Aging Cell (2007) **6**, pp421–423 Doi: 10.1111/j.1474-9726.2007.00309.x

VIEWPOINT

Long-lived dwarf mice: are bile acids a longevity signal?

David Gems

Department of Biology, University College London, London, UK

Summary

Pathways that control aging act via regulated biochemical processes, among which metabolism of xenobiotics (potentially harmful chemical agents encountered as environmental toxicants, for example, drugs, or produced internally) is one possible candidate. A new study of long-lived *Ghrhr* mutant mice reports that increased bile acid levels activate xenobiotic metabolism via the nuclear receptor, farnesoid X receptor. This increases resistance to xenobiotic stress, possibly contributing to longevity.
Key words: Aging; bile acids; metabolism; mouse; xenobiotic.

These days, many biogerontologists are tingling with optimism. One reason for this is the discovery of endocrine and intracellular signaling pathways that control longevity and aging. For example, studies with nematodes, fruit flies and mice have shown regulation of aging by insulin/insulin-like growth factor 1 (IGF-1) signaling (IIS) (Kenyon, 2005). These discoveries have opened paths that may lead on to a real understanding of aging, yet some difficult terrain could lie ahead. IIS and other longevity pathways seem to regulate downstream biochemical processes, which act directly on aging, but identifying these biochemistries and figuring out how they exert their effects is a tough challenge. This issue of *Aging Cell* contains a report from Gretchen Darlington's laboratory (Huffington Centre on Aging, Baylor, TX, USA) that sheds new light on one candidate downstream process: xenobiotic metabolism (Amador-Noguez *et al*., 2007). Their studies focus on a long-lived dwarf mutant mouse, the Little mouse (*Ghrhr*$^{lit/lit}$), which fails to secrete growth hormone (GH) and therefore has very low circulating levels of both GH and IGF-1 (Fig. 1).

Earlier studies have sought to exploit whole genome microarray analysis to identify downstream processes that influence lifespan, comparing long-lived animals with normal-lived controls to identify genes for which mRNA transcript levels are altered. A number of studies of this sort, looking at *Caenorhabditis elegans*, *Drosophila* or mouse (e.g. Amador-Noguez *et al*., 2004; McElwee *et al*., 2004; Tsuchiya *et al*., 2004), imply that genetic or dietary conditions that increase lifespan up-regulate sets of genes responsible for detoxification of xenobiotics. This biotransformation process involves a complex system of drug-metabolizing enzymes (DME) and cell surface pumps involved in detoxification and excretion of harmful molecules, as well as the biosynthesis of important metabolites (e.g. steroids). Major DME classes include the cytochrome P450 (CYP) oxidases and glutathione S-transferases (GST) (Fig. 1). It is often postulated that reactions involving toxic compounds, including reactive oxygen species, contribute substantially to the molecular damage that underlies aging. One possibility is that up-regulation of DME expression in long-lived milieus leads to enhanced clearance of toxins that cause aging (McElwee *et al*., 2004).

If the biotransformation system does help to prevent aging in these several animal models, this will not be good news for biogerontologists insofar as the biology of these detoxification processes is horribly complex. DMEs often show broad substrate specificities, and there are numerous isoforms of each DME type. These are encoded by large gene families that, in the main, expanded independently in the nematode, insect and mammalian lineages (Lespinet *et al*., 2002).

In an earlier study, Amador-Noguez *et al*. reported up-regulation of expression of a number of genes linked to xenobiotic metabolism in the liver of *Ghrhr* mutants (2004). Now they have gone on to test for increased xenobiotic metabolism at the phenotypic level, and demonstrate resistance to several xenobiotics that are known DME targets. For example, *Ghrhr* mutants are quicker to recover from paralysis with the muscle relaxant zoxazolamine, probably because this drug, a known CYP substrate, is detoxified more quickly. These findings extend the well-established correspondence between stress resistance and longevity to xenobiotic stress resistance.

