relevance of such information processing operations. The framework may be further extended to more complex devices by combining multiple SI schemes within a device and implementing layering strategies. We anticipate that further insight into RNA structure-function relationships (*25*), and improved predictions of RNA secondary and tertiary structures (*16*), may allow the development of improved modular assembly schemes, in which an important design challenge will be to insulate device functions across distinct components and control interactions between these components.

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Supporting Online Material

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Innate Immunity in *Caenorhabditis elegans* Is Regulated by Neurons Expressing NPR-1/GPCR

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A large body of evidence indicates that metazoan innate immunity is regulated by the nervous system, but the mechanisms involved in the process and the biological importance of such control remain unclear. We show that a neural circuit involving *npr-1*, which encodes a G protein–coupled receptor (GPCR) related to mammalian neuropeptide Y receptors, functions to suppress innate immune responses. The immune inhibitory function requires a guanosine 3′,5′-monophosphate–gated ion channel encoded by *tax-2* and *tax-4* as well as the soluble guanylate cyclase GCY-35. Furthermore, we show that *npr-1*– and *gcy-35*–expressing sensory neurons actively suppress immune responses of nonneuronal tissues. A full-genome microarray analysis on animals with altered neural function due to mutation in *npr-1* shows an enrichment in genes that are markers of innate immune responses, including those regulated by a conserved PMK-1/p38 mitogen-activated protein kinase signaling pathway. These results present evidence that neurons directly control innate immunity in *C. elegans*, suggesting that GPCRs may participate in neural circuits that receive inputs from either pathogens or infected sites and integrate them to coordinate appropriate immune responses.

Innate immune defense comprises a variety of mechanisms used by metazoans to prevent microbial infections. Activation of the innate immune system upon pathogen recognition results in a rapid and definitive microbicidal response to invading microorganisms that is fine-tuned to prevent deleterious deficiencies or excesses in the response. The nervous system, which can respond in milliseconds to many types of nonspecific environmental stimuli, has several characteristics that make it an ideal partner with the innate immune system to regulate nonspecific host defenses (*1*–*3*). However, even though a large body of evidence indicates that metazoan innate immunity is under the control of the nervous system, the mechanisms involved in the process and the biological importance of such control remain unclear. To provide insights into the neural mechanisms that regulate innate immunity, we have taken advantage of the simple and well-studied nervous and innate immune systems of *Caenorhabditis elegans.*

The powerful genetic approaches available to *C. elegans* research have been used to address central questions concerning the functions of the nervous system (*4*). With its 302 neurons and 56 glial cells, which represent 37% of all somatic cells in a hermaphrodite, the nervous system is perhaps the most complex organ of *C. elegans*. Ablation of different neurons has demonstrated that sensory neurons regulate a variety of physiological processes, including dauer formation and adult life span (*5*–*8*). In addition, *C. elegans* neurons are known to express numerous secreted peptides of the transforming growth factor–β (TGF-β) family, the insulin family, and neuropeptide families (*6*, *9*–*13*). This myriad of secreted factors has the potential to act at a distance to modulate various physiological processes by regulating the function of neuronal and nonneuronal cells throughout the animal.

Like other free-living nematodes, *C. elegans* lives in soil environments where it is in contact with soilborne microbes, including human microbial pathogens; it has evolved physiological mechanisms to respond to different pathogens by activating the expression of innate immune response genes that are conserved across metazoans (*14*–*19*). *C. elegans* also has behavioral responses to pathogenic bacteria such as *Bacillus thuringiensis* (*20*, *21*), *Microbacterium nematophilum* (*22*), *Photorhabdus luminescens* (*23*), *Pseudomonas aeruginosa* (*24*–*26*), and *Serratia marcescens* (*24*, *27*, *28*). Animals infected with these pathogens avoid lawns of the pathogen, or migrate away from pathogen odors. It is currently unknown how the nematode can sense pathogenic bacteria, although mutants in sensory-transduction molecules such as the Gi-like protein ODR-3 and the G protein–coupled receptor kinase GRK-2 are incapable of *S. marcescens* lawn avoidance (*28*). These results suggest that G protein–coupled receptors (GPCRs) may participate in neural circuits that receive inputs from either pathogens or infected sites and integrate them to coordinate appropriate defense responses.

