

Legends for supplementary figures

Supplementary Figure 1. Sequence alignment of Har-1 orthologs. ClustalW2 was used to align sequences using the setting shown.

Supplementary Figure 2. Sequence alignment of Spg-7 orthologs. ClustalW2 was used to align sequences using the setting shown.

Supplementary Figure 3. Glycolytic inhibitors did not protect wild type worms from the hemiasterlin analog. Approximately 400 synchronized *N2* L1 larvae were grown in liquid culture in the presence of increasing concentrations of the glucose analogs alone or the analog plus 1.3 μ M of the hemiasterlin analog. After 3 days of culture, healthy, morphologically normal and mobile L4 and adult worms were counted. Worms exposed to 1.3 μ M hemiasterlin analog alone die or develop as paralyzed and dumpy animals. In contrast to inhibitors of mitochondrial respiration, which rescued wild type worms from hemiasterlin, inhibitors of glycolysis could not protect wild type worms from hemiasterlin. Three wells were scored for each concentration, and average values are graphed with SEM. For most concentrations tested, the error bars are smaller than the symbol that indicates the data point. The experiment was reproduced twice.


Supplementary Figure 4. Resistance to the hemiasterlin analog does not correlate with hypersensitivity to paraquat. Some drug resistant mitochondrial mutants are hypersensitive to paraquat but *har-1* and *isp-1* worms are not. *isp-1* mutants are highly resistant to the hemiasterlin analog and also resistant to paraquat. Data represent the paraquat concentration that kills 90-100% of larvae within 5 days of exposure. Three wells were scored for each concentration, and average values are graphed with SEM indicated. Each experiment was reproduced independently three times.

Supplementary Figure 5. Hydrogen peroxide production by wild type *N2* and mitochondrial mutants does not significantly differ. Synchronized L1 larvae were grown for 2 days on agar dishes until the majority of animals become L4 and young adults, and hydrogen peroxide production was measured by an amplex red assay as described in Materials and Methods. Data are presented as amount of H_2O_2 produced in 1 hour by wild type worms and mitochondrial mutant strains. Average values of two independent experiments performed on different days were graphed and the SEM is shown. By two-tailed T test, compared to wild type, each of the mutants has $P > 0.05$.

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ClustalW2 Results

Results of search	
Number of sequences	4
Alignment score	1709
Sequence format	Pearson
Sequence type	aa
JalView	
Output file	clustalw2-20091231-0204271561.output
Alignment file	clustalw2-20091231-0204271561.aln
Guide tree file	clustalw2-20091231-0204271561.dnd
Your input file	clustalw2-20091231-0204271561.input

To save a result file right-click the file link in the above table and choose "Save Target As".
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Scores Table

Sequence Number ▼

SeqA	Name	Len (aa)	SeqB	Name	Len (aa)	Score
1	S.cerevisiae	156	2	C.elegans	154	31
1	S.cerevisiae	156	3	D.melanogaster	170	30
1	S.cerevisiae	156	4	H.sapiens	151	37
2	C.elegans	154	3	D.melanogaster	170	45
2	C.elegans	154	4	H.sapiens	151	39
3	D.melanogaster	170	4	H.sapiens	151	43

PLEASE NOTE: Some scores may be missing from the above table if the alignment was done using multiple CPU mode. Please check the output.

Sequence Number ▼

Alignment

CLUSTAL 2.0.12 multiple sequence alignment

```
C.elegans      MVRR-RTASPSPS----APVRSAPRPAAQSSFAAPPPRPAAPAAAPAYHPPAAPTIMGAPMG 55
D.melanogaster MVRGRSASPPPSTRRTAPVQARAPAPAPAPVQTRAPAPAASAPVPAPMSAP-PSAVGMP 59
H.sapiens      MPRGSRRT-----SRMAPPASRAPQMRAAPRPAPVAQPPAAAPPSPAVGSSAA--- 48
S.cerevisiae   MARSRGSSRP-----ISRSRPTQTRSASTMAAPVHPQQQQPNAYSHPPAAG-- 47
* * : : : . * . * : . . .

C.elegans      APSQGGLMKQMAATAGGVAIGSAVGHAVGG----MFTGGGSSHAEQAPAAAAAPAG-AP 110
D.melanogaster APQQ-PSMFQQMAATAGGVAIGSAVGHAVGG----MFTGGGSSHAEQAPAAAAAPAG-AP 118
H.sapiens      APRQ-PVLMAQMATAAGVAVGSAVGHAVGG----MFTGGGSSHAEQAPAAAAAPAG-AP 105
S.cerevisiae   AQTRQPGMFAQMASTAAGVAVGSAVGHAVGG----MFTGGGSSHAEQAPAAAAAPAG-AP 107
* : * :: **:* . **:* **:* **:* * * : * . . .

C.elegans      QASGYSQP-----CEFEWRQFVDCAQ-NQSDVSLCNGFNDFKQCKARYA-- 154
D.melanogaster YYAQQQQPNPEPQGACAWELKQFIQCAQ-GQADLTLCEGFNEALRQCKQSHHLQ 170
H.sapiens      QPAQQQQP-----CLYEIKQFLECAQ-NQGDIKLCEGFNEVLKQCRLANGLA 151
S.cerevisiae   TQTDQQLG----RTCEIDARNFTRCLDENNGNFQICDYLLQQLKACQEAAARQY 156
: . * : : * * : . . . : * : : : * :
```

