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NHR-49/PAARα and HLH-30/TFEB cooperate for C. elegans host defense via a flavin-containing monooxygenase

Khursheed A. Wani
University of Massachusetts Medical School

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Laboratory of Javier Irazoqui

Department of Microbiology and Physiological Systems

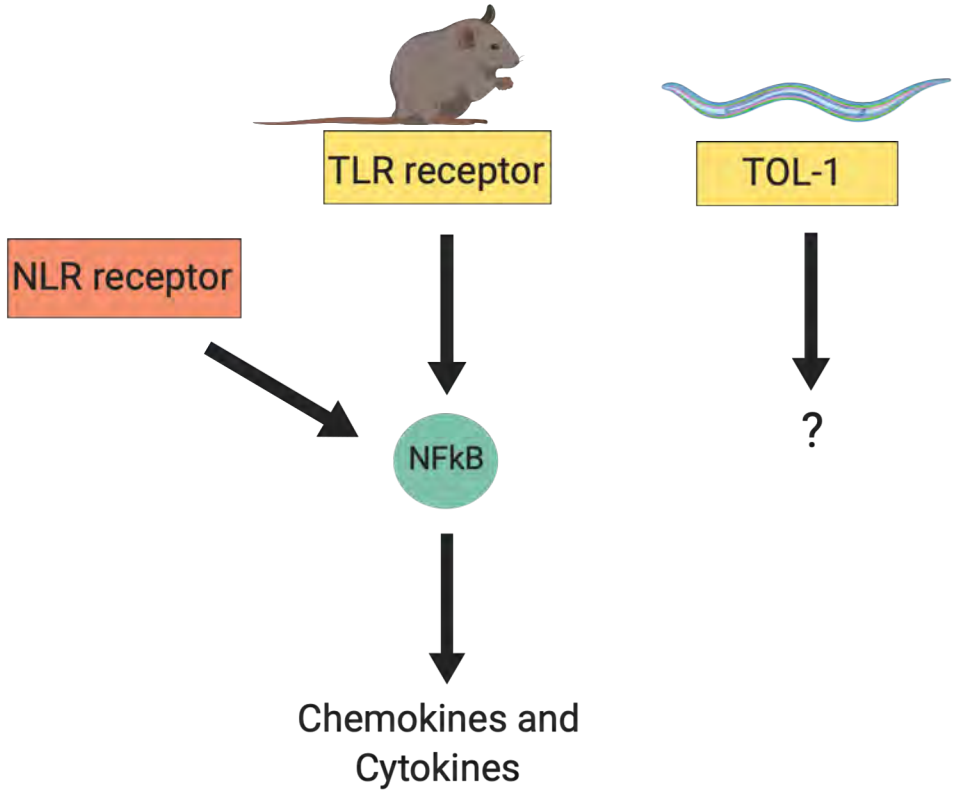
UMASS 2020 Retreat

C. elegans natural habitat poses a challenge to survive

Natural habitats and substrates of *C. elegans*

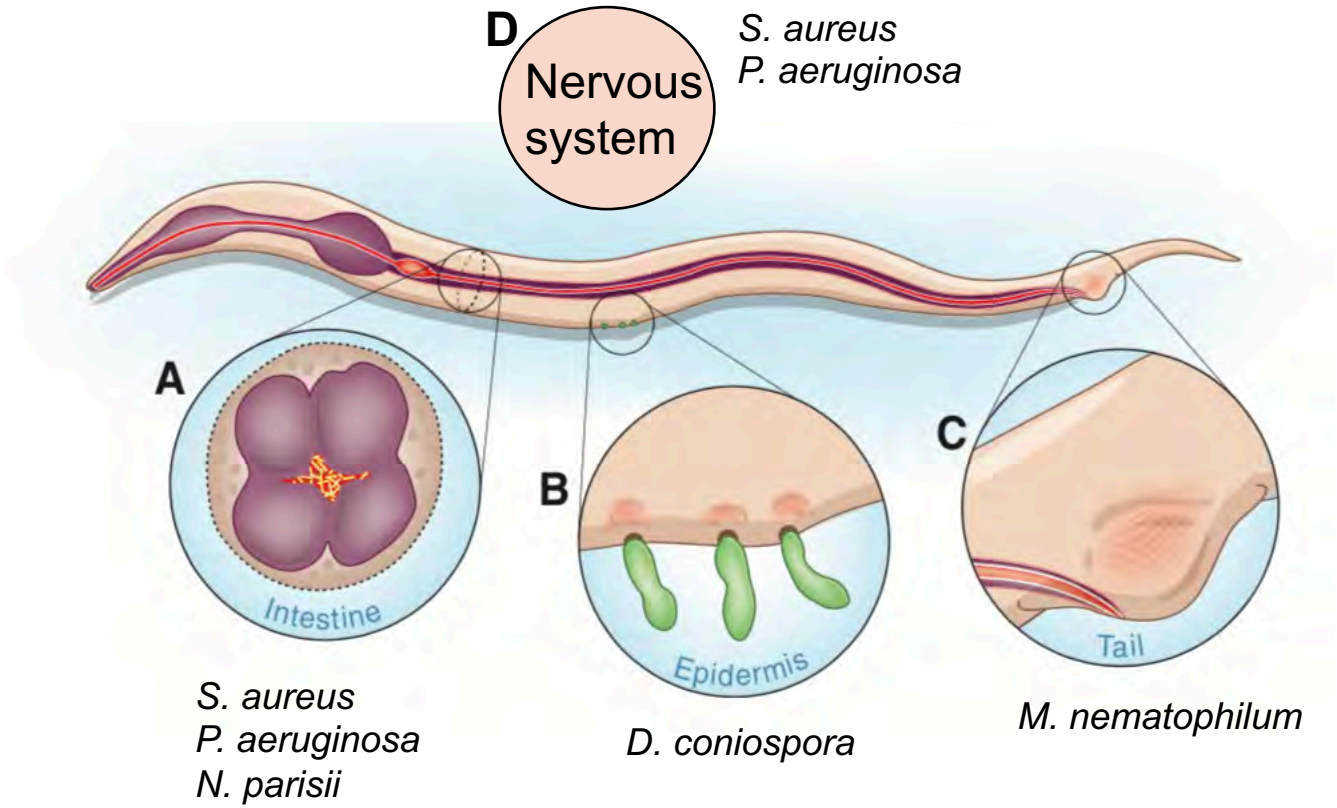
(Hinrich Schulenburg, and Marie-Anne Félix; 2017)

C. elegans lack conventional innate immune response pathways



- It is not clear whether *C. elegans* sole TLR, TOL-1, functions in innate immunity.
- *C. elegans* genome does not encode NFkB.
- Unlike mammals, *C. elegans* lack cell-mediated immunity.

C. elegans show transcriptional response to pathogens



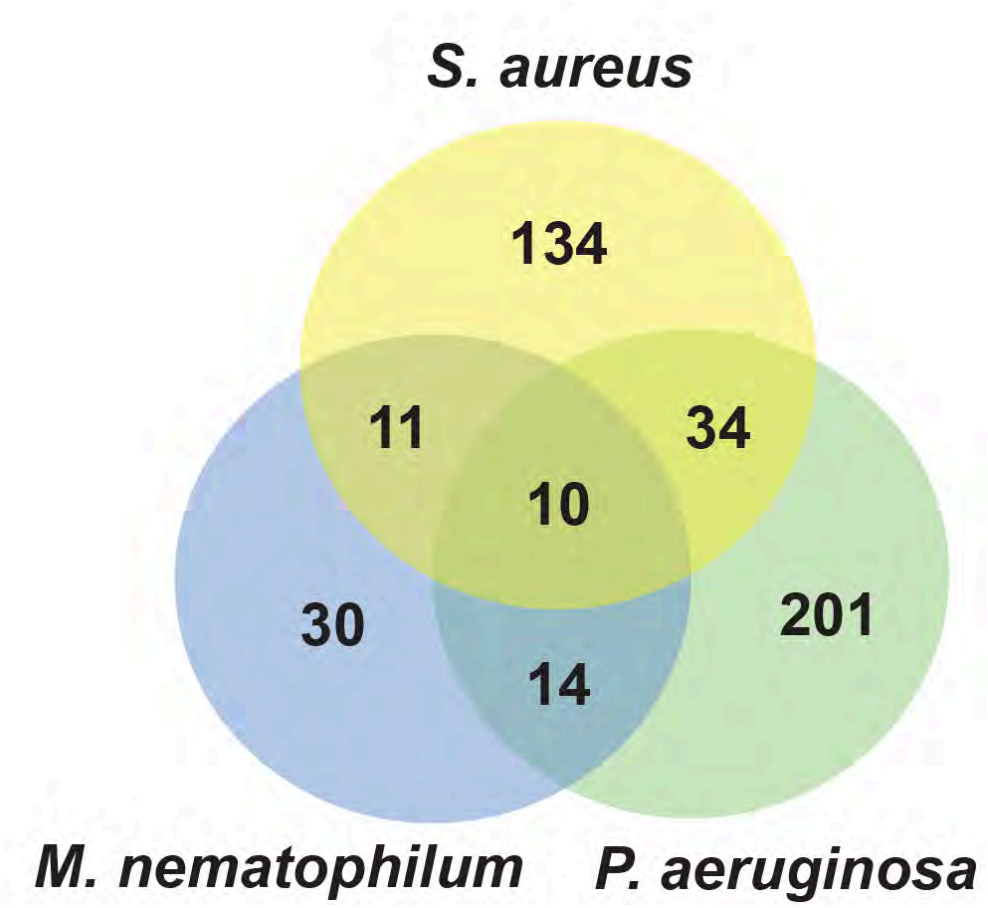
(Picture modified from Kim D, 2008)

Host defense genes:

- Anti-microbial peptides
- Lysozymes
- Lectins

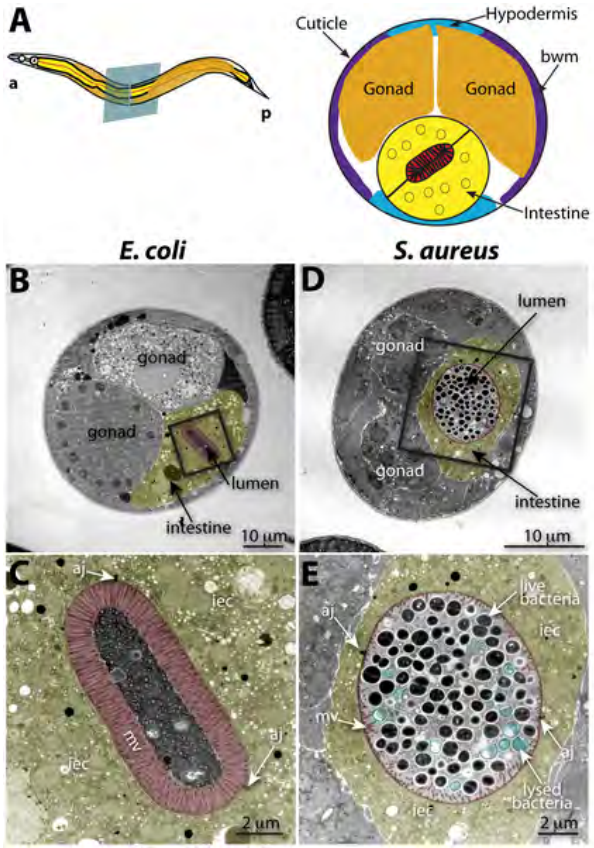
(Work carried out in Fred Asubel, Jonathan Hodgkin, Jonathan Ewbank, Dennis Kim, Alejandro Aballay, Emily Troemel, Read Pukkila-Worley, & Javier Irazoqui labs)

