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Abstract The human immune system is under great pathogen-mediated selective pressure. A combination of divergent infectious disease pathogenesis across human populations, and the overrepresentation of "immune genes" in genomic regions with signatures of positive selection suggests that pathogens have significantly altered the human genome. However, important features of the human immune system can confound searches for and interpretations of signatures of pathogen-mediated evolution. Immune system redundancy, immune gene

pleiotropy, host ability to acquire immunity and alter the immune repertoire of their offspring through “priming”, and host microbiome complicate evolutionary interpretations of host-pathogen interactions. The overall promiscuity and sensitivity of the immune system to local environments can also muddy assumptions about the origins of a selective pressure on a given set of genes. This review addresses how features of the immune system, the primary buffer between a pathogen and the human genome, affect evolutionary signal. Here, considerations that must be made when assessing how pathogens have contributed to human diversification are addressed.

Introduction

The human immune system is a complex and highly physiologically infiltrative organization of proteins, cells, tissues and organs that serves as the main interface between ourselves and the outside world. As such, it is under tremendous selective pressure mediated by pathogens and other micro-organisms (Barreiro and Quintana-Murci 2010; Filip and Mundy 2004; Fumagalli et al. 2011; Nakajima et al. 2008; Nedelec et al. 2016; Novembre and Han 2012; Sawyer et al. 2005). Genome-wide scans for evidence of natural selection in humans and other species have repeatedly found that immune genes are overrepresented in groups of genes associated with signatures of selection (Andersen et al. 2012; Cagan et al. 2016; Kosiol et al. 2008; Pickrell et al. 2009; Sabeti et al. 2006; Voight et al. 2006). Importantly, humans exhibit highly divergent clinical manifestations of disease between populations, suggesting that the immune system is diversifying within the species (Culhane et al. 2002; Dabelea et al. 2014; Feldman et al. 2013; Gelfand et al. 2005; Genovese et al. 2010; Haldane 1949; Karlsson et al. 2013; Nedelec et al. 2016; Richardson et al. 2016; Rubio-Tapia et al. 2012; Williams 2006). In the nearly 70 years since J.B.S. Haldane suggested that a microorganism may have strongly influenced the geographic distribution of human traits, distinct population level changes in immune genetic sequences have been paired with differences in immune responses to multiple major human pathogens (Dean et al. 1996; Haldane 1949; Johnson et al. 2007; Karlsson et al. 2013; Maier et al. 2003; Ogus et al. 2004; Stephens et al. 1998). Host-pathogen conflicts, therefore, have played an important role in the evolution of humans.

Given the strong evidence that pathogens have shaped the human genome, it is, perhaps, not surprising that human immune system evolution has, traditionally, been framed in precisely this way – pathogen-mediated selection on the genome that affects immune function. However,

some attributes of the human immune system can confound pathogen-mediated evolutionary signal. A host response to a pathogen involves a combination of strong and subtle expression alterations in many genes, as well as interactions between host and pathogen gene networks and the recruitment of circulating immune components (Schulze et al. 2015; Tierney et al. 2012). Very standard and powerful approaches for assessing pathogen-mediated diversification of the human genome, including highlighting genes physically proximal to a signature of selection, rely heavily on the definition of genes as "immune genes" (Deschamps et al. 2016; Prugnolle et al. 2005). A healthy dose of agnosticism about gene function, however, is important in the assessment of pathogen-mediated selection on the human genome as host-pathogen conflicts are complex, and immune system function is cross-referenced in other physiological systems and can be difficult to define. Importantly, pathogens can be limited by a broad range of host genes, the primary function of which are not immediately identifiable as immune defense (Hill et al. 1991; Sim et al. 1994; Verrelli et al. 2002). Moreover, human immune responses to pathogens are regulated by complex, multi-purpose and redundant gene networks, influenced by both evolutionary history and the multi-generational life experience of a population (Boscolo et al. 2012; Dopico et al. 2015; Hanson et al. 2003; Rose et al. 2016). All of these factors complicate searches for and interpretations of genomic signatures of pathogen-mediated adaptation in the human genome. This review addresses considerations that must be made when interpreting evolutionary interactions between pathogens and the human genome, given the complex nature of host-pathogen conflict and human immunity.

Infectious Diseases Have Shaped the Human Genome

Pathogens represent a tremendous burden on the reproductive fitness of humans, and are

a major selective force in the evolution of our species (Fumagalli et al. 2011; Hill 2012; Soto et al. 2010). In the nearly seven decades since J.B.S. Haldane first suggested that the occurrence of malaria may have influenced the frequency of thalassemias, the pathogenesis of multiple infectious diseases have been found to be affected by diversified genetic loci in human populations (Dean et al. 1996; Frodsham et al. 2006; Haldane 1949; Johnson et al. 2007; Karlsson et al. 2013; Maier et al. 2003; Ogus et al. 2004; Stephens et al. 1998; Thomas et al. 2009) (See Table 1). Since anatomically modern humans emerged over 200 000 years ago, the species has undergone major behavioural shifts that have altered their exposure to infectious pathogens(White et al. 2003). Our species' wanderlust and subsequent distribution across the globe has meant that humans have been subject to regionally-specific pathogens. While attempts to quantify the impact of local pathogen-mediated selection have had to rely on biased and incomplete recent records of detected pathogens to reconstruct a past pathogen-scape, innovative combinations of historical, immune function and selection data provide some evidence that particular broad types of micro-organisms have strongly affected regional genomic diversification and the health of humans (Cagliani et al. 2013; Fumagalli et al. 2010; Fumagalli et al. 2009; Fumagalli et al. 2011; Laayouni et al. 2014). Technological and economic innovation, including the adoption of agricultural economies and animal domestication approximately 10 000 years ago and heightening of trans-national migration and trade in the last 2500 years, has profoundly affected the pathogen exposure of humans as well. With these behavioural changes, human populations experience increases in size and continuity, consumption and physical association with animals and exposure to novel zoonotic pathogens including measles (rinderpest), smallpox and influenzas [reviewed in (Harper and Armelagos 2010; Harper and Armelagos 2013)]. Moreover, with the adoption of agricultural and animal

domestication practices, humans have committed *willful* changes to their environment such as the clearance of forested regions and alterations in irrigation that improve disease vector access to hosts. Human contact with *Plasmodium* (malaria), and *Trypanosoma* (sleeping sickness), which appear to have altered the coding regions of multiple genes such as *HBB, GYPA, GYPC* and *APOL1*, are thought to have increased in just such this manner (Baum et al. 2002; Genovese et al. 2010; Kwiatkowski 2005; Tishkoff et al. 2001; Wilder et al. 2009).

With the intensification of trans-national migration and trade over the last several hundred years, novel virulent pathogens emerged and distributed to new populations, helped along by the density and traffic of hosts in and out of urban centers. Indeed, pathogens at the center of some the deadliest pandemics in human history have been distributed to naïve populations via trade and military routes, including *Yersinia pestis* (plague), 1918 influenza, *Vibrio cholerae* (cholera), *Treponema palladium* (syphilis) and human immunodeficiency virus (Byerly 2010; Faria et al. 2014; Harper et al. 2011; Morelli et al. 2010)[reviewed in (Koch 2014)]. The genomic impact of these recently emerged diseases is thought to be significant. As an example, *Yersinia pestis* (plague) is estimated to have killed 30-50% of the European population during the first five years of its second pandemic (1345- 1876) (Benedictow 2004; Cohn 2008; Gage and Kosoy 2005). Several studies of human molecular evolution and disease modeling have implicated the second plague pandemic in the uneven distribution of human immune alleles, including polymorphisms in the bacteria-detecting gene cluster *TLR 1/6/10* and associated changes in peripheral blood mononuclear cell (PBMCs) cytokine responses to heat-inactivated *Y. pestis* (Laayouni et al. 2014; Mukherjee et al. 2014). Alleles that may confer plague infection resistance and are found in high frequency in plague-affected regions have also been highlighted as potentially the outcome of plague-mediated selection including alleles in

genes associated with hereditary hemochromatosis (*HFE, C282Y, H63D*) and the H red blood cell antigen (type O blood group) [reviewed in (Anstee 2010)] (Moalem et al. 2002). Further research is needed as, as yet, these alterations have not been tested for conferring a different host response to plague.

Genomic Changes Are the Outcome of Pathogens Matching Multiple Host Defenses for Successful Infection

The types of interactions that vertebrate hosts and microbial organisms may have are highly variable. Host-pathogen interactions, however, tend to be characterized by the occurrence or attempted avoidance of conflict. Much of our understanding of host-pathogen co-evolution is based on this notion of an ongoing war between host and pathogen in which the stakes are host bodily integrity and protection from non-self, and the pathogen's need for resources to replicate (Casadevall and Pirofski 1999). This image of battle is helped along by the ample tissue destruction often noted in symptomatic infections. One of the models of coevolution most frequently applied to host-pathogen interactions, the Red Queen Hypothesis (RQH), outlines the relationship between two closely associated species as one of intense competition or antagonism and speedy co-evolution, such that changes in one species produce a threat of survival to the other (Hamilton 1980; Van Valen 1973). Indeed, pathogens can restrict the reproductive fitness of a host and lead to quick changes in species phenotypes (Genovese et al. 2010; Ko et al. 2013; Thomson et al. 2014; Vilcinskas 2016).

Central to how host-pathogen conflict leads to genome diversification is natural selection – a process wherein phenotypes and related genetic variants that are beneficial to reproductive fitness will increase in frequency in a population, while deleterious variants will decrease. For

long-lived species, with lengthy reproductive trajectories and complex immune systems, such as humans, conflict-mediated phenotypic changes are assumed to occur more slowly than in the shorter-lived pathogen, whose replicative success relies on surviving a myriad of immune assaults and is, therefore, under much stronger selective pressure. The nature of this asymmetrical conflict is complex, occurring at multiple loci across the host genome with every interaction. This multi-locus conflict plays out through the well noted tendency of detected pathogens to set off a series of immune alarms in humans via sensing that redundantly triggers particular inflammasome pathways (i.e. NFKB) (Hagar et al. 2013; Hayashi et al. 2001; Kaparakis et al. 2010; Karlsson et al. 2013; Kayagaki et al. 2013; Kofoed and Vance 2011; Poltorak et al. 1998; Shimazu et al. 1999; Takeuchi et al. 1999; Zhao et al. 2011). Disease manifestation and resulting reduction in fitness in humans can, therefore, be thought of as the outcome of a pathogen's ability to "match" the host response at multiple loci on an allele by allele basis, and to "unlock" and escape immune defense by such "matching" (matching allele model) (Frank 1993; Frank 1994; Klein and O'Huigin 1994). Under this rubric, the success of cancer causing Kaposi Sarcoma associated Herpes Virus (KSHV), for example, in a human host is due to the virus' production of B cell lymphoma 1 protein (Bcl-2), which subsequently interacts with the human protein required to generate a common immune defense against viruses, autophagosomes (Atg6/Beclin-1), halting macroautophagy of the cell. This interaction allows the pathogen to escape destruction and subsequent MHC class I presentation (English et al. 2009; Pattingre et al. 2005). The resulting genomic signatures of host-pathogen conflict that arise in our species are, in part, dependent on how equally matched the host immune system is to the strategies of the pathogen in interactions just like this.

