Nilsson [6] has referred to eyes such as these as 'burglar alarms'. None of these eyes, including those of chitons, is a 'true' motion detector: that is, they do not compare sequential stimulation across the retina, as in insect or vertebrate eyes. Motion is detected simply as the dimming of one or more receptors, as the image of a dark object moves across the retinal array.

The photoreceptors involved in these unconventional eyes are interesting because they are usually different from those of the eyes borne on the head. Modern ideas about the evolution of photoreceptor types [7] indicate that the early bilaterians had two types of receptor: rhabdomeric receptors based on microvilli which depolarise to light, and ciliary receptors that hyperpolarise when illuminated and respond when darkened. In general the deuterostomes (incuding us and echinoderms) employ ciliary receptors and the protostomes (including molluscs, annelids and arthropods) employ rhabdomeric receptors in their main organs of sight.

In the molluscs, it seems that there are actually plenty of examples of both types of photoreceptor. Gastropod snails generally have a pair of cephalic eyes which direct locomotion. These are either simple pit eyes or have lenses of varying quality, and they invariably have microvillous on-responding receptors. The receptors that respond to shadow and cause withdrawal are not in the cephalic eyes, but located elsewhere on the body. The marine pulmonate slug *Onchidium verruculatum* has two types of eye: conventional cephalic eyes, and about 30 quite different eyes on papillae on its back. The latter have ciliary receptors and respond to shadow and probably movement [8]. The mantle eyes of bivalves are unlike cephalic eyes in optical structure (they tend not to have conventional lens optics), and in function, location and origin. They also typically have ciliary receptors that give off responses — although the opsins involved are not identical to the vertebrate opsins [7]. Chitons, which are only distant relatives of gastropods and bivalves, have no head and no cephalic eyes. The receptors in the dorsal ocelli seem to go against the general trend in that they are rhabdomeric [9], yet mediate shadow responses. This apparent anomaly might be worth another look.

The eyes of modern vertebrates, cephalopods and arthropods, backed up by impressive processing power, must all have originated in organs with a limited range of functions. Did they begin as devices for detecting prey, or predators, or mates, or for finding the right habitat, or for simply not bumping into things? Can the range of still-existing eyes with limited functions tell us much about the route or routes to visual multi-competence that must have occurred several times during the Cambrian and shortly thereafter? My guess is that the molluscan predator detectors were not on that route, but we still have few clues as to what was.

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DOI: 10.1016/j.cub.2011.03.006

Developmental Biology: Small RNAs Play Their Part

What mechanisms coordinate the sequential pattern of gene expression during development of specialized cells? A small RNA-based mechanism is proposed to repress expression of genes during oogenesis.

Eleanor M. Maine

Development of specialized cells typically requires the coordinated expression of genes as cells progress through developmental stages. During oocyte formation, coordinated gene expression allows germ cells to move through the stages of oogenesis and generate the numerous mRNAs and proteins that are stored in the oocyte for later use in the embryo. Various regulatory mechanisms have been implicated in the timely activation and repression of gene expression during germline development. In a recent issue of *Current Biology*, Maniar and Fire [1] provide an intriguing hypothesis for how small RNAs may participate in the coordinated repression of gene expression during *Caenorhabditis elegans* oogenesis.

Many components of the small RNA machinery promote development in plants, fungi, and animals, and it is becoming clear that small RNAs regulate developmental gene expression. In many organisms, RNA-dependent RNA polymerases (RdRPs) generate small RNAs during both RNA interference and normal development [2–8], and mutations in many RdRPs cause developmental defects (e.g., [5,9–15]). Unlike microRNAs, which are encoded by the genome, small RNAs have been particularly challenging to study because they are produced from RNA templates; consequently, it has not been possible to mutate specific small RNAs without also mutating the original, transcribed gene. Nonetheless, an appealing hypothesis, given the pleiotropic RdRP mutant phenotypes and the prevalence of endogenous small RNA sequences, is that these factors participate in mechanisms to limit the expression

of potentially numerous target genes during development.

