



# CDB SEMINAR

## Hiroaki Iwasa

Department of Molecular Biology and Biochemistry, Rutgers University

Tuesday, April 1, 2008

13:30~14:30 A7F Seminar Room

## RNAi screens for novel candidate insulin receptor-like proteins turned up an unexpected role of EGF signaling in aging

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## RNAi screens for novel candidate insulin receptor-like proteins turned up an unexpected role of EGF signaling in aging

### Summary

The DAF-2 insulin receptor functions as an upstream receptor in a kinase cascade that includes AGE-1 (PI-3 kinase) and ultimately phosphorylates forkhead transcription factor DAF-16 to inhibit its transcriptional activity. Decreased *daf-2* signaling promotes DAF-16 transcriptional functions and causes lifespan extension that depends on *daf-16* gene activity. It is somewhat puzzling that there are 39 insulin-like ligands encoded by the *C. elegans* genome, but only one clear insulin receptor homolog, DAF-2. Previously, bioinformatic analyses presented a list of 54 putative insulin receptor-like proteins in nematodes (Dlagic 2002). It should be noted, however, that these are sequence-related in the extracellular ligand-binding domain and contain secretion signal sequences, but lack the transmembrane domain present on classic receptor kinases--so they actually look more like secreted potential proteins. We constructed or obtained 54 clones for these candidates and used these for RNAi inactivation to test effects on healthspan of aging animals. We identified two candidates (*hpa-1* and *hpa-2*) for which RNAi confers **high performance in advancing age** (*hpa*) phenotype. We have also shown that RNAi directed against either candidate protein extends lifespan. We conclude that *hpa-1* and *hpa-2* are two new genes that influence healthspan and aging.

Interestingly, when we conducted our own bioinformatics analysis on HPA-1 and HPA-2, we find that both candidates more closely resemble EGF receptor than insulin receptor. We then showed that the healthspan-promoting effects are independent of the DAF-2 insulin-like receptor and the downstream insulin signalling transcription factor FOXO/DAF-16. These data prompted us to look at EGF pathway mutants for aging phenotypes. We found that a gain-of-function mutation in EGF receptor extends lifespan, and modestly lowers age pigment levels, consistent with a role of EGF signaling in *hpa* phenotype. Loss-of-function in the EGF receptor has the opposite effect. We conclude that the EGF pathway impacts aging--with pathway activation being associated with longevity and healthy aging.

### Reference

Dlagic M. *Curr Biol.* 2002 Mar 5;12(5):R155-7.

A new family of putative insulin receptor-like proteins in *C. elegans*.

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