CD163 Binding to Haptoglobin-Hemoglobin Complexes Involves a Dual-point Electrostatic Receptor-Ligand Pairing*

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The high affinity interaction between CD163 and Hp-Hb is $\text{Ca}^{2+}$-dependent and critically relies on the amino-terminal third of the extracellular SRCR region in CD163 (1, 19). Using a panel of truncated recombinant CD163 variants, we have previously shown that SRCR domains 1–5 bind Hp-Hb with an affinity similar to the entire extracellular region of CD163 (19). In the ligand, comparative binding analyses with human Hp, Hpr, and Hp/Hpr hybrids have shown that the so-called loop 3 of the Hp SP domain plays an essential function in CD163 recognition of Hp-Hb (20). The recently published crystal structure of porcine Hp-Hb reveals that this loop protrudes from the distal part of the Hp-Hb complex and small angle x-ray scattering measurements of human Hp-Hb in complex with recombinant CD163 SRCR domains 1–5 support the approximate zones of contact between the ligand and receptor (3). In contrast to the complex of Hp-Hb, Hb and Hp alone exhibit weak or no binding to CD163 in humans (1, 20, 21).

Mapping of the CD163-(Hp-Hb) interaction surfaces is so far restricted to the human system, but a recent study in mice has uncovered subtle and major evolutionary differences in the Hb scavenging mechanism. First, the binding of Hb alone to CD163 is of significantly higher affinity than the corresponding interaction in humans; and second, Hb fails to elicit high affinity receptor binding upon complex formation with Hb in the mouse system (22).

Ligand binding by the SRCR domain of the scavenger receptor MARCO also depends on $\text{Ca}^{2+}$, and this domain has been shown to harbor a metal ion binding site composed of three negatively charged residues that are involved in ligand binding (23). A corresponding motif for $\text{Ca}^{2+}$-coordinated clustering of acidic residues is present in SRCR domains 2, 3, 7, and 9 of CD163. Based on a series of binding experiments with mutated variants of both CD163 and Hb, we here present data pinpointing the contact region between CD163 and its high affinity ligand Hp-Hb and propose a common model for $\text{Ca}^{2+}$-dependent coupling and uncoupling of ligand.

**EXPERIMENTAL PROCEDURES**

**Plasmids**—We used a plasmid construct (18, 20) with human Hp1 cDNA inserted into the KpnI and XhoI sites of the mammalian expression vector pcDNA5/FRT (Invitrogen) as a template to generate mutants encoding Hp R252T; Hp E261A; Hp K262A; Hp T264A; and Hp E261A,K262A,T264A by means of the QuikChange site-directed mutagenesis kit (Stratagene). Likewise, the following human CD163 mutated variants were generated by site-directed mutagenesis using a pcDNA5/FRT construct that encodes the five amino-terminal SRCR domains of human CD163 (CD163 SRCR1–5; amino acids 1–574) (19) as a template in site-directed mutagenesis: CD163 SRCR1–5 D185A,D186A,E252A; CD163 SRCR1–5 D292A,D293A,E359A; CD163 SRCR1–5 D392A,D293A; CD163 SRCR1–5 E359A; CD163 SRCR1–5 D185A,D186A,D292A,D293A; and CD163 SRCR1–5 E252A,E359A. All plasmid constructs were verified by sequencing using the Eurofins MWG Operon (Ebersberg, Germany) sequencing service.

**Cell Lines**—Flp-In HEK293 cells (Invitrogen) were cultured in Dulbecco’s modified Eagle’s medium (Cambrex Bioscience, Verviers, Verviers, Belgium) supplemented with 10% fetal calf serum, 2 mM glutamine, and 100 μg/ml Zeocin (Invitrogen). Transfection with Hp mutant cDNA was performed using FuGENE 6 transfection reagent (Roche Diagnostics), and stable transfecants were selected with 150 μg/ml Hygromycin B (Invitrogen). Flp-In CHO cells (Invitrogen) were maintained in serum-free HyClone medium for CHO cells (Thermo Scientific). Stably transfected Flp-In CHO cells expressing CD163 variants were established by means of FuGENE 6 and subsequent selection with 750 μg/ml Hygromycin B (Invitrogen). Hp and CD163 expression products were visualized by subjecting growth medium and cell lysate to SDS-PAGE and subsequent Western blotting using a rabbit polyclonal anti-human Hp antibody (DAKOCytomation, Glostrup, Denmark) and a rabbit polyclonal anti-CD163 antibody (1), respectively.

