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Diversification of both *KIR* and *NKG2* natural killer cell receptor genes in macaques – implications for highly complex MHC-dependent regulation of natural killer cells

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Summary

The killer immunoglobulin-like receptors (KIR) as well as their MHC class I ligands display enormous genetic diversity and polymorphism in macaque species. Signals resulting from interaction between KIR or CD94/NKG2 receptors and their cognate MHC class I proteins essentially regulate the activity of natural killer (NK) cells. Macaque and human KIR share many features, such as clonal expression patterns, gene copy number variations, specificity for particular MHC class I allotypes, or epistasis between *KIR* and *MHC class I* genes that influence susceptibility and resistance to immunodeficiency virus infection. In this review article we also annotated publicly available rhesus macaque BAC clone sequences and provide the first description of the *CD94–NKG2* genomic region. Besides the presence of genes that are orthologous to human *NKG2A* and *NKG2F*, this region contains three *NKG2C* paralogues. Hence, the genome of rhesus macaques contains moderately expanded and diversified *NKG2* genes in addition to highly diversified *KIR* genes. The presence of two diversified NK cell receptor families in one species has not been described before and is expected to require a complex MHC-dependent regulation of NK cells.

Keywords: genomics; killer immunoglobulin-like receptors; MHC; natural killer cells.

Introduction

Macaques belong to the Cercopithecidae family (Old World monkeys) of primates with 23 currently known macaque species. The predominant macaque species for biomedical research are the rhesus macaque (*Macaca mulatta*), the long-tailed (or cynomolgus) macaque (*Macaca fascicularis*), the pig-tailed macaque (*Macaca nemestrina*), and the Japanese macaque (*Macaca fuscata*). Macaques are particularly used as non-human primate models of human infectious diseases.[1] For example, experimental infection with the simian immunodeficiency virus (SIV) is an excellent and established non-human primate model of HIV infection and AIDS.[2,3]

Natural killer (NK) cells play an important role in fighting infectious diseases through direct killing of infected cells and regulation of adaptive immune responses.[4,5] The activity of NK cells is regulated by expression of specific receptors that initiate stimulatory or inhibitory signal transduction. A fine-tuned balance of this signalling ensures tolerance against healthy cells and immune effector reactivity against unhealthy (e.g. infected or malignant) cells. Almost all NK cell receptors fall into two distinct protein families and harbour either immunoglobulin-like domains or C-type lectin-like domains in their extracellular part.[6] The activity of NK cells is particularly regulated by those receptors that bind to MHC class I proteins such as the killer immunoglobulin-like receptors (KIR), members of the leukocyte immunoglobulin-like receptors (LILR) or the killer cell lectin-like receptors (KLR). All these receptors come in two functionally distinct types and are either stimulatory or inhibitory. Hence, the presence or absence of MHC class I ligands on target cells is perceived through such receptors and this essentially determines the NK cells' effector functions.

A further characteristic feature of primate (and other mammalian) NK cell receptors is their variegated expression on NK cell and T cell subsets,[7,8] with most NK cells

expressing only a single receptor.[9] As the various receptors are specific for their cognate MHC class I ligands, this expression pattern considerably sharpens the ability of NK cells to recognize diseased cells. For example, infection may lead to virus-induced down-regulation of host MHC class I proteins and discontinuation of inhibitory receptor engagement and may lead to host cell-induced expression of certain MHC class I-like proteins (MIC and ULBP family members) that engage activating receptors and induce activating signalling.[10] Hence, the interplay between MHC class I ligands and their cognate NK cell receptors plays a central role in the regulation of NK cell activity. The interaction between inhibitory receptors and their cognate MHC class I ligands is important in two aspects: (i) binding of MHC class I proteins on other cells mediates tolerance of the NK cell, (ii) the absence of cognate MHC class I on the target cell is a strong trigger of NK cell activity. This latter point is known as the 'missing-self hypothesis'.[11] To avoid unwanted intolerance of those NK cell clones that clonally express a receptor for which the host does not encode an appropriate ligand, the NK cells undergo an educational process that requires the signalling via at least one inhibitory receptor specific for self MHC class I. This process produces so-called licensed or armed NK cells.[12,13]

Macaque NK cells were defined by absence of T cell and B cell markers (CD3, CD20) and specific expression of NKG2A/C or alternatively NKp80.[14] However, there are NKG2A/C-negative NK cells in macaques and a more complete definition was given by Webster and Johnson[15] who classified macaque NK cells as $CD3^-$ $CD8^{bright}$ $CD20^{-/dim}$ cells.

