The Essential Detail: The Genetics and Genomics of the Primate Immune Response

Shu Shen, Chul-Woo Pyo, Quyen Vu, Ruihan Wang, and Daniel E. Geraghty

Abstract

Next-generation sequencing technologies have led to rapid progress in the fields of human and nonhuman primate (NHP) genomics. The less expensive and more efficient technologies have enabled the sequencing of human genomes from multiple populations and the sequencing of many NHP species. NHP genomes have been sequenced for two main reasons: (1) their importance as animal models in biomedical research and (2) their phylogenetic relationship to humans and use in derivative evolutionary studies. NHPs are valuable animal models for a variety of diseases, most notably for human immunodeficiency virus/acquired immunodeficiency syndrome research, and for vaccine development. Knowledge about the variation in primate immune response loci can provide essential insights into relevant immune function. However, perhaps ironically considering their central role in infectious disease, the accumulation of sequence detail from genomic regions harboring immune response loci, such as the major histocompatibility complex and killer immunoglobulin-like receptors, has been slow. This deficiency is, at least in part, due to the highly repetitive and polymorphic nature of these regions and is being addressed by the application of special approaches to targeted sequencing of the immune response genomic regions. We discuss one such targeting approach that has successfully yielded complete phased genomic sequences from complex genomic regions and is now being used to resequence macaque and other primate major histocompatibility complex regions. The essential detail contained within the genomics of the NHP immune response is now being assembled, and the realization of precise comparisons between NHP and human immune genomics is close at hand, further enhancing the NHP animal model in the search for effective treatments for human disease.

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Introduction

During the last decade, improvements in next-generation sequencing technologies have led to rapid progress in the fields of human and nonhuman primate (NHP) genomics, extending detailed knowledge essential for the effective use of NHP animal models. These technologies enable the identification of all variants in a genomic region or even the whole genome as well as the sequencing of human genomes from multiple populations and the sequencing of many NHP species.

The essential rationale for this review is presented here, beginning with a description of the major uses of the NHP animal models for biomedical research. We next summarize the major genomic milestones that have been achieved and report recent changes in direction on the use of genomic data to identify causative genetic variation that contributes to common diseases. Given the evident importance of the immune response in infectious diseases in particular as well as in many other applications for biomedical research, we examine the state of the art in genomic studies of the immune response, highlighting the similarities and, importantly, the distinguishing features between the NHP immune response loci and orthologous regions in humans. Genomic data from the immune response loci in NHPs have lagged behind that of human immune response genomics, which itself is also substantially trailing the broader field of human genomics. As a direct remedy for this, our group has improved methods for acquiring genomic sequences from complex regions and applied them in resequencing projects of NHP major histocompatibility complex (MHC) regions. We discuss these efforts with a focus on advancing the state of the art of NHP immune response genomics.

NHPs as Animal Models

The close evolutionary relationship between NHPs and humans makes NHPs indispensible as models of disease in particular and for biomedical research in general. In comparison

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with other model organisms such as mice, NHPs show remarkable similarities to humans in behavior, neurologic function, development, and physiologic functions. Because of these similarities, primates are often used in behavioral research and for research of neurologic diseases such as Parkinson's disease or genetic diseases such as Huntington's disease (Emborg 2007; Yang et al. 2008). Primates are also the only mammals with reproductive cycles comparable with humans, making them the best models for reproduction and menopause (Braundmeier and Fazleabas 2009; Walker and Herndon 2008). In addition, NHPs are also used in research of chronic diseases such as diabetes and obesity (Bauer et al. 2011; Comuzzie et al. 2003; Harwood et al. 2012). Table 1 provides a partial summary of a wide range of disease research that uses NHPs as models. The NHP species are ranked from most to least respective counts for each disease. The order was determined by a search of the PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and PrimateLit (http://primatelit.library.wisc.edu/) databases to find the approximate number of studies of each disease using each model organism.

Detailed knowledge of the genomics of the immune response promises to have a major impact on studies of infectious diseases and on vaccine development. The NHP animal model is being applied to analyze human immunodeficiency virus type 1 (HIV-1) and HIV type 2 (HIV-2) infection through studies of the simian immunodeficiency virus (SIV) homologues (Morgan et al. 2008; Watkins et al. 2008). Whereas inbred mouse models have very limited genetic representation of allelic diversity at immune response loci, outbred NHPs are much more representative of the high polymorphism that is a hallmark of the major human immune response loci, providing a much more suitable animal model of human infectious disease. We discuss in more detail the use of four NHP models—sooty mangabeys (*Cerocebus atys*), rhesus macaques (*Macaca mulatta*), pig-tailed macaques (*Macaca nemestrina*), and cynomolgus macaques (*Macaca fascicularis*)—in regard to HIV/acquired immunodeficiency virus (AIDS) research and vaccine development.

Table 1 Human disease studied in nonhuman primate models

Disease[a]	Nonhuman primate species[b]
HIV/AIDS	Macaque Chimpanzee Sooty mangabey Baboon Gorilla
Parkinson's disease	Macaque Marmoset Squirrel monkey
Cancer	Macaque Chimpanzee Baboon Gorilla Squirrel monkey Marmoset
Diabetes	Macaque Baboon Chimpanzee
Malaria	Macaque Chimpanzee
Xenotransplantation	Baboon Macaque Chimpanzee
Alzheimer's disease	Macaque Chimpanzee Marmoset
Tuberculosis	Macaque Baboon Chimpanzee Squirrel monkey
Obesity	Macaque Baboon
Stroke	Macaque Baboon
Drug abuse	Macaque Squirrel monkey
Hepatitis C	Chimpanzee

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.
[a]Ranked in descending order of number of studies.
[b]Ranked from most used to least used in studies.

