BRANDX

A new MAP for miRNAs

Mature microRNAs (miRNAs) result from the cleavage of precursor miRNAs by the miRNA-generating complex, which in humans consists of Dicer and the HIV TAR RNA-binding protein (TRBP). Some mature miRNAs promote cell growth, whereas others suppress it. Qinghua Liu and colleagues now show that the mitogen-activated protein kinase (MAPK) extracellular signal-regulated kinase (ERK) pathway, which promotes growth, phosphorylates TRBP and enhances the capacity for miRNA biogenesis by stabilizing the miRNA-generating complex. Thus, this signalling pathway might regulate the miRNA machinery to achieve its desired biological response.

The authors found that TRBP is phosphorylated on Ser142, Ser152, Ser283 and Ser286. To investigate the function of these phosphorylation events, they generated isogenic cell lines expressing wild-type, phosphomutant or phosphomimic TRBP. Phosphomimic TRBP is expressed at a higher level and is more stable than wild-type or phosphomutant TRBP. Phosphomimic TRBP also enhances the stability of the miRNA-generating complex, which results in a higher level of miRNA-mediated silencing in these cells.

So, what kinase phosphorylates TRBP? Computational analysis of phosphorylated TRBP indicates that it contains amino acid motifs that have the potential to be phosphorylated by MAPK proteins. The ERK signalling pathway involves a cascade of phosphorylation events from a MAPK kinase kinase, to a MAPK kinase (MKK), to the MAPK ERK. Activated ERK then phosphorylates transcription factors that regulate the expression of genes that are important in cell growth and differentiation. The authors show that TRBP and phosphorylated ERK1 and ERK2 interact *in vivo*, and that recombinant MKK1 and ERK2 are required for the phosphorylation of TRBP *in vitro*. Furthermore, treatment of cells stably expressing TRBP with a mitogen that induces ERK activation causes the phosphorylation and accumulation of TRBP, and this is blocked by the MKK1 inhibitor U0126. These data suggest that TRBP is phosphorylated by the MKK1–ERK pathway.

The authors next sought to determine whether MAPK signalling regulates miRNA production to promote cell growth. They carried out miRNA microarray studies of cells expressing phosphomutant or phosphomimic TRBP to assess the effect of TRBP phosphorylation on global miRNA expression. miRNAs associated with growth promotion are among the miRNAs that are upregulated in cells expressing phosphomimic TRBP, but levels of miRNAs associated with growth suppression are lower in these cells. Treatment with mitogens results in similar growth-promoting miRNA profiles and preferentially enhances cell proliferation and survival in wild-type, relative to phosphomutant, TRBP-expressing cells. These findings indicate that ERK-induced phosphorylation of TRBP, and the subsequent alteration in the expression of miRNAs, might actively contribute to the growth-promoting actions of the ERK signalling pathway. Furthermore, as the level of growth-promoting miRNAs decreases (and that of growth-suppressing miRNAs increases) in cancer cell lines treated with U0126, this study might have therapeutic significance.

In short, the authors show that the ERK pathway enhances the stability of the miRNA-processing complex by phosphorylating TRBP and that the consequent reprogramming of miRNA expression might mediate ERK signalling.

Katharine H. Wrighton

> “ERK-induced phosphorylation of TRBP … might actively contribute to the growth-promoting actions of the ERK signalling pathway.”

ORIGINAL RESEARCH PAPER Paroo, Z. *et al.* Phosphorylation of the human microRNA-generating complex mediates MAPK/Erk signaling. *Cell* **139**, 112–122 (2009)
FURTHER READING Kim, V. N. *et al.* Biogenesis of small RNAs in animals. *Nature Rev. Mol. Cell Biol.* **10**, 126–139 (2009)