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Blocking Fcα Receptor I on Granulocytes Prevents Tissue Damage Induced by IgA Autoantibodies

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IgA represents the most prominent Ab class at mucosal surfaces and the second most prevalent Ab in human blood after IgG. We recently demonstrated that cross-linking of the granulocyte IgA FcR (FcαRI) by IgA induces a chemotactic-driven positive-feedback migration loop, hereby amplifying recruitment of granulocytes to IgA deposits. Therefore, we postulated that aberrant IgA–Ag complexes, which can be found in tissues in IgA-mediated diseases, are responsible for tissue damage by inducing continuous granulocyte migration and activation. Using an IgA-dependent skin-blistering disease as a model system, we demonstrated colocalization of FcαRI-positive granulocyte infiltrates with IgA in cryosections of lesional skin of patients suffering from this disease. Furthermore, we showed granulocyte migration to IgA deposits injected in human skin explants and in murine skin of FcαRI transgenic mice in vivo. Importantly, ex vivo migration and tissue damage were inhibited by blocking FcαRI, indicating that these events are dependent on the interaction of IgA autoantibodies with FcαRI. Thus, interrupting the granulocyte migration loop by blocking FcαRI reduces tissue damage in diseases with aberrant IgA–immune complexes. As such, our results may lead to development of new therapies for IgA-mediated chronic inflammatory diseases, hereby decreasing severe morbidity and improving quality of life for these patients.

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Abbreviations used in this article: BP, bullous pemphigoid; DES, dermal-epidermal separation; dIgA, dimeric IgA; ECP, eosinophil cationic protein; LABD, linear IgA bullous disease; mIgA, monomeric IgA; NHS, normal human serum; ROS, reactive oxygen species; RT, room temperature; SLgA, secretory IgA.
in great detail. In the current study, we used IgA-dependent skin-blistering diseases as a model system to investigate the role of IgA autoantibodies in recruitment of granulocytes and the involvement of FcαRI in inducing tissue destruction in diseases with aberrant IgA complexes.

**Materials and Methods**

**Isolation of human neutrophils and eosinophils**

Standard Lymphoprep (Axis-shield, Dundee, Scotland) density gradient centrifugation (800 × g, 25 min) was used to isolate granulocytes from heparinized peripheral blood samples, which were obtained from healthy donors. Erythrocytes were removed by hypotonic lysis (155 mM NHCl, 10 mM KHCO₃, 0.1 mM EDTA) for 10 min. Granulocytes were resuspended in RPMI 1640 (Life Technologies, Paisley, U.K.) supplemented with 10% heat-inactivated FCS, 1-glutamine, penicillin, and streptomycin. For the cryosection assay, human granulocytes were isolated from the peripheral blood of healthy donors. After 3% dextran sedimentation, remaining erythrocytes were lysed using a hypotonic solution of 0.2% NaCl. Human granulocytes were washed and resuspended in DMEM medium without supplements. Eosinophils were isolated from granulocyte suspension according to the manufacturer’s instructions using a MACS-Eosinophil Isolation Kit (Miltenyi Biotec, Bergisch Gladbach, Germany). Purity of isolated neutrophils (>95%) or eosinophils (>95%) was confirmed by cytopsin preparation. Studies were approved by the Medical Ethical Committee of VU University Medical Center and by the Ethics Committee of the Medical Faculty of the University of Freiburg, in accordance with the Declaration of Helsinki. All donors gave informed consent.

**Preparation of Ig-coated beads**

N-hydroxysuccinimide–activated Sepharose beads (GE Healthcare, Uppsala, Sweden) were coated under sterile conditions with either IgA or BSA, according to the manufacturer’s instructions. Briefly, beads were washed in 1 mM HCl and resuspended in 1 ml 0.2 M NaHCO₃/0.5 M NaCl (pH 8.3) containing 300 μg/ml serum IgA (Sigma-Aldrich, St. Louis, MO) or BSA and incubated overnight (4°C, head over head). Beads were washed with 0.5 M ethanolamine/0.5 M NaCl (pH 8.3) and 0.1 M sodium acetate/0.5 M NaCl (pH 4).