To study the role of GPCRs in the regulation of innate immune response, we first determined the susceptibility of 40 *C. elegans* strains carrying mutations in GPCRs to the human opportunistic pathogen *P. aeruginosa* strain PA14, a clinical isolate capable of rapidly killing *C. elegans* at 25°C

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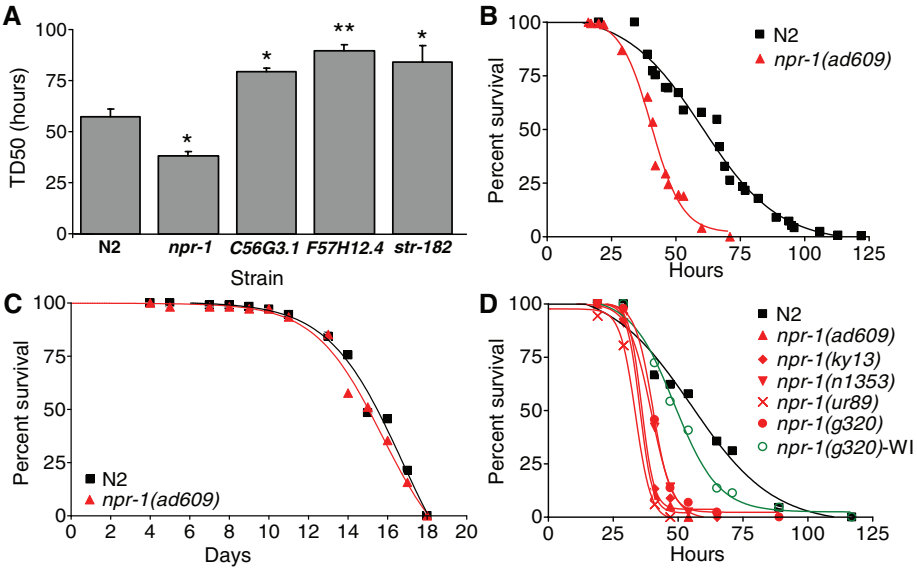

Fig. 1. *C. elegans* GPCR NPR-1 is involved in immunity to *P. aeruginosa*. (**A**) *C. elegans* strains carrying mutations in GPCRs were screened for altered survival on *P. aeruginosa*. *C56G3.1(ok1439)* (P = 0.0347), *F57H12.4(ok1504)* (P = 0.0071), and *str-182(ok1419)* (P = 0.0342) had enhanced resistance to *P. aeruginosa*, and *npr-1(ad609)* (P = 0.0246) had enhanced susceptibility to *P. aeruginosa*, relative to the wild type (N2). Shown is the time required for 50% of the nematodes to die (TD_{50}) as mean ± SEM corresponding to at least three independent experiments, each of which used at least 40 adult nematodes per strain. (**B**) Wild-type N2 and *npr-1(ad609)* (P = 0.0001) nematodes were exposed to *P. aeruginosa* and scored for survival over time. The graph represents combined results of four independent experiments ($n \geq 40$ adult nematodes per strain). (**C**) Wild-type N2 and *npr-1(ad609)* (P = 0.1411) nematodes were exposed to heat-killed *P. aeruginosa* and scored for survival over time. The graph represents the combined results of two independent experiments (n = 100 adult nematodes per strain). (**D**) Wild-type N2, *npr-1(ad609)* (P = 0.0001), *npr-1(ky13)* (P = 0.0001), *npr-1(n1353)* (P = 0.0001), *npr-1(ur89)* (P = 0.0001), *npr-1(g320)* (P = 0.0001), and the wild isolate *npr-1(g320)*-WI (P = 0.0922) were exposed to *P. aeruginosa* and scored for survival over time. Shown is a representative assay of at least three independent experiments (n = 48 adult nematodes per strain).

(*29*, *30*) (table S1). Of the 40 mutants studied, three mutants exhibited an enhanced resistance to *P. aeruginosa* and only one mutant exhibited an enhanced susceptibility to *P. aeruginosa* (Fig. 1, A and B). The strain exhibiting an enhanced susceptibility to *P. aeruginosa*–mediated killing carries a loss-of-function mutation in *npr-1*, which encodes a GPCR related to mammalian neuropeptide Y receptors (*31*).

To determine whether the enhanced susceptibility to *P. aeruginosa* exhibited by *npr-1(ad609)* animals (Fig. 1A) was due to a reduction in life span or a deficient response to potentially pathogenic bacteria, we fed *npr-1(ad609)* nematodes with heat-killed *P. aeruginosa* on plates supplemented with ampicillin. No difference in survival was seen between *npr-1(ad609)* and wild-type nematodes under these conditions, which suggests that the *npr-1* mutation affects the immune response to living pathogenic bacteria without altering the basic life span of the animals (Fig. 1C and fig. S1).