Sooty Mangabeys

More than 40 African NHP species are natural hosts of SIV, including sooty mangabeys, African green monkeys, and mandrills. They undergo a chronic SIV infection that generally does not result in clinical simian AIDS (Apetrei et al. 2004; Ling et al. 2004; Pandrea et al. 2001). Natural hosts offer an excellent opportunity for interpreting HIV pathogenesis because the AIDS pandemic originally arose as a consequence of zoonotic transmission of SIV from African species to humans. Evidence suggests that the HIV-1 epidemic originated from transmission of SIVcpz from chimpanzees to humans (Gao et al. 1999; Sharp et al. 1999). Similarly, the HIV-2 epidemic resulted from transmission of SIVsmm, found naturally infecting sooty mangabeys, to humans (Chen et al. 1997; Hahn et al. 2000). Moreover, passage of SIVsmm from mangabeys to macaques resulted in progressive infection and AIDS (McClure et al. 1989) and generated the SIV macaque animal model for HIV infection studies (Apetrei et al. 2004). In contrast, the nonpathogenic, persistent infections of African NHPs that are natural hosts of SIV have resulted from long-term coevolution between the viruses and their hosts. African NHPs infected with their species-specific viruses are therefore nonprogressive models of HIV pathogenesis. Comparisons between progressive and nonprogressive SIV models have revealed clues as to which

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viral and immunologic events are most important with regard to AIDS progression (Kornfeld et al. 2005; Muthukumar et al. 2005; Silvestri et al. 2003). Natural host species exhibit high levels of SIV replication and SIV plasma loads at levels comparable with HIV-positive patients. SIV-positive natural hosts also generally maintain healthy levels of $CD4^+$ T cells and low levels of aberrant immune activation during chronic infection, two characteristics which were both originally thought to be critical for the lack of opportunistic infections in these animals (Kornfeld et al. 2005; Silvestri 2005). Finally, relatively normal lymphoid architecture is maintained throughout SIV infection, potentially contributing to the ability of these monkeys to elicit effective immune responses (Muthukumar et al. 2004; Silvestri et al. 2003).

Rhesus Macaques

Currently the Indian rhesus macaque is one of the most widely used models for studying a variety of human health issues, ranging from diseases and disorders to potential therapies and preventive strategies (Table 1). It is also currently the best animal model for HIV vaccine testing (Johnson 1996; Stott and Almond 1995). Infection with SIV causes an AIDS-like disease in the majority of infected macaques by 1 year after inoculation (King et al. 1990). The nucleotide sequences of the SIVs are closely related to those of HIV-1 and HIV-2 (Chakrabarti et al. 1987; Franchini et al. 1987), and SIV and HIV have similar tropisms for CD4 (Daniel et al. 1985; Klatzmann et al. 1984). Therefore, SIV infection of macaques provides a cost effective animal model to test vaccine efficacy in vivo. Several vaccine studies in macaques have already suggested that a strong immune response to SIV can be generated in appropriately immunized monkeys (Benson et al. 1998; Desrosiers et al. 1989; Lehner et al. 1996; Murphey-Corb et al. 1989; Robinson et al. 1999). Furthermore, these studies provided the first demonstration that it may be possible to induce a protective immune response against the AIDS virus. The cell-mediated immune response to SIV may prove crucial for this vaccine protection. Because macaques and humans have similar immune systems, SIV infection of macaques is also an excellent model to study the immunology of HIV infection of humans. Many macaque genes that encode proteins important in the immune system are similar to those of humans. Orthologues of the human leukocyte antigen genes (HLA)-A, -B, -E, and -F have been isolated from rhesus monkeys (Watanabe et al. 1994), although there are nearly 10 times as many potentially functional macaque class I proteins as there are human class I proteins (Daza-Vamenta et al. 2004). Homologues of the human MHC class I (Boyson et al. 1996), MHC class II (Slierendregt et al. 1994), killer immunoglobulin-like receptor (KIR) genes, and TCR genes (Bontrop et al. 1995; Cohen 1988; Jaeger et al. 1993; Levinson et al. 1992) are found in macaques.

Studies in rhesus macaques could also provide insight into the roles of the MHC and KIR loci during HIV infection. In both human and NHP immune responses to HIV, variation in MHC and KIR genetics correlates with effects on susceptibility or resistance to HIV infection and disease progression (Fellay et al. 2007; Limou et al. 2009). In humans, both the HLA-B*57 and HLA-B*27 alleles have significant protective effects on HIV by controlling viral load and delaying disease progression (Kiepiela et al. 2004; Pereyra et al. 2008). In contrast, the HLA-B*35-Px allele is strongly associated with susceptibility to HIV infection (Gao et al. 2001; Itescu et al. 1992). There is also a strong association between the combination of KIR3DS1 and HLA-B Bw4-80I with a protective effect against HIV (Martin et al. 2007). In comparison, rhesus macaques with the manu-A*01 allele are more able to control viral replication and to survive longer (Mothe et al. 2003; Muhl et al. 2002). In addition, animals with the three class I alleles mamu-A*01, mamu-B*17, and mamu-B*29 were able to control the replication of a highly pathogenic SIV clone (O'Connor et al. 2003). The mamu-A*01 allele is present in 20–30% of the Indian rhesus macaque population, a fact that facilitated its discovery. However, the macaque MHC region is complex in its organization, and these studies have not necessarily accounted for many linked MHC class I loci.