**Granulocyte migration and activation assays**

**Two-dimensional migration assay.** The potentiality of eosinophils to migrate toward IgA-coated beads was assessed with a previously described assay (14). Briefly, isolated human eosinophils were labeled with PKH-26 (green fluorescence), according to the manufacturer’s instructions (Sigma-Aldrich). A total of 2.5 × 10⁶ eosinophils/well was seeded in 96-well flat-bottom plates (Greiner Bio-One North America, Monroe, NC), after which IgA-coated beads or BSA-coated beads as control were added. Eosinophils were incubated for 20 min at 37°C, after which supernatants were removed and beads were washed twice with PBS to remove unbound eosinophils. Beads were incubated with a buffer containing 2 g/ml hexadecyltrimethyl ammonium bromide, 1.0 g/ml TWEEN 20, 2.0 g/ml BSA, and 7.44 g/ml EDTA in PBS to lyse bound eosinophils. Fluorescence was measured using 485 nm excitation and 520 nm emission filters (Fluostar Galaxy, BMG Labtechnologies, Offenbach, Germany).

**Three-dimensional migration assay.** Collagen (isolated from rat tail tendons and dissolved in 0.1% acetic acid) was mixed with NaOH and DMEM (Sigma-Aldrich) as described (20). IgA- or BSA-coated beads (green beads 100 μg/ml) were added, and 1 ml of this mixture was plated in a 24-well plate and allowed to coagulate, after which 2 × 10⁶ granulocytes were added. After 4-h incubation (37°C), collagen gels were fixed and embedded in paraffin. Sections were stained with Mayer’s H&E stain (Klinpath, Mu¨ nster, Germany).

**Human skin migration assay.** Full-thickness mammary skin grafts (epidermis and dermis) were placed in an ex vivo tissue incubation chamber (method adapted from Oosterling (21)), with the dermis face up. IgA- or BSA-coated beads were injected intracutaneously via the dermis, followed by addition of PKH-67–labeled granulocytes (4 × 10⁶ cells/well) on the dermis in the absence or presence of 10 μg/ml MIP-8α. To allow detection of the injection spot, India ink was added to the beads. In alternative experiments, serum of patients with LABD was injected in the skin instead of beads. After 30 min, these granulocytes after isolation, cells were supplemented with IFN-γ to prevent early apoptosis (300 U/ml; Boehringer Ingelheim, Ingelheim am Rhein, Germany). Skin was incubated overnight at 37°C, after which biopsies of the injected skin were taken and snap frozen. Cryosections were analyzed with a Leica DM6000 microscope (Leica Microsystems, Rijswijk, The Netherlands).

**Autoantibody-induced granulocyte-dependent dermal-epidermal separation assay.** The potentiality of IgA autoantibodies to activate granulocytes and induce dermal-epidermal separation (DES) was assessed, with a previously described assay (22, 23). Briefly, 5 × 10⁶ granulocytes from healthy donors were added to cryosections of normal human skin, which had been incubated with serum of patients with LABD, BP (an IgG- and complement-mediated autoimmune bullous disease, used as control), or healthy donors. Incubation with granulocytes was performed in the absence or presence of 10 μg/ml MIP-8α, 100 μM apocynin (Sigma-Aldrich), or 100 μM N-(methyleneamino)-Ala-Ala-Pro-Val-chloromethyl ketone (Sigma-Aldrich). Cryosections were then incubated for 2 h at 37°C, followed by a 20-min wash in PBS and a standard H&E staining (Klinpath).

**ELISA**

The concentration of eosinophil cationic protein (ECP) in the supernatants of neutrophil/eosinophil migration assays was analyzed by ELISA (Uscn, Wuhan, China), according to the manufacturer’s instructions.

**Animal experiments**

Mice were bred and maintained at the Central Animal Facility of VU University under standard conditions. IgA- or BSA-coated beads were injected intracutaneously in nontransgenic or FcαRI transgenic mice (24) under isoflurane anesthesia. To allow detection of the injection spot, India ink was added to the beads. After 48 h, mice were sacrificed, and biopsies of injected skin were taken and snap frozen. All experiments were performed according to institutional and national guidelines. The animal ethical committee of VU University Medical Center approved all experiments.

