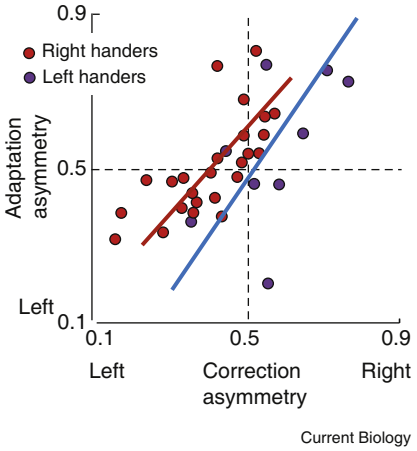

Figure 2. Learning to correct for motor errors.

Across a group of participants, asymmetry of corrections was correlated to the asymmetry of subsequent adaptation, with the non-dominant hand correcting and adapting more. Follow-up experiments demonstrated that this effect was dependent on the recent history of errors — the hand making more errors learns more. (Adapted from [7].)

Finally, White and Diedrichsen [7] addressed two alternative hypotheses to explain all these results. The motor system might bias responsibility for error to the arm for which it has less reliable information about performance. If predictions about the outcome of the dominant hand's action are better, because that hand is more reliable and more skilled, then ambiguous errors might be assigned to the less reliable, less predictable non-dominant hand (Figure 1A). And because prediction errors are an important training signal [9], the non-dominant hand would adapt more readily. Alternatively, the motor system might set the control gain higher for the less accurate hand, so that errors which are more likely to arise for that hand are more effectively corrected.

White and Diedrichsen [7] separated these two hypotheses with an experimental analogue of a gust of wind catching the tennis ball: the visual target, not the cursor, was suddenly shifted at movement onset. Now neither arm was responsible for the error, so inequality in the certainty of the two-state estimates should not result in asymmetric corrections, whereas inequality in control gains should. It turns out that the asymmetry of the responses does appear to be due to differences in control gain. This is a bit counter-intuitive, as much recent theory of motor control has shifted towards a more dominant role for prediction and state estimation [10–12]. However, the change in control gains is selective. Pre-training with target jumps did not affect later responses to cursor rotations, and *vice versa*.

This new paper [7] is neat, and may alter the way neuroscientists think about issues of generalization of skills from one hand to another [13]. It also opens some interesting new questions about neural representations in the motor system. We think the brain includes internal models that capture the response properties of the joints and muscles it controls [14], and probably has different models for different contexts — such as the behaviour of my arm with and without a tennis racquet in my hand. But do these models also code for the reliability of their internal estimates? Is the control gain set by this measure of reliability, so that a bad model has high gain, and must be pulled into line through a series of error corrections? Wolpert and Kawato [15] suggested that multiple internal models contribute to each motor command, combined according to their responsibility for control over the motor context. The model with high responsibility has more control. White and Diedrichsen's [7] results suggest an uncomfortable alternative: the models that are responsible for error, not for control, get the lion's share of the corrective task and of the learning that follows.

References

1. Kording, K.P., and Wolpert, D.M. (2004). Bayesian integration in sensorimotor learning. Nature *427*, 244–247.
2. Todorov, E., and Jordan, M.I. (2002). Optimal feedback control as a theory of motor coordination. Nat. Neurosci. *5*, 1226–1235.
3. Scott, S.H. (2004). Optimal feedback control and the neural basis of volitional motor control. Nature *5*, 534–546.
4. Flash, T., and Hogan, N. (1985). The coordination of arm movements: An experimentally confirmed mathematical model. J. Neurosci. *5*, 1688–1703.
5. Uno, Y., Kawato, M., and Suzuki, R. (1989). Formation and control of optimal trajectories in human multijoint arm movements: Minimum torque-change model. Biol. Cybern. *61*, 89–101.
6. Harris, C.M., and Wolpert, D.M. (1998). Signal-dependent noise determines motor planning. Nature *394*, 780–784.
7. White, O., and Diedrichsen, J. (2010). Responsibility assignment in redundant systems. Curr. Biol. *20*, 1290–1295.
8. Guigon, E., Baraduc, P., and Desmurget, M. (2007). Computational motor control: redundancy and invariance. J. Neurophysiol. *97*, 331–347.
9. Tseng, Y.W., Diedrichsen, J., Krakauer, J.W., Shadmehr, R., and Bastian, A.J. (2007). Sensory prediction errors drive cerebellum-dependent adaptation of reaching. J. Neurophysiol. *98*, 54–62.
10. Molinari, M., Restuccia, D., and Leggio, M.G. (2009). State estimation, response prediction, and cerebellar sensory processing for behavioral control. Cerebellum *8*, 399–402.
11. Miall, R.C., Christensen, L.O., Cain, O., and Stanley, J. (2007). Disruption of state estimation in the human lateral cerebellum. PLoS Biol. *5*, 2733–2744.
12. Frens, M.A., and Donchin, O. (2009). Forward models and state estimation in compensatory eye movements. Front. Cell Neurosci. *3*, 13.
13. Wang, J., and Sainburg, R.L. (2007). The dominant and nondominant arms are specialized for stabilizing different features of task performance. Exp. Brain Res. *178*, 565–570.
14. Miall, R.C., and Wolpert, D.M. (1996). Forward models for physiological motor control. Neural Netw. *9*, 1265–1279.
15. Wolpert, D.M., and Kawato, M. (1998). Multiple paired forward and inverse models for motor control. Neural Netw. *11*, 1317–1329.

