cannot enter until the trapped photon escapes. Imamoglu and colleagues call this a "photon (Kerr) blockade", by analogy with the electron (Coulomb) blockade[4]. In an electron blockade, the incident electron energy is just right to resonantly tunnel into the central island of a double-barrier tunnel diode. Once it is trapped, the resonant energy is shifted due to Coulomb repulsion, and electrons arriving later can't get in. This effect underlies various single-electron devices such as transistors, turnstiles and pumps[4].

Similarly, the photon blockade will probably be used in devices such as single-photon turnstiles[5] and single-photon quantum logic gates[6,7], which may be important for quantum cryptography and computation. Experimental demonstrations of the proposed giant Kerr nonlinearity and photon blockade are yet to be seen, but the work of Imamoglu *et al.* is an important step towards optical quantum information technologies. □

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Ageing

New mice for old questions

George M. Martin and I. Saira Mian

In 1733, Alexander Pope[1] wrote that man was "Created half to rise, and half to fall". In other words, "First we ripen, then we rot"! Pope, it seems, was 250 years ahead of his time in anticipating the modern evolutionary theory of ageing[2,3]. This theory states that organisms in age-structured populations senesce because of the weakening of the force of natural selection as they grow older, which allows certain gene actions to reach deleterious levels of expression. In human populations, common examples include cataracts, Alzheimer's disease and other dementias, type 2 diabetes mellitus, osteoporosis (brittle bones), many types of cancer and several types of arteriosclerosis (hardening of the arteries). On page 45 of this issue, Kuro-o and colleagues[4] describe a single mutation in a mouse gene that, when homozygous, appears to accelerate several types of pathology associated with late-life disorders in humans (but not in mice).

Like hundreds of labs that introduce bits of genetic material into mice in the hopes of getting expression of such foreign genetic information, these investigators inadvertently made a random 'hit' that crippled one of the host's normal genes. Unlike many such labs, however, they decided to alter course and to investigate what seemed to be a model of accelerated ageing in man. We can all be happy that they made this decision, as the results are of considerable interest, although not fully explained and of questionable relevance to mechanisms of human senescence. A special merit of their study is that they reintroduced a normal version of the gene into the mutant animals and essentially normalized the phenotype, thus satisfying a sort of genetic equivalent of Koch's postulates.

They named their gene *klotho* (*kl*) after one of the Fates of Greek mythology (Pope, a translator of Homer, would have approved). The gene encodes a cell-surface protein of 1,014 amino acids with a putative signal sequence at the amino terminus and a single transmembrane helix near the carboxy terminus. The extracellular domain is composed of two internal repeats (KL1, KL2), each of which has 20–40% sequence identity to the β-glucosidases of bacteria and plants as well as to mammalian lactase glycosylceramidase (Fig. 1).

The sequence similarity between Klotho and mammalian lactase glycosylceramidase suggests a role for Klotho in sphingolipid metabolism. From the diverse phenotypes of *kl* mutant mice, it seems that extracellular insults or agents such as hormones could activate Klotho, which might then act on membrane glycolipids and gangliosides to release ceramide — a molecule involved in cell replicative senescence, apoptosis and cell-cycle arrest. Given the predicted extracellular location of KL1 and KL2, Klotho probably acts on outer-leaflet membrane lipids. So, for ceramide generated by Klotho to initiate an intracellular response, it would need to diffuse through the membrane into the cytoplasm or alternatively to act extracellularly. The latter would require the existence of molecules on the cell surface and/or in the extracellular matrix that could interact with ceramide. Klotho may perhaps be involved (either directly or indirectly) with remodelling of the extracellular matrix.

