R
teroyine kinases (RTKs) that are bound to
appropriate growth factors activate PI3K, which initiates
Rac-induced cytoskeletal alterations. The signaling steps
between PI3K and Rac are uncovered on page 17 in an
article by Innocenti et al. that reveals the importance of complexes
in activating guanine nucleotide exchange factors (GEFs).

Genetic evidence has supported the
involvement of the GEF SOS-1 for
stimulating Rac activity in response to
growth factors. SOS-1 is found in complex
with Abi1 and Eps8, and interference
with any of these proteins is known to
block actin remodeling in response to
RTK activation. Innocenti et al. now
show biochemically that SOS-1 is
indeed the GEF that activates Rac in
response to PI3K.

Full GEF activation was a stepwise process. The physical
presence of PI3K itself stimulated low levels of the SOS-1 GEF
activity, perhaps by inducing a conformational change in SOS-1.
PI3K gets to the SOS-1 complex through Abi1. PI3K bound to
Abi1 in vitro and colocalized with Abi1 and Eps8 in PDGF-
induced membrane ruffles.

PI3K, the product of PI3K, further stimulated the basal SOS-1 GEF activity. Thus, strong GEF activity would be unleashed
only by activation of PI3K by growth factor-stimulated RTKs.
As expected, inhibition of SOS-1 GEF activity by interfering
with the interaction of PI3K and Abi1 blocked PDGF-induced
membrane ruffling. The assembly of the tetrameric complex
therefore allows for a number of biological consequences
important for growth factor responses, including two levels of
SOS-1 activation and the recruitment of both PI3K and PI3K to
sites where they are most needed for actin reorganization.

The complex life of a GEF

GF Sos-1

FRET-ing over scaffolds

Opposites really do attract. Results on
page 101 by Oliveria et al. show
that, although they perform opposing
functions, a kinase and a phosphatase
linked to synaptic plasticity are close
neighbors at the plasma membrane. The
two are brought together by the scaffolding
protein AKAP79 into a complex that may
be important for efficient learning.

The close proximity of the three proteins
is uncovered by a powerful microscopy
technique, fluorescence resonance energy
transfer (FRET). Using this technique in COS
cells, the group shows that protein kinase
A (PKA) and the phosphatase calcineurin
(CaN) bind to sites on membrane-targeted
AKAP79 that are spaced only nanometers
apart. In neurons, AKAP79 is known to
associate with SAP97, a scaffolding protein that links the signaling
complex to glutamate receptors. Now, using standard immuno-
fluorescence techniques, the authors show that expression of
SAP97 in COS cells brings a complex of PKA-AKAP-CaN and
SAP97 to the plasma membrane.

This complex may also be assembled at synapses in
neurons, indicating that scaffolds coordinate colocalization
of proteins that do not necessarily interact, but rather regulate
common downstream targets—in this case, glutamate receptors.
The proximity of the proteins—not necessarily to each other
but to their common target—is expected to regulate signaling
during long-term potentiation or depression by increasing
both efficiency (i.e., cAMP or Ca
2+
) increases will more rapidly
activate PKA or CaN, respectively) and specificity (e.g., only
Ca
2+
increases that occur near the receptors will activate
calcineurin).

RNA travels with ZBP1

On page 77, Farina et al. get a handle on RNA
localization machinery by proving that an RNA-binding
protein is essential for both mRNA transport and cell motility.

The cell motility connection comes about because localization
of the β-actin mRNA to the lamellae is required for cell polarity
and motility in fibroblasts. The new results show that this localization
depends on ZBP1, a protein associated
with cytoplasmic granules that contain
the actin mRNA. ZBP1 bound to the
mRNA through two COOH-terminal
KH domains that were required for granule formation and
attachment to the actin cytoskeleton. NH2-terminal regions
of ZBP1 were necessary for granule localization in the lamellae.

Dominant–negative ZBP1 constructs that mislocalized
actin RNA inhibited fibroblast motility. Since mRNAs for some
actin-associated proteins, such as ARP3, also contain ZBP1-
binding sequences, the authors believe that ZBP1 may link
several messages involved in motility to a transport complex.
But ZBP1 may be more than just a scaffold: a ZBP1 homologue has been
linked to translational repression of the insulin-related growth factor. Perhaps
ZBP1 also ensures that the actin mRNA
is not translated until it reaches its
ultimate destination.

The group plans to purify ZBP1-
associated proteins in the complex to identify the motor
responsible for actin-based transport. ZBP1 is also known to
be associated with microtubules in neurons, so it may connect
to different motors depending on the cell type.