We confirmed that NPR-1 is required for *C. elegans* defense against *P. aeruginosa* by exposing five additional *npr-1* mutants to the pathogen and comparing their survival with that of wild-type animals (Fig. 1D). Strains carrying loss-of-function alleles *npr-1(ky13)*, *npr-1(n1353)*, or *npr-1(ur89)* or the reduced-function allele *npr-1(g320)* were more susceptible to *P. aeruginosa* than were the wild type, confirming that NPR-1 is required for the defense response to this pathogen. Although the German wild isolate RC301, which contains the *npr-1(g320)* allele (*31*), is not particularly susceptible to *P. aeruginosa* as compared with the

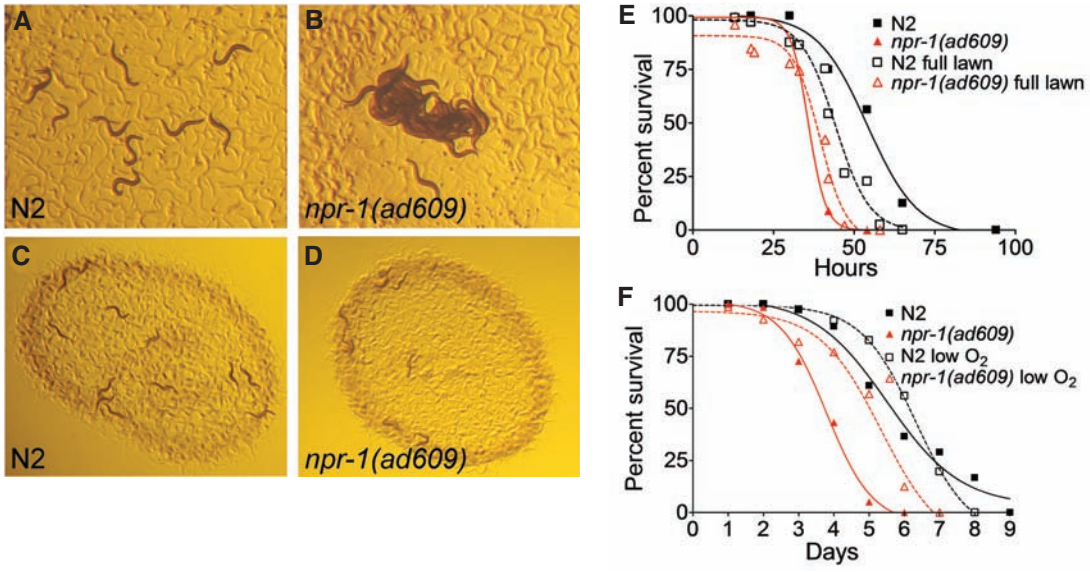

Fig. 2. Hyperoxia avoidance of NPR-1–deficient animals increases susceptibility to *P. aeruginosa*. (**A**) *C. elegans* wild-type N2 animals and (**B**) *npr-1(ad609)* mutants were propagated at 20°C as hermaphrodites on modified nematode growth agar plates seeded with *E. coli* strain OP50 and then visualized using a MZ FLIII stereomicroscope (Leica, Bannockburn, Illinois). The characteristic aggregate of *npr-1(ad609)* nematodes shown here is at the edge of the bacterial lawn. (**C**) Wild-type N2 and (**D**) *npr- 1(ad609)* nematodes (n = 12 each) were exposed to *P. aeruginosa* for 24 hours under standard killing assay conditions and visualized using a MZ FLIII stereomicroscope. Under these conditions, *npr-1(ad609)* nematodes do not form characteristic aggregates of the strain. (**E**) Wild-type N2 and *npr-1(ad609)* nematodes were exposed to either a full lawn or a center lawn of *P. aeruginosa* on a 3.5-cm-diameter plate and scored for survival over time. Under both conditions, *npr-1(ad609)* animals were more susceptible to *P. aeruginosa*–mediated killing (P = 0.0001). Wild-type animals on full lawns were more susceptible to *P. aeruginosa*–mediated killing than animals on center lawns (P = 0.0001); *npr-1(ad609)* animals were equally susceptible (P = 0.07). The graph represents combined results of three independent experiments ($n \geq 40$ adult nematodes per strain). (**F**) Wild-type N2 and *npr-1(ad609)* nematodes exposed to *P. aeruginosa* in either 21% or 8% oxygen at room temperature (~20° to 23°C) and scored for survival over time. Under both conditions, *npr-1(ad609)* animals were more susceptible to *P. aeruginosa*–mediated killing (P = 0.0001). *npr-1(ad609)* animals in 21% oxygen were more susceptible to *P. aeruginosa*–mediated killing than were animals in 8% oxygen (P = 0.0001); wild-type animals were equally susceptible (P = 0.95). The graph represents combined results of two independent experiments (n = 40 adult nematodes per strain).

wild type, the *npr-1(g320)* allele confers susceptibility to *P. aeruginosa* in an N2 background (Fig. 1D). These results suggest that the German isolate may have evolved a mechanism to compensate for the increased susceptibility to pathogens because of its reduced NPR-1 activity.