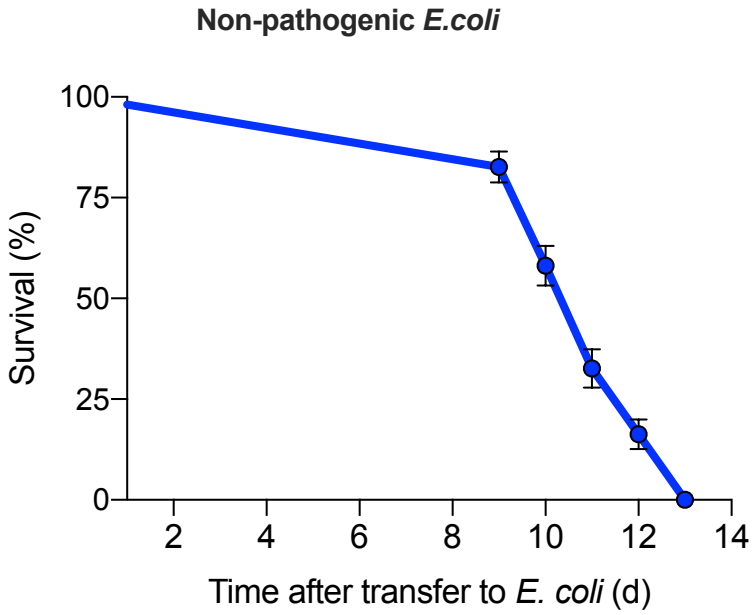
C. elegans show a pathogen-specific transcriptional response

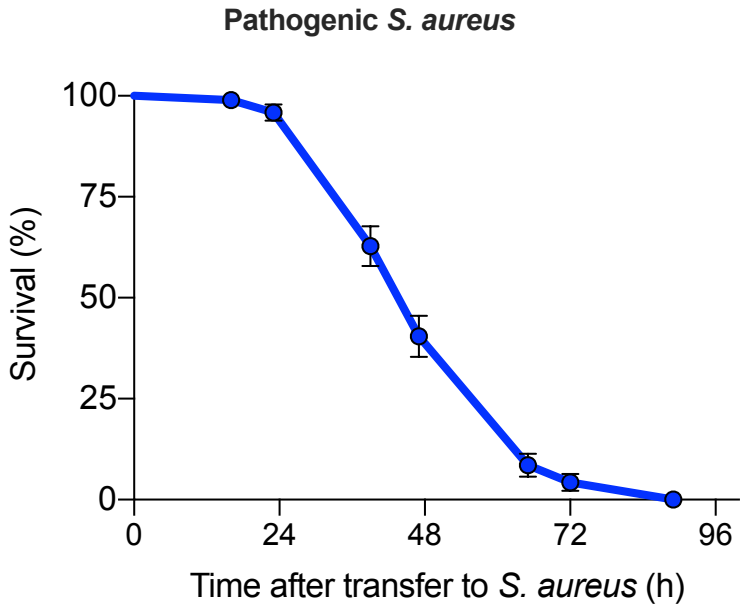


(Irazoqui JE et al; 2010)

S. aureus destroys *C. elegans* intestinal epithelial cells

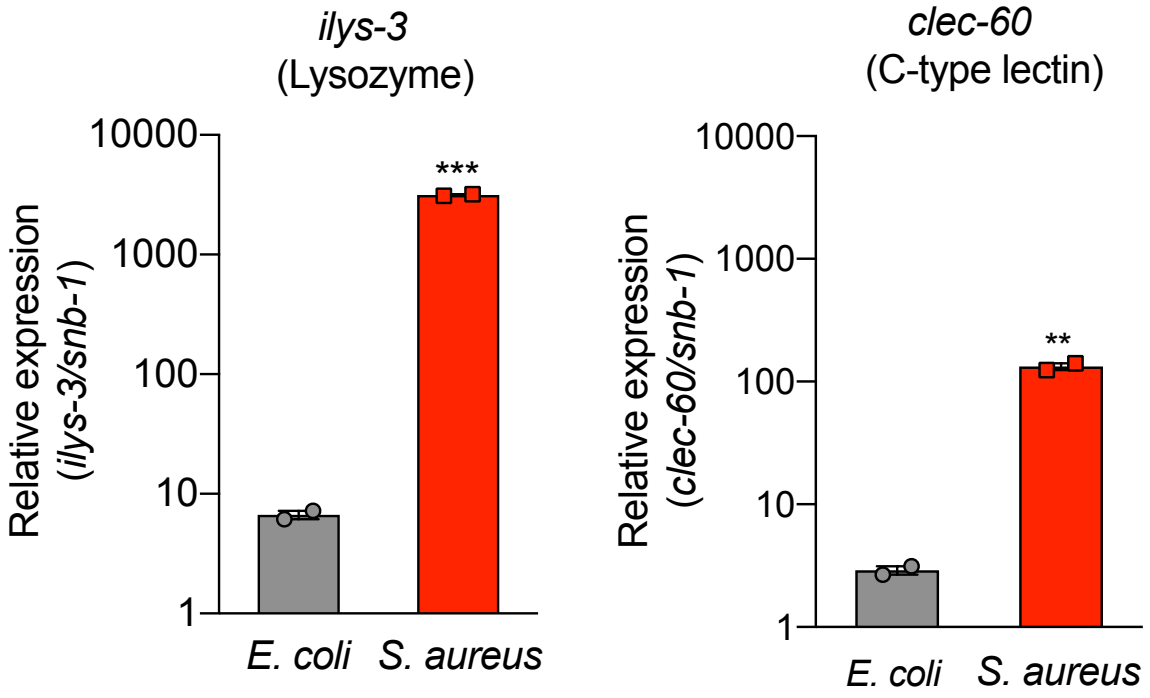


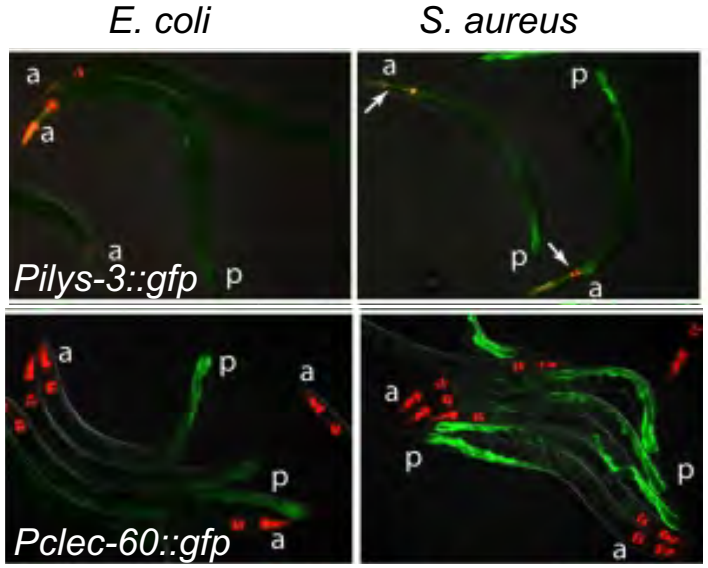




(Irazoqui et al, 2010)

C. elegans fight infection by the induction of host defense genes



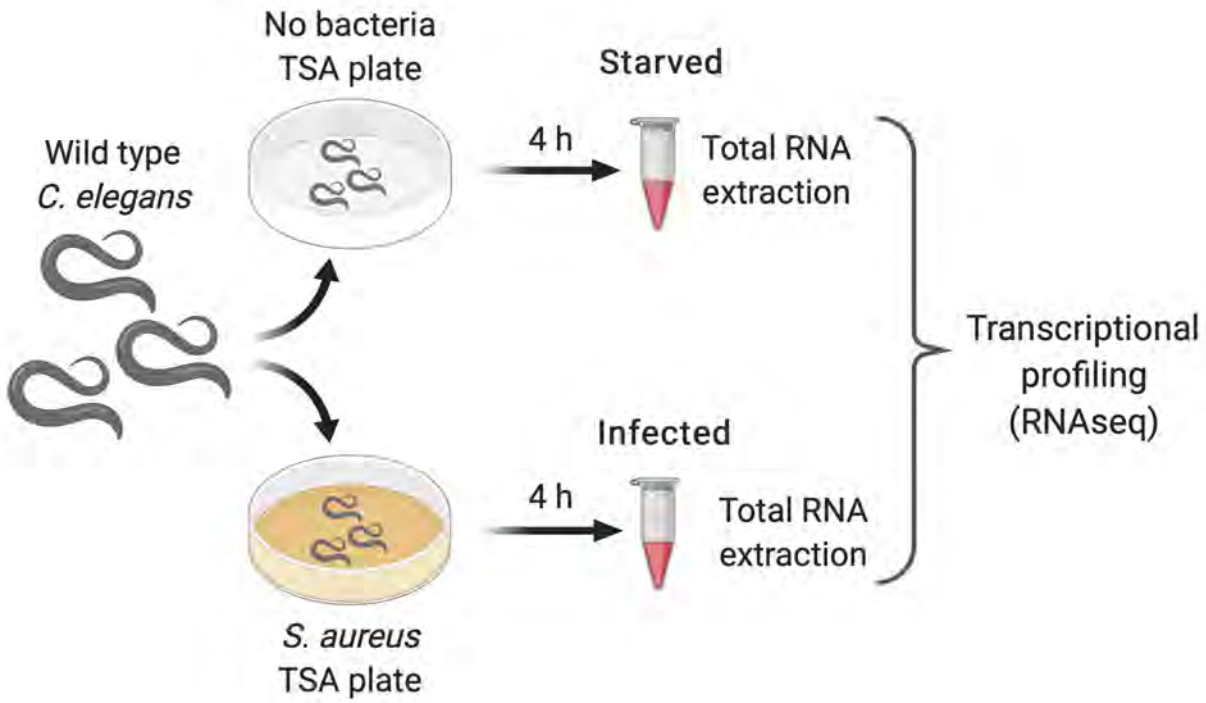


(Irazoqui JE et al; 2010)

S. aureus infection poses a nutritional challenge

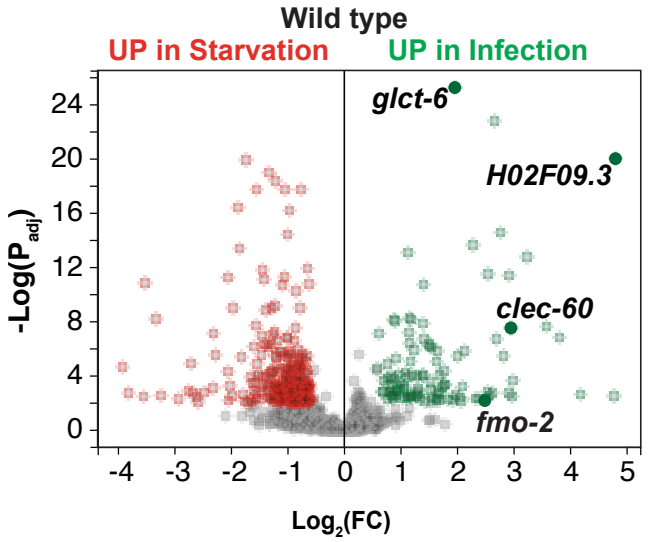
How much of the host response is due to infection as opposed to the nutritional challenge?

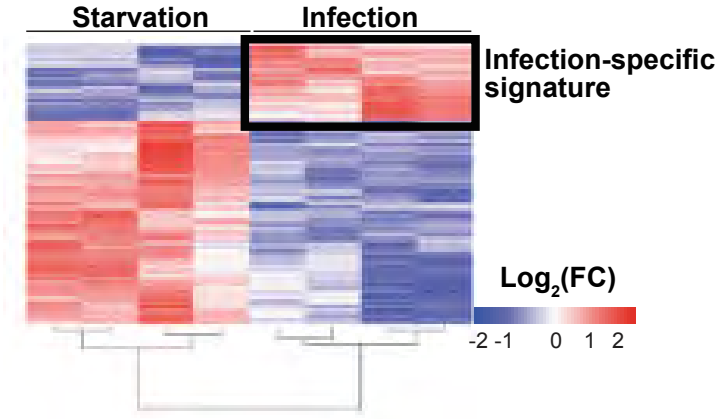
Can we separate metabolic stress from infection?