Pig-tailed Macaque

The pig-tailed macaque has several advantages over the rhesus macaque as a research model: (1) the average weight of pig-tailed macaques is about twice that of rhesus macaques, enabling larger volumes of blood sampling; (2) they are more adaptable to changes in environment; and (3) they are more accepting of oral therapeutics and treatments in general. In addition, pig-tailed macaques are defective for restriction factor TRIM5α (Kirmaier et al. 2010), which in rhesus macaques works to inhibit HIV-1 replication. In contrast with other NHPs, pig-tailed macaques are generally more susceptible to infection by lentiviruses, including HIV-1 and HIV-2 (Agy et al. 1992; Bosch et al. 2000; McClure et al. 2000). Researchers have been able to construct simian tropic (st)HIV-1 strains that differ from HIV only in the *vif* gene. Infection of pig-tailed macaques with this construct resulted in high viral replication and persistent infection (Hatziioannou et al. 2009). Evidence also suggests that compared with the rhesus macaque model, SIV infection in the pig-tailed macaque is more comparable with HIV infection in humans (Batten et al. 2006). Recently, Klatt and colleagues (2012) found that pig-tailed macaques infected with SIVmac239 progress more rapidly to AIDS than rhesus macaques. Considering the greater susceptibility of pig-tailed macaques to HIV-1 and stHIV-1 and the more rapid disease progression during SIV infection, pig-tailed macaques make an excellent model for HIV/AIDS research.

Cynomolgus Macaques

Because of their ready availability, their low cost, their extensive use in pharmacologic testing, and their susceptibility to

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SIV, cynomolgus macaques are becoming important for use in trials examining SIV pathogenesis and therapy as well as for other experimental uses (Gupta et al. 2005; Maggiorella et al. 2004; Misumi et al. 2006; Negri et al. 2006; Wiseman et al. 2006). Although the majority of these animals have been used for non-AIDS–related infectious disease research or other types of research, they have been used in AIDS research by a few investigators. A recent study in cynomolgus macaques demonstrated that individuals with a heterozygous HLA locus had lower viral loads and greater protection against disease progression (O'Connor et al. 2010).

Human and NHP Genomes

Human Genomes

Since the first sequenced human genome was published in 2001 (Lander et al. 2001), many human genomes from multiple populations have been sequenced, resulting in the identification of more than 10 million single nucleotide polymorphisms (SNPs) and structural variants (International HapMap Consortium 2005; Pang et al. 2010; Sachidanandam et al. 2001). The International HapMap Consortium has extended the catalogue to other types of variants, such as copy number polymorphisms, while also studying the frequency of variants, their population distribution, and their linkage disequilibrium patterns (International HapMap 3 Consortium 2010). The 1000 Genomes Project intends to sequence human genomes from multiple populations (Europe, East Asia, South Asia, West Africa, and the Americas) to identify 95% of genetic variants with a frequency of 1% or more (1000 Genomes Project Consortium 2010). A pilot experiment has found more than 15 million SNPs and structural variants, many of which had not been identified by previous studies.

Protein-coding genes cover only about 3% of the human genome; however, most SNPs found to be associated with diseases/traits occur outside of protein-coding regions. To help explain this apparent paradox, the Encyclopedia of DNA Elements (ENCODE) project has mapped the human genome to identify a comprehensive list of functional elements, which include protein-coding regions, noncoding RNA, protein-binding regions, chromatin structure, and histone modification sites (ENCODE Project Consortium 2012). They have assigned a function to 80% of the genome and found that many genetic variants associated with disease by genome-wide association studies (GWASs) are located within or near a functional element. Combining this annotated catalogue of functional elements with GWASs and extended genomic sequencing should lead us more directly to the causative genetic components of disease.

NHP Genomes

After drafts of the human and mouse genomes were completed, NHP genomes became a priority because of the close evolutionary relationship of NHPs to humans and their importance in biomedical research (Eichler and DeJong 2002). Comparisons of human and other primate genomes and comparisons between primate genomes have shed light on studies of human evolution, potentially leading to a better understanding of the genetic variants that are unique to human traits and diseases. Thus far, sequences of the primates with the closest evolutionary relationships to humans, such as chimpanzees, gorillas, orangutans, and gibbons, have been completed or are in assembly (Chimpanzee Sequencing and Analysis Consortium 2005; Locke et al. 2011; Scally et al. 2012). The first genome of the rhesus macaque was sequenced in 2007 (Gibbs et al. 2007). Multiple groups have begun to sequence macaques from different populations to discover a broader catalogue of SNPs and other genetic variants (Fawcett et al. 2011; Satkoski et al. 2008; Trask et al. 2011). New World monkeys such as squirrel monkeys and marmosets are also commonly used in studies of infectious diseases and behavior (Ward and Vallender 2012). New World monkeys have an advantage over Old World monkeys in their smaller body size and shorter reproductive span, which in some circumstances make them better research models, despite the fact that Old World monkeys are more closely related to humans. The marmoset and squirrel monkey genomes are being sequenced by the Marmoset Genome Sequencing Consortium and the Vertebrate Genome Biology Group, respectively.

The mapping of genetic variation in NHP populations has lagged behind efforts to map variation in the human population. Understanding genetic variation in model organisms is important for the development of truly effective translational models. For example, variation in the rhesus macaque affects the levels of SIV and simian-human immunodeficiency virus (SHIV) replication (Kirmaier et al. 2010), a fact that must be taken into consideration when testing vaccines. Tools developed for human genome sequencing can be used to study closely related NHP genomes. Whole-exome resequencing, originally used to identify variation in the coding regions of the human genome, has also been used by multiple groups to find variation in the coding regions of NHPs (Enard et al. 2010; Vallender 2011).