**Purification of Recombinant Proteins**—We purified Hp and Hp mutants from serum-free HEK293 cell culture medium (Invitrogen) by Hp (Sigma) affinity chromatography as detailed previously (20). Purification of human CD163 SRCR1–5 and mutated versions was performed by subjecting harvested cell culture medium containing secreted expression products to antibody affinity chromatography. The affinity column was generated by coupling 5 mg of the humanized anti-human CD163 antibody KN2/NRY (a gift from CytoGuide Aps, Aarhus, Denmark) to 1 ml of HiTrap NHS-activated HP (GE Healthcare) according to manufacturer’s instructions. The harvested culture medium was concentrated and filtered before application on the column. After allowing the expression products to bind to the immobilized antibody, the column was washed with phosphate-buffered saline, pH 7.4, before elution with a solution containing 50 mM acetate and 500 mM NaCl, pH 5.0. Secondary elution was performed with 100 mM glycine HCl, 500 mM NaCl, pH 4.0. The collected fractions were neutralized by a Tris buffer, pH 8.0, and the proteins were stabilized by addition of a protease inhibitor mixture (Roche Applied Science). Fractions were dialyzed against phosphate-buffered saline (137 mM NaCl, 2.7 mM KCl, 8.1 mM Na$_2$HPO$_4$, and 1.75 mM KH$_2$PO$_4$), pH 7.4, at 4 °C and analyzed by SDS-PAGE followed by silver staining.

**Pulldown Assay**—Bovine serum albumin (BSA) or complexes of human Hp (mixed phenotypes, Sigma) and human Hb A$_0$ (Sigma) were coupled to CNBr-activated Sepharose 4B beads (Amersham Biosciences) according to the manufacturer’s instructions. To test for interaction with CD163 variants, beads were washed twice in MB buffer (2 mM CaCl$_2$, 1 mM MgCl$_2$, 10 mM Heps, and 140 mM NaCl, pH 7.8) prior to incubation with growth medium harvested from CD163-transfected Flp-In CHO cells. Incubation was performed overnight at 4 °C, and the following morning beads were washed six times in MB buffer. Bound CD163 variant proteins were eluted by a lithium dodecyl sulfate-containing sample buffer and visualized by Western blotting using rabbit polyclonal anti-CD163 antibody (1).

**Surface Plasmon Resonance (SPR) Analyses**—The interaction between CD163 and complexes of Hb (Hp1-1 purified from human plasma (Sigma) or purified recombinant Hp variants) and Hb A$_0$ (Sigma) was studied by SPR analysis on a Biacore 3000 instrument, essentially as described (1, 18–20). Biacore...
sensor chips type CM5 were activated with a 1:1 mixture of 0.2 M N-ethyl-N’- (3-dimethylaminopropyl)carbodiimide and 0.05 M N-hydroxysuccimide in water according to instructions by the manufacturer. CD163 purified from human spleen (1) or purified truncated recombinant CD163 SRCR1–5 variants were immobilized in 10 mM sodium acetate, pH 4.0, and the remaining binding sites were blocked with 1 M ethanolamine, pH 8.5. A control flow cell was made by performing the activation and blocking procedure only. Samples were dissolved in 10 mM Hepes, 150 mM NaCl, 2.0 mM CaCl₂, 1.0 mM EGTA, and 0.005% Tween 20, pH 7.4. Sample and running buffers were identical. Regeneration of the sensor chip after each analysis cycle was performed with 10 mM glycine, pH 4.0, containing 20 mM EDTA and 500 mM NaCl.

RESULTS
Acidic Triads in CD163 SRCR Domains 2 and 3 Are Essential for Hp-Hb Binding—Fig. 1 shows an alignment of the MARCO SRCR domain and the nine SRCR domains of CD163 demonstrating that the metal binding residues of MARCO are conserved in CD163 SRCR domains 2, 3, 7, and 9.