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Guide Tree

[Show as Phylogram Tree](#) [Show Distances](#) [View DND File](#)

```
(
S.cerevisiae:0.36171,
(
C.elegans:0.28166,
D.melanogaster:0.26379)
:0.05587,
H.sapiens:0.26081);
```

Cladogram

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ClustalW2 Results

Results of search	
Number of sequences	4
Alignment score	13712
Sequence format	Pearson
Sequence type	aa
JalView	
Output file	clustalw2-20091231-1736287622.output
Alignment file	clustalw2-20091231-1736287622.aln
Guide tree file	clustalw2-20091231-1736287622.dnd
Your input file	clustalw2-20091231-1736287622.input

To save a result file right-click the file link in the above table and choose "Save Target As".
If you cannot see the JalView button, reload the page and check your browser settings to enable Java Applets.

Scores Table

SeqA	Name	Len (aa)	SeqB	Name	Len (aa)	Score
1	S.cerevisiae	825	2	C.elegans	782	43
1	S.cerevisiae	825	3	D.melanogaster	826	41
1	S.cerevisiae	825	4	H.sapiens	797	43
2	C.elegans	782	3	D.melanogaster	826	57
2	C.elegans	782	4	H.sapiens	797	56
3	D.melanogaster	826	4	H.sapiens	797	59

PLEASE NOTE: Some scores may be missing from the above table if the alignment was done using multiple CPU mode. Please check the output.

Alignment


```

**      *   :   :   *   .:::  ****:***::***** ..   :   :*****

D.melanogaster  ERVIAGMEKKTNVLAPEEKRTVAHHEAGHAVAGWFLEHADPLLKVSII PRGKG-LGYAQY 626
H.sapiens       ERVIGGLEKKTQVLQPEEKKTVAAYHEAGHAVAGWYLEHADPLLKVSII PRGKG-LGYAQY 608
C.elegans       ERVAGMEKKTQVLQKEEKKTVAAYHEAGHAIAGWFLQHADPLLKVSII PRGKG-LGYAQY 593
S.cerevisiae    ERVIGGVERKSKLLSPEEKKVVAAYHEAGHAVCGWYLKYADPLLKVSII PRGQ GALGYAQY 648
                ***:.*.*.*.*.:.*.  ***:.***:*****:.***:*.:*****:***:*.  *****

D.melanogaster  LPKDHILLSKEQLFDRMCMTLGGRAVEELFFNRITTTGAQDDLKKITDIAYSQVVRFGMNE 686
H.sapiens       LPKEQYLYTKEQLLDRMCMTLGGRAVEELFFGRITTTGAQDDLKRVTSAYAQIVQFGMNE 668
C.elegans       LPKEQYLYSKDQLLDRMCMTLGGRAVEELFFGRITTTGAQDDLQKVTQMAYSQVVKFGMSE 653
S.cerevisiae    LPGDIFLLTEQQLKDRMTMSLGGRVSEELHFPVTS GASDDFFKVTSMATAMVTELGMSD 708
                ** :  :*  :::**  ***  *:*****:.**:.  *  :*:**:**:*.  *  :  :.:.**:.

D.melanogaster  KVGQVSFDVQGADPVFSEKPYSEDTAQLIDNEVRSIIKCAHEATTSLLTKHKENVQKVAE 746
H.sapiens       KVGQISFDLPRQGMVLEKPYSEATARLIDDEVRI LINDAYKRTVALLTEKKADVEKVAL 728
C.elegans       KVGPLSFETPAPGEMAFDKPYSEATAQLIDQEVRLVMNARRTRDLLLEKRSDIERVAL 713
S.cerevisiae    KIGWVNYQK--RDDS LTKPFSDETGDIIDSEVYRIVQECHDRCTKLLKEKAEDVEKIAQ 766
                *:*  :.:.  .:  :  **:*  *  .  :**.*  :.  .  **  :.  :.:.:*

D.melanogaster  RLLQNEVLSRDDMIELLGPRPFKEKS-TYEEFVEGTGSFEEDTTLPEGLKSWNKEKERTE 805
H.sapiens       LLEKEVLDKNDMVELLGPRPFAEKS-TYEEFVEGTGSLDEDTSLPEGLKDWNKEREKEK 787
C.elegans       RLLEKEILNREDMIELVGKRPFVEKN-TYEEMVSGTGGLDENVLPKLENWNKESK 772
S.cerevisiae    VLLKKEVLTREDMIDLGKRPFPERNDAFDKYLN-----DYETEKIR-----KEEEKNE 815
                **:*  *  :.***:*.  *  ***  *  .  :.:.  :.  :.  .  **  *  :

D.melanogaster  PLDAGSTPSSPPTKPVT AQSS 826
H.sapiens       -----EPPGKVN--- 797
C.elegans       -----KDEEKKNDE--- 782
S.cerevisiae    -----KRNEPKPSTN--- 825