The Genetics and Genomics of the Primate Immune Response

As we emphasize throughout this review, detailed knowledge of the sequences of immune response loci is essential for understanding the innate and adaptive immune responses and the treatment of infectious diseases. To translate results from the NHP animal model to humans, a careful comparison is needed to understand the components of the genetics of the immune response that are unique to humans and to NHPs. For the purposes of this discussion, we submit a list of immune response genomic regions (Table 2), chosen based on the following features: (1) spanning hundreds of kilobases to megabases, (2) containing multiple loci with

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Table 2 Genomic immune response regions

Locus	Location	Length	No. of genes
B cell receptors	14q32.33 2p12 22q11.2	1.2 Mb 1.8 Mb 1 Mb	170–176 genes 82 genes 84–93 genes
Beta chemokine receptors	3p21.3	300 kb	6 genes at chromosome 3p21 11 genes total
Cytokine gene cluster	5q31	1 Mb	6 cytokine genes
Fc gamma receptors	1q23	200 kb	5 genes
Human leukocyte antigens (HLA)	6p21.3	4 Mb	45 HLA genes 208 non-HLA genes
Immunoglobulin-like transcript (ILT)/leukocyte immunoglobulin-like receptor (LIR)/monocyte-macrophage inhibitory receptor (MIR) cluster	19q13.4 (2 clusters)	125 kb 150 kb	12–13 genes total
Interleukin 1 family	2q14	400 kb	15 genes
Killer immunoglobulin receptors	19q13.4	150 kb	15 genes 2 pseudogenes
Regulators of complement activation	1q32	1.6 Mb	15 complement genes 60 genes total
T cell receptors	14q11.2 7q34 7p14	1 Mb 700 kb 160 kb	116 genes 64–67 genes 19-22 genes
Toll-like receptors	4p14	54 kb	3 genes at chromosome 4p14 10–15 genes total

related structures and immune functions, and (3) harboring relatively high genetic variability. Additional regions could certainly have been included, but for succinctness we limited the number of items listed. Because of their repetitive and polymorphic nature, detailed population studies of these genomic regions and genes have generally lagged in genome-wide efforts. These regions have yielded reliable sequences from the human genome primarily after focused efforts were applied, such as with the human MHC (MHC Consortium 1999) or the first sequence of the T cell receptor locus (Rowen et al. 1996).

Although all the regions listed in Table 2 were finished in the first human sequence by sequencing BAC clones and other specific approaches, few have been finished in the available NHP genomic sequences. A notable exception is the rhesus macaque MHC sequence discussed below (Daza-Vamenta et al. 2004). At population levels, even fewer detailed genomic regions have been described, with only a portion of the human MHC class II region (Raymond et al. 2005) and KIR (Pyo et al. 2010; Pyo et al. 2013) reporting more than 20 sequenced haplotypes. Thus far none have been reported at the population level in NHPs, although, as discussed below, similar efforts are underway. Detailed genomic compilations for all of these regions derived from multiple sequences from both human populations and each of the major NHP species used in infectious disease research are essential.

The regions containing the KIR and MHC genes are two of the most variable in both the human and NHPs genomes. The KIR locus encodes natural killer (NK) cell receptors, which together with their ligands (MHC class I molecules) are critical for NK cell development and function (Parham and Moffett 2013). NK cells function in innate immunity as defense against infections and cancer and may also play an important role during placentation. Because of their functional requirements, both the KIR and the MHC regions are highly polymorphic and evolve continuously (Parham et al. 2012). Variations in KIR and MHC genes have been found to be associated with susceptibility to infections, autoimmune diseases, and reproductive success (Kulkarni et al. 2008; Parham 2005). Accordingly, based on their status as the best studied immune response regions, the following discussion focuses on the MHC and KIR genomic regions.

The MHC

The MHC is central to the immune response, with more than 40% of some 200 resident genes playing an immunologic

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Human		Rhesus			
Gene	alleles	Gene	alleles	Gene	alleles
A	2132	A1	180	E	22
B	2798	A2	67	F	6
C	1672	A3	13	G	4
E	11	A4	23	I	32
F	22	A5	7	DQA1	25
G	50	A6	5	DQB1	77
DRB	1297	A7	4	DPA1	18
DQA1	49	AG	7	DPB1	33
DQB1	179	B	303	DRB	204
DPA1	36	B11L	13	**Total**	**1084**
DPB1	158	B16	10		
Total	**8496**	B17	27		
		B20	4		

Figure 1 The killer immunoglobulin-like receptor (KIR) and major histocompatibility complex (MHC) loci in primates. (A) The human MHC locus, located on chromosome 6p21.3, is divided into the class I, class II, and class III regions. The MHC region in rhesus macaque is longer by more than 1 Mb, the result of expansions in the mamu-A and mamu-B regions. The table insert lists the current number of class I and class II alleles in humans and rhesus macaques. (B) The KIR locus is located on chromosome 19q13.4 in humans within the leukocyte receptor complex. KIR genes are organized into two major haplotype groups, A and B, based on gene content. The expanded view of the KIR locus shows seven gene content haplotypes that resulted from recombination between four centromeric and two telomeric gene motifs. Haplotype A specific genes are blue, haplotype B specific genes are orange, shared genes are green, and framework genes are gray. The KIR loci of rhesus macque, chimpanzee, and orangutan are shown in comparison.

