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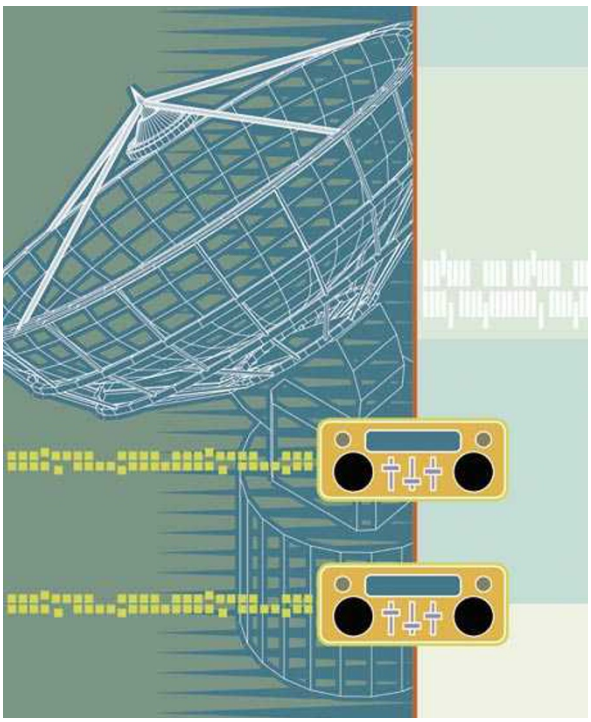
MEMBRANE TRAFFICKING

Endurance of the weakest signal

> …how weak signals can be transmitted effectively to the nucleus…

MET, the Tyr kinase receptor of hepatocyte growth factor (HGF), activates diverse signalling pathways, including AKT/protein kinase B (PKB), extracellular signal-regulated kinase (ERK), Rac and signal transducer and activator of transcription-3 (STAT3). But how are these different downstream pathways specifically regulated and coordinated? Reporting in *Journal of Cell Biology*, Stephanie Kermorgant and Peter Parker describe an unexpected link between the strength of the signalling response and the trafficking of the receptor and downstream signalling components.

CORBIS



STAT3 is thought to be phosphorylated (and subsequently activated) downstream of activated receptors at the plasma membrane. Activated STAT3 translocates to the nucleus, where it controls gene expression. Indeed, this is the case for the robust activation of STAT3 by the cytokine oncostatin M. By contrast, MET induces weak STAT3 activation. So, how can a weak STAT3 signal make it to the nucleus? Looking at live cells, the authors found that HGF stimulation caused MET and STAT3 to colocalize on endosomes at the perinuclear region, where STAT3 was phosphorylated.

Blocking microtubule trafficking of endosomes prevented phosphorylated STAT3 from accumulating in the nucleus, but it did not affect ERK1/2 nuclear translocation (which is indicative of signal specificity) or oncostatin-M-mediated STAT3 nuclear accumulation. These findings indicate that a strong STAT3 signal proceeds through cytosolic diffusion, whereas a weak signal (as seen in this study) for MET requires microtubule-dependent perinuclear accumulation of the activated receptor. In this manner, MET ensures that its weak STAT3 output is protected from the inactivating phosphatases that stand between the plasma membrane and the nucleus. In agreement with this hypothesis, endosome trafficking is not required in the presence of a phosphatase inhibitor.

This study elegantly highlights how weak signals can be transmitted effectively to the nucleus by exploiting endosomal compartments. Whether this strategy is also used by other receptors remains to be seen.

Ekat Kritikou

ORIGINAL RESEARCH PAPER Kermorgant, S. & Parker, P. J. Receptor trafficking controls weak signal delivery: a strategy used by c-Met for STAT3 nuclear accumulation. *J. Cell Biol.* **182**, 855-863 (2008)

FURTHER READING McShane, M. P.& Zerial, M. Survival of the weakest: signaling aided by endosomes. *J. Cell Biol.* **182**, 823-825 (2008)

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