To determine whether the immune deficiency due to mutation in the *npr-1* gene is specific for *P. aeruginosa* infection, we exposed *npr-1(ad609)* nematodes to *Salmonella enterica* and *Enterococcus faecalis*, two human pathogens known to kill *C. elegans* (*32*–*34*). As shown in fig. S3, A and B, *npr-1(ad609)* nematodes exhibited an enhanced susceptibility to these pathogens, suggesting that NPR-1 is required for immune responses to pathogens in general.

NPR-1 is involved in a neural circuit that integrates behavioral responses to environmental oxygen, food, and other animals. In nature, NPR-1 is found in two allelic forms that differ in a single amino acid at position 215, NPR-1(215V) and NPR-1(215F) (*31*). The NPR1(215V) allele, which is found in the standard laboratory strain, has high activity, whereas the NPR-1(215F) allele has low activity (*35*, *36*). Wild-type *npr-1(215V)* animals avoid oxygen levels above 10% when food is absent, but fail to avoid high oxygen in the presence of *Escherichia coli* bacteria, the food provided to *C. elegans* in the laboratory. In contrast, *npr-1(215F)* and *npr-1* animals carrying loss-of-function (*lf*) alleles have strong hyperoxia avoidance in the absence or presence of *E. coli* (*37*). As a result, *npr-1(215F)* and *npr-1(lf)* show a preference for the thickest part of a bacterial lawn, the region in which oxygen levels are the lowest (*35*). In addition, because nematode aggregation into feeding groups decreases local oxygen concentrations, *npr-1(215F)* and *npr-1(lf)* form aggregates of nematodes when the animals are grown at densities high enough to allow this behavioral response (*37*).

One potential explanation for the reduced life span of *npr-1(lf)* mutants grown on bacterial pathogens is that aggregation increases nematode susceptibility to pathogen infection. However, the animal density in the assays where the susceptibility to pathogens is tested was not sufficient to elicit aggregation, making this possibility unlikely (Fig. 2D). Even though *npr-1(ad609)* animals did not aggregate, they still exhibited a preference for the thickest part of the lawn, where oxygen concentrations are lower (Fig. 2, C and D). In addition, long-term exposure to *P. aeruginosa* caused wild-type animals to leave the bacterial lawn, a potentially protective behavioral response, but leaving was not observed in *npr-1(ad609)* animals. Thus, we examined whether the behavior of *npr-1(ad609)* animals could affect susceptibility to pathogens. The number of bacterial cells in *npr-1(ad609)* animals was not found to be greater than that in wild-type animals (fig. S2) at early stages of the infection, suggesting that the increased susceptibility to pathogens of *npr-1(ad609)* animals is not caused by a higher dose of bacteria. In addition, we grew animals on agar plates that were completely covered in *P. aeruginosa*, a condition that eliminates both the lawn border (favored by *npr-1* animals) and the ability to leave the lawn (favored by wild-type animals). As shown in Fig. 2E, wild-type animals grown on plates completely covered by *P. aeruginosa* died at a higher rate than did animals grown on plates containing a small lawn of *P. aeruginosa* in the center of the plate. *npr-1(ad609)* animals were equally susceptible to *P. aeruginosa* when grown on full or center lawns. Together, these results indicate that the lawn-leaving behavior of wild-type animals contributes to their increased survival. However, *npr-1(ad609)* animals still exhibited enhanced susceptibility to *P. aeruginosa* relative to the wild type when the infections were performed in plates containing full lawns (Fig. 2E). These results indicate that lawn avoidance is part of the *C. elegans* defense response to *P. aeruginosa* but cannot account for all of the differences between wild-type and *npr-1(ad609)* animals.

