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Human Immature Dendritic Cells Efficiently Bind and Take up Secretory IgA Without the Induction of Maturation

Heleen C. Heystek,1* Corinne Moulon, † Andrea M. Woltman, ‡ Pierre Garonne, § and Cees van Kooten ‡

Immature dendritic cells (DC) reside in peripheral tissues, where they pick up and process incoming pathogens via scavenger receptors or FcR such as FcγR and FcεR. At mucosal surfaces, IgA is the main Ig to protect the body from incoming pathogens. In addition, DC are present in high numbers at these sites. We detected expression of FcεRI (CD203c) on the CD11c+ population of CD34+ progenitor-derived DC and on monocyte-derived DC (MoDC). However, CD89 expression was strongly decreased upon differentiation from monocyte to DC. We found only minimal binding of serum IgA to MoDC but strong binding of secretory IgA (SIgA). The SIgA binding to MoDC could not be blocked by anti-CD89 blocking Abs. DC efficiently internalized SIgA, but not serum IgA, and uptake of SIgA could be blocked by specific sugars or partially by Ab reactive with mannose receptor. Importantly, binding and uptake of SIgA was not accompanied by signs of DC maturation, such as increased expression of CD86 and CD83 or induction of cytokine secretion. These data indicate that SIgA can interact with DC not via CD89, but via carbohydrate-recognizing receptors like mannose receptor and suggest that uptake of SIgA-containing immune complexes by immature DC may be a mechanism to modulate mucosal immune responses. The Journal of Immunology, 2002, 168: 102–107.

Mucosal tissues are heavily populated with cells of the immune system, including dendritic cells (DC)1, 2. In their immature state, DC are very efficient in Ag capture and can use several pathways such as macropinocytosis or phagocytosis of viruses, bacteria (3, 4), apoptotic, and necrotic cell fragments (5, 6), as well as intracellular parasites (7, 8). In addition, C-type lectin receptors (mannose receptor (MR), DEC-205; Refs. 9–11) or FcR such as FcγR such as FcγRI (CD64) and II (CD32; Refs. 12–14), and FcεRI (15, 16) are able to mediate endocytosis of immune complexes or opsonized particles for Ag-presentation in DCs. This event of Ag uptake, is thought to induce activation, migration, and maturation of the DC and represents the first critical step in the immune response. DC of mucosal surfaces have been described picking up Ag and migrating out of mucosal tissues to draining lymph nodes for Ag presentation to T cells (17). However, recent studies show that immature DC migrate constitutively from peripheral tissues in the absence of any antigenic or inflammatory stimuli (18).

A prominent feature of immune responses at mucosal sites is the synthesis of IgA. IgA is mainly expressed in two distinct forms: serum IgA, being predominantly monomeric, and secretory IgA (SIgA) in external fluids, which consists of dimeric IgA containing a joining J chain and secretory component as a result of the trans-cytosis process (19, 20). SIgA is considered the first line of defense to protect the body against incoming pathogens. Because responses against commensal bacterial flora and dietary Ags are harmful, SIgA is proposed as a non- or even anti-inflammatory Ab (21–24). SIgA is proposed as a non- or even anti-inflammatory Ab (21–24). In contrast, serum IgA was shown to initiate effector functions like complement activation, respiratory burst activity, or phagocytosis (19, 25).

Interaction of IgA with FcεRI are considered to play an important role in protection against infections. The first and best characterized specific receptor for IgA in humans is FcεRI (CD89). The expression of human FcεRI has been found on monocytes, macrophages, granulocytes, and eosinophils (20, 26, 27). However, little information exists concerning the CD89 expression on DC populations of myeloid origin. Myeloid DC have been characterized and in vitro cultures of DC from peripheral blood monocytes and CD34+ selected cells have been established (28, 29). In this study, we investigated how CD89 expression is regulated during DC development and studied whether DC can bind and take up IgA.

We detected low levels of CD89 expression on a distinct population of CD34+–derived DC and on monocyte-derived DC (MoDC). Binding of SIgA to DC was superior to binding of serum IgA and could not be inhibited by anti-CD89 blocking Abs. Interestingly, uptake of SIgA was not accompanied by DC maturation. Uptake of SIgA by DC was highly efficient and could be blocked by specific sugars or partially by Abs reactive with MR. These data indicate that SIgA can interact with DC not via CD89, but via carbohydrate-recognizing receptors such as MR.