```

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Guide Tree


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```

(
(
S.cerevisiae:0.35217,
C.elegans:0.21433)
:0.01718,
D.melanogaster:0.20407,
H.sapiens:0.20120);

```

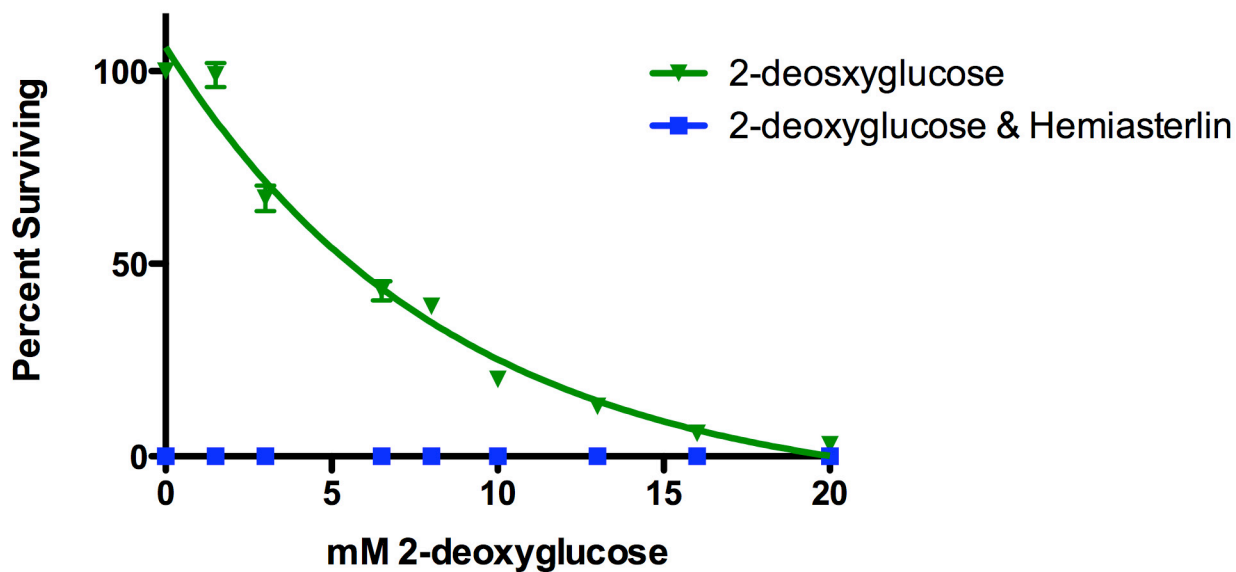