Wani et al; under revision

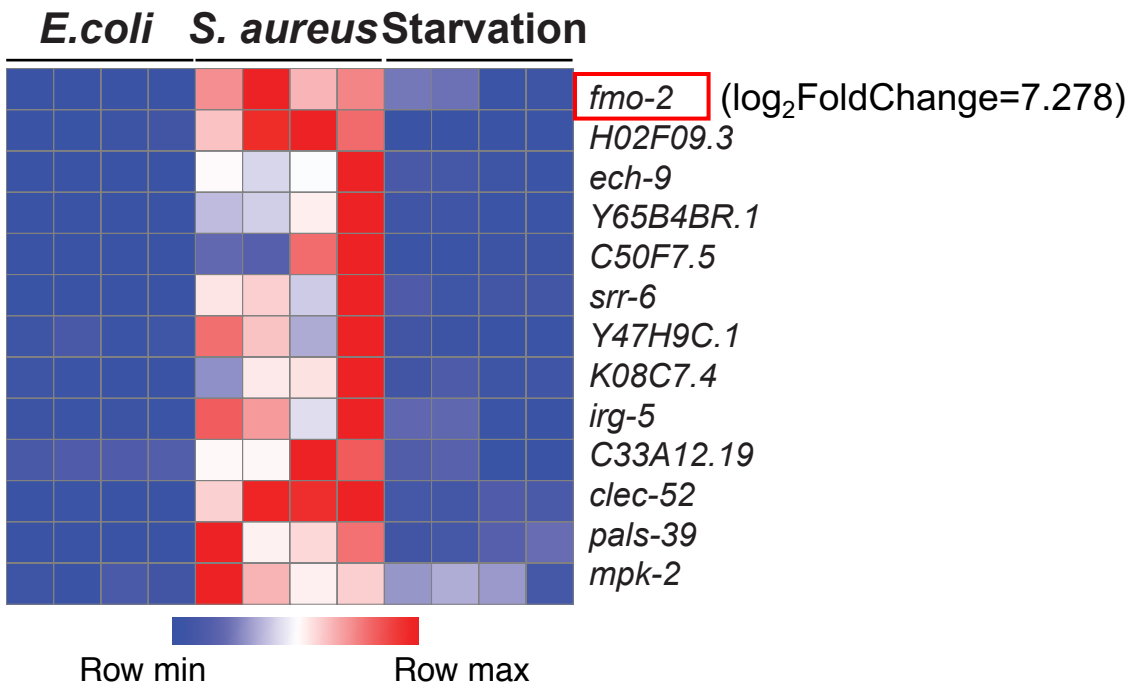
Identification of infection-specific gene signature



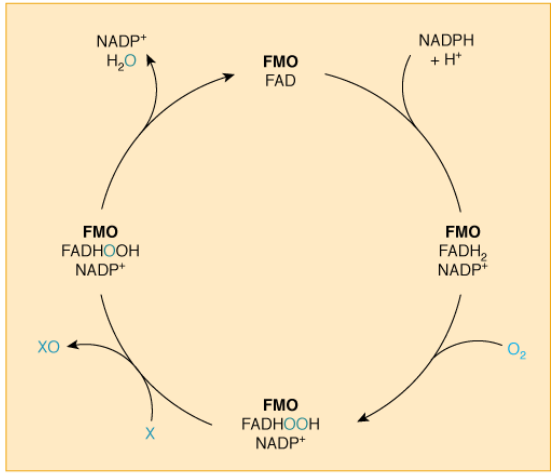


Wani et al; under revision

FMO-2 is a highly-induced infection-specific gene

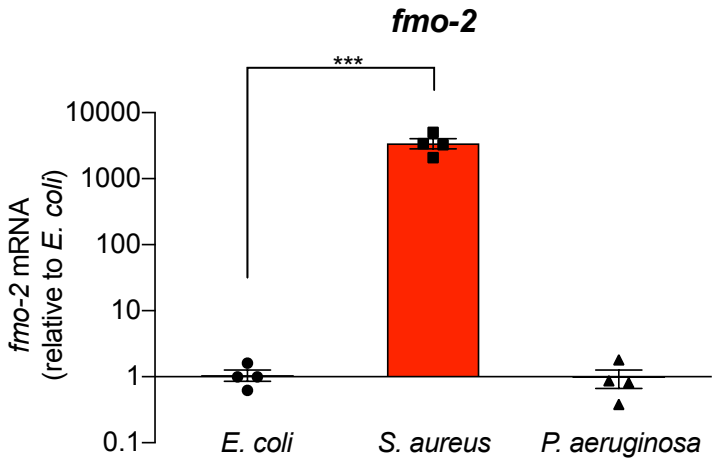


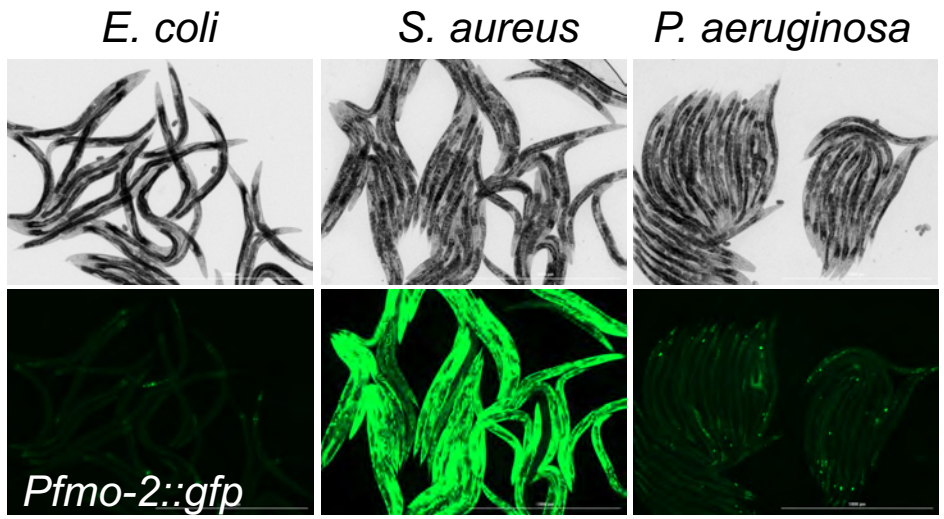
- *fmo-2* encodes flavin-containing monooxygenase
- Detoxification of xenobiotic substances
- In Arabidopsis, FMO1 functions in host defense

