in bats flying in their natural habitat. Further, navigation requires more than the hippocampal spatial signal: It also entails decision-making, goal-directed behaviors, sensory-motor integration, and other cognitive processes (mediated by brain structures such as the striatum, cerebellum, and prefrontal and parietal cortices). Thus, to elucidate the neural basis of real-life navigation in bats (27, 29), it would be essential to record neural activity from the hippocampal formation (and additional brain structures) in bats navigating over distances of kilometers.

References and Notes

Developmental Decline in Neuronal Regeneration by the Progressive Change of Two Intrinsic Timers

Yan Zou,* Hui Chiu,# Anna Zinovyeva,** Victor Ambros,† Chiu-Fen Chuang,‡ Chieh Chang††

Like mammalian neurons, Caenorhabditis elegans neurons lose axon regeneration ability as they age, but it is not known why. Here, we report that let-7 contributes to a developmental decline in anterior ventral microtubule (AVM) axon regeneration. In older AVM axons, let-7 inhibits regeneration by down-regulating LIN-41, an important AVM axon regeneration–promoting factor. Whereas let-7 inhibits lin-41 expression in older axons through the lin-41 3′ untranslated region, lin-41 inhibits let-7 expression in younger neurons through Argonaute ALG-1. This reciprocal inhibition ensures that axon regeneration is inhibited only in older neurons. These findings show that a let-7–lin-41 regulatory circuit, which was previously shown to control timing of events in mitotic stem cell lineages, is reutilized in postmitotic neurons to control postdifferentiation events.

We use Caenorhabditis elegans to study developmental decline in neuronal regeneration (Fig. 1A) (1). As in vertebrates, advancing development leads to decreased axon regenerative capacity in C. elegans (Fig. 1C) (2–4). The timing mechanism that controls developmental decline in neuronal regeneration is poorly understood (2–5). Because heterochronic genes are implicated in regulating developmental timing and aging in C. elegans (6), we hypothesized that they might regulate developmental decline in neuronal regeneration. The heterochronic pathway involves a number of microRNA-regulated posttranscriptional genetic circuits (7, 8), including an important interaction between the let-7 microRNA and its direct target, lin-41, which encodes a tripartite motif (TRIM) protein (9, 10). We show here that let-7 and lin-41 function in postmitotic neurons to time their differentiation and postdifferentiation events. Our study reveals that the intrinsic timing mechanism that controls developmental decline in neuronal regeneration depends on the progressive increase of let-7 and the progressive decrease of lin-41 in neurons, with let-7–lin-41 reciprocal inhibition having a role in this process.

MicroRNA expression is either spatially restricted or temporally regulated in neuronal development (11–14). To explore the role of microRNAs in neuronal regeneration, we examined anterior ventral microtubule (AVM) axon regeneration in mutants defective in microRNA biogenesis, dcr-1 and alg-1 (15). Although dcr-1 hypomorphic mutant animals displayed normal AVM axon regeneration (fig. S1A), regenerating AVM neurons of adult alg-1 mutants extended axons 2.5 times the length of those in adult wild-type animals (Fig. 1, B to D). In addition, regenerating axons of alg-1 mutants often displayed compact growth cones (fig. S1C). These regeneration phenotypes in adult alg-1 mutants are reminiscent of those in wild-type animals at an earlier developmental stage (Fig. 1, B to D, and fig. S1), which suggests that alg-1 mutations may retard a normal developmental decline in axon regeneration. Consistent with this conclusion, we observe that, although AVM axon regeneration in alg-1 mutants is similar to that of wild-type animals at the larval L2

1Division of Developmental Biology, Cincinnati Children’s Hospital Research Foundation, Cincinnati, OH 45229, USA.
2RNA Therapeutics Institute and Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, MA 01605, USA.
3Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec H3A 1B1, Canada.
*These authors contributed equally to this work.
†Corresponding author. E-mail: chiez.chang@cchmc.org (C.C.); chiu-fen.chuang@cchmc.org (C.-F.C.)
stage (Fig. 1, C and D), during advanced L3-YA (young adult) stages, AVM axon regeneration is significantly reduced in wild-type animals, but is unchanged in alg-1 mutants until day 4 of the adult stage (Fig. 1, C and D).

We hypothesize that ALG-1-dependent microRNAs are likely to be expressed late to contribute to the observed developmental decline in axon regeneration. Stem-loop reverse transcription polymerase chain reaction (RT-PCR) was used to globally survey mature microRNA expression in C. elegans (Fig. S2A). Among 90 microRNAs surveyed (Fig. S2), we identified 10 late-onset microRNAs whose expression coincides with the developmental decline in axon regeneration (Fig. 2A). Among the 10 late-onset microRNAs identified, only let-7, mir-84, and mir-241 are expressed in AVM neurons (Fig. 2, B to H, and fig. S3A). Out of those, only let-7 maturation is affected in alg-1 mutants (Fig. 2I and fig. S3B).