Materials and Methods

Biochemicals

An Alexa Fluor 488 protein labeling kit was obtained from Molecular Probes (Leiden, The Netherlands). Conjugation of different proteins with Alexa was done according to the protocol supplied by the manufacturer. BSA Fraction V; FITC-conjugated BSA; FITC-labeled mannosylated...
BSA; mannan derived from *Saccharomyces cerevisiae*; the monosaccharides N-galactose, D-glucose, L-fucose, and N-acetylgalactosamine; and human SIGA were purchased from Sigma-Aldrich (St. Louis, MO). Human serum IgA was obtained from ICN Pharmaceuticals (Aurora, OH).

**Isolation and culture of MoDC and CD34**\(^ \dagger \)** derived DC**

PBMCs were isolated by density gradient centrifugation of buffy coats from healthy donors using Lymphoprep (Nycomed, Oslo, Norway) and were cryopreserved in liquid nitrogen. Mononuclear cells were thawed and used immediately for immunomagnetic separation using a Monocyte Isolation kit (Miltenyi Biotec, Paris, France). Isolation of monocytes was performed as described by the manufacturer. Purified cells were typically >95% of CD14\(^\text{+}\) as determined by flow cytometry.

To obtain MoDC, as described, monocytes (6 x 10\(^6\) cells/well) were cultured in RPMI 1640 Glutamax-I medium containing kanamycin (100 µg/ml) and 10% FCS (Life Technologies, Cergy, France) and supplemented with 500 U/ml recombinant human GM-CSF and 250 U/ml recombinant human IL-4 (both cytokines were purchased from R&D Systems, Minneapolis, MN). In most experiments, except where noted, MoDC were harvested for use in assays after 5–7 days in culture. Analysis by flow cytometry revealed that preparations consisted of a homogeneous population of CD14\(^\text{+}\), CD14\(^\text{low/−}\), CD83 low/\(^\text{−}\), M R\(^\text{−}\), HLA class II \(^\text{−}\)expressing cells. This surface marker profile is characteristic of immature DC which are thought to efficiently take up and process exogenous Ags.

CD34\(^\text{+}\) hemopoietic progenitor cells were isolated from umbilical cord blood samples and used in cultures to generate immature DC as described before (28). In brief, CD34\(^\text{+}\) cells were isolated from mononuclear fractions through positive selection using anti-CD34-coated microbeads and Midi-Macs separation columns (both from Miltenyi Biotec). After cryopreservation, cells were cultured in RPMI 1640 containing 10% heat-inactivated FCS, 10 mM of HEPES, 2 mM of l-glutamine, 50 µM of 2-ME, and penicillin/streptomycin supplemented with GM-CSF (100 ng/ml; Schering-Plough, Kenilworth, NJ), stem cell factor (25 ng/ml; R&D Systems), TNF-\(\alpha\) (2.5 ng/ml; R&D Systems), and 5% AB\(^\text{+}\) pooled human serum. For FACS analysis, cells were collected after 6 days of culture.

The CD89-expressing cell line U937 (number CRL-1593.2; American Type Culture Collection, Manassas, VA; Ref. 30) was cultured in RPMI 1640 medium supplemented with 10% FCS.

**Antibodies and flow cytometry**

Cells were incubated for 30 min at 4°C in FACS buffer (PBS, 0.5% BSA, 0.02% azide) with a series of FITC- or PE-conjugated mAbs recognizing human Ags. The following mAbs were used for immunofluorescent staining: CD1a (T6), MR (3.29B1.10), CD83 (HB15a), CD14 (My4; all obtained from Beckman Coulter/Immunotech, Luminy, France), CD86 (FUN-1) and CD89 (A59; both obtained from BD Pharmingen, San Diego, CA). The CD89 mAbs A59 and 7D7 were both shown to react with the membrane-proximal extracellular 2 domain, whereas the blocking mAb 2D11 was shown to react with the extracellular 1 domain of FcRn (31). mAb reactive with MR (clone 19) for flow cytometry and inhibition studies of IgA binding was purchased from BD Pharmingen. After washing, the cells were analyzed by flow cytometry (Coulter EPICS XL; Beckman Coulter, Miami, FL or FACScan; BD Biosciences, San Jose, CA). Cells were electronically gated according to light scatter properties to exclude cell debris. Data analysis was performed by WinMDI software (http://faqs.scripps.edu/).

