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Characterization of the Ligand Binding Site of the Bovine IgA Fc Receptor (bFcαR)*

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Recently, we identified a bovine IgA Fc receptor (bFcαR), which shows high homology to the human myeloid FcαR, CD89. IgA binding has previously been shown to depend on several specific residues located in the B-C and F-G loops of the membrane-distal extracellular domain 1 of CD89. To compare the ligand binding properties of these two FcαRs, we have mapped the IgA binding site of bFcαR. We show that, in common with CD89, Tyr-35 in the B-C loop is essential for IgA binding. However, in contrast to earlier observations on CD89, mutation of residues in the F-G loop did not significantly inhibit IgA binding.

Circulating human phagocytes constitutively express an Fc receptor for immunoglobulin A (IgA),[1] which has been designated FcαRI or CD89. The binding of IgA-coated targets such as bacteria and viruses to CD89 has been shown to trigger a variety of cellular effector functions including phagocytosis, antibody-dependent cellular cytotoxicity, respiratory burst, and synthesis and release of cytokines. Furthermore, mounting experimental evidence suggests that CD89 is able to trigger cellular effector functions, at least as well as and perhaps even better than IgG Fc receptors (FcγRs). Therefore, CD89 provides a crucial link between the humoral and cellular arms of the immune system, which may in the future be exploited for therapeutic purposes (1).

A better understanding of the biological role of FcγRs has benefited greatly from the fact that cDNAs encoding the three receptor classes, FcγRI/CD64, FcγRII/CD32, and FcγRIII/CD16, have been cloned and characterized from several different species (2–4). Such comparative studies have not been possible for CD89, because only this human FcαR has been available for study. Recently, however, we cloned an FcαR homologous to CD89 from cattle and called it bFcαR (5).

CD89 and bFcαR are closely related to both the killer cell immunoglobulin-like receptors (KIRs) and the leukocyte immunoglobulin-like receptors. The human CD89, KIR, and leukocyte immunoglobulin-like receptors genes have been mapped to a region of chromosome 19 called the leukocyte receptor complex (LRC) (6). Similarly, the bFcαR gene has been localized to the bovine LRC on chromosome 18 (5). The closest FcR relative to CD89 and bFcαR is the bovine FcγR for IgG2 (bFcγ2R) whose gene is probably also located in the bovine LRC (7, 8).

CD89 and bFcαR are type I transmembrane glycoproteins, and each possesses two extracellular (EC) Ig-like domains (1, 9). They are both predicted to have a 19-amino acid transmembrane region containing a positively charged arginine residue, which at least for CD89 has been shown to be necessary for association with the common FcR γ-chain (10). Although much remains to be learned regarding the biological role of bFcαR, the presence of a charged transmembrane residue implies that this receptor is able to recruit specialized signaling molecules and thus probably represents a potent triggering molecule on bovine cells. Both receptors also have short cytoplasmic tails lacking other recognized signaling motifs. A further striking characteristic of CD89 (and also the closely related bFcγ2R) is that, in contrast to other FcRs, the ligand binding site is located in the membrane distal EC1 domain (11–14). In this study, we have used mutational analysis to map the IgA binding site of bFcαR. Our data revealed that mutation of a single residue in the B-C loop abolished the interaction with bovine IgA. In addition, the mutation of residues in the F-G loop, which have been shown to be important in ligand binding by CD89, did not appear to affect binding.

EXPERIMENTAL PROCEDURES

Cell Culture—COS-1 cells were maintained in Dulbecco's modified Eagle's medium (BioWhittaker, Walkserville, MD) supplemented with 10% fetal calf serum, 1 mM L-glutamine, and 50 μg/ml gentamycin (Invitrogen).

Immunoglobulin Preparations—Purified bovine IgA (bIgA) was purchased from Inter-Cell Technologies Inc. (Hopewell, NJ). The construction of the relevant expression vectors, generation of Ig secreting cell lines, and purification of recombinant anti-NIP bIgA have been described previously (15). Recombinant human anti-NIP IgA was also purified at LIIPAT and was kindly provided by Drs. R. Braathen and F.-E. Johansen (16).

Plasmid Construction and Generation of bFcαR Mutants—A plasmid containing an HA-tagged variant of the human FcRn cDNA subcloned immediately downstream of the murine major histocompatibility complex I Kb signal sequence (17) was kindly provided by Dr. F.-E. Johansen.