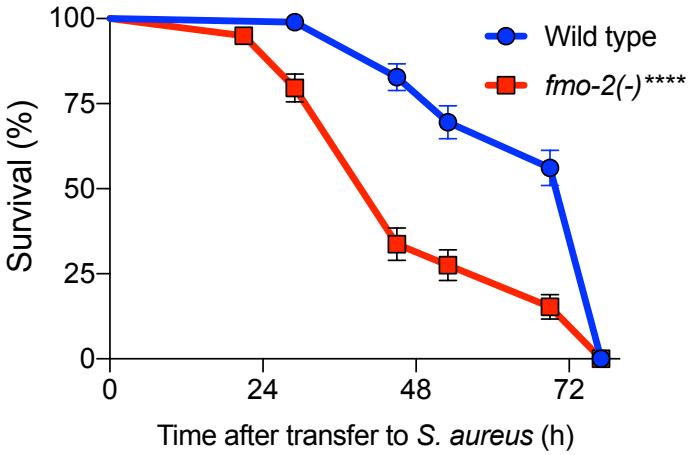


Wani et al; under revision

FMO-2 is a pathogen-specific host defense gene

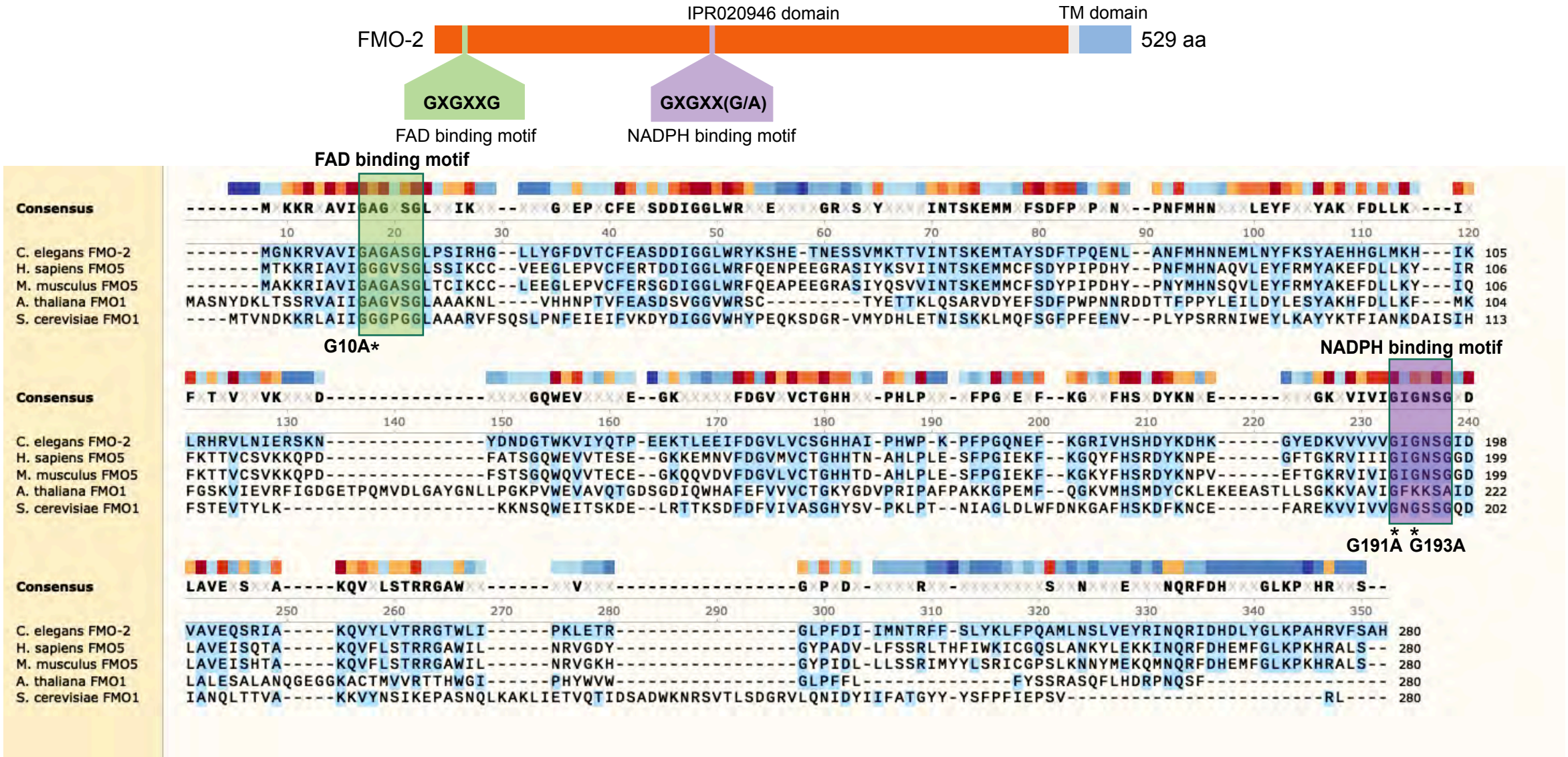




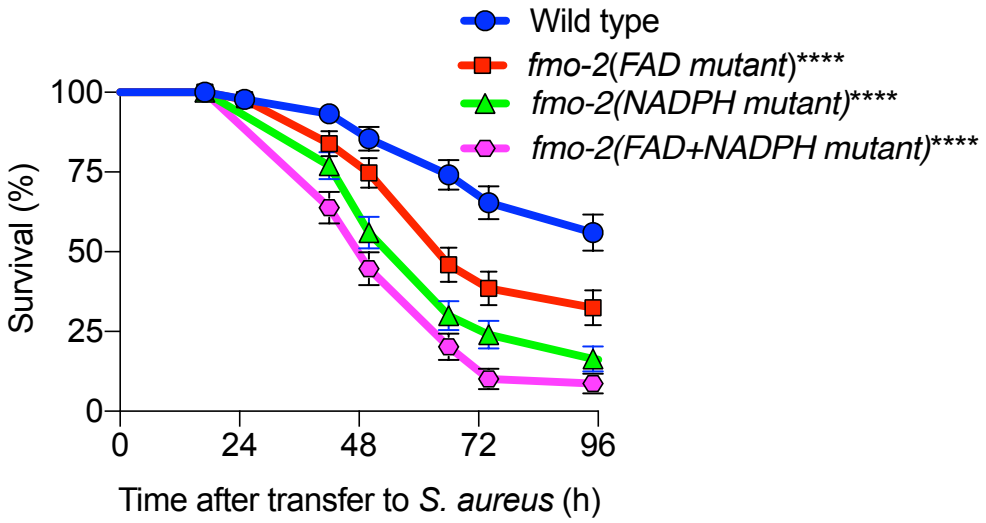


Wani et al; under revision

FAD and NADPH motifs are evolutionarily conserved

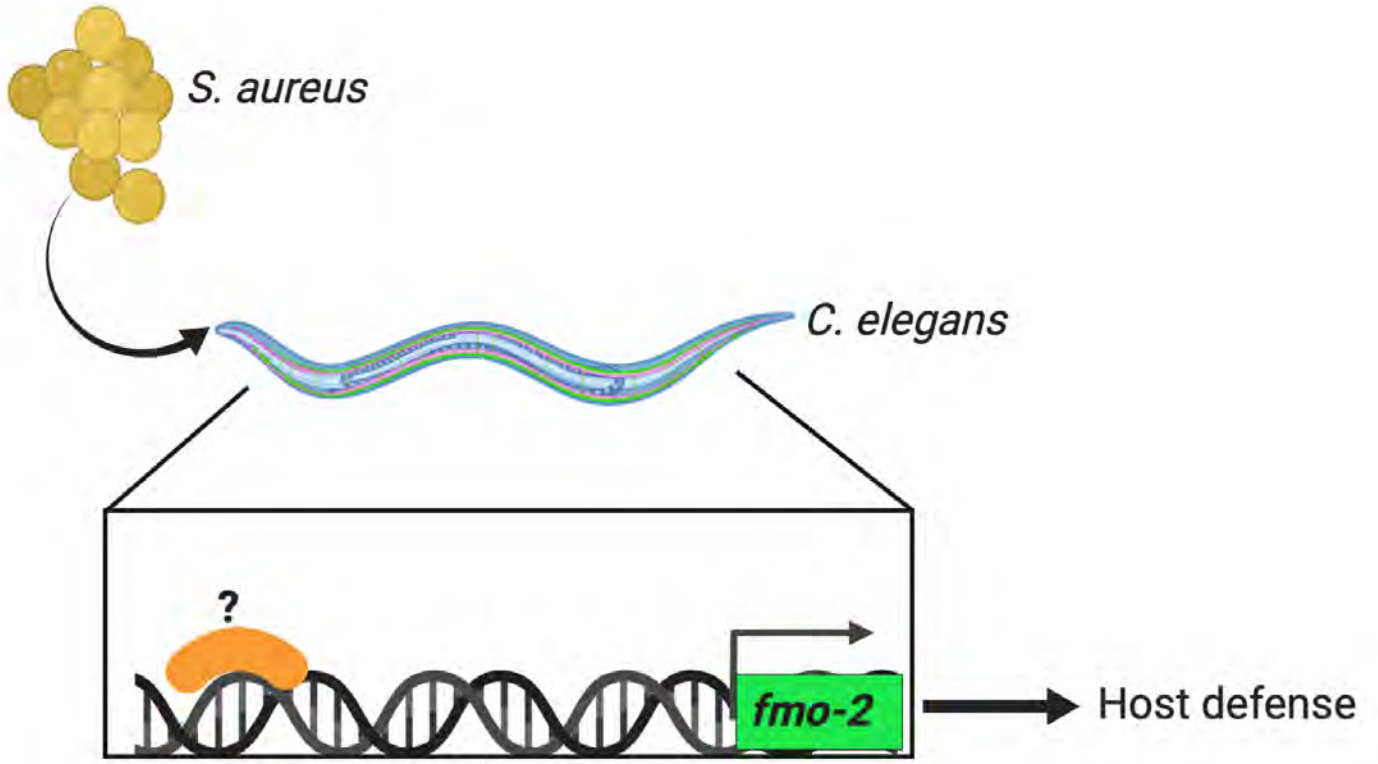


FMO-2 catalytic activity is required for host defense

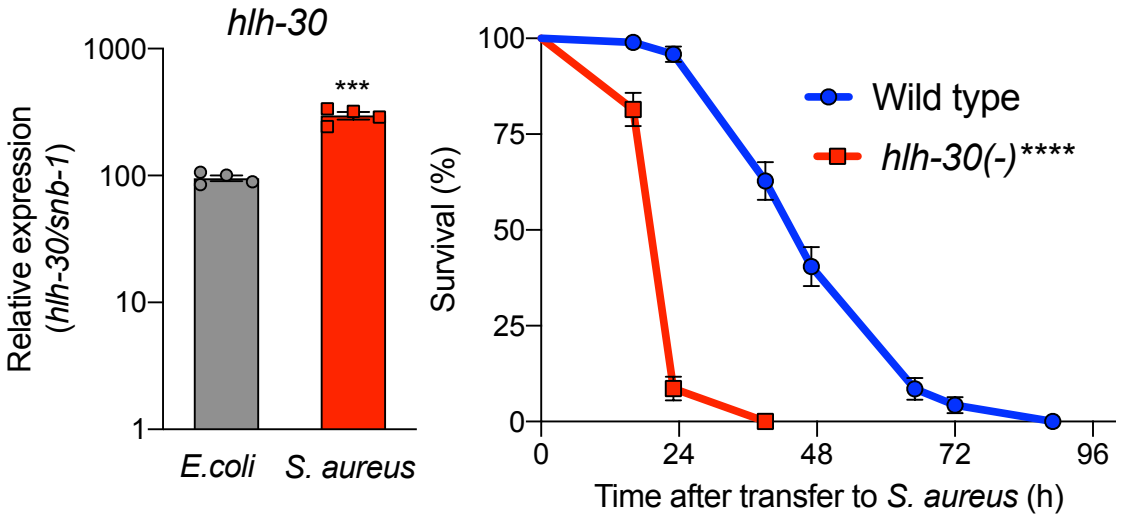


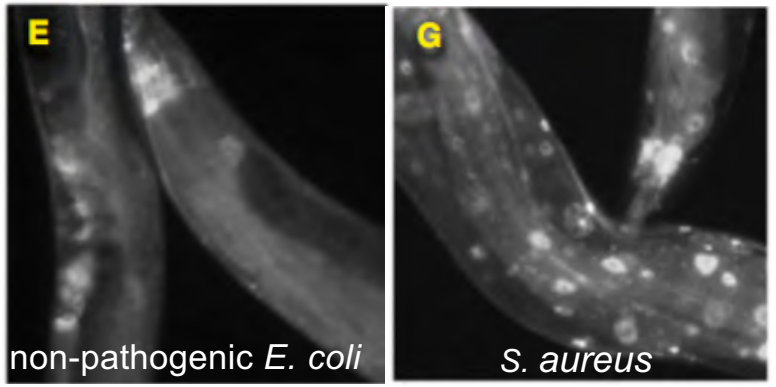
Wani et al; under revision

fmo-2 induction is required for host defense

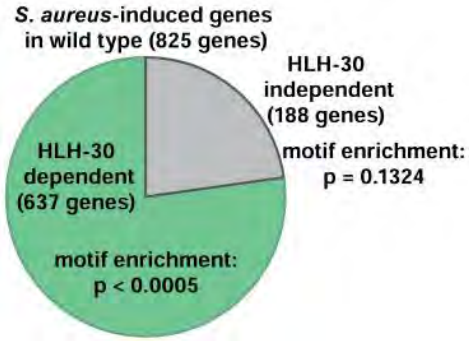


HLH-30/TFEB is important for host response to infection





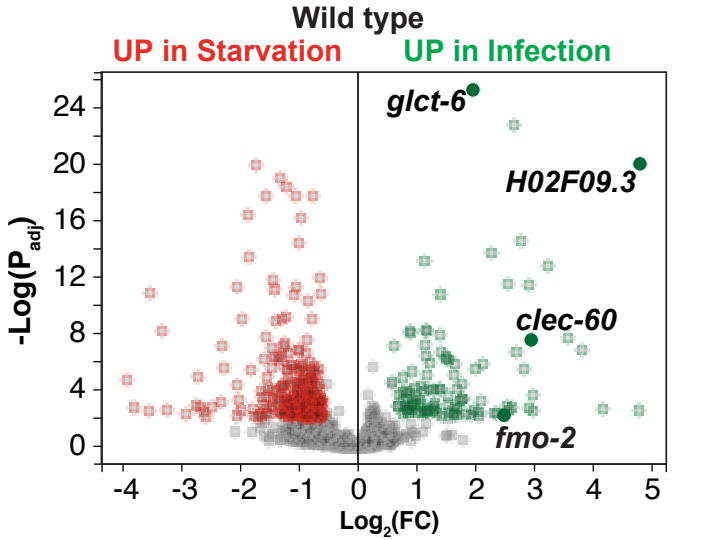
P*hlh-30::hlh-30::gfp*

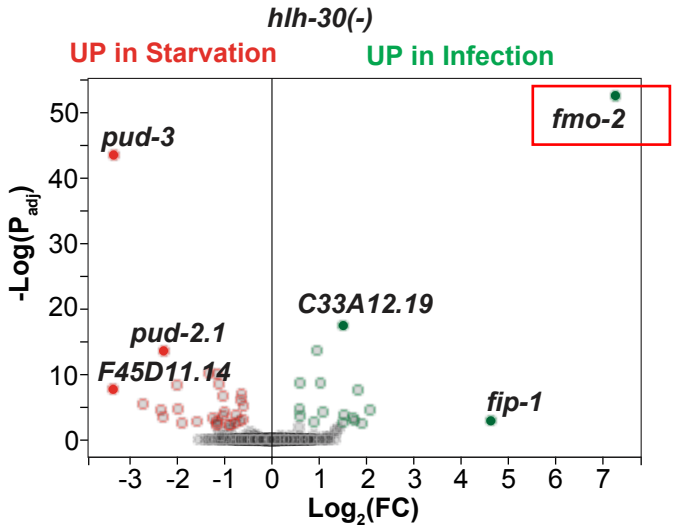


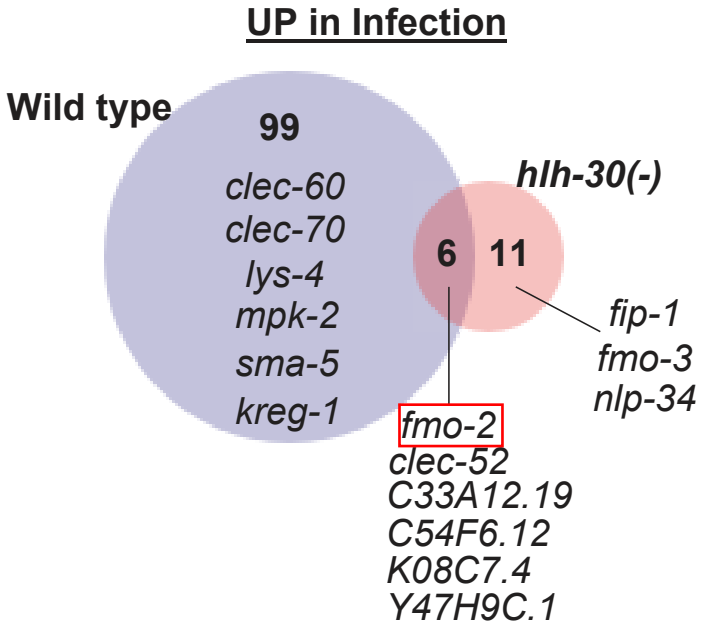
~80% HLH-30-dependent genes

(Visvikis O et al; 2014)

