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Human IgA-Inducing Protein from Dendritic Cells Induces IgA Production by Naive IgD⁺ B Cells

Mark A. Endsley,* Leo M. Njongmeta,§ Elisabeth Shell,† Matthew W. Ryan,‡¶ Alexander J. Indrikovs,‡ Seckin Ulualp,¶ Randall M. Goldblum,‡ Wai-thaka Mwangi,§ and D. Mark Estes2*§

Over the last several years, there has been a great deal of progress in characterizing the role of dendritic cells (DCs) in the activation and modulation of B cells. DC-secreted chemokines can induce B cell trafficking to the lymph nodes. DC-produced survival factors such as B cell-activating factor of the TNF family and a proliferation-inducing ligand have been shown to be essential for B cell maturation, but have also been implicated in class-switch recombination and B cell lymphoma survival. Recently added to this list of DC-derived factors effecting B cells is IgA-inducing protein (IGIP). In this study, we characterize production of IGIP by human DCs, and examine its capacity to induce IgA class switching and differentiation of naive B cells in vitro. Monocyte-derived DCs were cultured in vitro with TLR agonists (TLR3, 4, 5, and 9) and other factors, including CD40 ligand, GM-CSF, and IL-4 as well as the neuropeptide vasoactive intestinal peptide. Under in vitro stimulation with vasoactive intestinal peptide and CD40L, IGIP mRNA expression could be up-regulated as much as 35-fold above nonstimulated samples within 12–48 h. Naive B cells cultured with exogenous recombinant human IGIP produced IgA in greater quantities than nonstimulated controls. Finally, we demonstrate that IGIP stimulation drives the production of μ-α switch circles from IgM⁺IgD⁺ naive human B cells, indicating its role as an IgA switch factor.

I

mmunoglobulin A is the primary Ig isotype present in secretions, where it acts as the first line of defense against pathogens at mucosal sites. IgA also plays an important role in maintaining gut homeostasis by ensuring that the resident microflora does not invade the intestine (1). Numerous cytokines have been linked to the production of IgA at mucosal surfaces, including TGF-β, vasoactive intestinal peptide (VIP), IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-15, IFN-γ, B cell-activating factor of the TNF family (BAFF), and a proliferation-inducing ligand (APRIL) (2–8). Among these, only TGF-β and APRIL have been shown to promote IgA class switching independent of other cytokines. In addition, other factors not directly linked to IgA class switching, such as IL-2 and IL-10, can either increase the production of IgA in committed B cells or mitigate the negative effects of switch-directing cytokines (9, 10). This is particularly important for factors such as TGF-β, which has been shown to be antiproliferative (11), as progression through the cell cycle is required for class switching (12). Although TGF-β has been definitively shown to induce class switching to IgA, the ubiquitous expression of this cytokine suggests that other factor(s) may be responsible for the compartmental nature of IgA-secreting cells in the mucosa.

Dendritic cells (DCs) are potent regulators of the adaptive immune response, including the regulation of Ig, and particularly IgA, expression (13, 14). Interstitial DCs and monocyte-derived DCs (mDC) have the ability to regulate B cell differentiation through the expression of IL-10 and IL-12 following CD40 ligation (15–18) and have been linked to the regulation of Ab production both in the presence and absence of T cells. Recent studies have also shown that human DCs up-regulate BAFF and APRIL expression upon exposure to a variety of stimuli including IFN-α, IFN-γ, CD40L, or TLR-induced reactive oxygen species (19–23).

The role of neuropeptides such as VIP and pituitary adenylate cyclase-activating polypeptide (PACAP) in immune regulation may hold the key to our understanding of some aspects of host responses to infection. VIP has previously been shown to possess a number of potent immunomodulatory properties, including the capacity to inhibit cytokine and chemokine expression by macrophages (Mψ) and T cells and to induce a Th2 phenotype in the immune response (24–26). Recent studies have shown that VIP and PACAP also have a variety of effects on DCs dependent on their maturation states. Exposing immature DCs to VIP or PACAP has been shown to generate a Th2 response, while stimulation with either neuropeptide strongly inhibits the ability of LPS-induced DCs to prime naïve T cells (27). Furthermore, DCs differentiated from peripheral blood monocytes in the presence of VIP were shown to be tolerogenic, inducing a regulatory phenotype in both

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CD4+ and CD8+ T cells (28). Additionally, there is a well-established link between VIP and IgA production (29–31), and VIP has been considered a switch factor for IgA (32). Subsequent work, however, suggests that VIP modulation of B cells may be an indirect effect (33). In this study, we demonstrate that DC-derived IgA-inducing protein (IGIP) may be a vital link between VIP expression/signalizing and mucosal IgA production.

