Title
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Permalink
https://escholarship.org/uc/item/56r1k1x4

Journal
Cell reports, 14(7)

ISSN
2211-1247

Authors
Reddy, Kirthi C
Dunbar, Tiffany L
Nargund, Amrita M
et al.

Publication Date
2016-02-11

DOI
10.1016/j.celrep.2016.01.055

Peer reviewed
The *C. elegans* CCAAT-Enhancer-Binding Protein Gamma Is Required for Surveillance Immunity

### Graphical Abstract

- **P. aeruginosa infection**
- ToxA-induced translational inhibition in the intestine
- Perturbation in histone or mitochondrial function
- Increase in ZIP-2 protein levels
- ZIP-2/CEBP-2 activation of gene expression
- Transcription of *irg-1* and other infection response genes
- Reduction of pathogen load
- Increased survival

### Highlights

- CEBP-2, the *C. elegans* ortholog of mammalian C/EBP-γ, promotes resistance to infection
- CEBP-2, like the ZIP-2 transcription factor, defends against translational block
- CEBP-2 mediates a response to perturbation in histone and mitochondrial function
- CEBP-2 and ZIP-2 are potential heterodimeric partners in surveillance immunity

### Authors

Kirthi C. Reddy, Tiffany L. Dunbar, Amrita M. Nargund, Cole M. Haynes, Emily R. Troemel

### Correspondence

etroemel@ucsd.edu

### In Brief

Reddy et al. show that CEBP-2, the *C. elegans* ortholog of C/EBP-γ, acts together with the bZIP transcription factor ZIP-2 to promote host response against perturbation of core processes like mRNA translation. CEBP-2/ZIP-2 comprise a potential heterodimeric transcription factor that functions in surveillance immunity, a key aspect of epithelial defense.
The C. elegans CCAAT-Enhancer-Binding Protein Gamma Is Required for Surveillance Immunity

Kirthi C. Reddy,1 Tiffany L. Dunbar,1 Amrita M. Nargund,2,3 Cole M. Haynes,2,3 and Emily R. Troemel1,4
1Division of Biological Sciences, Section of Cell and Developmental Biology, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92037, USA
2Cell Biology Program, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA
3BCMBC Allied Program, Weill Cornell Medical College, New York, NY 10065, USA
4Correspondence: etroemel@ucsd.edu
http://dx.doi.org/10.1016/j.celrep.2016.01.055
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SUMMARY

Pathogens attack host cells by deploying toxins that perturb core host processes. Recent findings from the nematode C. elegans and other metazoans indicate that surveillance or “effector-triggered” pathways monitor functioning of these core processes and mount protective responses when they are perturbed. Despite a growing number of examples of surveillance immunity, the signaling components remain poorly defined. Here, we show that CEBP-2, the C. elegans ortholog of mammalian CCAAT-enhancer-binding protein gamma, is a key player in surveillance immunity. We show that CEBP-2 acts together with the bZIP transcription factor ZIP-2 in the protective response to translational block by P. aeruginosa Exotoxin A as well as perturbations of other processes. CEBP-2 serves to limit pathogen burden, promote survival upon P. aeruginosa infection, and also promote survival upon Exotoxin A exposure. These findings may have broad implications for the mechanisms by which animals sense pathogenic attack and mount protective responses.

INTRODUCTION

The innate immune system serves to defend hosts against pathogen infection, without the need for prior exposure to these pathogens (Kumar et al., 2011). A key component of the innate immune system is the detection of molecules characteristic of pathogens, so-called pathogen-associated molecular patterns or PAMPs. Hosts use pattern recognition receptors that are tuned to detect these PAMPs and trigger defense, often through upregulation of immune response gene expression. However, PAMPs are usually molecules found in broad classes of microbes and do not necessarily represent the presence of a pathogenic microbe. For example, lipopolysaccharide is a PAMP found in gram-negative bacterial species, both pathogenic and non-pathogenic alike. Thus, PAMPs may be more accurately defined as microbe-associated molecular patterns, or MAMPs. MAMPs provide hosts information about the presence of microbes, but not necessarily whether those microbes are pathogenic (Ausubel, 2005; Sanabria et al., 2010).