**Binding and detection of IgA**

To examine IgA binding, 5 x 10\(^4\) DC were incubated in FACS buffer with IgA (250 µg/ml) for 1 h at 4°C. After washing, cells were incubated for 1 h with PE-labeled F(ab\(^\prime\))\(_2\) of goat anti-human IgA (Southern Biotechnology Associates, Birmingham, AL). The stained cells were analyzed by flow cytometry. To define the specificity of the binding of IgA to CD89, blocking studies were performed using the anti-CD89 blocking mAb 2D11. Briefly, 2D11 mAb or an isotype-matched irrelevant control mAb was added to the cells and incubated at 4°C. After 15 min, IgA was added and the cells were stained and analyzed for IgA binding by FACS as described above.

**Quantitative analysis of ligand uptake by cells**

Cells were harvested and resuspended in RPMI 1640 medium (without serum) containing 0.5% BSA. Alexa-labeled ligands or FITC-conjugated ligands (1 U/ml) were diluted in RPMI medium, then added to 5 x 10\(^4\) cells, followed by 1 h incubation at either 37 or 4°C (negative control), as previously described (32). For binding inhibition studies mAbs or saccharides were added at the onset of incubation. Uptake was stopped by extensively washing the cells in ice-cold medium before examination by flow cytometry.

**Activation of DC for cytokine production and phenotypical analysis**

Immature DC were harvested, washed extensively, and stimulated with SIGA cross-linked with F(ab\(^\prime\))\(_2\) goat anti-human IgA (Southern Biotechnology Associates) or LPS (1 µg/ml) and IFN-\(\gamma\) (10 U/ml). After 20 h, cells were harvested and CD86 and CD83 expression was assessed by flow cytometry. At the same time, cell-free supernatants were collected and stored at −20°C before determination of IL-12p70, IL-6, and IL-10 levels by ELISA (Opt EIA; BD Pharmingen). The sensitivity of IL-12p70, IL-6, and IL-10 detection was 10 pg/ml.

**RNA isolation and RT-PCR analysis**

For PCR analysis, total RNA was isolated using RNAzol (Cambio, Cambridge, The Netherlands), a method based on the guanidinium chloride isolation according to the manufacturer’s instructions. Quantity and purity of RNA preparations were determined by measuring the OD at 260 and 280 nm. Fixed amounts of total cellular RNA (1 µg) were reverse transcribed into cDNA by oligo(dT) priming, using Moloney murine leukemia virus reverse transcriptase (Life Technologies). The amplification of cDNA by PCR was performed using the following CD89 specific primer sets: forward 5’-TGGGAGGAGCAAGGAAGG-3’, reverse 5’-TCTCTGGGTAACACC-3’ (product 370 bp), and forward 5’-CTACCTCTATGTGC-3’, reverse 5’-GTTT TACCACTGAGACC-3’ (product 515 bp), and the \(\beta\)-actin primer set: forward 5’-CTAAGGACTGCTGGTG-3’, reverse 5’-AAGGAGCTGGAAGGTG-3’ (product 527 bp). PCR amplification was performed under standard conditions (50 mM of KCl, 10 mM of Tris-HCl (pH 8.4), 2 mM of MgCl\(_2\), 0.06 mg/ml BSA, 0.25 mM of dNTPs, 25 pmol of each primer, and 1 U of Taq polymerase; PerkinElmer, Norwalk, CT) by 35 cycles of the following scheme: 1.5 min at 95°C, 2.5 min at 60°C, 1.5 min at 72°C, followed by 10 min of primer extension at 72°C. PCR products were analyzed on a 1% agarose gel containing ethidium bromide. Final results were registered using the Eagle Eye (Stratagene, San Diego, CA).

