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Note

Modulation of *Caenorhabditis elegans* Transcription Factor Activity by HIM-8 and the Related Zinc-Finger ZIM Proteins

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ABSTRACT

The previously reported negative regulatory activity of HIM-8 on the Sox protein EGL-13 is shared by the HIM-8-related ZIM proteins. Furthermore, mutation of HIM-8 can modulate the effects of substitution mutations in the DNA-binding domains of at least four other transcription factors, suggesting broad regulatory activity by HIM-8.

THE *Caenorhabditis elegans him-8* gene was identified on the basis of its *h*igh-*i*ncidence-of-*m*ales (*him*) phenotype where hermaphrodites produce a high proportion of male progeny due to meiotic nondisjunction of the X chromosome (Hodgkin *et al.* 1979; Broverman and Meneely 1994). HIM-8 is a C2H2 zinc-finger protein. In meiotic cells, it binds at or near the X chromosome pairing center and associates with the nuclear periphery (Phillips *et al.* 2005). HIM-8 functions to ensure pairing and subsequent synapsis of X chromosomes (Phillips *et al.* 2005). We recently demonstrated that HIM-8 has a broader function; it also acts in nonmeiotic cells to negatively regulate the activity of the Sox transcription factor EGL-13 (Nelms and Hanna-Rose 2006), which is encoded on the X chromosome and is important for maintenance of uterine-seam cell fate (Hanna-Rose and Han 1999; Cinar *et al.* 2003). The *co*nnection of *g*onad (Cog) morphology defect and the functional *egg-l*aying (Egl) defect that result from the lack of uterine-seam cell-fate maintenance in *egl-13* mutants are suppressed by mutation of the zinc-finger region of HIM-8 (Nelms and Hanna-Rose 2006).

HIM-8 is encoded in an operon with three similar proteins, ZIM-1 (*zi*nc finger in *m*eiosis), ZIM-2, and ZIM-3. Each of the four proteins has one C2H2 zinc finger with atypical spacing in the intervening region between the two cysteines and the two histidines, followed by a second typical C2H2 zinc finger (Phillips *et al.* 2005; Phillips and Dernburg 2006).

The ZIM proteins bind to the region of the chromosome-pairing center of specific subsets of autosomes. ZIM-1 binds to chromosomes II and III, ZIM-2 to chromosome V, and ZIM-3 to chromosomes I and IV. ZIM proteins also localize to the nuclear periphery and promote autosome pairing, analogous to the function of HIM-8 on the X chromosome (Phillips and Dernburg 2006). In this study, we report on suppression of *egl-13* mutant defects by mutations in *zim* genes. We also demonstrate that HIM-8 has broader regulatory activity on transcription factors other than EGL-13, acts in tissues other than the somatic gonad, and can affect genes that are encoded on an autosome.

Mutations in the *zim* genes suppress *egl-13(ku207)* phenotypes: Because of the strong similarity between HIM-8 and the ZIM proteins in the zinc fingers (Phillips *et al.* 2005; Phillips and Dernburg 2006), which are critical for HIM-8 suppression activity (Nelms and Hanna-Rose 2006), we asked if suppression of *egl-13* was specific to mutation of *him-8* or might be shared more broadly in this family of proteins. We tested deletion alleles of *zim-1*, *zim-2*, and *zim-3* (from the National Bioresource Project, Tokyo Women's Medical University) for the ability to suppress *egl-13(ku207)* phenotypes.

Mutations in the *zim* genes suppress the Cog morphology and the functional Egl defects of *egl-13(ku207)* (Figure 1). *zim-1(tm1813)* is as potent a suppressor as *him-8(e1489)*, but suppression by *zim-2(tm574)* appears to

