In This Issue

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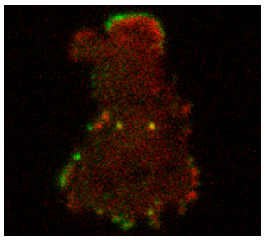
WASP takes the sting out of SCAR mutants



WASP (green) colocalizes with the Arp2/3 complex (red) at the leading edge of a SCAR knockout cell.

Veltman et al. reveal how one actin regulator can fill in for another to maintain cell protrusion and migration.

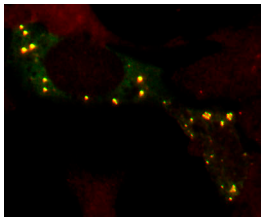
The Arp2/3 complex stimulates actin assembly at several different sites within the cell. WASP family proteins activate the complex at clathrin-coated pits undergoing endocytosis, whereas SCAR/WAVE proteins stimulate Arp2/3's activity at the leading edge to promote membrane protrusion and cell migration. Yet SCAR-deficient *Dictyostelium* cells still form protrusive pseudopods and migrate efficiently toward a chemoattractant. Veltman et al. wondered whether WASP might assume the responsibility of regulating cell protrusion in *Dictyostelium* cells lacking SCAR.

Sure enough, though WASP never localized to pseudopods in wild-type cells, the protein redeployed to the leading edge of SCAR knockouts, where it colocalized with the Arp2/3 complex. SCAR is usually recruited and activated by a quartet of regulatory proteins, but WASP didn't require any of these factors to localize to pseudopods. Instead, WASP was recruited to the leading edge by the Rac GTPase, a key regulator of cell migration that activates SCAR in wild-type protrusions. Rac was more active in SCAR knockouts, suggesting that SCAR usually induces a negative feedback loop to restrict Rac activity. In the absence of SCAR, Rac activity rises to the point that it can recruit WASP as a substitute activator of Arp2/3 and membrane protrusion.

Actin regulatory pathways therefore aren't as separate as previously thought. Author Robert Insall now wants to investigate what other upstream signals regulate SCAR or, if necessary, WASP to successfully guide *Dictyostelium* chemotaxis.

Veltman, D.M., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201205058.

GW220 seals the fate of mRNAs



GW220 (red) colocalizes with an miRNA-targeted mRNA (green) in cytoplasmic GW/P bodies.

Castilla-Llorente et al. identify a protein that determines the localization and fate of miRNA-targeted mRNAs.

miRNAs silence their target mRNAs by incorporating them into silencing complexes (miRISCs) that contain members of the Argonaute and GW families of proteins. Once inside an miRISC, an mRNA can be translationally repressed or permanently degraded, but how these alternative fates are coordinated is unclear. Castilla-Llorente et al. shed light on this question when they identified a unique GW protein splice variant called GW220.

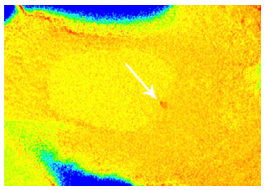
GW proteins have been associated with the formation of cytoplasmic ribonucleoprotein granules called P bodies, but Castilla-Llorente et al. found that not all P bodies contain GW proteins. Instead, GW220 localized to a distinct class of P bodies that also contained Argonaute proteins and miRNA-targeted mRNAs. These "GW/P bodies" were much more stable than other P bodies, suggesting that they might have a role in mRNA storage.

Overexpressing GW220 promoted GW/P body aggregation, whereas GW220 depletion reduced the formation of these granules. miRNAs suppressed protein expression in cells containing numerous GW/P bodies, but the target mRNA itself was fairly stable. In cells lacking GW/P bodies, however, miRNAs induced degradation of their target mRNAs.

GW220 therefore directs silenced mRNAs into GW/P bodies, where they are translationally repressed but protected from degradation. Senior author Jidong Liu now wants to identify additional RNA and protein components of GW/P bodies in order to determine the factors that regulate their formation and to establish which endogenous mRNAs are silenced within these granules.

Castilla-Llorente, V., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201201153.

Centrosomes are PKA's sensitive spot



A biosensor reveals that, despite lower local cAMP levels, PKA is more active at the centrosome (arrow) than in the surrounding cytosol.

Terrin et al. describe how protein kinase A (PKA) is uniquely regulated at the centrosome to control progression through the cell cycle.

The second messenger cAMP activates PKA to control a wide variety of cellular processes. PKA localizes to different parts of the cell by binding to A kinase–anchoring proteins like AKAP450, which recruits PKA to the centrosome. To investigate the function of centrosomal PKA, Terrin et al. developed a series of biosensors to monitor both cAMP levels and PKA activity at the centrosome.

In interphase cells, cAMP levels were lower around the centrosome than in the rest of the cytosol because AKAP450 also binds the cAMP-degrading phosphodiesterase PDE4D3. Surprisingly, however, PKA was more active at the centrosome. Terrin et al. found that binding to AKAP450 causes PKA to phosphorylate itself, raising the kinase's sensitivity to cAMP.

Centrosomal cAMP levels and PKA activity increased during mitosis, possibly because PDE4D3 can be phosphorylated and inhibited by MAP kinases. To determine whether this local regulation of PKA is important for cell cycle progression, Terrin et al. displaced PDE4D3 from centrosomes to raise centrosomal cAMP levels throughout the cell cycle. Cells accumulated in prophase, indicating that cell division is specifically regulated by centrosomal PKA activity.

Senior author Manuela Zaccolo says that centrosomal PKA's heightened sensitivity to lower cAMP levels may allow this population of the kinase to control the cell cycle independently of global changes in cAMP induced by extracellular signals. She now wants to investigate how centrosomal PKA arrests cells in prophase.

Terrin, A., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201201059.