Genomic Hallmarks of Pathogen-mediated Adaptations in Humans

There are a number of broadly accepted genomic hallmarks of host-pathogen conflict and subsequent host strategies to adapt to pathogen pressure (Table 2). Human strategies to cope with pathogen conflict generally fall into one of three partially overlapping categories of immune tactics: prevention (i.e. barriers, mucosa, transgenerational priming, adaptive immunity, behavioural immune system), recognition (i.e. non-self detection, receptor variation, antigen presentation, opsonization) and elimination (i.e. pore-forming proteins, cytotoxic effector cells, humoural responses, phagocytosis, apoptosis, inflammation). At the resolution of the genome these classic hallmarks of host-pathogen conflict can be detected near genes that directly or indirectly influence the efficacy of these strategies. Most famously, signatures of natural selection near "immune genes", such as pattern recognition receptors, of various human populations have been cited as evidence of interactions between humans and a range of pathogenic bacteria (Barreiro et al. 2009; Karlsson et al. 2013; Laayouni et al. 2014; Zhernakova et al. 2010) [methods reviewed in (Karlsson et al. 2014). Similarly, changes in coding regions that confer differences in protein binding sites or gross structure of a protein product known to interact with a pathogen are often considered adaptive outcomes of host-pathogen interactions. A 32 base pair deletion in the coding region of cc-motif chemokine receptor 5 (CCR5) that eliminates both its signaling domain and much of its extracellular domain, subsequently halting HIV-1 cellular infection, has been proposed to have risen in frequency in European populations due to a selective sweep hundreds of years ago by a prior pathogen (Galvani and Slatkin 2003). Expansions and narrowing of immune gene families and, more broadly, gene copy number variation of immune genes are often interpreted as gene replication and deletion events that are maintained because they are evolutionarily advantageous in the face of particular pathogens

(Grunhage et al. 2010; Hardwick et al. 2012; Krementsov et al. 2017; Polley et al. 2015). Increased copy number variation for the gene encoding salivary agglutinin in humans, for example, has recently been proposed as a response to an increased exposure to cariogenic bacteria with the adoption of agricultural-based diets (Polley et al. 2015). Inter-population differences in gene responses during cellular infection have been cited as evidence of pathogen-mediated change in humans (Nedelec et al. 2016; Pai et al. 2016). Grand alterations in genomic structure may also be indicative of host-pathogen conflict. There is evidence, for example, that chronic infection can lead to heritable shortening of telomere length (Asghar et al. 2015). The incorporation of retroviral nucleic acids into the human genome is also a hallmark of prior conflict, but also seems to confer phenotypic change in the host. Such sequences represent approximately 8% of the human genome sequence, and may have altered the physiology of the human placenta (Bannert and Kurth 2006; Dunlap et al. 2006). While these genomic signatures suggest pathogen-mediated change in immune function, their actual impact on immune phenotype is not straightforward. Host genetic factors are thought to explain perhaps 20-40% of the immune variation witnessed between populations. The remaining variation is likely the outcome of intrinsic factors (Liston et al. 2016). Any interpretation of a potential host-pathogen conflict that has contributed to genome change is deeply complicated by the plasticity, complexity and physiological promiscuity of the human immune system.

Phenotypes without a Genotype: How Immunity Affects Pathogens-mediated Change in Human Genomes

Between a pathogen exerting selective pressure on a population and the human genome stands highly plastic immune phenotypes. Pathogen-mediated selection tends to be described in

terms of an infectious disease exerting selective pressure on a human population and a subsequent increased frequency of beneficial alleles present via *standing genetic variation* (Cagliani and Sironi 2013; Fumagalli et al. 2011; Karlsson et al. 2014; Laayouni et al. 2014). However, several extremely important mechanisms of human immunity confer heritable phenotypes that are not DNA encoded or marked but can still alter the impact a pathogen might have on a species' genome. Such phenotypes are heavily influenced by environment and parental experience, and include acquired immunity from prior infections (and associated herd immunity) and trans-generational immune priming of offspring by parents for infections to which parents and grandparents have been exposed (i.e. transmission immunoglobulins across the placenta or via breast milk) [reviewed in (Hasselquist and Nilsson 2009)]. Variations in these mechanisms can be thought of as ***standing non-genetic variation.*** They are phenotypes without genotypes – they typically are not encoded and, if epigenetically marked, they are marked at a single cell level. These immune variations are tailored to microorganisms present in local environments and can protect otherwise vulnerable young offspring from virulent pathogens (Gasparini et al. 2001; Grindstaff et al. 2006). As such, these immune phenotypes can have a profound effect on how an infectious pathogen might reduce the reproductive fitness of individuals in a population. Acquired immunity to a prior pandemic influenza, for example, has been postulated to have significantly altered the mortality curve of the most severe infectious disease pandemic in recorded history, the 1918 influenza (Johnson and Mueller 2002). Along with typical "flu" victims, such as infants and the elderly, the 1918 influenza mainly killed healthy young adults. Reviews of contemporary medical reports suggest that most of these young people shared two characteristics 1) they died of secondary pneumonia (and likely associated strong cytokine responses) and 2) they were of an age where they were likely to have acquired immunity to a

closely related virus, the Russian influenza of 1890 (Frost 1919; Shanks and Brundage 2012). Shanks and Brundage (2012) have hypothesized that circulating memory lymphocytes stemming from this prior infection pre-disposed 1918 flu victims to pneumonia and sepsis, a finding circumstantially supported by the highly reactive memory B and CD8+ T cells found in humans and swine exposed to the 1918 flu or other H1N1 strains (Heinen et al. 2002; Yu et al. 2008).

Importantly, an individual or generation need not be exposed to a pathogen directly to experience altered immune responses and mortality as an outcome of acquired immunity. Parentally (often maternal) acquired immunity can be imprinted upon offspring T and B cell repertoires, affecting not just host responses to pathogens, but chronic inflammatory and autoimmune conditions in subsequent generations (Fink et al. 2008; Lemke et al. 2009; McKeever et al. 1997; Tanasa et al. 2010). Evidence of poor infant seroconversion in response to multiple vaccines while maternal antibodies remain in circulation suggests that trans-generational immune priming can also lessen offspring initial adaptive responses to pathogens and possibly enhance seroconversion later in childhood (Aaby et al. 2014; Appaiahgari et al. 2014; Faucette et al. 2015; Gans et al. 2001; Jones et al. 2014; Leineweber et al. 2004; Leuridan et al. 2010). As such acquired and transmitted immune phenotypes are pervasive and can diffuse or heighten the impact of a pathogen on reproductive fitness, they can readily be acted upon by natural selection and not necessarily leave an easily interpretable genomic signature (i.e. signature of selection associated with a particular immune locus). A pathogen can, therefore, affect the genomes of two human populations very differently if the very recent history of exposure to that pathogen or pathogens with similar recognized epitopes differs on a population basis.

Resident Microbiota Can Regulate Immune Responses Subject to Natural Selection

The microbiome can also contribute to immune phenotypes in ways that are both acquired and transgenerational. From conception on, humans are associated with microflora and microbial products. All body compartments, save, possibly, plasma and the central nervous system where microbial populations are more restricted, consists of billions of microhabitats in which well-developed ecological communities of micro-organisms reside(Costello et al. 2009). While acknowledgement that resident microbiota alter host immunity stretches back decades, in the last 15 years study of how the microbiome influences host immune response and health has intensified (Hagel et al. 1993; Kohashi et al. 1985; Lynch et al. 1983; Ownby et al. 2002). While much of the research on the resident microbiota of humans has been survey of what bacterial phyla and products are associated with immunological components, immune development, response and disease, there is sufficient functional information to conclude that microflora affects immune phenotypes that could be targeted by natural selection.

Microbiota is required for normal immune development and function. Micro-organisms have a profound effect on the development of secondary lymphoid tissue and, therefore, lymphocyte development and education (Bouskra et al. 2008; Drayton et al. 2006; Wesemann et al. 2013). Most famously, examinations of leukocyte development and function in germ-free vs specific pathogen-free and wild-type mice found that germ-free mice have substantially underdeveloped gut-associated lymphoid tissue (GALT) and muscosa-associated lymphoid tissue (MALT) broadly, fewer local lymph nodes, a loss of luminal integrity and deficits in antibody production (Abrams et al. 1963; Bouskra et al. 2008; Contractor et al. 1998; Ismail et al. 2009; Jain et al. 2016; Shroff et al. 1995). Similarly, microbiota in primary lymphoid tissues appears to be required for normal immune function. Micro-organisms sensed by the bone marrow, for

example, influence the generation of leukocyte precursor cells(Clarke et al. 2010; Takizawa et al. 2012; Zeng et al. 2016). In particular, such microbiota appear to be an important factor in production of "emergency" granulocytes (i.e. neutrophils) and could, therefore, affect host recovery from bacterial and parasitic infections (Gorjifard and Goldszmid 2016; Karmarkar and Rock 2013). They also appear to affect cell death and, therefore, energy requirements for white blood cell homeostasis. The lifespan of phagocytic cells, in particular, is altered by circulating microbial products sourced from gut microbiota (Hergott et al. 2016). Via regulation of immune cells, resident microbiota can impact reproductive fitness.

Resident microbiota can also be seen to serve as an extension of the immune system. Colonization by commensal bacteria provides a body compartment a competitive environment in which many invading pathogens will struggle to establish themselves. The composition of this population influences reproductive fitness and is highly sensitive to human diet and activity (Becattini et al. 2017; Stecher et al. 2007). The bacterial composition of the gut microbiome, for example, can contribute to low-grade systemic inflammation, a condition that is associated with a range of chronic diseases including diabetes and heart disease (Kasahara et al. 2017). A well demonstrated increase in Firmicutes:Bacteriodetes ratio that occurs in the gut in response to high fat diets can also contribute to this inflammation, as such a diet is associated with increased translocation of pyrogenic microbial components across the gut barrier and, eventually, into plasma (Everard et al. 2013; Kim et al. 2012; Moreira et al. 2012). Similarly, dietary-fiber deprived diets shift gut microbiome composition such that the mucous barrier of the colon degrades and allows increased passage of pathogens(Desai et al. 2016). Both of these phenomena can increase disease susceptibility and decrease reproductive fitness.

