Recruitment of reproductive features into other cell types may underlie extended lifespan in animals

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In the sense that organisms existing today are connected through a chain of life - through their parents, grandparents and other ancestors - almost a billion years back to the first animals of the pre-Cambrian era, an animal's reproductive cells can be considered to be immortal. These germline cells generate their offspring's somatic cells - other cells involved in all aspects of growth, metabolism and behavior, which have a set lifespan - and new germline cells that continue on, generation after generation.

Now in a dramatic finding, researchers from the Massachusetts General Hospital (MGH) Department of Molecular Biology have found that certain genetic mutations known to extend the lifespan of the *C. elegans* roundworm induce 'mortal' somatic cells to express some of the genes that allow the 'immortality' of reproductive germline cells. Their report will appear in the journal *Nature* and is receiving advance online release.

"*C. elegans* mutants with extreme longevity accomplish this feat, in part, by adopting genetic programs normally restricted to the germline into somatic cells," says Sean Curran, PhD, of MGH Molecular Biology, the study's lead author. "We know that germline cells are more stable than somatic cells - they live longer and are more resistant to stresses that damage other cells - and understanding the molecular pathways involved in that stability may someday allow us to devise therapies protective against age-related decline in other tissues."

Curran is a research fellow in the laboratory of MGH investigator Gary Ruvkun, PhD, whose work focuses on the development, longevity and metabolism of *C. elegans*, a tiny worm broadly used as a model for studying basic biological systems. Ruvkun and other researchers discovered that simple mutations in genetic pathways conserved throughout evolution can double or triple the lifespan of *C. elegans*, and that similar mutations in the corresponding pathways also dramatically extend mammalian lifespan.

Longevity-associated mutations have been shown to lead to enhanced immune response - including increased control of gene expression through RNA interference (RNAi) - in somatic cells. Since it is known that RNAi is among the mechanisms underlying germline cells' enhanced resistance to pathogens and other stresses, the researchers examined whether the reactivation of germline genetic programs was involved in the extended lifespan of *C. elegans* mutants.

A series of experiments demonstrated that worms with increased longevity induced by mutations in the insulin-like signaling pathway did exhibit somatic cell expression of genes usually active only in germline cells. The mutant worms also were protected from stresses that damaged the DNA of non-mutant worms. The researchers also found that inactivating germline-expressed genes in the mutant worms eliminated the increased lifespan and that longevity-associated mutations in two genes from a different metabolic pathway - one involved with detoxification and stress response - also increased the expression of germline markers.

"The idea that somatic cells can reacquire genetic pathways usually restricted to germline cells is fascinating, and since germline protection is seen across species, the activity of these genes may play a role in controlling mammalian lifespan," says Ruvkun, senior author of the *Nature* paper. "Understanding the mechanisms involved in this

transformation could help us develop new ways to repair and even regenerate key cells and tissues." A professor of Genetics at Harvard Medical School, Ruvkun was a co-recipient of the 2008 Lasker Award for Basic Medical Research for his role in discovering that tiny molecules of RNA can control the activity of critical genes

Source: Massachusetts General Hospital (news : web)