To determine whether other elements of the oxygen response contribute to the enhanced susceptibility of *npr-1(ad609)* nematodes, we compared animals grown in 21% oxygen with those grown in 8% oxygen, a favorable oxygen environment that suppresses most behavioral phenotypes of *npr-1* mutants. Under 8% oxygen, *npr-1(ad609)* animals do not exhibit a preference for the bacterial border and are capable of leaving the *P. aeruginosa* lawn. As shown in Fig. 2F, *npr-1(ad609)* animals were more resistant to

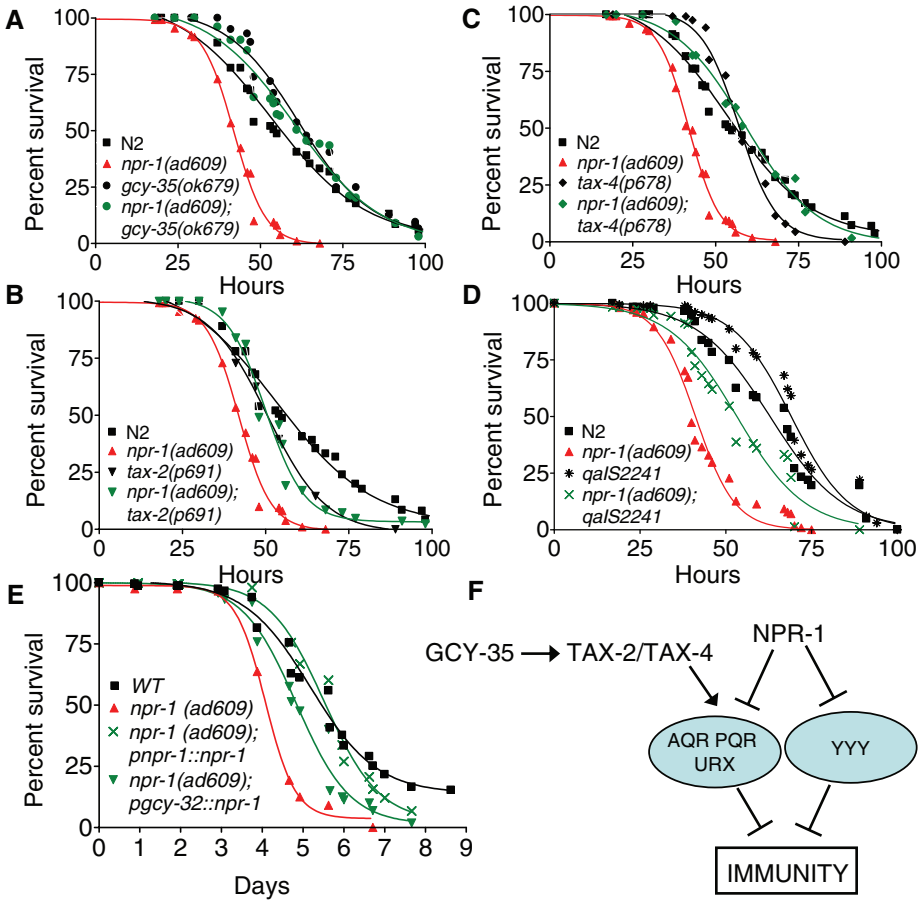

Fig. 3. The NPR-1 neural circuit regulates innate immunity. (**A**) Wild-type N2, *npr-1(ad609)* ($P = 0.0001$), *gcy-35(ok769)* ($P = 0.0125$), and *npr-1(ad609);gcy-35(ok769)* ($P = 0.0639$) were exposed to *P. aeruginosa*. (**B**) Wild-type N2, *npr-1(ad609)* ($P = 0.0001$), *tax-2(p691)* ($P = 0.0930$), and *npr-1(ad609);tax-2(p691)* ($P = 0.0031$) were exposed to *P. aeruginosa*. (**C**) Wild-type N2, *npr-1(ad609)* ($P = 0.0001$), *tax-4(p678)* ($P = 0.1673$), and *npr-1(ad609);tax-4(p678)* ($P = 0.3611$) were exposed to *P. aeruginosa*. (**D**) Wild-type N2, *npr-1(ad609)* ($P = 0.0001$), *qaIS2241* ($P = 0.0042$), a strain that lacks AQR, PQR, and URX neurons, and *npr-1(ad609);qaIs2241* ($P = 0.0001$) were exposed to *P. aeruginosa.* The graphs represent combined results of at least three independent experiments ($n \geq 40$ adult nematodes per strain). (**E**) Wild-type N2, *npr-1(ad609)* ($P = 0.0001$), *npr-1(ad609);pgcy-32::npr-1* ($P = 0.0001$), and *npr-1(ad609);pnpr-1::npr-1* ($P = 0.1939$) were exposed to *P. aeruginosa.* The graphs represent combined results of at least two independent experiments ($n \geq 100$ adult nematodes per strain). Killing assays were performed at 17°C, because low temperatures are known to increase the resolution of killing assays involving *P. aeruginosa.* (**F**) Model of the neural control of innate immunity in *C. elegans*. NPR-1 inhibits the activity of AQR, PQR, URX, and additional neuron(s) designated YYY that suppress innate immunity, whereas GCY-35, TAX-2, and TAX-4 are required for the activation of AQR, PQR, and URX neurons.