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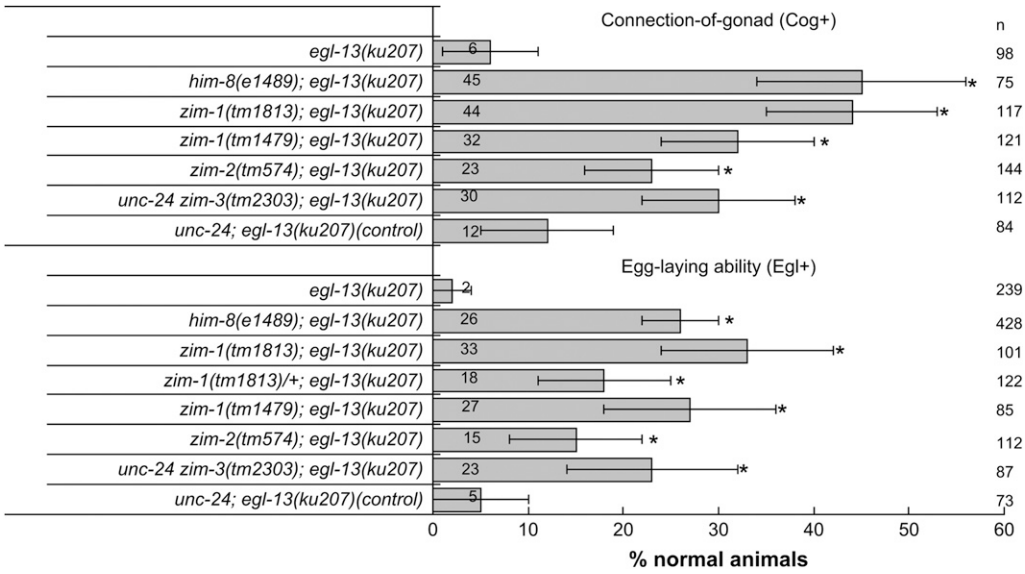

FIGURE 1.—Mutation of the *zim* genes suppresses the Cog and Egl defects of *egl-13(ku207)*. The histogram illustrates the Cog^+ and Egl^+ percentage of *egl-13(ku207)* and *suppressor; egl-13(ku207)* double mutants. The original *zim-3(tm2303)* chromosome was associated with linked mutations causing lethality (PHILLIPS and DERNBURG 2006). Thus, we used an *unc-24(e138) zim-3(tm2303)* recombinant chromosome, which causes less lethality (PHILLIPS and DERNBURG 2006), to assay suppression by *zim-3* and tested *unc-24(e138)* as a control. Cog and Egl phenotypes were scored as reported (HANNA-ROSE and HAN 1999). The *him-8(e1489)* data were published previously (NELMS and HANNA-ROSE 2006) and shown here for comparison. Note that wild-type animals have 100% normal gonad morphology and egg-laying ability. For Figures 1–3, basic principles of proportional analysis were applied as previously described to obtain 95% confidence intervals shown as error bars (NELMS and HANNA-ROSE 2006). Actual percentage is cited within each bar, and sample sizes (n) are indicated at the right in Figures 1–3. Asterisks indicate values for double mutants in Figures 1–3 that are significantly different from the relevant single mutants ($P < 0.005$, Fisher's exact test).

be weaker (Figure 1). We previously demonstrated that *him-8* mutations are semidominant suppressors due to haplo-insufficiency of the *him-8* locus (NELMS and HANNA-ROSE 2006). *zim-1(tm1813)* has a similar semidominant effect (Figure 1). As with suppression by *him-8* (NELMS and HANNA-ROSE 2006), suppression by *zim-1(tm1813)* is specific to non-null alleles of *egl-13*. *zim-1(tm1813); egl-13(ku194 null)* animals are not suppressed (0% Egl^+, $n = 70$). Thus, these related C2H2 zinc-finger proteins share another function in addition to their meiotic function: each appears to negatively regulate EGL-13 activity.

The high degree of protein sequence similarity among HIM-8, ZIM-1, ZIM-2, and ZIM-3 might suggest some degree of redundancy. However, the proteins play distinct roles in meiosis (PHILLIPS and DERNBURG 2006) and mutation of each gene results in suppression (Figure 1), indicating that the genes are not fully redundant. Partial redundancy in function is possible but is difficult to test due to the proximity of the genes in an operon.

