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CHEMOKINES

Moving on up

The consensus view of chemotaxis is that immune cells sense concentration differences of a chemoattractant across the cell diameter and thus respond to a spatial gradient. However, new work published in *Immunity* shows that dendritic cells and neutrophils require gradients with globally rising concentrations of CC-chemokine ligand 19 (CCL19) or CXC-chemokine ligand 12 (CXCL12), rather than temporally stable gradients, for persistent directional migration. This suggests that, at least for certain chemoattractants, temporal sensing is an important factor in controlling immune cell migration.

The authors used a previously developed microfluidic platform in which programmable syringe pumps can be used to establish defined 3D soluble gradients of chemokines across a collagen scaffold, with cell migration within the scaffold being assessed by time-lapse microscopy. Bone marrow-derived dendritic cells (BMDCs) exposed to CCL19 in the microfluidic chamber showed directional migration for approximately 30 minutes as the chemokine gradient was becoming established and CCL19 concentrations within the collagen matrix were rising, but this migration was lost once a stable CCL19 gradient had formed. When the CCL19 gradient was established before introducing the BMDCs to the chamber, the duration of directional migration decreased to approximately 10 minutes. There was no loss of BMDC homeostasis, viability or signalling capacity at later time points, so the authors conclude that persistent chemotaxis of BMDCs requires rising concentrations of CCL19 over time. BMDCs exposed to a continuously increasing source concentration of CCL19 migrated towards the source for the entire 1.5 hours of image capture.

> “persistent chemotaxis of BMDCs requires rising concentrations of CCL19 over time”

The requirement for a rising chemokine source could be explained by receptor desensitization, meaning that a stable chemokine gradient would fail to provide a sufficient signal to the cell over time. G protein-coupled receptor kinase 3 (GRK3) is known to be involved in desensitization of CC-chemokine receptor 7 (CCR7), the receptor for CCL19. *Grk3*$^{-/-}$ BMDCs showed persistent migration towards both stable and increasing sources of CCL19, presumably by limiting receptor desensitization. Thus, persistent directional migration of BMDCs in response to CCL19 depends on temporal sensing of an increasing chemokine source that can overcome the effects of receptor desensitization.

To explain how temporal sensing can direct cell migration up a chemokine gradient, the authors propose that polarization of a cell occurs during an initial period of spatial sensing, after which migration driven by temporal sensing occurs along that same orientation. BMDCs were pre-exposed to a homogeneous CCL19 concentration, resulting in a random distribution of cell polarity directions, then exposed to a CCL19 gradient with an increasing source. Whereas wild-type BMDCs maintained persistent migration in the random directions acquired during the pre-exposure period, *Grk3*$^{-/-}$ BMDCs (in which spatial sensing is not limited by receptor desensitization) were able to re-orient to migrate in the direction of the CCL19 source.

In summary, these data suggest a model whereby myeloid cells require temporal sensing of an increasing chemokine source for sustained migration, which could be a mechanism to determine whether an infection or inflammatory response is increasing or resolving. However, further studies showing that the requirement for temporal sensing differs between ‘intermediate’ chemoattractants (such as CCL19 and CXCL12) and end agonists (such as C5a) suggest that the nature of the chemoattractant signal is an important factor in determining the mode of migration.

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ORIGINAL ARTICLE Petrie Aronin, C. E. *et al.* Migrating myeloid cells sense temporal dynamics of chemoattractant concentrations. *Immunity* **47**, 862–874 (2017)