Major Histocompatibility Complex Class-I-Interacting Natural Killer Cell Receptors of Nonhuman Primates

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Key Words

Nonhuman primates • Killer cell immunoglobulin-like receptors • C-type lectin-like receptors • Coevolution • Major histocompatibility complex class I

Abstract

Human natural killer (NK) cell receptors are known to be highly polymorphic, to show complex genetics and to be associated with susceptibility to a variety of immunological diseases. Nonhuman primates are used as important models of these diseases, yet the knowledge of nonhuman primate NK cell receptors and ligands is not as advanced as in humans. Recently published data indicated that diversity and polymorphism of NK cell receptors are similar between nonhuman primates and humans. Comparative genomics revealed instructive insights into the evolution and function of primate NK cell receptor genes and contributed to the understanding of how present-day NK cell receptors and their ligands have evolved. Here, I review the current knowledge of nonhuman primate NK cell receptors that interact with major histocompatibility complex class I proteins.

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Introduction

Natural killer (NK) cells perform essential functions in the innate immune system against infected or malignant cells and play important roles in priming adaptive immune responses to viral, bacterial and eukaryotic pathogens [1, 2]. These lymphocytes are equipped with various germ line-encoded receptors that typically belong to two unrelated protein families: C-type lectin- and immunoglobulin (Ig)-like receptors. The activity of NK cells is regulated through integration of signals derived from inhibitory and stimulatory forms of these receptors, and activation results in killing of target cells and/or secretion of cytokines and chemokines [3, 4]. Another key component of the immune system, the family of major histocompatibility complex (MHC) class I proteins, serves as ligands for many C-type lectin- and Ig-like receptors. Therefore, this review focuses on those NK cell receptors that bind to MHC class I proteins.

Typical primate NK cell receptors capable of binding to MHC class I ligands are the families of killer Ig-like receptors (KIRs) and C-type lectin-like heterodimeric CD94/NKG2 receptors. Data from human and chim-

Fig. 1. Phylogenetic relationship of primates. mya = Million years ago. Figure adapted from Averdam et al. [38].

panzee showed that KIRs are expressed primarily on subsets of NK cells and CD8+ $\alpha\beta$ T and $\gamma\delta$ T cells. A special feature of KIRs is their variegated expression: NK cells with 0 or up to 4 different inhibitory KIR proteins have been described in human [5, 6] and common chimpanzee [7]. The actual number of KIR expression patterns is likely to be higher as no activating KIRs were included in these studies. Further characteristics of primate KIR are a high degree of polymorphism (allelic variability) and diversity (differential gene content) [8–11]. The various KIR genes have been assigned to lineages based on phylogenetic relationship: lineage Ia and Ib comprise *KIR2DL4* and *KIR2DL5*, respectively, lineage II contains *KIR3D* genes except *3DL3*, lineage III encompasses *KIR2D* genes except *2DL4* and *2DL5*, and lineage V harbors *KIR3DL3*. KIR genes evolve very fast [12–15], resulting in blurring intra- and intergenetic relationships and in the rapid loss of orthology of KIR genes, even between closely related species such as humans and chimpanzees.

The primate KIR molecules specifically react with MHC class I molecules of the MHC-A, MHC-B, MHC-C and MHC-G types [8]. In human, the spectrum of specificity of these interactions is broad: KIR3DL2 reacts only with 2 alleles of HLA-A (A*003, A*011), KIR3DL1 binds to class I molecules containing the Bw4 serological epi-

tope (roughly 30% of all HLA-B and only some HLA-A allotypes), KIR2DL1 and KIR2DS1 bind all HLA-C2 types and KIR2DL2/3 react with all HLA-C1 and certain C2 types, whereas KIR2DL4 reacts with all HLA-G alleles. The extraordinary polymorphism of the MHC class I ligands in combination with highly variable KIRs gives rise to differences between members of a population in terms of susceptibility to a couple of infectious [16] and autoimmune diseases [17] and can influence the success of bone marrow transplantation [18] and reproduction [19].

Contrasting the variable KIRs are the highly conserved CD94/NKG2 receptors in simian primates (Catarrhini and Platyrrhini; see fig. 1 for taxonomic designations and phylogenetic relationship). CD94 pairs either with NKG2A to form an inhibitory receptor, or with NKG2C or NKG2E, giving rise to stimulatory receptors. There is virtually no polymorphism or diversity seen for CD94 [7, 20, 21] and only limited polymorphism and some diversity for most NKG2 family members in simian primates [21]. All pairs of human CD94/NKG2A, CD94/NKG2C and CD94/NKG2E heterodimeric receptors bind to the non-classical and highly conserved HLA-E ligand. The activating NKG2D receptor is only distantly related to NKG2A, NKG2C, NKG2E and NKG2F. These homodimeric receptors interact with stress-induced ligands

of the MHC class-I-related MIC and ULBP families and mediate strong activation [22].

