

ABSTRACT

In harsh conditions *Caenorhabditis elegans* arrests development to enter a nonaging, resistant diapause state called the dauer larva. Olfactory sensation modulates the TGF- β and insulin-like signaling pathways to control this developmental decision. The dauer pheromone is required for formation of dauer larvae. This thesis shows that bacterial pathogenesis is an input into dauer formation in addition to the known inputs of starvation, overcrowding and high temperature. This was first suggested by the overabundance of innate immunity genes found in a screen for novel synthetic dauer formation mutants. A total of 21 genes were identified in this screen, only one of which, *srh-100*, was previously identified to influence dauer formation. This work also characterizes new genes and functions that define early, middle, and late steps in the dauer pathway. Epistasis analysis and a GFP-tagged reporter places DAF-25 (abnormal DAUER Formation) function in the sensory cilia. DAF-25 was shown to be required for DAF-11 cilia localization as well as proper olfaction to various cues. *daf-25* and *daf-11* mutants have similar phenotypes and epistatic order. Intraflagellar transport is not defective in *daf-25* mutants although the ciliary localization of DAF-25 itself is altered in a mutant that is defective in retrograde IFT. A Daf-c enhancing mutant originally isolated as a double mutant with a novel *daf-2* allele was also identified. *m708* is allelic with *sdf-9* (Synthetic Dauer Formation). Epistasis analysis and allele-specific interactions place it in the *daf-2* pathway as a possible DAF-2 interactor. The molecular lesion in *m708* was identified to be an insertion of the mariner transposon *Cemar1*. This is the first identified hopping event described for this transposon family, the largest in *C. elegans*. Finally, *zip-5* (initially identified as a candidate DAF-16/FOXO target by serial analysis of gene expression) was shown to be a basic-leucine zipper transcription factor (bZIP) that is down regulated in a *daf-2* background. *zip-5* mutants show an extension of life span that is dependent on SKN-1, a bZIP-like transcription factor. ZIP-5 expression is dependant on the longevity-associated DAF-16 transcription factor and the *zip-5* GATA binding sites.

BIOGRAPHICAL NOTES

Born: March, 28, 1977, Vancouver, BC
Academic Studies: B. Sc. (1st Class Hon.), Simon Fraser University, 2004

GRADUATE STUDIES

Field of Study: Development, Aging and Olfactory Signaling, Department of Medical Genetics

Courses (500 level and above) for example:

MEDG 505 Genome Analysis
MEDG 520 Advanced Human Molecular Genetics
MEDG 521 Molecular and Cell Biology of Cancer
MEDG 530 Human Genetics
MEDG 545 Current Topics in Genomics
MEDG 548 Directed Studies

Instructors

Dr. S. Jones
Dr. C. Brown
Dr. P. Hoodless
Dr. L. Clarke
Dr. A. Brooks-Wilson
Dr. D. Riddle

AWARDS

Graduate Entrance Scholarship (2004)
NSERC CGS (2005)
MSFHR JGS (2005)
NSERC PGS (2006)
MSFHR SGS (2008)
Genetics Society of America Poster Award (2009)

PUBLICATIONS

Jensen, V.L., Bialas, N.J., Bishop-Hurley, S., Molday, L.L., Kida, K., Blacque, O.E., Nguyen, T.P., Molday, R.S., Leroux, M.R., Riddle, D.L. (2009). The novel cilia protein DAF-25 is required for DAF-11 guanylyl cyclase localization in chemosensory neurons. Accepted, PLoS Genetics.

Jensen, V.L., Albert, P.S., and Riddle, D.L. (2007) *Caenorhabditis elegans* SDF-9 Enhances Insulin/Insulin-Like Signaling Through Interaction With DAF-2. *Genetics* 177 (1): 661–666.

Jensen*, V.L., Gallo*, M., and Riddle, D.L. (2006) Targets of DAF-16 involved in *Caenorhabditis elegans* adult longevity and dauer formation. *Experimental Gerontology*. 41 (10):922-927. *Authors contributed equally.