Vitamin metabolites such as retinoic acid (RA), a vitamin A metabolite, have also been shown to play a role in mucosal IgA secretion. RA has been shown to induce the expression of mucosal homing chemokine receptors such as CCR9, as well as the mucosa-specific αiβ7 integrin (34). Although RA was not sufficient to induce IgA expression in naive B cells in these experiments, it did synergize with as yet unidentified DC-derived factors to enhance IgA production.

Recent work in our laboratory has added another member to the list of IgA regulatory factors. Austin et al. (35) described a novel protein, IGIP, isolated from a bovine Peyer’s patch and mesenteric lymph node combined cDNA library with cells activated under various conditions (35). Bovine IGIP, like BAFF and APRIL, was found to be produced primarily by DCs in response to CD40L stimulation. Furthermore, we found that recombiant bovine IGIP enhances IgA expression in IgM+ peripheral blood B cells in an in vitro culture system. In this study, we demonstrate the effects of this peptide on human B lymphocytes and characterize the conditions under which IGIP is expressed and the conditions required for IGIP function.

**Materials and Methods**

**Reagents**

The following reagents were used for mDC or B cell stimulation experiments and are listed with their working concentrations and suppliers. Tripalmitoylated lipopeptide 3CySerLy54 (Pam3CSK4) (TLR2 ligand, 1 μg/ml; Alexa Biochemicals), poly(I:C) (TLR3 ligand, 10 μg/ml; Sigma-Aldrich), LPS (TLR4 ligand, 100 ng/ml; Sigma-Aldrich), flagellin (TLR5 ligand, 1 μg/ml; Alexa Biochemicals), CpG oligodeoxynucleotide 2006 (TLR9 ligand, 10 μg/ml; IDT DNA), or CD40L (30 ng/ml; Alexa Biochemicals), VIP (1 μM; CalBiochem), recombiant human (rh) TGF-β (10 ng/ml; R&D Systems), transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI)-Fc (soluble BAFF- and APRIL-neutralizing receptor, 20 ng/ml; R&D Systems), rhIL-10 (25 ng/ml; R&D Systems), anti-TGF-β mAb (30 μg/ml; R&D Systems), PMA (10 ng/ml; Sigma-Aldrich), and ionycin (1 μg/ml; Sigma-Aldrich). Treatment with PMA and ionycin is abbreviated PMAI.

**Isolation of naive human B cells from peripheral blood**

Total PBMCs were isolated from 100 ml of whole blood from normal healthy donors via AccuPrep (Accurate Chemical and Scientific) gradient centrifugation. Total PBMCs were isolated from 100 ml of whole blood from normal healthy donors via AccuPrep (Accurate Chemical and Scientific) gradient centrifugation. Isolated populations were shown to be >98% pure by FACS analysis (data not shown).

**Isolation of PBMC subsets**

PBMCs were isolated by density gradient centrifugation. Populations of T cells, B cells, monocytes, and NK cells were isolated with anti-human CD3, CD19, CD14, and CD56 Microbeads, respectively, by double-column sorting with an AutoMACS magnetic cell sorter (Miltenyi Biotec). All reactions were conducted in sorting buffer (PBS (pH 7.4), 0.5% BSA, 2 mM EDTA) at 4°C. Surface IgD+ B cells were then purified with an automated magnetic cell sorter (AutoMACS; Miltenyi Biotec). The purity of sorted surface IgD+ cells, tested by flow cytometry and the absence of RT-PCR for IgM and IgA transcripts as previously described, exceeded 95% in all experiments (data not shown).