**Immunofluorescence and immunohistochemistry**

Human normal or LABD skin cryosections (6 μm) were fixed in anhydrous acetone and air dried, and nonspecific binding was blocked by incubation (15 min, room temperature [RT]) with 10% normal rabbit serum diluted in 0.5% BSA in PBS. Skin sections were stained as indicated in figures with FITC- or PE-conjugated anti-human CD68, IgA, and FcαRI mAbs (BD Biosciences, Franklin Lakes, NJ) (1 h, RT). Detection of serum autoantibodies was performed, as described by Sitaru et al. (25). Briefly, cryosections of normal human skin were incubated with serum of patients with LABD, BP, or healthy donors (1 h, RT), after which they were washed and subsequently incubated with FITC-anti-human IgA (Dako Nederland, Heverlee, Belgium), anti-IgG, or an irrelevant isotype control (BD Biosciences). Granulocyte presence in mouse skin cryosections was determined by staining sections with rat-anti-mouse GR-1 mAb (BD Biosciences) and HRP-labeled goat anti-rat Abs. The 3-amo-9-ethylcarbazole (Zymed, San Francisco, CA) was used as a peroxidase substrate. Cryosections were analyzed with a Leica DM6000 microscope (Leica Microsystems).

**Statistical analysis**

Data are shown as mean ± SD. Statistical differences were determined using two-tailed unpaired Student test (comparing two groups) or ANOVA (2 or more groups). Significance was accepted when p < 0.05.

**Results**

**Colocalization of IgA deposits and FcαRI-expressing granulocytes in skin of LABD patients**

Cryosections of skin lesions of LABD patients, or of normal healthy skin as control, were analyzed by immunofluorescence microscopy to evaluate colocalization of IgA deposits and FcαRI-expressing cells. Neither IgA deposits nor FcαRI expression was...
observed in normal skin (Fig. 1A, upper panels). In contrast, in cryosections of LABD patients, IgA (shown in green) was deposited along the basement membrane in a linear pattern, as also described in Sitariu and Zillikens (19) (Fig. 1A, lower panels). Interestingly, an infiltrate of FcαRI-expressing cells (shown in red) was observed in the dermis adjacent to the basement membrane of the skin (Fig. 1A, lower panels). Importantly, the overlay panel shows colocalization of IgA and FcαRI (Fig. 1A inset; yellow staining). Furthermore, double staining for the granulocyte marker CD66b (green) and FcαRI (red) (Fig. 1B, colocalization; yellow staining), or IgA (green) and CD66b (red) (Fig. 1C), demonstrated that FcαRI-positive cells consisted of granulocytes, which were situated adjacent to IgA deposits. Thus, FcαRI-expressing granulocytes were located in contact with IgA–immune complexes at the epidermal basement membrane of lesional skin of LABD patients.

**IgA induces both neutrophil and eosinophil migration**

Granulocyte infiltrates of lesional skin of LABD patients consisted mostly of neutrophils and to a lesser extent eosinophils (Fig. 2A, eosinophils; arrowheads), as earlier described (26, 27). When collagen gels containing IgA-coated beads or BSA-coated beads as control were incubated with granulocytes and stained with H&E to distinguish neutrophils from eosinophils, neither neutrophils nor eosinophils migrated toward BSA-coated beads. However, granulocytes that were recruited toward IgA-coated beads consisted of both neutrophils and eosinophils (Fig. 2B). We previously demonstrated rapid neutrophil migration to IgA-coated beads with a two-dimensional migration assay (14). Because eosinophils also express a functional FcαRI (28, 29), we now investigated whether eosinophils were equally capable of migrating to IgA-coated beads. Therefore, we first performed a two-dimensional migration assay in which IgA or control (BSA) beads were added to a monolayer of fluorescently labeled eosinophils. The amount of bound cells was quantified by measuring fluorescence after the cells had been lysed, which confirmed that only a few eosinophils had bound to control beads, whereas a large number of eosinophils had migrated toward and adhered to IgA-coated beads (Fig. 2C). Next, cell-tracking experiments were performed with a granulocyte suspension to compare neutrophil versus eosinophil migration in response to IgA-coated beads (Fig. 2D, Supplemental Video 1). Neutrophils (green fluorescent cells) responded within 2 min after addition of IgA-coated beads (Fig. 2D, upper panels; arrows), whereas eosinophils (red fluorescent cells) were still inactive at this time point. After 4 min, eosinophils became active (Fig. 2D, lower panels; arrows). Both neutrophils and eosinophils specifically traveled in the direction of IgA-coated beads, indicating induction of chemotaxis instead of random chemokinesis (Fig. 2E, 2F). Traveled distances were similar between neutrophils and eosinophils (Fig. 2G, left panel). However, neutrophils migrated with higher speed, compared with eosinophils (Fig. 2G, right panel). To assess whether eosinophils may contribute to the pathogenesis of IgA-mediated tissue damage, we analyzed the concentration of ECP as a marker of eosinophil degranulation. The concentration of ECP was significantly higher in supernatants of the granulocyte suspension in response to IgA-coated beads compared with BSA-coated beads (Fig. 2H), which support that eosinophils had degranulated.

