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IN BRIEF

CELL SIGNALLING

A RAG dissociation inhibitor

Mammalian target of rapamycin complex 1 (mTORC1) couples nutrient availability to cell growth and homeostasis, and its dysregulation is often pathological. Nutrient-sensing RAG GTPases were shown to be crucial for mTORC1 activation, whereas sestrins were implicated as mTORC1 repressors. Peng *et al*. show that sestrins directly interact with RAG GTPases and inhibit RAG-dependent lysosomal translocation of mTORC1. In addition, sestrins prevented RAG·GDP dissociation, which suggests that they function as guanine nucleotide dissociation inhibitors (GDIs) for RAGs. Indeed, a GDI consensus motif was identified in sestrins that is crucial for mTORC1 inhibition. Finally, sestrin-knockout mice were defective in mTORC1 inhibition following prolonged amino acid starvation, indicationg that sestrins regulate RAGs *in vivo*. Thus, inhibiting RAG GTPases is a potential novel therapeutic strategy.

ORIGINAL RESEARCH PAPER Peng, M., Yin, N. & Li, M. O. Sestrins function as guanine nucleotide dissociation inhibitors for Rag GTPases to control mTORC1 signaling. *Cell* **159**, 122–133 (2014)

TECHNOLOGY

RNA targeting by Cas9

Cas9, a component of the genome editing tool CRISPR–Cas9, is a DNA endonuclease. It is targeted by guide RNAs (gRNAs), and its activity depends on recognizing a short sequence known as the protospacer adjacent motif (PAM). O'Connell *et al*. show that Cas9 also targets single-stranded RNA (ssRNA) with high affinity, if PAM-presenting oligonucleotides (PAMmers) are provided. Cleavage experiments *in vitro* revealed that deoxyribonucleotide (but not ribonucleotide)-based PAMmers activated Cas9 to cleave ssRNA, and that this depended on the stability of the PAMmer–ssRNA duplex. Similar to DNA cleavage, ssRNA cleavage by Cas9–gRNAs was specific and programmable. Importantly, incubating dsDNA targets lacking a PAM with PAMmer–ssRNA substrates resulted in the selective cleavage of the ssRNA, demonstrating that when targeting RNA transcripts, genomic loci could be excluded. Tailored RNA recognition and cleavage have immense potential for RNA research and therapeutics.

ORIGINAL RESEARCH PAPER O'Connell M. R. *et al.* Programmable RNA recognition and cleavage by CRISPR/Cas9. *Nature* http://dx.doi.org/10.1038/nature13769 (2014)