To generate bFcαR containing an NH$_2$-terminal HA tag (5′-YPYDVP-DYA-3′), overlap extension PCR was performed to fuse the major histocompatibility complex I Kb signal sequence and HA tag in-frame with the nucleotide sequence encoding the mature bFcαR protein. The resultant PCR product was then subcloned into the pcDNA3.1/V5-His-TOPO

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[1] The abbreviations used are: IgA, immunoglobulin A; bFcαR, bovine IgA Fc receptor; FcαR, IgA Fc receptor; KIR, killer cell immunoglobulin-like receptors; LRC, leukocyte receptor complex; bFcγ2R, bovine FcγR for IgG2; EC, extracellular; bIgA, bovine IgA; HA, hemagglutinin; GFP, green fluorescent protein; CMV, cytomegalovirus; FACS, fluorescence-activated cell sorter; mAb, monoclonal antibody; NIP, 4-hydroxy-3-iodo-5-nitrophenylacetate.

vector. Plasmids containing the HA-bFcαR cDNA in the correct orientation were selected by restriction enzyme digestion, and the nucleotide sequence was verified by sequencing. Prior to the generation of additional mutants, the functionality of the wild-type HA-bFcαR cDNA was further verified by transfection into COS-1 cells. This finding demonstrated that HA-bFcαR was expressed at the cell surface and was able to bind IgA. Point mutations were introduced into HA-bFcαR with the QuikChange mutagenesis kit (Stratagene) and appropriate synthetic oligonucleotides. The integrity of all of the mutants was confirmed by sequence analysis prior to transfection.

The pCMV-GFP plasmid, encoding the green fluorescent protein, was constructed by inserting the cytomegalovirus (CMV) promoter region from pCDNA3 (Invitrogen) into the multiple cloning site of the pEGFP-1 vector (Clontech, Palo Alto, CA).

Transfections—COS-1 cells were transiently transfected with 1 μg of bFcαR cDNA constructs by means of FuGENE 6 transfection reagent (Roche Applied Science) according to the manufacturer's instructions. Cells to be used for Ig binding assays were co-transfected with 0.05 μg of the pCMV-GFP plasmid in addition to the bFcαR constructs. Cells were incubated at 37 °C in a humidified CO_2 atmosphere for 48 h prior to harvesting.

Ig Binding Assays—Uncoated magnetic M-450 Dynabeads (Dynal, Oslo, Norway) were coated with NIP-bovine serum albumin according to the manufacturer's instructions. To prepare beads coated with recombinant human or bovine (anti-NIP) IgA, NIP-bovine serum albumin-coated beads were incubated with 100 μg/ml IgA for 1 h at room temperature. These beads were washed three times in phosphate-buffered saline prior to rosetting analysis. In our rosetting procedure, COS-1 cells were co-transfected with a bFcαR construct and pCMV-GFP. In this way, the COS-1 cells, which had taken up DNA during the transfection procedure, could be readily identified by their green fluorescence. In addition, untransfected cells that did not take up DNA and were thus not green served as an internal negative control of binding.

The binding assays were performed as follows: ~0.5 × 10⁵ transfected COS-1 cells were mixed with Ig-coated Dynabeads in a final volume of 50 μl per well in V-bottomed microtiter plates. After a 20-min incubation at room temperature, the plate was spun at 50 × g for 1 min and incubated for an additional 45 min at room temperature. Cells and beads were then carefully resuspended and examined for the presence of rosettes in a Nikon Eclipse E800 microscope, combining ordinary light and fluorescence.

FACS Analysis—To assess the expression of the HA-bFcαR mutants at the cell surface, COS-1 cells transfected with only the HA-bFcαR cDNAs (and not the GFP construct) were washed with FACS buffer (phosphate-buffered saline, 0.5% bovine serum albumin, 0.02% azide) and incubated with the HA.11 anti-HA tag monoclonal antibody (mAb) (mIgG1; Biosite, Täby, Sweden) or an irrelevant mIgG1 mAb (Southern Biotechnology, Birmingham, AL) as control for 30 min at 4 °C. Cells were next washed twice with FACS buffer and incubated for 30 min at 4 °C with goat anti-mouse IgG1-fluorescein isothiocyanate conjugate (Southern Biotechnology). After washing twice with FACS buffer, cells were analyzed on a FACScan (BD Biosciences). Data acquisition was conducted with CELLQuest software (BD Biosciences), whereas the analysis was performed with WinMDI software (available from the Scripps Research Institute, La Jolla, CA).