fmo-2 induction is independent of HLH-30/TFEB







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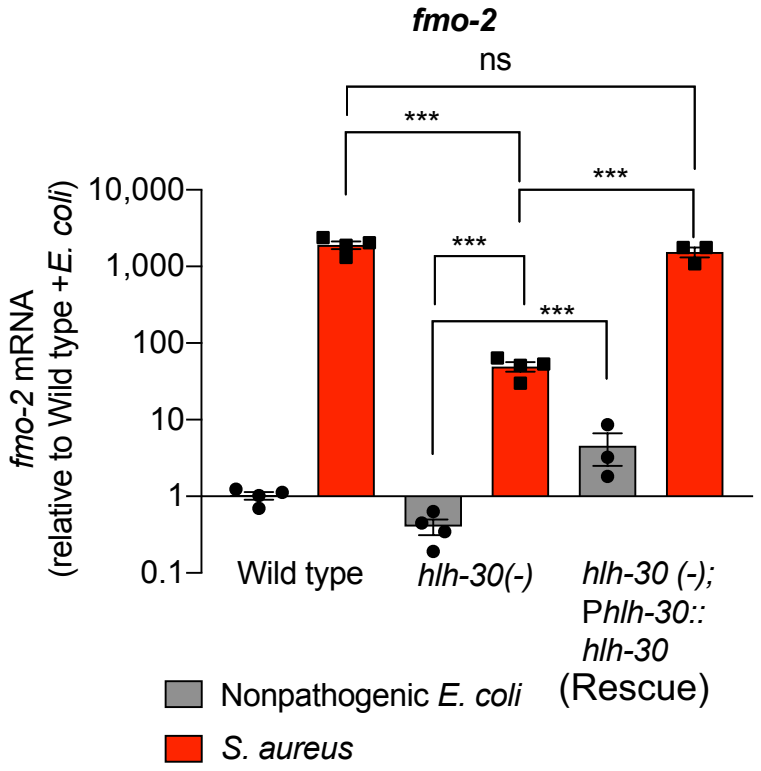
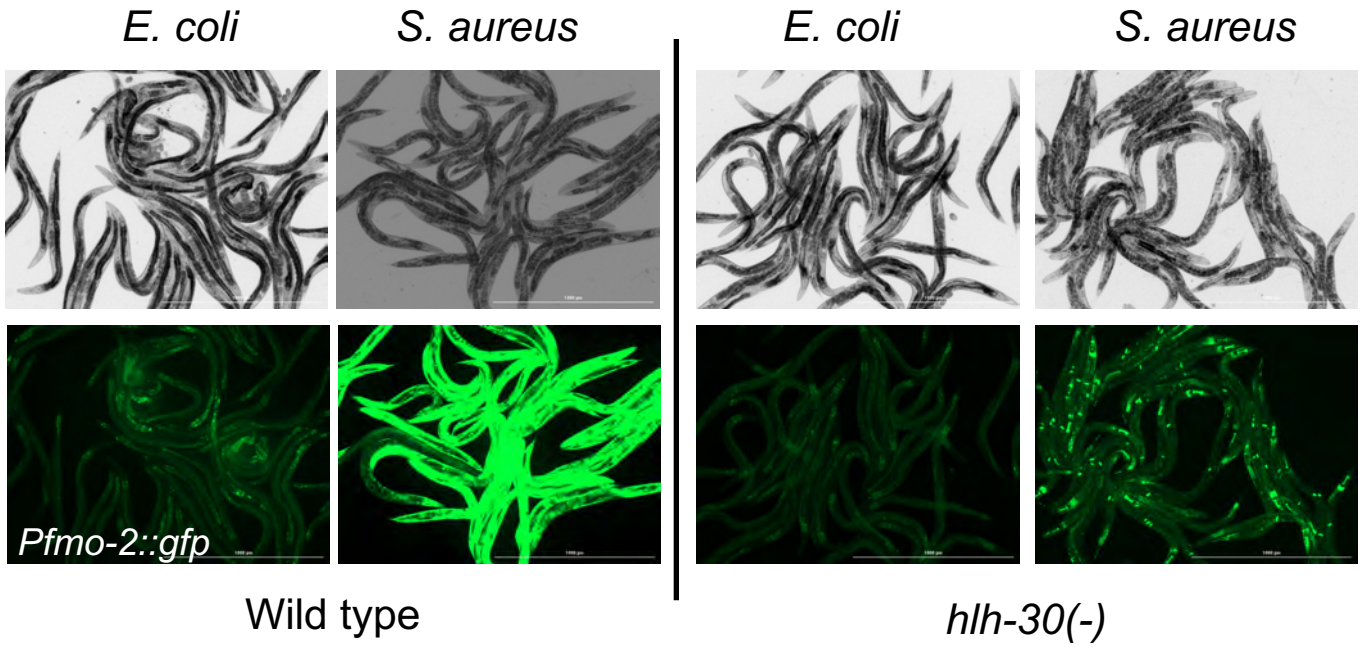
HLH-30/TFEB is partially required for *fmo-2* induction during infection





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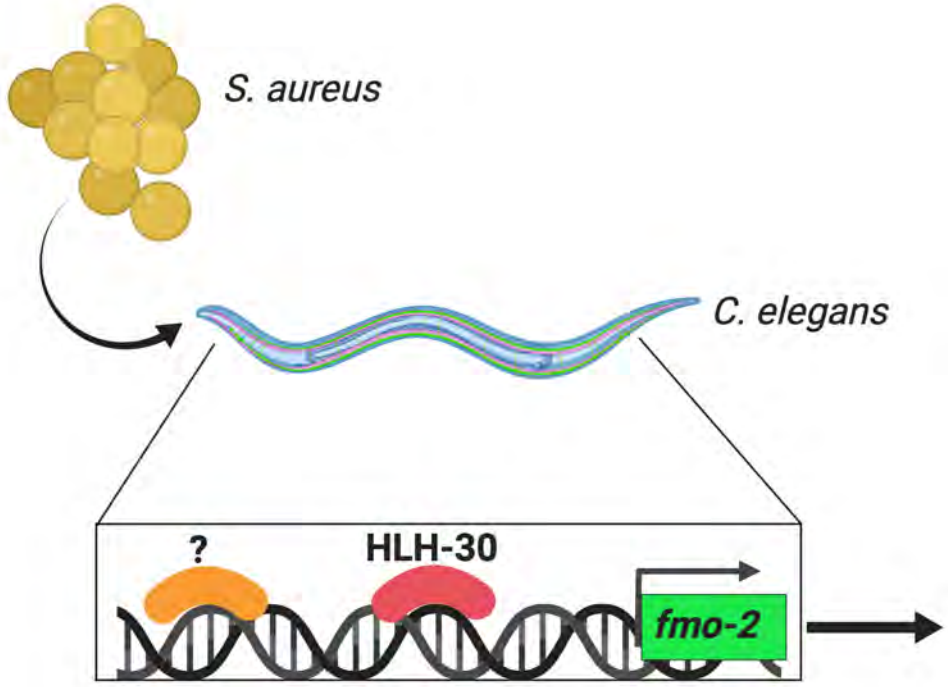
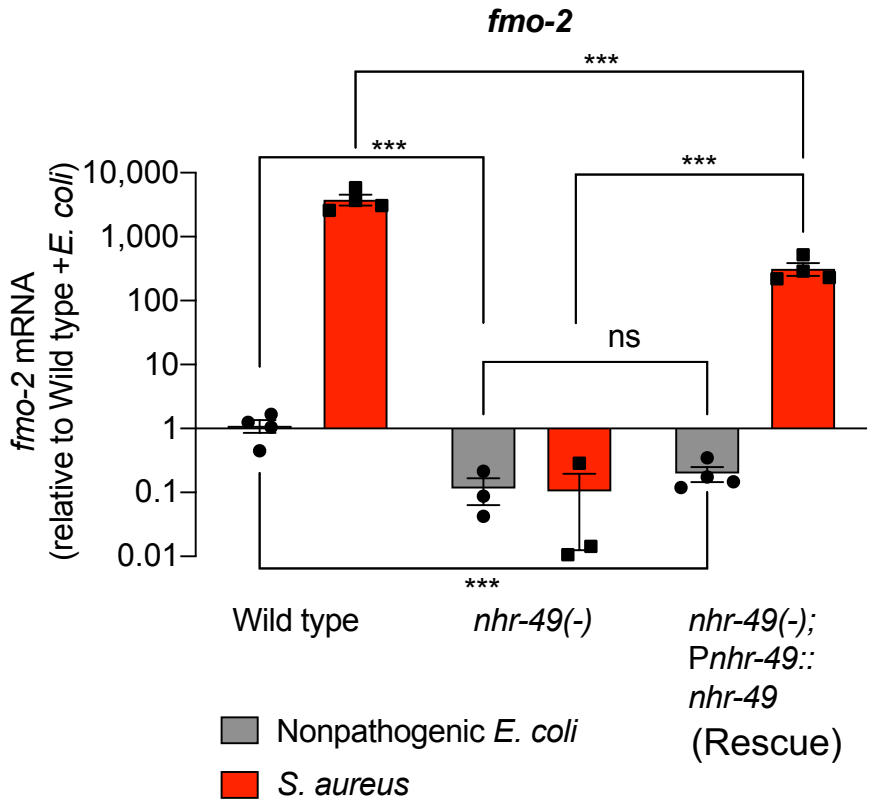
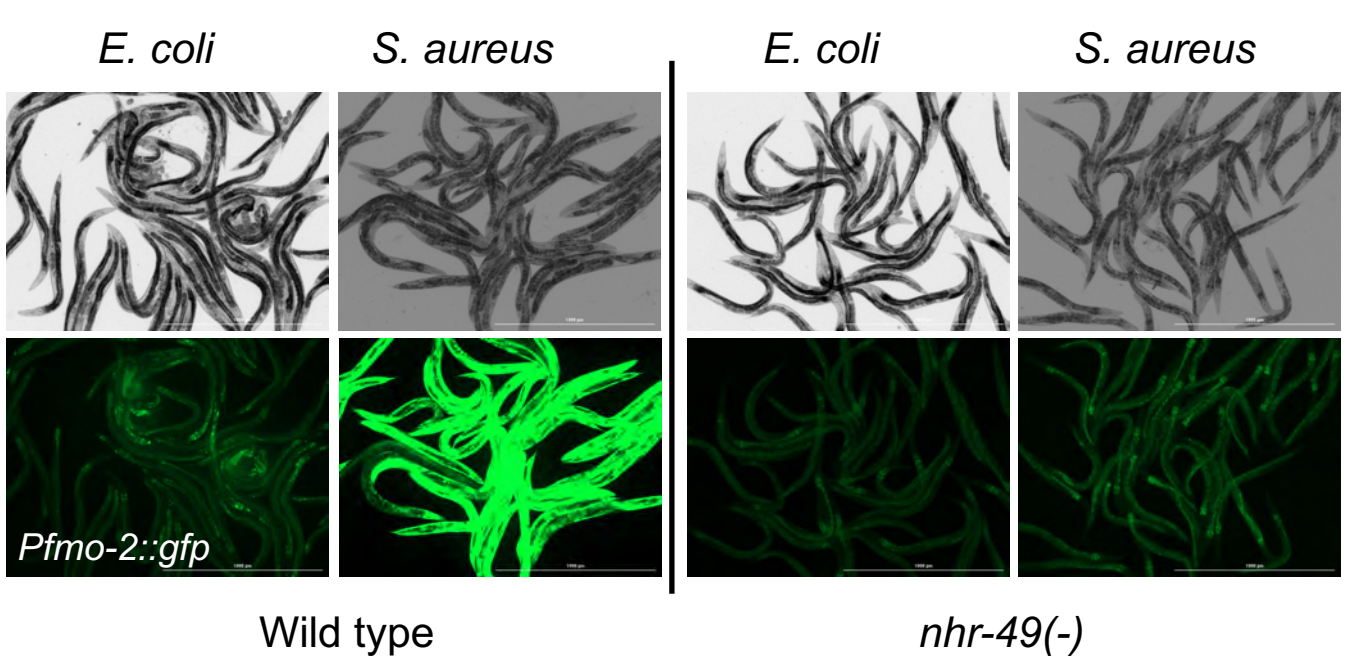
What else does regulate *fmo-2* induction during infection?