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role (Bashirova et al. 2011; Parham 2005; Trowsdale 2011). In primates, the MHC is divided into three regions—the class I, class II, and class III regions (Figure 1A) – and in humans, the hallmark genes of the MHC are the class I (HLA-A, -B, -C) and class II (HLA-DP, -DQ, and -DR) loci, which encode the antigen-presenting molecules fundamental to the recognition of self and nonself. Together with the KIR loci discussed below, the classic MHC class I and II genes are the most polymorphic genes in primate genomes. As examples, in humans there are currently 2798 HLA-B alleles (the most polymorphic HLA gene) listed in the IMGT/HLA database (www.ebi.ac.uk/imgt/hla) (Robinson et al. 2013b), whereas 303 mamu-B like alleles are listed in the IPD-MHC database (http://www.ebi.ac.uk/ipd/mhc/) (Robinson et al. 2013a).

The early success of the human genomic efforts provided impetus to better understand the genetic diversity and genomics of the immune response in rhesus macaques to advance our understanding of the evolutionary history of primates and to aid the design and conduct of AIDS vaccine experiments in the rhesus SIV animal model. Previously, we isolated overlapping BAC clones containing a complete macaque MHC and obtained finished high-quality sequence data spanning the entire region (Daza-Vamenta et al. 2004). Two major differences between rhesus macaque and human emerged from these studies. First, there was a major expansion from six class I genes per haplotype (three nonclassical) in humans to as many as 28 MHC class I genes on a single haplotype in rhesus macaque, combined with levels of sequence divergence of 2–6% throughout extended portions of class I, some 10-fold higher than found in a similar human comparison. Second, alignment of two nearly complete haplotype sequences from the class II region revealed similarly high levels of sequence polymorphisms overall and specifically within most immune-related genes in this region.

The MHC region in rhesus macaques is expanded to 5.3 Mb, the result of internal duplications in the mamu-A and mamu-B regions. In the mamu-A region, there is an expansion in the number of genes and pseudogenes, but the function of the genes has remained largely similar between rhesus macaques and humans (Figure 1A). Although the mamu-G genes are pseudogenes, the mamu-AG genes—duplications of the mamu-A genes—appear to act as functional homologues to HLA-G. The mamu-B region underwent an even greater expansion, swelling to approximately 1.3 Mb from about 100 kb in humans. For Indian-origin rhesus macaques, there are varying numbers of class I and II loci; for example, for mamu-B there are up to 14 potentially active loci per haplotype (Daza-Vamenta et al. 2004). Further, different haplotypes contain different loci, essentially blurring the distinction between a locus and an allele. Outside of these two regions, gene content and function in rhesus macaques are similar to that of their orthologues in humans, although a higher level of copy number variation exists in the mamu class II region. In addition to high allelic polymorphism, rhesus MHC-I and MHC-II genes gain diversity through gene content and combinations of expressed genes (Otting et al. 2005).

A consideration of the evolutionary context and the functional consequences of the expansion of mamu-B loci was summarized in the article containing the original description of the rhesus macaque MHC (Daza-Vamenta et al. 2004). There we discussed the likelihood that evolutionary constraints are limiting the numbers of class I loci functioning in antigen presentation to far less than the 20 per haplotype found in macaques. Indeed, copy number may be compensated for by reduced numbers of expressed genes, as evidenced by the numbers of cDNAs found from any individual animal (Wiseman et al. 2009). However, it is worth restating here that, although several genes within an animal may be functionally silenced or expressed at low levels (Budde et al. 2011), it is not clear what mechanisms are operating to control expression because there are no evident structural defects in most of the genomic sequences. If differential methylation controls expression, then that leaves the question of whether the methylation is sequence specific—all versions of a particular genomic sequence in a population are similarly controlled—or whether, perhaps more likely, control of expression might be developmental or even possibly change during an animal's lifetime in response to pathogens. This latter idea might allow for a limited number of expressed alleles at any particular time while still retaining a larger reservoir of potential diversity for antigen presentation. Such a possibility would, of course, require explanations of how T cell education and tolerance would be operating if MHC-I were changed midlife, and that consideration may rule out the possibility in the first place. However, the control(s) of macaque MHC class I expression requires an explanation both for basic understanding of MHC plasticity in evolutionary biology among other basic immunologic considerations and for supporting the utility of the macaque as an animal model for human infectious disease.

The KIR Family

NK cell receptors in mammals belong mainly to two protein families, the KIRs and the killer cell lectin-like receptors (KLRs). In humans NHPs, the NK cell receptors are represented by the KIR locus, which appears to have expanded from a single copy of KIR3DL (Averdam et al. 2009; Guethlein, Abi-Rached, et al. 2007). The KIR locus in humans is located on chromosome 19q13.4 within the leukocyte receptor complex and is highly variable with regard to both gene content and allelic polymorphism (Figure 1B). A total of 15 human KIR genes and two pseudogenes, separated into centromeric and telomeric regions by the framework *KIR3DP1* and *KIR2DL4*, have been identified (Bashirova et al. 2006). Two other framework genes, which are genes present in all haplotypes, are *KIR3DL3* at the centromeric end and *KIR3DL2* at the telomeric end.

KIR genes are organized into the major haplotype groups A and B based on gene content. Haplotype A is constant in gene content, consisting of five inhibitory genes and one activating gene, whereas haplotype B contains a variable number of inhibitory and activating genes (Kulkarni et al. 2008).

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Recently, we sequenced 24 common human KIR haplotypes, leading to the identification of seven major gene content haplotypes, each representing different combinations of four centromeric and two telomeric gene motifs (Figure 1B) (Pyo et al. 2010). Further work examining 9024 chromosomes identified a total of 37 KIR haplotypes based on gene content—far more when considering allelic variation—containing various gene deletion, gene insertions, and gene hybridizations (Pyo et al. 2013).

