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MICROFLUIDIC DEVICE FOR EXAMINING DIRECTIONAL SENSING IN DENDRITIC CELL CHEMOTAXIS

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Abstract

Dendritic cell chemotaxis is an important process involved in the acquisition of adaptive immunity. Despite several studies, our understanding of this process remains limited. One of the reasons for this is the lack of experimental models that give us real-time information on dendritic cell locomotion. Here, using tools in microfluidics, we have fabricated a microdevice that allows us to monitor dendritic cell migration in a chemokine gradient in real time. We successfully observed the migration of dendritic cells derived from a myeloid leukemia cell line (MUTZ-3) in a soluble chemokine (CCL-19) gradient. Our experiments suggest the utility of microdevices in monitoring dendritic cell chemotaxis in real time and getting important information regarding migration speeds and distances previously not available from conventional chemotaxis assays. This kind of data is useful for building mechanistic mathematical models of dendritic cell chemotaxis that may give us novel insights to the process of dendritic cell chemotaxis.

Keywords

Chemotaxis; dendritic cells; BioMEMs; migration; CCL-19

1. Introduction

Dendritic cells are antigen-presenting cells residing in peripheral epithelial tissues, where they act as sentinels protecting the body from potentially harmful antigens and insults.¹ On encountering an antigen, the dendritic cells mature, process the antigen and then migrate to the local draining lymph nodes.^{2,3} In the lymph node, these cells present the antigen to naïve T-cells, which in turn get activated and mount an immune response resulting in inflammation.^{4,5} As described above, the migration of dendritic cells to the lymph node is crucial for the initiation of inflammation. This is achieved by chemotaxis, a process by which cells migrate in response to a chemical cue.⁶ Once activated, dendritic cells express CCR-7^{7,8} and migrate in response to gradients of CCL-19 and CCL-21,⁹ which are expressed in lymphatic vessels and T-cell areas of the lymph nodes.¹⁰

Several *in vivo* and *in vitro* experimental models have been used successfully for studying dendritic cell migration.^{11–13} However, most of these assays are endpoint assays and do not

give real-time information about how dendritic cells migrate. For example, several *in vivo* mouse models of dendritic cell migration comprise sensitization of peripheral tissue and then recovery of the activated dendritic cells in the lymph node.¹⁴ These experimental models give us information about the number of activated dendritic cells that have migrated to the lymph node. Similarly, the most common *in vitro* assay for chemotaxis, the Boyden Chamber assay, is also an endpoint assay that gives us the number of cells that have migrated to the chemokine source.¹⁵ This issue has partially been solved by other chemotaxis assays such as the Dunn chamber assay and under Agarose gel assays as they do allow us to monitor chemotaxis in real time.^{16,17} However, the gradients generated in these assays cannot be sustained for a long period of time. In a matter of hours, the chemokine gradient is lost due to diffusion from the chemokine source to the cell chamber. Maintenance of steady state gradients is crucial for studying the mechanism of dendritic cell motility. Furthermore, both of these assays follow cells moving freely in a two-dimensional surface, which is not a good physical mimic of dendritic cell chemotaxis since these cells crawl through narrow interstitial spaces to reach the lymph node from peripheral tissue.

Microscale technologies are potentially powerful tools and can be used to address some of these challenges.¹⁸ MEMS (Microelectromechanical systems) can be used to control features at a micron scale, which gives us the ability to control and fine tune cellular microenvironments in which cell behavior can be observed in real time.^{19,20} Recent advances in soft lithography and microfluidics have allowed the development of microfluidic chemotaxis chambers.^{21–23} These chambers enable the creation of precise and stable chemokine gradients and also allow monitoring of cell migration in real time. These microdevices have been used successfully to study neutrophil chemotaxis in gradients of IL-8²¹ and fMLP.²² Similarly, these microfluidic chambers have been used to quantitatively analyze migration of breast cancer cells in EGF gradient.²³