Because genes in an operon share transcriptional regulatory sequences (BLUMENTHAL and GLEASON 2003), we considered the possibility that the mutations in the upstream *zim* genes act as suppressors due to indirect negative effects on expression of *him-8*, the last gene in the operon. If this were the case, the strong *zim-1(tm1813)* suppressor would be predicted to reduce *him-8* activity significantly, similar to the *him-8(e1489)* mutant, and to cause a Him phenotype as a result. In contrast, none of the *zim* mutants cause a highly penetrant Him phenotype (PHILLIPS and DERNBURG 2006). We cannot rule out the scenario that disruption of *him-8* expression could be making a contribution to the suppression phenomenon, but additional direct effects of the *zim* mutations seem most likely.

Mutation of *him-8* suppresses a non-null mutation in the DNA-binding domain of POP-1: We next investigated the question of whether mutation of *him-8* might have effects on genes other than the *egl-13* gene. We first tested for suppression of a mutation in a transcription factor related to EGL-13. POP-1 is the *C. elegans* TCF-1/LEF-1 family protein (LIN *et al.* 1995; KORSWAGEN 2002), which are downstream effectors of canonical wnt signal transduction pathways (BRANTJES *et al.* 2002). TCF-1/LEF-1 proteins bind to DNA via an HMG box motif related to the Sox (*S*ry-related HMG b*ox*) domain of EGL-13 (LAUDET *et al.* 1993). POP-1 is encoded on chromosome I and functions in multiple tissues (LIN *et al.* 1995; HERMAN 2001; SIEGFRIED and KIMBLE 2002). *pop-1(q624)* causes a substitution of an isoleucine for asparagine 224 within the HMG box (SIEGFRIED and KIMBLE 2002). Asparagine 224 is conserved in the TCF/LEF proteins but is not a conserved residue of the HMG box motif in general (LAUDET *et al.* 1993). Thus, *q624* is likely to have an adverse effect on DNA binding or target-site specificity but is unlikely to be a null, consistent with the incompletely penetrant phenotypes, including extra anchor cells, missing gonad arms, and lethality of first larval stage animals (SIEGFRIED and KIMBLE 2002). Mutation of *him-8* suppresses the gonad arm and anchor cell defects of *pop-1(q624)* animals (Figure 2). We conclude that mutation of *him-8* can increase the effective activity of at least one other mutant transcription factor other than EGL-13 in the