**Preparation of mDCs**

PBMCs were labeled with anti-CD14 Microbeads (Miltenyi Biotec) and monocytes were separated by AutoMACS (Miltenyi Biotec). CD14+ monocytes were cultured with 10 ng/ml rhIL-4 (R&D Systems) and 1400 U/ml rhGM-CSF (Leukine; Immunix) for 6 days as previously described (37, 38). Nonadherent cells were removed and cultured for an additional 14 h in complete RPMI 1640 (cRPMI), with or without 300 ng/ml soluble rhCD40L. Purity of isolated mDC populations was verified by flow cytometry with Abs to DC-SIGN (R&D Systems) and HLA-DR (Southern Biotechnology Associates).

**Amplification of human IGIP**

Pure mDC cultures were stimulated with 500 ng/ml rhCD40L (Axxora), 20 ng/ml LPS, or 10 ng/ml PMA and 1 μg/ml ionycin for 14 h. Total RNA was extracted with an RNeasy RNA extraction kit (Qiagen) and DNase treated with a DNA Free DNase kit (Ambion) as per the manufacturer’s instructions. Human IGIP transcripts were amplified with a Titan One Tube RT-PCR kit (Roche) according to the manufacturer’s instructions with forward primer 5′-AAATATCAATTTGTCATG-3′ and reverse primer 5′-TTTGGCTACTTATTTACCA-3′. Temperature cycling conditions were as follows: 50°C for 50 min; 95°C for 5 min; 35 cycles of 95°C for 30 s, 50°C for 1 min; 72°C for 2 min; 72°C for 7 min; and 4°C hold. Fragments were visualized in a 1% w/v agarose gel containing 0.5 μg/ml ethidium bromide.

**RT-PCR assays**

RT-PCR for human IGIP, BAFF, APRIL and IL-10 was performed at the University of Texas Medical Branch Real-Time PCR Core Facility with primer and probe sets from BD Biosciences as follows: human IGIP: Fwd, 5′-CCCCATCTCGTCTGGAGAAA-3′, Rev, 5′-CTGATGCACAACGGTTTGCT-3′, and probe, 5′-CACCATCTGGGAAAC-3′; BAFF: Fwd, 5′-ACCGCGGGACTGAAAATCT-3′, Rev, 5′-GTTCTGACTGGATTTGTGGTCTTT-3′, and probe, 5′-TGAACCCAACAACCTGCC-3′; APRIL: Fwd, 5′-CATCTGTCGTCACCTGGTTTT-3′, Rev, 5′-TCTCCATGATCGGTCACTCC-3′, and probe, 5′-CATTACCGCACCCTCC-3′; and IL-10: Fwd, 5′-CCCCAAGTGTGAGAACAG-3′, Rev, 5′-TCCCCAGGGAGTTCAACA-3′, and probe, 5′-CAGACATCAAGGGC-3′.

**Densitometry**

Densitometry measurements were made with AlphaEaseFC Software (Alphalnnotech). Integrated density values (IDVs) were determined for each band in the gel, with the software correcting for background. Relative expression (RE) was calculated for each band by dividing the IDV of IGIP by the IDV of G3PDH (housekeeping gene) in the same sample and PCR (RE_IGIP = IDV_IGIP/IDV_G3PDH).

**Expression of rhIGIP**

Human IGIP proved to be difficult to express in vitro due to issues with RNA stability. To stabilize the mRNA, it was necessary to link it to another protein mRNA and express the pair as a chimera joined by an inert linker. CD40L was chosen as the stabilizing protein, as it is required for IGIP-induced class switch recombination (CSR) and would already be present in all cultures. Human IGIP cDNA was ligated into the multiple cloning site of the pCND5A expression vector (Invitrogen) containing an N′-terminal FLAG tag. Human CD40L was then ligated into the multiple cloning site at the 3′ end of human IGIP, with a short inert linker in between. Sequence was verified and the plasmid was transfected into HEK 293F cells with the Lipofectamine transfection reagent (Invitrogen) according to the manufacturer’s instructions. Cells were cultured for 3 days in DMEM supplemented with 10% FBS and supernatants were collected. Recombinant IGIP was purified with an affinity column specific for the FLAG peptide DYKDDDDK, constructed with anti-FLAG M2-agarose beads (Sigma-Aldrich) and dialyzed in sterile double-distilled water overnight. Concentration was determined with the bicinchoninic acid protein assay (Pierce) according to the manufacturer’s protocol. It should be noted here that the CD40L portion of the IGIP-CD40L chimeric protein lacked any activity, as it was found to be unable to induce IgA CSR in the absence of additional rhCD40L.