In our assay using RNA preparations from staged animals, expression of the mature let-7 microRNA is almost undetectable from embryonic to L2 stages and becomes apparent at L3 (Fig. 2A). In let-7(n2853ts) mutants at 20°C, AVM axons regenerated to twice the length of those regenerated in wild-type animals (Fig. 2M), which suggested that let-7 mutations recapitulate the let-7 mutant phenotype in enhancing A VM axon regeneration (Fig. 2M). let-7(n2853ts) likely represents a loss-of-function mutation in A VM at 20°C, because let-7(n2853ts) mutants display a similar degree of AVM axon regeneration at 23°C as at 20°C (average axon regeneration is 105 μm at 23°C and 100 μm at 20°C, P = 0.32). Like alg-1 mutants, let-7(n2853ts) animals also display a retarded developmental decline in AVM axon regeneration (fig. S4, A and B). Regenerating AVM neurons in let-7(n2853ts) mutants not only extended longer axons, they also frequently displayed compact growth cones (fig. S1D), a phenotype shared by alg-1 mutants (fig. S1C). Some regenerating axons in alg-1 mutants only stop outgrowth as they are about to enter the nerve ring (Fig. 2L). The effect of let-7 mutations on AVM axon regeneration appears to be cell autonomous, as expression of let-7 in A VM significantly rescues the let-7 mutant phenotype of enhancing A VM axon regeneration (Fig. 2M).

lin-4, like let-7, is a developmental timing microRNA and is expressed strongly in A VM (14). AVM axon regeneration in lin-4 mutants is not significantly different from that in wild-type animals (fig. S5A), which suggests that different developmental-timing microRNAs play different roles in A VM: lin-4 is used to time AVM axon connectivity as reported previously (14); let-7 is used to time developmental decline in AVM axon regeneration.

To determine whether the effect of let-7 on axon regeneration represents a prior role for let-7 during development of the AVM to establish its regenerative potential or, rather, an acute requirement for let-7 during the process of regeneration, we performed temperature-shift experiments. We observed that let-7(n2853ts) animals shifted to the nonpermissive temperature after injury exhibit better axon regeneration than wild-type animals (fig. S5). These data indicate that let-7 has an immediate effect in regenerating AVM neurons to inhibit their regenerative capacity.

let-7 is expressed only weakly in AVM and anterior lateral microtubule (ALM) mechanosensory neurons at the L1 stage (Fig. 2J) when AVM and ALM axon development is under way, which suggests that a low level of let-7 may be necessary for normal axon development. To test whether elevated let-7 would inhibit AVM and ALM axon outgrowth in development, we forced early expression of let-7 in AVM and ALM using a cell-specific mec-4 promoter, which enables gene expression from the late embryonic stage onward. Forced early expression of let-7 in AVM and ALM limits their axon outgrowth during

stage (Fig. 1, C and D), during advanced L3-YA (young adult) stages, AVM axon regeneration is significantly reduced in wild-type animals, but is unchanged in alg-1 mutants until day 4 of the adult stage (Fig. 1, C and D).

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In our assay using RNA preparations from staged animals, expression of the mature let-7 microRNA is almost undetectable from embryonic to L2 stages and becomes apparent at L3 (Fig. 2A). To study specifically the expression of let-7 in AVM, we developed a 2.9-kilobase let-7 promoter reporter that stably expresses in AVM and whose expression levels in the whole animal at different stages correlate very well with the whole-animal stem-loop RT-PCR results (Fig. 2A and Fig. S3C). This let-7 reporter is expressed at relatively low levels in AVM at L1 and L2 stages (Fig. 2, C and J) but is significantly elevated from L3 onward (Fig. 2, F and J). This indicates that let-7 is expressed at the right place and right time to contribute to the developmental decline in AVM axon regeneration. Several lines of evidence indicate that the effect of alg-1 mutations on AVM axon regeneration can be attributed to let-7 inactivation in AVM. First, let-7 mutants display enhanced AVM axon regeneration to a similar extent to alg-1 mutants (Fig. 2, K to M). Second, the effect of alg-1 mutations on AVM axon regeneration is rescued by the let-7 overexpression in AVM (Fig. 2M). Last, although the let-7 RNA interference (RNAi) causes enhanced AVM axon regeneration, it does not further enhance regeneration in let-7 mutants (Fig. 2M).

