FUNCTIONAL GENOMICS

Insulin — meet the family

When the going gets tough, the nematode *Caenorhabditis elegans* enters a developmentally arrested state called the dauer stage. Dauer entry is under the control of the insulin and transforming growth factor-β (TGF-β) signalling pathways. But the endogenous ligand for the worm insulin pathway has not been found. Using a sophisticated genomic analysis, Sarah Pierce, Michael Costa and colleagues have now identified a collection of insulin-like ligands in *C. elegans*, among which is a strong candidate for a ligand that controls dauer entry. But here's the twist — it's an antagonist of insulin signalling.

A key aspect of this work is that the search for new insulin homologues incorporated information about protein structure that is conserved among insulin molecules. Thirty-seven insulin family members were found by screening the *C. elegans* genome for these structural features, 25 of which were novel.

Because of its close relationship to human insulin, one of the *C. elegans* genes, *ins-1*, was the focus for genetic analysis. Insulin signalling is required to keep the worms in an active state — switch off signalling and worms enter the dauer state. Surprisingly, overexpression of *ins-1* increased dauer entry, which indicates that INS-1 might be an antagonist of the insulin receptor *DAF-2*. Knocking out *ins-1* produced no phenotype, and so there might be other signalling molecules the function of which overlaps with INS-1. One of the other insulins, INS-18, was indeed shown to function as an antagonist of insulin signalling. Even human insulin behaved as an antagonist of insulin signalling in *C. elegans*.

So, there are now some strong candidates for endogenous insulin signals in *C. elegans*, but is there an endogenous agonist of insulin signalling? Further analysis of this large group of molecules should tell. And for those interested in the role of insulin signalling in disease, the possibility that the vertebrate insulin family is also much larger than expected, and the demonstration that insulin can function as a signalling antagonist, suggest some attractive lines of inquiry.

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References and links

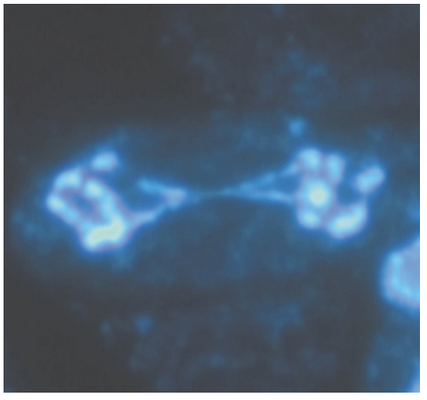
ORIGINAL RESEARCH PAPER Pierce, S. *et al*. Regulation of DAF-2 receptor signalling by human insulin and *ins-1*, a member of the unusually large and diverse *C. elegans* insulin gene family. *Genes Dev*. **15**, 682–686 (2001)

WEB SITE Gary Ruvkun's lab

CHROMOSOME BIOLOGY

Plastic plants

Plant genomes betray a past characterized by vast chromosomal rearrangements and changes in ploidy, often caused by the union of genomes of different plant varieties. In their recent report, Riha and colleagues uncover further evidence of the plasticity and resilience of plants towards genomic changes by showing that *Arabidopsis* can better withstand the erosion of telomeres — the chromosome ends — than animals can.



Anaphase-staged chromosomes from G_5 of telomerase-deficient *Arabidopsis*. Two anaphase bridges are shown here. Photo courtesy of Karel Riha, Texas A&M University, USA.

Chromosomes need to protect themselves from the wear and tear that results from the inefficient replication of their ends. As a protective measure, both ends of eukaryotic chromosomes are capped by a nucleoprotein complex — the telomere. These ends are replicated by a reverse-transcription mechanism catalysed by the enzyme telomerase. Without telomerase, telomeres gradually shorten until cells, sensing an emergency, activate DNA checkpoints that lead to cell-cycle arrest, senescence and apoptosis.

In this study, the fate of four lines of telomerase-deficient *Arabidopsis* plants was examined over ten generations. Physiologically, the mutant plants appeared normal until generation 5 (G_5), after which their condition gradually worsened. The first defects were seen in vegetative structures such as leaves, whereas later-generation phenotypes affected the reproductive organs. Unexpectedly, although these plants are sterile, their vegetative shoot meristems (from which gametes derive) expand into an amorphous mass of dedifferentiated cells. This growth is unusual for a phenotype that is normally characterized by cell-cycle arrest and death, but is consistent with the increased tumour incidence seen in telomerase-deficient mice.

At the molecular level, genomes are destabilized by the absence of telomerase — a phenomenon that can be gauged in plants by the number of end-to-end fusions that occur between the shortened chromosomes, and from the chromosome bridges that form during anaphase. These bridges were apparent in plants from G_5 onwards, although anaphase was not delayed as a result. Chromosome ends were clearly beginning to erode in early-generation plants, but surprisingly, some telomeres became longer from one generation to the next. This indicates that the plants might be able to engage telomerase-independent mechanisms for lengthening the telomeres. The fate of telomerase-deficient mice is very different: their fertility and development decline over several generations until the mice become sterile by the sixth generation. At this stage, cells have ceased cycling in the face of total genomic catastrophe.

Although metazoans wouldn't swap their dynamic lives for one rooted in the ground, the genome organization of plants and their response to genomic stresses might teach us a thing or two about telomeres and genome stability.

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References and links

ORIGINAL RESEARCH PAPER Riha, K. *et al.* Living with genome instability: plant responses to telomere dysfunction. *Science* **291**, 1797–1800 (2001)

ENCYCLOPEDIA OF LIFE SCIENCES Telomeres

WEB SITE Dorothy Shippen's lab