Resident microbiota can have a profound effect on immune cell pathogen detection and signaling and, therefore, infection survival. One of the best functionally substantiated microorganism-mitigated immune responses is endotoxin tolerance and priming. In both tolerance and priming, prior exposure to small amounts of endotoxin [(lipopolysaccharide (LPS)] induces innate immune cells to develop blunted (tolerance) or potentiated (priming) pro-inflammatory responses to a second challenge with LPS(Rocksen et al. 2004; Vaknin et al. 2008). The cellular "decision making" required to either make an innate immune cell tolerant to very high doses of LPS, or primed to respond strongly to very small doses is not well understood, though the *TRIF,* and *MyD88* genes in the toll-like receptor 4 (TLR4) pathways and anti- and pro-inflammatory pathway cross-talk appear to play important roles (Deguchi et al. 2013; Vartanian et al. 2011). Tolerance and priming both matter in the grand scheme of human genome evolution, because they affect responses to Gram-negative bacterial infection. An individual primed for strong anti-LPS response may clear a Gram-negative bacterial infection effectively, but may also respond so overtly as to trigger deadly sepsis. Alternatively, an individual whose macrophages, for example, have been made LPS tolerant via prior contact with low-levels of LPS will require higher doses of that molecule to initiate a response to Gram-negative bacteria that leads to infection clearance. This latter scenario could be an adaptation in individuals with pervasive endotoxin exposure to prevent an overt and dangerous pro-inflammatory response typical of sepsis (Li et al. 2000). Endotoxin-induced alterations in immune response, likely contribute to persistent low levels of circulating LPS. Such levels of LPS in human blood have been associated with a number of conditions that impact reproductive fitness, including altered wound healing, diabetes, and atherosclerosis(Creely et al. 2007; Szeto et al. 2008; Yuan et al. 2016). Importantly, individuals maintaining blood and tissue

microbiomes with differing levels of Gram-negative bacteria could be differently primed or made tolerant to infection and, therefore, subject to different selection intensity by Gram-negative pathogens. With resident microbiota as a factor in whether an anti-inflammatory or pro-inflammatory pathway is triggered by a Gram-negative pathogen, for example, the microbiome can influence which pathway comes under selection. Moreover, host genetic variants that provision for resident microbiota that induce tolerance or priming may also undergo selection, which can make evolutionary signal difficult to interpret.

Immune System Pleiotropy Means Pathogen-mediated Selection Can Affect Other Physiological Systems and Vice Versa

Detecting and interpreting evolutionary signal stemming from pathogen-mediated adaptation in the human genome is further complicated by the redundancy and physiological promiscuity of the immune system. The human immune system is highly redundant. There are multiple receptor gene families, for example, that strongly overlap in the pathogens that they recognize. Multiple immune proteins can sense a given pathogen. Such is the case with major families of innate immune receptors, such as Toll-like receptors (TLRs), RIG-I-like receptors, Nucleotide Oligomerization Domains –like receptors (NODs) and Tumour-necrosis factor receptors. *Staphylococcus aureus*, for example, is sensed by TLR2/TLR1, NOD2, TNFR1 (Gomez et al. 2006; Hruz et al. 2009; Ozinsky et al. 2000; Takeuchi et al. 2000). Two of these receptors (TLR2 and NOD2) detect *S. aureus* via the same pathogen-associated molecular pattern, peptidoglycan. Like many other pathogen-receptor interactions, these three receptors activate pro-inflammatory responses via the same transcription factors, including interferon

regulatory factor (IRF), nuclear factor kappa-B (NFκB), and activator protein (AP-1) [reviewed in (Lee and Kim 2007)].

Within gene families there can also be considerable functional redundancy. Chemotaxic cytokines, or "chemokines", and their receptors are the outcome of multiple copy events stemming from the emergence of an ancestral gene over 650 million years ago (DeVries et al. 2006). Human chemokine and chemokine receptor genes are engaged in cell migration, activation and differentiation [reviewed in (Qidwai 2016). They share high identity, and many appear to be functionally redundant. There are, for 18 human chemokine receptors, 42 chemokines. While some of these proteins are uniquely involved in the migration of particular cell types (i.e. CXCL8, CXCR2 cooperate to specifically traffic neutrophils; CCR7 is required for lymphocyte homing to secondary lymphoid tissues) many appear to be involved in precisely the same cell migration activities (DeVries et al. 2006; Forster et al. 1999; Laing and Secombes 2004; Middleton et al. 1997; Rainger et al. 1997; Smith et al. 2004). How this redundancy affects pathogen-mediated selection on the human genome depends on the benefit of repetitive function to reproductive fitness. Multiple sensing mechanisms for the same molecular motif may act to initiate transcription factor activity at an optimal level not achievable via a single sensing mechanism and pathway [reviewed in (Nish and Medzhitov 2011)]. Redundancy may also act as a kind of insurance against the failure of pathway or gene to limit a pathogen. Chemokines are tasked with the extremely important business of trafficking leukocytes to sites of infection/inflammation (Oppenheim et al. 1991). Redundant chemokines and receptors may ensure cells are trafficked in the event of pathogen or mutation blocking the activity of a given chemokine. In either of these scenarios it is likely that pathogens exerting selective pressure on humans are targeting multiple genes that serve similar functions. Moreover, the multiple innate

immune pathways involved in sensing singular pathogen associated molecular motif means that target genes for a given pathogen are very likely to have been the target genes of *any number of other pathogens*. Attribution of diversified immune responses or signatures of selection in humans to a particular microbe is, therefore, very challenging, even with lengthy functional characterization of genetic variants to an extant proxy pathogen.

A much more complex wrinkle in interpreting how pathogens affect the human genome stems from the promiscuous manner in which the immune system has evolved in eukaryotic life – co-opting and "borrowing" genes and structures that serve other physiological functions [reviewed in (Dzik 2010)]. Human immune genes are very pleiotropic and are cross-referenced in the development and maintenance of other physiological systems that are important to reproductive fitness, including the nervous and reproductive systems (Bhurke et al. 2016; Bussmann et al. 2011; Chen et al. 1999; Meng et al. 1999; Semple et al. 2010; Sharkey et al. 1995; Stumm and Hollt 2007). Moreover, these highly multi-purpose genes engage in gene networks that are also pleiotropic and can be involved in multiple physiological activities simultaneously (Andreassen et al. 2015; Eagleson et al. 2017; Raj et al. 2013). This is the case for cytokines, which tend to be viewed as proteins governing important immune functions such as cell-to-cell communications, inflammation, cell differentiation and apoptosis within immunity, but are also key proteins in the maintenance of "non-immune" physiological processes that have a strong impact on reproductive fitness including ovulation, spermatogenesis, neurogenesis and neuronal function, lung development and bone development (Joyce et al. 2001; Marz et al. 1998; Ochsner et al. 2003; Sarkar et al. 2008) (Meola et al. 2013; Sabatini et al. 1988; Zhu et al. 2007). Chemokines also guide neural crest and neuronal cell migration during embryogenesis and regulate the development of the circulatory system [reviewed in (Mayor and Theveneau

2013)](Bussmann et al. 2011). Transcription factors JUN, FOS and STAT3, for example, are key to innate immune regulation of inflammation and apoptosis and also work in networks to regulate uterine epithelial proliferation and embryo implantation [reviewed in (Bhurke et al. 2016). An examination of previously published data on human cell whole genome responses to one of three pathogens to which humans have had prolonged evolutionary exposure reveals that the reported five most strongly upregulated genes are highly pleiotropic (See Table 3) (Li et al. 2016; Pacis et al. 2015; Thomas et al. 2014). These genes are not just involved in infection responses, but activities that can strongly impact reproductive fitness such as embryo implantation, spermatogenesis, menstruation, and intestinal organization. Key considerations regarding pathogen-driven diversification of the human genome, therefore, include that 1) factors exerting a selective effect on immune genes (i.e. chemokine CXCL8) could drive the evolution of other physiological systems (i.e. reproductive system) and vice versa and 2) the redundancy of the immune system may loosen any evolutionary constraint on a given gene to conform to roles in both the immune system and any other physiological systems. Importantly, functional redundancy in immunity may grant flexibility in the evolution of genes under demand in multiple systems. Factors exerting evolutionary pressure in another physiological system may alter genomic signatures around immune genes.

Immunity Is Not Always the Target

Important to the assessment of how infectious disease has affected the human genome is the acceptance that many analyses of genomic hallmarks of host-pathogen conflict may suffer from a less than agnostic approach to apparently affected genomic regions. When a signature of selection, for example, is found in a genomic region where well-established immune genes are

located, there may be an impulse to highlight those genes and exclude non-immune genes as potentially affected by a pathogen. Most of the time, this impulse is likely the correct action. However, not only are immune system genes often redundant and highly pleiotropic, but they are sometimes not the target of pathogen-mediated selection at all. The most famous examples of genetic variants that confer infectious disease resistance in human populations occur in genes whose primary function is concerned with non-immune activities. Variations in red blood cell structure are known to lend *Plasmodium* (malaria) resistance to hosts, but have little to do with the immune system directly. The HbS allele of the hemoglobin subunit beta gene (*HBB*), for example, confers changes in charge and folding of haemoglobin that then changes the overall structure of red blood cells to a sickle shape (Gouagna et al. 2010; Williams et al. 2006). Similarly, deletions of α –globin genes confer thalasemmia microcytic anemia (Wambua et al. 2006). Alterations to these features, however, have knock on effects that engage immune system components. *Plasmodium* resistance stemming from these mutations seems to be at least partially the outcome of increased splenic clearance of unusually shaped red blood cells [reviewed in(Kwiatkowski 2005)]. Neither red blood cell shape nor splenic blood filtering is typically included in the canonical perception of immunity. When considering pathogen-mediated selection on human genomes, therefore, it becomes important to consider that either changes in non-immune genes have functional consequences for immunity, or that our current perception of what constitutes the immune system is not broad enough. If shifts in a gene conformation or function lead to a change in response to a pathogen, is that sufficient to consider the gene and the affected tissues part of the immune system? Most importantly, such changes in traditionally non-immune genes suggest that an agnostic approach to interpreting apparently affected genomic

regions is very important until animal model-based functional confirmation of a locus' involvement in pathogenesis can be attained.

Conclusions

The human immune system is under great selective pressure by pathogens. As such, it is expected that pathogen-mediated selection has modified the human genome. As a bulwark between pathogens and host genomes, the human immune system and its phenotypic variations directly inform the impact a pathogen will have on the human genome. When assessing how pathogens have affected human evolution care must taken as host-pathogen conflicts are complex and features inherent to the human immune system, such as adaptive immunity, trans-generational immune priming, microbiome, immune protein redundancy and pleiotropy can diffuse or heighten evolutionary signal. As such, assessments of how pathogens shape host genomes requires a carefully curated assemblage of genomic, immune function, immune phenotyping information and, when possible, historical information. Recent approaches to pathogen impact on human variation have included the use of serotyping in surviving populations (Yu et al. 2008), recovery of ancient pathogen genomes(Bos et al. 2016; Feldman et al. 2016), pathogen-stimulation of immune cells recovered from a population showing evidence of selection(Laayouni et al. 2014) and could involve gene editing to assess the functional impact of polymorphisms thought to be associated with an infectious disease. All such multi-disciplinary/multi-technique approaches to determining how infectious pathogens have contributed to the diversification of the human genome are worthy of exploration, as they can help us clarify the gene networks engaged in disease progression, identify therapeutic targets for current infectious disease and help explain disease disparities in modern populations.