Although the authors argue that their *kl* mutants develop normally, it is clear that the appearance of symptoms as early as 3–4 weeks after birth means that their mice have not fully 'ripened'. (The equivalent human age is six years.) But for each locus identified on the basis of a strong mutational effect, there could exist 'leaky' mutants and, perhaps of more general importance to the pathobiology of ageing, polymorphic variants. Such genetic variants could result in significant modulation of phenotypes that emerge after the reproductive phase of life is finished. At the level of precise phenotypic analysis, however, there are important

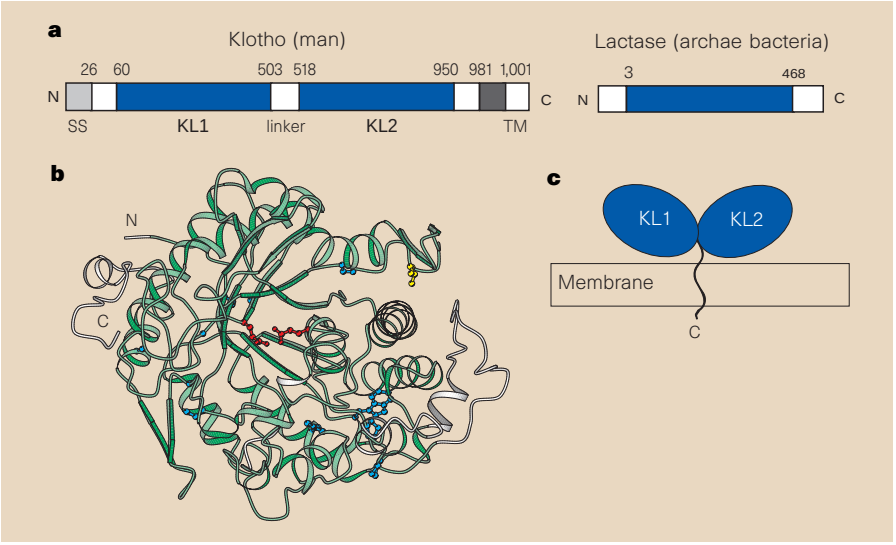

Figure 1 a, **Comparison of human Klotho and archaeal lactase, proteins that contain β-glycosidase domains (labelled KL1 and KL2 in Klotho).** b, **The three-dimensional structure of archaeal lactase is shown as a ribbon diagram (conserved residues are turquoise, glutamic-acid residues in the active site are red, and the regions present in KL1 and KL2 but absent in lactase are yellow). Although KL1 and KL2 domains in Klotho are likely to have tertiary structures similar to that of lactase, subtle differences in the active site and other residues may exist.** c, **The spatial proximity of the amino and carboxy termini of lactase and the relatively short linker region between KL1 and KL2 suggest that Klotho may have a butterfly shape. (The common features of these proteins were compared using a hidden Markov model[7–9]. The model is at URL http://genome.wustl.edu/eddy/hmm.html; software is at URL http://www.cse.ucsc.edu/research/compbio/sam.html)**

caveats that lead one to question the relevance of the *kl* mutation to normal human ageing. For example, osteopenia (decreased bone mass) in mutant mice cannot be immediately equated with human osteoporosis. Moreover, the conclusion that there is atrophy of anterior pituitary cells and associated deficiency of growth hormone requires quantitative morphological and biochemical assessments. In any case, there is evidence that mice that are genetically deficient in growth hormone live longer than controls[5].

What is known about β-glucosidase mutations in man? Perhaps the closest (but quite imperfect) match to the *kl* mutant phenotype is Gaucher's disease[6]. Patients are homozygous for a rare point mutation at the (lysosomal) β-glucocerebrosidase locus on the long arm of human chromosome 1. Klotho appears to have a different subcellular localization (plasma membrane). Unlike the classical forms of Gaucher's disease, *kl* mutant mice have only sparse numbers of cells engorged with unmetabolized substrate. These mice also show progressive cardiovascular calcification, hydrocephalus, selective neuronal loss, opaque corneas, deafness and deformed toes. One wonders if the abnormal strides of *kl* mutant mice are suggestive of subtle foot deformities rather than of Parkinson's disease, as the authors suggest. The strong *kl* expression in the choroid plexus hints that some degree of hydrocephalus might have been missed in these mutant animals.