**ELISA**

Sandwich capture ELISA was performed as previously described (39). Briefly, Immulon II 96-well round-bottom plates (Dynatech) were coated overnight at 4°C with 1 μg/well polyclonal goat anti-human IgM(μ), IgG(γ) or IgA(α) (Southern Biotechnology Associates). Plates were then washed three times with PBS (pH 7.4) containing 0.1% Tween 20 (PBST) and blocked with Superblock (Pierce) for 2 h at 37°C and washed three times with PBST. Fifty microliters of B cell culture supernatants, diluted 1/1 in PBST, were added to each well and incubated for 1 h at 37°C and washed three times. Purified human IgM, IgG, or secretory IgA (SIA; Sigma-Aldrich) from 1.0 μg/ml to 16 ng/ml and assayed in parallel with the culture supernatants. Plates were then incubated with HRP-conjugated...
polyclonal goat anti-human IgM(μ), IgG(γ) or IgA(α) (Southern Biotechnology Associates) at room temperature for 30 min and wash three times. ABTS substrate (100 μl; Molecular Devices) after a 15-min incubation. Supernatant IgM, IgG, and IgA concentrations were calculated based on the standard curve and analysis by linear regression with purified human protein for each respective isotype (Sigma-Aldrich). Correlation coefficients were >95% for each evaluation. Results are presented as the mean and SEM for triplicate treatments and are representative of three experiments with similar results.

**Switch circle PCR**

PCR for the joining region of the μ-α switch circle was performed as previously described (40). Briefly, phenol/chloroform extracted DNA was amplified with the following primers designed to span the intron joint of the switch circle: 5′-TCAGGCTTCTCCTTGCCGAC-3′ and 5′-TGGTTCCTACATCTTGAGTCCCG-3′. A two-step PCR profile was used with the following temperature conditions: 94°C for 10 min, 68°C for 10 min, then 30 cycles of 94°C for 1 min, 68°C for 2 min, and 72°C for 3 min. Products of this reaction were used as the template for a second reaction with the following primers, which are internal to those used in the previous reaction: 5′-TGAGTGGCCTCTACTCTTGAGTCCCG-3′. Two-step PCR profile was used with the following temperature conditions: 94°C for 10 min, 68°C for 10 min, then 30 cycles of 94°C for 1 min, 68°C for 2 min, and 72°C for 3 min. Products of this reaction were used for the presence of IGIP transcripts by RT-PCR.

**Results**

The major source of IGIP in humans is the DC

To define the cellular sources of human IGIP transcripts, different cell populations were isolated from normal blood donors and stimulated with mitogens, calcium ionophore, or other key agonists, and RNA was collected at optimal time points. mDCs were differentiated from peripheral blood monocytes as previously described (37, 38). T cells (CD3+), B cells (CD19+), and NK cells (CD56+) were stimulated for 24 h with PMA/I. Monocytes (CD14+) were stimulated for 24 h with LPS. mDCs were stimulated for 24 h with VIP (Calbiochem). RNA was collected with an RNeasy RNA extraction kit and IGIP transcripts were quantified by RT-PCR. mDCs were shown to be the primary producers of IGIP, with relatively low levels of transcription detected in purified B cells (Fig. 1a). IGIP production by population and activation condition is summarized in Table I. To establish the kinetics of IGIP expression, mDCs were stimulated with VIP (1 μM) and rhCD40L (30 ng/ml) and harvested at 12, 18, 24, 48, and 72 h. IGIP expression was first detected 12 h after stimulation, peaking at 24 h, and was no longer detectable by 72 h (Fig. 1b).

