When c-Met can’t shout, it moves closer to get its signal heard, according to Kermorgant and Parker. c-Met is the plasma membrane receptor for hepatocyte growth factor (HGF), and signals by phosphorylating the transcription factor STAT3. But it’s a weak activator of STAT3, and STAT3 faces a gauntlet of inactivating phosphatases that stand between the plasma membrane and the nucleus. This suggested to the authors that c-Met may not rely on long-distance diffusion of STAT3 to get its message across.

Looking at live cells, the team found that HGF stimulation caused c-Met and STAT3 to colocalize on endosomes at the periphery, where STAT3 became phosphorylated. But blocking microtubule trafficking of endosomes prevented active STAT3 from accumulating in the nucleus, confirming that diffusion was insufficient to get it there, and that its transport within endosomes, along with c-Met, was needed to deliver the signal. Not surprisingly, endosome trafficking was not required if the gauntlet of phosphatases was inactivated.

“Information flow from receptors is not simply a switch thrown at the cell surface,” says PI Peter Parker. “The spatial distribution of signaling components is important, and a Western blot doesn’t necessarily tell you much about what the pathway is doing in the cell.” Although strong signal activators may be able to rely on peripheral signaling alone to get their message across, Parker suggests, for weaker ones, where they signal from may determine whether they are heard at all.

SRC1, central to the nuclear periphery
In yeast a handful of transcription-coupled export (TREX) factors, which package nascent mRNAs and eject them from the nucleus, have been identified. But Grund et al. were on the search for more. Grund et al. discovered SRC1’s potential role in the TREX pathway by showing that it could compensate for the lack of certain TREX factors in yeast. Because little was known about SRC1, the next step was to remove it from yeast to see how it affected transcription. Only a small number of genes were misregulated, but interestingly these were skewed toward genes residing near telomeres. Members of the PHO family of genes, for example, which are located in subtelomeric regions, were up-regulated in the Src1 mutant strain.

Chromatin immunoprecipitation showed that the SRC1 protein was enriched at telomeres and subtelomeres. Analysis of the structure and localization of SRC1 showed that it was an integral membrane protein that appeared to be specifically embedded in the inner nuclear membrane. It was possible that by interacting with both telomeres and inner nuclear membrane, SRC1 might bring genes, such as the PHO family, into the proximity of transcription repressors at the periphery—a region previously considered a site of silencing. Without SRC1, however, the active PHO genes remained at the nuclear periphery.

Exactly how SRC1 might repress PHO genes is thus so far unclear. And exactly why a potential TREX pathway factor would be working as a transcription repressor is also unclear. Although the periphery was historically considered as a site of silencing, recently it has been found that certain genes relocate there for activation, and it is thought that patches of inactive heterochromatin (such as telomeres) alternate with active chromatin near the nuclear pores (for easy mRNA export). The authors propose that SRC1 might somehow act at the interface between the two.