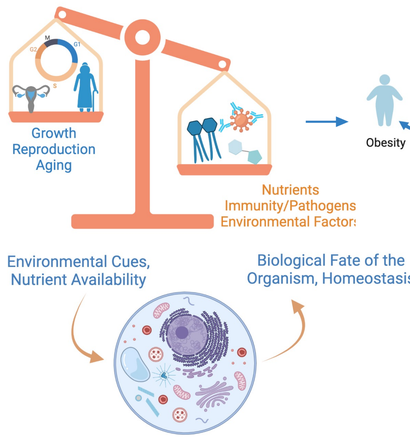
A forward genetic screen identifies mutants that suppress the effects of a gene-diet interaction in *C. elegans*

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Sarah K. Torzone, Robert H. Dowen

The University of North Carolina at Chapel Hill, Department of Biology

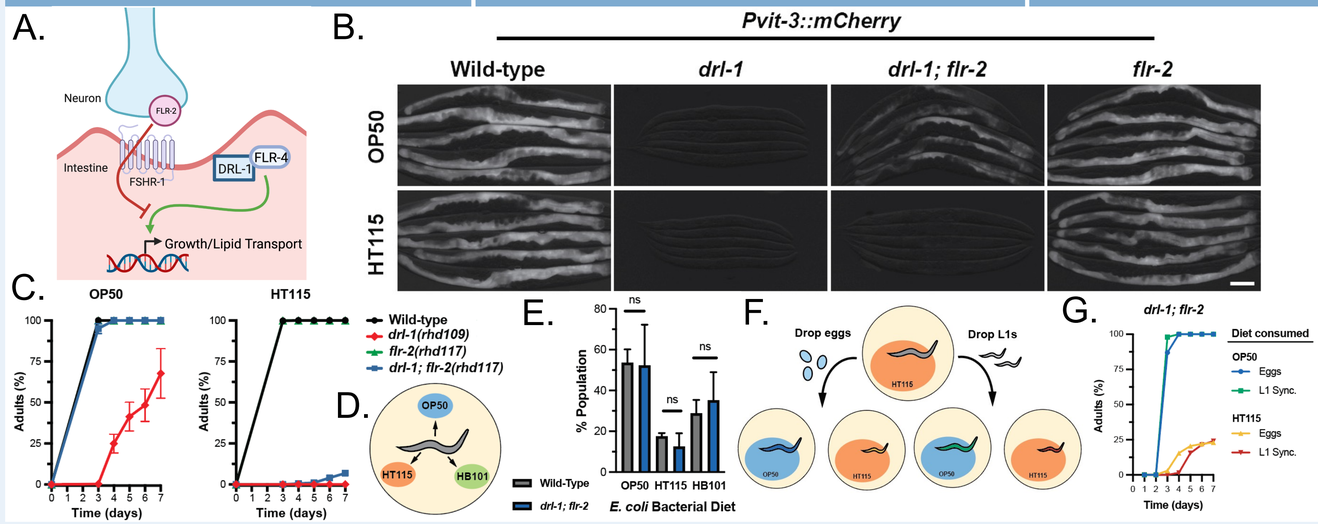
Background



Organisms metabolize energetic resources in response to nutritional and environmental conditions to balance biological processes. Misregulation of lipid metabolism results in disease.

Lipids are essential biomolecules which are transported between tissues via lipoprotein particles. In the model organism *C. elegans*, lipids are reallocated from the intestine to the germline by vitellogenesis. One key regulator of this process is the DRL-1 MAP kinase, which is also a key regulator of growth.

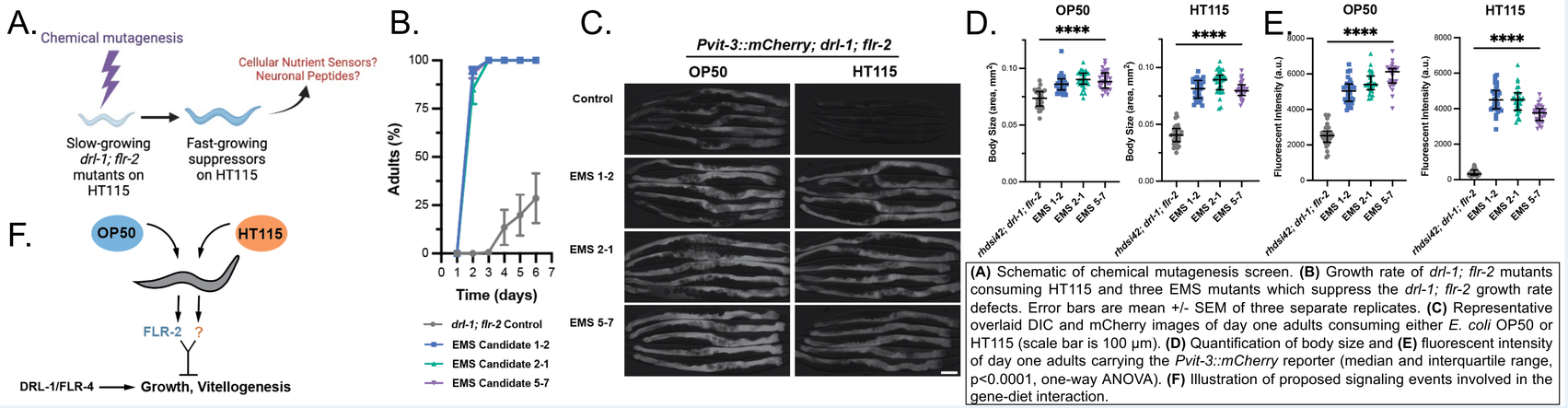
Glycoprotein hormone signaling opposes MAPK-mediated growth and lipid reallocation in a diet-specific manner