School of Psychology, University of Birmingham, Birmingham B15 2TT, UK.
E-mail: r.c.miall@bham.ac.uk

DOI: 10.1016/j.cub.2010.05.030

MicroRNAs: Genetically Sensitized Worms Reveal New Secrets

Why do many microRNA gene mutants display no evident phenotype? Multiply mutant worms that are selectively impaired in genetic regulatory network activities have been used to uncover previously unknown functions for numerous *Caenorhabditis elegans* microRNAs.

Victor Ambros

MicroRNAs are fascinating and still rather mysterious agents of gene regulation in metazoan cells. These small (~22 nucleotide) RNAs regulate the production of specific proteins through base-pairing to messenger

RNAs (mRNAs). The human genome contains several hundred genes for microRNAs, and our favorite experimental stand-in for humans, the nematode *Caenorhabditis elegans*, possesses a hundred-odd microRNA genes, many of which are evolutionarily related to human microRNAs. *C. elegans* has taught us a lot about microRNAs, for example by revealing the first identified microRNAs, the products of the worm *lin-4* and *let-7* genes [1,2]. Loss-of-function mutations in either *lin-4* or *let-7* cause distinct and easily detectable developmental abnormalities in the worm, and so these two microRNA genes were originally identified in screens for visible morphological phenotypes.

However, after the *lin-4* and *let-7* mutant worms revealed the existence of microRNAs, and after additional microRNAs were identified in the worm through cDNA cloning and computational approaches [3,4], *C. elegans* seems to have become more secretive about the functions of its other microRNAs. What happens when one deletes the gene for a worm microRNA other than *lin-4* or *let-7*? Practically nothing. When a set of mutant worm strains were generated, each with a different microRNA gene knocked out, it was discovered that most microRNAs in *C. elegans* are individually dispensable — this is so even for microRNAs that are well conserved evolutionarily [5].

Part of the reason for the apparent irrelevance of an individual microRNA gene is family redundancy. Indeed, the original *let-7* gene belongs to a family of four paralogous genes in *C. elegans* encoding a set of similar microRNAs that function together to repress common target mRNAs. Mutation of any one of the other three of these genes has marginal effects on phenotype, but simultaneous loss of two or more members of the *let-7* family can cause severe defects [6]. This theme of familial redundancy extends to at least three other microRNA gene families in *C. elegans*. As reported in a recent issue of *Current Biology* by Alvarez-Saavedra *et al.* [7], a systematic genetic survey of 15 *C. elegans* microRNA gene families showed that for 3 of these 15 families, simultaneous removal of all members of the family caused pronounced developmental or behavioral phenotypes.

Nevertheless, what about the other 12 families of microRNAs tested by Alvarez-Saavedra *et al.* [7], and the other single microRNA genes that appear to be dispensable to the worm? This question is particularly compelling for the microRNAs in the worm that are evolutionarily conserved in sequence, and hence clearly under strong selection. In an exciting paper in this issue of *Current Biology*, Brenner *et al.* [8] report the results of two innovative genetic strategies that reveal functions in the worm for many of these conserved microRNAs. The Brenner *et al.* study is predicated on the idea that microRNAs can function redundantly with any of a range of other gene regulatory systems. Brenner *et al.* specifically explored the idea that a microRNA can function redundantly with microRNAs of other families or with other gene regulatory processes, particularly chromatin modification and transcriptional regulation.

