OUTLOOK

A sense-able microRNA

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In this issue of *Genes & Development*, Drexel and colleagues (pp. 2042–2047) present a beautiful example of how microRNAs (miRNAs) can regulate tissue-specific gene expression in a biologically relevant setting. They found that miR-791 is expressed in only three types of carbon dioxide (CO₂)-sensing neurons in *Caenorhabditis elegans*, and its primary function there seems to be repression of two target genes that interfere with the behavioral response to CO₂. Interestingly, these two targets are broadly expressed across other tissues. Thus, restricted miRNA expression can lead to target repression in select tissues to promote distinct cellular physiologies.

Virtually all cells in a multicellular organism possess the entire genetic code for the organism. However, each cell type expresses only a subset of these genes, allowing different tissues to develop distinct morphologies and physiologies. One way to establish unique gene expression domains is to control activation at the transcriptional level. The decision to turn a gene on or off or tune it to the spectrum in between usually involves a complex assembly of transcription factors and chromatin modifiers that ultimately regulate the ability of a gene to be transcribed into the messenger RNA (mRNA) that will encode the gene product. Alternatively, the mRNA itself can be the target of regulation at the post-transcriptional level. MicroRNAs (miRNAs) bind specific target mRNAs through base-pairing interactions and repress their translation and stability (Pasquinelli 2012). Thus, genes with broad transcriptional domains can be selectively regulated in certain tissues depending on the presence of a targeting miRNA.

The expression pattern of a miRNA can provide important clues toward its function. For example, temporal control of the first discovered miRNAs, *lin-4* and *let-7*, enables them to repress key targets in the developmental timing pathway in *Caenorhabditis elegans* (Bartel 2009). Thus, a potential function for *C. elegans* miR-791 was revealed when Drexel et al. (2016) observed that its expression is restricted to three pairs of neurons involved in sensing carbon dioxide (CO₂) levels (Fig. 1). Normally, high CO₂ levels signal an approaching predator, and

worms respond by moving in the opposite direction (Bretscher et al. 2008; Hallem and Sternberg 2008). This specific behavior was found to depend on miR-791, as deletion mutants have a muted response even though they exhibit no obvious defects in neuronal development or sensing another gas (Drexel et al. 2016). These results suggested that miR-791 activity is dedicated to the regulation of genes that interfere with CO₂ sensation and possibly the avoidance response to it.

Since miRNAs use limited sequence complementarity to recognize their targets, it can be difficult to identify genes directly regulated by a particular miRNA (Pasquinelli 2012). However, a daunting list of predicted targets can be filtered by focusing on genes that might be relevant to a particular pathway. With the knowledge that miR-791 likely regulates genes involved in neuronal signaling, two candidates rose to the top of the target list: AKAP-1 (A kinase anchor protein 1), which acts in subcellular signaling pathways, and CAH-3 (carbonic anhydrase 3), which metabolizes CO₂. Indeed, Drexel et al. (2016) demonstrated that *akap-1* and *cah-3* are the physiologically relevant direct targets of miR-791 in the CO₂-sensing neurons. Remarkably, though, these genes are broadly expressed in worms and seem to function in various pathways (Maeda et al. 2001; Benner et al. 2011). Thus, repression of *akap-1* and *cah-3* is limited to the miR-791-expressing neurons to enable a complex sensory behavior (Fig. 1).

In addition to providing an elegant new example of a miRNA regulatory pathway, the study by Drexel et al. (2016) also puts forth two broader implications for the field. First, miRNAs with identical 5' end sequences comprise families and have been proposed to target the same genes (Bartel 2009). While this may be true in some instances, a role in CO₂ sensing was not detected for miR-790, which is identical to miR-791 at positions 2–10 and is expressed in the same neurons (Drexel et al. 2016). Furthermore, loss of miR-791 alone resulted in misregulation of the *akap-1* and *cah-3* targets and consequent defective avoidance behavior. Thus, in this biological context, the miR-790/791 family members are not redundant. This in vivo example lends credence to recent

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Figure 1. Restricted expression of miR-791 (green) in three sets of CO₂-sensing neurons results in tissue-specific repression of the target genes *akap-1* (*A kinase anchor protein 1*) and *cah-3* (*carbonic anhydrase 3*) (blue) through several complementary sequences in their 3' untranslated regions (UTRs). This regulation allows worms to avoid CO₂ (left), and the behavior is lost in its absence (right).

biochemical studies that have shown specific target-binding activity by distinct miRNA family members (Moore et al. 2015; Broughton et al. 2016). The second implication of this study is that a single miRNA, even a poorly conserved one, can have a function essential to animal survival in the wild. Previously, a broad screen for miRNA function indicated that deletion of individual miRNA genes results in no obvious phenotypes, except in rare cases (Miska et al. 2007). A current perception is that many miRNAs act redundantly or combinatorially to sculpt

gene expression, buffering the loss of individual miRNAs (Miska et al. 2007; Bartel 2009). The study by Drexel et al. (2016) now provides a compelling demonstration that a single miRNA can have a biologically relevant function that may be apparent only in certain contexts. Given the lesson of miR-791, perhaps the idea that miRNAs exert largely redundant fine-tuning functions merits reconsideration.

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