In this work, we developed a microfluidic device to observe dendritic cell chemotaxis in a gradient of CCL-19 in real time. We used dendritic cells that were derived from a cytokine responsive myeloid leukemia cell line (MUTZ-3). One novel aspect in this device was the introduction of a neck in the transversal channels to mechanically constrain mature dendritic cells during cell loading. This allowed us to selectively load mature dendritic cells that are bigger in size than the MUTZ-3 precursors. We were successfully able to generate stable chemokine gradients as well as monitor the migration of the dendritic cells in real time. Interestingly, we observed that on switching on the gradient, the cells first send out projections in multiple directions and sense their surroundings before starting to migrate. This led to a lag in their response before moving in the direction of the gradient with a constant velocity. Furthermore, based on their speed and migration distance, we detected two different populations of migrating dendritic cells. Our data suggest the utility of using microdevices in monitoring dendritic cell chemotaxis in real time and getting important information regarding migration speeds and distances previously not available from conventional chemotaxis assays. This kind of data is useful for building mechanistic mathematical models of dendritic cell chemotaxis that may give us novel insights to the process of dendritic cell chemotaxis.

2. Materials and Methods

2.1. Cell culture

The human myeloid leukemia cell line MUTZ-3 (ACC295) and bladder carcinoma cell line 5637 (ACC 35) were acquired from the Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ, Germany). The 5637 cells were cultured in RPMI supplemented with 10% fetal bovine serum and the cells were grown to confluence. After reaching confluence,

fresh media was replaced and it was harvested after 42–43 h. This conditioned media was used for culture of MUTZ-3 cells as described below.

MUTZ-3 cells were routinely cultured in growth medium, which is α -mem (Invitrogen, Carlsbad, CA, USA) supplemented with 20% Fetal bovine serum, 50 μ M *b*-mercaptoethanol and 10% 5637 conditioned media. For generation of dendritic cell progenitors, MUTZ cells (10^5 cells/ml, 2 ml medium/well) were cultured in 12 well plates in growth media supplemented with GM-CSF (100 ng/ml, R&D Systems), TGF- β (10 ng/ml, R&D systems) and TNF- α (2.5 ng/ml, R&D systems) for 7 days.

The dendritic cell progenitors were then spun down and reseeded in 12 well plates (2×10^5 cells/ml, 2 ml/well) in α -MEM medium (without 5637-conditioned media) supplemented by a cocktail of inflammatory cytokines consisting of PGE₂ (1 μ g/ml Sigma), IL-6 (100 ng/ml R&D systems), TNF- α (50 ng/ml) and IL-1 (25 ng/ml). These cells were cultured for two days resulting in maturation of dendritic cell precursors.

2.2. Flowcytometry and labeling of the cells

Mature cells or immature cells were characterized by antibodies to mature dendritic cell markers CD86, CD83, langerhans cell marker CD207 and CCR-7 the receptor for CCL-19. For staining with CD83 or CD86, either mature or immature cells were harvested by spinning them down. They were then incubated either by FITC-conjugated mouse antihuman CD83 (BD pharmingen), FITC-conjugated mouse antihuman CD86 (BD pharmingen), PE-conjugated Rat antihuman CCR-7 (BD pharmingen) or PE-conjugated mouse antihuman langerin (R&D systems) for 30 min on ice. After the incubation, cells were washed twice with phosphate buffered saline and the surface expression was quantified using a flowcytometer. For staining of langerin and CCR-7, the cells were fixed by 4% formaldehyde. Since langerin is in the cytoplasm, the fixed cells were further permeabilized using Triton X-100 before incubating them with the antibody.

2.3. Fabrication of microdevice

The microfluidic device was fabricated using standard microfabrication technologies. Briefly, two PDMS (polydimethyl siloxane) layers were bonded together on top of a glass slide, one layer 200 μ m thin (network layer) and one 4 mm thick (control layer). The thick layer was made by casting PDMS on a master silicon wafer with photolithographically defined photoresist features. This layer was bonded after exposure to oxygen plasma on top of the network layer, cast on a second wafer, by spinning PDMS and curing overnight at 65°C. Microfluidic valves were defined in the network layer and pneumatically controlled using the channels in the control layer, as previously described in detail.²² Four valves are placed symmetrically at the ends of a parallel array of $10 \times 10 \times 150$ μ m channels. One original element in the current design is represented by the narrowing of the transversal channels, which serves the purpose of mechanically trapping dendritic cells at the beginning of the experiment.