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Literature Cited

Aaby, P., C. L. Martins, M. L. Garly et al. 2014. Measles vaccination in the presence or absence of maternal measles antibody: Impact on child survival. *Clin. Infect. Dis.* 59:484–492.

Abrams, G. D., H. Bauer, and H. Sprinz. 1963. Influence of the normal flora on mucosal morphology and cellular renewal in the ileum. A comparison of germ-free and conventional mice. *Lab. Invest.* 12:355–364.

Andersen, K. G., I. Shylakhter, S. Tabrizi et al. 2012. Genome-wide scans provide evidence for positive selection of genes implicated in Lassa fever. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 367:868–877.

Andreassen, O. A., R. S. Desikan, Y. Wang et al. 2015. Abundant genetic overlap between blood lipids and immune-mediated diseases indicates shared molecular genetic mechanisms. *PLoS One* 10:e0123057.

Angiolillo, A. L., C. Sgadari, D. D. Taub et al. 1995. Human interferon-inducible protein 10 is a potent inhibitor of angiogenesis in vivo. *J. Exp. Med*. 182:155–162.

Angres, B., L. Kim, R. Jung et al. 2001. LI-cadherin gene expression during mouse intestinal development. *Dev. Dyn*. 221:182–193.

Anstee, D. J. 2010. The relationship between blood groups and disease. *Blood* 115:4,635–4,643.

Appaiahgari, M. B., R. Glass, S. Singh et al. 2014. Transplacental rotavirus IgG interferes with immune response to live oral rotavirus vaccine ORV-116E in Indian infants. *Vaccine* 32:651–656.

Asghar, M., D. Hasselquist, B. Hansson et al. 2015. Hidden costs of infection: Chronic malaria accelerates telomere degradation and senescence in wild birds. *Science* 347:436–438.

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

Barreiro, L. B., M. Ben-Ali, H. Quach et al. 2009. Evolutionary dynamics of human Toll-like receptors and their different contributions to host defense. *PLoS Genet.* 5:e1000562.

Barreiro, L. B., and L. Quintana-Murci. 2010. From evolutionary genetics to human immunology: How selection shapes host defence genes. *Nat. Rev. Genet.* 11:17–30.

Baum, J., R. H. Ward, and D. J. Conway. 2002. Natural selection on the erythrocyte surface. *Mol. Biol. Evol.* 19:223–229.

Becattini, S., E. R. Littmann, R. A. Carter et al. 2017. Commensal microbes provide first line defense against Listeria monocytogenes infection. *J. Exp. Med.* 214:1,973–1,989.

Benedictow, O. 2004. *The Black Death 1346–1353: The Complete History.* Woodbridge, England: Boydell Press.

Bhurke, A. S., I. C. Bagchi, and M. K. Bagchi. 2016. Progesterone-regulated endometrial factors controlling implantation. *Am. J. Reprod. Immunol.* 75:237–245.

Bodnar, R. J., C. C. Yates, and A. Wells. 2006. IP-10 blocks vascular endothelial growth factor-induced endothelial cell motility and tube formation via inhibition of calpain. *Circ. Res.* 98:617–625.

Bos, K. I., A. Herbig, J. Sahl et al. 2016. Eighteenth century Yersinia pestis genomes reveal the long-term persistence of an historical plague focus. *eLife* 5:e12994.

Boscolo, P., L. Forcella, M. Reale et al. 2012. Job strain in different types of employment affects the immune response. *Work* 41:2,950–2,954.

Bouskra, D., C. Brezillon, M. Berard et al. 2008. Lymphoid tissue genesis induced by commensals through NOD1 regulates intestinal homeostasis. *Nature* 456:507–510.

Brass, A. L., I. C. Huang, Y. Benita et al. 2009. The IFITM proteins mediate cellular resistance to influenza A H1N1 virus, West Nile virus, and dengue virus. *Cell* 139:1,243–1,254.

Burant, C. F., J. Takeda, E. Brot-Laroche et al. 1992. Fructose transporter in human spermatozoa and small intestine is GLUT5. *J. Biol. Chem.* 267:14,523–14,526.

Bussmann, J., S. A. Wolfe, and A. F. Siekmann. 2011. Arterial-venous network formation during brain vascularization involves hemodynamic regulation of chemokine signaling. *Development* 138:1,717–1,726.

Byerly, C. R. 2010. The U.S. military and the influenza pandemic of 1918–1919. *Public Health Rep.* 125:82–91.

Cagan, A., C. Theunert, H. Laayouni et al. 2016. Natural selection in the great apes. *Mol. Biol. Evol.* 33:3,268–3,283.

Cagliani, R., U. Pozzoli, D. Forni et al. 2013. Crohn's disease loci are common targets of protozoa-driven selection. *Mol. Biol. Evol.* 30:1,077–1,087.

Cagliani, R., and M. Sironi. 2013. Pathogen-driven selection in the human genome. *Int. J. Evol. Biol.* 2013:204,240.

Casadevall, A., and L. A. Pirofski. 1999. Host-pathogen interactions: Redefining the basic concepts of virulence and pathogenicity. *Infect Immun.* 67:3,703–3,713.

Caws, M., G. Thwaites, S. Dunstan et al. 2008. The influence of host and bacterial genotype on the development of disseminated disease with Mycobacterium tuberculosis. *PLoS Pathog.* 4:e1000034.

Chen, H. F., J. Y. Shew, H. N. Ho et al. 1999. Expression of leukemia inhibitory factor and its receptor in preimplantation embryos. *Fertil. Steril.* 72:713–719.

Clarke, T. B., K. M. Davis, E. S. Lysenko et al. 2010. Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. *Nat. Med.* 16:228–231.

Coelho, L. F., G. Magno de Freitas Almeida, F. J. Mennechet et al. 2005. Interferon-alpha and -beta differentially regulate osteoclastogenesis: Role of differential induction of chemokine CXCL11 expression. *Proc. Natl. Acad. Sci. U. S. A.* 102:11,917–11,922.

Cohn, S. K., Jr. 2008. Epidemiology of the Black Death and successive waves of plague. *Med. Hist. Suppl.* (27):74–100.

Contractor, N. V., H. Bassiri, T. Reya et al. 1998. Lymphoid hyperplasia, autoimmunity, and compromised intestinal intraepithelial lymphocyte development in colitis-free gnotobiotic IL-2-deficient mice. *J. Immunol.* 160:385–394.

Costello, E. K., C. L. Lauber, M. Hamady et al. 2009. Bacterial community variation in human body habitats across space and time. *Science* 326:1,694–1,697.

Creely, S. J., P. G. McTernan, C. M. Kusminski et al. 2007. Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. *Am. J. Physiol. Endocrinol. Metab.* 292:E740–747.

Culhane, J. F., V. Rauh, K. F. McCollum et al. 2002. Exposure to chronic stress and ethnic differences in rates of bacterial vaginosis among pregnant women. *Am. J. Obstet. Gynecol.* 187:1,272–1,276.

Dabelea, D., E. J. Mayer-Davis, S. Saydah et al. 2014. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA* 311:1,778–1,786.

Dantzig, A. H., J. A. Hoskins, L. B. Tabas et al. 1994. Association of intestinal peptide transport with a protein related to the cadherin superfamily. *Science* 264:430–433.

de Koning, P. J., J. A. Kummer, S. A. de Poot et al. 2011. Intracellular serine protease inhibitor SERPINB4 inhibits granzyme M-induced cell death. *PLoS One* 6:e22645.

Dean, M., M. Carrington, C. Winkler et al. 1996. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. *Science* 273:1,856–1,862.

Deguchi, A., T. Tomita, T. Omori et al. 2013. Serum amyloid A3 binds MD-2 to activate p38 and NF-kappaB pathways in a MyD88-dependent manner. *J. Immunol.* 191:1,856–1,864.

Desai, M. S., A. M. Seekatz, N. M. Koropatkin et al. 2016. A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. *Cell* 167:1,339–1,353.e21.

Deschamps, M., G. Laval, M. Fagny et al. 2016. Genomic signatures of selective pressures and introgression from archaic hominins at human innate immunity genes. *Am. J. Hum. Genet.* 98:5–21.

DeVries, M. E., A. A. Kelvin, L. Xu et al. 2006. Defining the origins and evolution of the chemokine/chemokine receptor system. *J. Immunol.* 176:401–415.

DiVietro, J. A., M. J. Smith, B. R. Smith et al. 2001. Immobilized IL-8 triggers progressive activation of neutrophils rolling in vitro on P-selectin and intercellular adhesion molecule-1. *J. Immunol.* 167:4,017–4,025.

Dopico, X. C., M. Evangelou, R. C. Ferreira et al. 2015. Widespread seasonal gene expression reveals annual differences in human immunity and physiology. *Nat. Commun.* 6:7,000.

Drayton, D. L., S. Liao, R. H. Mounzer et al. 2006. Lymphoid organ development: From ontogeny to neogenesis. *Nat. Immunol.* 7:344–353.

Du, L., and A. P. Heaney. 2012. Regulation of adipose differentiation by fructose and GluT5. *Mol. Endocrinol.* 26:1,773–1,782.

Dunlap, K. A., M. Palmarini, M. Varela et al. 2006. Endogenous retroviruses regulate periimplantation placental growth and differentiation. *Proc. Natl. Acad. Sci. U. S. A.* 103:14,390–14,395.

Dzik, J. M. 2010. The ancestry and cumulative evolution of immune reactions. *Acta Biochim. Pol.* 57:443–466.

Eagleson, K. L., Z. Xie, and P. Levitt. 2017. The pleiotropic MET receptor network: Circuit development and the neural-medical interface of autism. *Biol. Psychiatry* 81:424–433.

English, L., M. Chemali, J. Duron et al. 2009. Autophagy enhances the presentation of endogenous viral antigens on MHC class I molecules during HSV-1 infection. *Nat. Immunol.* 10:480–487.

Everard, A., C. Belzer, L. Geurts et al. 2013. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc. Natl. Acad. Sci. U. S. A.* 110:9,066–9,071.

Everitt, A. R., S. Clare, T. Pertel et al. 2012. IFITM3 restricts the morbidity and mortality associated with influenza. *Nature* 484:519–523.

Faria, N. R., A. Rambaut, M. A. Suchard et al. 2014. HIV epidemiology. The early spread and epidemic ignition of HIV-1 in human populations. *Science* 346:56–61.

