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Ly49 Gene Expression in Different Inbred Mouse Strains*

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Abstract

Mouse natural killer cells express receptors for class I MHC in the form of the Ly49 family of proteins. The Ly49 family contains at least 13 expressed members (A, B, C, D, E, F, G, H, I, J, L, O, and P) and is further subdivided into activating and inhibitory subfamilies based on intracellular and transmembrane characteristics. The level of sequence identity between different members varies dramatically. However, comparison of the extracellular domain has revealed that several of the Ly49 molecules also form "pairs," where one member is activating and the other is inhibitory. Until recently, most Ly49 molecules described have come from the C57Bl/6 strain of inbred mice. Using molecular cloning and immunochemical analysis we have found that different mouse strains express novel Ly49 molecules. Comparison of the allelic forms of some Ly49 molecules has shown that the dividing line between different genes and different alleles is blurred.

Key Words

Natural killer cells
Ly49
Cell surface molecules
Signal transduction
Inbred mouse strains

Introduction

Natural killer (NK) cells are necessary for constant surveillance against viral infection and cellular transformation. The basis of this surveillance strategy is referred to as the "missing self" hypothesis. Briefly, this hypothesis states that NK cells screen host cells for the expression of certain ubiquitously expressed self-antigens such as class I major histocompatibility (MHC) molecules (reviewed in

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ref. *1*). This hypothesis was put forward after the observation that NK cells preferentially kill cells that lack self-MHC. This disruption in expression could be due to an alteration in MHC expression because of mutation or viral down regulation of gene expression. One would expect that allogeneic cells could also serve as targets because of the lack of self MHC, and this has proven to be true (reviewed in ref. *2*).

The identity of the "self-receptor" on NK cells has been the goal of many laboratories. This interest has led to the identification of many receptors found on both human and mouse NK cells. The best-characterized group of receptors in mice, and the subject of this article, is the Ly49 family. Ly49 molecules are type II transmembrane cell surface proteins expressed mainly on NK cells and on a small percentage of T cells *(3)*. The extracellular domain of the Ly49 receptors is homologous to the C-type lectin superfamily that includes CD94, CD69, NKRP1, and the NKG2 family. The currently known Ly49s range from Ly49A to P with the possible exceptions of Ly49K, M, and N, which have not been shown to express functional full-length gene products *(4–7)*. The genes for *Ly49o* and *p* have yet to be identified and are only known by their cDNA sequence *(7)*. The Ly49 genes are clustered together on mouse chromosome 6 in the region known as the NK cell gene complex. The NK complex harbors other NK-related genes such as the *Nkrp1* cluster, *Cd94*, and *Cd69 (8)*. Interestingly, resistance to ectromelia and mouse cytomegalovirus infection has also been genetically mapped within the NK complex *(9,10)*.

All members of the Ly49 family can be subdivided into inhibitory or activating groups. The inhibitory Ly49 proteins (A, B, C, E, F, G, I, J, and O) possess in their cytoplasmic domain a peptide sequence known as an intracellular tyrosine-based inhibitory motif (ITIM) of the form I/VxYxxL. Studies have shown that cross-linking of inhibitory receptors such as Ly49A, C, and G2 leads to recruitment of the cytoplasmic tyrosine phosphatase SHP-1 and the down regulation of NK cell function *(11,12)*. The "activating" members of the Ly49 family (D, H, L, and P) lack the ITIM motif and instead have a positively charged residue (arginine) in their transmembrane domain. This charged residue requires the activating Ly49 molecules D, H, and P to associate with a small adaptor protein called DAP12 for stable surface expression *(7,13,14)*. DAP12 contains an immunoreceptor tyrosine-based activation motif (ITAM). Antibody-mediated cross-linking of activating Ly49s has been shown to result in an increase in intracellular calcium ion levels and tyrosine phosphorylation of the associated DAP12 molecule *(7,13,14)*. Further downstream signaling events include tyrosine phosphorylation and activation of Cγ1, Erk, Cbl, and Syk *(15)*. Such biochemical events are thought to be linked to biological outcomes of activating-Ly49 ligation such as cytotoxicity and cytokine production/secretion *(14,16)*.