P. aeruginosa–mediated killing in 8% oxygen than 21% oxygen, but were still more susceptible than were wild-type animals in 8% oxygen. These results indicate that animals deficient in NPR-1 activity are more susceptible to *P. aeruginosa* because of two factors: decreased pathogen avoidance and decreased innate immune responses.

The increased susceptibility of *npr-1(ad609)* to *S. enterica* (fig. S3A), a pathogen that does not elicit an avoidance behavior (*38*), is consistent with a role of NPR-1 in the regulation of immune responses that are independent of pathogen avoidance. Because a small amount of *S. enterica* that passes through the pharyngeal grinder proliferates and colonizes the intestine in a process that is independent of the dose (*32*), and the pumping rates of *npr-1(ad609)* animals are comparable with those of the wild type (fig. S4), the results further support the function of NPR-1 in the regulation of immune responses.

Genetic studies have identified a chemosensory circuit that coordinates oxygen preference and aggregation in *npr-1* mutants (*35*, *37*, *39*–*42*). Aggregation and bordering of *npr-1(ad609)* nematodes depend on functional *gcy-35*, *tax-2*, or *tax-4* genes (*31*, *40*, *43*). GCY-35 is a soluble guanylyl cyclase (sGC) that binds directly to molecular oxygen, and TAX-2 and TAX-4 are two subunits of a guanosine 3′,5′-monophosphate–gated ion channel (*31*, *40*, *43*). Through the activity of GCY-35 and other guanylate cyclases and the subsequent activation of TAX-2/TAX-4, the AQR, PQR, and URX sensory neurons drive avoidance of high oxygen; these neurons are thought to be hyperactive in *npr-1* mutants (*40*). To determine whether this part of the NPR-1 neural circuit regulates innate immune response, we studied the pathogen susceptibility of *npr-1(ad609)* animals carrying loss-of-function mutations in *gcy-35*,