We here review the current knowledge of MHC class I-dependent regulation of NK cells in macaques with focus on the KIR and CD94/NKG2 family.

The *KIR* and *MHC class I* gene families of macaques

Macaque KIR and MHC class I genes

Analyses of rhesus macaque cDNA and genomic DNA revealed the presence of 22 *KIR* genes (Table 1), which can all be assigned to established KIR lineages. Phylogenetic analyses suggest that cynomolgus macaques and pig-tailed macaques have similar sets of *KIR* genes with few species-specific differences.[16,17] Similar to human *KIR* haplotypes, macaque *KIR* haplotypes also vary in gene content, giving rise to a substantial degree of genomic diversity, in particular of the *KIR3D* genes.[17–20] The *MHC class I* genes of macaques have undergone significant expansions during evolution.[21] Although an *HLA-C* orthologue is not present, multiple copies of *HLA-A* and *HLA-B* paralogues can be found in macaques. Contrasting a fixed number of *class I* genes on *HLA* haplotypes in humans are extreme copy number variations of *MHC-A* and *MHC-B* genes of macaque *MHC* haplotypes.[22–25] In addition, the degree of their polymorphism (allelic variation) is usually much smaller compared with their human paralogues, suggesting that variability of the macaque *MHC class I* system is more focused on copy number variation than on allelic polymorphism.[21]

Table 1. Rhesus macaque killer immunoglobulin-like receptor (KIR) genes

Receptor	KIR lineage	Putative function
Mamu-KIR1D	III	n.d. (no cytoplasmic domain)
Mamu-KIR2DL4	I	Activation/Inhibition
Mamu-KIR3DL01	II	Inhibition
Mamu-KIR3DL02	II	Inhibition
Mamu-KIR3DLW03	II	Inhibition
Mamu-KIR3DL04	II	Inhibition
Mamu-KIR3DL05	II	Inhibition
Mamu-KIR3DL06	II	Inhibition
Mamu-KIR3DL07	II	Inhibition
Mamu-KIR3DL08	II	Inhibition
Mamu-KIR3DL10	II	Inhibition
Mamu-KIR3DL11	II	Inhibition
Mamu-KIR3DL20	V	Inhibition
Mamu-KIR3DS01	II	Activation
Mamu-KIR3DS02	II	Activation
Mamu-KIR3DS03	II	Activation
Mamu-KIR3DS04	II	Activation
Mamu-KIR3DS05	II	Activation
Mamu-KIR3DS06	II	Activation
Mamu-KIR3DS07	II	Activation
Mamu-KIR3DSW08	II	Activation
Mamu-KIR3DS09	II	Activation

KIR and MHC class I in macaque disease models

In rhesus macaques experimentally infected with SIV, several *MHC class I* alleles were identified that influence the disease in this important animal model (for review see ref. 26). Among the alleles with a beneficial effect in SIV infection were *Mamu-A1* alleles *001, *002, *011 and *Mamu-B* alleles *008, *017, *029, *047, and *069, whereas A1*004 and B*001 were associated with susceptibility.[27–32] Recently, also the presence/absence of *KIR* genes was included in such SIV disease association studies. Hellmann *et al.*[33] reported an association of high copy numbers of activating *KIR3DS* genes with lower peak viral load in animals negative for *Mamu-A1*001* and positive for a protective *TRIM5* allele. In a further study, this group demonstrated high *KIR2DL4* copy numbers to be associated with a better preservation of $CD4^+$ T cells and an increased interferon-γ production of stimulated $CD56^-$ $CD16^-$ NK cells in SIV-infected rhesus macaques.[34] Albrecht *et al.*[32] identified individual *KIR* genes