**Results**

**Expression of CD89 on DC derived from CD34\(^\dagger\)** precursor cells

At day 6, CD34\(^\text{+}\)-derived cells cultured in the presence of GM-CSF and TNF-\(\alpha\) expressed low but significant levels of CD89 (Fig. 1A). With two different mAbs against CD89, a similar expression...
was found. It has been shown that CD34<sup>+</sup> hematopoietic progenitor cells differentiate along two distinct DC pathways based on the reciprocal expression of CD1a or CD14 Ags (33). To better characterize CD89 expression on the two CD34<sup>+</sup>-derived DC populations, a triple staining was performed allowing specific analysis of both CD14<sup>-</sup>/CD1a<sup>-</sup> and CD14<sup>+</sup>/CD1a<sup>-</sup> expressing cells. Interestingly, the CD1a<sup>-</sup> precursors expressed lower levels of CD89 compared with the CD14<sup>+</sup> precursors (Fig. 1B). Expression remained low until the stage of fully differentiated DC was reached at day 12 of culture (data not shown). The CD14<sup>+</sup> precursors have features of dermal DC and blood DC (33) and are likely linked to the monocytic lineage.

**Expression of CD89 on CD14<sup>+</sup>-derived DC**

We investigated regulation of CD89 expression during monocyte-derived DC differentiation. High expression of CD89 was detected on monocytes at the onset (day 0) of DC culture and on the U937 cell line used as a positive control (Fig. 2A). However, CD89 expression was strongly down-regulated upon differentiation to MoDC (Fig. 2A). Kinetic experiment showed that the strongest decrease at the protein level was found between days 2 and 6 of DC development (Fig. 2B).

RT-PCR analysis showed a similar decrease in CD89 mRNA expression during DC development (Fig. 3). Comparable results were found with two different primer pairs, resulting in the expected size of PCR products, excluding alternative splicing or contamination of chromosomal DNA. RT-PCR of the myeloid cell line U937 was used as a positive control.

**SIgA binds to MoDC but the binding is not mediated via CD89**

The IgA binding potential of MoDC was analyzed by flow cytometry. The cell line U937 was taken along as a positive control. Incubation of U937 cells or MoDC with serum IgA revealed high binding of serum IgA to U937 cells but minimal binding to MoDC (Fig. 4A), which is compatible with higher CD89 expression on U937 cells as compared with MoDC (Fig. 2A). We next studied SIgA binding to U937 cells or MoDC. In this case, SIgA showed better binding to MoDC than to U937 cells (Fig. 4A). To determine whether the binding of SIgA to MoDC was mediated by CD89, cells were exposed to SIgA in the presence and absence of the anti-CD89 blocking mAb 2D11 and subsequently assessed for binding of IgA. The anti-CD89 blocking mAb 2D11 did not reduce the binding of SIgA to MoDC, suggesting the involvement of another receptor (Fig. 4B). Binding of serum IgA to U937 cells could nearly completely be blocked by the 2D11 mAb (Fig. 4B). No inhibition was found with an isotype-matched control Ab.

**FIGURE 2.** Expression of CD89 is strongly down-regulated during MoDC generation but still detectable when cells reach DC stage. A, Expression of CD89 was analyzed on U937 cells, MoDC days 0 and 8. B, During MoDC generation, the expression of CD89 was analyzed by flow cytometry. This result represents mean fluorescence intensity ± SD of four different donors.

**FIGURE 3.** PCR analysis of CD89 expression during development from monocyte to MoDC. Total RNA was isolated from monocytes before and during culture in GM-CSF plus IL-4 at indicated time points. Total RNA was reverse transcribed, and PCR for CD89 and β-actin were performed using specific primer sets. Shown is the ethidium bromide staining of PCR products analyzed on a 1% agarose gel.

**FIGURE 4.** SIgA binding to MoDC cannot be inhibited by functional blocking anti-CD89 Ab. MoDC (left panel) or U937 cells (right panel) were incubated with serum IgA or SIgA (A). Subsequently, cells were washed and stained with goat anti-human IgA F(ab')<sub>2</sub>-PE conjugate (bold line). Cells incubated with only the secondary reagent served as negative control (thin line). B, Before incubation with SIgA for MoDC or serum IgA for U937 cells, the cells were incubated with control mAb (thin line) or anti-CD89 blocking mAb 2D11 (bold line). Subsequently, cells were washed and stained with goat anti-human IgA F(ab')<sub>2</sub>-PE conjugate. The dotted lines indicate mean staining obtained with cells incubated with only the secondary reagent. Fluorescence was analyzed by flow cytometry.
Human DC efficiently internalize SIgA