NHR-49/PPARα is essential for *fmo-2* induction during infection





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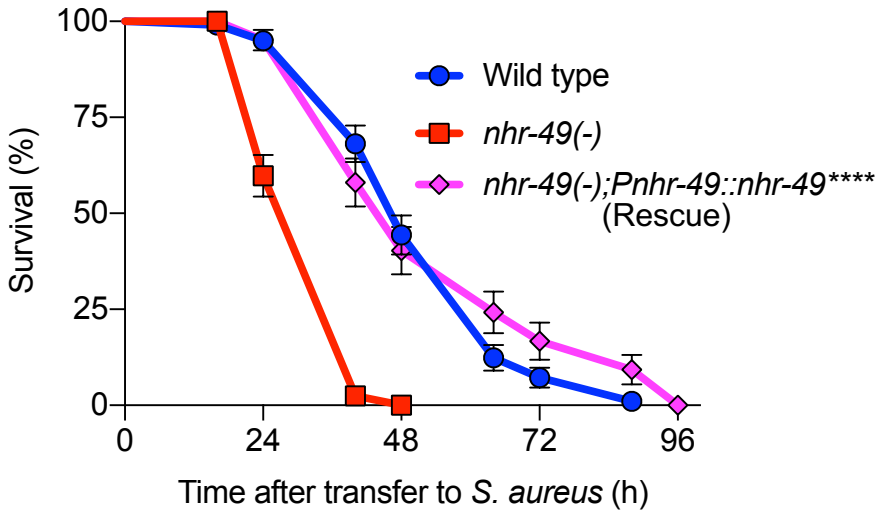
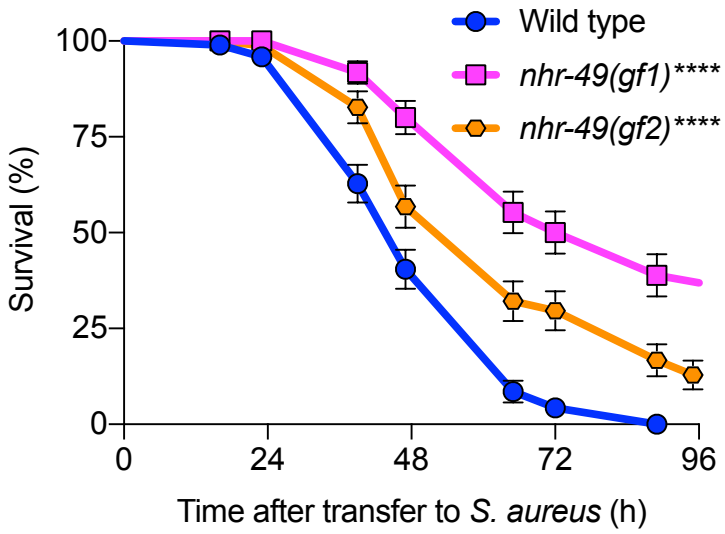
NHR-49/ PPARα is necessary and sufficient for host survival





gf= gain of function

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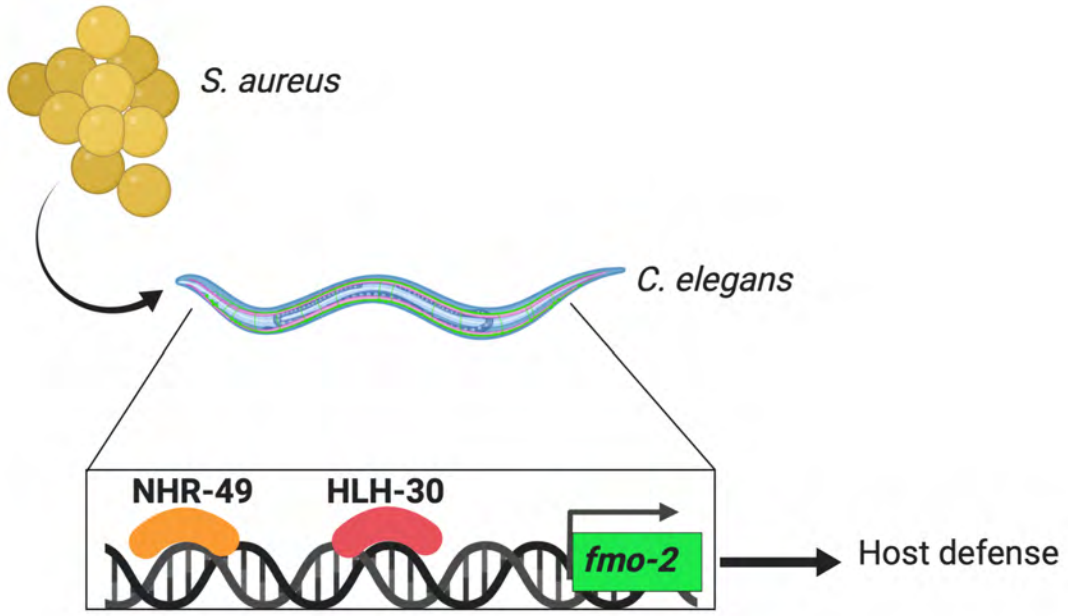
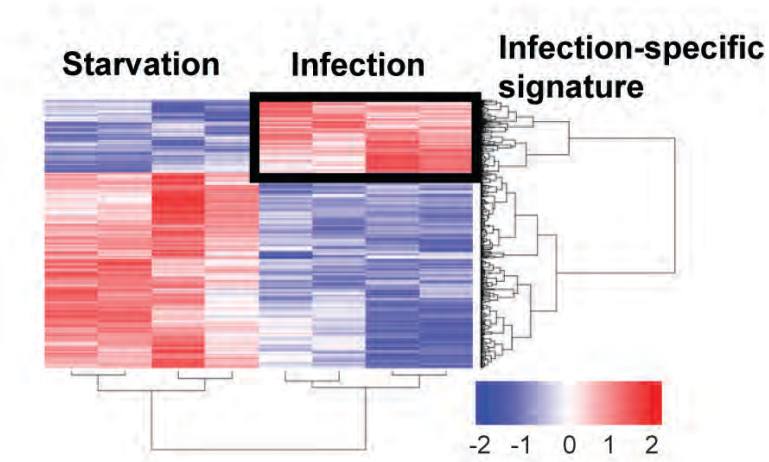
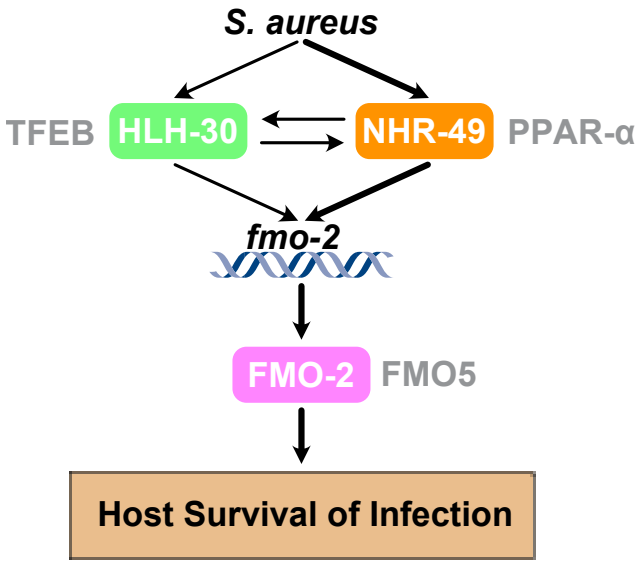
HLH-30 and NHR-49 regulate host defense via *fmo-2* induction



Summary





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Acknowledgements

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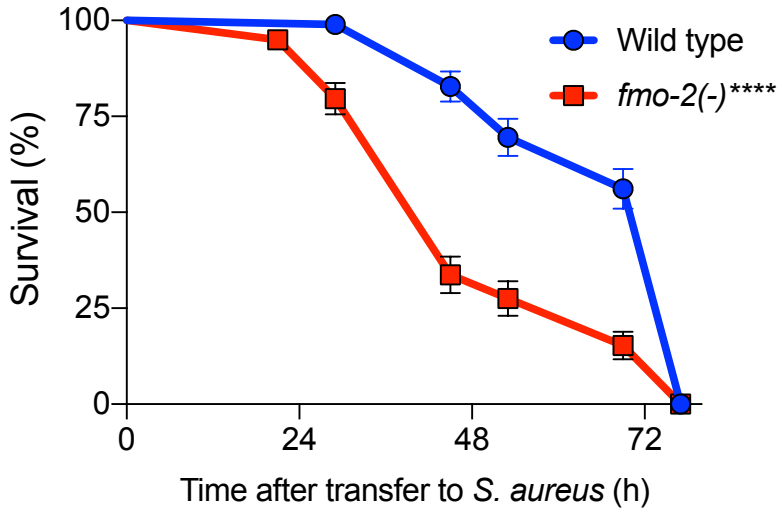
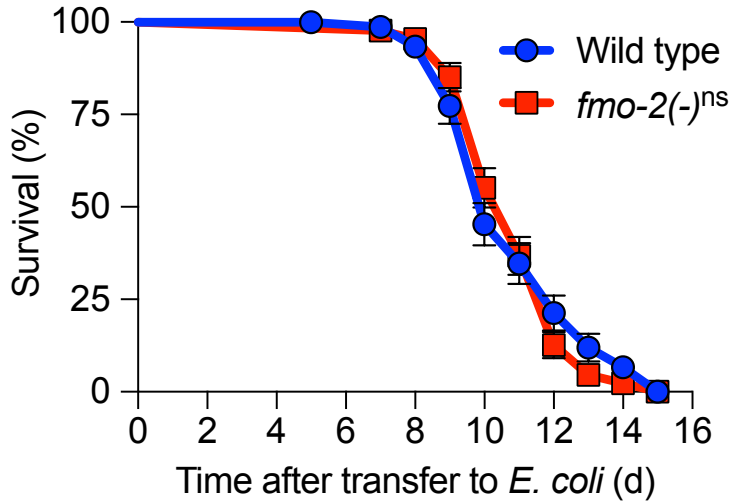
- Mehran Najibi
- Joseph Moreau
- Xavier Gonzales
- Havisha Honwad

Collaborators:

- Stefan Taubert (Univ. of British Columbia)
- Arjumand Ghazi (Univ. of Pittsburgh)
- Ramesh Ratnappan (Ghazi lab)

fmo-2 mutants are hypersensitive to infection





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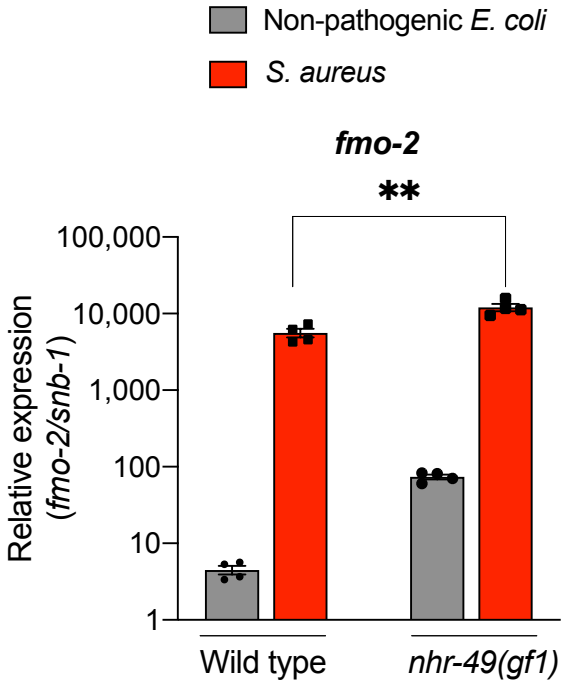
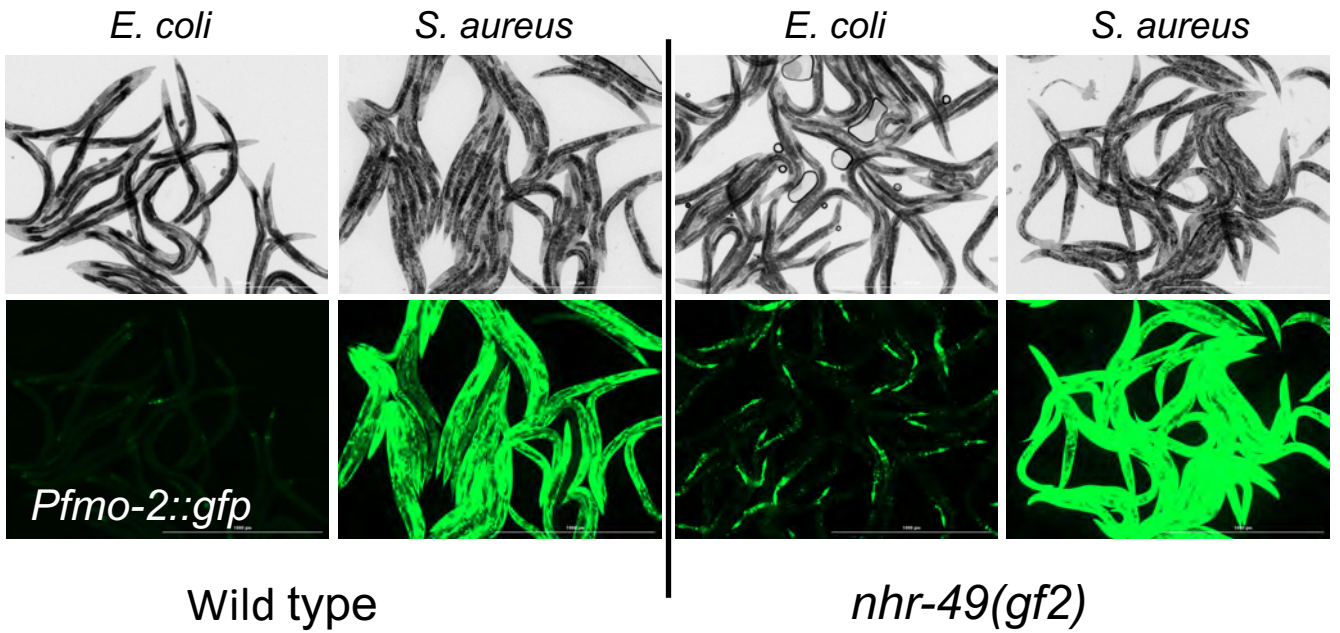
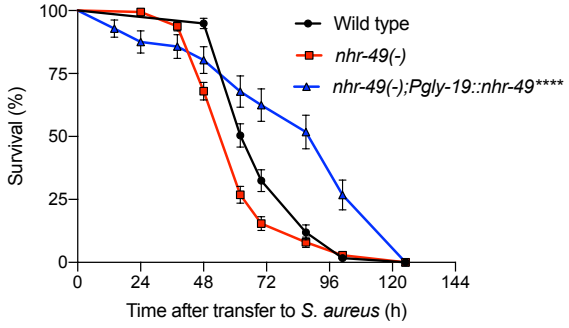
NHR-49 gain-of-function causes *fmo-2* overexpression

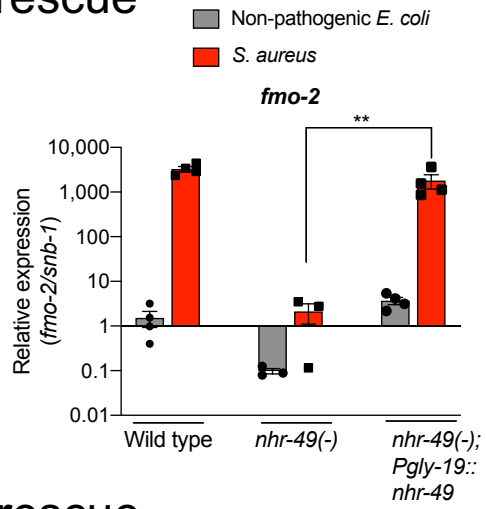




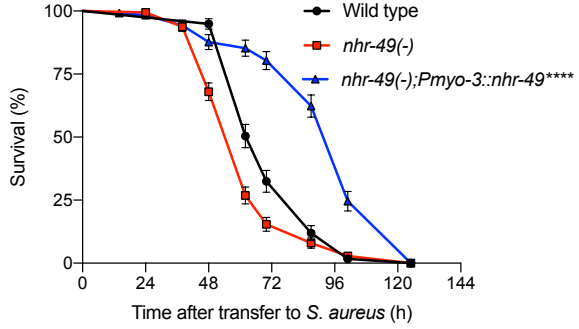
NHR-49 functions cell non-autonomously for host defense and *fmo-2* induction