Only a few individual animals from several primate species have been sequenced, leading to an incomplete picture of KIR variability (Figure 1B). Thus far, 13 KIR genes have been identified in chimpanzees, including the framework genes and variable centromeric genes, leaving the telomeric region empty (Abi-Rached et al. 2010). In chimpanzees, KIR variability is similar to that of humans, but unlike in humans where there is recombination between the centromeric and telomeric regions, variability in chimpanzee KIR gene content arises from recombination among the centromeric genes only. Chimpanzee haplotypes are closer to human haplotype group A, with no haplotype group B counterpart evidently present in populations. Orangutan KIR haplotypes also resemble the chimpanzee haplotypes and human haplotype group A. As in chimpanzees, the orangutan KIR locus contains the framework genes and genes in the centromeric region only (Guethlein, Older Aguilar, et al. 2007). Rhesus macaques are evolutionarily more distant from humans than either chimpanzees or orangutans, and mamu KIR loci are more divergent as well. Five KIR genes have been identified in the rhesus macaque, three orthologous to the human framework genes and one gene each located in the centromeric and telomeric regions (Sambrook et al. 2005). These comparisons between human and NHP sequences demonstrate the rapid evolution of the KIR in primates.

Genetic Variation and Disease

A central rationale motivating the genome sciences is the identification of the causative genetic variation that underlies common diseases. The large majority of genome-wide searches in the genetics of complex disease have tested the common disease/common variant hypothesis using GWASs that examined the association of common variants with disease in case–control models. However, growing evidence suggests that common human diseases with a genetic component are more often caused by rare variants that cannot be identified by GWASs (McClellan and King 2010; Olson 2012). Indeed, it appears that most human diseases are characterized by genetic heterogeneity, where a complex disease may be caused by any one of a variety of collections of rare alleles in an individual (McClellan and King 2010). New alleles are constantly produced with each generation and together vastly outnumber the common variants. Deleterious mutations are likely to be the rare alleles because they are less likely to be passed on to the next generation. Therefore, the identification of rare alleles is likely essential to identifying causative genetics that underlie common disease. Consequently, extended genomic regions associated with disease need to be sequenced to high resolution in large numbers of individuals to identify rare, disease-causing alleles. Although inexpensive, high-fidelity, whole-genome sequencing is still in development, some new approaches are now available to obtain high-resolution data over extended regions, as discussed below.

When considered in the context of the immune response genetics, the rare variant hypothesis has particular appeal. Consider, in primates both the MHC and KIR loci have extensive allelic polymorphism, and most alleles are rare by genome standards, especially when taking into account variation over each complete locus (i.e., high-resolution genotyping). This variation affects protein structure and antigen binding, expression levels, and epistatic interactions between receptors and ligands. How to best combine these considerations on a particular disease pathway requires, first, a detailed knowledge of relevant variation and, second, analysis based on flexible models that explore interactions among those variations. For the most part, such detail is lacking in studies of infectious disease for both humans and NHPs, and analysis is usually restricted to standard approaches for other genome regions. As a result, much of the functional detail has been missed (e.g., most GWAS platforms detect only a few KIR alleles among the aggregate thousands present in a population).

The genotyping needs of the diverse NHP immunologic and infectious disease research community, including the special needs of solid organ, tissue, and bone marrow/stem cell transplantation research, are all essentially the same. That is, the more information about complex immune genetics made available—regardless of the clinical outcome being studied—the more precise are potential comparisons. In that regard, different approaches are needed to acquire genetic and genomic data, with both the breadth and depth of allelic information, from immune response loci and related genomic regions. As a framework for that capability, we discuss below more recent developments of alternative approaches applicable at the genomic level.

Targeted Sequencing of Immune Response Genomic Regions

As the human genome project has repeatedly demonstrated, the establishment of framework genomic DNA sequences can provide fundamental support for, and an extension of, a plethora of basic and clinical research studies that are now advancing human health. However, as the human genome project has also shown, establishing framework DNA sequences for regions of the genome harboring immune response genes, especially the MHC region, is difficult and has largely been excluded from those efforts. The difficulty is because of the complex repetitive structure of those regions within an individual genome and the high levels of allelic polymorphism within populations. Fortunately,

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intelligently focused efforts using state-of-the-art technology can resolve such complex genomic sequences, as demonstrated by the completed rhesus macaque MHC sequence. These approaches, combined with new advancements in sequencing technology, can now yield completed phased genomic DNA from such complex regions, providing a framework for future studies and an opportunity for comparative analysis among macaque populations. Such comparisons, in turn, will provide direction for functional testing of genetic factors that, for example, relate to long-term nonprogression of SIV infection in rhesus macaques and then to the same phenotype for HIV-1 infection in humans. Evidently, the identification of causative host genetic factors that control HIV-1 infection in humans would have important implications for disease treatment and vaccine design.

An illustrative example of the need for high-quality finished sequence is evident from the rhesus MHC sequences. An essential step in functional studies of SIV disease progression and vaccine trials is to identify the structure of all of the class I genes potentially expressed in an animal. Many of these studies are focused on cytotoxic T lymphocyte responses and are looking in detail at the MHC–peptide complexes that are associated with viral escape and disease progression (Greene et al. 2012; Wu et al. 2011). The consideration of all of the antigen-presenting genes that are available for participation in a specific immune response could reveal in more detail how that response is initiated, how it progresses, and under what circumstances it is ultimately evaded or completed. In this regard, the higher levels of polymorphism in immune-related genes in the rhesus MHC outside of the class I and II regions could affect immune function in other ways that are qualitatively distinguishable from those in human. For example, the higher level of polymorphism in the TAP genes in the rat has functional consequences for peptide selection, a feature not mirrored in humans (Powis et al. 1996).