Faucette, A. N., B. L. Unger, B. Gonik et al. 2015. Maternal vaccination: Moving the science forward. *Hum. Reprod. Update* 21:119–135.

Feldman, M., M. Harbeck, M. Keller et al. 2016. A high-coverage Yersinia pestis genome from a sixth-century Justinianic Plague victim. *Mol. Biol. Evol.* 33:2,911–2,923.

Feldman, C. H., L. T. Hiraki, J. Liu et al. 2013. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000–2004. *Arthritis Rheum*. 65:753–763.

Filip, L. C., and N. I. Mundy. 2004. Rapid evolution by positive Darwinian selection in the extracellular domain of the abundant lymphocyte protein CD45 in primates. *Mol. Biol. Evol.* 21:1,504–1,511.

Fink, K., R. Zellweger, J. Weber et al. 2008. Long-term maternal imprinting of the specific B cell repertoire by maternal antibodies. *Eur. J. Immunol.* 38:90–101.

Forster, R., A. Schubel, D. Breitfeld et al. 1999. CCR7 coordinates the primary immune response by establishing functional microenvironments in secondary lymphoid organs. *Cell* 99:23–33.

Frank, S. A. 1993. Specificity versus detectable polymorphism in host-parasite genetics. *Proc. Biol. Sci.* 254:191–197.

Frank, S. A. 1994. Recognition and polymorphism in host-parasite genetics. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 346:283–293.

Frodsham, A. J., L. Zhang, U. Dumpis et al. 2006. Class II cytokine receptor gene cluster is a major locus for hepatitis B persistence. *Proc. Natl. Acad. Sci. U. S. A.* 103:9,148–9,153.

Frost, W. H. 1919. The epidemiology of influenza. *Public Health Reports* 34:1,823–1,926.

Fry, A. E., M. J. Griffiths, S. Auburn et al. 2008. Common variation in the ABO glycosyltransferase is associated with susceptibility to severe Plasmodium falciparum malaria. *Hum. Mol. Genet.* 17:567–576.

Fu, Y., L. Maianu, B. R. Melbert et al. 2004. Facilitative glucose transporter gene expression in human lymphocytes, monocytes, and macrophages: A role for GLUT isoforms 1, 3, and 5 in the immune response and foam cell formation. *Blood Cells Mol. Dis.* 32:182–190.

Fumagalli, M., U. Pozzoli, R. Cagliani et al. 2009. Parasites represent a major selective force for interleukin genes and shape the genetic predisposition to autoimmune conditions. *J. Exp. Med.* 206:1,395–1,408.

Fumagalli, M., U. Pozzoli, R. Cagliani et al. 2010. The landscape of human genes involved in the immune response to parasitic worms. *BMC Evol. Biol.* 10:264.

Fumagalli, M., M. Sironi, U. Pozzoli et al. 2011. Signatures of environmental genetic adaptation pinpoint pathogens as the main selective pressure through human evolution. *PLoS Genet.* 7:e1002355.

Gage, K. L., and M. Y. Kosoy. 2005. Natural history of plague: Perspectives from more than a century of research. *Annu. Rev. Entomol.* 50:505–528.

Galvani, A. P., and M. Slatkin. 2003. Evaluating plague and smallpox as historical selective pressures for the CCR5-Delta 32 HIV-resistance allele. *Proc. Natl. Acad. Sci. U. S. A.* 100:15,276–15,279.

Gans, H., L. Yasukawa, M. Rinki et al. 2001. Immune responses to measles and mumps vaccination of infants at 6, 9, and 12 months. *J. Infect. Dis.* 184:817–826.

Gasparini, J., K. D. McCoy, C. Haussy et al. 2001. Induced maternal response to the Lyme disease spirochaete Borrelia burgdorferi sensu lato in a colonial seabird, the kittiwake Rissa tridactyla. *Proc. Biol. Sci.* 268:647–650.

Gelfand, J. M., R. S. Stern, T. Nijsten et al. 2005. The prevalence of psoriasis in African Americans: Results from a population-based study. *J. Am. Acad. Dermatol.* 52:23–26.

Genovese, G., D. J. Friedman, M. D. Ross et al. 2010. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 329:841–845.

Genton, B., F. al-Yaman, C. S. Mgone et al. 1995. Ovalocytosis and cerebral malaria. *Nature* 378:564–565.

Gomez, M. I., M. O'Seaghdha, M. Magargee et al. 2006. Staphylococcus aureus protein A activates TNFR1 signaling through conserved IgG binding domains. *J. Biol. Chem.* 281:20,190–20,196.

Gorjifard, S., and R. S. Goldszmid. 2016. Microbiota-myeloid cell crosstalk beyond the gut. *J. Leukoc. Biol.* 100:865–879.

Gouagna, L. C., G. Bancone, F. Yao et al. 2010. Genetic variation in human HBB is associated with Plasmodium falciparum transmission. *Nat. Genet.* 42:328–331.

Gresnigt, M. S., and F. L. van de Veerdonk. 2013. Biology of IL-36 cytokines and their role in disease. *Semin. Immunol.* 25:458–465.

Grindstaff, J. L., D. Hasselquist, J. K. Nilsson et al. 2006. Transgenerational priming of immunity: Maternal exposure to a bacterial antigen enhances offspring humoral immunity. *Proc. Biol. Sci.* 273:2,551–2,557.

Grunhage, F., J. Nattermann, O. A. Gressner et al. 2010. Lower copy numbers of the chemokine CCL3L1 gene in patients with chronic hepatitis C. *J. Hepatol.* 52:153–159.

Hagar, J. A., D. A. Powell, Y. Aachoui et al. 2013. Cytoplasmic LPS activates caspase-11: Implications in TLR4-independent endotoxic shock. *Science* 341:1,250–1,253.

Hagel, I., N. R. Lynch, M. Perez et al. 1993. Modulation of the allergic reactivity of slum children by helminthic infection. *Parasite Immunol.* 15:311–315.

Haldane, J. B. 1949. The rate of mutation in human genes. *Proc. VIII Int. Cong. Genet. Hereditas* 35:267–273.

Hamilton, W. D. 1980. Sex versus non-sex versus parasite. *Oikos* 35:282–290.

Hanson, L. A., M. Korotkova, S. Lundin et al. 2003. The transfer of immunity from mother to child. *Ann. N. Y. Acad. Sci.* 987:199–206.

Hardwick, R. J., W. Amogne, S. Mugusi et al. 2012. Beta-defensin genomic copy number is associated with HIV load and immune reconstitution in sub-saharan Africans. *J. Infect. Dis.* 206:1,012–1,019.

Harper, K., and G. Armelagos. 2010. The changing disease-scape in the third epidemiological transition. *Int. J. Environ. Res. Public Health* 7:675–697.

Harper, K. N., and G. J. Armelagos. 2013. Genomics, the origins of agriculture, and our changing microbe-scape: Time to revisit some old tales and tell some new ones. *Am. J. Phys. Anthropol.* 152:135–152.

Harper, K. N., M. K. Zuckerman, M. L. Harper et al. 2011. The origin and antiquity of syphilis revisited: An appraisal of Old World pre-Columbian evidence for treponemal infection. *Am. J. Phys. Anthropol.* 146:99–133.

Hasselquist, D., and J. A. Nilsson. 2009. Maternal transfer of antibodies in vertebrates: Trans-generational effects on offspring immunity. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 364:51–60.

Hayashi, F., K. D. Smith, A. Ozinsky et al. 2001. The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5. *Nature* 410:1,099–1,103.

He, C., E. Peatman, P. Baoprasertkul et al. 2004. Multiple CC chemokines in channel catfish and blue catfish as revealed by analysis of expressed sequence tags. *Immunogenetics* 56:379–387.

Heinen, P. P., F. A. Rijsewijk, E. A. de Boer-Luijtze et al. 2002. Vaccination of pigs with a DNA construct expressing an influenza virus M2-nucleoprotein fusion protein exacerbates disease after challenge with influenza A virus. *J. Gen. Virol.* 83:1,851–1,859.

Hergott, C. B., A. M. Roche, E. Tamashiro et al. 2016. Peptidoglycan from the gut microbiota governs the lifespan of circulating phagocytes at homeostasis. *Blood* 127:2,460–2,471.

Hill, A. V. 2012. Evolution, revolution and heresy in the genetics of infectious disease susceptibility. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 367:840–849.

Hill, A. V., C. E. Allsopp, D. Kwiatkowski et al. 1991. Common west African HLA antigens are associated with protection from severe malaria. *Nature* 352:595–600.

Hruz, P., A. S. Zinkernagel, G. Jenikova et al. 2009. NOD2 contributes to cutaneous defense against Staphylococcus aureus through alpha-toxin-dependent innate immune activation. *Proc. Natl. Acad. Sci. U. S. A.* 106:12,873–12,878.

Intemann, C. D., T. Thye, S. Niemann et al. 2009. Autophagy gene variant IRGM -261T contributes to protection from tuberculosis caused by Mycobacterium tuberculosis but not by M. africanum strains. *PLoS Pathog.* 5:e1000577.

Isaacs, A., J. Lindenmann, and R. C. Valentine. 1957. Virus interference. II. Some properties of interferon. *Proc. R. Soc. Lond. B. Biol. Sci.* 147:268–273.

Ishida, K., T. Matsumoto, K. Sasaki et al. 2010. Bone regeneration properties of granulocyte colony-stimulating factor via neovascularization and osteogenesis. *Tissue Eng. Part A* 16:3,271–3,284.

Ismail, A. S., C. L. Behrendt, and L. V. Hooper. 2009. Reciprocal interactions between commensal bacteria and gamma delta intraepithelial lymphocytes during mucosal injury. *J. Immunol.* 182:3,047–3,054.

Jain, R., S. Waldvogel-Thurlow, R. Darveau et al. 2016. Differences in the paranasal sinuses between germ-free and pathogen-free mice. *Int. Forum Allergy Rhinol.* 6:631–637.

Johnson, C. M., E. A. Lyle, K. O. Omueti et al. 2007. Cutting edge: A common polymorphism impairs cell surface trafficking and functional responses of TLR1 but protects against leprosy. *J. Immunol.* 178:7,520–7,524.

Johnson, N. P., and J. Mueller. 2002. Updating the accounts: Global mortality of the 1918–1920 "Spanish" influenza pandemic. *Bull. Hist. Med.* 76:105–115.

Jones, C., L. Pollock, S. M. Barnett et al. 2014. The relationship between concentration of specific antibody at birth and subsequent response to primary immunization. *Vaccine* 32:996–1,002.

Joyce, I. M., F. L. Pendola, M. O'Brien et al. 2001. Regulation of prostaglandin-endoperoxide synthase 2 messenger ribonucleic acid expression in mouse granulosa cells during ovulation. *Endocrinology* 142:3,187–3,197.

