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ABSTRACT
This paper describes a chips-on-a-plate (COP) device for monitoring the migration of Raji cells in the Caco-2/Raji coculture. To generate a model of the human intestinal follicle-associated epithelium (FAE), the coculture method using a conventional Transwell cell culture insert was established. Due to the structural limitations of the Transwell insert, live-cell tracking studies have not been performed previously using the existing FAE model. In this study, we designed a COP device to conduct long-term live-cell tracking of Raji cell migration using a microchannel-based FAE model. The COP device incorporates microfluidic chips integrated on a standard well plate, consistent humidity control to allow live-cell microscopy for 2 days, and microchannels connecting the two cell culture chambers of the COP device, which serve as a monitoring area for cellular migration. Using the COP device, we provide the first analysis of various migratory characteristics of Raji cells, including their chemotactic index in the microchannel-based FAE model. We showed that the migration of Raji cells could be controlled by modulating the geometry of the connecting microchannels. Cellular treatments with cytokines revealed that the cytokines increased the permeability of an FAE model with a detachment of Caco-2 cells. Live-cell monitoring of Raji cells treated with a fluorescent reagent also indicated exocytosis as a key agent of the Caco-2/Raji interaction. The COP device allows live-cell tracking analyses of cocultured cells in the microchannel-based FAE model, providing a promising tool for investigating cellular behavior associated with the recruitment of Raji to Caco-2 cells.

INTRODUCTION
The human intestines, containing the largest number of immune cells in the body, are exposed to a variety of antigens, including commensal and pathogenic microorganisms.1 Gut-associated lymphoid tissue (GALT) consists of follicles of immune cells and associated tissues, which orchestrate the intestinal immune system.2 Different from the majority of the intestinal epithelium, the follicle-associated epithelium (FAE), which covers GALT, senses luminal antigens and translocates them into GALT.3 The FAE is considered to be an entrance for pathogens and drugs, thus attracting recent scientific investigation into its involvement in pathogenesis and drug delivery.

Kernéis et al. established the first in vitro FAE model, consisting of two immortalized cell lines, Caco-2 and Raji cells, cocultured in a Transwell insert.4 Caco-2 cells, a human intestinal epithelial cell line derived from colorectal adenocarcinoma, were selected to model intestinal epithelial cells; Raji cells, a human B lymphocyte cell line derived from Burkitt’s lymphoma, were selected to model intestinal lymphocytes of GALT. The Transwell in vitro model simplifies the complexity of the FAE tissue, facilitating studies focused on various cellular mechanisms. For example, Transwell-based studies were used to characterize genetic similarities between the in vitro model and the human FAE.5 In addition, various Transwell-based models were used to investigate hypotheses deduced from in vivo studies, elucidating surface markers and antigen translocation mechanisms of the FAE.6,7 Nevertheless, the Transwell apparatus has limitations, which have prevented the analysis of Raji cell migration; instead, studies have focused on Caco-2 cells for the FAE model. As in vivo studies have illuminated lymphocytic migration and contact with intestinal epithelial cells to differentiate the FAE,3 the migratory behavior of Raji cells in Caco-2/Raji coculture could be
informative about the formation of the FAE-like phenotype in Caco-2 cells. Additionally, the translocation of Raji cells through 3-μm pores of the Transwell membrane would signify active migration toward Caco-2 cells. Live-cell monitoring is required to investigate the migration of and cellular interaction between cocultured Caco-2 and Raji cells. However, Transwell assays allow only indirect visualization. Accordingly, end-point visualization techniques such as immunohistochemical imaging, confocal microscopy, and transmission electron microscopy have been used in Transwell-based models.

To investigate live monitoring of cellular migration, basic principles of microfabrication were applied to develop cell culture devices. Heralded by the invention of soft lithography, advancements in microfluidics and microfabrication technologies have resulted in the development of numerous cell culture devices made of poly(dimethylsiloxane) (PDMS) for live-cell monitoring. Previously, PDMS-based microfluidic cell culture devices were used to measure the migratory rate and directionality against soluble stimulants of Raji cells. However, a comparable analysis of Raji cells in Caco-2/Raji coculture has not been reported. The Caco-2/Raji coculture requires a long culture period in a hydrostatic environment. Although existing microfluidic cell culture devices enabled long-term culture, customized perfusion pumps are required to provide a hydrostatic environment. Recently, an open well-based microfluidic device was used successfully in long-term culture; however, its dimensions were specific for the coculture of mammalian and bacterial cells.