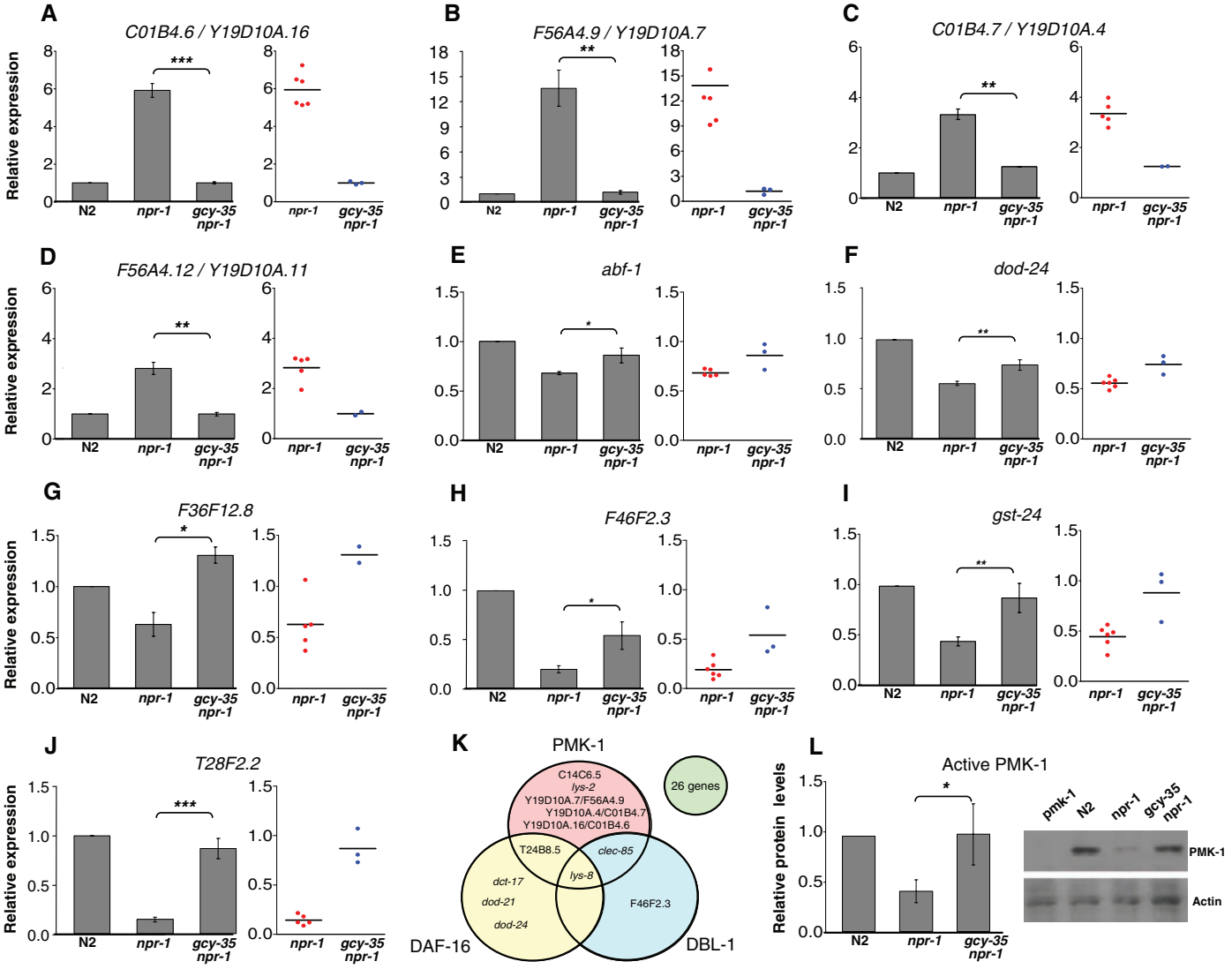

Fig. 4. The NPR-1 neural circuit regulates expression of innate immune genes. (**A** to **J**) QPCR analysis of *C01B4.6/Y19D10A.16*, *F56A4.9/Y19D10A.7*, *C01B4.7/Y19D10A.4*, *F56A4.12/Y19D10A.11*, *abf-1*, *dod-24*, *F36F12.8*, *F46F2.3*, *gst-24*, and *T28F2.2* expression in *npr-1(ad609)* and *npr-1(ad609);gcy-35(ok769)* nematodes relative to wild-type nematodes exposed to *P. aeruginosa*. Data were analyzed by normalization to pan-actin *(act-1,-3,-4)* and relative quantification using the comparative-cycle threshold method. Student's exact *t* test indicates that differences among the groups are significantly different; bar graphs correspond to mean ± SEM. Point graphs correspond to gene quantification in independent isolations of *npr-1(ad609)* ($n = 6$ independent experiments) and *npr-1(ad609);gcy-35(ok769)* ($n = 3$ independent experiments). (**K**) The Venn diagram lists the genes identified by microarray analysis to be regulated by both NPR-1 and one or more known innate immune pathways in *C. elegans*. Genes that lie within two or three circles are regulated by multiple innate immune pathways in addition to NPR-1. Twenty-six genes have not been previously connected to any of the innate immune pathways and are depicted in the solitary circle. (**L**) Immunological detection of active PMK-1. Active PMK-1 was detected in wild-type N2, *npr-1(ad609)*, and *npr-1(ad609);gcy-35(ok769)*. Animals were grown at 20°C until 1-day-old adult and whole-worm lysates were used to detect active PMK-1 with Western blotting using an antibody to human p38 (Promega). Actin was detected using a polyclonal antibody (Sigma). Quantity One analysis software (BioRad) was used to scan and analyze the Western blot.

tax-2, or *tax-4*. As shown in Fig. 3, the enhanced susceptibility to *P. aeruginosa* of *npr-1(ad609)* animals was rescued by mutations in *gcy-35*, *tax-2*, or *tax-4*. Similar results were obtained when the infections were performed in plates containing full lawns of *P. aeruginosa* (fig. S5).

