

Charest, P.G. and R.A. Firtel (2006). Feedback signaling controls leading-edge formation during chemotaxis. *Curr. Opin. Genet. Devel.* 16:339-347.

Chemotactic cells translate shallow chemoattractant gradients into a highly polarized intracellular response that includes the localized production of PI(3,4,5)P<sub>3</sub> on the side of the cell facing the highest chemoattractant concentration. Research over the past decade began to uncover the molecular mechanisms involved in this localized signal amplification controlling the leading edge of chemotaxing cells. These mechanisms have been shown to involve multiple positive feedback loops, in which the PI(3,4,5)P<sub>3</sub> signal amplifies itself independently of the original stimulus, as well as inhibitory signals that restrict PI(3,4,5)P<sub>3</sub> to the leading edge, thereby creating a steep intracellular PI(3,4,5)P<sub>3</sub> gradient. Molecules involved in positive feedback signaling at the leading edge include the small G-proteins Rac and Ras, phosphatidylinositol-3 kinase and F-actin, as part of interlinked feedback loops that lead to a robust production of PI(3,4,5)P<sub>3</sub>.