Here, we report a microfluidic cell culture chips-on-a-plate (COP) device for live-cell monitoring of the Caco-2/Raji coculture. The device consists of microfluidic chips for cell culture, integrated on a 6-well plate for live-cell microscopy. The open-well design of the COP device is compatible with a common culture plate and ensures consistent prevention of media evaporation, allowing maintenance of long-term culture and live-cell monitoring. The small molecule diffusion properties and the apparent permeability of Caco-2 cells cultured in the COP device were analyzed to validate the establishment of the in vitro microchannel-based FAE model consisting of the Caco-2/Raji coculture. This study demonstrated visual tracking and analyses of the migratory behavior of Raji cells cocultured with Caco-2 cells in the COP device. This device will facilitate investigations of key characteristics of the microchannel-based FAE model.

**MATERIALS AND METHODS**

**Design and fabrication of a COP device**

A COP device was fabricated using soft lithography of PDMS. To prepare the mold, the negative photoresist SU-8 (MicroChem Corp., Newton, MA, USA) was spin-coated on a bare silicon wafer and developed into microstructures using photolithography. The PDMS elastomer was mixed with a curing agent at a ratio of 10:1 (w/w). The PDMS mixture was cast onto the mold and cured on a hot plate at 120 °C for 2 h to complete the cross-linking. Cured chips were sterilized with 70% ethanol and autoclaved. The COP devices and the surfaces of a glass-bottomed confocal 6-well plate (SPL Life Sciences Co., Ltd., Pocheon, Korea) were plasma-activated and bound together. The bonding was completed by placing the assembly in a dry oven at 85 °C for 30 min. The COP device was filled with media prior to use.

**Caco-2/Raji coculture**

Caco-2 and Raji cells were obtained from the American Type Culture Collection (Manassas, VA, USA) and maintained in Dulbecco’s modified Eagle’s medium supplemented with 4.5 g/l glucose, 50 U/ml penicillin, 50 U/ml streptomycin, and 10% fetal bovine serum (media components purchased from Corning Inc., Corning, NY, USA). The cells were cultured to confluence in T25 flasks. The Caco-2 cells were collected by trypsinization while the Raji cells were collected by centrifugation, and the cell numbers were counted using an automated hemocytometer (Logos Biosystems, Inc., Anyang, Korea). Following a seeding method described previously, Caco-2 cells were introduced into the Caco-2 chamber of the COP device at a concentration of 200 000 cells/ml. The Caco-2 cells were cultured up to 14 days (∼7 days after confluence) to promote their epithelial phenotype. Subsequently, Raji cells were seeded at a concentration of 200 000 cells/ml into the Raji cell chamber. The COP device was placed upright (e.g., perpendicular to the floor) in a humidified 37 °C incubator for 15 min to allow settling of the Raji cells at the entrances of the connecting microchannels between the two cell culture chambers.

**Characterization of diffusional transport**

The connecting microchannels were reconstituted on a 2D plane and analyzed with computational fluid dynamics (ESI Group SA, Paris, France). The COP device was filled with distilled water, and one drop of 100 μM 10 kDa fluorescein isothiocyanate-dextran (FD-10) was introduced into the Caco-2 chamber. The diffusional transport of FD-10 through the connecting microchannels was recorded using a fluorescent microscope (AX10; Carl Zeiss AG, Jena, Germany). The acquired images were analyzed with ImageJ (https://imagej.nih.gov/ij/) to measure the gradient of fluorescent intensity over the middle section of the connecting microchannels at 10 min. The fluorescent intensity was compared to a mathematical prediction expressed by the equations listed below. The diffusion coefficient of FD-10 in water at 37 °C was calculated using the Stokes–Einstein equation [Eq. (1)], where $D_{FD-10}$ is the diffusion coefficient of FD-10, $k_B$ is Boltzmann’s constant, $T$ is the temperature in Kelvin, $\eta_{water}$ is the dynamic viscosity of water at 37 °C, and $r_{FD-10}$ is the radius of FD-10 reported as 2.9 nm.