with either a protective or a detrimental effect in SIV-infected rhesus macaques. *KIR3DL02*, *KIR3DSW08* and most probably also *KIR3DS01* are associated with slow disease progression, longer survival times, higher numbers of blood NK cells, and higher lytic capability of NK cells.[32] In contrast, *KIR3DS02*, *KIR3DL10* and *KIR3DL05* were more frequently found in animals with fast disease progression, shorter survival times, lower numbers of blood NK cells, and decreased lytic capability of NK cells.[32] Furthermore, analyses of epistasis identified combinations of certain *KIR* and *MHC class I* genes with progression to AIDS: *KIR3DL05*, *KIR3DS05* as well as *KIR3DL10* are associated with faster progression to AIDS, but only in combination with presence of *Mamu-B*012* or absence of *Mamu-A1*001*.[32]

KIR-mediated regulation of NK cell activity

Rhesus macaque KIR proteins are expressed in a clonal manner, but in contrast to humans the frequencies of rhesus macaque KIR-expressing NK cells do not appear to depend on the presence of their cognate MHC class I ligands.[8,10] Specific interactions between macaque KIR3D proteins and MHC class I ligands have been described for rhesus and pig-tailed macaques (Table 2). *Mamu*-A1 allotypes are ligands of the activating receptor KIR3DS05[35] (Table 2), but unlike inhibitory KIR, these interactions are characterized by low avidity. Lower avidity of activating receptors for their cognate ligands is also evident for activating human KIR and activating Ly49 of mice.[36]

In comparison to human inhibitory KIR (iKIR), the iKIR–MHC class I interactions in macaques are characterized by lower avidity and broader reactivity.[17,35,37,38] Although the Bw4/Bw6 motifs play a role in binding macaque KIR3D proteins,[17,35,37] there are some KIR3D with restricted specificity for Bw4 such as KIR3DL01[37] or KIR3DLW03,[35] whereas other iKIR bind to both motifs such as KIR3DL05[35,38] or KIR049-4.[17] One reason for this broader reactivity of some iKIR might be the enormous genetic diversity and copy number variation in macaque species that might favour the evolution of KIR with broad interaction specificity.

The KIR-mediated NK cell activity is also modulated by antigenic peptides presented by MHC class I proteins, e.g. HLA-B- or HLA-C-bound peptides were shown to modulate binding of their cognate KIR.[39] Support for the role of peptides in modulation of KIR-mediated NK cell responses came from a study that demonstrated certain HIV-1 amino acid polymorphisms to be particularly frequent in KIR2DL2-positive individuals.[40] Peptides containing such a polymorphic position mediated particularly strong inhibition of KIR2DL2-expressing NK cells.[40] Hence, mutation of HIV-1 peptides resulted in increased avidity of HLA-C (presenting these HIV-1 peptides) to inhibitory KIR2DL2. This is interpreted as a strategy to avoid immune recognition and underscores the importance of NK cells in the defence of HIV-1.[40] An influence of MHC class I-bound peptides on binding avidity of KIR3D proteins was also demonstrated in rhesus and pig-tailed macaques.[17,37,38,41] Hence, there is accumulating evidence that the repertoire of presented peptides is an important factor in the KIR-mediated control of NK cell activity and that viruses might exploit this. On the other hand, primate activating *KIR* genes originate from inhibitory *KIR* genes and are rapidly evolving.[42] The reason for this is probably an important role of activating KIR in fighting pathogens. Consistent with this assumption are the above-mentioned epidemiological studies showing a beneficial role of activating *KIR3DS* genes in infections with immunodeficiency viruses in humans[43] and macaques.[32] In line with this, the interaction between human KIR3DS1 and its ligand $Bw4^+$ HLA-B*57 is restricted and is dependent on the presence of B*57-bound peptides with aromatic residues (tryptophan, phenylalanine or tyrosine, but not histidine) at P8.[44] It is thought that theses residues might compensate the interaction disabling arginine residue at position 166 of KIR3DS1 and that the frequency of such peptides increases in diseased (infected, transformed) cells.[44] Hence, the activating receptor KIR3DS1 does not interact with B*57 of healthy cells and thereby ensures immune tolerance, but engages B*57 upon disease-mediated changes of the peptide repertoire ('altered-self' recognition).