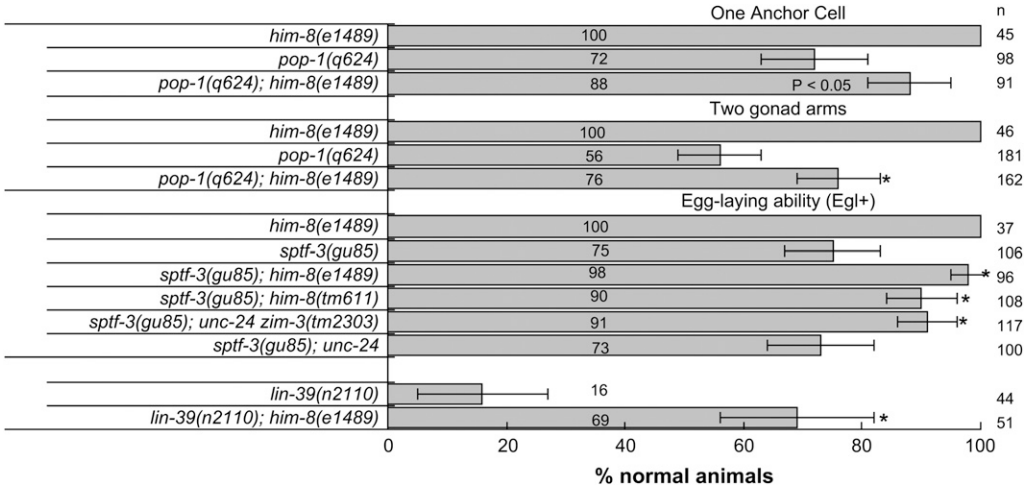

FIGURE 2.—Mutation of *him-8* suppresses non-null mutations in the DNA-binding domains of POP-1, SPTF-3, and LIN-39. The histogram illustrates the percentage of normal phenotypes. The percentage of normal *pop-1(q624)* animals reported here agrees closely with previously published data (SIEGFRIED and KIMBLE 2002). We also scored these phenotypes in *pop-1(q624); syIs50*[*cdh-3*::GFP] and *pop-1(q624);e1489; syIs50*[*cdh-3*::GFP] animals and obtained similar results (data not shown). *cdh-3*::GFP is strongly expressed in the anchor cell, allowing easier scoring of the double-anchor cell defect. Note that 100% of wild-type animals are Egl^+ and have one anchor cell and two gonad arms.

somatic gonad. Furthermore, mutation of *him-8* can affect a gene encoded on an autosome. Interestingly, *him-8(e1489)* has no effect on the penetrance of larval lethality caused by *pop-1(q624)*. *pop-1(q624)* mutants are 61% ($n = 319$) L1 lethal and *pop-1(q624); him-8(e1489)* double mutants are 62% ($n = 719$) L1 lethal.

Mutation of *him-8* suppresses non-null mutations in an Sp1-related zinc-finger protein and a Hox domain transcription factor: SPTF-3, which is encoded on chromosome I, is a transcription factor with three C2H2 zinc fingers related to Sp1 (S. F. SLEIMAN and H. M. CHAMBERLIN, unpublished results). *sptf-3(gu85)* is a missense mutation of an invariant phenylalanine in zinc finger 2. *sptf-3(gu85)* causes an incompletely penetrant Egl defect that is suppressed by *him-8(e1489)* and *him-8(tm611)*, as well as by *zim-3(tm2303)* (Figure 2). *sptf-3*(*tm607*), which is a deletion allele and a putative null that disrupts the first two zinc fingers, causes embryonic lethality that is not suppressed by *him-8(e1489)*. Neither *sptf-3(tm607)/hT2[qIs48 GFP+]* nor *sptf-3(tm607)/hT2[qIs48 GFP+]; him-8(e1489)* animals have viable *sptf-3(tm607)* (GFP-negative) progeny.

LIN-39, which is encoded on chromosome III, is a Hox family DNA-binding factor (CLARK *et al.* 1993). *lin-39(n2110)* is a missense mutation, E179K, in the Hox domain that results in a highly penetrant Egl defect (CLARK *et al.* 1993). *lin-39(n2110)* is efficiently suppressed by *him-8(e1489)* (Figure 2). However, the Egl phenotype of *lin-39(n1880)*, a putative null allele that introduces a stop at codon 100 prior to the Hox domain (CLARK *et al.* 1993), is not suppressed by *him-8(e1489)*. Both *lin-39(n1880)* and *lin-39(n1880); him-8(e1489)* are 0% Egl^+. We conclude that mutation of *him-8* can increase the effective activity of compromised transcription factors with DNA-binding domains other than an HMG box but cannot compensate for the loss of these factors.

Mutation of *him-8* has tissue-specific effects on a non-null mutation in EGL-38: EGL-38, which is encoded on chromosome IV, is a *C. elegans* Pax 2/5/8 family protein (CHAMBERLIN *et al.* 1997). Reduction-of-function mutations in *egl-38* have defects in uv1 cell-fate specification, vulval morphology, egg laying, hindgut development (including hindgut expression of a *lin-48*::GFP reporter), and male tail morphology (CHAMBERLIN *et al.* 1997; JOHNSON *et al.* 2001; ZHANG *et al.* 2005; RAJAKUMAR and CHAMBERLIN 2007). Different mutations within the EGL-38 DNA-binding domain can have specific effects on one or more of the phenotypes, but do not necessarily affect each phenotype equally (ZHANG *et al.* 2005). *egl-38(gu22)* causes a substitution in the DNA-binding domain of isoleucine for methionine 29, which is conserved but not invariant within the Pax 2/5/8 family of proteins (ZHANG *et al.* 2005).