To investigate whether the acidic triads in CD163 SRCR domains 2 and 3 play a role in Hp-Hb binding, we expressed recombinant CD163 SRCR1–5 mutated in the candidate metal-binding residues of SRCR domains 2 and 3 (Fig. 2A). Expression of a variant carrying mutations in the acidic triad of SRCR domain 2 (D185A,D186A,E252A) revealed a stable protein but absent Hp-Hb binding as measured by Hp-Hb-mediated pulldown analysis (data not shown). Mutation of the entire acidic triad of SRCR domain 3 rendered the protein unstable, but single (E359A) and double mutations (D292A,D293A) in this acidic triad completely abrogated Hp-Hb-mediated pulldown (Fig. 2B and data not shown). In line with these results, single mutation of one or two residues in each of the acidic triads of SRCR domains 2 and 3 (SRCR1–5 E252A,E359A and SRCR1–5 D185A,D186A,D292A,D293A) led to stable expression products but inactivity in terms of Hp-Hb binding (Fig. 2B).

To study the Hp-Hb binding properties in a more sensitive assay, three of the mutants (SRCR1–5 D185A,D186A,E252A; SRCR1–5 D292A,D293A; and SRCR1–5 E359A) were purified by antibody affinity chromatography (Fig. 2C) for use in SPR experiments. The resulting data showed that the SRCR domain 2 mutant protein (D185, D186A,E252A) has a significant reduction in affinity compared with the WT counterpart, and that effects of the single (E359A) and double mutations (D292A, D293A) in SRCR domain 3 are equally dramatic (Fig. 2D). Collectively, these binding analyses disclosed an essential role for the acidic triads of CD163 SRCR domains 2 and 3 in Hp-Hb recognition.

Two Positively Charged Residues in Hp Loop 3 Are Crucial for the CD163-(Hp-Hb) Interaction—In this part of the study we tested the hypothesis that basic residues in the ligand pair with Ca²⁺-coordinated acidic triads in CD163, an electrostatic pairing mechanism, that has previously been proposed to be a common theme of Ca²⁺-dependent ligand-receptor interactions (24). In this model, Ca²⁺ plays an indirect role in ligand binding by positioning two or three negatively charged residues from the acidic triad for direct interaction with one positively
Basic residues in the CD163 binding region in Hp loop 3 were subsequently subjected to mutagenesis to identify potential Arg/Lys residues involved in receptor binding. A strong candidate was Lys-262 because a previous comparison of Hp and Hpr has shown that simultaneous substitution with Hpr-specific residues in positions 261, 262, and 264 in Hp loop 3 completely abrogates binding of Hp-Hb to CD163 (20) and Fig. 3, A and C). Analysis of single mutants (Hp E261A; Hp K262A; and Hp T264) (Fig. 3B) in SPR binding experiments revealed that the K262A substitution alone accounted for the eliminated binding of the Hp-Hb complex to CD163 (Fig. 3C). For comparison, the triple mutant with mutations corresponding to Hpr-specific residues (Hp E261K,K262W,T264A (Fig. 3A)) and a triple mutant with Ala substitutions (Hp E261A,K262A,T264A) were also included in this analysis (Fig. 3, B and C).

To hunt down a second positively charged Hp residue with a crucial role in receptor interaction, we again turned to the previous mutational analysis of Hp/Hpr hybrids which had furthermore revealed that the triple substitution of Hp residues Asp-248, Gln-249, and Arg-252 into the corresponding residues of Hpr (Fig. 3A) resulted in inhibition of receptor binding (20). These residues are positioned in an α-helix located in the loop 3 region. Mutation of Arg-252 on its own gave rise to a significant reduction in receptor affinity (Fig. 3, B and C).

We also investigated the effect of substitution of surface-exposed Hb residues that are positioned closely to the Hp loop 3 in the recently solved crystal structure of the Hp-Hb complex (3). Neither of the following Hb mutations affected the high affinity contact between ligand and receptor. This summary, these mutational studies identified Arg-252 and Lys-262 in Hp loop 3 as essential residues in the CD163-(Hp-Hb) interaction. The three-dimensional model in Fig. 3D illustrates the position of these two positively charged residues within the Hp molecule.