A growing theme in animal immunity is that hosts specifically detect pathogen attack with surveillance or “effector-triggered” immune pathways, which detect the effects of pathogen-delivered toxins and virulence factors, rather than recognizing the molecular structure of the factors themselves (Cohen and Troemel, 2015; Rajamuthiah and Mylonakis, 2014; Spoel and Dong, 2012; Stuart et al., 2013). For example, many bacterial toxins inhibit host mRNA translation elongation (Beddoo et al., 2010; Lee et al., 2013; Lemaitre and Girardin, 2013; Lemichez and Barbieri, 2013; Mohr and Sonenberg, 2012), and these toxins are quite prevalent in the environment, with up to 29% of soil samples in one study harboring DNA for translation-blocking Shiga toxin (Casas et al., 2009). Translation-blocking toxins are made by diverse bacterial pathogens including P. aeruginosa (Iglewski et al., 1977), Corynebacterium diphtheriae (Pappenheimer, 1977), Vibrio cholerae (Jorgensen et al., 2008), Legionella pneumophila (Belyi et al., 2006), Shigella spp, and Shiga toxin-producing E. coli (Pacheco and Sperrandio, 2012). Because these toxins are diverse in structure, it is arguably an efficient defense strategy for hosts to detect the common block in translation elongation caused by these toxins to trigger defense.

Recent findings indicate that C. elegans uses surveillance pathways for defense against toxins delivered by the bacterial pathogen P. aeruginosa that block not only mRNA translation but also mitochondria, the proteasome, and histones (Dunbar et al., 2012; Liu et al., 2014; McEwan et al., 2012; Melo and Ruvkun, 2012; Pellegrino et al., 2014). P. aeruginosa causes a lethal intestinal infection in its nematode host, and in the early response to infection, C. elegans upregulates mRNA expression of many defense genes, including candidate anti-microbial peptides, detoxifying enzymes, and efflux pumps (Shapira et al., 2006; Troemel et al., 2006). We identified the bZIP transcription factor ZIP-2 as a key mediator of this infection-induced gene expression and showed that it promotes a defense response (Estes et al., 2010). The transcriptional response to P. aeruginosa infection appears to be predominantly a response to pathogenicity, triggered in part by the translation-blocking Exotoxin A (ToxA) (Dunbar et al., 2012; Estes et al., 2010; McEwan et al., 2012). In previous studies, we showed that C. elegans intestinal cells appear to endocytose ToxA, which blocks mRNA translation specifically in the intestine, and this
block is sensed by the host to upregulate defense gene expression. Surprisingly, this translational block appears to trigger an increase in protein levels of ZIP-2, apparently through regulation in cis by an upstream open reading frame (Dunbar et al., 2012). Thus, ZIP-2 appears to function in effector-triggered immunity in C. elegans to respond to the translational block caused by P. aeruginosa-delivered ToxA. However, ZIP-2 does not have an obvious mammalian ortholog, which made it unclear which transcription factor might be involved in this type of immunity in mammals.

Here, we show that ZIP-2 acts together with another bZIP transcription factor called CEBP-2 in C. elegans surveillance immunity. Intriguingly, CEBP-2 is the C. elegans ortholog of mammalian CCAAT-enhancer-binding protein gamma (C/EBP-γ), which plays a role in the acute response to infection and inflammation in mammals, together with other C/EBP transcription factors (Gao et al., 2002; Parkin et al., 2002; Tsukada et al., 2011), although its role in effector-triggered defense has not been shown. We show that CEBP-2 is required to upregulate a transcriptional response to ToxA in C. elegans and promote defense against insult by this toxin as well as against pathogen infection. We also show that CEBP-2 is required for upregulation of defense gene expression in response to RNAi against genes that function in the mitochondria and transcription-related processes and that perturbation of these processes increases levels of ZIP-2 protein, similar to perturbation of translation (Dunbar et al., 2012). Thus, ZIP-2/CEBP-2 appears to be a key transcription factor in C. elegans surveillance immunity that promotes defense against pathogenic microbes.