Brenner *et al.* bring to bear two rather innovative approaches to test these hypotheses. To explore whether microRNAs in *C. elegans* could function redundantly with members of other microRNA families, they tested for synthetic phenotypes caused by combining microRNA gene deletion mutations with a mutation compromising the overall microRNA machinery. Specifically, by deleting one member of two redundant genes for the microRNA Argonaute (ALG-1), leaving the other microRNA Argonaute gene (ALG-2) intact, Brenner *et al.* created a sensitized genetic background with the microRNA machinery partially disabled. By crossing microRNA gene mutations into this *alg-1* mutant background, the authors show developmental phenotypes caused by loss of certain specific microRNAs. Importantly, these phenotypes are manifest only if other microRNAs are partially disabled by the mutant ALG-1. These results indicate that these microRNAs function redundantly with other microRNAs. Together with the results of Alvarez-Saavedra *et al.* [7] showing that many of these same microRNAs are not redundant with members of their own families, these latest results strongly point to important functional interactions between distinct microRNA families in the worm. In these cases, distinct microRNA families may act on distinct mRNA targets in parallel genetic pathways or could act together to redundantly regulate the same targets (Figure 1A).

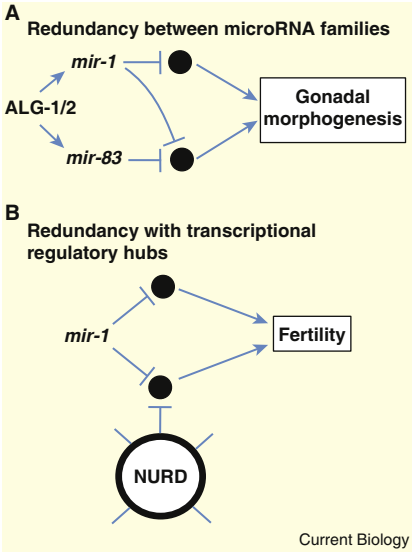

Figure 1. Models for functional redundancy in gene regulatory networks involving microRNAs in *C. elegans*.

Depicted are models for potential gene regulatory network topologies underlying genetic interactions between mutations in microRNA genes and the RISC component ALG-1 (A) or transcriptional regulatory hub genes (B), such as EGL-27, a component of the nucleosome remodeling and histone deacetylation (NURD) complex. These hypothetical network topologies provide explanations for the apparent redundancy observed between pathways revealed by these studies. (A) Mutation of *agl-1* causes a general reduction in microRNA activity, sensitizing the worm to further reduction of any single microRNA among an otherwise redundant set, so that, for example, mutation of either *mir-1* or *mir-83* alone reveals defects in gonadal morphogenesis. In this example, *mir-1* and *mir-83* may regulate separate targets in redundant pathways, or may redundantly regulate the same targets. (B) Similarly, mutation of a transcriptional regulatory hub protein, such as a NURD component, results in general disruption of NURD target gene expression, so that otherwise undetected phenotypes are revealed for mutation of a microRNA functioning redundantly with NURD. In this example, *mir-1* could post-transcriptionally regulate targets in the same pathway as NURD or a parallel pathway.

Interestingly, some microRNA mutations suppressed the developmental timing defects of *alg-1* mutant animals. This suggests that these microRNAs could regulate targets in the developmental timing pathway in a fashion opposite to the *lin-4* or *let-7* family miRNAs (which largely underlie the *alg-1* developmental defects). Brenner *et al.* also suggest the intriguing possibility that suppression of *alg-1* phenotypes by loss of certain microRNAs could reflect a derepression of microRNA targets that are themselves components of the RNA-Induced Silencing Complex (RISC) or RISC modulators, such as NHL-2 [9].

In a parallel set of experiments, Brenner *et al.* [8] employed microRNA mutations in a different sort of genetically sensitized background. In this approach, genetic sensitization was achieved using mutants compromised for a set of core gene regulatory pathways, which the authors refer to as 'hubs' in recognition of their extensive functional interactions across the gamut of cellular processes. The disabled hubs tested here included, notably, components of chromatin modification and transcriptional regulatory complexes. By crossing microRNA gene mutations into these sensitized backgrounds, the authors discovered synthetic phenotypes for particular microRNAs. These results provide key leads into the functions of these microRNAs in essential pathways that also involve 'hub' activities. Interactions with transcriptional and chromatin modification machinery could reflect a convergence on common targets, in this case on both the transcriptional and post-transcriptional levels. For example, some of the microRNAs that genetically interact with the NURD complex may regulate post-transcriptionally sets of mRNAs whose transcription is modulated by the NURD (Figure 1B).

The Brenner *et al.* [8] results will help lay the foundation for the next stage of detailed analysis of microRNA pathways in *C. elegans*. As the authors point out, these novel genetic interactions among microRNAs could point the way to sorting among the dizzying lists of computationally predicted targets for those targets of most impact physiologically. It should be noted that since Brenner *et al.* concentrated on phylogenetically conserved microRNAs for this study, their data will serve as a platform for important genetic analysis of these conserved microRNAs using the powerful *C. elegans* system.

