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DENR-MCT-1 promotes translation reinitiation downstream of uORFs to control tissue growth

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ABSTRACT: During cap-dependent eukaryotic translation initiation, ribosomes scan messenger RNA from the 5' end to the first AUG start codon with favourable sequence context. For many mRNAs this AUG belongs to a short upstream open reading frame (uORF), and translation of the main downstream ORF requires re-initiation, an incompletely understood process. Re-initiation is thought to involve the same factors as standard initiation. It is unknown whether any factors specifically affect translation re-initiation without affecting standard cap-dependent translation. Here we uncover the non-canonical initiation factors density regulated protein (DENR) and multiple copies in T-cell lymphoma-1 (MCT-1; also called MCTS1 in humans) as the first selective regulators of eukaryotic re-initiation. mRNAs containing upstream ORFs with strong Kozak sequences selectively require DENR-MCT-1 for their proper translation, yielding a novel class of mRNAs that can be co-regulated and that is enriched for regulatory proteins such as oncogenic kinases. Collectively, our data reveal that cells have a previously unappreciated translational control system with a key role in supporting proliferation and tissue growth.

STATEMENT: *Eukaryotic mRNAs contain a cap structure at their 5' ends that guides the ribosome to the mRNA. From there, the ribosome translocates towards the 3' end until it encounters an AUG start codon, at which point it initiates translation. However, for many animal mRNAs, the first AUG is located in a short upstream open reading frame (uORF), which means that translation of the main coding region of the mRNA requires a re-initiation event at its AUG. In this study, we have now identified the first factor specific for this re-initiation process. This initiation factor, DENR-MCT-1, allows bypass of some factors required for canonical, cap-dependent initiation. We could demonstrate that many cell proliferation and growth genes that are involved in cancer are dependent on the re-initiation factor for their translation. Our study also reveals for the first time that the DENR-MCT-1 re-initiation factor complex plays a key role in regulation of tissue growth in vivo in animals. Thus, two important implications of this paper are: 1) cells have a previously unappreciated translational control system that can be regulated independently to control the level of synthesis of specific proteins; 2) this system seems to be much more important in proliferative cells, suggesting that it might be an interesting target for cancer therapy. Indeed, work from other groups has already provided evidence that one of the complex components is an oncogene.*

BACKGROUND: The UKE researchers are in the ZMNH Neuronal Translational Control Research Group, led by Dr. Kent Duncan since 2010. The group is interested in how regulated translation contributes to organismal biology in health and disease, with special emphasis on the nervous system. The project was a collaboration with the group of Dr. Aurelio Teleman at the DKFZ, Heidelberg, who co-supervised the interdisciplinary study, and in whose group first author Sibylle Schleich is based. The UKE team was supported in part by the Hans und Ilse Breuer Stiftung and a grant from the Fritz Thyssen Stiftung to Dr. Duncan.