2.4. Chemotaxis assay

The device was first primed with phosphate buffered saline. The inlets and the outlets were all connected using tygon tubing. The inlets were clamped and PBS was pushed from the outlet to remove all the bubble in the microdevice. Once all the bubbles were removed, the inlets were opened and the cells were introduced from the outlet. Two diagonally opposite valves were closed and the remaining two were left open. This ensured flow through the channels and made the cells go in the channels. The bigger dendritic cells (either immature or mature) were stuck in the neck that was introduced in the middle of the channels. After sufficient cells were captured, all the valves were opened to balance the flow in the device.

The two inlets were then connected to syringes containing either the media or media containing CCL19 (250 ng/ml) and fluorescein. The syringes were loaded on a syringe pump and the two flow lines were started. Flow was adjusted such that there was no mixing at the inlet and no pressure drop in the channels resulting in no flow in the channels. The migration of the cells was captured by time lapse microscopy using a Nikon microscope with a heated stage. The images and the migration of cells were quantified using Image J.

3. Results

3.1. Generation and characterization of dendritic cells

We used a cytokine responsive CD34⁺ human acute myeloid leukemia cell line (MUTZ-3) for the generation of dendritic cells as described previously.²⁴ We cultured MUTZ-3 cells for 7 days in the presence of GM-CSF (100 ng/ml), TGF- β (10 ng/ml) and low levels of TNF- α (2.5 ng/ml) (Fig. 1(a)). After seven days in culture, the cells grew in clusters (Fig. 1(b), **Immature dendritic cells**) and they had dendritic cell like projections (Fig. 1(c)) and these cells were termed as immature dendritic cells. These immature dendritic cells were further treated by a cocktail of inflammatory cytokines (IL-6, TNF- α , IL-1 and PGE₂) to induce their activation and maturation for two days. Once the cells get activated, they break apart from these clumps and migrate out as single cells (Fig. 1(b), **Mature dendritic cells**) as has been described previously.²⁵ In addition, we found that MUTZ-3 cells maintained a spherical profile with a cell diameter of 8–12 μ m (Table 1). On the other hand, upon maturing the cells differentiated into a larger diameter (Table 1, 15–25 μ m) and show many variation in shapes including spherical, elongated profiles and dendritic cell like extensions (Fig. 1(c)).

We characterized the mature dendritic cell population by staining them with different dendritic cell markers e.g., CD83 and CD86. The mature dendritic cells expressed several markers of mature dendritic and langerhans cells. While about 60% of the cell population was expressing CD83 and CD86 (Fig. 2), a small population of the cells also expressed the langerhans cell-specific marker langerin (CD207, 22%). Furthermore, we also assessed the expression of CCR-7 (CD-197), a receptor for CCL-19 which is expressed primarily on mature dendritic cells and found that about 48% of the cells were expressing this marker (Fig. 2). These data suggest that we were able to successfully generate mature dendritic cells.

3.2. Generation of a microdevice with stable chemokine gradient

We used microfluidic ladder chamber consisting of several small transversal channels as shown in Fig. 3(a). We introduced a “neck” (10 μ m long and 10 μ m wide at about 60 μ m and 90 μ m from each of the larger transversal channels) in the channels to capture the dendritic cells once they are introduced by flow (Fig. 3(b)). This neck was large enough to let the MUTZ-3 cells flow through while capturing the bigger differentiated MUTZ-3–derived dendritic cells. The cells were introduced from the outlet of the device (Fig. 3(b)). The microfluidic device has four valves controlled by air and they were used during loading of the cells (Fig. 3(b)). During loading, two valves (Fig. 3(b), valves 2 and 3) were closed and the remaining two valves (Fig. 3(b), valves 1 and 4) were left open. This ensures flow in the channels and hence loading of the cells (Fig. 3(c)). After introduction of the cells, all the valves were opened and we started the two flow lines at the inlet (chemokine and buffer) using a syringe pump. The flow rates were adjusted so that there is no mixing at the interface, which yields a gradient of the chemokine by diffusion as described previously in the lab (Fig. 4).²²

For visualizing the chemokine gradient, we added fluorescein in the chemokine flow line. After capturing enough number of cells, we started both the chemokine and buffer lines. The flow of both lines was adjusted in such a manner so that there was no mixing at the inlet and no convective flow in the transversal channels (Fig. 4). This yielded a stable gradient of the chemokine purely due to diffusion at steady state. Furthermore, since the cells occluded the channel they were exposed to the chemokine only on one side (termed as the front end) leading to polar stimulation (Fig. 4).

