

**P019** An H<sub>2</sub>O<sub>2</sub>/PI 3-kinase/FOXO feedback mechanism may function in starvation responses at the cost of longevity  
David Weinkove, Francesca Milano, Jonathan R. Halstead, Ronald H. Plasterk\* and Nullin Divecha  
Division of Cellular Biochemistry, Netherlands Cancer Institute, Amsterdam. \*Hubrecht Laboratory, Utrecht, The Netherlands

Mutations in the *C. elegans* AGE-1 Class IA PI 3-kinase extend lifespan. However, the *age-1(hx546)* mutant cannot compete with the wild type during repeated rounds of starvation and feeding. The *age-1(hx546)* allele has no mutation in the predicted open reading frame but we have discovered a defect in H<sub>2</sub>O<sub>2</sub>-stimulated PIP<sub>3</sub> production in starved L1 (first stage) larvae, a diapause state distinct from the better-characterised dauer. Our novel assay for the resistance of L1s to H<sub>2</sub>O<sub>2</sub> showed that starvation caused resistance in a manner dependent on the FOXO homologue, *daf-16*. We also found that H<sub>2</sub>O<sub>2</sub> causes DAF-16 to leave the nucleus. Further, after two days of starvation, DAF-16 translocated to the cytoplasm without external stimulus, and both translocations were defective in the *age-1(hx546)* mutant. Despite the DAF-16 cytoplasmic translocation, wild type larvae remained resistant to H<sub>2</sub>O<sub>2</sub>, suggesting that *daf-16*-dependent transcription on the first day of starvation is sufficient for long-term resistance and that excessive DAF-16 activity in the *age-1* mutant extends lifespan but compromises responses to starvation. We propose that an endogenous H<sub>2</sub>O<sub>2</sub> signal from *daf-16*-activated gene products causes a feedback inhibition of DAF-16 via AGE-1 PI 3-kinase activation.