A *lin-48*::GFP reporter is expressed in four hindgut cells in wild-type animals but expression is absent from one or more hindgut cells in *egl-38(gu22)* mutants (JOHNSON *et al.* 2001; ZHANG *et al.* 2005). Although *egl-38(gu22)* mutants lack efficient *lin-48*::GFP expression, they have largely normal vulval morphology and egg-laying function (ZHANG *et al.* 2005). The proportion of the population of *egl-38(gu22)* mutants that completely lack *lin-48*::GFP hindgut expression is eliminated in *egl-38(gu22) him-8(e1489)* double mutants (Figure 3) and the intensity of expression relative to the *egl-38* mutants with expression is increased as well (Figure 4). Thus, *him-8(e1489)* is a potent suppressor of *egl-38(gu22)* in the hindgut. *him-8(e1489)* also completely suppresses the Mab (*m*ale *ab*normal development) defect of *egl-38(gu22)* (Figure 3). Surprisingly, *him-8(e1489)* had an opposite effect on the vulval morphology and the related egg-laying defects of *egl-38(gu22)*. *him-8(e1489)* dramatically exacerbates these defects (Figure 3).

The opposite effects on *egl-38(gu22)* in the hindgut and the male tail *vs.* the vulva could be due to different effects of *him-8* in each tissue or, more likely, due to the complicated tissue-specific activities of *egl-38* (ZHANG

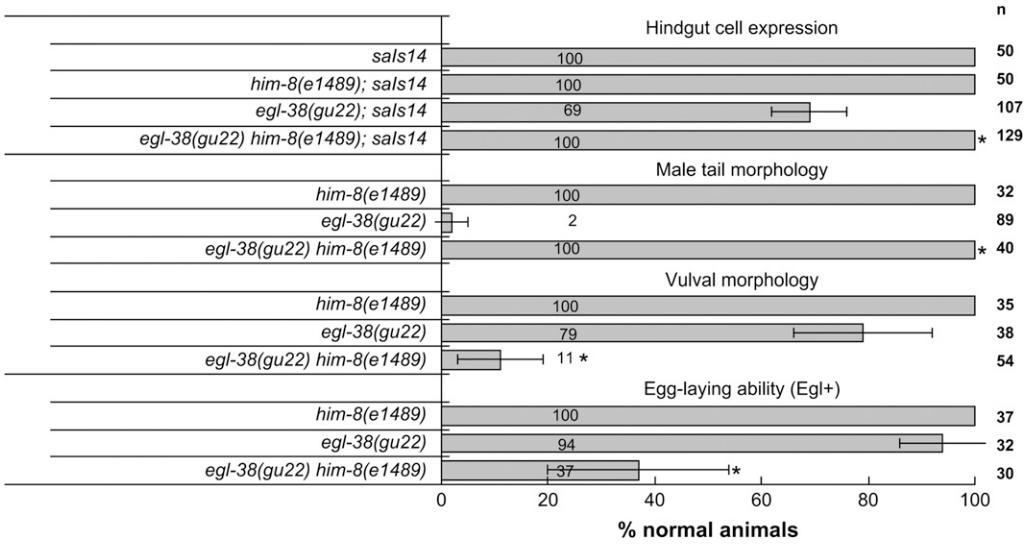

FIGURE 3.—*him-8(e1489)* suppresses the male tail defect and defective hindgut expression of a *lin-48*::GFP reporter but exacerbates the vulval development and egg-laying defects caused by *egl-38(gu22)*. The histogram illustrates the percentage of animals that express *lin-48*::GFP in at least one of the four hindgut cells with normal male tail morphology, normal vulval morphology, or normal egg-laying activity (Egl^+). Phenotypes were assayed as reported (CHAMBERLIN *et al.* 1997; JOHNSON *et al.* 2001; ZHANG *et al.* 2005; RAJAKUMAR and CHAMBERLIN 2007).

et al. 2005). For example, mutation of *him-8* could act to increase the activity of *egl-38* in both tissues, but increased activity of the EGL-38(M29I) mutant in the vulva would have a different and deleterious effect as opposed to the positive effect of increased activity of EGL-38(M29I) in the hindgut. In general, it is clear that, although mutation of *him-8* can suppress a range of mutations in a range of tissues, the phenotypic suppression effect is not universal, and phenotypic enhancement is possible.