**IGIP transcription is induced by VIP**

mDCs were stimulated with Pam3CSK4, poly(I:C), LPS, CpG DNA, CD40L, secretory IgA (SIgA), and VIP. Interestingly, TLR stimulation depressed IGIP expression below constitutive levels (Fig. 2a), as did stimulation with CD40L, SIgA, and PMA/I (Fig. 2b). Only VIP stimulation induced IGIP expression above basal levels. IGIP expression in response to VIP stimulation was found to increase in a dose-dependent manner up to 20 μM, the highest concentration tested (Fig. 3). Interestingly, mDC expression of BAFF and IL-10 were shown to respond to VIP stimulation in a dose-dependent manner, with optimal expression achieved at 5 μM. Induction of IGIP transcripts by VIP stimulation was detected by 18 h, peaked at 24 h, decreased substantially by 48 h, and was undetectable by 72 h, while very high concentrations (20 μM) reduced expression below constitutive levels.

**CD40L acts synergistically with VIP to induce IGIP expression**

To investigate the role of mDC activation/maturation in VIP-induced IGIP expression, mDCs were treated with various TLR ligands, or CD40L trimer to cross-link CD40, in addition to VIP. mDCs were cultured for 24 h with Pam3CSK4, poly(I:C), LPS, CD40L, secretory IgA (SIgA), and VIP. Interestingly, TLR stimulation depressed IGIP expression below constitutive levels (Fig. 2a), as did stimulation with CD40L, SIgA, and PMA/I (Fig. 2b). Only VIP stimulation induced IGIP expression above basal levels. IGIP expression in response to VIP stimulation was found to increase in a dose-dependent manner up to 20 μM, the highest concentration tested (Fig. 3). Interestingly, mDC expression of BAFF and IL-10 were shown to respond to VIP stimulation in a dose-dependent manner, with optimal expression achieved at 5 μM. Induction of IGIP transcripts by VIP stimulation was detected by 18 h, peaked at 24 h, decreased substantially by 48 h, and was undetectable by 72 h, while very high concentrations (20 μM) reduced expression below constitutive levels.

**rhIGIP induces expression of IgA in the presence of IL-10**

To determine the effects of IGIP on IgA expression, naïve B cells were cultured with rhIGIP and compared with cells cultured with TGF-β. Additionally, since IL-10 has a well-established role as an accessory factor in IgA expression but not CSR (40, 41), IL-10 was added to some cultures to assess any possible effect on IGIP-dependent IgA expression. Briefly, IgA+ B cells were isolated from peripheral blood and cultured at 10^6/well in a 96-well plate in cRPMI with CD40L, IL-2, and TACI-Fc. Additionally, cells were stimulated with rhIGIP (1 μg/ml), rhTGF-β, rhIL-10, rhIGIP plus IL-10, or rhTGF-β plus IL-10. An anti-TGF-β mAb was added to cultures not receiving exogenous TGF-β to eliminate any IgA CSR it may have initiated. Supernatants were collected at day 14 and
IgA concentration was measured by sandwich capture ELISA. In the presence of IL-10, rhIGIP plus CD40L stimulation yielded an IgA concentration of 307 ng/ml, as opposed to 3.35 ng/ml for CD40L alone (Fig. 5). In this regard, IGIP was found to have a similar capacity to induce IgA expression as TGF-β/H9252 plus IL-10, which yielded 260 ng/ml in the same experiment. In the absence of IL-10, IGIP stimulation yielded an IgA concentration that was consistently, but not significantly (p<0.052), greater than control wells stimulated with CD40L alone. Culture supernatants were also assayed for IgM and IgG. IGIP was found to have no effect on either IgM or IgG expression under these stimulation conditions (data not shown).