To study the fate of SIgA bound to MoDC, we analyzed the uptake of IgA by immature MoDC. The cells were incubated with Alexa-labeled ligands at either 37° or 4°C, as described previously (32). Uptake of SIgA by MoDC after incubation for 1 h at 37°C was more efficient than using the same concentration of serum IgA (Fig. 5A). Labeling occurred only at 37°C, and not at 4°C, suggesting that the ligand is internalized by MoDC at 37°C. No labeling was found after incubation of U937 cells (Fig. 5B) or EBV-transformed B cells (data not shown) with either SIgA or serum IgA for 1 h at 37°C.

Uptake of SIgA can be inhibited by some monosaccharides and Abs against MR

Because the secretory component in SIgA is abundantly glycosylated (19), we hypothesized that a receptor with lectin-like properties may be required for binding and internalization of SIgA. To further characterize the interaction of SIgA with DC, Alexa-labeled uptake of SIgA and BSA was measured in the presence of 100 mM of monosaccharides (Fig. 6). Uptake of SIgA was blocked by mannose and fucose, and to a lesser extent by N-acetylgalactosamine. Galactose was unable to inhibit uptake of SIgA. None of the monosaccharides were able to inhibit the uptake of BSA, which is in line with the fact that DC take up BSA via fluid phase endocytosis.

The pattern of inhibition of SIgA internalization is consistent with uptake being mediated by MR, as shown previously (34). High expression of MR could be detected on immature MoDC, as has been described in previous studies (9), whereas U937 cells completely lack surface expression of MR (Fig. 7A). Internalization of SIgA by MoDC in the presence of 10 μg/ml blocking Ab against MR was only partially inhibited (Fig. 7B). Percentage of inhibition of SIgA uptake by MoDC did not change using blocking MR Abs at higher concentration (data not shown). The anti-CD89 blocking mAb 2D11 did not reduce SIgA uptake by MoDC (Fig. 7A), which is in line with the binding studies depicted in Fig. 4.

Binding and uptake of SIgA does not induce DC activation or maturation

We next investigated whether internalization of SIgA by DC would induce DC activation and maturation, as described for serum IgA (35). Cross-linking of SIgA failed to activate DC as the expression of CD86 did not change (Fig. 8A) and CD83 was not induced (data not shown). As a positive control, DC incubated with LPS plus IFN-γ showed increased CD83 and CD86 expression (Fig. 8A). In addition, we examined whether preincubation of DC with SIgA-complexes could induce DC to produce cytokines. No increased production of IL-10, IL-12p70, or IL-6 by DC could be detected after SIgA cross-linking, while LPS plus IFN-γ induced strong IL-12p70 and IL-6 and low IL-10 production by the same DC (Fig. 8B).

Discussion

The most abundant isotype of Ab in secretions is SIgA and its role in the mucosal immune system is very important. It provides an immune barrier to keep exogenous substances, like microbial pathogens, from penetrating the mucosae. To keep homeostasis, IgA should not trigger inappropriate inflammation. In the present study, we show for the first time that SIgA binds to DC, which play a crucial role in the immune system (36). In addition, we show that SIgA is efficiently taken up by DC and that this internalization is primarily mediated via MR without inducing DC maturation.
A better understanding of IgA-mediated mucosal immunity requires insights into the interaction between IgA and receptors present at mucosal surfaces. A number of different cell types have been previously shown to bind IgA, but only one receptor, specific for IgA, has been cloned. The expression of FcεRI (CD89) seems to be largely restricted to cells of the myeloid lineage (20, 26, 27). In the present study, we show low levels of CD89 expression on MoDC and the CD14⁺-expressing subpopulation of CD34⁺-derived DC but we could not detect CD89 expression on the CD1a⁺ subpopulation of CD34⁺-derived DC that resemble Langerhans cells. Our data are in line with recent in vitro studies that showed CD89 expression on a subpopulation of MoDC resembling dermal DC but absence of CD89 on monocyte-derived Langerhans cell-type DC (35). In addition, in vivo studies on frozen skin sections showed the presence of CD89 on dermal DC but no staining of CD89 on Langerhans cells (35).