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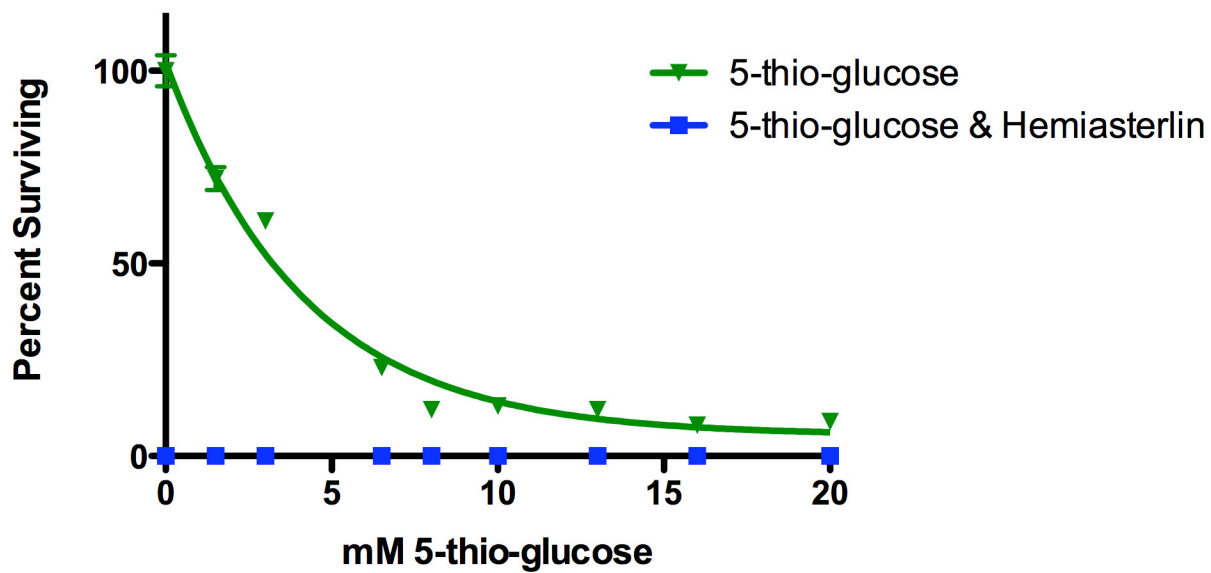
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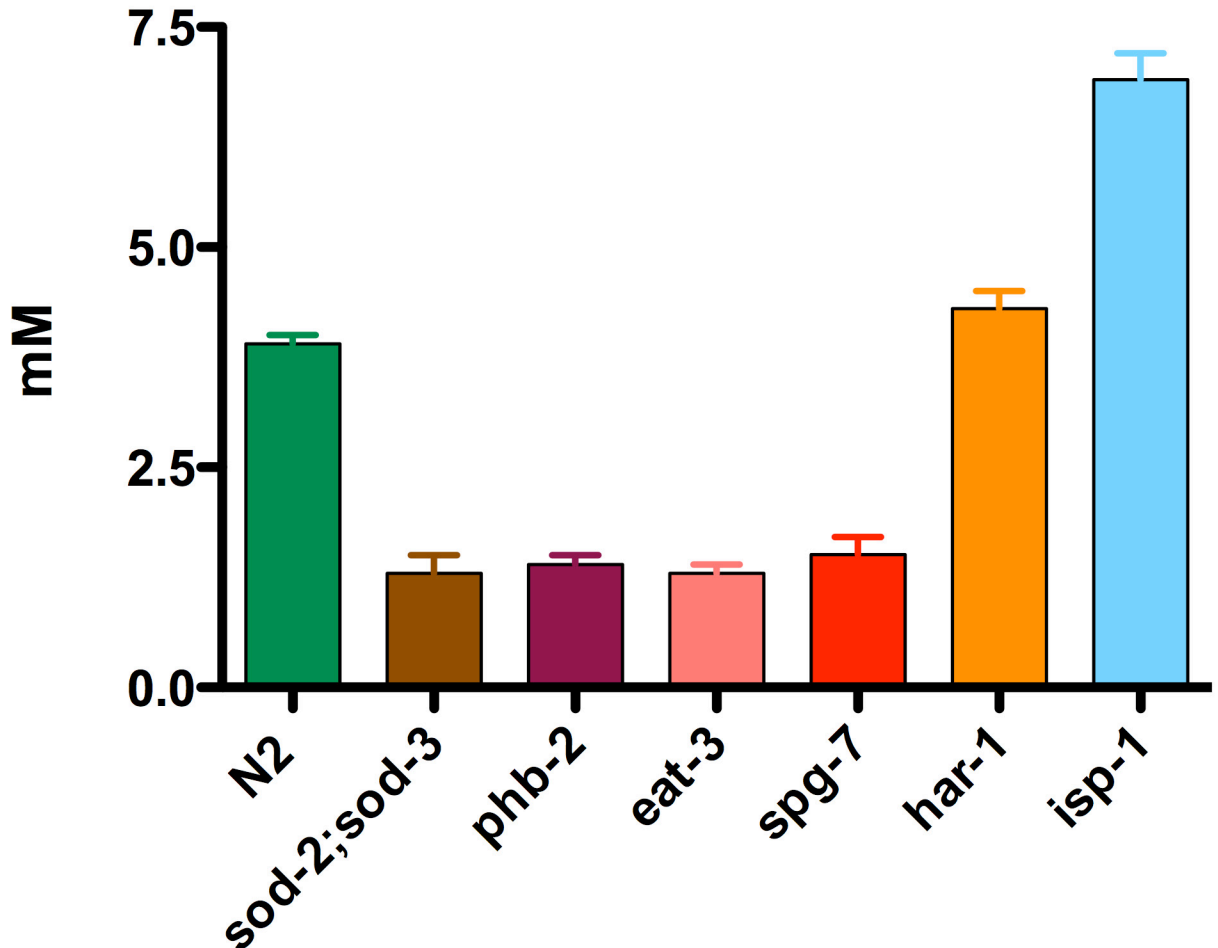
2-deoxyglucose + Hemiasterlin



5-thio-glucose + Hemiasterlin



Lethal Dose of Paraquat



H2O2 Production