**FcαRI mediates IgA-induced granulocyte migration in ex vivo human skin and in vivo**

To mimic granulocyte migration toward aberrant IgA–Ag complexes in skin, we next established an ex vivo migration assay. Full-thickness human skin grafts were injected with BSA- or IgA-coated beads and incubated for 24 h with fluorescently labeled granulocytes. Bright field analyses of skin sections showed localization of the injected BSA- or IgA-coated beads (Fig. 3A, left panels). Random migration of a small number of granulocytes (green fluorescence) at the top of the dermis was observed in skin sections in which BSA-coated beads had been injected. In contrast, massive granulocyte infiltration was observed toward IgA-coated beads. Overlay images showed no binding of granulocytes to BSA-coated beads, but extensive binding of cells to IgA-coated beads (Fig. 3A, middle and right panels). When an anti-FcαRI mAb was added to the culture that blocks the binding site for IgA on FcαRI (MIP8a), migration of granulocytes was strongly reduced (Fig. 3B, lower panels). Thus, the presence of IgA beads induced granulocyte migration, which was dependent on FcαRI. To confirm that IgA autoantibodies of LABD patients induce granulocyte migration, ex vivo skin experiments were repeated after injection of serum of LABD patients into skin samples. Similarly, without blocking FcαRI, granulocytes migrated toward injected serum of LABD patients (Fig. 3C, left panel). Blocking FcαRI with MIP8a, however, inhibited migration of granulocytes almost completely (Fig. 3C, right panel).

In vivo studies investigating the role of IgA have been restricted because mice do not express an FcαRI homolog (2, 13). To overcome this limitation, human FcαRI transgenic mice were generated, in which FcαRI expression, regulation, interaction with human IgA, and function mimic the human situation (24). Human IgA-coated
beads (or BSA-coated beads as control) were injected in the skin of human FcαRI transgenic mice or nontransgenic littermates to study the in vivo role of FcαRI in IgA-induced granulocyte migration in skin. Mice were sacrificed after 48 h. Only minimal influx of granulocytes was observed in skin of nontransgenic mice injected with either BSA- or IgA-coated beads (Fig. 3DI, 3DIII), or in the skin of FcαRI transgenic mice injected with BSA-coated beads (Fig. 3DII). In contrast, massive granulocyte infiltration was observed in skin of human FcαRI transgenic mice that had been injected with IgA-coated beads (Fig. 3DIV). Thus, only aberrant IgA deposits in the skin of human FcαRI transgenic mice induced massive granulocyte migration and infiltration.

Blocking FcαRI prevents IgA-induced tissue damage

To analyze whether blocking FcαRI would prevent tissue damage, normal human skin was incubated with serum from healthy donors, patients with LABD, or patients with BP as control. The latter is an autoimmune blistering disorder of the skin similar to LABD, but mediated by IgG autoantibodies against collagen XVII (30). First, we analyzed the presence of autoreactive Abs to the epidermal basement membrane in human sera with immunofluorescence microscopy. No specific staining was detected in skin cryosections incubated with normal human serum (NHS) of healthy donors (Fig. 4A, left panel). In contrast, IgG or IgA autoantibodies from patients with BP or LABD, respectively, stained the basement