Much of the knowledge on NK cells and their receptors is derived from studies in mice and humans. Despite the fact that mice provide excellent tools for studying functions of genes via respective knock-out or transgenic animals, they are not suitable to model certain human infectious diseases. Nonhuman primates fill this gap due to their closer phylogenetic relationship with humans.

Polymorphic NK Cell Receptors of Hominoid Primates

Hominoid primates encompass humans, great apes (common chimpanzee, bonobo, gorilla, orangutan) and smaller apes (gibbons). All *KIR* lineages are found in hominoid primates, but the number of *KIR* genes per individual lineage can vary between species. For example, humans and great apes have particularly expanded lineage III *KIRs*, i.e. *KIR2D* genes, but such an expansion is not evident in gibbon species [23]. A plausible explanation for this observation is that *KIR2D* proteins interact with *MHC-C*-encoded ligands, and an *MHC-C* gene locus is present only in humans and great apes, but not in gibbons [23–25].

Considerable diversity is seen for human *KIR* haplotypes, yet all of them can be assigned in a rather simple way to two groups termed ‘haplotype group A and B’ [20]. The two groups differ in number of activating *KIR* genes, being either low (group A) or high (group B). So far, this distinction has not been observed in any other primate species, and hence, might be specific to humans. Nevertheless, common chimpanzee [7, 26], bonobo [27], gorilla [15] and orangutan [28] *KIR* genotypes and haplotypes are also highly diverse. Among the bonobo *KIR* haplotypes there is one haplotype comprising only the three genes *KIR2DL4*, *KIR3DL3* and *KIR3D* [27]. Such haplotypes were called ‘minimal essential *KIR* haplotypes’ [27] as they contain only those types of *KIR* genes that are present on all human haplotypes, so-called ‘framework *KIR* genes’. Gibbons deviate from other hominoid primates in that all gibbon *KIR* haplotypes identified so far are small; the only framework gene is *KIR3DL3*, and *KIR2DL4* is a frequent target of deletion [23].

Human, chimpanzee and orangutan *KIR* molecules specifically interact with MHC class I molecules of the MHC-A, MHC-B and MHC-C types [7, 29]. In humans, these encompass *KIR2DL1* (interacting with HLA-C2 types), *KIR2DS1* (HLA-C2), *KIR2DL2/3* (HLA-C1 and

certain HLA-C2), *KIR2DL4* (HLA-G), *KIR2DS4* (certain HLA-C1 and HLA-C2, HLA-A*11), *KIR3DL1* (Bw4 epitope-carrying HLA class I) and *KIR3DL2* (HLA-A*003, HLA-A*011). Similar to human, also the common chimpanzee *MHC-C* gene, designated ‘*Patr-C*’, encodes the main ligand of chimpanzee *KIR* molecules: lineage III *KIRs* *KIR2DL6* and *KIR2DL8* are specific for *Patr-C1* types, and *KIR2DL7* is specific for *Patr-C2* types [30]. In contrast to human, specificity for MHC-C ligands is also found for chimpanzee *KIR3D* molecules *3DL4* and *3DL5*, which interact with *Patr-C2* types [30]. However, it should be noted that these types of *KIR3D* proteins represent unusual members of *KIR* lineage III. A further difference between human and chimpanzee refers to number and types of genes at the telomeric side of the *KIR* locus, i.e. the region between *KIR2DL4* and *FCAR*, which in chimpanzee harbors only a single gene, *KIR3DL1/2*. Chimpanzees and gorillas have only single lineage II *KIR* genes, gorilla *KIR3DLa* and chimpanzee *KIR3DL1/2* [15, 31]. The latter encodes a protein with specificity for both Bw4 and Bw6 ligands [7]. Phylogenetic analysis suggested that chimpanzee *KIR3DL1/2* is more closely related to human *KIR3DL1/3DS1* and gorilla *KIR3DLa* to human *KIR3DL2* [15]. Interestingly, the D1 domain of *KIR3DLa* is assigned to *KIR* lineage III. Besides unequal crossing-over and formation of hybrid genes [23, 32], such shuffling of exons represents a characteristic mechanism to increase the genetic diversity of *KIR* [15, 33]. Gorilla lineage III *KIR2D* can also bind to MHC-C1 and MHC-C2 types. In contrast, all orangutan MHC-C allotypes are of the MHC-C1 type [29], and consequently, orangutan *KIR2D* molecules have only specificity for MHC-C1. An exception is orangutan *KIR2DLB*, which is specifically interacting with both HLA-C1 and HLA-C2 types. This receptor is seen as an evolutionary intermediate in the development of MHC-C1- and MHC-C2-specific lineage III *KIRs* in other hominoid primates [29]. Notably, the *MHC-C* gene is not fixed in orangutan populations, with 25% of individuals being negative for this gene [25]. Thus, fixation of the *MHC-C* gene obviously accompanied formation of MHC-C1- and MHC-C2-specific *KIRs* in hominoid primates – a further instructive example of MHC class I and *KIR* co-evolution. As a result of various deletion events, all present-day *KIR* haplotypes in gibbon species tested so far are rather small, with only 2–5 functional *KIR* genes [23]. Moreover, gibbon *KIR* haplotypes are atypical compared to other hominoid primates, with *KIR3DL3* being the only conserved framework *KIR* gene, with *KIR2DL4* being a recurrent target of deletion, and with lack of *KIR* lineage III expansion [23]. Here again, a view on the MHC class I

