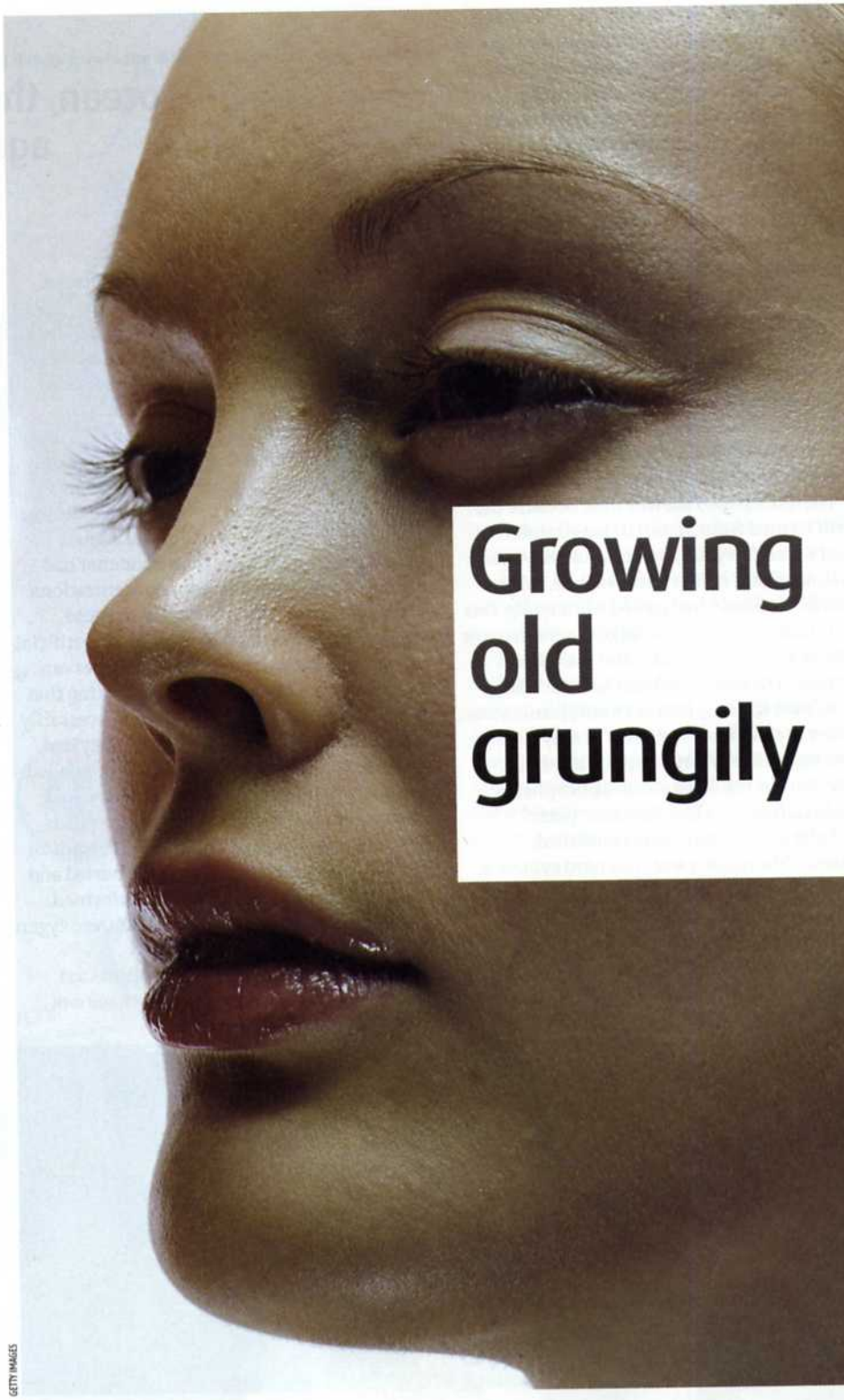
Growing old grungily



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MY ATTIC is a sad sight, a jumble of frayed carpet offcuts, half-empty cans of congealed paint, broken videos, dead computers and inoperative exercise bikes. Just the thought of dragging it all to the dump tires me out.

Something similar is happening inside my body's cells – at least according to a new theory about why we age. The rubbish is piling up, and while I could clear it all out, that would take a lot of effort. So my metabolic cleaning systems are set to "don't bother", and the result is that harmful garbage is accumulating.

Junk plays a central role in many theories of ageing. The "free radical" theory, for example, suggests that ageing is caused by highly reactive oxygen species that gradually turn DNA and proteins into toxic rubbish. But now there is a new take on junk, where it comes from, and how it causes us to get old. By analysing unusually long-lived variants of the tiny nematode worm *Caenorhabditis elegans*, David Gems and Josh McElwee of University College London's Centre for Research on Ageing have found that free radicals are just one part of a much bigger story.