FIGURE 2. IgA induces both neutrophil and eosinophil migration. (A) Paraffin sections of lesional skin of LABD patients were stained with H&E to distinguish neutrophils from eosinophils. Inset, Higher magnification of neutrophils and eosinophils. Arrows, Eosinophils. Original magnification ×10. (B) Paraffin sections of collagen gels, in which IgA-coated beads (*) had been embedded and had been incubated with granulocytes, were stained with H&E. Inset, Higher magnification of neutrophils and eosinophils. Arrows, Eosinophils. Original magnification ×40. (C) Control (BSA) or IgA-coated beads (IgA) were added to monolayers of resting fluorescently labeled eosinophils for 20 min. Cells were lysed, after which fluorescence was determined as measure of the number of cells that had adhered to the beads. (D) Cell-tracking experiments were performed with a mixture of PKH-67-labeled neutrophils (upper panels, green) and PKH-26-labeled eosinophils (lower panels, red). White spheres indicate location of IgA-coated beads. Arrows, Activated neutrophils (green) or eosinophils (red). (E) Migratory direction of neutrophils is indicated by green arrows, eosinophils by red arrows. White spheres indicate location of IgA-coated beads. (F) IgA-coated beads after 20 min. Both neutrophils (green) and eosinophils (red) have attached. Original magnification ×40. (G) Distance traveled in 20 min (left panel) and speed (right panel) of neutrophils (white bars) and eosinophils (black bars) to control beads (BSA) and to IgA-coated beads (IgA). (H) ECP was measured as indication of eosinophil degranulation. Data are represented as mean ± SD. A representative experiment of three is shown. *p < 0.05.
membrane of human skin cryosections (Fig. 4A, middle and right panels). Subsequently, cryosections were incubated with granulocytes. No blister formation was observed in cryosections incubated with NHS (Fig. 4B, left panel). However, DES was observed when skin cryosections were incubated with serum of either BP or LABD patients in the presence of granulocytes (Fig. 4B, middle and right panels).

Next, we investigated the therapeutical potential of blocking FcαRI. When cryosections of human skin were incubated with patients’ sera, and granulocytes in the presence of an irrelevant isotype control (Fig. 4C, upper panels), DES was not inhibited. In addition, blister formation was not abolished when skin cryosections were incubated with sera from patients with BP and granulocytes in the presence of MIP8α (Fig. 4C, lower, middle panel). Importantly, IgA autoantibodies against the basement membrane did not induce granulocyte-dependent DES in cryosections of human skin, when granulocytes were incubated with MIP8α (Fig. 4C, lower, right panel). Thus, blocking FcαRI prevented ex vivo tissue damage in skin induced by LABD IgA autoantibodies and granulocytes.

To successfully kill microbes after their phagocytosis and in the pericellular tissue environment, granulocytes use efficient weapons, such as reactive oxygen species (ROS), and serine proteases like neutrophil elastase (31). Although intracellular killing of pathogens by ROS and serine proteases is a beneficial function for the host, extracellular spillage can result in significant collateral damages of tissues. To assess whether ROS or neutrophil elastase is responsible for the tissue damage observed in patients, granulocytes were incubated with inhibitors for NADPH oxidase (apocynin), which is involved in ROS production, or neutrophil elastase (chloromethyl ketone), and added to normal human skin, incubated with serum from healthy donors or patients with LABD. Inhibition of ROS production resulted in ∼50% reduction of DES (Fig. 4E). Additionally, blocking elastase activity (Fig. 4F) resulted in decreased DES as well, albeit to a lesser extent. Thus, both pathways contributed to blister formation in the skin.