RESULTS

Construction and Expression of HA-bFcαR—COS-1 cells transfected with bFcαR cDNA are able to form rosettes with beads coated with bovine and human IgA (5), but a specific antibody reagent recognizing the bFcαR protein is not available. Therefore, we were unable to independently verify surface expression of bFcαR. Consequently, we decided to generate a bFcαR containing an NH₂-terminal HA tag that would allow detection of the expressed protein with a mAb against HA. Following the transfection of HA-bFcαR into COS-1 cells, we showed that the protein was indeed expressed at the cell surface and was recognized by a mAb specific for the HA tag (Fig. 1). In addition, we showed that COS-1 cells expressing HA-bFcαR were able to bind to beads coated with either bovine or human IgA. Moreover, the pattern of binding was indistinguishable from that observed with cells transfected with the wild-type bFcαR (Fig. 2). Altogether, these result strongly suggested that the incorporation of the HA tag into the NH₂-terminal of bFcαR did not adversely affect its ability to bind IgA.
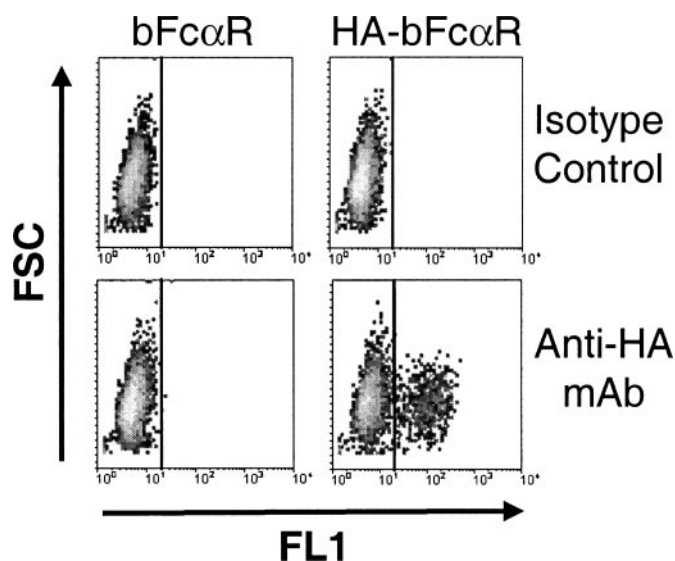

FIG. 1. **Surface expression of HA-tagged bFcαR.** COS-1 cells were transfected with either wild-type bFcαR or HA-bFcαR. Transfected COS-1 cells were then harvested and stained with an irrelevant isotype-matched control antibody (*top two panels*) or with an anti-HA mAb (*bottom two panels*) followed by an appropriate fluorescein isothiocyanate-labeled secondary reagent. *FSC*, forward scatter.
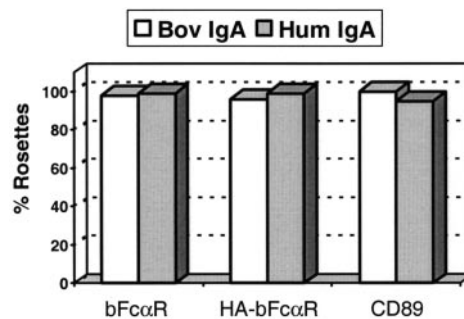

FIG. 2. **IgA binding by bFcαR, HA-bFcαR, and CD89.** Rosetting analysis was performed with COS-1 cells expressing the indicated FcαR. The beads were coated with either bovine (*Bov IgA, white bars*) or human IgA (*Hum IgA, gray bars*). The results shown are representative of at least three separate experiments.

Identification of Residues Important for IgA Binding—Previous mutational analysis of FcRs most closely related to bFcαR, namely CD89 and bFcγ2R, has identified several residues within their EC1 domains important for ligand binding (11, 13, 14). For CD89, these studies have shown that residues Tyr-35 (in the B-C loop) and Arg-82 (in the F-G loop) are essential for IgA binding, whereas His-85 (also in the F-G loop) contributes to the binding (Fig. 3). Similarly, for bFcγ2R, two residues in the F-G loop, Phe-82 and Trp-87, have been shown to be critical for the binding of bIgG2. The amino acid alignment of the protein sequence of CD89 and bFcαR showed that the tyrosine residue at position 35 is conserved. Notably, the arginine and histidine residues within the F-G loop of bFcαR are also conserved, although due to a two-amino acid deletion earlier in the domain, they are designated Arg-80 and His-83, respectively (Fig. 3). In addition, the residues toward the end of the bFcαR EC1 F-G loop are actually more similar to the corresponding residues of bFcγ2R (WSAPSE compared with WSEPSE, respectively).