Table 2. Interactions between macaque KIR3D and MHC class I proteins

Receptor	Ligands	Ref.
Mamu-KIR3DL01	Mamu-B*007:01, -B*041:01, -B*058:02, -B*065:01	36
Mamu-KIR3DLW03	Mamu-A1*001:01, -A1*008:01, -A1*011:01	35
Mamu-KIR3DL05	Mamu-A1*001:01, -A1*002:01, -A3*13:11	35, 37
Mamu-KIR3DL11	Mamu-A1*008:01	35
Mamu-KIR3DS05	Mamu-A1*001:01, -A1*011:01	35
Mane-KIR049-4	Mane-A1*082, -A1*084	17

The *CD94/NKG2* gene family of macaques

The NKG2 genes of macaques revisited

The human inhibitory NKG2A as well as both the activating NKG2C and NKG2E form heterodimers with CD94. The function of NKG2F is less clear. The distantly related NKG2D forms homodimers and binds stress-inducible ligands of the MHC class I-related families of MIC and ULBP proteins. In contrast to CD94/NKG2A and CD94/

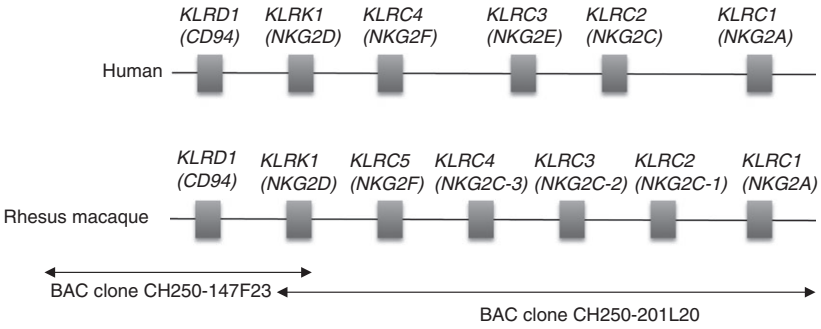

Figure 1. Genomic organization of the human and rhesus macaque *CD94* and *NKG2* region. The maps are not to scale. Orthologous genes *CD94*, *NKG2D*, *NKG2F*, and *NKG2A* are ordered vertically.

NKG2C, the CD94/NKG2E heterodimer is not expressed at the cell surface but is retained intracellularly due to hydrophobic residues at the C terminus, which do not exist in other human NKG2 molecules.[45] All human CD94/NKG2 heterodimers bind the non-polymorphic HLA-E ligand.[46]

Although the rhesus macaque genome is sequenced, regions containing immune gene families are in general often incomplete and incorrectly displayed in genome browsers due to high sequence similarities of gene family members, difficulties in automated gene annotations, or gene copy number variations. Hence, also the rhesus macaque *CD94-NKG2* genomic region is not properly represented in the rhesus macaque reference genome. We identified two overlapping rhesus macaque BAC clones from the GenBank sequence database and annotated the *CD94-NKG2* genomic region (Fig. 1). Besides *CD94* and *NKG2D*, we identified *NKG2A*, *NKG2F*, and three genes that we tentatively named *NKG2C-1*, *NKG2C-2* and *NKG2C-3* (Fig. 1). A summary of the putative functions of the rhesus macaque *NKG2* genes is shown in Table 3. According to phylogenetic analyses these three rhesus macaque *NKG2C* genes appear to be more closely related to human *NKG2C* than to *NKG2E*, both in trees based on the complete amino acid sequences (Fig. 2a) and on the cytoplasmic and transmembrane part (Fig. 2b). The extracellular C-type lectin-like domains show the known clustering by species (Fig. 2c) as the exons encoding these domains most likely underlie homogenization.[47] The *NKG2A* and *NKG2F* genes of human and rhesus macaque both form separate clusters with high bootstrap support when the complete sequences or the cytoplasmic/transmembrane parts are considered (Fig. 2a,b), indicating that these genes are orthologous between human and rhesus macaque.