To further investigate the interaction of IgA with DC, we concentrated on MoDC because they represent a more homogeneous cell population and they can be obtained more easily. Our data suggest that CD89 on MoDC is not involved in SlgA binding because this binding could not be inhibited by the functional blocking CD89 Ab 2D11. The fact that SlgA bound to MoDC suggests that another receptor for IgA exists on MoDC next to CD89. We found higher binding of SlgA to MoDC than serum IgA, which might implicate either a stronger affinity of SlgA for the receptor, higher levels of cell surface expression of the receptor, or higher specificity of the receptor for SlgA.

Interestingly, MoDC efficiently internalized SlgA and this uptake could be partially inhibited by ligands known to interact with MR. Lack of complete inhibition indicates that secondary mechanisms for uptake of SlgA may be involved, like macropinocytosis or another receptor. As MR is highly efficient in uptake and recycling, we cannot rule out the possibility that the blocking Ab itself is internalized as well. The complete lack of SlgA uptake by U937 cells might be explained by the fact that they do not express MR or that the cells miss the internalization machinery that DC do have.

Recently, several new C-type lectins, like the DC immunoreceptor Langerin, the DC-specific ICAM-3 grabbing nonintegrin, DC-associated C-type lectin-2 (Decin-2), and C-type lectin receptor 1, have been described to be specifically expressed by DC (reviewed in Ref. 37). Interestingly, the DC immunoreceptor has the capacity to bind glycosylated ligands and DC-specific ICAM-3 grabbing nonintegrin and Langerin display mannose-binding capacity. Whether these C-type lectin receptors play a role in SlgA binding and uptake by DC needs further investigation.

It has been shown that FcR such as FcγRI (CD64) and II (CD32) (12–14), FcεRI (15, 16), and FcαRI (35) are able to mediate endocytosis of immune complexes for Ag-presentation by DCs. This internalization process leads to activation that further allows migration and final maturation of the DC. No cross-linking of SlgA was needed for internalization into MoDC in our studies. In addition, we could not induce up-regulation of costimulatory molecules, like CD86 or CD83, nor in mature to secrete cytokines after SlgA cross-linking with goat anti-human IgA, suggesting that uptake of SlgA did not lead to maturation of DC.

Recent studies showed that uptake of glycosylated Ag was mediated by MR and that the glycosylated form of the Ag failed to prime Th cells (38). It could be possible that uptake of the heavily glycosylated SlgA by DC in our studies may be presented without induction of maturation of the DC. Previous studies showed that the use of immature DC results in Ag-specific inhibition of effector T cell functions or induction of IL-10-producing CD4⁺ T cells after repetitive stimulation with immature DC (39, 40). In addition, a subpopulation of DC was shown to transport apoptotic intestinal epithelial cells and migrate constitutively to T cell areas of mesenteric lymph nodes in the absence of any antigenic or inflammatory stimuli (18). These immature DC containing self-Ag were suggested to play a role in inducing and maintaining peripheral self-tolerance.

The in vivo relevance of our findings remains to be established. It is not clear how in vitro generated DC are related to in vivo populations of DC. There is evidence however, that CD14⁺ cells can differentiate into DC in vivo (41) and can even be recruited into mucosal tissues, particularly under inflammatory conditions (2, 42). In addition, expression of MR by DC populations in situ has been controversial and needs further investigation (43, 44). Although SlgA and mucosal DC seem to be present in different body compartments and occurrence of trace levels of SlgA in the circulation is not a regular finding in healthy individuals (45), transepithelial transport of SlgA via specialized Ag-handling cells called microfold cells (46) or retrograde transport via vesicles (47) suggests that SlgA could interact with DC at mucosal surfaces. Moreover, mucosal DC can open tight junctions between epithelial cells and send their dendrites outside the epithelium to sample the gut lumen (48).

In conclusion, we have shown that immature DC can very efficiently take up SlgA independent of CD89 but via a C-type lectin pathway, without the induction of DC maturation or activation. Therefore, we hypothesize that SlgA not only plays an anti-inflammatory role by adhering to microbes in the intestinal lumen, but may also modulate mucosal immune responses.