and similar L enantiomeric excesses in isovaline and α-methylnorvaline, thus challenges the accepted view that the Strecker pathway produced the Murchison α-amino acids. The nearly equivalent L enantiomeric excesses for these α-dialkyl amino acids suggest that they formed in an environment where an asymmetric influence was present in the synthetic environment, something that would appear to be unlikely on meteorite parent bodies. Cronin and Pizzarello propose (*4*) that α-amino-*n*-butamoic acid and norvaline are racemic, whereas their α-dialkyl analogs show an L enantiomeric excess could indicate that the enantiomeric excess in α-hydrogen amino acids was erased by subsequent racemization during parent body aqueous alteration (see figure). They also suggest that the α-dialkyl amino acids may have been produced in presolar environments, whereas the α-hydrogen amino acids were synthesized on meteorite parent bodies by way of the Strecker pathway. This latter proposal appears to me to be unlikely because both α-hydrogen and α-dialkyl amino acids are readily synthesized in laboratory-based abiotic simulations of the Strecker synthesis (*6*).

A number of possible mechanisms for generating enantiomeric excesses in cosmogeochemical environments have been suggested (*1*). Cronin and Pizzarello focus on the proposal that circularly polarized light associated with the synchrotron radiation of neutron stars could result in asymmetric organic synthesis or degradation, but other processes such as spontaneous physical symmetry breaking in β decay and in weak neutral currents seem equally plausible from the theoretical point of view. None of the proposals are overly compelling, and there is a general lack of convincing experimental evidence for any of them. Although very small enantiomeric excesses (~2%) have been generated from racemic leucine irradiated with circularly polarized ultraviolet light, there was extensive decomposition (59 to 75%) during the experiment (*7*). This implies that amino acid survival during this type of enantiomeric enrichment process would be extremely poor. The findings of Cronin and Pizzarello are probably the first demonstration that there may be a natural L-enantiomeric enrichment process in certain cosmochemical environments. This discovery of L enantiomeric excesses for the α-dialkyl amino acids in Murchison, if verified, is certain to generate a flurry of new experiments and proposals by theorists.

Could these enantiomeric excesses be linked to the origin of L amino acid homochirality in life on Earth? First of all, the enantiomerically enriched α-dialkyl amino acids would have to be delivered to Earth without extensive decomposition. Whether exogenous delivery could have provided sufficient amounts of organic compounds necessary for the origin of life, or to sustain life once it started, is largely unknown, although extraterrestrial organic compounds, including racemic (within the precision of the measurements) isovaline, have been detected in deposits associated with impact events (*8*). The reported L amino acid excesses are very small and would need to be amplified by some process in order to generate homochirality. Even if this did take place, the L amino acid homochirality would be associated with α-dialkyl amino acids, which are not major players in modern protein biochemistry. If α-dialkyl amino acids had an important role during the origin of biochemistry, then initially life may have been based on a different protein architecture because peptides made primarily of these amino acids tend to form 3_{10}-helical structures rather than the α-helical conformation associated with proteins made of α-hydrogen amino acids (*5*, *9*). Finally, the homochirality of α-dialkyl amino acids would need to be somehow transferred to the α-hydrogen protein amino acids either during the origin or early biochemical evolution of life on Earth.

If the origin of the homochirality of amino acids in terrestrial life was preordained, then extinct or extant life elsewhere in the solar system would likely be based on the same amino acid handedness. If this is the case, it will make it more difficult to ascertain whether life arose independently elsewhere in the solar system, especially Mars, unless the extraterrestrial life was based on a different suite of L amino acids, such as α-dialkyl amino acids.

An enhanced version of this Perspective, with live links, can be seen in *Science* Online at http://www.sciencemag.org/

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AGING

What Makes Us Tick?

Leonard Guarente

What determines how long an animal can live? Some have argued that the life-span of a species is limited by a fixed total metabolic potential that is consumed over a lifetime. This follows from the observation that smaller animals have faster metabolic rates and generally shorter life-spans (*1*). Consistent with this idea, rats or mice that have existed on a diet reduced in calories live longer than animals that were allowed to eat as much as they liked. A corollary of this view is that the "clock" that times aging might be cumulative damage that is generated by toxic by-products of metabolism, such as oxygen radicals. Others have suggested that life-span may be genetically determined and that these genetic factors override any simple metabolic readout. This could explain why bats and mice, mammals of roughly the same size, have life-spans that differ by a factor of 5 to 10. This view also suggests that the clock is a genetic program set at a different rate in each species. The cloning and sequencing of the *clk-1* gene of *Caenorhabditis elegans* reported in this issue (*2*), along with recent findings discussed below, suggests how both of these propositions may be true.

Worms that have a mutant form of *clk-1* enjoy life-spans that are up to 50% longer than those of wild-type worms (*3*, *4*) and also display a decreased rate of embryonic

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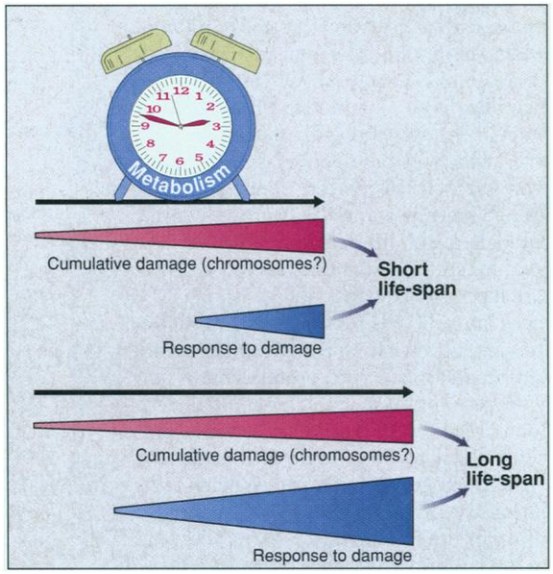
development and a slowing of certain rhythmic behaviors in adults. The mutations show a maternal effect, in which heterozygous mothers with one wild-type and one mutant *clk* gene produce progeny that are phenotypically wild type, even if the offspring are homozygous for the *clk* mutation. This implies that *clk* genes exert their effect in the egg or in early development.