$$D_{FD-10} = \frac{k_B T}{6 \pi \eta_{water} r_{FD-10}} = 1.131548 \times 10^{-10} \text{m}^2 \text{s}^{-1}. \quad (1)$$

For mathematical prediction, the measured middle section of the connecting microchannels was simplified as a straight line, and the mathematical prediction of the concentration of FD-10 was modeled as diffusion in a semi-infinite medium [Eq. (2)],

$$C(x, t) = C_0 \text{erfc} \left( \frac{x}{2 \sqrt{Dt}} \right). \quad (2)$$

**Measurement of media evaporation**

The COP device was filled with 220 μl of 100 μM erioglaucine aqueous solution and humidified using integrated humidity control.
or conventional wet tissue paper humidification. The COP device was placed in a conventional humidified incubator at 37 °C, and samples were taken every 12 h. A microplate spectrophotometer (Molecular Devices, LLC, San Jose, CA, USA) was used to measure the concentration of erioglaucine from which the volume loss was calculated. The differences were considered significant at \( p < 0.05 \).

**FD-10 permeability assay**

FD-10 (100 \( \mu \)M) in Hank’s balanced salt solution (Corning Inc.) was added into the Caco-2 chamber of the COP device with Caco-2 cells cultured for 14 days. The opposite chamber contained Raji cells cocultured for 3 days, and the control condition contained a single culture of Raji cells without coculture. The cells were incubated at 37 °C for 2 h. Samples were taken from the Raji chamber, and the fluorescent intensity of FD-10 was measured using a multilabel plate reader (PerkinElmer, Inc., Waltham, MA, USA). The apparent permeability coefficient \( (P_{\text{app}}) \) was calculated, where \( \frac{dQ}{dt} \) is the flux for 2 h, \( A \) is the total area of the entrances of the connecting microchannels, and \( C_0 \) is the initial concentration of FD-10 [Eq. (3)]. Differences were considered significant at \( p < 0.05 \).

\[
P_{\text{app}} = \frac{dQ}{dt} \times \frac{1}{A \times C_0}
\]  

**Live-cell tracking analysis**

Caco-2 cells were cultured for 14 days in the Caco-2 chamber, and Raji cells were introduced into the Raji chamber as described in the Caco-2/Raji coculture section. The COP device was mounted on a microscope stage-top incubator (Live Cell Instrument, Seoul, Korea) for live-cell tracking. Images were acquired every 10 min for 48 h, and the observed migration of Raji cells was tracked as coordinates on an \( xy \) plane using the MTrackJ plugin of ImageJ. The migration speed was calculated by dividing the absolute distance between the initial and final position of the Raji cells over their total migratory distance. Differences were considered significant at \( p < 0.05 \).

**Chemical treatment of Caco-2 and Raji cells in a COP device**

Tumor necrosis factor-\( \alpha \) (TNF-\( \alpha \)) and lipopolysaccharide (LPS) from \( E. coli \) O26:B6 (Sigma-Aldrich, St. Louis, MO, USA) were used for the proinflammatory cytokine treatments of Caco-2 cells. Caco-2 cells cultured to confluence in a COP device were exposed to LPS (10 \( \mu \)g/ml) or TNF-\( \alpha \) (100 ng/ml) solubilized in Hank’s balanced salt solution (Corning Inc.) for 1 day. The cytokine solution was replaced with the growth medium for subsequent Raji seeding. For visualization in fluorescent microscopy, Raji cells were stained with 5-chloromethylfluorescein diacetate (CMFDA; Thermo Fisher Scientific, Inc., Waltham, MA, USA).