IGIP is an IgA switch factor and not an accessory factor

To determine whether IGIP is a switch factor or an accessory factor that aids in IgA expression, we assayed whole genomic DNA of rhIGIP-stimulated B cells for the presence of switch circles, the circular fragments of IgH genomic DNA that are excised during CSR. IgD/H11001 B cells were isolated from peripheral blood and cultured at 10^6/well in a 24-well plate in cRPMI with rhCD40L, anti-TGF-β-neutralizing mAb, and TACI-Fc, with or without rhIGIP (1 

CD40L alone (Fig. 5). In this regard, IGIP was found to have a similar capacity to induce IgA expression as TGF-β plus IL-10, which yielded 260 ng/ml in the same experiment. In the absence of IL-10, IGIP stimulation yielded an IgA concentration that was consistently, but not significantly (p = 0.052), greater than control wells stimulated with CD40L alone. Culture supernatants were also assayed for IgM and IgG. IGIP was found to have no effect on either IgM or IgG expression under these stimulation conditions (data not shown).

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FIGURE 6.  IGIP is an IgA switch factor. IgD+ B cells were cultured for 5 days with rhCD40L (30 ng/ml), anti-TGF-β-neutralizing mAb (30 μg/ml), and TACI-Fc (20 ng/ml) in the presence or absence of rhIGIP (1 μg/ml). Positive control cells were incubated for 5 days with rhCD40L (30 ng/ml) and rhTGF-β (1 ng/ml). DNA was collected at day 5 and assayed for switch circles by nested PCR. The PCR product of 1182 bp indicates the presence of μ-α switch circles (confirmed by sequencing) and IgA CSR. Data presented are one representative experiment of three with similar results. Lane 1, 100-bp ladder; lane 2, IGIP plus CD40L; lane 3, TGF-β plus CD40L; lane 4, CD40L alone; and lane 5, no template control.

Discussion

Despite the localized IgA production at mucosal sites, the total amount of this isotype produced by the body on a daily basis and its role in defense against mucosal infection, the regulation of IgA expression and secretion in humans and other species is not fully understood. To date, only TGF-β and APRIL have been definitively shown to induce CSR at the molecular level independent of other factors. Other DC-derived cytokines, such as BAFF, have been implicated in IgA CSR, providing the necessary NF-κB signaling in T-independent Ag-induced CSR (21). Although it was not tested, the effects of PACAP are likely to be similar to VIP with regard to IGIP and BAFF expression. It has previously been shown that mouse mDCs express VPAC1 and VPAC2, two receptors shared by VIP and PACAP, and that stimulation with these two neuropeptides results in mDCs with the same phenotype (27).

As previously stated, there is a well-established, but indirect, link between VIP and IgA production (29–33). In this study, we present strong evidence that IGIP may be the missing link in this mucosal IgA regulation scheme. Among the other stimuli tested for their ability to induce IGIP expression was SlgA (Sigma-Aldrich), the rationale being that signaling through CD89 (FcγR) may up-regulate the expression of IgA regulatory proteins in response to the presence of SlgA. Interestingly, although the addition of SlgA did not significantly effect the expression of IGIP, it did up-regulate BAFF expression by ~2-fold (Fig. 2).

In addition to characterizing IGIP expression, we have also examined the effects of IGIP stimulation on B cells and IgA expression. Under the influence of exogenous IGIP stimulation, CD40L-activated IgD+ B cells were shown to increase IgA production above CD40L-activated controls without IGIP (Fig. 5). The addition of IL-10 was shown to greatly enhance IGIP-dependent production of IgA, as has been shown for other cytokines involved in IgA expression (40, 41). IGIP was also shown to be a bona fide IgA switch factor. In the presence of IGIP and CD40L alone, IgD+ B cells were shown to undergo μ-α CSR by the presence of IgA switch circles (confirmed by sequencing) and IgA CSR (21).

In summary, our data support a role for VIP to regulate expression of IgA via IGIP production from DCs. This clarifies the role of VIP in regulation of IgA responses. This pathway is unique in that IGIP expression does not appear to be regulated via recognition of pathogen-associated molecular pattern receptors on the DCs. Our observations in these studies may provide a link between VIPergic fibers and innervation of GALT with homeostatic production of IgA (independent of TLR stimulation) and potentially with natural baseline mucosal IgA production.

Disclosures

The authors have no financial conflict of interest.

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