Next, they ask whether up-regulation of DME gene expression in *Ghrhr* mutants is mediated by any of three known DME gene regulators, all nuclear receptors: the constitutive androstane receptor (CAR), the pregnane X receptor (PXR) and the farnesoid X receptor (FXR). Here, the mouse has advantages as a model relative to *C. elegans* and *Drosophila* in that murine regulation of DME gene expression is relatively well characterized. Darlington's laboratory has now shown that, of these three potential regulators, only FXR is critical for up-regulation of DME gene expression in *Ghrhr* mutants. This is interesting because FXR is known to be activated by bile acids, and earlier work on *Ghrhr* mutants had shown changes in mRNA levels of several enzymes that affect bile acid metabolism (Amador-Noguez *et al*., 2004). Bile acids are oxidized cholesterol derivatives that are secreted from the gall bladder into the intestine to aid lipid uptake by the intestine. The new study reports that levels of bile acids, particularly cholic acid (Fig. 1), are increased in *Ghrhr* mutants

Correspondence
David Gems, Department of Biology, University College London, Gower Street, London WC1E 6BT, UK. Tel.: 020 7679 4381; fax: 020 7679 7096; e-mail: david.gems@ucl.ac.uk

Accepted for publication *3 May 2007*

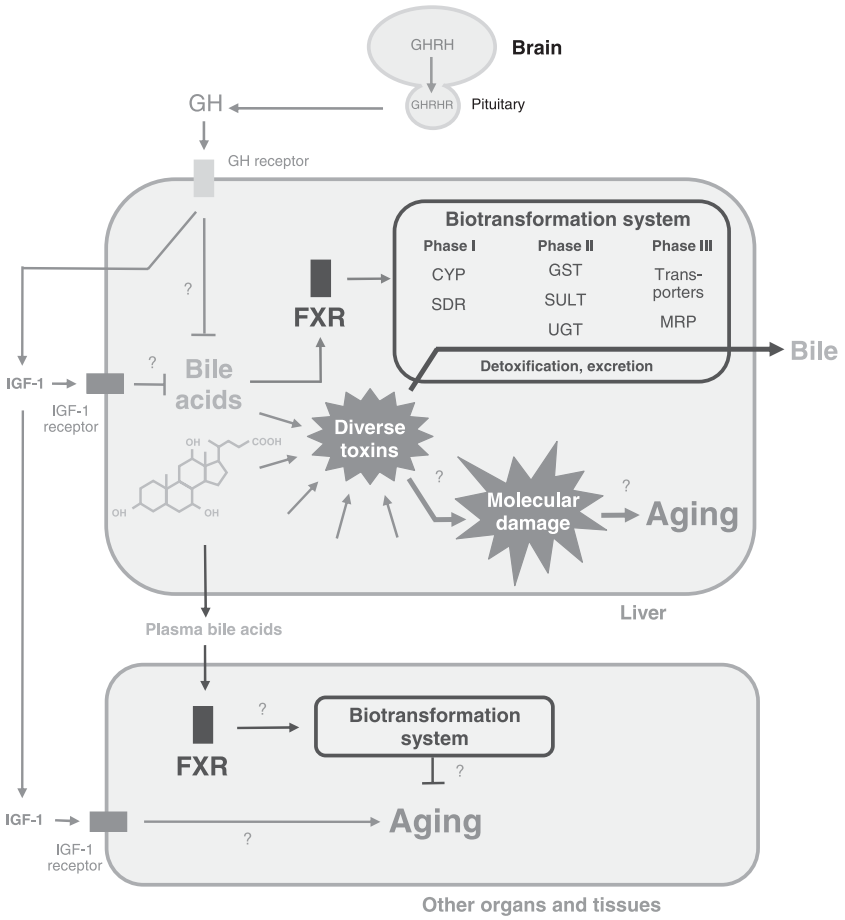

Fig. 1 Hypothetical model of aging-regulatory systems in the Little mouse. This model depicts GH as promoting aging by elevating IGF-1 levels and lowering bile acid levels. As depicted for the liver, a broad spectrum of toxins of various origins are either cleared by the biotransformation system, or react with molecular constituents of the cell, thereby contributing to aging. A simplified version of this is shown for other organs and tissues. This model includes a number of untested hypotheses (indicated by question marks), for example, that bile acids might stimulate biotransformation in peripheral tissues and that detoxification retards aging. The bile acid depicted is cholic acid. Arrows denote either stimulation or movement of signaling molecular. T bars represent inhibition. CYP, cytochrome P450; FXR, farnesoid X receptor; GH, growth hormone; GHRH, GH-releasing hormone; GHRHR, GHRH receptor; GST, glutathione S-transferase; IGF-1, insulin-like growth factor 1; MRP, multidrug resistance associated protein; SDR, short-chain dehydrogenase/reductase (e.g. carbonyl transferases); SULT, sulfotransferase; UGT, UDP-glucuronosyltransferase. For a general review of xenobiotic metabolism, see Gibson and Skett (2001).

in liver, bile and serum. Moreover, administering cholic acid to wild-type mice largely reproduces the changes in DME gene expression seen in *Ghrhr* mutants.