Considering that as many as 28 mamu-B loci and four mamu-A loci may be expressed in a heterozygous animal raises questions about not only which class I loci are most important to a particular cytotoxic T lymphocyte response but also the interaction of class I molecules with the innate immune response. As discussed above, an essential component of the latter response is the interaction between the KIR and their MHC class I ligands. In humans, specific class I antigens interact with specific KIR loci to yield both inhibitory and activatory responses from NK cells. However, the expansion of class I in the macaque was apparently not associated with an expansion of the number of KIR gene products (Hershberger et al. 2001). This raises the question of whether an increase in the number of mamu-B proteins has affected the corresponding inhibitory or activatory network. Among the details provided by the finished high-quality rhesus genomic sequence was that of the 19 mamu-B genes present on one haplotype; four of them were predicted to be nonfunctional because of a single nucleotide substitution that introduced a stop codon in the open reading frame. Therefore, out of more than a megabase of sequence, a specific 4 base pairs were essential to distinguish these pseudogenes. This essential detail was in addition to the precise structures of the 14 intact sequences on the same haplotype, most of which encode functional proteins as supported by cDNA and transfection analysis (Evans et al. 2000; Mothe et al. 2002).

Over the past several years, four efforts have resequenced long tracts of phased DNA from complex immune regions from multiple individuals. The Sanger Institute used BAC cloning and ABI sequencing to complete three MHC sequences of some 4 Mbp each and compiled several portions of five additional haplotypes over a period of 8 years before closing that effort in 2007 (Horton et al. 2004; Horton et al. 2008; Stewart et al. 2004). The rhesus macaque MHC sequences our laboratory completed contribute a second example (Daza-Vamenta et al. 2004). The situation is little better on shorter distance scales. The University of Washington Genome Center's publication of 20 new human haplotypes across a 100-kbp segment of the HLA class II region was by far the deepest study of any MHC region extending for more than a few kilobase pairs (Raymond, Kas, et al. 2005). That effort is also closed as of 2007. Our laboratory has since used the approach they pioneered to establish a third dataset in the sequencing of 24 phased KIR haplotypes in our initial effort (Pyo et al. 2010) and supplemented with a comprehensive population study and the sequences of several additional haploytpes (Pyo et al. 2013).

The challenge in establishing highly accurate sequences from complex repetitive regions lies in the acquisition of DNA spanning the targeted region. As mentioned above and evidenced by the MHC (Raymond, Kas, et al. 2005) and KIR (Pyo et al. 2010; Pyo et al. 2013) sequences, fosmid libraries solve this problem where other methods fail. No other method, outside of BAC cloning, has produced complete, contiguous, high-fidelity MHC or KIR sequences. The highly duplicated structures of these regions simply cannot be assembled from shotgun methods without some higher scale order placed on the data such as that accomplished through the use of fosmids.

Our laboratory has advanced the original approach described by Raymond and colleagues (Raymond, Subramanian, et al. 2005) for fosmid acquisition and sequencing to obtain in-phase sequences of complex genomic regions efficiently and inexpensively. The method, summarized in Figure 2, starts with the construction of fosmid libraries from genomic DNA. Libraries are diluted over wells to reduce the complexity of each well to about 5% of that of the whole genome. Improvements over the original approach are largely due to the use of next-generation sequencing technology, which enables the use of multiplexing sequencing to quickly identify wells containing target fosmids. Because each well has a mixture of different fosmids, the isolation of the target fosmid is accomplished by recombineering (Nedelkova et al. 2011). For the final step of sequence analysis, hundreds of individual fosmids can be sequenced in one or a few sequencing runs, providing finished high-quality data that is phased over the approximately 40 kb region covered by each fosmid. Individual fosmid sequences can then be assembled

