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TRANSLATION

DENR–MCT1 reinitiates translation

Translation initiation involves scanning of the 5′ untranslated region (UTR) for initiation codons. In many cases the first initiation codon belongs to an open reading frame (ORF) upstream of the main ORF; the main ORF then requires translation reinitiation by an incompletely understood mechanism. Schleich *et al.* now identify the fly homologues of density-regulated protein (DENR; known as CG9099 in flies) and malignant T cell-amplified sequence 1 (MCT1; known as CG5941 in flies) as the first specific regulators of translation reinitiation in metazoans, and reveal that they co-regulate the translation of a specific set of mRNAs.

The authors generated a fly knockout of the DENR homologue to identify the function of the DENR–MCT1 complex. These knockout flies die as pharate adults owing to the impaired proliferation of histoblast cells. Although the DENR homologue is expressed ubiquitously, its loss had a larger effect on proliferating than on quiescent cells. Moreover, some of the characteristics of *DENR*-homologue-knockout flies were not observed in mutants with generally impaired translation, but were found in flies with reduced levels of cell cycle regulators, which suggests that DENR affects the translation of mRNAs involved in cell proliferation. Similar phenotypes were observed in flies in which the MCT1 homologue was depleted by RNAi.

The profiling of actively translated mRNAs revealed ~100 mRNAs that require the DENR homologue for efficient translation. Analysis of one mRNA that depended particularly strongly on the DENR homologue revealed that its 5′ UTR was sufficient to impart DENR-homologue-translation dependence to a reporter gene. Moreover, three upstream ORFs with strong Kozak sequences (stuORFs) were identified to be necessary and sufficient for DENR-homologue-translation dependence of the main ORF. Together with other experimental analyses, these findings indicate that the DENR homologue promotes translation reinitiation of the main ORFs after translation termination of stuORFs. Introducing synthetic stuORFs into a control reporter gene was sufficient to impart DENR homologue dependence, which was affected by the number and length of upstream ORFs, as well as by their Kozak sequence strength. Additional computational and experimental analyses established that 5′ UTRs with stuORFs are mostly DENR-dependent, thus identifying a new class of translationally co-regulated transcripts.

In summary, the authors found a new translational control system that is dependent on stuORFs and the DENR–MCT1 complex, which is not required for standard initiation, and that regulates the translation of a specific set of mRNAs.

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ORIGINAL RESEARCH PAPER Schleich, S. *et al.* DENR–MCT-1 promotes translation re-initiation downstream of uORFs to control tissue growth. Nature http://dx.doi.org/10.1038/nature13401 (2014)

FURTHER READING Jackson, R. J., Hellen, C. U., Pestova, T. V. *et al.* The mechanism of eukaryotic translation initiation and principles of its regulation. *Nature Rev. Mol. Cell Biol.* **11**, 113–127 (2010)