A single target for microRNA regulation

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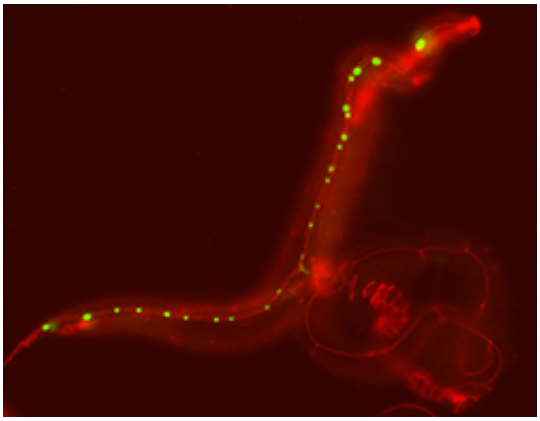

Bursting roundworm. Due to a defect in regulation of the let-7 target lin-41 the worm bursts and dies at the larval to adult transition. Green: seam cell nuclei, red: cell membranes.

It has generally been believed that microRNAs control biological processes by simultaneously, though modestly, repressing a large number of genes. But in a study published in *Developmental Cell*, a group of scientists led by Helge Grosshans have now shown that miRNAs can control the development of a roundworm through regulation of a single target.

The discovery, some 15 years ago, of the small RNA molecule let-7 opened up a whole new field of research. It became apparent that genes in a wide variety of organisms – from roundworms to humans – are regulated by a host of so-called microRNAs (miRNAs). In the development of the roundworm, let-7 plays a key role: if it is defective,

the worm bursts and dies as a result of abnormal development of the sexual organs. Although in the meantime, much has been learned about the molecular mechanisms underlying miRNA function, it remained unclear how this dramatic effect of let-7 was to be explained.

An elegant study by a group led by Helge Grosshans at the FMI has now revealed how let-7 controls normal vulval development in the roundworm. Moreover, by showing that miRNAs can produce significant biological effects through regulation of one single target gene, these findings make a substantial contribution to current theories on the functioning of miRNAs.

It is known that miRNAs can bind many different messenger RNAs (mRNAs), thus repressing protein translation or facilitating mRNA degradation. However, as the effect is usually modest, it was assumed that the biological activity of miRNAs is mediated by coordinated repression of numerous different mRNAs.

The new study demonstrates that the dramatic effect of let-7 is attributable to interaction with lin 41 mRNA alone, although let-7 also regulates other mRNAs. These other interactions are, however, dispensable and inconsequential. Grosshans comments: "The finding that a microRNA can have such a dramatic effect through interaction with a single gene is new. What our study also shows is that it is not enough to measure the interaction of RNA molecules – we need to elucidate how such interactions influence a specific function."

Here, the scientists benefited from a new genome editing technology known as CRISPR-Cas9, which allows base pairs to be replaced in a targeted fashion. As first author Matyas Ecsedi explains, "We were able to modify the binding of let-7 to specific mRNAs and then directly observe what effect this had on the development of the sexual organs." As well as providing new insights into the functioning of miRNAs, this

approach has the potential to advance the safe and effective use of miRNAs for therapeutic purposes.

Evolutionarily conserved: let-7 and LIN-41

The rise of microRNA research was largely due to the fact that let-7 is evolutionarily well conserved – i.e., it occurs in many different animals. It was thus clear that let-7 is not peculiar to the roundworm, but plays a role in various species. Over the years, let-7 was found to be universally important as a regulator of stem cell processes.

LIN-41/TRIM71 likewise occurs in various organisms, assuming a similar function in each case. In stem and progenitor cells, LIN-41 promotes cell division and prevents cell differentiation, while let-7 serves the opposite function and represses LIN-41. As a pair, let-7 and LIN-41 are therefore of great interest in the quest to improve our understanding of stem cell processes.

More information: Ecsedi M, Rausch M, Grosshans H. (2015) "The let-7 microRNA directs vulval development through a single target." *Dev Cell* 32:335-44 dx.doi.org/10.1016/j.devcel.2014.12.018.

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