

The thread of life

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Christmas seems to come around faster each year. And with it, the inevitable sensation that time is truly passing and – though we may be getting a little wiser – we are getting none the younger. Like it or not, we are stuck with life the way we are stuck with the prospect of death. We can trick the traces of the passage of time with plastic surgery but underneath, our bodies are ageing without mercy. How? And is it genetic? Environmental? Both? Neither? A child's development into a full-grown adult bears a strong genetic component. It is not yet clear, though, whether the process of 'just getting old' does too – although a number of disorders which bring on premature ageing would suggest something of the like. A protein named Klotho, discovered by chance in the late 1990s, is helping to unveil the process involved in an individual's longevity.

Numerous models have been proposed for ageing, amongst which the existence of genes related to a maximum number of cell divisions, excessive posttranslational modifications of proteins, and the accumulation of toxic substances in cells. Such events cause all sorts of dysfunctions which in the long run portray old age as we observe it in the elderly: arteriosclerosis, osteoporosis, senile atrophy of the skin, defective hearing, microvascular changes and even diabetes or Alzheimer's disease. Whether such dysfunctions are to be blamed on the environment, genes or indeed just time is still impossible to say. However, with the discovery of a protein such as Klotho, it looks like some of our wrinkles are the work of a protein or two. Klotho was named after a Greek goddess. She was one of the numerous offspring of Nyx, the goddess of the night who gave birth to the gods and goddesses of doom, deceit, death, pain, love, blame... as well as to the goddesses of fate, one of whom was Klotho who spun the thread of life.

The Klotho protein was discovered by chance in mice. When its gene was disrupted, the mice that carried the mutation showed signs of premature ageing of the kind you would find in humans. A particular variant of Klotho – known as KL-VS – was found in three populations of humans, and KL-VS also seemed to contribute to an individual's lifespan. Those who were homozygous for the variant lived shorter lives; this was deduced from the fact that only babies carried both copies, but no adults over 65 did. Surprisingly, one of the populations heterozygous for Klotho saw their life expectancy increased. It is not known why but it

could be that heterozygosity for Klotho has a positive effect on individuals much in the same way as individuals who are heterozygous for the sickle cell mutation bear a greater protection against malaria.



'Sometimes Broadway, sometimes catskills'
Judy Somerville

Courtesy of the artist

Klotho is just over 1000 amino acids long, and there is both a membrane-bound and a secreted form. It belongs to the alpha-glucosidase family, although it can't be shown to have glucosidase activity. Klotho is only really expressed in the placenta, kidney, prostate and small intestine, yet its effects are systemic, which led scientists to

believe that there must be a humoral factor, i.e. either Klotho itself or a relay.

Besides the 'ageing' phenotypes observed in mice due to dysfunctional Klotho, what could be going on inside? One hypothesis is that Klotho is involved in calcium homeostasis. It would do this by regulating an enzyme – 1alpha-hydroxylase – which controls the synthesis of vitamin D, which in turn has an effect on calcium levels. And what do calcium levels have to do with ageing? Cell death can be brought on by calcium-dependent proteolysis. When the level of calcium is increased, proteolysis occurs. One of the roles of Klotho would be to check the level of cellular calcium, thereby preventing proteolysis. However, with the passing of time, the expression of Klotho decreases. As a result, calcium levels increase and calcium-dependent proteolysis can have a ball.

Not much is known about how Klotho functions on the molecular level. It is taken for granted that some substance must make its way around our system for Klotho to have an effect. As to what that substance could be, there are three possibilities. Either the membrane-bound form of Klotho undergoes posttranslational modifications allowing the extracellular domain to be secreted and function as a humoral factor, or Klotho acts as an enzyme which converts a circulating inactive precursor into

an active one, or it acts as a receptor which mediates a signal to fire off another humoral factor.

We know what happens when Klotho is dysfunctional. What happens, though, when it is overproduced? Recently, researchers managed to tinker mice that synthesized more Klotho than the norm. And they lived a year longer than their wild-type counterparts... However, the male rodents presented an increase in insulin suggesting insulin resistance – which could be a symptom of diabetes. Despite this, the fact that an increase in Klotho production is linked with the check of insulin signalling is exciting to some, because the suppression of insulin signalling coupled with that of the related hormone insulin-like growth factor-1 is known to extend the life span of many species.

Is there any chance that future findings on Klotho will have the power to extend our life's guarantee? Not so sure. All observations have been made on mice... not on humans. Who says that what scientists have referred to as 'signs of premature ageing in mice' are not just signs of sick mice whose symptoms resemble ageing in humans? What is more, it is very unlikely that one sole protein is at the heart of so many symptoms linked with old age. The pathways leading to senescence are complex and numerous. So let us just enjoy the Christmas season – and the next one – regardless of Klotho and its doings.

Cross-references to Swiss-Prot

Klotho, *Homo sapiens* (Human) : Q9UEF7

Klotho, *Mus musculus* (Mouse) : O35082

Klotho, *Rattus norvegicus* (Rat) : Q9Z2Y9

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