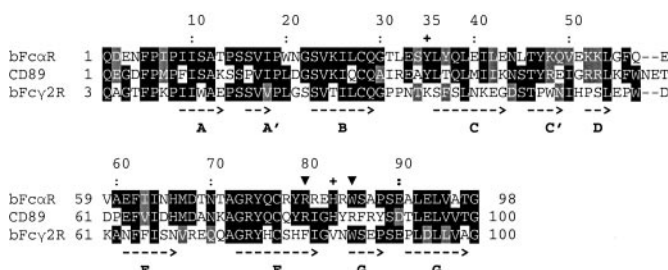Therefore, to identify the IgA binding site of bFcαR, we decided to mutate residues corresponding to those amino acids

FIG. 3. *A*, alignment of the protein sequences of the EC1 domains of bFcαR, CD89, and bFcγ2R (NCBI protein accession numbers AAP41842, CAA38089, and CAA85736, respectively). B-sheet regions of CD89 (designated A to F) by *broken arrows* under the sequence (based on data from Refs. 19 and 20). The numbering system used for the amino acid sequence of bFcαR in this report is indicated in detail above the text. Note that the numbering of CD89 is identical to bFcαR up to amino acid 57, after which there is a two-residue insertion in CD89. The numbering system used for bFcγ2R is consistent with that used in earlier publications and reflects the prediction that the bFcγ2R leader peptide is two amino acids shorter than those of bFcαR and CD89 (see Refs. 7 and 14). The amino acids previously identified as important for the binding of IgA to CD89 only are marked with a +. The amino acids previously identified as important for binding of IgA and bIgG2 to CD89 and bFcγ2R, respectively, are indicated with a ▼ (see Refs. 11, 13, and 14).

within CD89 and bFcγ2R that had been previously identified as important for ligand binding. A panel of four mutants was generated. Tyr-35, Arg-80, His-83, and Trp-85 were all replaced with Ala residues to generate the Y35A, R80A, H83A, and W85A mutants, respectively. Mutated HA-bFcαR cDNAs were then transfected into COS-1 cells, and their surface expression was confirmed by staining with the anti-HA mAb (Fig. 4). Although the W85A mutant appears to be expressed on a lower percentage of cells than the other mutants, the expression levels were more than sufficient for rosette analysis.

COS-1 cells expressing the mutated HA-bFcαR cDNAs were assayed for their ability to form rosettes with IgA-coated beads. We found that cells expressing the R80A, H83A, and W85A mutants were still able to bind to beads coated with either bovine or human IgA. In fact, only the cells expressing the Y35A mutant proved completely unable to form rosettes with IgA-coated beads (Fig. 5). These results showed that Tyr-35, which is predicted to lie within the B-C loop of the EC1 domain of bFcαR, is essential for IgA binding. Interestingly, the mutation of residues within the F-G loop, namely Arg-80, His-83, and Trp-85, did not appear to adversely affect ligand binding by bFcαR.

DISCUSSION

Here, we report that mutation of a single residue (Tyr-35) in the B-C loop of the EC1 domain of bFcαR was sufficient to abolish the interaction with IgA. Somewhat surprisingly and in contrast to previous reports describing similar mutations of CD89, we also showed that mutation of residues in the F-G loop region (Arg-80, His-83, and Trp-85) had no or little apparent effect on IgA binding in our assay system.

The bFcαR, CD89, and bFcγ2R represent a unique class of FcRs and are only distantly related to other mammalian FcRs such as FcγRI, FcγRII, FcγRIII, and FcεRI (1). In fact, they are more closely related to the family of genes that includes the KIRs, the leukocyte immunoglobulin-like receptors, and NKp46. In humans, the CD89 gene is located close to the KIR, leukocyte immunoglobulin-like receptor, and NKp46 genes within the so-called LRC on chromosome 19q13.4 (18, 19). It has been shown that the KIR and NKp46 genes are present in cattle, and these genes are also located in the bovine LRC on chromosome 18 (20, 21). Recently, we have also mapped the bFcαR gene to the bovine LRC (5).
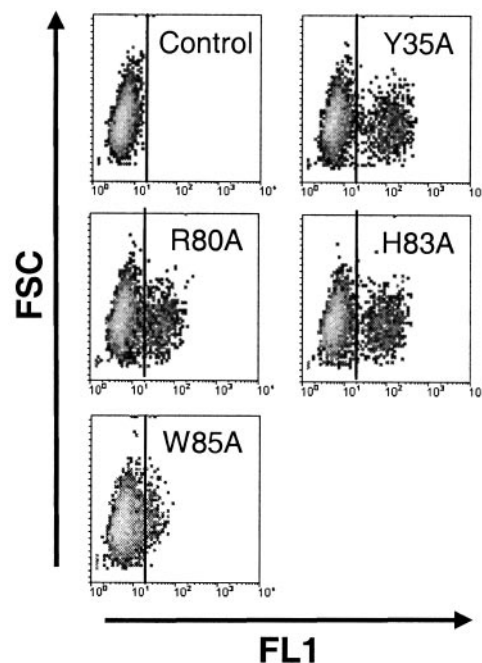