Because cell growth and development were slowed in *clk* mutants, it was inferred that the molecular basis of the defects may be an alteration in cellular metabolism. The *clk-1* sequence (*2*) tends to validate this suspicion. A 1.9-kb fragment of DNA that rescues the mutant phenotypes, including the extension in life-span, is homologous to *CAT5/COQ7*, a gene in *Saccharomyces cerevisiae* (*5*). This gene has been implicated in transcriptional regulation of genes that allow yeast cells to grow on nonfermentable carbon sources, although the precise function of the gene product is not known. In *cat5/coq7* mutants, genes that are normally turned on by a shift from glucose to nonfermentable carbon sources are not activated. These include genes required for gluconeogenesis, as well as genes necessary for synthesis of the electron carrier, coenzyme Q. The functional relatedness of the C. *elegans* and yeast genes is underscored by the ability of *clk-1* to partially complement a *cat5* mutant.

These new results show that life-span in the worm can be extended by a slowing in the metabolic rate, although the molecular mechanism is not yet clear. Negative effects of metabolism might also be inhibited, and long life promoted, in organisms that have an enhanced capacity to prevent oxidative damage when it occurs. In fact, there is a correlation between the levels of superoxide dismutase (SOD) and catalase—compounds that can decrease amounts of oxygen free-radicals—and life-span in different species of mammals or in different strains of *Drosophila* and C. *elegans* (*1*).

How might cumulative damage deriving from metabolism result in aging? Several findings suggest that damage to chromosomes might be important (*6*), including the identification of the gene product mutated in the human premature aging disease, Werner's syndrome, as a putative DNA helicase (*7*). A defect in this helicase could cause an unusually rapid accumulation of chromosomal damage that mimicks the damage that normally accrues during aging.

However, the fact that bats live 5 to 10 times longer than mice—a difference not accounted for by differences in metabolic rate—suggests that metabolism cannot be the whole story (see figure). A second process contributing to the determination of life-span may be a genetic response to aging that cells mount to counteract damage and thus promote longevity. Any longevity-promoting response mechanism would be selected in evolution, and such mechanisms might therefore be quite general in eukaryotic species. The life-span of an organism would then be determined by the sum of these two counteracting forces.



How we age. Damage resulting from metabolism and a counteracting response that can repair the damage may interact to determine life-span. For two species with similar rates of metabolism, a more robust response gives rise to a longer life-span.

The notion of genetic mechanisms that promote longevity by responding to damage contrasts with models of aging in which a genetic program causes senescence. What evidence exists in favor of responses playing a part in controlling life-span? Many of the known means of altering life-span, including genetic mutations, can be interpreted within this framework. In this model, delay of aging can be achieved by cells in two ways: by slowing the accumulation of damage or by heightening the response to damage. The newly cloned *clk-1* gene in C. *elegans* or the insertion of SOD and catalase transgenes in *Drosophila* (*8*) extends life-span by slowing the accumulation of damage.

In other examples of extended life-span, the response to damage is increased: Mutations that affect life-span in the budding yeast, *S. cerevisiae*, likely define response pathways. In this organism, life-span is defined by the number of times that mother cells can bud and give rise to daughter cells. Life-span is determined, in part, by the silent information regulator (SIR) complex, which mediates silencing of entire regions of chromosomes. Loss-of-function mutations in any one of the *SIR* genes shorten life-span, and a gain-of-function mutation in *SIR4* extends life-span (*9*). This latter mutation may direct the SIR complex away from known sites of silencing—that is, telomeric regions of chromosomes—to another novel locus important in determining the life-span. The activity of the SIR complex at this locus may be a part of a response mechanism that promotes longevity. Another response may be Ras2p and its target, cyclic AMP–dependent protein kinase, because increasing the expression of *RAS2* also extends life-span in yeast (*10*).

Yet another response pathway may exist in C. *elegans*. The constitutive activation of regulatory genes of the dauer larvae pathway of this organism can also extend life-span (*11*). Early larvae can enter the dauer state when overcrowded or deprived of nutrients and can remain dormant and viable for long periods of time. Because the activation of certain dauer regulatory genes in adults by mutation extends life-span, these same genes may be a part of a longevity-response program in wild-type adults.

Clearly, a major component of aging occurs at the cellular level and may be quite general in different organisms. The sequence of the *clk-1* gene (*2*) and its yeast homolog suggests that metabolism may be one determinant of life-span. Key questions to be addressed are the nature of the metabolism-generated damage that is relevant to aging and how the proposed genetic response mechanism copes with this damage and delays aging. The analysis of additional genes germane to the aging process in C. *elegans*, *S. cerevisiae*, and mammals will help to illuminate the answers. One wonders whether the pace of aging research will accelerate to the point of overtaking aging itself. The race is on!

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