Nature Reviews Molecular Cell Biology | AOP, published online 12 September 2012; doi:10.1038/nrm3438

CYTOSKELETON

Actin regulator substitution

The functions of the actin regulators SCAR (suppressor of cyclic AMP receptor) and Wiskott–Aldrich syndrome protein (WASP) are usually clearly delineated in eukaryotic cells. SCAR regulates actin polymerization in pseudopods, whereas WASP (in mammalian cells the universal homologue is N-WASP) promotes filamentous actin formation, which helps to mediate clathrin-mediated endocytosis. However, SCAR mutants of *Dictyostelium discoideum*, a model organism in which SCAR, its regulatory complex and WASP are conserved and are easily manipulated, migrate fairly normally. Veltman *et al.* now provide an explanation for this puzzle, showing that WASP can substitute for SCAR during cell protrusion and migration.

First, the authors transfected SCAR mutants with fluorescently labelled versions of the actin nucleating ARP2/3 (actin-related protein 2/3) complex and WASP and saw that ARP2/3-positive pseudopods all contained WASP at the leading edge, where SCAR would normally be. Fewer pseudopods were seen in the SCAR mutants, but they behaved normally, and WASP even occurred in patches and caused pseudopod splitting, as does SCAR. However, Veltman *et al.* found that the SCAR regulatory complex was not required to recruit WASP, as pseudopods in mutants lacking each of the SCAR complex subunits still contained colocalized WASP and ARP2/3.

So, how is WASP recruited to the pseudopods? RHO family GTPases activate both SCAR and WASP, whereas the GTPase RAC binds the SCAR regulatory complex and also the WASP CRIB (CDC42- and RAC-interacting and -binding) domain, so the authors focused on RAC as a likely candidate for mediating recruitment of WASP. They found that wild-type SCAR localized to sites of RAC activation around the leading edge of pseudopods and, importantly, that WASP colocalized with active RAC in SCAR mutants. They also observed that the pseudopods in SCAR mutants were enriched for active RAC. Expression of dominant-active RAC1A in cells carrying wild-type SCAR led to recruitment of WASP to the leading edge of pseudopods, whereas expression of dominant-negative RAC1A in SCAR mutants prevented recruitment of WASP and inhibited pseudopod formation.

The authors propose that, in wild-type cells, once recruitment of SCAR to patches of activated RAC has led to pseudopod formation, SCAR negatively regulates RAC1. However, in the absence of SCAR, this negative feedback loop is lost, and the resulting high levels of RAC1 allow recruitment of WASP to substitute for SCAR function.

Ezzie Hutchinson

ORIGINAL RESEARCH PAPER Veltman, D. M. *et al.* SCAR knockouts in *Dictyostelium*: WASP assumes SCAR's position and upstream regulators in pseudopods. *J. Cell Biol.* **198**, 501–508 (2012)