Now, Maniar and Fire [1] report the identification of small RNA and mRNA populations whose levels are altered in females lacking the RdRP EGO-1. The *ego-1* female germ line has defects throughout germline development, including meiotic progression and oogenesis, that might result from these changes [9,13,14,16]. Using deep sequencing and bioinformatics, the authors identified hundreds of genes whose corresponding small RNAs were reduced, consistent with the more limited data reported by Claycomb *et al.* [15], and infer that the loss of EGO-1 activity leads directly to the absence of these small RNAs. For the majority of these genes, the authors also identify an increase in mRNA level in the *ego-1* mutants. This relationship is exactly what one would expect if the small RNAs participate in a mechanism to repress gene expression during development. The majority of EGO-1-dependent small RNAs include sequences that are antisense to introns, consistent with having been produced from mRNA templates. Interestingly, the fold-increase in mRNA levels varied widely from gene to gene, and the effect was relatively modest in many cases, suggesting that many small RNAs partially repress, but do not eliminate, gene expression.

To better understand how small RNAs function in the germline, Maniar and Fire also investigated the relationship between EGO-1-dependent small RNAs and the activity of several other proteins that have been linked functionally to EGO-1 in genetic and molecular studies. These proteins include: an Argonaute protein, CSR-1; an RNA helicase, DRH-3; and a Tudor domain protein, EKL-1 [4,15,17,18]. Consistent with a previously published report that DRH-3 and EKL-1 activities promote accumulation of a class of small RNA called 22 G RNAs [4], Maniar and Fire observed that the general pool of small RNAs is reduced in *drh-3* and *ekl-1* mutants. Moreover, they found that CSR-1 associates with approximately two-thirds of EGO-1-dependent small RNAs, confirming previous work [15]. Hence, a significant proportion of small RNAs generated by EGO-1 apparently function to recruit CSR-1 to specific targets. The authors also showed that various components of the exogenous RNAi machinery and/or endogenous pathways such as the enhanced RNAi (ERI) pathway are not required for production of EGO-1-dependent small RNAs. These findings fit with the emerging picture of a set of interlocking yet distinct small RNA pathways actively regulating gene expression during development.

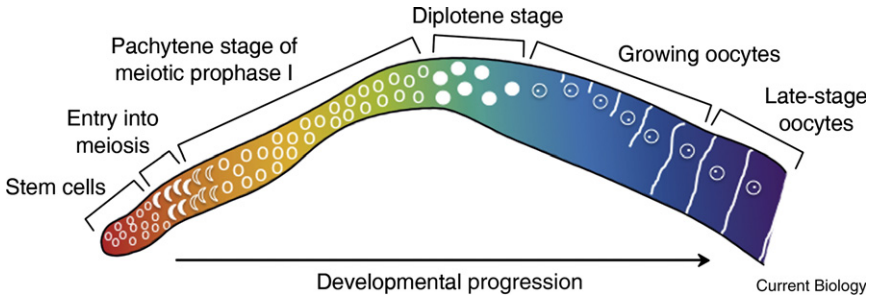

Figure 1. A sequential, tightly regulated pattern of gene expression is required for *C. elegans* oogenesis.

The illustration represents the female germline. Landmark developmental events are indicated schematically, and rising/falling mRNA levels are indicated via colored shading. Multiple mechanisms are known to regulate transcription and translation of genes during *C. elegans* oogenesis. Maniar and Fire propose an additional mechanism wherein EGO-1 RdRP utilizes certain germline mRNAs as templates for the production of small RNAs. Eventually, these small RNAs lead to downregulation of the template mRNAs, presumably as the protein products they encode are no longer required.

