EXPERIMENTAL MODEL

Decoy receptor fine tunes insulin signaling in *C. elegans*Martinez, B, A et al. *elife* 9, e49917 (2020)

Given that many components of the insulin/IGF1 signaling (IIS) pathway are evolutionary conserved, researchers can turn to simple and manipulable invertebrate models such as *Caenorhabditis elegans* to gain insights into IIS cascade and outputs. In the nematode, *daf-2* encodes a receptor with sequence homology to mammalian insulin receptors, which is involved in fundamental biological processes such as development and aging. By revealing that alternative splicing in the *daf-2* locus leads to the expression of a truncated isoform of the insulin-like receptor that can counteract the action of the full-length receptor and fine-tune IIS pathway, a new study in *C. elegans* calls for further investigation into the role of truncated decoy receptors in other species.

In the study, the team of investigators from the Scripps Research Institute in Florida showed that the *daf-2b* isoform encodes a protein that retains the complete extracellular ligand binding domain of the insulin receptor but lacks the intracellular

signaling domain present in the full-length protein encoded by *daf-2a* and *daf-2c* isoforms. Using isoform-specific fluorescent splicing reporters, the investigators showed that *daf-2b* splicing is spatially and temporally regulated through reproductive development and mainly occurs at the L1 and L2 stages.

Daf-2b splicing was also detected in dauer larvae, an arrested stage specialized for survival in adverse conditions that is known to be regulated by insulin signaling. Previous studies have shown that hypomorphic *daf-2* mutant worms show increased dauer entry compared with wild-type worms. Given the role of insulin signaling in the formation of the dauer larva, the investigators hypothesized that DAF-2B isoform could have an important role in modifying entry and/or exit from dauer. DAF-2B overexpression increased dauer entry caused by hypomorphic insulin signaling, whereas loss of *daf-2b* reduced dauer formation. The findings suggest that DAF-2B reduces insulin signaling either by

sequestering insulin peptides away from full length DAF-2A or by acting in a dominant negative manner via the formation of DAF-2A/DAF-2B heterodimers. “DAF-2B can promote dauer entry by changing availability of agonist insulin peptides, thereby further reducing insulin signaling,” explain the investigators in their report.

The investigators also showed that DAF-2B can sequester antagonist insulin peptides, thereby revealing several new layers of complexity in IIS regulation. Given that alternatively spliced isoforms of the insulin receptor have been reported in mammals, future investigations are needed to determine if this decoy mechanism is conserved across species and regulates biological processes such as aging or pathological conditions such as insulin resistance.

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