FIG. 4. **Surface expression of the HA-tagged bFcαR mutants.** COS-1 cells were transfected with four differently mutated HA-tagged bFcαR cDNAs as indicated. Two days thereafter, the cells were harvested and stained with an anti-HA mAb. Mock-transfected cells were used as control. *FSC*, forward scatter.
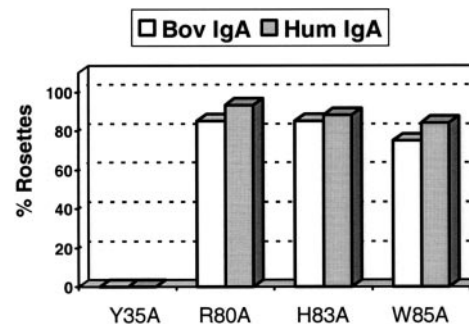

FIG. 5. **IgA binding by HA-bFcαR mutants.** Rosetting analysis was performed with COS-1 cells expressing HA-bFcαR with the indicated mutations. The beads were coated with either bovine (*Bov IgA*, *white bars*) or human IgA (*Hum IgA*, *gray bars*). The results shown are representative of at least three separate experiments.

Reflecting this differential evolution, it had previously been shown that CD89 and bFcγ2R shared various characteristics, which further distinguished them from other FcRs. One such unique feature is that the Ig binding site of these two FcRs lies in the EC1 domain (12), whereas that of other FcRs (FcγRs and FcεRI) lies predominantly in the EC2 domain (22–24). Specific residues within the EC1 domains of CD89 and bFcγ2R have been identified by site-directed mutagenesis studies. Thus, for CD89 expressed at the cell surface, it has been shown that Tyr-35 in the B-C loop and Arg-82 in the F-G loop are essential for binding to IgA (11, 13). Biosensor data have also suggested that His-85 is critical for IgA binding, but the effect of mutation of this residue on binding by cell surface-expressed receptor has not been reported (11, 13).

In the case of bFcγ2R, ligand binding appears to depend on two residues in the F-G loop region and mutation of either Phe-82 or Trp-87 abolishes binding to bovine IgG2 (14). Thus, by comparison with other closely related FcRs, we identified a number of residues that we believe may be important for IgA

binding by bFcαR. Therefore, we chose to mutate Tyr-35, Arg-80, His-83, and Trp-85 and investigate the effect on the interaction with IgA. Although slightly different numbering systems were used for these three FcRs, the sequence homology predicted that Arg-80 and His-83 of bFcαR correspond to Arg-82 and His-85 of CD89. Similarly, bFcαR Trp-85 corresponds to Trp-87 of bFcγ2R (see Fig. 3).

To correctly interpret our IgA binding assays, we required an independent method to confirm the surface expression of the bFcαR mutants. Traditionally, such mutagenesis studies of FcRs have depended on specific anti-FcR mAbs to confirm surface expression of the mutated receptors (13, 14). However, in the case of bFcαR, there was no specific mAb available. Therefore, we decided to introduce an HA tag into the NH$_2$ terminus of the receptor. Previously, it has been shown that the NH$_2$ terminus of CD89 does not contribute in any way to the IgA binding site and we reasoned that this would most likely also be the case for the highly homologous bFcαR (13). Indeed, our data showed that the introduction of the HA tag into bFcαR had no apparent effect on the ability of transfected COS-1 cells to bind IgA-coated beads. Consequently, we proceeded to introduce the previously specified mutations into the HA-tagged version of bFcαR.