gene family provides a plausible explanation: gibbons lack genes encoding MHC-G and MHC-C, the putative ligands of KIR2DL4 and lineage III KIRs, respectively.

Polymorphic NK Cell Receptors of Old and New World Monkeys

KIR genes have been described in the Old World monkey species rhesus and cynomolgus macaques and African green monkey and show a considerable degree of polymorphism and diversity [10, 11, 34, 35]. Data on KIR protein expression in lymphocyte subsets are not yet available due to lack of appropriate monoclonal antibodies and lack of cross-reactivity of antihuman KIR antibodies. So far, only a single *KIR* haplotype has been completely sequenced in Old World monkeys. This rhesus macaque *KIR* haplotype contains the *KIR3DL3*-corresponding gene *KIR3DL20*, a *KIR* gene encoding only a single Ig-like domain (*KIR1D*), *KIR2DL4*, *KIR3DL1* and *KIR3DL10* [31]. Methods for specific genotyping based on mRNA [11, 34] and on genomic DNA [10] have recently been published for macaques. These studies revealed that rhesus macaque *KIR* haplotypes show extensive allelic and genomic variation with up to 11 segregating *KIR* genes per haplotype [10, 34]. Furthermore, these studies indicated that the sequenced rhesus macaque *KIR* haplotype was rather small and unusual. A striking difference to hominoid primates is a considerable expansion of lineage II *KIR* genes and lack of lineage III *KIR* genes, which is most probably due to extensive expansion of MHC class I genes of the *MHC-A* and *MHC-B* types [36] and lack of an *MHC-C* gene, respectively. However, so far, specific interactions of rhesus macaque inhibitory and activating KIR3D were detected only with class I proteins of the *MHC-A* and not the *MHC-B* type [37]. Similar to human KIR3DL1, rhesus macaque KIR3DLW03 binds to the Bw4 epitope of Mamu-A ligands, whereas rhesus macaque KIR3DL05 interacts with both Bw4 and Bw6 epitopes of Mamu-A [37].

Cynomolgus macaques (also designated 'long-tailed macaques' or 'crab-eating monkey') and rhesus macaques have several *KIR* genes in common such as *KIR1D*, *KIR2DL4*, *KIR3DL1*, *KIR3DL2* and *KIR3DL20* [11]. Not surprisingly, differences between both macaque species are particularly found among the rapidly evolving lineage II *KIR3D* genes. A common feature of activating KIR proteins in Old World monkeys and in gibbons is the presence of an arginine residue in the transmembrane region as opposed to a lysine residue in humans and great apes.

