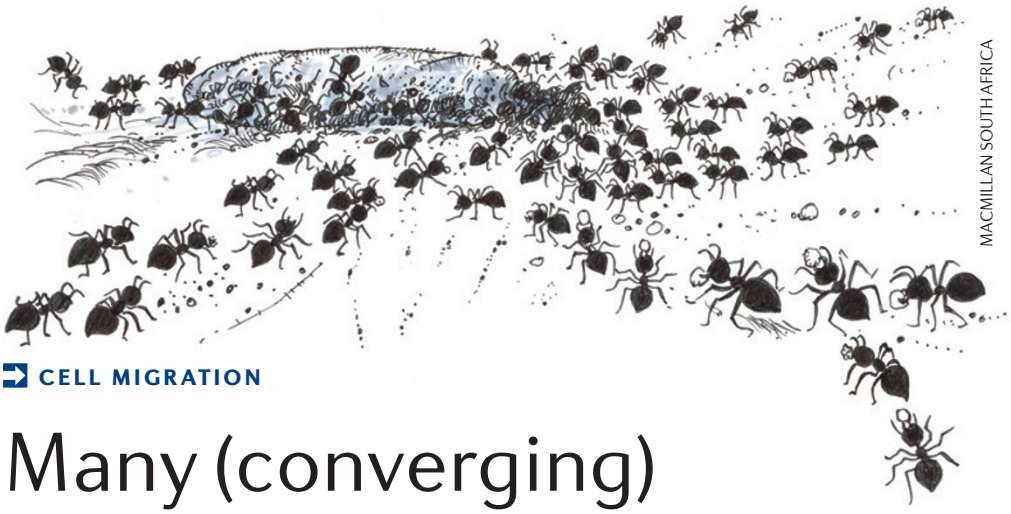

MACMILLAN SOUTH AFRICA

CELL MIGRATION

Many (converging) pathways, one destination

Elucidating how the ever-increasing number of pathways that reportedly affect cell migration are spatially and temporally regulated to influence the molecular migration machinery is a challenge. For example, how does RALB signalling to the exocyst complex, which controls secretory vesicle trafficking, regulate cell motility? Mechanisms that are likely to contribute to migration have been described, but Parrini *et al.* now report a direct link between the RALB–exocyst pathway and the small GTPase RAC1.

A yeast two-hybrid screen had previously indicated binding between the exocyst and SH3 domain-binding protein 1 (SH3BP1; also known as SH3BGRL3), a RHO-specific GTPase-activating protein (GAP). This was confirmed by Parrini *et al.*, who also established the importance of the SH3BP1 Bin–amphiphysin–Rvs (BAR) domain for the interaction. They then showed, using RNA interference, that the exocyst complex and SH3BP1 are mutually dependent on each other for localization at the leading edge of migrating cells.

So, the absence of exocyst compromises SH3BP1 recruitment to the leading edge, but how might it affect cell behaviour? SH3BP1-deficient cells showed reduced migration in wound healing and Boyden chamber assays, and both the BAR domain and a functional GAP domain were required to restore normal motility.

To identify the physiological RHO GTPase target of SH3BP1 in this context, the authors initially assessed CDC42 activity, using reorientation of the microtubule-organizing centre (MTOC) in front of the nucleus as a marker of cell polarization. Depletion of SH3BP1, RALB or the exocyst components did not affect MTOC reorientation, leaving RAC1 as the probable target, as a previous study had demonstrated that SH3BP1 shows no GAP activity towards RHOA. Parrini *et al.* confirmed this by monitoring the spatiotemporal activation of RAC1 following SH3BP1 silencing in motile cells: global levels of active RAC1 were not significantly affected by loss of SH3BP1, but the gradient of RAC1 activity markedly increased from the nucleus to the leading edge. Re-expressing wild-type, but not GAP-defective, SH3BP1 restored normal spatial RAC1 activity.

Normally, then, SH3BP1 downregulates RAC1 at the leading edge to avoid the occurrence of what the authors describe as 'anarchic protrusions'. Upregulated RAC1 activity at the leading edge in SH3BP1-deficient cells resulted in increased numbers of protrusions that formed more quickly than those of control cells but were less persistent and partially delocalized. Similarly, cells expressing the constitutively active (hydrolysis-deficient) RAC Gly12Val mutant showed unstable membrane dynamics and severe migration defects, indicating that RAC1 inactivation at the leading edge is necessary for cell migration.

On the basis of these findings and what is known about other RAC1 regulators, the authors propose a model for how SH3BP1 links RALB and RAC1 pathways to regulate cell motility. RALB promotes the assembly of the exocyst and its localization at the leading edge, where SH3BP1 is recruited through interactions with certain exocyst subunits; here, SH3BP1 inactivates RAC1, but other guanine nucleotide exchange factors activate it. This RAC1 activation–inactivation cycle, accompanied by its regulation at the spatial and kinetic levels, is essential for driving cell migration.

Katrin Legg, Gateway Assistant Editor,
Cell Migration Gateway

ORIGINAL RESEARCH PAPER Parrini, M. C. *et al.* SH3BP1, an exocyst-associated RhoGAP, inactivates Rac1 at the front to drive cell motility. *Mol. Cell* **42**, 650–661 (2011)