Our results showed that, in common with CD89, Tyr-35 in the B-C loop of the EC1 domain of bFcαR appears to be essential for the binding of IgA. Surprisingly, however, the substitution of residues in the F-G loop region with alanine did not inhibit binding to IgA-coated beads. The mutation of Arg-82 to alanine in CD89 has been reported to abolish IgA binding, so we had expected that the corresponding mutation in bFcαR (R80A) would have a similar effect. However, although alanine substitutions in the F-G loop of bFcαR did not abolish binding, we cannot exclude that residues in this region contribute somewhat to the interaction with ligand. Previously, the biosensor analysis of CD89 mutants also identified Arg-52 as a residue that appeared to contribute to IgA binding. Biosensor data showed that the mutation of Arg-52 to alanine produced an 8-fold reduction in affinity. However, when this mutant was expressed at the cell surface, it still bound the same amounts of IgA as wild-type CD89 (13). Thus, biosensor measurements with mutated soluble proteins, which show even a relatively large reduction in affinity, may not necessarily indicate how the binding reaction will proceed when a mutated FcR is expressed at the cell surface and assayed for binding to Ig-coated particles, a situation presumably mimicking more closely FcR-mediated cellular triggering *in vivo*. In this respect, the sensitivity of our rosetting method may be advantageous because it allows us to detect mutations that completely abolish binding and are thus essential for promoting the CD89-IgA interaction. Unfortunately, however, this assay does not readily detect very small changes in affinity so we cannot rule out the possibility that residues in the F-G loop do make a minor contribution to the interaction with IgA. However, our data clearly show that the residues in the F-G loop, which were mutated in this study, are not essential for the binding of IgA-coated particles to CD89-expressing cells.

Recently, the three-dimensional structure of CD89 was solved (25, 26). More interestingly, the structure of CD89 in complex with the IgA Fc and the stoichiometry of the reaction were elucidated (25, 27). Unlike the FcγRs and FcεRI, which bind Ig with a 1:1 stoichiometry, two CD89 molecules were shown to bind one IgA Fc region. The co-crystal data further confirmed that residues such as Tyr-35 and Arg-82, which had previously been shown to be involved in IgA binding by mutagenesis, do indeed directly contact the IgA Fc.
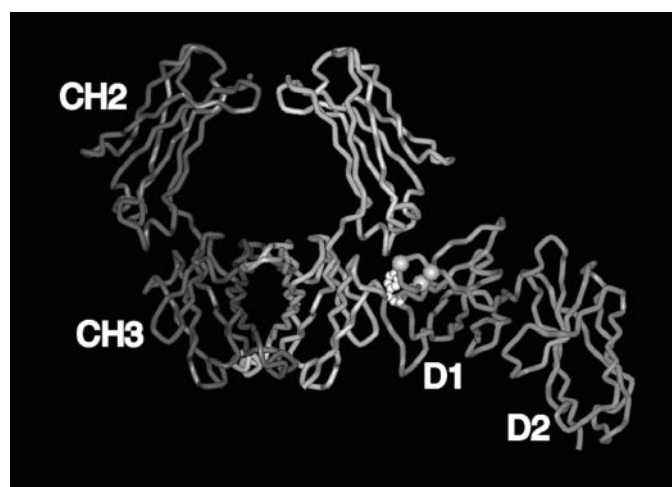

FIG. 6. **Structure of the complex of human IgA1 Fc and human CD89 with the receptor residues equivalent to those mutated here highlighted.** The IgA Fc is shown on the *left* with one heavy chain in *dark gray* and the other in *light gray*. The extracellular domains of CD89 are shown on the *right*. The membrane distal domain (*D1*) of the receptor interacts with the interface of domains CH2 and CH3 of IgA Fc. Residue Tyr-35 is shown in *white* (space-filled representation). The locations of residues Arg-82, His-85, and Arg-87 (the equivalents of Arg-80, His-83, and Trp-85 in bFcαR) are shown as large spheres. X-ray crystal coordinates were taken from the Protein Data Bank entry 1OW0.

The high level of homology between CD89 and bFcαR suggests that their overall structures will be similar. In addition, the residues within the Fc region of human IgA, which have been shown to interact with CD89, are also conserved in the bovine IgA Fc (15). Taken together, these data suggest that bFcαR binds IgA in a manner broadly similar to CD89 (Fig. 6). However, our results suggest that in contrast to the situation for CD89, the F-G loop of the EC1 domain of bFcαR may not play an essential role in IgA binding.

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Ligand Binding Site of Bovine FcαR

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