Table 3. Summary of rhesus macaque *NKG2* receptors

Receptor	Putative function
NKG2A	Inhibition
NKG2C-1	Activation
NKG2C-2	Activation
NKG2C-3	Activation
NKG2D	Activation
NKG2F	Activation

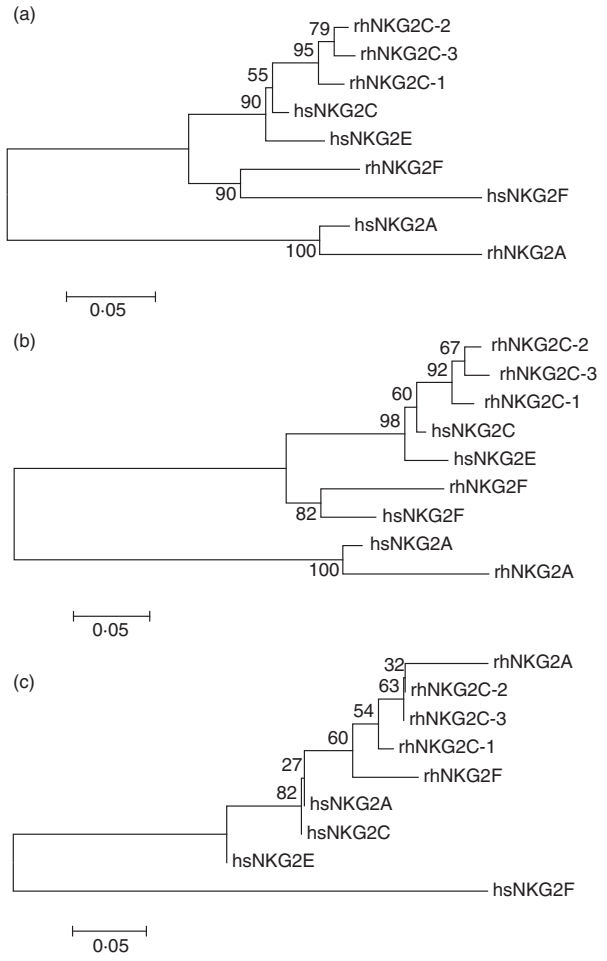

Figure 2. Phylogenetic tree analysis of human (hs) and rhesus macaque (rh) NKG2 amino acid sequences. Sequences were aligned and neighbour-joining trees using the Jones–Taylor–Thornton model with 1000 bootstraps were constructed. Scale bars denote substitutions per site and bootstrap support in per cent is indicated at nodes. Trees were based on (a) complete amino acid sequences, (b) transmembrane and cytoplasmic regions only, (c) C-type lectin-like domains only.

How do previously published rhesus macaque *NKG2* sequences relate to these BAC clone-derived sequences? The rhesus macaque *NKG2A* and *NKG2C* alleles identified by Biassoni *et al.*[48] show 96% and 99% (one non-synonymous substitution) sequence similarity with the BAC clone-derived *NKG2A* and *NKG2C-1* alleles. Kravitz *et al.*[49] identified several *NKG2* clones from a rhesus macaque decidua cDNA library: the *NKG2A* allele shows 97% sequence similarity with the *NKG2A* allele of the BAC clone, and *NKG2C* clones 65 and 74 display 99% identity with the BAC clone-derived alleles of *NKG2C-1* and *NKG2C-2*, respectively. LaBonte *et al.*[50,51] described a single *NKG2A* sequence and a couple of transcripts that were similar to human *NKG2C*, *NKG2E* and *NKG2F*: the

