GENETICS

A new mouse model to study miRNA biology

La Rocca, G., King, B. et al. *eLife* **10**, e70948 (2021)

MicroRNAs (miRNAs) are small molecules of 18–22 nucleotides that repress gene expression through the recruitment of the miRNA-induced silencing complex (miRISC) to target RNAs. miRNAs are abundantly expressed in most tissues, and regulate many, if not all, biological processes. Despite the importance of these regulatory molecules, determining the role of individual miRNAs remains technically challenging.

A new study reports the development of a mouse model to investigate the effects of global inhibition of miRNA function in vivo.

Previous studies have used single-gene knockouts (KO) strategies to determine individual miRNA function, but most KO animals showed no detectable mutant phenotypes, which could be partially explained by the functional redundancy between miRNAs. In other studies, researchers have generated KO models lacking core miRNA biogenesis factors, but other pathways than miRNA biogenesis were

affected in the animals, complicating the analysis of the phenotypes.

Here, the investigators generated a novel mouse strain allowing inducible and reversible global inhibition of miRNA-guided gene silencing. The strategy used to create the mice relies on the inducible expression of a T6B peptide that competes with endogenous trinucleotide repeat-containing gene 6 (TNRC6) proteins, binds to the Argonaute proteins (AGO) and prevents the assembly of a functional miRISC, thereby resulting in effective inhibition of miRISC-mediated gene repression. The model was designed to switch on/off miRNA-mediated gene repression without affecting miRNA biogenesis.

Upon doxycycline administration in adult mice, T6B was strongly expressed across most tissues. Mice remained healthy and appeared normal upon macroscopic examination, which suggests that miRISC function can be suppressed with minimal consequences on tissue homeostasis.

However, in certain tissues such as the colon, miRNA activity appeared essential during regeneration following acute injury. These findings are in line with previous studies where the phenotype caused by targeted deletion of individual miRNAs manifested only after the mutant animals were subjected to stress.

In their report, the researchers explain that the same strategy can be applied to study the effects of acute inhibition of miRISC activity in other organisms such as zebrafish and sea urchin in which, similar to the mouse model, T6B expression in embryos induced developmental defects.

“These findings are not unexpected, yet they highlight the usefulness of the T6B system for dissecting the miRNA pathway in a variety of animal models,” conclude the investigators.

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Published online: 11 October 2021
<https://doi.org/10.1038/s41684-021-00879-9>

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