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Synthetic spatially graded Rac activation drives directed cell polarization and locomotion

Benjamin Lin, William R. Holmes, ChiaoChun Wang, Tasuku Ueno, Andrew Harwell, Leah Edelstein-Keshet, Takanari Inoue, Andre Levchenko and

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Migrating cells possess intracellular gradients of Rho GTPases, but it is unknown whether these shallow gradients themselves can induce motility. Here we describe a new method to present cells with induced linear gradients of active, endogenous Rac without receptor activation. Gradients as low as 15% were sufficient to not only trigger cell migration up the synthetic gradient, but also to induce both cell polarization and repolarization. Response kinetics were inversely proportional to Rac gradient values, in agreement with a new mathematical model, suggesting a role for natural input gradient amplification upstream of Rac. Increases in Rac levels beyond a well-defined threshold dramatically augmented polarization and decreased sensitivity to the gradient value. The threshold was governed by initial cell polarity and PI3K activity, supporting a role for both in defining responsiveness to natural or synthetic Rac activation. Our methodology suggests a general way to investigate processes regulated by intracellular signaling gradients.

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