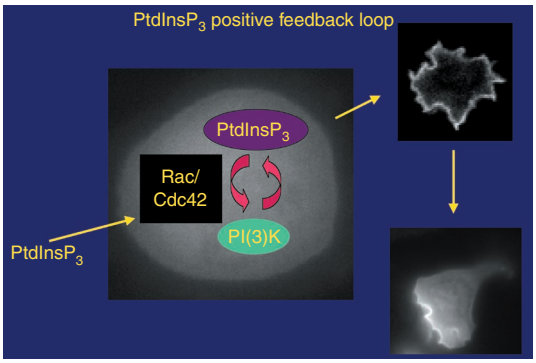
Leading the way

The ability to chemotax, that is, to sense and move in the direction of chemical signals, is a feature of a wide variety of eukaryotic cells. Chemotaxis is important for many biological responses, from the movement of leukocytes towards sites of infection or inflammation to the aggregation of *Dictyostelium discoideum* amoebae to form a multicellular organism. Recent work has firmly established the importance of the phosphatidylinositol 3-OH kinase (PI(3)K) pathway in mediating directional movement in response to chemoattractants. Insight into the mechanism that translates a shallow gradient of chemoattractant into cytoskeletal polarization and directional movement first came from work using *Dictyostelium* cells, and subsequently from studies with leukocytes and fibroblasts. These studies identified the importance of localized signalling by demonstrating that green fluorescent protein (GFP) fusions of a subfamily of pleckstrin homology (PH) domain-containing proteins, which specifically bind to the phosphoinositide products of PI(3)K, preferentially localized to the leading edge of chemotaxing cells. These findings strongly suggested that PI(3)K functions at the leading edge of the cell to mediate directional movement by using its products PtdIns(3,4,5)P_3 and PtdIns(3,4)P_2 as second messengers.

Two manuscripts in this issue of *Nature Cell Biology* (Wang, F. *et al. Nature Cell Biol* **4**, XXX–XXX (2002) and Weiner, R. *et al. Nature Cell Biol* **4**, XXX–XXX (2002)) report positive feedback loops in neutrophils that could provide the amplification mechanisms necessary for the conversion of a shallow extracellular gradient of chemoattractant into a steep intracellular second messenger gradient. In neutrophils, uniform stimulation with chemoattractant eventually results in spontaneous polarization. Wang *et al.* demonstrate that a membrane-permeable PtdIns(3,4,5)P_3 complex can elicit the same response. Using a pharmacological approach, the authors go on to show that this response is dependent on endogenous PI(3)K activity and requires a Rho family GTPase activity. Their studies suggest a model for chemotaxis in which a directional chemoattractant signal results in a small initial activation of PI(3)K, triggering a Rho GTPase-dependent feedback loop that amplifies the signal, contributing to the observed steep intracellular PtdIns(3,4,5)P_3 gradient.

Weiner *et al.* provide further evidence that inhibition of PI(3)K activity impairs the ability to maintain stable pseudopodia, resulting in poor chemotactic fidelity. In addition, the authors provide compelling evidence that actin polymerization at the leading edge, which drives pseudopod extension and



occurs downstream of PtdIns(3,4,5)P_3 accumulation, is in turn necessary for the maintenance of the localized accumulation of PtdIns(3,4,5)P_3 at the leading edge. Actin dynamics as part of a positive feedback loop may provide neutrophils with the ability to spontaneously polarize in response to an initially diffuse stimulus and start moving, only later homing in on their target. Thus, the amplification of the response to a chemoattractant gradient by the combination of Rho GTPase and actin feedback loops provides an attractive mechanism for how an initial small response results in strong cell polarization and persistent chemoattractant movement. What is unknown in this model are the mechanisms positioning the initial response that result in the first accumulation of PtdIns(3,4,5)P_3 at the site of the cell closest to the chemoattractant source. Future studies to define the biochemistry of this step, as well as to flesh out the feedback loops outlined in these two papers, are necessary to understand how cells sense and respond to directional signals.

RUEDI MEILI AND RICHARD A. FIRTEL

[AU: Please include the full address of both authors and an e-mail address for correspondence.]