3.3. Dendritic cell chemotaxis

Mature dendritic cells activated in the peripheral tissue migrate in a gradient of CCL-19 to reach the lymph nodes *in vivo*. So we monitored the migration of dendritic cells by creating a gradient of CCL19 in our device. First, we introduced immature dendritic cells (dendritic cell precursors) in the microfluidic chamber and then switched on the lines containing buffer and CCL-19. The immature dendritic cells did not respond to the gradient and showed no displacement or extension of dendrites (Fig. 5(b)). On the other hand, activated dendritic cells responded to polar stimulation in minutes. These cells started to extend dendrites in the direction of the gradient and then started moving in that direction as well. There was significant activity on the leading cell surface in contact with CCL-19 compared to the lagging cell surface (Figs. 5(c) and 5(d)). Interestingly, this response was not uniform in all the cells. Some cells (termed as slow cells) showed dendrite activity at the leading edge but failed to migrate as fast as others or did not migrate at all. We quantified the displacement of the cells with time and found that overall there were two populations of cells (Figs. 5(c)–5(d)), one that was moving relatively fast and reached the end of the channel and the other that was moving slow or not moving at all (Fig. 5(e)). We quantified the speeds of these two populations and found that the speeds of the cells in both populations were uniform (Fig. 5(e)). Furthermore, we measured the cell diameter of the cells in the two populations and found that the cell sizes between the two populations were fairly similar (Fig. 5(f)), suggesting that the difference in the speeds is not because of difference in cell sizes.

4. Discussion

Dendritic cell chemotaxis is crucial to adaptive immunity and our understanding of this process remains limited. One major hurdle for understanding this process is the lack of experimental assays that allow monitoring of dendritic cell chemotaxis in real time. Most of these assays quantify the number of dendritic cells migrated to the chemokine source.^{3,14,26} However, they fail to give us information as to how the cells got there. The ability to observe dendritic cells migration in real time gives us the power to not only get information about changes in cell morphology and speeds during migration but also monitor the expression and spatial distribution of several proteins during cell movement. Moreover, generation of real time data for cell migration is particularly useful for building mathematical models that may provide further insights to dendritic cell migration.

Here, we demonstrate the development of a microfluidic platform that allows us to monitor migration of dendritic cells derived from a myeloid leukemia cell line in a gradient of CCL19 in real time. Our device was able to generate stable chemokine gradients over extended periods of time and mechanically constrain the cells in 3D channels. Furthermore, since the cells occluded the channels they were exposed to distinct environments at the front and back, leading to polar stimulation. We observed clear formation of dendrites at the leading edge of the cells which was absent at the lagging edge since it was not exposed to the chemokine. This is a unique capability different than the existing assays for dendritic cell migration as they lack the control of environment at the front and back of the cells.²⁷ Hence, these controlled morphology changes cannot be observed in real time. This is extremely

useful because this device gives us the power of identifying different proteins acting at the leading and lagging edge of the cell through immune-staining.

One novel design in our microdevice is the introduction of a neck in the transversal channels. This allowed the mature dendritic cells that are much bigger in size than their precursors to get mechanically constrained during cell loading. Since mature dendritic cells cannot be cultured most protocols involve differentiating them from their precursors isolated from bone marrow,²⁷ blood²⁶ or myeloid leukemia cell lines.²⁴ These protocols always result in a heterogeneous population of cells. For example, our differentiation protocol yielded about 60% of dendritic cells from MUTZ cell precursors (Fig. 2). Since, MUTZ cells are smaller than dendritic cells, the neck in the transversal channels acted as a “sieve” and only entrapped the bigger dendritic cells while letting the smaller MUTZ cells through. Furthermore, on “switching on” the gradient the dendritic cells squeezed through the neck which is a good physical mimic of the chemotactic events *in vivo* where the cells need to crawl and squeeze through narrow interstitial spaces to get to their destinations.