The story begins in 1993 when Cynthia Kenyon of the University of California, San Francisco, discovered that some strains of *C. elegans* with mutations in a gene called *daf-2* lived more than twice as long as normal. This appeared to show that ageing was controlled by genes, contradicting the widespread view that it was largely the result of wear and tear inflicted by free radicals. Not surprisingly the results caused a stir. Many researchers were puzzled about how genes for ageing could evolve through natural selection.

However, similar genes were soon found in flies and mice. There is now good evidence that flies can live longer as a result of mutations in these genes, and early results in mice point the same way. Most researchers now accept that flies and nematode worms possess genes which can exert a powerful influence on lifespan, and that similar genes could be important for humans too. But what do all those genes actually do? This has been the big question ever since.

A few years after Kenyon's discovery, researchers at Massachusetts General Hospital in Boston worked out what the *daf-2* gene does. They found that it specifies a cell-surface receptor that recognises a signalling protein called IGF-1 (insulin-like growth factor 1). Like many such receptors, daf-2 turned out to be at the apex of a powerful signalling cascade. When IGF-1 binds to the receptor, it transmits a message to the inside of the cell, switching on another gene, *daf-16*, which Kenyon's group found could also influence longevity. It turned out that *daf-16* codes for a "suppressor" protein that binds to genes and turns them off. Mutations in *daf-2* apparently extend life by suppressing this suppression, keeping numerous genes active that would otherwise be switched off.

But which genes was *daf-2* affecting? Kenyon's group tried to find out using one of the latest technologies for probing gene expression: microarrays or "gene chips" that pack huge numbers of short DNA sequences onto a glass slide. By taking RNA molecules – the direct transcriptions of any gene – from living cells and seeing which DNA sequence these bind to, microarrays can tell you which genes are active. Kenyon's idea was to compare gene expression in normal *C. elegans* with that of long-lived *daf-16* mutants, and two years ago she showed that mutations in *daf-16* affect more than 300 genes.

Then she looked to see if any of these genes might be linked with longevity. Three kinds stood out. Some directed the cell to make

If life's a beach, then ageing is an unmanageable tide of junk washing over you. **Jon Turney** explains

antibacterial enzymes, which are vital for a worm that dines on bacteria that can also kill it. Others coded for heat-shock proteins, which protect cells against damage from high temperatures. A third type shielded against free radicals.

Gems and his colleagues, however, doubted that this was the full story. Kenyon was focusing on these genes, they suggested, because they fitted in with established theories of ageing, particularly the free-radical theory. What about all the others? And so they did the same experiment, but picked out the important genes using a statistical analysis designed to eliminate any bias toward the usual suspects (*Mechanisms of Ageing and Development*, vol 126, p 381).

They identified two main groups of genes that are more active in the long-lived worms. One group codes for proteins known as chaperonins, which are involved in helping proteins keep their shapes under stress and include the heat-shock genes flagged in Kenyon's study. The other, larger set covers a variety of enzymes involved in breaking down toxic by-products of metabolism.

Most of these enzymes were already known from mammalian liver cells, where they neutralise drugs, toxins and carcinogens. But they also help dispose of harmful chemicals that occur naturally inside all cells. As Gems sees it, this second battery of enzymes comprises a general detox and maintenance system that deals with all manner of molecular junk.

Some of this junk is generated by free radicals, but by no means all of it. Cells are constantly breaking down and rebuilding complicated chemicals, and as Gems puts it, "there are an infinite number of ways for things to go wrong". So cells need huge families of garbage-disposal enzymes to deal with all the junk they create. But the system carries a heavy overhead. It consumes lots of energy the organism could use elsewhere – particularly in reproduction.

And that gives natural selection something to work on. Individuals that damp down their garbage disposal systems and use the energy for reproduction gain a short-term competitive advantage over those that keep on detoxing. Of course, the price they pay is ageing more rapidly and dying younger, but on the whole natural selection couldn't care less what happens to an organism after it has reproduced.

The end result is that evolution has favoured cells that opt out of the detox business and allow molecular detritus to pile up. Gems and McElwee now believe that ageing is largely due to a breakdown in routine waste disposal and maintenance – what they call the "green theory" of ageing. In the end, the crud piles up and poisons your cells.

Others in the field are taking notice, but are not yet convinced. "It pushes a lot of the right buttons," says Mark Viney of the University of Bristol, UK. But he warns that it will be laborious to test: you would have to deactivate each gene one by one to see what effect it has. "There are hundreds of genes," Gems admits.

And what of the prospects for using the green theory to combat the problem of human ageing? As it is more general than, say, free-radical theories of damage, you'd probably have to do lots of different things to keep the junk at bay. But the hope is that one or two of the genes involved in this system will turn out to have big effects all by themselves. Then, perhaps, we can learn to harness their effects, and live longer lives. Maybe I'd even find the time to clean out my attic. ●

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