**RESULTS AND DISCUSSION**

The COP device for monitoring cellular migration in a microchannel-based FAE model

The COP device was designed to study cellular migration in the Caco-2/Raji coculture, representing in vitro microchannel-based FAE. Using the device, Caco-2 cells were cultured to confluence, and then Raji cells were seeded into the opposite chamber. The connecting microchannels linked the two cell culture chambers and served as passages for migration of Raji cells to interact with Caco-2 cells [Fig. 1(a)]. A PDMS disk with micropatterned structures and punched inlets was bound on a glass-bottomed 6-well plate to form the COP device [Fig. 1(b)]. In the complete COP device, diffusive transport of FD-10 through the connecting microchannels was characterized, as it was assumed that chemokines secreted by Caco-2 cells regulate Raji migration. The computational simulation of the fluorescent tracer diffusing through the connecting microchannels was comparable to the fluorescent images of actual diffusion [Fig. S1(a) in the supplementary material], and the measured fluorescent intensity was comparable to the mathematical prediction of diffusion [Fig. S1(b) in the supplementary material].

Figure 1(c) shows a photograph of six COP devices integrated on a conventional 6-well plate. The peripheral area in each well was used as an internal water bath to maintain optimal humidity during several days of live-cell microscopy. Furthermore, the remaining area in each well acted as a humidity controller that prevented rapid media evaporation, which is problematic when maintaining a microvolumetric cell culture. The COP device was designed to study cellular migration in the Caco-2/Raji coculture device could introduce a critical failure causing a dramatic decrease in media osmolality, which affects cellular behavior and viability. However, a few studies on evaporation have been performed aimed at increasing the duration of monitoring.

In this study, the peripheral area of the 6-well plate attached to the COP device served as an integrated humidity controller with consistent geometry. Caco-2 and Raji cells were easily maintained.
in the open-well design, while maintaining the internal humidity with the closed lid of the 6-well plate. The preventive efficacy of the COP device was compared to the use of wet tissue paper surrounding the COP device. We compared the three humidity configurations (no source of external humidity, the integrated humidity controller, and wet tissue paper) [Fig. 2(a)] in a 37°C humidified incubator for 48 h. Whereas the lack of proximal humidity resulted in complete evaporation, the media volume was maintained within 3% of its...
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As summarized in a review of various studies investigating the development of new TEER equipment for non-Transwell microfluidic cell culture devices, a different electrical measurement setup is required to conduct a TEER assay on a COP device. For the coculture of Caco-2 and Raji cells in a Transwell insert, the establishment of the FAE model was confirmed by the apparent permeability (P_app) of Caco-2 cells and the migration of Raji cells into the Caco-2 cell layer. In this respect, P_app was measured instead of TEER, representing the amount of a Raji cell invasion in a COP device.

P_app is generally used to evaluate the permeation of the tracer molecules across the Caco-2 cell culture. Here, 10 kDa FD-10 was chosen as the tracer, as it represented the molecular mass of chemokines. As shown in Figs. 3(a) and 3(b), permeation of FD-10 occurred from the Caco-2 cell chamber into the Raji cell chamber at 2 h. The Caco-2 cells cultured in the COP device behaved as a barrier against permeation, and thus the amount of FD-10 in the Raji chamber could not be measured from images acquired using a fluorescent microscope. Therefore, a multilabel plate reader was used to measure the low concentration of FD-10 in the Raji chamber to calculate P_app. The P_app values were measured for FD-10 across the Caco-2 monolayer with or without the Raji cell coculture. The Caco-2 monolayer cocultured with Raji cells for 3 days showed a 1.76-fold increase in the P_app value [Fig. 3(c)]. Moreover, the invasion of Raji cells into the Caco-2 cell culture was observed [Fig. 3(d)]. The increased permeability in the coculture was similar to that described in previous reports. The increased P_app and Raji cell invasion suggest that Caco-2 cells acquired an FAE-like phenotype. Thus, the application of the coculture protocol in the COP device displayed the two characteristics of in vitro FAE. Therefore, Raji cell migration toward Caco-2 cells could be visually tracked using the COP device.

### Live-cell tracking analysis of Raji cells

The migratory characteristics of Raji cells in the coculture were studied using live-cell microscopy. A single culture of Raji cells in the Raji chamber of the COP device was set as a negative control [Fig. 4(a), Multimedia view] and compared to the Raji cells of the microchannel-based FAE model [Fig. 4(b), Multimedia view]. Time-lapse imaging was used to monitor Raji cells migrating inside the connecting microchannels of the COP device [Figs. 4(c) and 4(d)]. Raji cells introduced into the Raji chamber showed a tendency to congregate in clusters from which the migrating cells moved out. The majority of Raji cells in the control condition returned to the clusters [Fig. 4(e)]. On the other hand, Raji cells in the microchannel-based FAE model displayed migration toward the Caco-2 layer [Fig. 4(f)], infiltrating the Caco-2 culture. Such behavior was comparable to that of the Raji cells found within the membrane or the Caco-2 layer of the Transwell-based FAE model.