The authors have mapped the human *kl* gene to the long arm of chromosome 13. It is therefore possible that a yet-to-be-described mutation at this locus could give a phenotype in man that is more closely related to the lesions seen in mice homozygous for the *kl* mutation. If so, some variants at this locus may satisfy Pope's conception of proper ageing. □

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Evolutionary biology

Sex and synergism

Emily J. Lyons

"In short, it seems certain — and here we must simply grit our teeth and swallow — that it is impossible to understand the function of sex without both a firm grasp of the rival hypotheses, their assumptions, logical development and consequences, and also a reasonably comprehensive knowledge of the nature, occurrence and correlates of sexual systems in nature." Graham Bell[1] wrote this 15 years ago. His comments illustrate, in a nutshell, the reasons behind a conference held late this summer to examine the enduring mystery of the prevalence of sexual reproduction*.

The event was marked by the first synthesis of ideas in the field since 1988 (ref. 2), and by a shift from theoretical approaches to empirical tests of both the function of sex in natural populations and of the assumptions underlying the various explanations for it. The meeting culminated primarily in consensus and a clear agenda for future research. However, some key theories for the maintenance of sex hinge on the rate at which deleterious mutations accumulate in the genome of an organism, and there was much debate about the measurement of this rate.

How is it that there are so many sexual organisms when a female could have twice as many grandchildren if she reproduced asexually? Over a century ago, Weismann proposed that the significance of sexual reproduction is "the creation of hereditary individual characters to form the material upon which natural selection may work"[3]. Contemporary workers agree with Weismann, for all of the current, plausible theories hold that sex is advantageous because it creates variation, the raw material for evolution by natural selection, and results in either the assembly of mutations that confer an advantage or the clearance of those that do not (L. Hurst, Univ. Bath; G. Bell, McGill Univ.).

The usefulness of one model of mutation clearance, the 'mutational deterministic' hypothesis (A. Kondrashov, Cornell Univ.) received close attention. According to this view, if deleterious mutations interact synergistically (that is, each successive mutation has progressively larger effects on the decline in an organism's fitness), then asexual populations will have a higher mutation load than sexual populations at equilibrium — the point at which the accumulation of mutations is equal to their removal by natural selection. If the rate at which deleterious mutations occur is greater than about one per genome per generation, then this load should result in an advantage for sexuality[4,5].

It was originally thought that the beauty of this model lay in its falsifiability; clearly, if the mutation rate in a sexual population is less than one per genome per generation, then the model cannot explain why sex is maintained. The difficulty arises with the fact that one cannot simply look at an organism and know its deleterious mutation rate — at best, that rate can be measured only indirectly.

The issue is further complicated by disagreement about the mutational process in general. For example, is the deleterious mutation rate roughly constant across the genome of an organism (A. Kondrashov; B. Tautz, Univ. Munich)? Or are some genes in regions of the genome with a very low mutation rate whereas other regions are prone to higher rates (Hurst)?

The measurement of the rate, constant or otherwise, is similarly contentious. Typically, the measurement is made by calculating the proportion of the genome that is constrained by selection, and the mutation rate per base pair in that constrained region. Tautz estimates the size of the region using the number of amino acids coded for, assuming that the greater the number of the latter, the more highly constrained the region. Kondrashov, however, believes that estimates of this sort may be highly conservative. Not surprisingly, these disparate views on the mutation process and how best to measure mutation rates led to estimates that ranged from 0.06 to 10 per genome per generation, making the mutational deterministic model less easily falsifiable than originally thought.

On the other side of the coin (mutations that are advantageous in themselves or when assembled together), the Red Queen hypothesis postulates that host–parasite coevolution is the critical force. Sex and recombination are favoured because they allow for the production of new, rare genotypes that are expected to have a greater chance of escaping parasites or, in the case of parasites, of infecting new hosts[6]. The operation of this model is perhaps best seen in natural populations of a New Zealand freshwater snail, *Potamopyrgus antipodarum*, where the frequency of sex is highest in lakes and habitats within lakes where parasites are most prevalent (C. Lively, Indiana Univ.). Parasites can play the same game, only in reverse, as evidenced in their increased sexual reproduction when faced with host immunity. Specifically, parasitic nematode larvae from rat hosts that have acquired immune protection are more likely to develop into sexual adults than those from unprotected hosts (A. Read, Univ. Edinburgh).

Nonetheless, there are systems where sex

*Summer School on the Evolution and Maintenance of Sex, Max Planck Institute for Behavioural Physiology, Seewiesen, Germany, 10–17 August 1997.