The temperature-sensitive allele used in this study, let-7(n2853ts), is a point mutation in the 5′ seed region of the let-7 microRNA. let-7(n2853ts) animals have normal let-7 activity at the permissive temperature of 15°C but have reduced let-7 activity at the nonpermissive temperature of 20°C. In let-7(n2853ts) mutants at 20°C, AVM axons regenerated to twice the length of those regenerated in wild-type animals (Fig. 2M), which suggested that let-7 mutations recapitulate the alg-1 mutant phenotype in enhancing AVM axon regeneration (Fig. 2M). let-7(n2853ts) likely represents a loss-of-function mutation in AVM at 20°C, because let-7(n2853ts) mutants display a similar degree of AVM axon regeneration at 23°C as at 20°C (average axon regeneration is 105 μm at 23°C and 100 μm at 20°C, P = 0.32). Like alg-1 mutants, let-7(n2853ts) animals also display a retarded developmental decline in AVM axon regeneration (Fig. S4, A and B). Regenerating AVM neurons in let-7(n2853ts) mutants not only extended longer axons, they also frequently displayed compact growth cones (Fig. S1D), a phenotype shared by alg-1 mutants (Fig. S1C). Some regenerating axons in let-7 mutants only stop outgrowth as they are about to enter the nerve ring (Fig. 2L). The effect of let-7 mutations on AVM axon regeneration appears to be cell autonomous, as expression of let-7 in AVM significantly rescued the let-7 mutant phenotype of enhancing AVM axon regeneration (Fig. 2M).

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To determine whether the effect of let-7 on axon regeneration represents a prior role for let-7 during development of the AVM to establish its regenerative potential or, rather, an acute requirement for let-7 during the process of regeneration, we performed temperature-shift experiments. We observed that let-7(n2853ts) animals shifted to the nonpermissive temperature after injury exhibit better axon regeneration than wild-type animals (Fig. S5). These data indicate that let-7 has an immediate effect in regenerating AVM neurons to inhibit their regenerative capacity.

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Fig. 1. alg-1 mutations slow developmental decline in AVM axon regeneration. (A) AVM axon before, immediately after, and 24 hours after laser surgery in a wild-type animal. D (dorsal end) and P (proximal end) of severed axons. Red arrow points to the focus of laser plasma. Anterior is left, dorsal up. (B) The positions of regenerating axon termini in wild-type L2-stage animals, wild-type YAs, and alg-1 YAs. In each scatter plot, the top line (dorsal nerve cord), the bottom line (ventral nerve cord), and the wild-type AVM morphology before surgery (green) are shown. (C and D) Average AVM axon length in wild type (C) and alg-1 mutants (D) at different stages. Asterisks indicate cases in which latter stage animals differ from L2-stage animals at **P < 0.01; ***P < 0.001. Error bars indicate SEM.
development (Fig. S6, A to G), which suggests that premature let-7 expression closes early the window of plasticity for axon outgrowth.

hbl-1 and lin-41 are critical direct targets of let-7 in C. elegans developmental timing (10, 16). hbl-1 encodes a transcription factor and LIN-41 is a member of TRIM family of proteins. Analysis of the promoter activity of hbl-1 and lin-41 genes by using green fluorescent protein–fused promoter (promoter::GFP) reporters showed that lin-41 is expressed in AVM and ALM, but hbl-1 is not (Fig. 3A). Also, lin-41 mutants (but not hbl-1 mutants) display significantly reduced AVM axon regeneration (Fig. 3C and E). lin-41 mutations suppress the let-7 mutant phenotype of enhancing AVM axon regeneration, which suggests that lin-41 acts downstream of let-7 in AVM (Fig. 3E). Consistent with a positive role for lin-41 in promoting axon regeneration, overexpressing lin-41 in AVM enhanced AVM axon regeneration (Fig. 3D and E).

Consistent with a developmental down-regulation of lin-41 in AVM by rising let-7, an engineered genomic reporter containing the 5′, coding, and 3′ fragments of the lin-41 gene showed a stage-dependent decline in AVM (Fig. 3B). This down-regulation of lin-41 is likely via direct interaction of let-7 with the lin-41 3′ untranslated region (3′UTR), as the expression of a GFP::lin-41 3′UTR sensor in adult AVM was higher in let-7 mutants than in wild-type animals (Fig. S7), and ectopic expression of let-7 in younger AVM was sufficient to repress GFP::lin-41 3′UTR (fig. S8).

lin-29, a zinc finger transcription factor of the C2H2 type (17), is known to be inhibited by let-7 (10). We show that lin-29 mutations cause enhanced AVM axon regeneration but do not further enhance regeneration in let-7 mutants (Fig. 3E). In addition, lin-29 mutations suppress the lin-41 mutant phenotype of reducing AVM axon regeneration (Fig. 3E). Further, the level of the LIN-29::GFP fusion protein in AVM at the L1 stage is significantly higher in lin-41 mutants than in wild-type animals (Fig. 3F). Together, our results indicate that let-7/lin-41 is acting via lin-29 to control AVM axon regeneration.