FLR-2 opposes DRL-1 in the presence of *E. coli* OP50 but not *E. coli* HT115.
(A) The FLR-2 neurohormone and its putative receptor FHSR-1 oppose the DRL-1 and FLR-4 kinases to regulate growth and vitellogenesis. Mutation of *flr-2* suppresses *drl-1* mutant **(B)** *vit* gene and **(C)** body size defects when the animal consumes *E. coli* OP50 but fails to suppress these defects when consuming *E. coli* HT115 (scale bar is 100 µm).

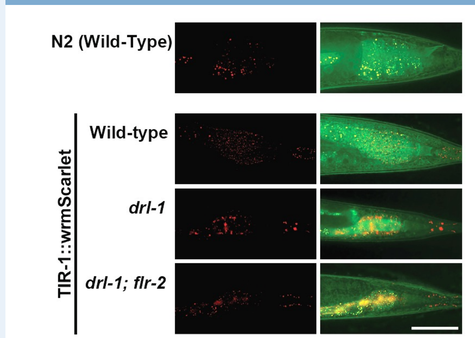
***drl-1; flr-2* animals do not choose different nutrient sources than wild-type animals and are not influenced by the diet of their parents.**
Schematic **(D)** and results **(E)** of food choice experiment in which a population of synchronized L1 animals were allowed to migrate between food sources on a single plate and scored at the L4 stage (error bars are mean with SEM of three replicates, two-tailed t-test between genotypes on respective food sources was not significant, ns). Schematic **(F)** and results **(G)** of a population of eggs or synchronized L1s obtained from adults consuming *E. coli* HT115 which were allowed to grow for 7 days and scored as having reached adulthood upon gravidity.

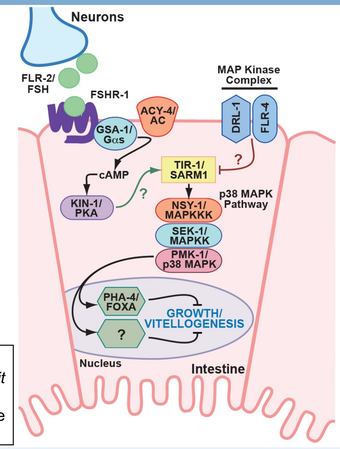
Three unique mutants suppress the growth and *vit* gene defects in *drl-1; flr-2* mutants consuming HT115



(A) Schematic of chemical mutagenesis screen. **(B)** Growth rate of *drl-1; flr-2* mutants consuming HT115 and three EMS mutants which suppress the *drl-1; flr-2* growth rate defects. Error bars are mean +/- SEM of three separate replicates. **(C)** Representative overlaid DIC and mCherry images of day one adults consuming either *E. coli* OP50 or HT115 (scale bar is 100 µm). **(D)** Quantification of body size and **(E)** fluorescent intensity of day one adults carrying the *Pvit-3::mCherry* reporter (median and interquartile range, p<0.0001, one-way ANOVA). **(F)** Illustration of proposed signaling events involved in the gene-diet interaction.

Future Directions





- Is the oligomerization of TIR-1/SARM1 dependent on *E. coli* diet?
- Does HT115 supplementation with vitamin B12 rescue growth/ *vit* gene defects in *drl-1; flr-2* mutants?
- Identify causative mutations in EMS suppressors by whole genome sequencing, RNAi, and genetic crosses

Acknowledgements

theDowenlab METABOLISM | DEVELOPMENT | AGING

OFFICE FOR UNDERGRADUATE RESEARCH

NIH National Institute of General Medical Sciences

bio RENDER honors CAROLINA

Scan for references