NPR-1 is expressed in at least 20 different neurons, including the *gcy-35*–expressing sensory neurons AQR, PQR, and URX (*35*). To confirm that at least AQR, PQR, and URX neurons are part of a neural network that inhibits innate immunity, we studied the susceptibility to *P. aeruginosa* of a strain in which these neurons were genetically ablated by expressing the cell-death activator gene *egl-1* under the control of the *gcy-36* promoter (*42*). The strain lacking AQR, PQR, and URX neurons exhibited a significantly increased survival on *P. aeruginosa* (Fig. 3D), indicating that AQR, PQR, and URX neurons suppress innate immunity. In addition, lack of AQR, PQR, and URX neurons partially rescued the enhanced susceptibility to *P. aeruginosa* of *npr-1(ad609)* animals (Fig. 3D). Expression of *npr-1* under the control of the *gcy-32* promoter, which drives the expression of *npr-1* to the AQR, PQR, and URX neurons, also rescued the enhanced susceptibility to *P. aeruginosa* of *npr-1(ad609)* animals (Fig. 3E), providing additional evidence of the role of these neurons in the regulation of innate immunity. Consistent with the idea that additional NPR-1–expressing neurons regulate innate immunity (Fig. 3F), *npr-1* expression under the regulation of its own promoter fully rescued the enhanced susceptibility to *P. aeruginosa* phenotype of *npr-1(ad609)* animals (Fig. 3E). Taken together, these results indicate that genes and cells involved in the NPR-1 neural circuit modulate innate immune responses.

As in mammals, peristalsis, low pH, and antimicrobial substances prevent microbial colonization of the *C. elegans* intestine. In addition, accumulating evidence indicates that different genetic pathways regulate the expression of *C. elegans* genes that are markers of immune response (*14*–*19*). To provide insight into the immune function of the NPR-1 neural circuit, we used gene expression microarrays to find clusters of genes up-regulated or down-regulated in *npr-1(ad609)* mutants relative to wild-type animals grown on live *P. aeruginosa* (tables S2 and S3). There is a substantial enrichment in NPR-1–regulated genes that have at least one of three features: they are up-regulated by *P. aeruginosa* infection in wild-type animals, expressed in the intestine, and/or have already been linked to the *C. elegans* p38 mitogen-activated protein kinase PMK-1, which plays a crucial role in innate immunity (*17*, *44*–*47*) (table S4). Further analysis revealed that five of the genes most highly down-regulated by NPR-1 are found in a cluster on chromosome V that appears to have been duplicated further downstream on that chromosome (table S3). Of these five genes, three are also known to be down-regulated by the *C. elegans* PMK-1/p38 pathway. Overall, most of the genes regulated by pathways linked to innate immunity correspond to PMK-1–regulated genes (Fig. 4K). In addition, these genes are similarly misregulated in animals deficient in NPR-1 or PMK-1 function (tables S2 and S3). Because *pmk-1* is not transcriptionally regulated by NPR-1 (tables S2 and S3), we studied whether NPR-1 regulates PMK-1 at the post-transcriptional level. As shown in Fig. 4L, *npr-1 (ad609)* nematodes exhibited lower levels of active PMK-1 than did wild-type nematodes, suggesting that the NPR-1 neural circuit modulates the activation of PMK-1. Inhibition of *pmk-1* gene expression by RNA interference in *npr-1(ad609)* nematodes resulted in increased susceptibility (fig. S6), indicating that although the NPR-1–mediated immune pathway has overlapping targets with the PMK-1–mediated immune pathway, NPR-1 regulates both PMK-1–dependent and PMK-1–independent immune responses.

To obtain insight into the mechanism by which *gcy-35* mutation rescues the enhanced susceptibility to *P. aeruginosa* of *npr-1(ad609)* animals (Fig. 3A), we used quantitative real-time polymerase chain reaction (QPCR) to compare the expression levels of selected genes of *npr-1(ad609)* with that of *npr-1(ad609);gcy-35(ok769)* animals. As shown in Fig. 4, a *gcy-35* mutation in *npr-1(ad609)* animals rescues the altered expression of 10 out of 19 genes tested that are markers of the *C. elegans* immune response. These results indicate that the NPR-1 neural circuit modulates the expression of immune-related genes, many of which are known to be expressed in tissues that are in direct contact with pathogens during infection.

Our results provide evidence that specific genes and neurons in the nervous system are responsible for effective innate immune responses that are independent of behavioral phenotypes and may take place in tissues that are in direct contact with pathogens. It has recently been postulated that cell-nonautonomous signals from different neurons may act on nonneural tissues to regulate processes such as fat storage (*48*) and longevity (*8*). *C. elegans* neurons can regulate physiological processes through conserved neuroendocrine signals, including insulin-related peptides, TGF-β peptides, and neuropeptides. The URX, AQR, and PQR neurons that are part of the NPR-1 neural circuit that regulates innate immunity are exposed to the pseudocoelomic body fluid, which could communicate neuroendocrine signals to nonneural tissues involved in defense responses. The identification and characterization of the specific neuroendocrine signals that regulate innate immune responses in *C. elegans* should yield several insights into the mechanisms used by the nervous system to regulate similar processes across metazoans.

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