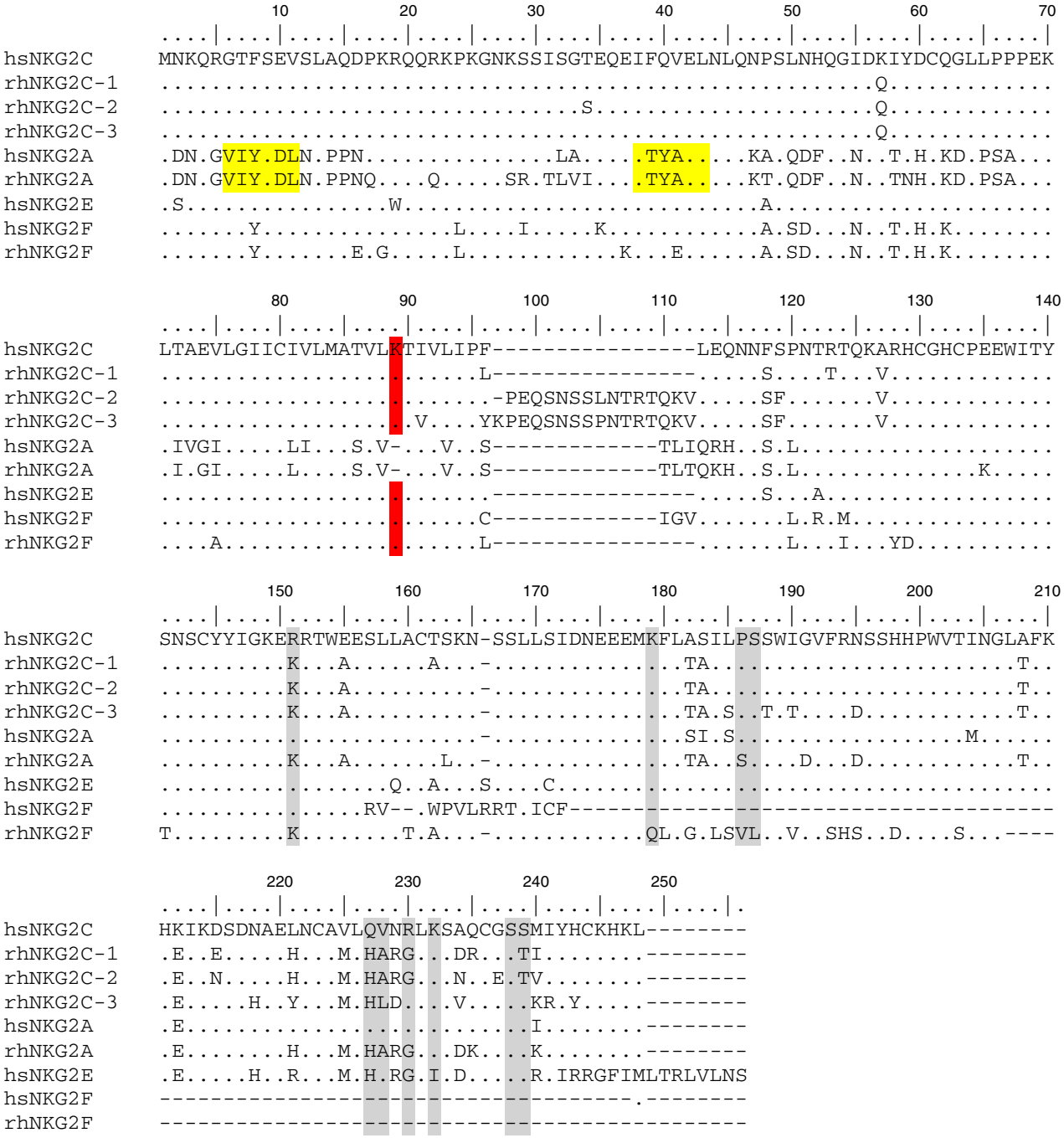

Figure 3. Amino acid sequence alignment of human (hs) and rhesus macaque (rh) NKG2 sequences. Identical residues are indicated by a dot and gaps by a dash. Residues known to be involved in binding of human NKG2A to HLA-E[53–55] are marked. The ITIM motifs of inhibitory receptors and the lysine residue in the transmembrane region of activating receptors are marked in yellow and red, respectively.

NKG2C sequences (clones 10/1#66 and 10/1#2) display sequence similarities of 99% and 97% with BAC-derived *NKG2C1*, the *NKG2-C2* sequences (clones 10/1#69 and 10/1#81) are 99% identical with the BAC-derived *NKG2C-2*, the *NKG2Ce2* sequence is 99% identical with the BAC-derived *NKG2C-3*, and the *NKG2Fe2*, *NKG2F2* and *NKG2F3* sequences are almost identical (97–99%) to *NKG2F*.