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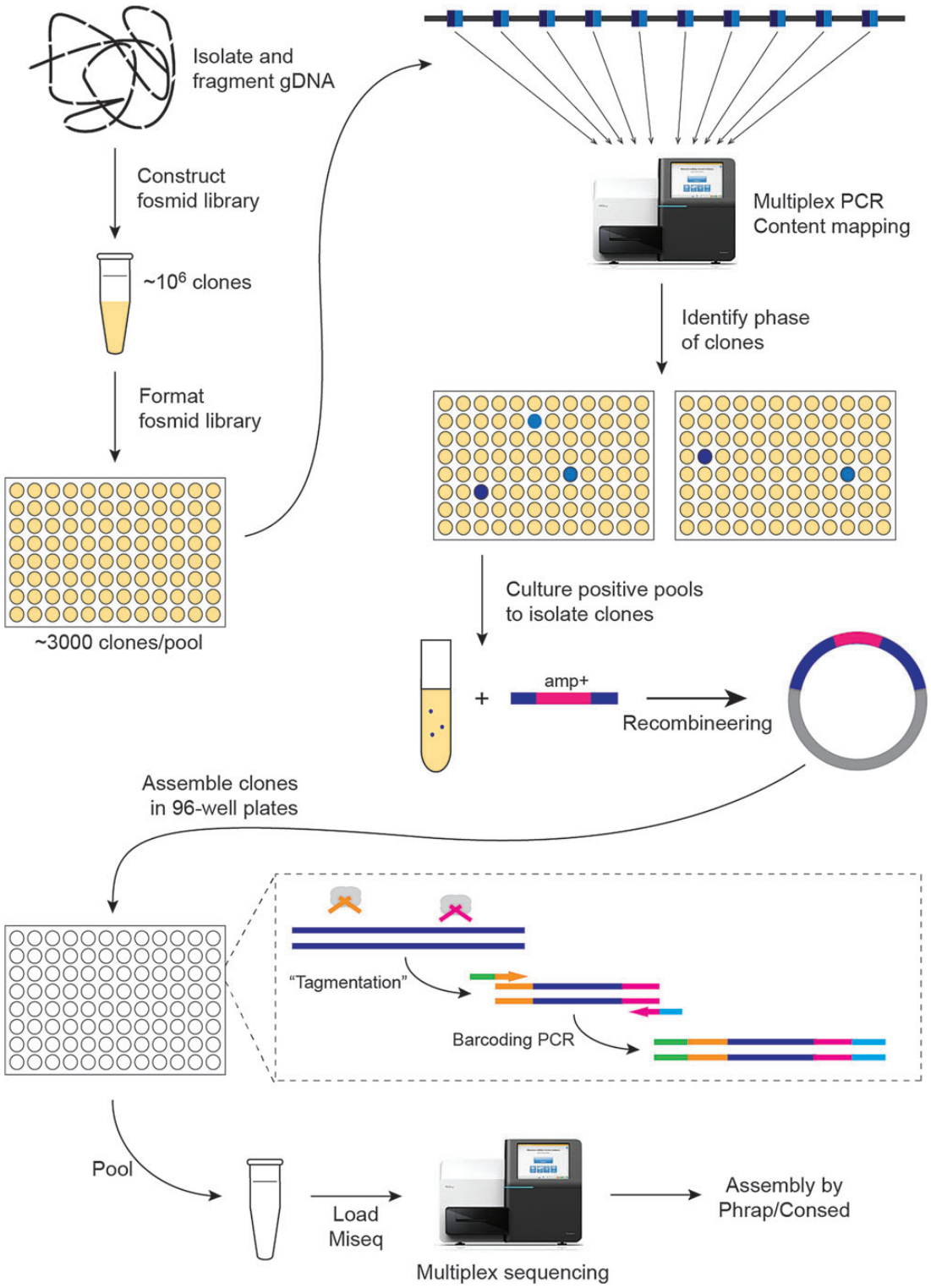

Figure 2 Generation of phased genomic sequences using fosmids. Fosmid libraries are constructed by inserting fragmented genomic DNA into vectors to create approximately 10^6 clones, which are formatted into 96-well plates containing approximately 3000 clones/well. Content maps are created using multiplex sequencing that identifies targeted clones over extended regions and allows phase to be determined. Clones of interest are isolated using a recombineering approach, where an ampicillin-resistant marker is inserted into the regions of interest by homologous recombination and selection isolates the targeted fosmid from the mixture of fosmids within a well. Isolated fosmids are sequenced by shotgun sequencing using the Nextera DNA Sample Preparation kit from Illumina. DNA formatted into 96-well plates is treated with Nextera transposomes that fragment DNA and at the same time tag them with unique adaptor sequences. The fragmented DNA is then subjected to limited cycle polymerase chain reactions, which add sequencing primers and indexing sequences on either side of the fragment. After being tagged with unique indexes, DNA is pooled together and loaded onto an Illumina Miseq instrument for multiplex sequencing.

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using overlaps to reconstruct long phased sequences on the megabase scale.

We are currently using this approach to resolve several MHC regions from macaques and the sooty mangabey. The overall objectives include the establishment of high quality, phased genomic sequences from the MHC from multiple samples taken from rhesus macaques, cynomolgus macaques, and pig-tailed macaques. The macaque sequences will include a minimum of 20 approximately 1.6 Mbp of total phased sequence and highest quality haplotype sequences, fully annotated, from the class IB and class II regions. These sequences will provide an unprecedented resource of complex immune genomic regions (among any genomic dataset now available, including from humans). This project is now ongoing, and individual fosmid sequences will be deposited in GenBank in the second half of 2013, with annotation and complete phasing over the megabase regions following in subsequent years. This comprehensive dataset will enable more knowledge of the immune loci that are central to both the adaptive and innate immune responses, furthering basic and clinical research of infectious disease, autoimmunity, and transplantation. It will also be available for use in developing methods and tools that will allow for genotyping and haplotyping of MHC class I and class II in macaques at a superior depth and, consequentially, be much more informative than current methods allow.

Summary

One of the goals of genomics is to understand the full range of genetic variation as it affects various phenotypes. Growing evidence indicates common disease is primarily caused by rare alleles that may occur in only one individual or one family and that different rare mutations affect the same disease processes in different individuals, collectively resulting in the observed disease in a population. Therefore the identification of rare alleles has significant implications for the treatment of disease in individuals, as well as for advancing our understanding of the pathology of common diseases. Next-generation sequencing technologies, combined with advancements in methods to acquire targeted regions of the genome, unlike approximate methods such as GWASs, are capable of identifying all variants in a region and may be the only method available to obtain sufficient detail from genomic regions containing immune response genes.

NHP disease models are widely used in biomedical research, especially in HIV/AIDS research and vaccine development. The genomes of primate species most closely related to humans (chimpanzee, gorilla, and orangutan) as well as several species heavily used in biomedical research (macaque, baboon, and squirrel monkey) have been sequenced or are in progress. Although the data obtained from sequencing these species have led to a better understanding of primate evolution and have been useful in understanding disease processes, variations within and among populations need to be catalogued and accordingly accounted for in the design of experiments. The essential detail contained within the genomics of the NHP immune response is now being assembled, and the realization of precise comparisons between NHP and human immune genomics is close at hand, further enabling the NHP animal model in our search for effective treatments for human disease, including HIV-1 infection and AIDS.

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