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LIPIDS

Cofilin set free

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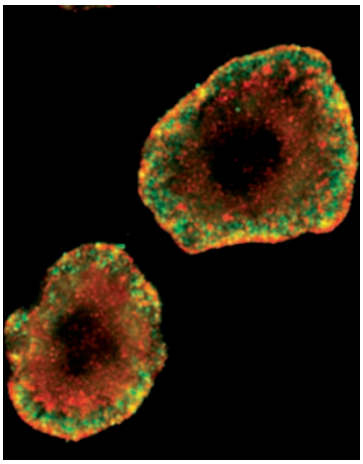
Epidermal growth factor (EGF) stimulates both chemotaxis and the metastatic activity of mammary carcinoma cells. It regulates actin polymerization and promotes cellular protrusion by activating cofilin — an effect known to require phospholipase C (PLC). In the *Journal of Cell Biology*, Jacco van Rheenen *et al*. now report that in rat MTLn3 carcinoma cells, cofilin is activated by its release from the plasma membrane as a result of reduced levels of phosphatidylinositol-4,5-bisphosphate ($PtdIns(4,5)P_2$).

> “…cofilin is activated by its release from the plasma membrane as a result of reduced levels of phosphatidylinositol-4,5-bisphosphate…”



$PtdIns(4,5)P_2$ (green) and cofilin (red) are associated *in vivo* in a compartment at the plasma membrane that releases active cofilin in response to stimulation of EGF receptors.

Using a fluorescence resonance energy transfer (FRET)-based $PtdIns(4,5)P_2$ assay, the authors first showed that EGF stimulation led to an increase in cell protrusion, which was accompanied by a substantial drop in $PtdIns(4,5)P_2$ levels. Both cell protrusion and $PtdIns(4,5)P_2$ hydrolysis were blocked on PLC inhibition, suggesting that EGF-induced protrusion may result from PLC-catalysed hydrolysis of $PtdIns(4,5)P_2$.

The authors found that non-phosphorylated cofilin colocalized with $PtdIns(4,5)P_2$ at the plasma membrane in fixed cells, but that following a reduction in $PtdIns(4,5)P_2$ levels, cofilin became activated and enriched at the leading edge of newly formed lamellipodia. When PLC activity was blocked, EGF was unable to induce the drop in $PtdIns(4,5)P_2$ levels and cofilin remained at the plasma membrane. These data suggest that non-phosphorylated cofilin is sequestered and inactivated at the plasma membrane by $PtdIns(4,5)P_2$, and that EGF-induced $PtdIns(4,5)P_2$ hydrolysis causes the release and activation of cofilin, which then translocates to the filamentous (F)-actin compartment.

Using fluorescence imaging approaches, the authors observed the rapid translocation of cofilin from the plasma membrane that was dependent on PLC-mediated $PtdIns(4,5)P_2$ hydrolysis. Cofilin was also released from the membrane on PLC-independent $PtdIns(4,5)P_2$ reduction.

They further showed that endogenous cofilin binds to actin filaments shortly after EGF stimulation in fixed MTLn3 cells. Binding was reduced on PLC inhibition, indicating that F-actin-bound cofilin originated from the plasma membrane. Local application of EGF resulted in a local translocation of cofilin from the plasma membrane compartment to the F-actin compartment. Finally, the authors found that the actin-severing activity of cofilin increased after EGF treatment or $PtdIns(4,5)P_2$ reduction.

Taken together, this work provides the first *in vivo* evidence that cofilin is locally activated on release from the plasma membrane as a result of a reduction in $PtdIns(4,5)P_2$ levels. Free active non-phosphorylated cofilin can then rapidly translocate to the cell front where it binds and severs F-actin to promote cell protrusion.

Kim Baumann, Editor,
Cell Migration Gateway

ORIGINAL RESEARCH PAPER van Rheenen, J. *et al*. EGF-induced PIP2 hydrolysis releases and activates cofilin locally in carcinoma cells. *J. Cell Biol.* **179**, 1247–1259 (2007)

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