The MHC specificity of some members of the Ly49 family has been deduced through various assays including conjugate formation, cytotoxicity, and soluble class I MHC flow cytometric analysis. For example, the Ly49D-transfected RNK.16 tumor line has been shown to recognize and lyse target cells bearing H-2D^d (D^d) *(17)*. Similarly, Ly49D^+ NK cells have been shown to kill target cells expressing D^r and D^{sp2} *(18)*. Interestingly, Ly49D has also been implicated in the killing of xenogeneic target cells, presumably through cross-reactive xeno-MHC structures *(19)*. Ly49A binds D^k, D^d, and D^p *(20–22)*. Ly49C binds K^b, D^b, K^d, D^d, and D^k *(21)*. Ly49G2 inhibits the killing of D^d-, L^d-, and D^r-bearing target cells *(18,23)*. However tetramer binding studies have not shown binding of L^d to Ly49G2-expressing cells, the reason for the inconsistency between the cytotoxicity and

Table 1. Nucleotide identity between Ly49 gene coding regions

	A^{B6}	B^{B6}	C^{B6}	$D1^{B6}$	E^{B6}	F^{B6}	$G2^{B6}$	$H1^{B6}$	I^{B6}	J^{B6}	$L2^{CBA}$	O^{129}	P^{129}
A^{B6}	–	69.8	80.7	88.2	82.8	82.3	87.7	77.9	80.7	80.5	86.2	96.7	90.9
B^{B6}	–	–	70.9	68.9	69.9	70.9	70.8	69.7	70.9	69.8	68.5	70.1	69.6
C^{B6}	–	–	–	76.8	89.1	90.9	80.0	90.5	95.9	96.3	77.4	80.7	77.8
$D1^{B6}$	–	–	–	–	78.8	78.3	84.3	78.6	77.8	76.6	89.8	90.0	93.3
E^{B6}	–	–	–	–	–	91.9	81.8	85.4	90.0	88.9	79.5	82.7	79.5
F^{B6}	–	–	–	–	–	–	82.5	86.5	91.8	91.3	79.9	82.4	79.3
$G2^{B6}$	–	–	–	–	–	–	–	77.9	80.4	80.0	89.2	87.7	85.9
$H1^{B6}$	–	–	–	–	–	–	–	–	91.9	91.1	79.8	78.0	79.3
I^{B6}	–	–	–	–	–	–	–	–	–	96.9	78.4	80.7	78.7
J^{B6}	–	–	–	–	–	–	–	–	–	–	77.5	80.5	77.7
$L2^{CBA}$	–	–	–	–	–	–	–	–	–	–	–	86.4	90.2
O^{129}	–	–	–	–	–	–	–	–	–	–	–	–	89.4
P^{129}	–	–	–	–	–	–	–	–	–	–	–	–	–

tetramer studies for Ly49G2 are unknown *(21)*. Ly49I can bind K^d and D^d *(21)*.

Interfamily Similarity

The sequence homology (at the nucleotide level of the coding region) of the various members of the Ly49 family varies dramatically (Table 1). The average homology between different genes is roughly 80%. *Ly49b* stands out as the most different Ly49 with an average of 70% homology to all the other family members. It is interesting to note that the *Ly49b* gene, while still residing in the NK complex, is very far removed from the other family members. The average distance between Ly49 genes is 5–20 kb *(6)*, while *Ly49b* is over 1 Mb away from the last gene of the cluster *(10)*. These findings suggest that *Ly49b* is not part of the immediate *Ly49* gene family.

On the other end of the homology spectrum, the *c*, *i,* and *j* genes are very closely related and on average share 96.5% identity. One not familiar with the Ly49 field would assume that these might represent alleles except for the fact that their respective genes have all been mapped and found to be independent of each other *(6)*. In fact, *Ly49i* was initially thought to be the B6 allele of *Ly49c* (which was originally found in Balb/c mice) due to their close sequence homology. The isolation of the actual B6 *Ly49c* allele was subsequently reported *(24)*. This exemplifies the taxonomic problems in dealing with such a highly related family of genes. Another striking match found in this table is that of *Ly49a* and *Ly49o* at 96.7% homology. Since both of these receptors are of the inhibitory type and *Ly49o* was initially described in the 129/J strain of mice (7), it is possible that *Ly49o* might simply be the 129/J allele of *Ly49a*. Another highly homologous pair of receptors is *Ly49d* and *Ly49p* at 93.3%. Our laboratory has recently sequenced the cDNA of the 129/J allele of *Ly49d* and so we can confidently say that these are in fact separate genes without mapping the location of the *Ly49p* gene (Anderson, unpublished data).

Genomic mapping of the *Ly49* locus in different mouse strains may be required to differentiate between Ly49 alleles and genes of different mouse strains. However, this approach assumes that the arrangement of the Ly49 genes within the cluster is constant between different strains of mice. While this intuitively should appear to be true, McQueen et al. have shown

that Southern blotting of genomic DNA from different mouse strains with a *Ly49c* single exon probe results in a very different pattern and number of bands in each strain *(6)*. This suggests that the number and perhaps type of *Ly49* genes is different between strains of mice.