Alignment of available Hp sequences revealed that Lys-262 is highly conserved whereas Arg-252 only is present in primate Hp (Fig. 4). Some primates such as Macaca fascicularis have a Lys corresponding to Arg-252 and an Arg corresponding to Lys-262. Hp from this primate species showed similar induction of high affinity binding of human Hb to human CD163 in the SPR binding assay (data not shown).

**DISCUSSION**

The present mutagenesis study now reveals the essential receptor and ligand residues involved in high affinity binding of the Hp-Hb complex to CD163 in humans. In CD163, the identified ligand contact region comprises two triplets of acidic residues in SRCR domains 2 and 3, respectively, both of which conform to the calcium- and ligand-binding motif described in MARCO (23). In the CD163 ligand, the two basic residues Arg-252 and Lys-262 residing in loop 3 of Hp are crucial for binding to CD163. As further described below, we suggest that electrostatic interactions between the Ca$^{2+}$-coordinated acidic residues in CD163 and the basic residues in Hp loop 3 are crucial for the high affinity contact between ligand and receptor. This also corresponds with the well described calcium dependence.

**charged residue from the ligand. In compliance with Lys/Arg playing an essential role in the CD163-(Hp-Hb) interaction, the presence of free Lys or free Arg efficiently inhibited Hp-Hb binding to CD163 in SPR binding experiments (data not shown). In contrast, free His was severalfold less efficient in inhibiting Hp-Hb binding to CD163.**
Amino acid residue differences between Hp and Hpr are shown in Figure 3. Lys-262 and Arg-252 in Hp loop 3 are critically involved in the Mechanism of CD163-(Haptoglobin-Hemoglobin) Binding.

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FIGURE 3. Lys-262 and Arg-252 in Hp loop 3 are critically involved in CD163 binding. A, sequence alignment of human Hp1 and human Hpr. Amino acid residue differences between Hp and Hpr are shown in black, and loop 3 is framed in a box. The cleavage sites of the 18-residue Hp signal peptide and between the CCP and SP domains are indicated by arrows. Concurrent substitution of Glu-261, Lys-262, and Thr-264 (highlighted in blue) into the corresponding Hpr residues was previously shown to eliminate Hp-Hb binding. B, SPR analyses of mutants were analyzed for binding to CD163 immobilized on a Biacore sensor chip. The recombinant Hp protein analyzed is indicated above each panel. D, model of the human Hp1 monomer based on the structure of the porcine Hp-Hb complex (3). Arg-252 and Lys-262 are shown as sticks. The Hp loop 3 is shown in blue.

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one site (Asn-182) is positioned in the vicinity of loop 3 (3). Abrogation of this glycosylation site by mutation of Ser-184 does not change apparent receptor binding affinity (20).

Interestingly, Hp Arg-252 seems specific for primates, and this coincides with the observation that human and monkey Hp, when complexed with Hb, elicits a pronounced increase in CD163 affinity. Other striking Hp and CD163 features specific for primates or for humans are: (i) a high Hp level in plasma, (ii) human-specific Hp multimerization induced by the Hp2 gene product, (iii) evolution of the Hpr protein (for review, see Refs. 8, 28), and (iv) duplication of the CD163 gene giving rise to the gene encoding the macrophage surface protein CD163-L1 (29).

Hpr is known to play a major role in the innate defense against the
Trypanosoma brucei brucei
parasites causing sleeping sickness. It is tempting to speculate that the other genetic expansions also rely on the evolution of novel defense mechanisms against infectious diseases that have been a major threat to survival during evolution of the primates.

As presented in the alignment in Fig. 1, the Ca$^{2+}$-coordinated ligand-binding residues of MARCO are conserved not only in CD163 SRCR domains 2 and 3, but also in SRCR domains 7 and 9. Based on previous binding studies with truncated CD163, SRCR domains 7 and 9 are not part of the Hp-Hb binding regions (19). However, it is possible that these domains bind free Hb, as well as other ligands. Multiligand preference is a general feature of macrophage scavenger receptors, and other ligands such as the cytokine TWEAK, erythroblasts, as well as some bacteria and viruses have been reported to bind to CD163 (reviewed in detail in Ref. 30). Compared with the binding of Hp-Hb to CD163, these other reported ligand-CD163 interac-
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CD163-L1 (29, 33). Ligands that bind to these putative Ca\(^{2+}\) sites await identification.

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