How do RdRP-generated small RNAs act to reduce mRNA levels? Many EGO-1 RdRP products span exon–exon splice junctions, indicating they were generated from mRNA templates, and the majority of EGO-1 products are antisense to exon sequences, likewise consistent with having been generated from mRNA templates. It is theoretically possible for many of these small RNAs to target CSR-1 activity to mRNA or primary (chromatin-associated) RNA for degradation and/or to effect transcriptional silencing or chromatin modification. Each mechanism would result in reduced mRNA levels, as observed. Maniar and Fire propose the reduction in mRNA levels could be a mechanism for repressing gene expression during development. As developmentally important genes are activated and their mRNA levels rise, certain mRNAs would trigger biogenesis of small RNAs by EGO-1; these small RNAs would then act together with an Argonaute protein (in many cases, presumably CSR-1) in a negative feedback mechanism to down-regulate mRNA levels (Figure 1). This is an attractive model, especially given the already established importance of translational regulation in the *C. elegans* germ line. Other mechanisms have been defined to regulate the translation of specific mRNAs during germline development. For example, the GLD-1 protein represses translation of numerous mRNAs to promote distinct aspects of germline development, including entry into meiosis, meiotic progression, the sperm-to-oocyte switch, and oogenesis [19]. Perhaps some aspects of the *ego-1* germline phenotype arise due to delayed repression of developmental gene expression, leading to the observed delays in the ability of cells to execute subsequent developmental stages [9].

In the *C. elegans* soma, a small RNA-based, two-step mechanism represses gene expression [5–8]. In this case, distinct RdRPs produce small RNAs from mRNA targets: RRF-3 produces 26 G RNAs required to initiate the process, and RRF-1 produces 22 G RNAs required to accomplish the repression. Interestingly, somatic development is not radically impaired in *rrf-3* and *rrf-1* mutants, suggesting the two-step mechanism may have a relatively small effect on developmental gene expression [12,20]. In the germline, where EGO-1 is responsible for biogenesis of a significant pool of 22 G RNAs [1,4], drastic phenotypic effects are associated with the loss of *ego-1* function [9,13–15]. Maniar and Fire provide evidence that this phenotypic difference between soma and germline may arise because EGO-1 RdRP targets a relatively large set of genes whose products are required for many developmental processes.

Recent analyses of *C. elegans* RdRP function highlight the utility of

combining deep sequencing and bioinformatic approaches with genetic analysis to investigate gene regulatory mechanisms [1,4–8]. By showing that the loss of *ego-1* activity results in over-expression of developmentally important mRNAs, Maniar and Fire provide evidence that small RNAs function to limit mRNA levels in the germ line and also identify candidate mRNAs whose mis-regulation may contribute directly to the *ego-1* mutant phenotype. As deep sequencing technologies continue to be developed in coming years, it seems likely such data will continue to complement genetic approaches to yield major insights into developmental mechanisms.

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DOI: 10.1016/j.cub.2011.03.014

Neural Networks: More about Flexibility Than Synaptic Strength

The leech heartbeat neural network is famous for its constancy in both architecture and functional output across animals. A recent study, however, has found that the synaptic strengths underlying this constancy are quite variable across animals.

Jean-Marc Goaillard

A large body of recent work now argues that there is a great deal of animal-to-animal variation in the biophysical properties that contribute to neural circuit dynamics [1–7]. In a recent study of the central pattern generator (CPG) that controls the leech heartbeat, Norris *et al.* [8] found that precisely predicting the output of a neuron on the basis of the strength of its synaptic inputs is not possible. Their new work suggests that additional, non-synaptic parameters introduce significant animal-to-animal variations in the biophysical solutions underlying physiological output.

The leech hearbeat CPG is composed of seven identified bilateral pairs of heart interneurons (HN1–HN7) located in the first seven rostral segments of the animal projecting onto pairs of motorneurons located in the segments 3 to 18 [9]. The activity of the heartbeat network displays alternatively a synchronous or a peristaltic sequence (the left side being synchronously active when the right side is peristaltically active, and *vice versa*). In the peristaltic sequence, motorneurons are activated in a rear-to-front wave of firing: motorneurons located in caudal segments fire before motorneurons located in more rostral segments (Figure 1A). This wave of activity is determined by the activity of the heart interneurons (the CPG pacemaker), which are themselves activated in a rear-to-front sequence (Figure 1A). Norris *et al.* [8] focused on the activity of the three pairs of motorneurons located in segments 8, 10 and 12. These neurons are interesting because they are solely driven by the activity of the four interneurons HN3, 4, 6 and 7. The activity of each motorneuron (HE8–HE12) is therefore supposedly