Activating and Inhibitory Receptor Pairs

The range of similarities displayed in Table 1 are even more striking when the sequences are arranged according to identity in a phylogenetic dendogram. This "tree" was divided into intracellular/transmembrane (ATG in exon 2 to the end of exon 3) and extracellular (exon 4 to the termination codon in exon 7) portions to minimize the complexities caused by the apparent recombinations the Ly49 genes have undergone. Where possible, the B6 allele of each gene was used for tree construction to minimize differences due to strain variation. When the intracellular/transmembrane domains are analyzed in this fashion, the four activating receptors are found grouped together, and the inhibitory receptors are in two subgroups, A, G2, and O in one group, and C, E, F, I, and J in the other (Fig. 1). Thus, from this standpoint it appears that there were three Ly49 gene progenitors during mouse evolution. This figure also suggests that the activating Ly49s appeared after the inhibitory Ly49s; however, this is speculative.

Comparison of the extracellular Ly49 sequences shows a totally different grouping pattern than the intracellular/transmembrane tree (Fig. 2). This tree shows that recombination between genes, along with duplication, is responsible for the diversity of the mouse Ly49 family (Fig. 2). Interestingly, each activating Ly49 co-segregates with an inhibitory Ly49, for example, Ly49P groups with A, Ly49D groups with O, Ly49L2 groups with G2, and Ly49H groups with Ly49I. The immediate conclusion from this pairing of the domains involved in MHC binding is that for a given MHC molecule a receptor exists that both activates and suppresses NK cytotoxicity. While inhibitory receptors fit into the missing-self theory of NK function, the activating receptors have no known function other than allo- and xeno-recognition as studied in vitro.

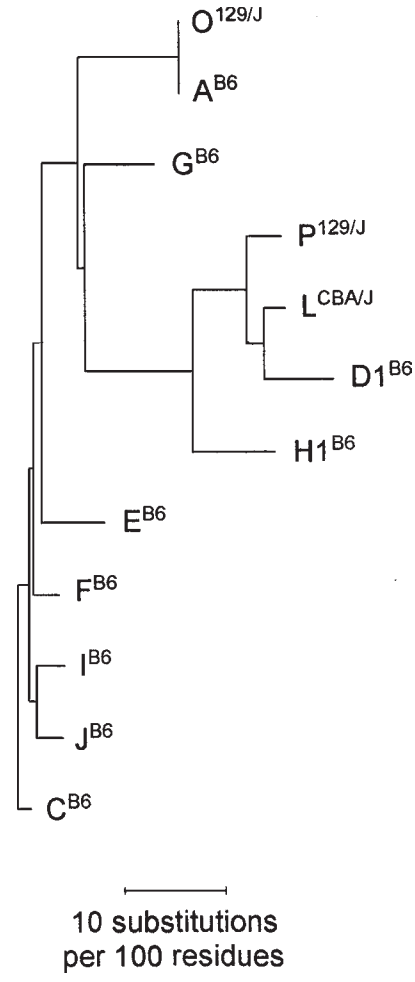

Fig. 1. Phylogenetic dendogram of the intracellular and transmembrane coding region of the known Ly49 genes. Nucleotide sequences from the ATG initiation codon in exon 2 to the end of the predicted third exon boundary were compared using SeqWeb Version 1.1 sequence analysis software. The strain of the Ly49 allele used in the analysis is denoted in superscript.

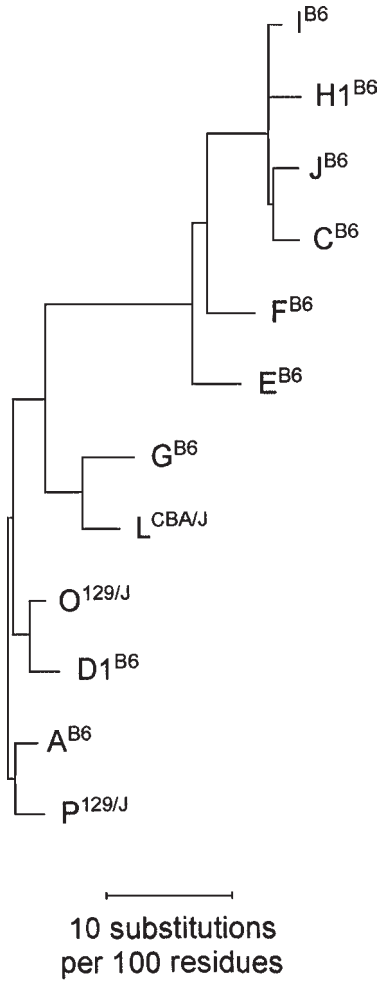

Fig. 2. Phylogenetic dendogram of the extracellular coding region of the known Ly49 genes. Nucleotide sequences from beginning of the predicted fourth exon to the termination codon were compared using SeqWeb Version 1.1 sequence analysis software. The strain of the Ly49 allele used in the analysis is in superscript.