Brenner *et al.* suggest that the apparent pervasive redundancy between microRNA families and between microRNAs and other gene regulatory processes could reflect modes of gene regulatory network organization that have evolved to ensure robustness of gene expression programs against environmental and physiological contingencies.

MicroRNAs may in many situations function to buffer developmental or physiological processes against stresses, and/or to coordinate multiple gene regulatory pathways in the context of variable physiological conditions. Perhaps one reason why it has been difficult to uncover functions for certain microRNAs is that we have not yet learned how to properly query the phenotypes of these other microRNA mutants. More attention to conditions that stress cells could reveal functions for microRNAs in physiological contingencies.

Examples of conditional functions for microRNAs have been demonstrated in several cases. For example, worm mutants lacking the abundant, evolutionarily conserved muscle-specific microRNA *mir-1* exhibit no overt phenotypes. However, if neuromusculature signaling is compromised pharmacologically, a role for *mir-1* in modulating synaptic function was revealed [10]. Similarly, miR-206 knockout mice are normal for the development of neuromuscular synapses, but the mutant mice exhibit accelerated neurodegenerative disease and poor regeneration of neuromuscular synapses after nerve injury [11].

The use of sensitized genetic backgrounds to uncover layers of gene function may be particularly useful in the case of microRNAs, if this class of regulators commonly function in combination with other gene regulatory pathways, as is suggested by the Brenner *et al.* [8] findings. Therefore, for other animals, in addition to *C. elegans*, a useful strategy for exploring microRNA function may be to follow the lead of Brenner *et al.* and screen for phenotypes in the context of genetic- or environmental-sensitizing strategies.

References

1. Lee, R.C., Feinbaum, R.L., and Ambros, V. (1993). The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell *75*, 843–854.
2. Reinhart, B.J., Slack, F.J., Basson, M., Pasquinelli, A.E., Bettinger, J.C., Rougvie, A.E., Horvitz, H.R., and Ruvkun, G. (2000). The 21-nucleotide let-7 RNA regulates developmental timing in Caenorhabditis elegans. Nature *403*, 901–906.
3. Lau, N.C., Lim, L.P., Weinstein, E.G., and Bartel, D.P. (2001). An abundant class of tiny RNAs with probable regulatory roles in Caenorhabditis elegans. Science *294*, 858–862.
4. Lee, R.C., and Ambros, V. (2001). An extensive class of small RNAs in Caenorhabditis elegans. Science *294*, 862–864.
5. Miska, E.A., Alvarez-Saavedra, E., Abbott, A.L., Lau, N.C., Hellman, A.B., McGonagle, S.M., Bartel, D.P., Ambros, V.R., and Horvitz, H.R. (2007). Most Caenorhabditis elegans microRNAs are individually not essential for development or viability. PLoS Genet. *3*, e215.
6. Abbott, A.L., Alvarez-Saavedra, E., Miska, E.A., Lau, N.C., Bartel, D.P., Horvitz, H.R., and Ambros, V. (2005). The let-7 MicroRNA family members mir-48, mir-84, and mir-241 function together to regulate developmental timing in Caenorhabditis elegans. Dev. Cell *9*, 403–414.
7. Alvarez-Saavedra, E., and Horvitz, H.R. (2010). Many families of C. elegans microRNAs are not essential for development or viability. Curr. Biol. *20*, 367–373.
8. Brenner, J.L., Jasiewicz, K.L., Fahley, A.F., Kemp, B.J., and Abbott, A.L. (2010). Loss of individual microRNAs causes mutant phenotypes in sensitized genetic backgrounds in C. elegans. Curr. Biol. *20*, 1321–1325.
9. Hammell, C.M., Lubin, I., Boag, P.R., Blackwell, T.K., and Ambros, V. (2009). nhl-2 modulates microRNA activity in Caenorhabditis elegans. Cell *136*, 926–938.
10. Simon, D.J., Madison, J.M., Conery, A.L., Thompson-Peer, K.L., Soskis, M., Ruvkun, G.B., Kaplan, J.M., and Kim, J.K. (2008). The microRNA miR-1 regulates a MEF-2-dependent retrograde signal at neuromuscular junctions. Cell *133*, 903–915.
11. Williams, A.H., Valdez, G., Moresi, V., Qi, X., McAnally, J., Elliott, J.L., Bassel-Duby, R., Sanes, J.R., and Olson, E.N. (2009). MicroRNA-206 delays ALS progression and promotes regeneration of neuromuscular synapses in mice. Science *326*, 1549–1554.

Department of Molecular Medicine, University of Massachusetts Medical School, 373 Plantation St, Worcester, MA 01605, USA.
E-mail: victor.ambros@umassmed.edu

DOI: 10.1016/j.cub.2010.05.054