RESULTS AND DISCUSSION

CEBP-2 Is Required for Induction of ZIP-2-Dependent Genes in Response to P. aeruginosa Infection

Previously, we demonstrated that the bZIP protein ZIP-2 mediates induction of candidate defense genes and promotes survival upon P. aeruginosa infection (Estes et al., 2010). As bZIP proteins canonically act as dimers, we were interested in identifying a heterodimeric partner that could act together with ZIP-2 in C. elegans host defense. A comprehensive study of bZIP transcription factor protein-protein interactions in vitro identified C. elegans C48E7.11 as the highest-affinity binding partner for ZIP-2 (Reinke et al., 2013). C48E7.11 is the top BLAST hit in the C. elegans genome for human C/EBP-γ transcription factor (NP_001797). It shares 37% amino acid identity with the human protein and has a similar domain structure, with most of the protein being composed of a bZIP domain. Therefore, we renamed C48E7.11 CEBP-2, for CCAAT/enhancer-binding protein 2.

We investigated whether CEBP-2 mediates a protective response to P. aeruginosa strain PA14 infection of C. elegans, which would support the hypothesis that CEBP-2 acts together with ZIP-2 as a heterodimeric transcription factor in mediating defense against infection in vivo. First, we examined whether cebp-2 regulates expression of target genes known to be induced by zip-2 upon infection. In particular, we examined P. aeruginosa-induced expression of a GFP reporter for infection response gene-1 (irg-1p::GFP) in cebp-2-deficient animals, using either cebp-2 RNAi-treated animals or cebp-2(tm5421) mutant animals, and found greatly reduced induction of GFP compared to control, similar to that seen in worms lacking zip-2 function (Figures 1A–1F). This result indicates that cebp-2, like zip-2, regulates irg-1 induction in response to P. aeruginosa infection.

We next confirmed that cebp-2 controls pathogen induction of endogenous irg-1 mRNA expression by using qRT-PCR to measure RNA levels in cebp-2-deficient animals. We found that cebp-2 RNAi-treated animals had decreased induction of irg-1 in response to P. aeruginosa, as compared to control, as well as decreased induction of two other zip-2-dependent genes, F11D11.3 and oac-32 (Figure 1G). However, induction of another zip-2-dependent gene, infection response gene 2, irg-2, was not decreased in cebp-2 RNAi-treated animals (Figure 1G). cebp-2(tm5421) mutant animals had a stronger phenotype, with greatly reduced mRNA induction of irg-1, irg-2, F11D11.3, and oac-32 (Figure 1H). We also tested a panel of infection response genes whose induction in response to P. aeruginosa infection does not require zip-2 and found that most of these genes were induced normally in cebp-2-deficient animals (Figures 1G and 1H). The fact that cebp-2 is required for induction of the infection response genes that also require zip-2 for their induction supports the model that CEBP-2 and ZIP-2 work together as a transcription factor to mediate a transcriptional response to P. aeruginosa infection in C. elegans.

CEBP-2 and ZIP-2 Promote Resistance against P. aeruginosa Infection

Our previous studies indicated that zip-2-mediated gene expression promotes a defense response, as zip-2-defective animals have modestly decreased survival upon infection with P. aeruginosa (Estes et al., 2010). To determine whether cebp-2 is also important for defense against killing by P. aeruginosa, we tested the survival of cebp-2-defective animals upon infection with P. aeruginosa. Indeed, we found that cebp-2 RNAi-treated animals, like zip-2 RNAi-treated animals, had a modest but significant decrease in survival upon infection (Figure 2A), indicating that cebp-2, like zip-2, promotes host defense. In addition, we found that cebp-2 and zip-2 mutants had a modest decrease in survival upon PA14 infection (Figure 2B). cebp-2 mutants had slightly decreased survival compared to zip-2 mutants, perhaps due to the decreased overall health of these animals (see results below). If, however, cebp-2 and zip-2 were working together to regulate gene expression that promotes survival upon PA14 infection, then a cebp-2;zip-2 mutant should not have a further decrease in survival compared to the cebp-2 single mutant alone. Consistent with this model, we found that cebp-2;zip-2 mutants did not have a greater decrease in survival compared to the single cebp-2 mutant (Figure 2B).