Kaparakis, M., L. Turnbull, L. Carneiro et al. 2010. Bacterial membrane vesicles deliver peptidoglycan to NOD1 in epithelial cells. *Cell Microbiol.* 12:372–385.

Karlsson, E. K., J. B. Harris, S. Tabrizi et al. 2013. Natural selection in a Bangladeshi population from the cholera-endemic Ganges River Delta. *Sci. Transl. Med.* 5:192ra186.

Karlsson, E. K., D. P. Kwiatkowski, and P. C. Sabeti. 2014. Natural selection and infectious disease in human populations. *Nat. Rev. Genet.* 15:379–393.

Karmarkar, D., and K. L. Rock. 2013. Microbiota signalling through MyD88 is necessary for a systemic neutrophilic inflammatory response. *Immunology* 140:483–492.

Kasahara, K., T. Tanoue, T. Yamashita et al. 2017. Commensal bacteria at the crossroad between cholesterol homeostasis and chronic inflammation in atherosclerosis. *J. Lipid Res.* 58:519–528.

Kayagaki, N., M. T. Wong, I. B. Stowe et al. 2013. Noncanonical inflammasome activation by intracellular LPS independent of TLR4. *Science* 341:1,246–1,249.

Kim, K. A., W. Gu, I. A. Lee et al. 2012. High fat diet-induced gut microbiota exacerbates inflammation and obesity in mice via the TLR4 signaling pathway. *PLoS One* 7:e47713.

Klein, J., and C. O'Huigin. 1994. MHC polymorphism and parasites. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 346:351–357; discussion 357–358.

Ko, W. Y., P. Rajan, F. Gomez et al. 2013. Identifying Darwinian selection acting on different human APOL1 variants among diverse African populations. *Am. J. Hum. Genet.* 93:54–66.

Koch, T. 2014. 1831: The map that launched the idea of global health. *Int. J. Epidemiol.* 43:1,014–1,020.

Kofoed, E. M., and R. E. Vance. 2011. Innate immune recognition of bacterial ligands by NAIPs determines inflammasome specificity. *Nature* 477:592–595.

Kohashi, O., Y. Kohashi, T. Takahashi et al. 1985. Reverse effect of gram-positive bacteria vs. gram-negative bacteria on adjuvant-induced arthritis in germfree rats. *Microbiol. Immunol.* 29:487–497.

Kosiol, C., T. Vinar, R. R. da Fonseca et al. 2008. Patterns of positive selection in six Mammalian genomes. *PLoS Genet.* 4:e1000144.

Krementsov, D. N., L. K. Case, O. Dienz et al. 2017. Genetic variation in chromosome Y regulates susceptibility to influenza A virus infection. *Proc. Natl. Acad. Sci. U. S. A.* 114:3,491–3,496.

Kwiatkowski, D. P. 2005. How malaria has affected the human genome and what human genetics can teach us about malaria. *Am. J. Hum. Genet.* 77:171–192.

Laayouni, H., M. Oosting, P. Luisi et al. 2014. Convergent evolution in European and Rroma populations reveals pressure exerted by plague on Toll-like receptors. *Proc. Natl. Acad. Sci. U. S. A.* 111:2,668–2,673.

Laing, K. J., and C. J. Secombes. 2004. *Chemokines. Dev. Comp. Immunol.* 28:443–460.

Lee, M. S., and Y. J. Kim. 2007. Signaling pathways downstream of pattern-recognition receptors and their cross talk. *Annu. Rev. Biochem.* 76:447–480.

Leineweber, B., V. Grote, U. B. Schaad et al. 2004. Transplacentally acquired immunoglobulin G antibodies against measles, mumps, rubella and varicella-zoster virus in preterm and full term newborns. *Pediatr. Infect. Dis. J.* 23:361–363.

Lemke, H., R. I. Tanasa, A. Trad et al. 2009. Benefits and burden of the maternally-mediated immunological imprinting. *Autoimmun. Rev.* 8:394–399.

Leuridan, E., N. Hens, V. Hutse et al. 2010. Early waning of maternal measles antibodies in era of measles elimination: Longitudinal study. *BMJ* 340:c1626.

Li, L., S. Cousart, J. Hu et al. 2000. Characterization of interleukin-1 receptor-associated kinase in normal and endotoxin-tolerant cells. *J. Biol. Chem.* 275:23,340–23,345.

Li, Y., S. Shah-Simpson, K. Okrah et al. 2016. Transcriptome remodeling in Trypanosoma cruzi and human cells during intracellular infection. *PLoS Pathog.* 12:e1005511.

Li, H. T., T. T. Zhang, Y. Q. Zhou et al. 2006. SLC11A1 (formerly NRAMP1) gene polymorphisms and tuberculosis susceptibility: A meta-analysis. *Int. J. Tuberc. Lung Dis.* 10:3–12.

Lindesmith, L., C. Moe, S. Marionneau et al. 2003. Human susceptibility and resistance to Norwalk virus infection. *Nat. Med.* 9:548–553.

Liston, A., E. J. Carr, and M. A. Linterman. 2016. Shaping variation in the human immune system. *Trends Immunol*. 37:637–646.

Loos, T., A. Mortier, M. Gouwy et al. 2008. Citrullination of CXCL10 and CXCL11 by peptidylarginine deiminase: A naturally occurring posttranslational modification of chemokines and new dimension of immunoregulation. *Blood* 112:2,648–2,656.

Lynch, N. R., R. Lopez, G. Isturiz et al. 1983. Allergic reactivity and helminthic infection in Amerindians of the Amazon Basin. *Int. Arch. Allergy Appl. Immunol.* 72:369–372.

Maier, A. G., M. T. Duraisingh, J. C. Reeder et al. 2003. Plasmodium falciparum erythrocyte invasion through glycophorin C and selection for Gerbich negativity in human populations. *Nat. Med.* 9:87–92.

Malide, D., T. M. Davies-Hill, M. Levine et al. 1998. Distinct localization of GLUT-1, -3, and -5 in human monocyte-derived macrophages: Effects of cell activation. *Am. J. Physiol.* 274:E516–526.

Marz, P., J. G. Cheng, R. A. Gadient et al. 1998. Sympathetic neurons can produce and respond to interleukin 6. *Proc. Natl. Acad. Sci. U. S. A.* 95:3,251–3,256.

Mayor, R., and E. Theveneau. 2013. The neural crest. *Development* 140:2,247–2,251.

McKeever, U., S. Khandekar, M. Jesson et al. 1997. Maternal immunization with a soluble TCR-Ig chimeric protein: Long term, V beta-8 family-specific suppression of T cells by maternally transferred antibodies. *J. Immunol* 159:5,936–5,945.

Meng, S. Z., A. Oka, and S. Takashima. 1999. Developmental expression of monocyte chemoattractant protein-1 in the human cerebellum and brainstem. *Brain Dev.* 21:30–35.

Meola, D., Z. Huang, and J. M. Petitto. 2013. Selective neuronal and brain regional expession of IL-2 in IL2P 8-GFP transgenic mice: Relation to sensorimotor gating. *J. Alzheimers Dis. Parkinsonism* 3:1000127.

Metcalf, D. 1985. The granulocyte-macrophage colony-stimulating factors. *Science* 229:16–22.

Middleton, J., S. Neil, J. Wintle et al. 1997. Transcytosis and surface presentation of IL-8 by venular endothelial cells. *Cell* 91:385–395.

Miller, L. H., S. J. Mason, D. F. Clyde et al. 1976. The resistance factor to Plasmodium vivax in blacks. The Duffy-blood-group genotype, FyFy. *N. Engl. J. Med.* 295:302–304.

Miyata, T., M. Nangaku, D. Suzuki et al. 1998. A mesangium-predominant gene, megsin, is a new serpin upregulated in IgA nephropathy. *J. Clin. Invest.* 102:828–836.

Moalem, S., M. E. Percy, T. P. Kruck et al. 2002. Epidemic pathogenic selection: An explanation for hereditary hemochromatosis? *Med. Hypotheses* 59:325–329.

Moreira, A. P., T. F. Texeira, A. B. Ferreira et al. 2012. Influence of a high-fat diet on gut microbiota, intestinal permeability and metabolic endotoxaemia. *Br. J. Nutr.* 108:801–809.

Morelli, G., Y. Song, C. J. Mazzoni et al. 2010. Yersinia pestis genome sequencing identifies patterns of global phylogenetic diversity. *Nat. Genet.* 42:1,140–1,143.

Mukherjee, S., D. Ganguli, and P. P. Majumder. 2014. Global footprints of purifying selection on Toll-like receptor genes primarily associated with response to bacterial infections in humans. *Genome Biol. Evol.* 6:551–558.

Mulero, J. J., A. M. Pace, S. T. Nelken et al. 1999. IL1HY1: A novel interleukin-1 receptor antagonist gene. *Biochem. Biophys. Res. Commun.* 263:702–706.

Nakajima, T., H. Ohtani, Y. Satta et al. 2008. Natural selection in the TLR-related genes in the course of primate evolution. *Immunogenetics* 60:727–735.

Nedelec, Y., J. Sanz, G. Baharian et al. 2016. Genetic ancestry and natural selection drive population differences in immune responses to pathogens. *Cell* 167:657–669.e21.

Nish, S., and R. Medzhitov. 2011. Host defense pathways: Role of redundancy and compensation in infectious disease phenotypes. *Immunity* 34:629–636.

Noma, T., K. Fujisawa, Y. Yamashiro et al. 2001. Structure and expression of human mitochondrial adenylate kinase targeted to the mitochondrial matrix. *Biochem. J.* 358:225–232.

Nordgren, J., E. Kindberg, P. E. Lindgren et al. 2010. Norovirus gastroenteritis outbreak with a secretor-independent susceptibility pattern, Sweden. *Emerg. Infect. Dis.* 16:81–87.

Novembre, J., and E. Han. 2012. Human population structure and the adaptive response to pathogen-induced selection pressures. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 367:878–886.

Numata, A., K. Shimoda, K. Kamezaki et al. 2005. Signal transducers and activators of transcription 3 augments the transcriptional activity of CCAAT/enhancer-binding protein alpha in granulocyte colony-stimulating factor signaling pathway. *J. Biol. Chem.* 280:12,621–12,629.

Ochsner, S. A., D. L. Russell, A. J. Day et al. 2003. Decreased expression of tumor necrosis factor-alpha-stimulated gene 6 in cumulus cells of the cyclooxygenase-2 and EP2 null mice. *Endocrinology* 144:1,008–1,019.

Ogus, A. C., B. Yoldas, T. Ozdemir et al. 2004. The Arg753GLn polymorphism of the human toll-like receptor 2 gene in tuberculosis disease. *Eur. Respir. J.* 23:219–223.

Oppenheim, J. J., C. O. Zachariae, N. Mukaida et al. 1991. Properties of the novel proinflammatory supergene "intercrine" cytokine family. *Annu. Rev. Immunol.* 9:617–648.