The in vivo role of activating Ly49 receptors has not yet been determined. It seems highly unlikely that activating Ly49s are an artifact of evolution, since four distinct genes are currently known to be expressed. Furthermore, each well-studied strain of mouse has been found to have at least one activating Ly49 receptor: Ly49D and H are found in B6; Ly49 D and P are found in 129; and CBA mice express Ly49L (*7*, Makrigiannis and Anderson, unpublished results).

Ly49 Expression is Strain Dependent

Most of the Ly49 sequences have been obtained from C57Bl/6 (B6) mice. The exceptions are *Ly49O* and *P*, which to date have only been found in the 129/J strain of mice *(7)*. Recently, we have found that a functional version of Ly49L, a novel activating receptor, is expressed in CBA/J and C3H but not in B6 mice (Makrigiannis and Anderson, unpublished results). We have found multiple isoforms of Ly49L including those with and without an insert in the stalk domain analogous to the Ly49G1 insert. We have also found some forms of Ly49L with or without a small intracellular insert found in Ly49D1 and H1. The Ly49L2 referred to above does not contain the large Ly49G1-type insert (making it analogous to Ly49G2) but does contain the small Ly49D1/H1 insert. *Ly49l* was originally described as two genomic fragments from B6 mice *(6)*.

The close similarities between some Ly49 sequences seen in Table 1 leads one to ponder the difference between an allele and a gene. In order to determine a numerical boundary, if one exists, between sequences of different Ly49 genes and alleles, the sequences of all known Ly49 alleles were compared within a particular gene group and the percentage identity determined (Table 2). Different allele sequences are only known for Ly49A, C, D, F, G, and I. The level of homology between various alleles within a particular group seems to vary between 97% and 100%. Interestingly in Table 1, we found that the highest level of homology between separate genes is also approximately 97% (Ly49C, I, and J). If genetic drift is a function of time, this suggests that Ly49C, I, and J are the most recent gene dupli-

Table 2. Nucleotide identity between alleles of Ly49 gene coding regions

Ly49A	B6	Balb/c-ByJ	CBA/J
B6	–	98.9	98.9
Balb/c –ByJ	–	–	100
CBA/J	–	–	–

Ly49C	Asn	Balb/c	CB17	CBA/J	B6
Asn	–	100	100	100	99.3
Balb/c	–	–	100	100	99.3
CB17	–	–	–	100	99.3
CBA/J	–	–	–	–	99.3
B6	–	–	–	–	–

Ly49D1	129/J
B6	97.1

Ly49F	129/J
B6	96.4

Ly49G2	CB17	CBA/J	129/J	B6
CB17	–	99.8	99.6	97.9
CBA/J	–	–	99.6	97.9
129/J	–	–	–	98.0
B6	–	–	–	–

Ly49I	129/J	B6	NZB
129/J	–	97.8	97.6
B6	–	–	97.8
NZB	–	–	–

cations in mouse evolution. Interestingly, the B6 alleles for Ly49A, C, D1, F, and G2 are the least homologous members of their individual groups. This suggests that the B6 mouse has been genetically isolated for a longer period of time than the other inbred mouse strains. Furthermore, we cannot rule out the possibility that the Ly49F 129/J clone isolated in our lab is a distinct gene (Anderson, unpublished data).

Many of the alleles display great variation between strains. It is possible that these sequence differences are translated into differing biological activities of the various alleles. This is not unprecedented; for example, mouse FasL seems to have two alleles. mFasL.1 is expressed by B6, C3H, MRL, SJL, NOD, NZB, and NZW mice, while mFasL.2 is found in BALB/c, DBA/1, and DBA/2 mice. Interestingly, mFasL.2 binds with much greater affinity to Fas than mFasL.1 *(25)*. One study has shown that the B6 and Balb/c alleles for Ly49C display similar binding affinities *(21)*. However, a wider sampling of the Ly49 alleles needs to be conducted before a definitive

answer is found. While mouse MHC antigens are broadly grouped as H-2b, k, d (and other) haplotypes, it is known that in the human system each of the main haplotypes has many different alleles. It is possible that in wild mice populations, Ly49 genes are co-evolving with MHC genes. This may account for the Ly49 allele variation seen in the inbred mouse strains discussed here.

