the microorganisms that exploited our prokaryotic and

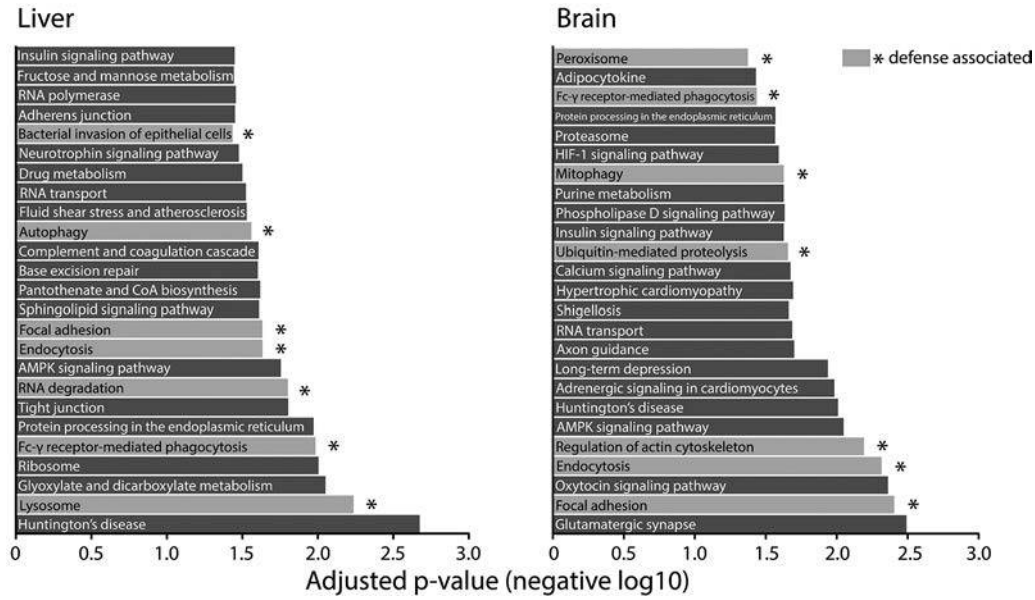


Figure 3. Cell-Autonomous Defenses in Nonimmune Tissues Have Diverged Between Closely Related Primates

Approximately 28% of the 25 KEGG pathways most significantly overrepresented in the significantly differentially expressed genes between human and rhesus macaque liver and brain transcriptomes are cell-autonomous defenses, with multiple pathways associated with phagocytosis occurring in the top 5 overrepresented pathways. See the online edition for a color version of this figure.

single-celled ancestors, and continuing to diversify under the pressure of the great pathogens of human history in recent millennia. This antiquity provides an opportunity to more formerly broaden the way in which human evolutionary studies address the human evolutionary story. Cell-autonomous defenses demonstrate that we, as a species, are connected to a prokaryotic and single-celled life past that is relevant if not decisive in the most frequent environmental interactions we have—microbial. In this sense, microbial conflicts that precede the emergence of humans, primates, and even multicellular life are intrinsic to questions of the evolution of human immune function. For human evolutionary biologists, using outputs such as immune cell transcriptomics or cytokine expression as biological markers to better understand human evolution or variation, the chronological window for interpreting the functional meaning of these outputs is actually millions to billions of years wide.

Importantly, *the ubiquity of these defenses blurs definitions of immune and nonimmune systems.* Since cell-autonomous defenses are hardwired into each cell, and each cell interacts with pathogens known and unknown, every physiological system bears the mark of direct past pathogen interactions. For decades, it has been understood that microorganisms and cell-autonomous immune responses to them alter human behavior and vice versa (Dantzer and Kelley 1989; Chiu et al. 2013; Liu et al. 2014; Stock et al. 2017; Del Giudice 2019). Incorporation of the same biological relationships between pathogens, cell-autonomous defenses, and body system X extended to other physiological systems or traits at the center of the classic questions of human evolutionary biology (e.g., why does skin color vary in humans, why do primate placentae vary in shape and size, how did human bipedal locomotion evolve, how does primate bone and dental microstructure vary) can enrich and improve our understanding of why such features evolved (Robbins and Bakardjiev 2012). Explorations of how the pathogens thought to have had the most profound effect on human evolution have potentially

altered human cell biology and have shown that nonimmune cells have been evolutionarily impacted at molecular and immunological levels (e.g., gut: *V. cholerae*, bladder: UPEC; Karlsson et al. 2013; reviewed in Terlizzi et al. 2017). For this kind of information to contribute to a better understanding of the gross features of human evolution, however, requires researchers in this area to increase integration of molecular and morphological methods or findings in human evolutionary studies. Importantly, it requires a radical shift in how researchers in human evolutionary studies frame the emergence of our species—from the descendent of the bipedal ape that arises in an African woodland at the end of the Miocene to a life form with a history much more ancient, whose life and death is heavily dependent on mechanisms that arose before the emergence of primates, or mammals, or multicellular life. It requires acknowledgement that in the human evolutionary story, we are a bipedal ape with a rich intergenerational backstory of past and ongoing conflict with microorganisms that have exploited every type of cell in every body system for eons. As our ancient immune mechanisms honed by this attempted exploitation over time are integrated into every other aspect of human physiology, any examination of human evolutionary biology, regardless of physiological system and when possible, should consider autonomous immunity of the cells in that system and how microorganisms have shaped them.

Materials and Methods

Data sharing is not applicable to this article as no new data were created or analyzed in this study. All genomic sequences were previously published and the Gene Expression Omnibus database accession numbers are provided here.

RNA-seq mapping and differential expression analysis

RNA-seq data was downloaded from the Gene Expression Omnibus database (GSE50782; human brain: SRR976225, SRR976227, SRR976228, SRR976229, SRR976230; human liver: SRR976238, SRR976241, SRR976242, SRR976243, SRR976244; rhesus macaque brain: SRR976250, SRR976251, SRR976252, SRR976253, SRR976254; and rhesus macaque liver: SRR976264, SRR976265, SRR976266, SRR976267, SRR976268). RNA isolation, library preparation (Illumina NlaIII DGE) for this data was completed in batches by tissue, with species randomized in library preparation and sequencing on Illumina Genome Analyzer II. Reads were mapped to species-specific references genomes (GRCh38.96, Mmul8.0.1.96, GRCm38.96) using STAR aligner 2.7.0. (Dobin et al. 2013). Counts per gene for all samples were generated using featurecounts in the Subread 1.6.3 package (Liao et al. 2013). Gene orthology was assessed using Ensembl Genes 96 and orthologs identified via the biomaRt package in the R environment (Durinck et al. 2009; Zerbino et al. 2018). Gene expression was normalized by counts per million using edgeR, with genes filtered such that 20% of the total samples had >1 cpm (Robinson et al. 2010). Differential expression (DE) was calculated using DESeq2, and assessed as minimum 20% fold change in expression at a false discovery rate (fdr) or 10% or less (Love et al. 2014).

Overrepresentation analysis

Genes that were found to be significantly DE by tissue between species were submitted to the Enrichr database for overrepresentation analysis and graphs developed using a combination of Prism and R (Kuleshov et al. 2016).

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