Table 1. Combinatorial diversity of CD94/NKG2 receptors in primates

Species	CD94/NKG2 receptors	Receptor numbers	Known or putative ligand(s)
Human	CD94, NKG2A, NKG2C, NKG2E	3	HLA-E
Common chimpanzee	CD94, NKG2A, NKG2CI, NKG2CII, NKG2E	4	Patr-E
Orangutan	CD94, NKG2A, NKG2CE	2	Popy-E
Common marmoset	CD94, NKG2A, NKG2CE	2	Caja-E
Mouse lemur	CD94-1, CD94-2, CD94-3, NKG2-1, NKG2-2, NKG2-3, NKG2-5, NKG2-8	15	unknown, many possible
Ruffed lemur	CD94-1, CD94-2, CD94-3, NKG2-1, NKG2-2, NKG2-3, NKG2-4, NKG2-5, NKG2-6, NKG2-7, NKG2-8	24	unknown, many possible

Recently, *KIR* genes have been described in a New World monkey species, the owl monkey [33]. While rapid evolution has wiped off close phylogenetic relationships to catarrhine *KIR* coding sequences, owl monkey *KIR* genes still contain repetitive elements typical of primate *KIR* lineages. However, the most obvious difference is that owl monkeys possess transcribed *KIR* genes encoding a protein with 4 Ig-like domains (KIR4D). This expansion of Ig domains stems from duplication of D0 domain-encoding exon 3 [33].

Polymorphic NK Cell Receptors of Lemurs

An analysis of strepsirrhine primates (fig. 1) indicated the presence of a novel system of polymorphic NK cell receptor genes [38]. Sequencing of the complete *KIR* locus revealed only a single *KIR* pseudogene, which represents the ancestral type of *KIR3D* genes in platyrrhine and catarrhine primates. Intriguingly, lemurs considerably expanded their *CD94* (3 copies) and *NKG2* (5–8 copies) genes. In addition, these genes are also highly polymorphic and the polymorphism is biased towards residues involved in binding of MHC class I ligands and their presented peptides. All copies of *CD94* and *NKG2* can form

proper heterodimeric receptors expressed on the cell surface [38], giving rise to remarkable combinatorial diversity (table 1). Notably, so far, such a type of diversity has not been found for any other NK cell receptor system. The emergence of CD94/NKG2 as main and polymorphic NK cell receptors was accompanied by major deviations of their putative ligands. All functional lemur MHC class I genes were translocated to a different chromosome and the MHC-containing chromosome harbors only MHC class I pseudogenes [38]. Orthologous relationships between strepsirrhine and catarrhine/platyrrhine MHC class I genes are not evident [39]. In the light of the polymorphic and diverse CD94/NKG2 receptors, one would anticipate several *MHC-E*-like genes in lemurs. However, neither phylogenetic analysis nor inspection of peptide-binding residues indicated the presence of any *MHC-E*-like gene in lemurs [38]. Thus, emergence of polymorphic KIRs (and Ly49 in rodents) was accompanied by a conserved MHC-E (Qa1 in rodents) and CD94/NKG2 system in the lineage leading to catarrhine and platyrrhine primates, and vice versa, emergence of a polymorphic CD94/NKG2 system in lemurs came along with an inactivated KIR system.

Remarkably, expanded *CD94* genes are not restricted to lemurs, which are endemic to Madagascar, but were also found in the African galago and even in the tarsier from Southeast Asia [38]. The latter is particularly interesting as tarsiers as well as Catarrhini and Platyrrhini belong to the suborder Haplorrhini (fig. 1). Strepsirrhini account for roughly one third of all primate species, and therefore, a considerable amount of primate species make use of polymorphic and diverse CD94/NKG2 receptors.

Unusual Ligands and Functions of KIRs

The function and specific ligands of a couple of KIR proteins are not known, including human *KIR3DL3*, *KIR2DL5*, almost all activating *KIR*, as well as the ancient *KIR3DX1*. The *KIR3DL3* gene stands out in its characteristics [40] because: (1) it represents the only conserved *KIR* gene in humans and apes (and possibly extending to Old World monkeys as well), (2) it is the most polymorphic human *KIR* gene, (3) its transcription is restricted to CD56^{bright} NK cells, and (4) so far, despite mRNA transcription, a *KIR3DL3* protein has not been found on the cell surface. An unexpected function was recently reported for human *KIR3DL2*, which binds CpG oligonucleotides and shuttles to the endosomal

compartment where the cargo induces potent interferon- γ responses via Toll-like receptor 9 [41]. Interestingly, mRNA of the mouse X-chromosomal KIR-related gene *Kirl* has not only been identified in NK cells but also in certain regions of the brain with high synaptic plasticity, suggesting a putative role of the KIRL protein in this process [42].

Conclusions

Primates have evolved either KIRs or CD94/NKG2 as their polymorphic MHC class-I-interacting NK cell receptors. Both receptors and ligands are subject of extensive coevolution, allowing for detailed and instructive views on the evolution of whole gene families. Elucidation of the biological properties of nonhuman primate NK cells and their receptors is strictly required for efficient and ethically justified use of nonhuman primates as models of those human diseases where NK cells play crucial roles.

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