The creation of the inbred mouse strains facilitated the identification of the various MHC antigens. However, in addition to capturing a specific assortment of MHC genes, it is becoming increasingly apparent that each mouse strain has a specific assortment of expressed Ly49 genes as well. For example, Ly49P was identified in 129/J mice, yet does not seem to be present in B6 mice *(7)*. Similarly, Ly49L was found to be expressed in CBA/J and C3H mice but not B6 (Makrigiannis and Anderson, unpublished data). We have recently conducted a study showing that in comparison to B6 mice, DX-5$^+$, CD3$^-$ splenic NK cells from different mouse strains display wide variation in cell surface staining with Ly49-specific mAb *(26)*. Many strains were found to display little or no staining with a given mAb compared with B6 mice. This suggests that either certain Ly49s are expressed in particular strains or that the mAb used are strain specific. In contrast, Ly49G was found in 11/11 different inbred strains suggesting that some Ly49s seem to have a "universal" expression *(26)*. In our experience with CBA/J and 129/J mice, the various Ly49 alleles found reacted with the corresponding antibody, suggesting that in general, the lack of antibody reactivity indicates the absence of a given Ly49.

Activating and inhibitory Ly49 molecules can be detected by immunoprecipitation of pervanadate-stimulated NK cell extracts with Ly49-specific mAb and subsequent immunoblotting for phosphotyrosine. In this type of assay, inhibitory Ly49s will appear at approx 100 kDa due to phosphorylation of the tyrosine residue contained within the ITIM, while the presence of activating Ly49s can be inferred by observing multiple bands between 20 and 30 kDa formed by the associated DAP12 homodimer. For example, immunoprecipitation of NK extracts from B6 and 129/J mice with Ly49A-reactive mAb (YE1/48 and YE1/32) revealed the expected inhibitory Ly49 band in B6 mice but this was absent in 129/J extracts. Instead DAP12 was found to be associated with a YE1/48-reactive molecule in 129/J mice, and this observation led to the discovery of the cross-reactive activating Ly49P *(7)*. In addition, an inhibitory 4E5-reactive Ly49 was detected in 129/J mice, which likely represents the Ly49O protein (McVicar and Anderson, unpublished observations). We have since performed similar experiments in CBA/J mice to see if this was an anomaly with 129/J mice. CBA/J mice seem to express a third type of Ly49 repertoire. Like B6 mice, CBA/J NK extracts were observed to contain typical inhibitory 4D11, 5E6, and YE1/48-reactive molecules (Ly49G, C, and A, respectively). However, activating 4E5 and 1F8 complexes (Ly49D and H) were not detected (Ortaldo and Mason, unpublished data). The only activating complexes were seen with 4D11 and YE1/48. Our cloning studies in this mouse strain have borne out the biochemical studies with the isolation of cDNAs for Ly49A, C, G and the novel activating Ly49L molecule. Ly49L was subsequently shown to be cross-reactive with the 4D11 and YE1/48 mAb, thus accounting for the unusual banding patterns seen with the immunoprecipitation experiment. Ly49L was previously known from two gene fragments in B6 mice. RT-PCR experiments have shown that Ly49L is not expressed in B6 mice. As expected from the above-described immunoprecipitation data, no cDNA clones of Ly49D or H were found in CBA/J

mice (Makrigiannis, unpublished data). The investigation of the unusual reactivity of Ly49 mAb in certain mouse strains has led us to the discovery of novel Ly49 molecules in strains other than the well-characterized B6 strain.

Conclusion

The studies described herein have shown that for at least three mouse strains (B6, 129/J, and CBA/J) the Ly49 repertoires are clearly different. It has been shown that Ly49 expression is modulated when the host also expresses the MHC ligand to which it can bind *(27)*. However, differences in Ly49 expression between mouse strains cannot be wholly attributed to development in a particular MHC background, as B6 and 129 mice are both of the H-2^b haplotype. One possibility is that certain Ly49 genes have become inactivated due to mutation, such that they are present in all inbred mouse strain genomes but do not produce functional products. This has recently been shown to be the case for *Ly49k* and *n (28)*. This possibility will be better assessed once the B6 *Ly49l, o,* and *p* genes, as well as the CBA/J *Ly49d* and *h* genes have been fully sequenced.

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