Models for HIM-8/ZIM suppression: HIM-8 has more global effects on gene activity than might be expected from its primarily X-specific activity in meiosis. Although we have not tested the ZIM proteins as widely as HIM-8, they behave similarly to HIM-8 where examined (in modulation of EGL-13 and SPTF-3). How might these proteins be mediating their effects? Our previous results implicated the DNA-binding domain of HIM-8 in suppression activity. At the same time, we showed that increasing the level of mutant EGL-13 protein could mimic suppression (NELMS and HANNA-ROSE 2006). Thus, a possible scenario for suppression is that eliminating or reducing HIM-8/ZIM protein activity results in upregulation of EGL-13, and increased levels of mutant protein can increase the level of function.

This model predicts that mutant *him-8* might suppress a wide range of mutations that would benefit from increased gene dose. *lin-15(n765ts)* is an X-linked, temperature-sensitive, hypomorphic mutation, which can be almost completely suppressed by elevated X chromosome expression caused by mutations in the dosage compensation genes *dpy-21* and *dpy-26* (MENEELY and WOOD 1987; HSU and MEYER 1994). However, *him-8(e1489)* cannot suppress *lin-15(n765ts)*. *lin-15(n765)*

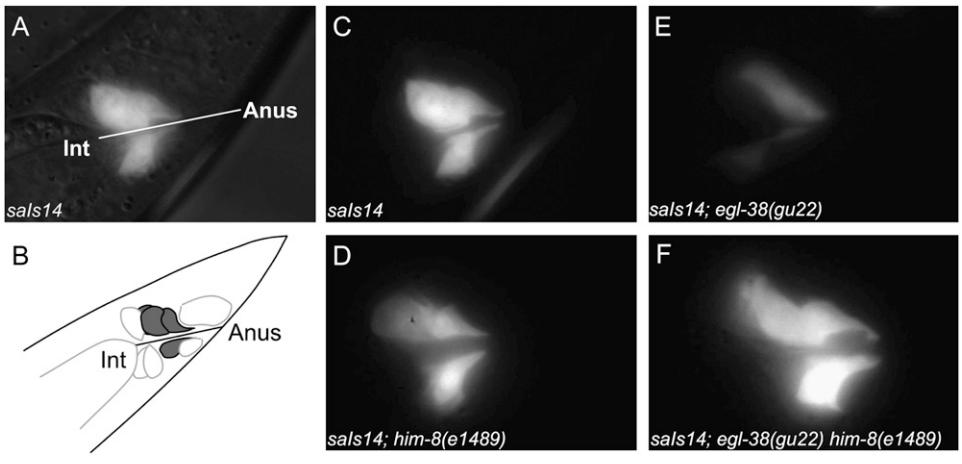

FIGURE 4.—*him-8(e1489)* increases the intensity of *lin-48::GFP* expression in the hindgut of an *egl-38(gu22)* mutant. (A) Fluorescent image of the hindgut region of an *saIs14*[*lin-48*::GFP] hermaphrodite overlaid on the corresponding DIC image. (B) *lin-48*::GFP expression is visible in four hindgut cells that flank the rectum. (C) Expression is consistently detected in all four cells at similar intensities in the transgenic parent strain. (D) The intensity of *lin-48*::GFP expression in *him-8(e1489); saIs14*[*lin-48*::GFP] animals is not detectably different from that of the parent strain. (E) Thirty-one percent of *egl-38(gu22); unc-119(e2498); saIs14*[*lin-48*::GFP] animals lack all hindgut expression of *lin-48*::GFP (Figure 3), and the intensity of *lin-48*::GFP expression is weaker than that of the parental strain in all animals that have expression. (F) In addition to an increase in the percentage of the population that expresses the reporter faithfully (Figure 3), all suppressed *egl-38(gu22) him-8(e1489)*; *saIs14*[*lin-48*::GFP] animals have an increase in the intensity of *lin-48*::GFP expression relative to the parental strain. Image exposure conditions were identical for A and C–F.