Interestingly, we also observed two different populations of dendritic cells based on their speeds and migration distance. It is not very clear how these two cell populations are formed. One possibility could be that the cells may differ in sizes and since they are made to squeeze through the neck, this difference can determine how fast or slow the cell can move through. However, an analysis of cell sizes of the two populations revealed no difference in cell size (Fig. 5(f)), ruling out this possibility. So it is very likely that these cell populations may be biologically distinct and further experiments are required to characterize these populations. Interestingly, previous studies have reported the presence of distinct mature dendritic cells populations.²⁸ It further suggested that not all mature stages of dendritic cells are destined to migrate to lymphoid organs. Interestingly, our microdevice was able to capture this differential behavior. This is a useful feature of the device because these two populations can be separated based on their migration characteristics and be used for further analysis. Furthermore, analyzing the migration capability of dendritic cells may have important implications in immunotherapy.

In conclusion, we report a novel experimental platform for studying dendritic cell chemotaxis. Our experiments show the utility of microfluidic devices in studying this important process central to the induction and regulation of most adaptive immune responses. The described microfabricated device is unique in its application to the study of dendritic cell chemotaxis. Furthermore, the introduction of the neck in the device allowed us to separate cells based on size. This is useful when cells are generated through an *in vitro* maturation protocol, which invariably results in heterogeneous populations of mature and immature cells. Moreover, the cells need to squeeze through the neck during chemotaxis which is a good physical mimic of chemotactic events *in vivo*, where the cells crawl and squeeze through narrow spaces. Hence, these enabling microfluidic technologies may assist us in understanding several mechanisms of dendritic cell migration which was previously not possible, further revolutionizing the field of dendritic cell chemotaxis and biology.

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Fig. 1. Generation of dendritic cells from MUTZ-3 cell line: (a) Schematic of the *in vitro* protocol for generation of mature dendritic cells; (b) Bright field images of cells during different stages of differentiation. Bar = 100 μ m; (c) Brightfield image of a dendritic cell. Note the dendritic cell like projections. Bar = 20 μ m.

Fig. 2.

Characterization of the generated dendritic cells. Either MUTZ-3 cells (shaded histogram) or mature dendritic cells (open histogram) were labeled with the indicated markers of dendritic cells. The expression was quantified by running the cells through a flowcytometer. The number indicates the percentage of the cells in the population expressing the marker.

Fig. 3. Capturing cells in the microdevice: (a) Scanning Electron Micrograph (SEM) of the microdevice. The microdevice was fabricated as described in Sec. 2; (b) Diagram representing the microdevice. It consists of an array of channels with a neck for capturing the dendritic cells. During cell loading valves, 1 and 4 are opened while valves 2 and 3 are closed. The cells are introduced from the outlet and due to the valves are forced to go through the channels where they are captured. After cell capture, all the valves are opened and the chemoattractant and buffer are introduced at the two inlet channels; (c) Image of a captured dendritic cell at the “neck” of the channel.

Fig. 4.

Generation of stable chemokine gradient in the microdevice. Panel 1 shows the inlet of the device where the buffer and chemokine streams come in contact. Panel 2 shows the array of capillaries where cells are captured and undergo chemotaxis. Fluorescein was added in the chemokine line to visualize the gradient. After cells were captured the chemokine and buffer lines were turned on. Note the no mixing at the inlet and the occlusion of the channels by the cells leading to polar stimulation.

Fig. 5.

Monitoring of dendritic cell migration: (a) Image showing the start point of migration of the cell, with the cell moving upwards. Displacement curves of dendritic cell precursors; (b) and mature dendritic cells (c) and (d). The Y axis is normalized to the maximum distance that the cells can travel which is the distance from the bottom of the neck to the top end of the channel; (e) Average velocity of slow and fast mature dendritic cells. The velocity value was obtained from the slope of the displacement curves. A total of 15 individual cells from 3 independent experiments were used for these experiments ($n = 15$); (f) Average cell diameter of the fast and slow moving populations.

Table 1

Size comparison of MUTZ-3 and MUTZ-3 derived dendritic cells.

Cells	Effective Diameter of Cell (In Microns)
Mutz Cells	8–12
MUTZ-Immature DC	15–25
MUTZ-Mature DC	15–25