Ovsyannikova, I. G., R. B. Kennedy, M. O'Byrne et al. 2012. Genome-wide association study of antibody response to smallpox vaccine. *Vaccine* 30:4,182–4,189.

Ownby, D. R., C. C. Johnson, and E. L. Peterson. 2002. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. *JAMA* 288:963–972.

Ozinsky, A., D. M. Underhill, J. D. Fontenot et al. 2000. The repertoire for pattern recognition of pathogens by the innate immune system is defined by cooperation between toll-like receptors. *Proc. Natl. Acad. Sci. U. S. A.* 97:13,766–13,771.

Pacis, A., L. Tailleux, A. M. Morin et al. 2015. Bacterial infection remodels the DNA methylation landscape of human dendritic cells. *Genome Res*. 25:1,801–1,811.

Pai, A. A., G. Baharian, A. Pagé Sabourin et al. 2016. Widespread shortening of 3' untranslated regions and increased exon inclusion are evolutionarily conserved features of innate immune responses to infection. *PLoS Genet.* 12:e1006338.

Paiva, P., M. G. Lockhart, J. E. Girling et al. 2016. Identification of genes differentially expressed in menstrual breakdown and repair. *Mol. Hum. Reprod.* 22:898–912.

Pattingre, S., A. Tassa, X. Qu et al. 2005. Bcl-2 antiapoptotic proteins inhibit Beclin 1-dependent autophagy. *Cell* 122:927–939.

Pickrell, J. K., G. Coop, J. Novembre et al. 2009. Signals of recent positive selection in a worldwide sample of human populations. *Genome Res.* 19:826–837.

Polley, S., S. Louzada, D. Forni et al. 2015. Evolution of the rapidly mutating human salivary agglutinin gene (DMBT1) and population subsistence strategy. *Proc. Natl. Acad. Sci. U. S. A.* 112:5,105–5,110.

Poltorak, A., X. He, I. Smirnova et al. 1998. Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: Mutations in Tlr4 gene. *Science* 282:2,085–2,088.

Prugnolle, F., A. Manica, M. Charpentier et al. 2005. Pathogen-driven selection and worldwide HLA class I diversity. *Curr. Biol.* 15:1,022–1,027.

Puiffe, M. L., I. Lachaise, V. Molinier-Frenkel et al. 2013. Antibacterial properties of the mammalian L-amino acid oxidase IL4I1. *PLoS One* 8:e54589.

Qidwai, T. 2016. Chemokine genetic polymorphism in human health and disease. *Immunol. Lett.* 176:128–138.

Rainger, G. E., A. C. Fisher, and G. B. Nash. 1997. Endothelial-borne platelet-activating factor and interleukin-8 rapidly immobilize rolling neutrophils. *Am. J. Physiol.* 272:H114–122.

Raj, T., M. Kuchroo, J. M. Replogle, et al. 2013. Common risk alleles for inflammatory diseases are targets of recent positive selection. *Am. J. Hum. Genet.* 92:517–529.

Richardson, L. C., S. J. Henley, J. W. Miller et al. 2016. Patterns and trends in age-specific black-white differences in breast cancer incidence and mortality — United States, 1999–2014. *MMWR Morb. Mortal. Wkly. Rep.* 65:1,093–1,098.

Rocksen, D., B. Koch, T. Sandstrom et al. 2004. Lung effects during a generalized Shwartzman reaction and therapeutic intervention with dexamethasone or vitamin. *E. Shock* 22:482–490.

Root, R. K., and D. C. Dale. 1999. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor: Comparisons and potential for use in the treatment of infections in nonneutropenic patients. *J. Infect. Dis.* 179:S342–352.

Rose, D. R., M. Careaga, J. Van de Water et al. 2016. Long-term altered immune responses following fetal priming in a non-human primate model of maternal immune activation. *Brain Behav. Immun.* 63:60–70.

Rubio-Tapia, A., J. F. Ludvigsson, T. L. Brantner et al. 2012. The prevalence of celiac disease in the United States. *Am. J. Gastroenterol.* 107:1,538–1,544; quiz 1,537, 1,545.

Ruwende, C., S. C. Khoo, R. W. Snow et al. 1995. Natural selection of hemi- and heterozygotes for G6PD deficiency in Africa by resistance to severe malaria. *Nature* 376:246–249.

Sabatini, M., B. Boyce, T. Aufdemorte et al. 1988. Infusions of recombinant human interleukins 1 alpha and 1 beta cause hypercalcemia in normal mice. *Proc. Natl. Acad. Sci. U. S. A.* 85:5,235–5,239.

Sabeti, P. C., S. F. Schaffner, B. Fry et al. 2006. Positive natural selection in the human lineage. *Science* 312:1,614–1,620.

Sarkar, O., P. P. Mathur, C. Y. Cheng et al. 2008. Interleukin 1 alpha (IL1A) is a novel regulator of the blood-testis barrier in the rat. *Biol. Reprod.* 78:445–454.

Sawyer, S. L., L. I. Wu, M. Emerman et al. 2005. Positive selection of primate TRIM5alpha identifies a critical species-specific retroviral restriction domain. *Proc. Natl. Acad. Sci. U. S. A.* 102:2,832–2,837.

Schulze, S., S. G. Henkel, D. Driesch et al. 2015. Computational prediction of molecular pathogen-host interactions based on dual transcriptome data. *Front Microbiol.* 6:65.

Semple, B. D., T. Kossmann, and M. C. Morganti-Kossmann MC. 2010. Role of chemokines in CNS health and pathology: A focus on the CCL2/CCR2 and CXCL8/CXCR2 networks. *J. Cereb. Blood Flow Metab.* 30:459–473.

Shanks, G. D., and J. F. Brundage. 2012. Pathogenic responses among young adults during the 1918 influenza pandemic. *Emerg. Infect. Dis.* 18:201–207.

Sharkey, A. M., K. Dellow, M. Blayney et al. 1995. Stage-specific expression of cytokine and receptor messenger ribonucleic acids in human preimplantation embryos. *Biol. Reprod.* 53:974–981.

Sharma, S., G. Godbole, and D. Modi. 2016. Decidual control of trophoblast invasion. *Am. J. Reprod. Immunol.* 75:341–350.

Shimazu, R., S. Akashi, H. Ogata et al. 1999. MD-2, a molecule that confers lipopolysaccharide responsiveness on Toll-like receptor 4. *J. Exp. Med.* 189:1,777–1,782.

Shroff, K. E., K. Meslin, and J. J. Cebra. 1995. Commensal enteric bacteria engender a self-limiting humoral mucosal immune response while permanently colonizing the gut. *Infect. Immun.* 63:3,904–3,913.

Sim, B. K., C. E. Chitnis, K. Wasniowska et al. 1994. Receptor and ligand domains for invasion of erythrocytes by Plasmodium falciparum. *Science* 264:1,941–1,944.

Smith, M. L., T. S. Olson, and K. Ley. 2004. CXCR2- and E-selectin-induced neutrophil arrest during inflammation in vivo. *J. Exp. Med.* 200:935–939.

Soto, P. C., L. L. Stein, N. Hurtado-Ziola et al. 2010. Relative over-reactivity of human versus chimpanzee lymphocytes: Implications for the human diseases associated with immune activation. *J. Immunol.* 184:4,185–4,195.

Stecher, B., R. Robbiani, A. W. Walker et al. 2007. Salmonella enterica serovar typhimurium exploits inflammation to compete with the intestinal microbiota. *PLoS Biol.* 5:2,177–2,189.

Stephens, J. C., D. E. Reich, D. B. Goldstein et al. 1998. Dating the origin of the CCR5-Delta32 AIDS-resistance allele by the coalescence of haplotypes. *Am. J. Hum. Genet.* 62:1,507–1,515.

Stumm, R., and V. Hollt. 2007. CXC chemokine receptor 4 regulates neuronal migration and axonal pathfinding in the developing nervous system: Implications for neuronal regeneration in the adult brain. *J. Mol. Endocrinol.* 38:377–382.

Szeto, C. C., B. C. Kwan, K. M. Chow et al. 2008. Endotoxemia is related to systemic inflammation and atherosclerosis in peritoneal dialysis patients. *Clin. J. Am. Soc. Nephrol.* 3:431–436.

Takeuchi, O., K. Hoshino, and S. Akira. 2000. Cutting edge: TLR2-deficient and MyD88-deficient mice are highly susceptible to Staphylococcus aureus infection. *J. Immunol.* 165:5,392–5,396.

Takeuchi, O., K. Hoshino, T. Kawai et al. 1999. Differential roles of TLR2 and TLR4 in recognition of gram-negative and gram-positive bacterial cell wall components. *Immunity* 11:443–451.

Takizawa, H., S. Boettcher, and M. G. Manz. 2012. Demand-adapted regulation of early hematopoiesis in infection and inflammation. *Blood* 119:2,991–3,002.

Tanasa, R. I., A. Trad, H. Lange et al. 2010. Allergen IgE-isotype-specific suppression by maternally derived monoclonal anti-IgG-idiotype. *Allergy* 65:16–23.

Taub, D. D., D. L. Longo, and W. J. Murphy. 1996. Human interferon-inducible protein-10 induces mononuclear cell infiltration in mice and promotes the migration of human T lymphocytes into the peripheral tissues and human peripheral blood lymphocytes-SCID mice. *Blood* 87:1,423–1,431.

Thomas, J. M., Z. Pos, J. Reinboth et al. 2014. Differential responses of plasmacytoid dendritic cells to influenza virus and distinct viral pathogens. *J. Virol.* 88:10,758–10,766.

Thomas, D. L., C. L. Thio, M. P. Martin et al. 2009. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature* 461:798–801.

Thomson, R., G. Genovese, C. Canon et al. 2014. Evolution of the primate trypanolytic factor APOL1. *Proc. Natl. Acad. Sci. U. S. A.* 111:E2,130–2,139.

Tierney, L., J. Linde, S. Muller et al. 2012. An interspecies regulatory network inferred from simultaneous RNA-seq of Candida albicans invading innate immune cells. *Front. Microbiol.* 3:85.

Tishkoff, S. A., R. Varkonyi, N. Cahinhinan et al. 2001. Haplotype diversity and linkage disequilibrium at human G6PD: Recent origin of alleles that confer malarial resistance. *Science* 293:455–462.

Uzumaki, H., T. Okabe, N. Sasaki et al. 1989. Identification and characterization of receptors for granulocyte colony-stimulating factor on human placenta and trophoblastic cells. *Proc. Natl. Acad. Sci. U. S. A.* 86:9,323–9,326.

Vaknin, I., L. Blinder, L. Wang et al. 2008. A common pathway mediated through Toll-like receptors leads to T- and natural killer-cell immunosuppression. *Blood* 111:1,437–1,447.

Van Valen, L. 1973. A new evolutionary law. *Evol. Theor.* 1:1–30.