A conserved mitogen-activated protein kinase (MAPK) pathway, including the DLK-1–MAPK kinase and p38 kinase–PMK-3, controls axon regeneration in C. elegans (4). This pathway is negatively regulated by the conserved protein RPM-1 (4). We show that dkl-1 and pmk-3 mutations suppress the enhanced AVM axon regeneration of let-7 mutants, which suggests that let-7 may act upstream of dkl-1 and pmk-3 (Fig. S9A). Further, lin-41 mutations do not suppress the enhanced AVM axon regeneration of rpm-1 mutants, whereas pmk-3 and dkl-1 mutations do, which suggests that lin-41 may act upstream of or in parallel to rpm-1 (Fig. S9A). Analysis of the RPM-1 level shows no difference between lin-41 mutants and wild-type animals (Fig. S9B), which indicates that either LIN-41 is acting in parallel to RPM-1 or LIN-41 is acting through a posttranscriptional mechanism to indirectly regulate RPM-1 activity but not its level.

In wild-type animals, mature let-7 microRNA is expressed at low levels before the L3 stage (Figs. 2A and 4A). In let-7 mutants, let-7 is precociously expressed at the L1 stage (Fig. 4A), which indicates that let-7 prevents the early-onset expression of let-7. The expression intensity of a Plet-7::GFP reporter in the whole animal or in AVM is slightly lower instead of higher in lin-41 mutants than in wild-type animals at L1 to L3 stages (Fig. 4, B and C), which suggests that lin-41 inhibits early expression of let-7 posttranslationally.

Recent studies of mouse stem cells showed that mLin41 E3 ubiquitin ligase activity regulates...
Argonaute2 turnover (18). Our study shows that the ALG-1 Argonaute is required for let-7 maturation in C. elegans (Fig. 2I). To test whether LIN-41 inhibits the early-onset expression of let-7 through negative regulation of ALG-1, alg-1 mutations were examined for their effects on let-7 expression in lin-41 mutants. In lin-41:alg-1 double mutants, let-7 levels were restored to late-onset expression (Fig. 4A). Because only the ectopic (early) expression but not the normal (late) expression of let-7 was affected by alg-1 mutations in lin-41 mutants, this result suggests that LIN-41 may inhibit ALG-1 only at the early stage to repress early-onset let-7 expression. Indeed, LIN-41 is no longer able to down-regulate let-7 expression in the adult stage (Fig. 4D).

Consistent with this interpretation, the level of the ALG-1::GFP fusion protein in AVM at the L1 stage was significantly higher in lin-41 mutants than in wild-type animals (Fig. 4E). Using a lin-41 promoter construct that drives the FLAG-tagged LIN-41 protein expression mainly in neurons (Fig. 3A), we tested whether immunoprecipitation (IP) of ALG-1 would co-precipitate the FLAG-tagged LIN-41 protein. Co-IP of FLAG::LIN-41 with ALG-1 was observed (Fig. 4F and fig. S10A), which suggests that these two proteins may form a complex in neurons. The relatively low LIN-41::FLAG signal points to the terminus of regenerating axons. Anterior is left, dorsal up. (E) Average AVM axon length. Asterisks indicate cases in which mutants or transgenic animals significantly differ from wild-type or a comparison between mutants is significantly different at ***P < 0.001. (F) Analysis of the level of the LIN-29::GFP fusion protein in AVM in lin-41 mutants versus wild-type animals at L1. Images shown are expression of the LIN-29::GFP fusion protein in the AVM nucleus.