Therefore, we conclude that the rhesus macaque genome contains genes that encode *CD94*, *NKG2A*, *NKG2C-1*, *NKG2C-2*, *NKG2C-3*, *NKG2D* and *NKG2-F*. Interestingly, none of the rhesus macaque NKG2 sequences contains the hydrophobic amino acids that are present at the C terminus of human (see Fig. 3), chimpanzee, or orang-utan NKG2E and we hypothesize that none of the three rhesus macaque NKG2C proteins is retained intracellularly.

Biassoni *et al.*[48] reported a cynomolgus macaque *NKG2C* sequence. Sequence comparison indicates that it is most closely related to the rhesus macaque genomic sequence *NKG2C-1* reported here (not shown).

CD94/NKG2-mediated regulation of macaque NK cell responses

Experiments by Biassoni *et al.*[48] showed that both rhesus and cynomolgus macaque CD94/NKG2A as well as CD94/NKG2C-1 heterodimers are expressed at the cell surface upon transfection and react with anti-human NKG2A antibody Z199. Hence, unlike in humans, this monoclonal antibody does not discriminate between NKG2A and NKG2C in macaques.[48] These data were confirmed and extended by LaBonte *et al.*,[52] who showed that also CD94/NKG2C-2 (alias NKG2-C2) are expressed at the cell surface and react with Z199. Hence, besides the inhibitory CD94/NKG2A heterodimer, at least two stimulatory CD94/NKG2C can be expressed at the cell surface and react with Z199. LaBonte *et al.* also expressed NKG2Ce, which is an alternatively spliced and C-terminally shorter form of NKG2Ce2 (= NKG2C-3), but did not detect binding of Z199.[52] A possible reason for the lack of antibody binding might be that the shorter isoform was used.

The three-dimensional structure of the human CD94/NKG2A heterodimer in contact with its ligand HLA-E was reported by different groups.[53–55] Comparison of the known interacting amino acid residues of human NKG2A and its ligand HLA-E with those residues present in rhesus macaque NKG2A, NKG2C-1, NKG2C-2 and NKG2C-3 suggests that Mamu-E is the ligand of the respective heterodimeric CD94/NKG2 receptors (Fig. 3). In accord with this hypothesis, previous experiments with HLA-E tetramers folded with an HLA-A2 leader peptide showed binding to rhesus macaque $CD3^-$ $CD16^+$ cells.[56] Interestingly, the putative MHC-E ligand is moderately polymorphic in macaque species, yet the polymorphisms appear to map outside of peptide-binding regions.[57,58]

Published reports on the involvement of CD94/NKG2 heterodimers in the regulation of macaque NK cell responses are rather scarce, which is probably due to the lack of specific antibodies that distinguish between macaque NKG2A and the various NKG2C proteins. However, Reeves *et al.*[59] demonstrated recently that a specific memory NK cell response (killing) of SHIV- or SIV-infected macaques against Gag- and Env-pulsed dendritic cells is dependent on NKG2A/C but not on NKp46. These data indicate an essential role of NKG2A and/or NKG2C molecules in the regulation of NK cell memory responses.

A moderately diversified (*NKG2*) combined with a highly diversified (*KIR*) NK cell receptor system is interesting and to the best of our knowledge has not been described in any other mammal. Such a highly diversified NK cell receptor system implicates a complex MHC-dependent regulation of NK cells and possibly of other lymphocytes expressing these receptors such as $CD8^+$ T cells. Reasons for the development of expanded and diversified *NKG2C* genes in macaques might be that the complex genetic systems of *KIR* and *MHC class I* with numerous gene copy number variations of both systems requires additional activating receptors without extensive copy number variations. Alternatively, the Mamu-E ligand plays a more prominent role in macaque immunology compared with its human orthologue HLA-E, requiring the expansion and evolution of *NKG2* genes in macaques. Another scenario could be that the system of two diverse NK cell receptors was the original state in the evolution of catarrhine primates. Selection during evolution of Hominidae may have forced the development of restricted immunological functions of the *MHC-E/NKG2* system and of extended immunological functions of the *MHC-I/KIR* system, coming along with a reduced set of *NKG2* genes, a highly diverse set of *KIR* genes, and fixed numbers of *MHC class I* genes in humans and apes.

Disclosures

The authors do not have any competing interests.

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