mutants are 100% ($n = 18$) Multivulva (Muv) at 20°, and *him-8(e1489); lin-15(n765)* animals are still highly Muv (97%, $n = 34$). Moreover, if mutation of *him-8* suppresses *egl-13(ku207)* simply by increasing *egl-13* gene expression, mutations in dosage compensation genes, which are responsible for reducing expression from the X chromosome in hermaphrodites (Meyer 2000), might be expected to suppress *egl-13(ku207)* as well. However, we detected no suppression by the dosage compensation mutants *dpy-28(y1)* or *dpy-21(e428)* (B. L. Nelms and W. Hanna-Rose, unpublished results). Thus, we have accumulated no evidence in support of an upregulation of gene transcription model.

An alternative model is that the suppression is uniquely specific to missense mutations affecting the DNA-binding domain of transcription factors (and perhaps other proteins that interact with the chromosome). This model is consistent with the failure of *him-8(e1489)* to suppress *egl-13*, *sptf-3*, or *lin-39* null mutants or to suppress non-null mutations in genes that do not encode transcription factors (below).

In addition to failing to suppress *lin-15(n765)* (above), *him-8(e1489)* does not suppress missense mutations in several other genes that encode proteins without DNA-binding activity. First, *him-8(e1489)* does not suppress *egl-26(n481)*, a missense mutation (S275F) in a putative acyltransferase (Estes *et al.* 2007). *egl-26(n481)* is 35% ($n = 206$) Egl$^+$, and *egl-26(n481); him-8(e1489)* is 35% ($n = 83$) Egl$^+$.

Second, *him-8(e1489)* cannot suppress *sur-6(ku123)*, a missense mutation (C302Y) in a regulatory subunit of protein phosphatase 2A (Sieburth *et al.* 1999). *sur-6(ku123)* suppresses the Muv phenotype of animals harboring one copy of the ras gain-of-function transgene *kuIs14*. *kuIs14*/+ animals are 68% ($n = 71$) Muv whereas *sur-6(ku123); kuIs14*/+ animals are 51% ($n = 77$) Muv. However, the presence of *him-8(e1489)* has no effect on *sur-6(ku123)* activity. *sur-6(ku123); kuIs14/+; him-8(e1489)* are indistinguishable from *sur-6(ku123); kuIs14*/+ at 51% ($n = 85$) Muv.

Third, *him-8(e1489)* cannot suppress *unc-37(e262)*. *unc-37(e262)* is a missense mutation (H539Y) in a WD repeat motif of UNC-37, a Groucho-like corepressor protein (Pflugrad *et al.* 1997). All *unc-37* animals and all *unc-37(e262); him-8(e1489)* animals abnormally coil instead of backing in response to a head touch ($n > 60$). Although UNC-37 Groucho is involved in transcriptional regulation, it does not bind directly to the DNA (Pickles *et al.* 2002). Our results suggest that mutation of the zinc fingers of HIM-8 specifically modulates the activity of DNA-binding transcription factors with compromised DNA-binding activity.

A DNA-binding-domain-specific model suggests that suppression occurs not due to direct changes in the suppressed gene, but rather due to altered activity of the protein product on its transcriptional targets. For example, disruption of HIM-8 might alter chromosome structure, allowing greater access to DNA targets, or otherwise enhance the *in vivo* DNA-binding activity of the compromised proteins. As most of the transcriptional targets responsible for the phenotypes assayed in this study are not known, it is possible that the difference between phenotypes that are suppressed and those that are enhanced could be the relative sensitivity of the target to the mutant protein or its genomic location. Our experiments leave open the possibility of direct interactions between the suppressed protein products and the suppressors as well. However, if protein–protein interactions between HIM-8 and transcription factors play a role in the mechanism, the transcription factors do not appear to alter HIM-8 meiotic activity since our double-mutant strains have Him phenotypes similar to that of *him-8* single mutants. Future experiments will be required to better clarify the underlying mechanism for this unique function of HIM-8.

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