Migratory characteristics were analyzed and compared between the control (a single culture of Raji cells) and the microchannel-based FAE model in the COP device with 3- or 8-μm high connecting microchannels. The change in height of the connecting microchannels revealed the importance of structural hindrance for migrating cells. At the onset of live-cell monitoring, Raji cells were observed inside the 8-μm high connecting microchannels.

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**FIG. 2.** Prevention of media evaporation in the COP device. (a) Images of the COP device operated with or without the integrated humidity controller and wet tissue paper. Scale bar: 1 cm. (b) Changes during the evaporation of the medium over 48 h (n = 5). *p < 0.05.
As the measured average diameter (10.83 ± 1.64 μm) of Raji cells is similar to the 8-μm height, a considerable number of Raji cells randomly entered the connecting microchannels without geometric constraints. The migration rates of the Raji cells were recorded in the range of 0.75–1.25 μm/min under the three conditions [a single culture of Raji cells (control) and in coculture in the COP device with 3- or 8-μm high microchannels] [Fig. 5(a)]. Visual tracking was initiated when a Raji cell entered the connecting microchannels and terminated when the observed cell returned to a cluster of Raji cells or infiltrated the Caco-2 culture. The tracking time of the Raji cells of the microchannel-based FAE model in the COP device with 3-μm high connecting microchannels showed greater consistency than that under the other two conditions [Fig. 5(b)]. The low chemotactic index observed in the control condition was consistent with the reported value obtained from a microfluidic chemotaxis assay.23 Indeed, the chemotaxis value obtained in the COP device increased fourfold in the coculture [Fig. 5(c)]. Consistent and directed migration of Raji cells toward the Caco-2 layer was observed in the 3-μm high connecting microchannels. This report is the first demonstration of live-cell monitoring; however, our results showed that the migratory tendency of Raji cells of the microchannel-based FAE model in the COP device with 3-μm high connecting microchannels showed greater consistency than that under the other two conditions [Fig. 5(b)]. The low chemotactic index observed in the control condition was consistent with the reported value obtained from a microfluidic chemotaxis assay.23 Indeed, the chemotaxis value obtained in the COP device increased fourfold in the coculture [Fig. 5(c)]. Consistent and directed migration of Raji cells toward the Caco-2 layer was observed in the 3-μm high connecting microchannels. This report is the first demonstration of live-cell monitoring; however, our results showed that the migratory tendency of Raji cells of the microchannel-based FAE model in the COP device with 3-μm high connecting microchannels showed greater consistency than that under the other two conditions [Fig. 5(b)]. The low chemotactic index observed in the control condition was consistent with the reported value obtained from a microfluidic chemotaxis assay.23 Indeed, the chemotaxis value obtained in the COP device increased fourfold in the coculture [Fig. 5(c)]. Consistent and directed migration of Raji cells toward the Caco-2 layer was observed in the 3-μm high connecting microchannels.

**Fig. 3.** Apparent permeability values ($P_{app}$) measured for FD-10 across a Caco-2 monolayer with or without Raji cell coculture. (a) Schematic of the FD-10 permeability assay. The amount of FD-10 that permeated the Raji chamber over 2 h was measured. (b) Microscope images of FD-10 diffusing through the connecting microchannels in a blank COP device (left) and with Caco-2 cells cultured for 14 days (right). Scale bar: 100 μm. (c) $P_{app}$ for the Caco-2 single culture and the Caco-2/Raji coculture ($n = 3$). *p < 0.05. (d) The invasion of a single Raji cell into the Caco-2 layer was monitored. A Raji cell body is emphasized with white borderlines. Scale bar: 10 μm.
cells toward the Caco-2 layer was not dominant. The majority of Raji cells seeded inside the connecting microchannels migrated toward the seeding inlet. Removing the Raji cells clustered in the inlet will allow visualization of Raji migratory behaviors in relation to the connecting microchannels.