Next, we investigated whether zip-2 and cebp-2 promote increased survival upon infection with P. aeruginosa by restricting pathogen accumulation in the intestine or by improving tolerance of the pathogen (Medzhitov et al., 2012). To distinguish between these possibilities, we measured fluorescence levels of P. aeruginosa PA14-dsRed (Djnović et al., 2013) in animals deficient for either zip-2 or cebp-2 at 16 hr post-infection and found that zip-2- and cebp-2-deficient animals accumulated
significantly more intestinal PA14-dsRed than control animals (Figures 2C–2F and S1A–S1D). This result indicates that both zip-2 and cebp-2 likely contribute to defense against killing by P. aeruginosa in part by controlling pathogen burden in the intestine. In addition, we found that the cebp-2;zip-2 double mutant had a similar increase in PA14-dsRed levels in the intestine as the single mutants (Figure 2F). Together, these results indicate that zip-2 and cebp-2 act to promote resistance to the pathogen P. aeruginosa, perhaps functioning together as a heterodimeric transcription factor to induce genes that limit pathogen accumulation in the intestine and promote survival upon infection.
CEBP-2 and ZIP-2 Are Both Expressed in Intestinal Nuclei during *P. aeruginosa* Infection

Previous studies indicated that much of the *P. aeruginosa*-mediated induction of infection response genes such as *irg-1* was due to pathogen-induced perturbation of core processes, including inhibition of mRNA translation (Dunbar et al., 2012; McEwan et al., 2012). Indeed, a key trigger of *irg-1* induction appears to be the *P. aeruginosa* translational inhibitor Exotoxin A (ToxA), because heterologous expression of ToxA in non-pathogenic *E. coli* is sufficient to induce *irg-1* mRNA expression in *C. elegans*, in a zip-2-dependent manner (McEwan et al., 2012). The induction of *irg-1* mRNA upon infection is likely mediated by an increase in ZIP-2 protein levels, which could then serve to increase *irg-1* transcription. Indeed, ZIP-2 protein levels increase upon *P. aeruginosa* infection and also with pharmacological inhibition of translation by the elongation inhibitor cycloheximide (Dunbar et al., 2012). Consistent with this model, we show here that ZIP-2 protein levels increase upon exposure to ToxA. Animals carrying a ZIP-2::GFP transgene had virtually no GFP expression when feeding on *E. coli* carrying the empty expression vector but had strong GFP expression with nuclear
localization in intestinal cells when feeding on *E. coli* expressing ToxA (Figures S2A, S2B, and S2E).

Next, we investigated whether *cebp-2* was required for the increased ZIP-2 protein levels seen after exposure to ToxA, because one possible explanation for the similar defects seen in *zip-2*- and *cebp-2*-deficient animals in response to *P. aeruginosa* infection is that *cebp-2* is required for ZIP-2 protein expression. However, we found that *cebp-2* was not required for ZIP-2 protein expression in response to ToxA, as *cebp-2* RNAi-treated animals had robust induction of ZIP-2::GFP in intestinal nuclei after feeding on *E. coli* expressing ToxA (Figures S2C–S2E). This result indicates that the similar phenotypes of *zip-2*- and *cebp-2*-deficient animals are not due to regulation of ZIP-2 expression by CEBP-2.

If CEBP-2 and ZIP-2 function together in the response to *P. aeruginosa* infection, then these proteins should be expressed at the same time and in the same location. To test this model, we generated a transgene that contains 1.1 kb of genomic DNA upstream of the predicted *cebp-2* ATG start site followed by the *cebp-2* genomic coding region with GFP fused to the C terminus. We found that animals carrying this CEBP-2::GFP transgene express GFP broadly in somatic tissues including the intestine, with strong nuclear localization (Figure 3A). We did not see any change in CEBP-2::GFP expression or localization in animals infected with *P. aeruginosa* (Figure 3B), indicating that CEBP-2 is constitutively expressed, unlike ZIP-2. In addition, we did not find that *zip-2* was required for CEBP-2 expression, as CEBP-2::GFP expression did not change after zip-2 RNAi treatment (Figures 3C and 3D).
**P. aeruginosa** infection

ToxA-induced translational inhibition in the intestine  
Block in histone or mitochondrial function

Increase in ZIP-2 protein levels  
ZIP-2/CEBP-2 activation of gene expression

Transcription of *irg-1* and other infection response genes

Reduction of pathogen load

Increased survival

(legend on next page)
Furthermore, there was not a change in cepb-2 mRNA expression (or other genes in the cepb-2 operon) after zip-2 RNAi (Figure 3E), further supporting the conclusion that zip-2 is not required for cepb-2 expression.