**Fig. 4. LIN-41 inhibits let-7 expression through ALG-1 at the early stage.** (A) Analysis of temporal expression of mature let-7 microRNA in wild-type and lin-41 mutants by the stem-loop RT-PCR assay. Analysis of the let-7 promoter activity in the whole animal (B) and AVM (C) in lin-41 mutants versus wild-type animals. (D) Stem-loop RT-PCR analysis of the mature let-7 microRNA in wild-type and Ex[Pin-41::lin-41]. (E) Analysis of the expression of the ALG-1::GFP fusion protein in AVM in lin-41 mutants versus wild-type animals at L1. (F) IP of ALG-1 coprecipitates FLAG-tagged LIN-41. (G) Model of let-7–signaled developmental decline in AVM axon regeneration.
intensity in the ALG-1 IP suggests that only a subpopulation of LIN-41 is in complexes with ALG-1. Similarly, IP of GFP-tagged LIN-41 pulled down a subset of the ALG-1 protein population (Fig. S10B). IP of small subsets of protein populations with components of microRNA-induced silencing complex has precedents (15, 19).

Even though let-7 levels decline significantly by day 4 in the adult stage (fig. S11, A and B), AVM axon regeneration significantly enhanced in aged animals that either express lin-41 or contain let-7 mutations (fig. S11, C and D), which indicates that the let-7/lit-41 pathway regulates axon regeneration even in aged AVM. Furthermore, let-7 mutations significantly enhance, whereas lin-41 mutations significantly reduce, axon regeneration in several neurons that coexpress both genes, which suggests that the role of let-7/lit-41 in regulating axon regeneration can be extended beyond AVM neurons (fig. S12).

In this study, we show that let-7 contributes to a developmental decline in AVM axon regeneration. We identify LIN-41 as an important AVM axon regeneration-promoting factor. let-7 represses lin-41 expression to inhibit AVM axon regeneration in older neurons. Our results suggest a negative regulatory loop between let-7 and lin-41 (Fig. 4G). In younger neurons, lin-41 inhibits let-7 expression through negative regulation of ALG-1. In older neurons, up-regulation of let-7 overcomes the lin-41 inhibition and, in turn, represses the lin-41 expression through the lin-41 3' UTR. Like C. elegans, mammals also exhibit a developmental decline in axon regeneration. Our findings suggest that it may be possible to enhance axon regeneration after injury through therapeutic inhibition of the let-7 microRNA in neurons and, thereby, to restore their youthful regenerative capacity.

**References and Notes**


**A Neural Marker of Perceptual Consciousness in Infants**

Sid Kouider,§,1* Carsten Stahlhut,1 Sofie V. Gelskov,1,3 Leonardo S. Barbosa,1 Michel Dutat,1 Vincent de Gardelle,2 Anne Christophe,6 Stanislas Dehaene,4,5,6,7 Ghislaine Dehaene-Lambertz2,6,7

Infants have a sophisticated behavioral and cognitive repertoire suggestive of a capacity for conscious reflection. Yet, demonstrating consciousness in infants remains challenging, mainly because they cannot report their thoughts. Here, to circumvent this problem, we studied whether the neural signatures of infant consciousness and its neural correlates in adults can already be obtained in the developing brain. We capitalize on visual masking, a psychophysical phenomenon whereby a brief display, when followed by a second picture, vanishes from awareness. Previous research in adults has shown that the perception of masked displays to report the presence or absence of a stimulus, either by touching the location of a stimulus on a screen or by touching an alternative key to indicate that no stimulus had been presented. After a unilateral lesion in V1, they consistently press the “absent” key for stimuli contralateral to the lesioned side, although they remain able to localize them with high accuracy, which suggests that they undergo a “blindsight” phenomenon similar to that of human patients (6). However, it seems much more difficult to train infants to report similarly about their thoughts and percepts, which renders the issue of infant consciousness particularly challenging.

In this study, we follow an alternative strategy: examining whether the neural signatures of perceptual consciousness that are observed in adults can already be obtained in the developing brain. We capitalize on visual masking, a psychophysical phenomenon whereby a brief display, when followed by a second picture, vanishes from awareness. Previous research in adults has shown that the perception of masked displays

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1Laboratoire de Sciences Cognitives et Psycholinguistique, EHESS/CNRS/ENS-DEC, 75005 Paris, France. 2Section for Cognitive Systems, Department of Informatics and Mathematical Modeling, Technical University of Denmark, 2800 Kongens Lyngby, Denmark. 3Barish Research Center for Magnetic Resonance, Copenhagen University Hospital, 2650 Hvidovre, Denmark. 4Collège de France, 75231 Paris, France. 5INSERM, U992, Cognitive Neuroimaging Unit, 91191 Golf-sur-Yvette, France. 6CEA, NeuroSpin Center, 91191 Golf-sur-Yvette, France. 7Université Paris XI, 91405 Orsay, France.

*Corresponding author. E-mail: sid.kouider@ens.fr
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Yan Zou et al.
Science 340, 372 (2013);
DOI: 10.1126/science.1231321

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