**Effects of proinflammatory cytokines and a fluorescent dye on the in vitro FAE cellular behaviors**

Caco-2 cells of the microchannel-based FAE were treated with LPS or TNF-α to study the effect of proinflammatory cytokines on Raji cell migration. At the beginning of the time-lapse imaging,
Caco-2 cells detached from the entrances of the connecting microchannels were observed in both treatments [Fig. 6(a), Multimedia views]. Reattachment of Caco-2 cells to the entrances indicated cellular viability maintained with the cytokine treatments. No Raji cells entering the connecting microchannel were observed, and the motility of the Raji cells residing in their culture chamber decreased with the cytokine treatments [Fig. 6(b)]. Stimulating Caco-2 with TNF-α was reported to increase the secretion of an in vivo FAE...
chemokine CCL2.46 However, Raji does not express CCR6, which is the receptor of CCL2.44,47 The reduced Raji motility measured in this study agreed with the inability of Raji to recognize CCL2 and disputed its role as an FAE protagonist in the Caco-2/Raji coculture. With no mean for live-cell monitoring, changes in cellular behavior of a Transwell-based FAE were inferred from the measurements of Caco-2 permeability. Increased permeability of the Caco-2 culture by TNF-α treatment implied a stronger FAE-like function established in a Transwell-based FAE.48 On the other hand, the COP device provided direct observational data from both Caco-2 and Raji cells in the microchannel-based FAE coculture. The result of studying cellular behavior under the influence of proinflammatory cytokines suggested that the increased Caco-2 permeability was due to the detachment from the interconnecting passage rather than the strengthened FAE-like function.

Live-cell monitoring of nontabeled cells is considered as a gold standard assay because labeling reagents often interfere with cellular behavior. Nevertheless, fluorescent stains help locate cells that are hardly seen with brightfield microscopy. To enhance cell visibility, the FAE coculture in a COP device was constructed with Raji cells infused with a fluorescent tracking reagent, CMFDA. Fluorescent live-cell monitoring also revealed streams of granular bodies originating from Raji cells and migrating toward Caco-2 [Fig. 6(c), Multimedia view]. Using a COP device, the reported exocytosis of the fluorescent label from Raji cells was observed.49 The observed streams of granular bodies suggested a bigger role of exocytosis than cellular migration in the Caco-2/Raji interaction of the FAE model.

CONCLUSIONS

Raji cell migration toward Caco-2 has been reported previously, however, the migratory characteristics were unclear due to the structural limit of the Transwell insert used. Microfluidic cell culture devices for live-cell analysis have often been optimized for assays shorter than 1 day. However, Raji cell migration in the cocultured FAE model requires at least 3 days to verify the endpoint position. In this study, we developed a COP device to provide live-cell tracking for an extended period. During continuous live-cell tracking over 2 days, Raji cell migration was observed from beginning to end. This is the first report of Raji cell migration using a microchannel-based FAE model. The migration rate, actual tracking time, and chemotactic index were obtained from the live-cell tracking conducted with the COP device. Changing the height of the connecting microchannels elucidated the role of structural hindrance in reducing the random migration of Raji cells inside the COP device. The dominant self-clustering behavior of Raji cells observed in this study suggests that the COP device structure provides an effective microenvironment for promoting the interaction between Caco-2 and Raji cells. When the microchannel-based FAE model was influenced by proinflammatory cytokines, Caco-2 cells were detached from the entrances of the connecting microchannels, and Raji cells displayed reduced motility. This result suggested that the cytokines increased the permeability of an FAE model with morphological changes in Caco-2 culture, rather than the induction on FAE-like function. The involvement of exocytosis in the Caco-2/Raji interaction was inferred from the observation of massive streams of granular bodies emanating from Raji cells. The COP device for live-cell analyses of the microchannel-based FAE model is expected to help elucidate the cellular migration of Raji cells as an immunological response against stimulants such as microorganisms and cytokines.

SUPPLEMENTARY MATERIAL

See the supplementary material for a detailed description of the diffusive transport of the fluorescent tracer through the connecting microchannels (Fig. S1) and an image of Raji cells located inside the 8-μm high connecting microchannels (Fig. S2).

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