Vartanian, K. B., S. L. Stevens, B. J. Marsh et al. 2011. LPS preconditioning redirects TLR signaling following stroke: TRIF-IRF3 plays a seminal role in mediating tolerance to ischemic injury. *J. Neuroinflamm.* 8:140.

Verrelli, B. C., J. H. McDonald, G. Argyropoulos et al. 2002. Evidence for balancing selection from nucleotide sequence analyses of human G6PD. *Am. J. Hum. Genet.* 71:1,112–1,128.

Vilcinskas, A. 2016. The role of epigenetics in host-parasite coevolution: Lessons from the model host insects Galleria mellonella and Tribolium castaneum. *Zoology (Jena)* 119:273–280.

Voight, B. F., S. Kudaravalli, X. Wen et al. 2006. A map of recent positive selection in the human genome. *PLoS Biol.* 4:e72.

Wambua, S., T. W. Mwangi, M. Kortok et al. 2006. The effect of alpha+-thalassaemia on the incidence of malaria and other diseases in children living on the coast of Kenya. *PLoS Med.* 3:e158.

Wang, X., T. L. Yue, E. H. Ohlstein et al. 1996. Interferon-inducible protein-10 involves vascular smooth muscle cell migration, proliferation, and inflammatory response. *J. Biol. Chem*. 271:24,286–24,293.

Wesemann, D. R., A. J. Portuguese, R. M. Meyers et al. 2013. Microbial colonization influences early B-lineage development in the gut lamina propria. *Nature* 501:112–115.

White, T. D., B. Asfaw, D. DeGusta et al. 2003. Pleistocene Homo sapiens from Middle Awash, Ethiopia. *Nature* 423:742–747.

Wilder, J. A., E. K. Hewett, and M. E. Gansner. 2009. Molecular evolution of GYPC: Evidence for recent structural innovation and positive selection in humans. *Mol. Biol. Evol.* 26:2,679–2,687.

Williams, T. N. 2006. Red blood cell defects and malaria. *Mol. Biochem. Parasitol.* 149:121–127.

Williams, G., M. P. Rosen, J. A. Parker et al. 2006. Splenic implants detected by SPECT images of Tc-99m labeled damaged red blood cells. *Clin. Nucl. Med.* 31:467–469.

Wong, S. H., S. Gochhait, D. Malhotra et al. 2010. Leprosy and the adaptation of human toll-like receptor 1. *PLoS Pathog.* 6:e1000979.

Yu, X., T. Tsibane, P. A. McGraw et al. 2008. Neutralizing antibodies derived from the B cells of 1918 influenza pandemic survivors. *Nature* 455:532–536.

Yuan, R., S. Geng, K. Chen et al. 2016. Low-grade inflammatory polarization of monocytes impairs wound healing. *J. Pathol.* 238:571–583.

Yue, Y., W. Huang, J. Liang et al. 2015. IL4I1 is a novel regulator of M2 macrophage polarization that can inhibit T cell activation via L-Tryptophan and arginine depletion and IL-10 production. *PLoS One* 10:e0142979.

Zeng, M. Y., D. Cisalpino, S. Varadarajan et al. 2016. Gut microbiota-induced immunoglobulin G controls systemic infection by symbiotic bacteria and pathogens. *Immunity* 44:647–658.

Zhang, F. R., W. Huang, S. M. Chen et al. 2009. Genomewide association study of leprosy. *N. Engl. J. Med.* 361:2,609–2,618.

Zhao, Y., J. Yang, J. Shi et al. 2011. The NLRC4 inflammasome receptors for bacterial flagellin and type III secretion apparatus. *Nature* 477:596–600.

Zhernakova, A., C. C. Elbers, B. Ferwerda et al. 2010. Evolutionary and functional analysis of celiac risk loci reveals SH2B3 as a protective factor against bacterial infection. *Am. J. Hum. Genet.* 86:970–977.

Zhu, N. L., C. Li, H. H. Huang et al. 2007. TNF-alpha represses transcription of human Bone Morphogenetic Protein-4 in lung epithelial cells. *Gene* 393:70–80.

Table 1. Example putative pathogen-mediated alterations of the human genome and the extant pathogens affected by them

Pathogen	**Disease**	**Putative alteration**	**Evidence (association/experimental)**
Hepatitis B Virus	Hepatitis B	- IFN-AR2-F8S and IL-10RB-K47E	- major haplotypes associated with HBV clearance (Frodsham et al. 2006)
Hepatitis C Virus	Hepatitis C	- rs12979860 C/C genotype near IL28	- enhances spontaneous clearance of HCV (Thomas et al. 2009)
Influenza A	Influenza	- IFITM3 - rs12252 C/C genotype near IFITM3	- expression is associated with viral restriction. - associated with increased infection severity (Brass et al. 2009; Everitt et al. 2012)
Plasmodium sp.	Malaria	- HbS allele of HBB gene, DARC mutation - SLC4A1 band 3 deletion - α –globin deletions and G6PD-deficiency - ABO group O	- associated with malaria resistance (Gouagna et al. 2010; Miller et al. 1976; Williams 2006) - protects against parasitemia (Genton et al. 1995) - associated with malaria regions (Ruwende et al. 1995; Wambua et al. 2006) - associated with decreased susceptibility to severe infection (Fry et al. 2008)
Mycobacterium leprae	Leprosy	- HLA-DR/DQ rs9271366 variants - TLR1 I602S S mutation - C13orf31 rs3764147 and rs10507522 variants - CCDC122 rs9533634 and rs3088362 variants	- associated with susceptibility and resistance (Zhang et al. 2009) - protective against leprosy (Wong et al. 2010) - associated with susceptibility (Zhang et al. 2009) - associated with susceptibility (Zhang et al. 2009)
Mycobacterium tuberculosis	Tuberculosis	- IRGM 261TT - SLC11A1 multiple polymorphisms - TLR2 T597C C mutation	- resistant against MTBC lineage 4 (Intemann et al. 2009) - associated with pulmonary tuberculosis (Li et al. 2006) - associated with increased infection by MTBC lineage 2 (Caws et al. 2008)

Norovirus	Norovirus	- FUT2 null mutation homozygosity	- protects against some strains of virus (Lindesmith et al. 2003; Nordgren et al. 2010)
Trypanosoma brucei	Sleeping Sickness	-APOL1 variants 342G and 3384M	- confer resistance to sleeping sickness (Genovese et al. 2010)
Variola virus	Smallpox	-Multiple population-specific loci	- associated with success of seroconversion (Ovsyannikova et al. 2012)
Vibrio cholerae	Cholera		- Five genomic regions of selection in resistant population (Karlsson et al. 2013)
Yersinia pestis	Plague	-TLR10/TLR1/TLR6 locus	- under strong selection, and polymorphisms in this region confer different *in vitro* responses to *Y. pestis* stimulation (Laayouni et al. 2014)

Table 2. Classic genomic hallmarks of pathogen-host conflict

Hallmark type	**Example hallmarks (affected extant pathogen)**
Signatures of natural selection	- TLR10/TLR1/TLR6 region under positive selection in European populations (Barreiro et al. 2009; Laayouni et al. 2014)(Gram-positive bacteria, *Yersinia pestis*) - Five genomic regions under selection in cholera resistant Bangladeshi people (*Vibrio cholera*)(Karlsson et al. 2013)
Coding region mutations	- CCR5Δ32 deletion (HIV-1) (Dean et al. 1996) - HbS allele of HBB gene (*Plasmodium falciparium*) (Gouagna et al. 2010; Williams 2006)
Gene family expansion and narrowing	- Species-specific expansion of chemokine receptor family (unknown)(DeVries et al. 2006; He et al. 2004; Laing and Secombes 2004)
Changes in copy number variation	- Increased CNV of DMBT1 gene (cariogenic bacteria)(Polley et al. 2015)
Population differences in genetic response to infection	- European and African Americans generate different whole genome responses to *Listeria monocytogenes* and *Salmonella typhimurium* (Nedelec et al. 2016)
Telomere shortening	- Heritable shortening of telomere length occurs in a wild vertebrate chronically infected with malaria (Asghar et al. 2015)
Host genomic incorporation of pathogen nucleic acids	- Retroviruses represent approximately 8% of the human genome sequence and may have altered human placental development (Bannert and Kurth 2006; Dunlap et al. 2006)

Table 3. The immune and non-immune functions of the top five upregulated genes in response to three major infectious pathogens: *Mycobacterium tuberculosis*, Influenza A virus and *Trypansoma cruzi* (fdr <0.1).

Pathogen (host cell type)	Time point	Upregulated gene	Immune function	Non-immune function
Mycobacterium tuberculosis (monocyte-derived dendritic cells) (Pacis et al. 2015)	18 hours	BAALC-AS2 (C8orf56)	-	-
		SERPINB4	Natural killer cell activity(de Koning et al. 2011)	Implicated in menstruation(Paiva et al. 2016)
		SERPINB7	-	Kidney development and function(Miyata et al. 1998)
		IL36RN	Anti-inflammatory(Mulero et al. 1999)	Skin homeostasis [reviewed in (Gresnigt and van de Veerdonk 2013)]
		CSF3	Granulocyte and monocyte differentiation and development(Metcalf 1985; Numata et al. 2005)	Embryo implantation enhancement (Root and Dale 1999; Uzumaki et al. 1989) Osteogenesis(Ishida et al. 2010)
H1N1 Influenza A virus (plasmacytoid dendritic cells) (Thomas et al. 2014)	6 hours	CXCL10	Monocyte and T-cell activation and chemotaxis(Loos et al. 2008; Taub et al. 1996)	Muscle development(Wang et al. 1996) Angiogenesis(Angiolillo et al. 1995; Bodnar et al. 2006)
		CXCL11	Activated T cell chemotaxis(Loos et al. 2008)	Bone development/osteoclastogenesis(Coelho et al. 2005)
		IFNA17	Antiviral activity(Isaacs et al. 1957)	-
		IFNA4	Antiviral activity(Isaacs et al. 1957)	-
		IFNA1	Antiviral activity(Isaacs et al. 1957)	-
Trypansoma cruzi (human foreskin fibroblasts) (Li et al. 2016)	4 hours	CDH17(LI)	Cell adhesion(Dantzig et al. 1994)	Liver and intestine organization(Angres et al. 2001)
		SLC2A5	Macrophage differentiation(Fu et al. 2004; Malide et al. 1998)	Fructose metabolism(Burant et al. 1992) Spermatogenesis (Burant et al. 1992) Adipose differentiation(Du and Heaney 2012)
		CXCL8	Neutrophil trafficking(DiVietro et al. 2001)	Trophoblast implantation [reviewed in (Sharma et al. 2016)]
		IL4I1	Macrophage polarization(Yue et al. 2015) Antibacterial activity (Puiffe et al. 2013)	-
		AK4	-	GTP:ATP phosphotransferase activity**(**Noma et al. 2001)

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