To confirm that the CEBP-2::GFP expression construct was functional and thus likely to reflect endogenous expression of CEBP-2 protein, we analyzed whether this could rescue the cepb-2 mutant phenotype. Indeed, we found that this CEBP-2::GFP construct could rescue the defects in gene induction in response to P. aeruginosa in the cepb-2(tm5421) mutant (Figure 3F). This result also confirms that the cepb-2 gene induction phenotype in the cepb-2(tm5421) mutant strain is not due to a background mutation and rather due to a mutation in the cepb-2 gene itself.

Taken together, these results indicate that ZIP-2 and CEBP-2 do not function to regulate expression or localization of each other and are both present in intestinal nuclei during infection with P. aeruginosa when there is robust gene induction of irg-1 and other infection response genes. These results are consistent with the model that ZIP-2 and CEBP-2 function together as a heterodimeric transcription factor to induce genes in the context of pathogen infection.

cebp-2 Mutants Have a Decrease in Body Size and Reproductive Output

Although zip-2 and cepb-2 mutants appear to have nearly identical phenotypes in terms of their response to pathogen infection, they do differ in terms of overall health and vigor. In particular, cepb-2(tm5421) mutants had reduced body size compared to wild-type animals during normal well-fed conditions (Figure S3A), a defect that was rescued by the CEBP-2::GFP transgene. In contrast, zip-2(tm4248) mutants had no decrease in body size compared to wild-type animals. We also found that cepb-2(tm5421) mutants had a significantly reduced brood size compared to wild-type animals, whereas zip-2(tm4248) mutants had no reduction in brood size (Figure S3B). These differences in overall health between cepb-2 and zip-2 mutants may be due to CEBP-2 acting in a dimer with a different bZIP transcription factor to regulate growth and reproduction. Notably, mammalian C/EBP-gamma does not appear able to regulate transcription on its own but rather partners with several different C/EBP factors to regulate distinct outputs (Tsuakada et al., 2011). Indeed, CEBP-2 has been shown in vitro to interact with several other binding partners (Reinke et al., 2013) and recently was shown to have a role in fat metabolism as well (Xu et al., 2015), which may explain its effects on body size and reproduction.

CEBP-2 Mediates a Transcriptional Response to Inhibition of mRNA Translation and Inhibition of Other Core Processes, which Increases ZIP-2 Protein Expression

As mentioned above, previous studies indicate that ToxA-mediated translational inhibition appears to be responsible for a subset of the P. aeruginosa infection-induced transcriptional response in C. elegans. This gene induction is partially dependent on zip-2, and the zip-2-signaling pathway was shown to protect C. elegans from killing by ToxA. We therefore investigated whether cepb-2 is similarly required for ToxA-mediated gene induction and for survival after exposure to ToxA. We first examined whether cepb-2 is required for ToxA-induced expression of the irg-1::GFP reporter. In both cepb-2 RNAi-treated animals and cepb-2(tm5421) mutant animals, we found greatly reduced induction of irg-1::GFP after exposure to ToxA as compared to control, similar to that seen in worms lacking zip-2 function (Figures 4A–4H). This result indicates that cepb-2, like zip-2, regulates irg-1 induction after ToxA treatment. We next tested whether cepb-2 regulates endogenous irg-1 induction as well as induction of two other zip-2-dependent genes, oac-32 and F11D11.3, in response to ToxA exposure. We used qRT-PCR to measure RNA levels in cepb-2-deficient animals and found that cepb-2, like zip-2, is required for induction of irg-1, oac-32, and F11D11.3 after ToxA-mediated translational inhibition (Figures 4I and 4J). We also tested an additional three genes whose induction in response to ToxA treatment does not require zip-2 (McEwan et al., 2012) and found that these genes were induced normally in cepb-2-deficient animals (Figures 4I and 4J).

Surveillance pathways in C. elegans monitor not only mRNA translation but also core processes mediated by mitochondria, the proteasome, and transcriptional machinery (Bakowski et al., 2014; Dunbar et al., 2012; Liu et al., 2014; Melo and Ruvkun, 2012). Our previous screen found RNAI clones against not only translation factors, but also mitochondrial pathways and histones can induce irg-1::GFP in a ZIP-2-dependent manner.
Thus, we investigated whether cepb-2 was required for surveillance of these processes. Indeed, we found that RNAi against the histone H2A his-57 and the mitochondrial enzyme dihydrolipoamide dehydrogenase dlat-1 no longer induced ig-1p::GFP in cepb-2 mutants (Figures S4A–S4F). Thus, cepb-2 appears to be important for gene induction upon perturbation of multiple core processes.