**Discussion**

Granulocytes are the first cells that migrate into tissues to engulf and kill microorganisms at sites where the skin or mucosal barriers are damaged (32). They arrive within 1 h of tissue damage, and their number increases significantly over time, particularly when the lesion is infected (33, 34). Release of antimicrobial products by granulocytes efficiently kills pathogens, but can also lead to serious collateral damage to normal host cells. It is therefore imperative that activation is tightly regulated and that granulocytes are removed from the tissue as soon as the infection is cleared (35–37). We recently demonstrated that cross-linking of granulocyte FcαRI by IgA induces the release of leukotriene B4, which is a strong chemotaxant for granulocytes. This induces a positive migration loop that can be very efficient for killing invading bacteria at mucosal sites where IgA is the predominant Ab (14). Moreover, we also showed that targeting FcαRI very effectively induced leukotriene B4-dependent neutrophil recruitment into tumor colonies, which led to destruction (38). Thus, we postulated that FcαRI may promote tissue damage in diseases...
mediated by IgA autoantibodies. We now show that granulocyte migration and activation are deranged in diseases in which aberrant IgA–Ag complexes are formed. Because granulocytes are not able to clear such complexes, newly recruited granulocytes are continuously activated, leading to perpetuating inflammation and tissue damage. For instance, anti-collagen type XVII IgA Abs that are deposited at the basement membrane of the skin induce continued granulocyte activation, resulting in separation of the dermis and epidermis, which constitutes a pathological hallmark of LABD. Importantly, blocking FcαRI with a mAb prevented ex vivo skin cleavage. Furthermore, both the respiratory burst and elastase were responsible for tissue damage, as separation of the dermis and epidermis was (partly) blocked when these pathways were inhibited. The infiltrates of LABD patients often also contain eosinophils, but the role of these cells in the pathology of LABD is not completely understood. We demonstrated that eosinophils had degranulated after migration toward IgA-coated beads, as indicated by increased ECP concentration, which supports the hypothesis that eosinophils most likely contribute to the pathology of LABD. Eosinophils were previously shown to express FcαRI (36). It was furthermore shown that cross-linking of FcαRI on eosinophils induced respiratory burst activity, albeit smaller compared with the response of neutrophils (37). This may be due to the fact that FcαRI is inactive on resting eosinophils, and has to be primed by cytokines to become fully active (29).

FcαRI-induced tissue damage may also apply to other diseases characterized by aberrant IgA–Ag complexes and granulocyte infiltrates, such as Henoch-Schönlein purpura, IgA pemphigus, and dermatitis herpetiformis. However, this mechanism may also play an important role in diseases, which are generally not considered as strictly mediated by granulocytes. Rheumatoid arthritis, for instance, is characterized by chronic joint inflammation, in which mononuclear cells like T and B lymphocytes and macrophages play a prominent role (39). Infiltration of granulocytes into the synovial membrane and fluid compartment is, however, also observed. Moreover, it was shown that patients with elevated levels of serum IgA immune complexes or IgA rheumatoid factor have worse prognosis, as this is associated with development of rheumatoid vasculitis and predicts development of active, erosive disease of the joints (40–43). It was, furthermore, suggested that granulocyte recruitment to inflamed joints was mediated by leukotriene B4 (44). Thus, IgA–FcαRI interactions may induce granulocyte recruitment to the joints of rheumatoid arthritis patients, leading to increased destruction of joint tissues.

Furthermore, also in mucosal diseases in which aberrant IgA complexes have not yet been recognized as potentially damaging, IgA-induced migration of neutrophils may contribute to the pathogenesis of disease. Ulcerative colitis is a chronically remitting and relapsing disorder, characterized by severe inflammation of the intestinal tract (45). One of the hallmark features of ulcerative colitis are large granulocytic infiltrates. Because the mucosal barrier...
is impaired in these patients, leading to translocation of luminal contents, it is likely that excessive IgA–Ag complexes are formed. Because we previously demonstrated that granulocytes in the colon of ulcerative colitis patients had taken up IgA complexes (14) and we now demonstrate that excessive IgA deposits lead to an expanding inflammation loop of infiltrating granulocytes and tissue damage, we hypothesize that cross-linking of FcεRI by aberrant IgA–Ag complexes might be a key process in causing severe tissue damage in this disease.

In conclusion, although the origins of aberrant IgA–Ag complexes in most diseases are currently unknown and our data as such do not clarify the initiation of disease, this study clearly demonstrates that abnormal depostitions of IgA–Ag complexes in tissues induce sustained granulocyte recruitment through cross-linking of FcεRI. As a consequence, our results provide an explanation for the constant activation and infiltration of granulocytes, which cause severe tissue damage and aggravation of the symptoms of these diseases. Importantly, we now demonstrate that blocking IgA–FcεRI interactions abolishes the perpetuating inflammatory loop of granulocytes, hereby significantly reducing damage and morbidity. As such, these results hold promise for development of new therapeutics for diseases associated with aberrant tissue deposits of IgA–Ag complexes. 

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Disclosures

The authors have no financial conflicts of interest.

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