Taken together, these findings suggest a new picture of how GH, and perhaps other elements of IIS pathways, control murine aging (Fig. 1). Lowered GH seems to alter the biotransformation system at two levels. First, there is a change in biosynthetic activity in the liver, leading to altered bile acid levels within the liver. These then act as autocrine or paracrine signals, stimulating DME gene expression via the bile acid-regulated transcription factor FXR. Possibly the resulting increase in DME levels protects against molecular damage and slows aging, at least within the liver. It is tempting to speculate that circulating bile acids might act in a systemic endocrine fashion, stimulating DME expression in peripheral tissues, although this remains unexplored.

The possible role of bile acids as endocrine regulators of aging echoes findings in *C. elegans*, where bile acid-like steroids influence lifespan via the DAF-12 nuclear receptor (Held *et al*., 2006; Gerisch *et al*., 2007). Alternatively, one could see this as a hormetic response to internally generated chemical stress. Hormesis is the beneficial effect at low levels of an agent that is harmful at higher levels. Bile acids are potentially toxic: as this study shows, the elevated bile acid levels in *Ghrhr* mutants are toxic in the absence of FXR. Hormetic effects can increase lifespan; for example, transient heat stress can increase lifespan in *C. elegans* (Cypser *et al*. 2006).

Of course, many questions remain: does the increase in DME activity contribute to the extended lifespan of *Ghrhr* mutants? Does administration of cholic acid increase lifespan (and for that matter, xenobiotic resistance)? Are bile acid levels elevated in other tissues, other long-lived mouse mutants, or in response to dietary restriction? Overexpression GST-10, which detoxifies the lipid peroxidation product 4-hydroxynonenal (HNE), increases lifespan in *C. elegans* (Ayyadevara *et al*. 2005), demonstrating that at least one DME can promote longevity. Notably, murine mGstA4, which also clears HNE, also increases lifespan if expressed in *C. elegans*, and this gene is also up-regulated in *Ghrhr* mutants.

References

Amador-Noguez D, Dean A, Huang W, Setchell K, Moore D, Darlington G (2007) Alterations in xenobiotic metabolism in the long-lived Little mouse. *Aging Cell* **6**, doi: 10.1111/j.1474-9726.2007.00300.x.

Amador-Noguez D, Yagi K, Venable S, Darlington G (2004) Gene expression profile of long-lived Ames dwarf mice and Little mice. *Aging Cell* **3**, 423–441.

Ayyadevara S, Engle MR, Singh SP, Dandapat A, Lichti CF, Benes H, Shmookler Reis RJ, Liebau E, Zimniak P (2005) Lifespan and stress resistance of *Caenorhabditis elegans* are increased by expression of

glutathione transferases capable of metabolizing the lipid peroxidation product 4-hydroxynonenal. *Aging Cell* **4**, 257–271.

Cypser JR, Tedesco P, Johnson TE (2006) Hormesis and aging in *Caenorhabditis elegans*. *Exp. Gerontol*. **41**, 935–939.

Gerisch B, Rottiers V, Li D, Motola DL, Cummins CL, Lehrach H, Mangelsdorf DJ, Antebi A (2007) A bile acid-like steroid modulates *Caenorhabditis elegans* lifespan through nuclear receptor signaling. *Proc. Natl Acad. Sci. USA* **104**, 5014–5019.

Gibson GG, Skett P (2001) Introduction to Drug Metabolism. Bath, UK: Nelson Thornes.

Held JM, White MP, Fisher AL, Gibson BW, Lithgow GJ, Gill MS (2006) DAF-12-dependent rescue of dauer formation in *Caenorhabditis elegans* by (25S)-cholestenoic acid. *Aging Cell* **5**, 283–291.

Kenyon C (2005) The plasticity of aging: insights from long-lived mutants. *Cell* **120**, 449–460.

Lespinet O, Wolf Y, Koonin E, Aravind L (2002) The role of lineage-specific gene family expansion in the evolution of eukaryotes. *Genome Res*. **12**, 1048–1059.

McElwee JJ, Schuster E, Blanc E, Thomas JH, Gems D (2004) Shared transcriptional signature in *C. elegans* dauer larvae and long-lived *daf-2* mutants implicates detoxification system in longevity assurance. *J. Biol. Chem*. **279**, 44533–44543.

Tsuchiya T, Dhahbi J, Cui X, Mote P, Bartke A, Spindler S (2004) Additive regulation of hepatic gene expression by dwarfism and caloric restriction. *Physiol. Genomics* **17**, 307–315.