Anyanful, A., Ono, K., Johnsen, R.C., Ly, H., **Jensen, V.**, Baillie, D.L., and Ono, S. (2004) The RNA binding protein SUP-12 controls muscle-specific splicing of the ADF/cofilin pre-mRNA in *Caenorhabditis elegans*. *Journal of Cell Biology* 167 (4): 639- 647.

McKay, S. J., Johnsen, R., Khattra, J., Asano, J., Baillie, D.L., Chan, S., Dube, N., Fang, L., Goszczynski, B., Ha, E., Halfnight, E., Hollebakk, R., Huang, P.,



Hung, K., **Jensen, V.**, Jones, S.J.M, Kai, H., Li, D., Mah, A., Marra, M., McGhee, J., Newbury, R., Pouzyrev, A., Riddle, D.L., Sonnhammer, E., Tian, H., Tu, D., Tyson, J.R., Vatcher, G., Warner, A., Wong, K., Zhao, Z., and Moerman, D.G., (2003) Gene Expression Profiling of Cells, Tissues and Developmental Stages of the Nematode *C. elegans*. Cold Spring Harbor Symposia on Quantitative Biology 68:159-169.

SELECTED PRESENTATIONS

- Center for Molecular Medicine and Therapeutics, The University of British Columbia (Vancouver, BC, Canada), "The novel cilia protein DAF-25 is required for guanylyl cyclase localization in chemosensory neurons" (Talk, 2009)
- Michael Smith Laboratories Colloquium (UBC), "A screen of putative DAF-16/FOXO target genes for novel SynDaf genes reveals a connection between dauer formation and innate immunity" (Talk, 2008)
- VanWoRM (Vancouver Worm Research Meeting), Simon Fraser University (Burnaby, BC, Canada), "A screen of putative DAF-16/FOXO target genes for novel SynDaf genes reveals a connection between dauer formation and innate immunity" (Talk, 2008)
- C. elegans* Topic Meeting: Aging, Stress, Pathogenesis and Heterochrony, (Madison, Wisconsin), "A screen of putative DAF-16/FOXO target genes for novel SynDaf genes reveals a connection between dauer formation and innate immunity" (Talk, 2008)
- European Worm Meeting (Carmona, Spain), "A screen of putative DAF-16/FOXO target genes for novel SynDaf genes reveals a connection between dauer formation and innate immunity" (Talk, 2008)
- European Worm Meeting (Carmona, Spain) "The maternal-effect Daf-c gene *daf-25* is expressed in ciliated neurons and functions in neurosecretion" (Talk, 2008)
- Michael Smith Laboratories Colloquium (UBC), "Mutation of the DAF-16 Target ZIP-5 Extends Longevity." (Talk, 2007)
- VanWoRM (Vancouver Worm Research Meeting), Simon Fraser University (Burnaby, BC, Canada), "Loss of ZIP-5 results in *daf-2* dependent extended longevity" (Talk, 2007)

In addition, eleven posters were presented at various conferences.

SUPERVISORY COMMITTEE

- Dr. Donald L. Riddle, Research Supervisor (Medical Genetics)
- Dr. Donald G. Moerman (Zoology)
- Dr. Robert S. Molday (Ophthalmology and Visual Sciences)
- Dr. Stefan Taubert (Medical Genetics)

PROGRAMME

The Final Oral Examination
For the Degree of

DOCTOR OF PHILOSOPHY
(Medical Genetics)

VICTOR JENSEN

B.Sc. (1st Class Hon.), Simon Fraser University, 2004

Monday, December 6, 2010, 12:30 pm
Leon's Lounge, Graduate Student Centre

"Novel Components of the Dauer Larva Developmental Signaling Pathway in *Caenorhabditis elegans*"

EXAMINING COMMITTEE

Chair:

Dr. Richard Tees (Psychology)

Supervisory Committee:

Dr. Donald Riddle, Research Supervisor (Medical Genetics)

Dr. Stefan Taubert (Medical Genetics)

University Examiners:

Dr. Catharine Rankin (Psychology)

Dr. Orson Moritz (Ophthalmology and Visual Sciences)

External Examiner:

Professor Gert Jansen

Department of Cell Biology and Genetics

Erasmus MC

Rotterdam, Netherlands