Previously, we had found that either genetic or chemical inhibition of mRNA translation caused an increase in ZIP-2 protein levels (Dunbar et al., 2012), explaining how translational inhibition could lead to an induction of ZIP-2-dependent gene expression. Here, we extend those analyses to blockade of other core processes, such as mitochondrial function and histone function. In particular, we found that RNAi against the histone H2A his-57 and the mitochondrial enzyme dihydrolipoamide dehydrogenase dlat-1 caused an increase in ZIP-2::GFP protein expression (Figures S4G–S4L). Thus, perturbation of several core processes appears to increase ZIP-2 protein expression, where it could act together with the constitutively expressed CEBP-2 to promote a transcriptional response to xenobiotic insults.

**CEBP-2 Mounts a Protective Response against ToxA-Mediated Killing**

Previous studies found that wild-type animals mount a defense response against ToxA, as ToxA treatment does not compromise survival unless immune pathways are defective (McEwan et al., 2012). zip-2 mutants have a substantially shorter lifespan when fed *E. coli* expressing ToxA as compared to control. To determine whether cepb-2 is important for defense against killing by ToxA, we exposed cepb-2(tm5421) mutant animals to *E. coli* expressing either a vector control or ToxA. We found that cepb-2 mutants, like zip-2 mutants, have greatly decreased survival upon treatment with ToxA, with relatively normal survival on the vector control (Figure 4K). Thus, cepb-2 is required for the defense response against the pathogen-derived toxin ToxA. Furthermore, we found that the cepb-2;zip-2 double mutant had a similar decrease in survival upon ToxA exposure as the cepb-2 and zip-2 single mutants (Figure 4K). Together, these results support the model that cepb-2 is acting together with zip-2 to mount a protective response against ToxA-mediated killing (Figure 4L).

**Concluding Remarks: CEBP-2 and ZIP-2 Act Together in Surveillance Immunity in C. elegans**

A growing theme in animal innate immunity is that hosts are able to discriminate pathogens from other microbes through the use of surveillance pathways that monitor disruption of host processes commonly targeted by pathogens. This effector-triggered immunity is critical for epithelial cells that encounter a wide variety of microbial species. In addition to the responses to the bacterial pathogen *P. aeruginosa* described here and in other publications, recent findings suggest that defense against natural eukaryotic pathogens in *C. elegans* can also be triggered by perturbing core processes (Bakowski et al., 2014). Our discovery that CEBP-2 and ZIP-2 act as a potential heterodimeric transcription factor in surveillance immunity against *P. aeruginosa* in *C. elegans* sheds light on this process and also provides a mammalian connection to be explored. CEBP-2 is the ortholog of C/EBP-gamma in mammals, which is a bZIP transcription factor that heterodimerizes with several other bZIP transcription factors to regulate upregulation of cytokines such as IL-6 and IL-8 in response to classic PAMPs like LPS (Gao et al., 2002), although it has not yet been shown to play a role in effector-triggered immunity. Interestingly, interindividual variation in C/EBP-y transcript expression levels has been implicated as a risk factor for altered severity of lung disease in cystic fibrosis (Gu et al., 2009)—a genetic disease in which chronic *P. aeruginosa* pneumonia is a pathological hallmark. Future studies could investigate the role that C/EBP-gamma and its binding partners play in surveillance immunity in mammals in order to better understand how animals discriminate pathogens from other microbes to fight off infection.
ACKNOWLEDGMENTS

Some C. elegans strains were provided by the Caenorhabditis Genetics Center (CGC), which is funded by NIH Office of Research Infrastructure Programs (P40 OD010440). We thank the National BioResource Project for the cebp-2(tm5421) deletion strain. Supported by NIH T32 GM07240 training grant to T.L.D.; NIH R01AI087528, R01GM114139, the Searle Scholars Program, Packard Foundation, and Burroughs Wellcome Fund fellowships to E.R.T.; and NIH R01AG040061 to C.M.H.

AUTHOR CONTRIBUTIONS

K.C.R., T.L.D., A.M.N., C.M.H., and E.R.T. designed the experiments. K.C.R., T.L.D., and A.M.N. performed the experiments. K.C.R. and E.R.T. wrote the manuscript. C.M.H. and E.R.T. secured funding.

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