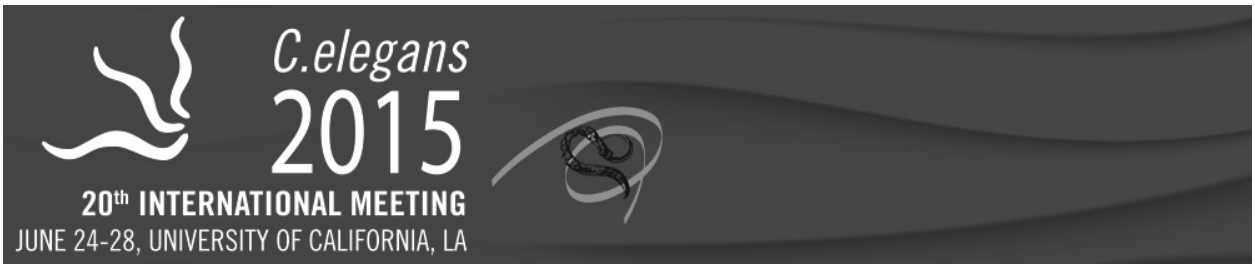
Genetics Society of America Conferences



FULL ABSTRACTS

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elegans, SKN-1 translocates to the nucleus in response to electrophiles in order to turn on genes to mount an appropriate oxidative stress response. In homeostasis, SKN-1 is kept inactive by WDR-23. Nrf2 is the mammalian equivalent of SKN-1, and the underlying molecular mechanisms that regulate its activity and abundance are similar to SKN-1, but utilize a different protein, Keap1. Despite sharing a conserved biological function, Keap1 and WDR-23 are structurally dissimilar. Intriguingly, mammals also have a protein homologous to worm WDR-23. Although mammals have evolved the Keap1 mechanism for Nrf2 regulation, Wdr23 has nonetheless been retained in the genome over evolutionary time, indicating an essential reason for Wdr23's role. We have uncovered two important functions of Wdr23: (1) its role in the Nrf2 oxidative stress response, and (2) its involvement in other cytoprotective pathways in *C. elegans* that maintain genomic integrity. We have strong evidence that the loss of Wdr23 in cell culture turns on Nrf2 target genes, indicating it has a role as a negative regulator of Nrf2. Importantly, we believe that this regulation has a greater impact when cells are in the presence of oxidative stress. These present a new axis of Nrf2 regulation and further define the essential roles for WDR-23.

278A. A metabolomic perspective of the impact of mitochondrial prohibitin on *C. elegans* longevity. **Artur B. Lourenço[1]**, Celia Muñoz Jiménez[1], David Cabrerizo Granados[1], Mónica Venegas Calerón[2], Mary Doherty[3], Phillip Whitfield[3], Marta Artal-Sanz[1]. 1) Andalusian Centre for Developmental Biology (CABD), Sevilla; 2) Instituto de la Grasa, Sevilla; 3) Department of Diabetes and Cardiovascular Science, University of the Highlands and Islands.

The mitochondrial prohibitin complex is a context-dependent modulator of longevity. Specifically, prohibitin deficiency shortens the lifespan of otherwise wild type worms, while it dramatically extends lifespan under compromised metabolic conditions, as in the case of the diapause *daf-2(e1370)* mutant. This extremely intriguingly phenotype has been linked to alterations in mitochondrial function and in fat metabolism. Nevertheless, the true function of the mitochondrial prohibitin complex remains elusive. With the ultimate goal of understanding how mitochondrial prohibitin complex affects longevity, we have employed several metabolomic approaches to characterize the changes elicited upon prohibitin depletion by RNAi on the metabolome of wild type and *daf-2* mutant worms.Metabolic analysis by gas chromatography coupled to a flame ionization detector and ^{1}H-NMR spectroscopy reveals that prohibitin depletion leads to an alteration in the overall fatty acid composition of the worm, as well as in carbohydrate and amino acid metabolism. To enlarge the coverage of the metabolome, we employed a lipidomic mass spectrometry-based approach. We identify that prohibitin has a differential effect in the content of various species of triglycerides and phospholipids in wild type and in *daf-2* mutant animals. In particular, we find that prohibitin affects not only the amount but also the composition of fat storage lipids. Overall, prohibitin depletion has a more pronounced effect on the metabolic profiles of wild type worms than of *daf-2* mutants indicating that *daf-2* mutants are more robust to the changes elicited upon prohibitin depletion. We are currently exploring the relevance of identified metabolites in the context of the effect of prohibitin on the *C. elegans* longevity.

279B. Comparing regulation and function of DAF-16/FOXO in different longevity pathways in *C. elegans*. **Hildegard Mack[1]**, James Moresco[2], John R. Yates[2], Cynthia Kenyon[1]. 1) Department of Biochemistry and Biophysics, University of California, San Francisco, San Francisco, CA; 2) Department of Chemical Physiology, The Scripps Research Institute, La Jolla, CA, USA.

The FOXO transcription factor is required for longevity in response to reduced insulin-like signaling in many organisms. In the nematode *Caenorhabditis elegans*, the FOXO ortholog, DAF-16, is also required for the lifespan increase that occurs when germline stem cells are ablated while the somatic gonad remains intact. Interestingly, previous work from our group has found that removing the germline precursor cells from long-lived insulin-receptor (*daf-2*) mutant worms extends their lifespan even further, giving rise to the hypothesis that DAF-16 regulation and function differs between the Insulin signaling- and the germline longevity pathway. To address this issue and to elucidate how DAF-16 is activated and extends lifespan in the absence of germline stem cells, we used mass spectrometry to identify and compare the sets of proteins that interact with DAF-16 in the intestine (the tissue in which DAF-16 activity is required to extend lifespan upon germline removal) of wild type and long-lived *daf-2* and *glp-1* (germline-deficient) mutant animals. In agreement with a previous DAF-16 co-immunoprecipitation study, we find that the majority of proteins bind to DAF-16 in its activated state (i.e. in the *daf-2* and/or the *glp-1* background). However, our preliminary data indicates that *daf-2* and *glp-1* mutants share only about 50 % of their DAF-16 interactomes while substantial fractions are specific to either condition, thus supporting our hypothesis for different modes of DAF-16 regulation and function in the two longevity pathways. We are currently in the process of further validating our mass spectrometry results and of examining the role for selected *glp-1* specific DAF-16 candidate interactors in lifespan extension of germline deficient animals.

280C. Chronic proteasome dysfunction in *C. elegans* activates a compensatory response involving *skn-1*, *elt-2*, and lysosome activity. **Sarah K. Maddux[1,2]**, Scott A. Keith[3], Yayu Zhong[1,2], Annabel A. Ferguson[3], Arjumand Ghazi[4], Alfred L. Fisher[1,2,5]. 1) Center for Healthy Aging, Barshop Institute for Longevity and Aging Studies, UTHSCSA, San Antonio, TX; 2) Division of Geriatrics, Gerontology, and Palliative Medicine, Department of Medicine, UTHSCSA, San Antonio, TX; 3) Division of Geriatric Medicine, Department of Medicine, University of Pittsburgh, Pittsburgh, PA; 4) Department of Pediatrics, University of Pittsburgh, Pittsburgh, PA; 5) San Antonio GRECC, South Texas VA Healthcare System, San Antonio, TX.