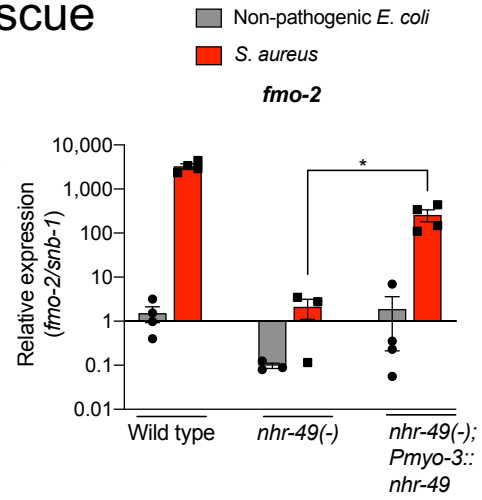
Intestinal rescue



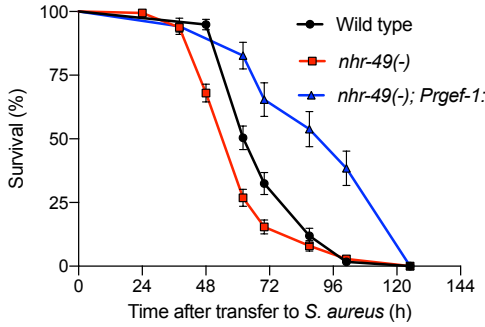


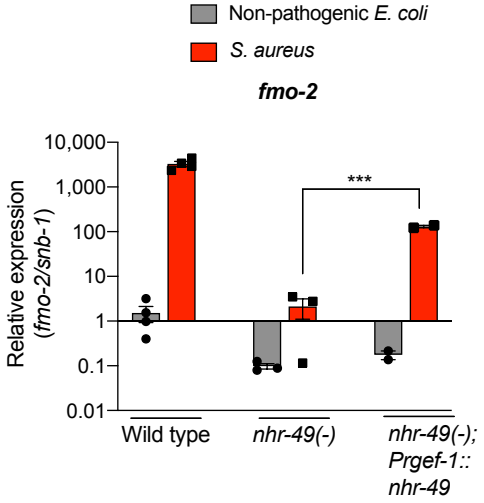
Muscle rescue



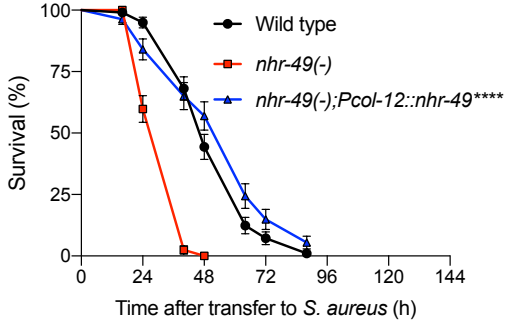


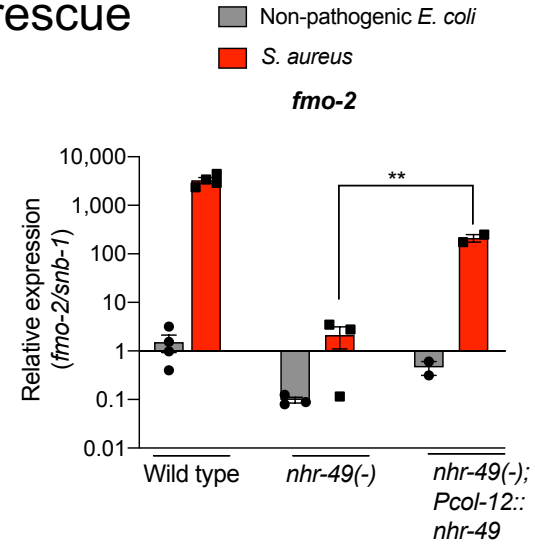
Neuronal rescue



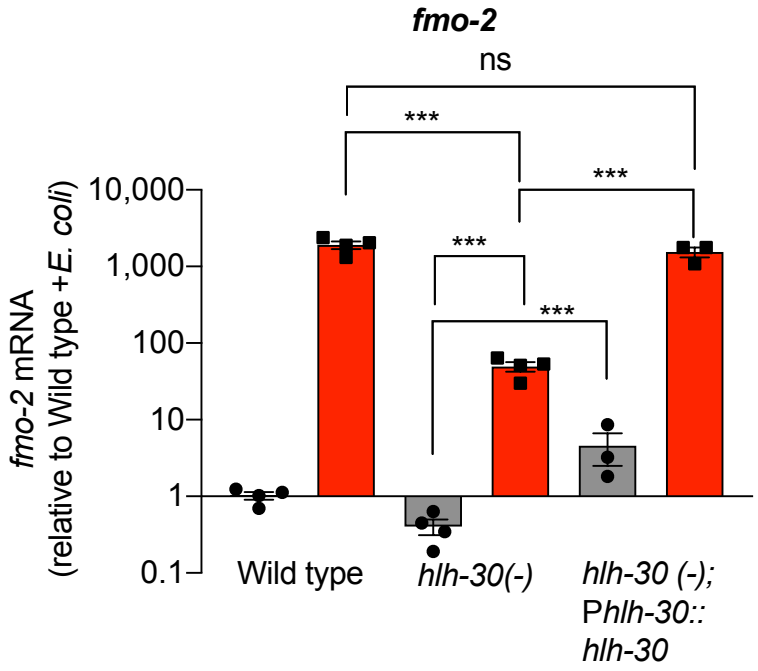


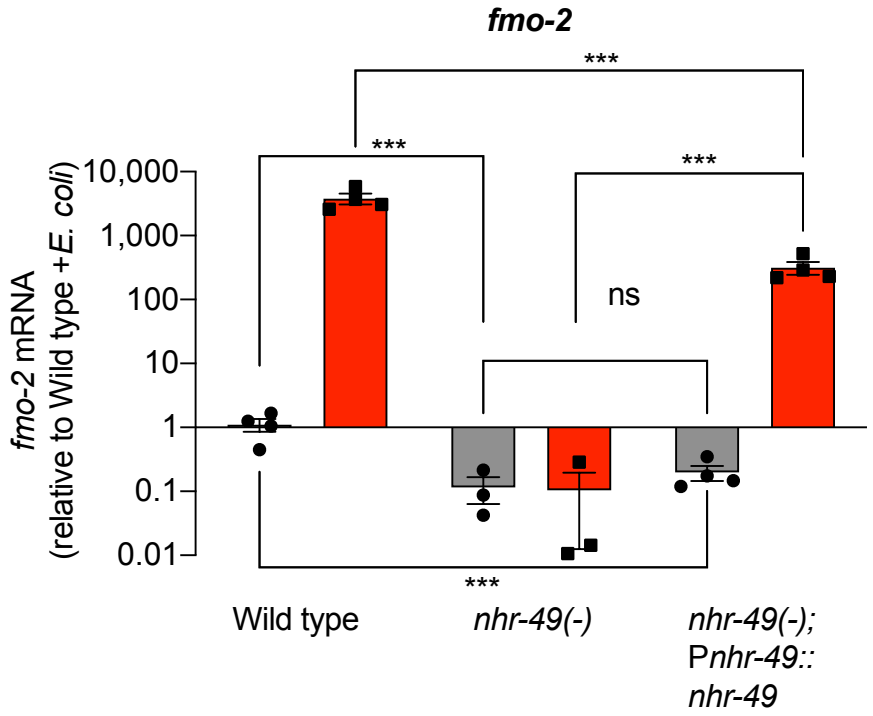
Epidermis rescue





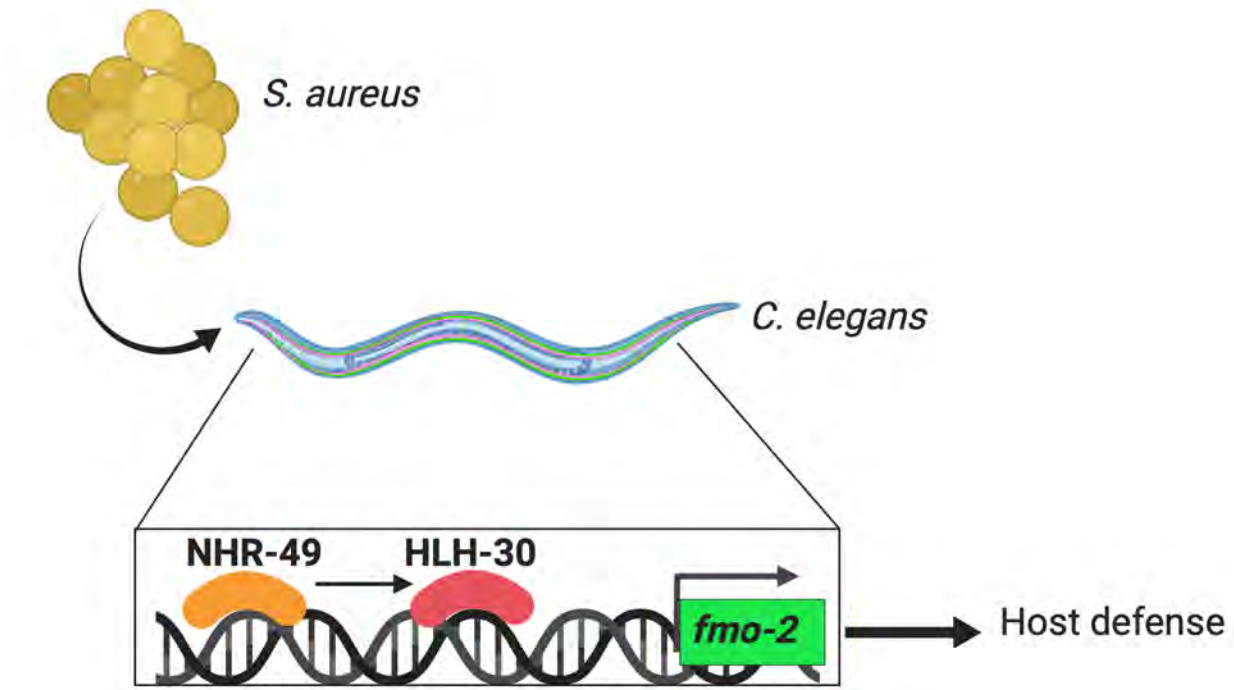
Loss of NHR-49 is stronger than loss of HLH-30



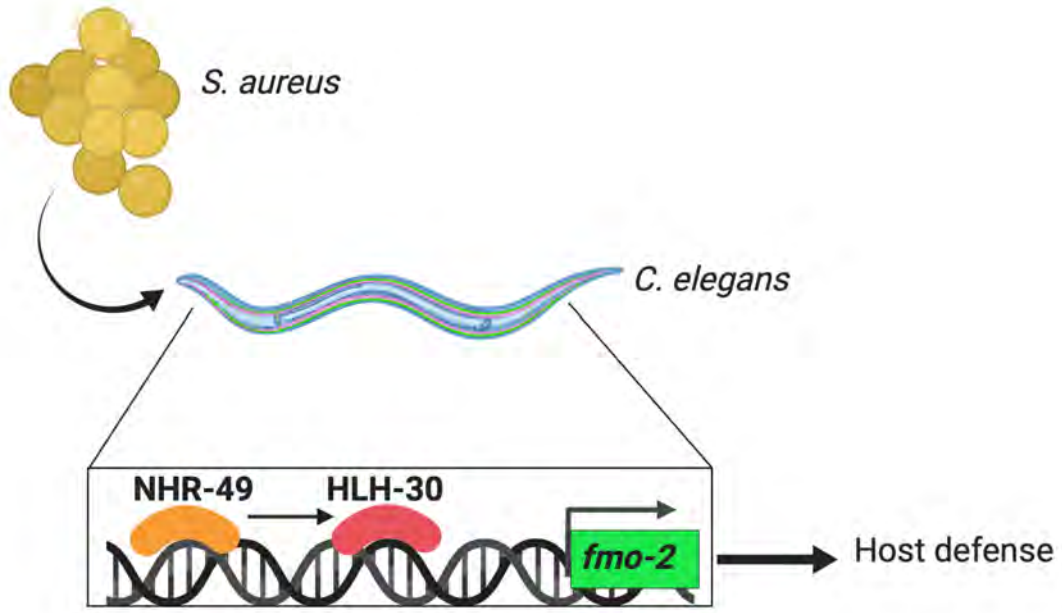


Wani et al; under revision

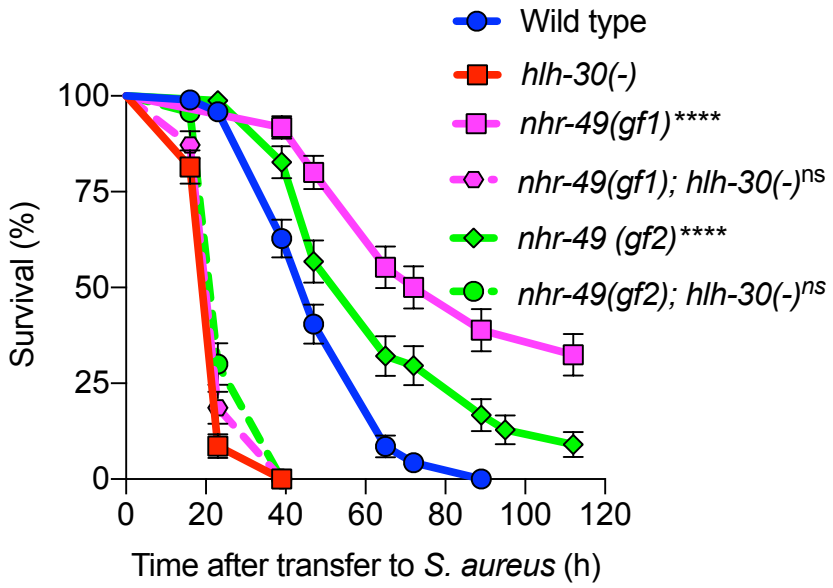
HLH-30 functions downstream/parallel to NHR-49 for host defense and *fmo-2* induction

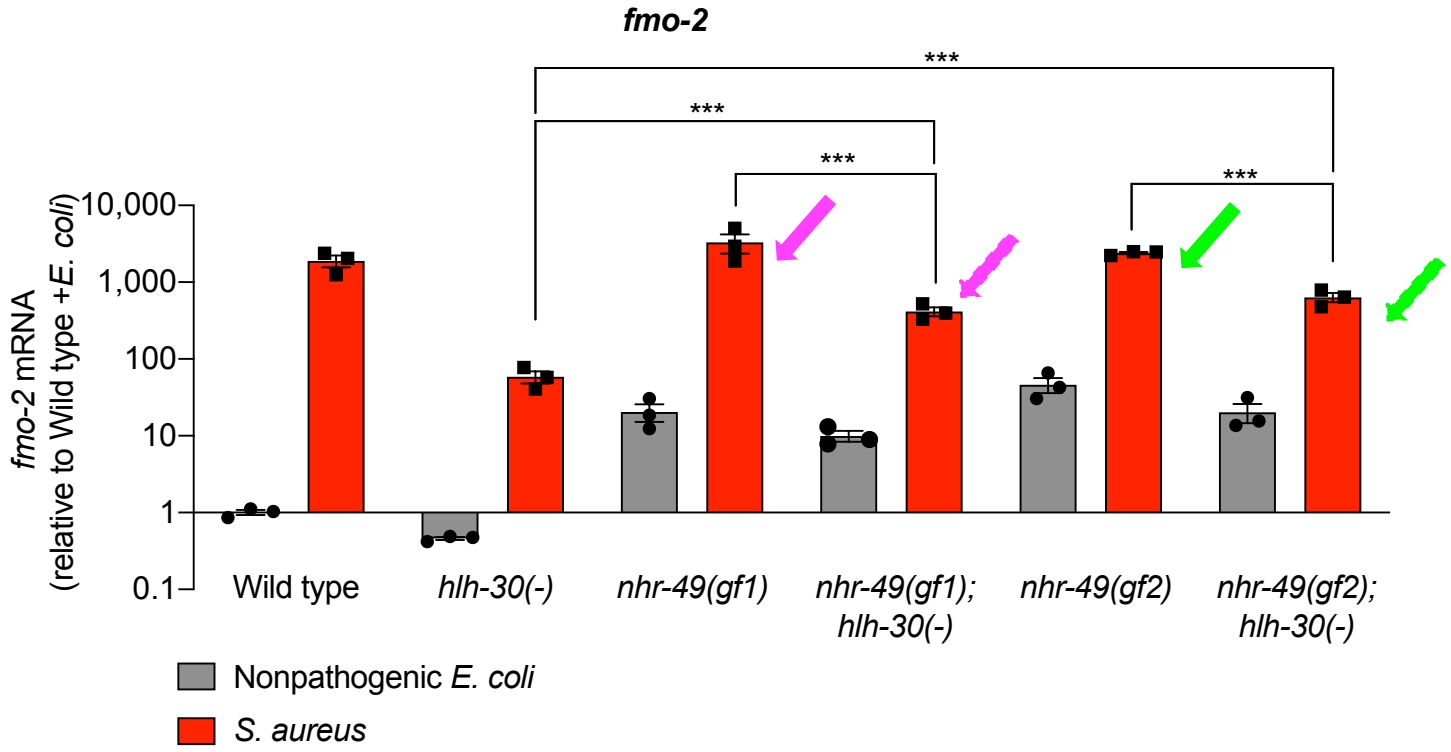


Does HLH-30 function downstream/parallel to NHR-49?



HLH-30 functions downstream/parallel to NHR-49 for host defense and *fmo-2* induction





Wani et al; under revision