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The energy trade-off between growth and longevity

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ABSTRACT

Understanding the trade-offs between organisms' life history traits has been a major goal of physiology, ecology and evolution. In the last few decades, two types of intra-specific studies have highlighted the trade-off between growth and longevity. First, diet restriction (DR), as an environmental intervention, has been shown to suppress growth and extend the lifespan of a broad range of animals. Second, genetic studies have also shown that mice, whose growth hormone function is genetically modified (GM), grow slower and live longer than their wild-type siblings. Despite a wealth of empirical data, still largely missing is a theoretical framework that specifies and makes quantitative predictions on this trade-off. Here, I present a mechanistic model based on the principles of energy conservation. The model quantifies explicitly how DR and GM alter the animal's energy budget, and channel metabolic energy to somatic maintenance by suppressing growth, thereby extending lifespan. Data from a diverse set of empirical studies on small rodents supports the predictions of the model. More importantly, the model reveals that although DR and GM are two different methods to extend lifespan, i.e., environmental vs. genetic, the underlying mechanisms of them are the same from the energetic viewpoint.

1. Introduction

Evolutionary theory suggests that the development of organisms' life history traits, such as growth, reproduction, and survival, are constrained by the trade-offs between them (Stearns, 1992). When resource supply is limited, a beneficial change in one trait will cause a detrimental change in another (Sibly and Calow, 1986; Stearns, 1992; Zera and Harshman, 2001). One of the most important trade-offs is between growth and longevity (Hou et al., 2011a; Metcalfe and Monaghan, 2001; Ricklefs, 2006; Rollo, 2002). In the last 80 years, a negative correlation between these two traits has been observed in numerous intra-specific studies, in which the growth of animals is usually suppressed by dietary restriction (DR) or by genetic modification (GM) of the function of growth hormone (GH). DR, designed to induce "under nutrition without malnutrition", has been shown since the 1930s to extend the lifespan of a broad range of organisms (Mair and Dillin, 2008; Masoro, 2005; McCay et al., 1935; Merry, 2002; Sinclair, 2005; Weindruch and Walford, 1988). Genetic studies in the last two decades have also shown that mutant mice with GH deficiency and GH-receptor knock-out mice with GH resistance live longer than their wild-type siblings (Bartke, 2005; Brown-Borg, 2003; Brown-Borg et al., 1996). However, despite decades of intensive study and a wealth of empirical data, theoretical efforts to understand this trade-off remain either descriptive, such as a few statistical models (Merry, 2002; Rollo, 2002; Ross et al., 1976; Turturro et al., 1994), or qualitative, such as the theories of oxidative free radical damage (Barja, 2004; Bartke, 2005; Merry, 2002; Monaghan et al., 2009), protein synthesis alteration (Kapahi, 2010), membrane fatty acid alteration (Hulbert et al., 2007; Merry, 2002), and hormesis (Masoro, 2005). Here, I present a quantitative and predictive framework based on the principle of energy conservation, which explicitly quantifies the alteration of energy allocation of animals under DR or genetic modification (GM), and reveals a common pattern of the trade-off between growth and longevity in both DR and GM animals from an energetic viewpoint.

I assume that the longevity of an organism is correlated to the energetically costly pathways of somatic maintenance, which are involved in repairing oxidative damage of protein, membrane lipid and DNA (Barja, 2004; Bartke, 2005; Bokov et al., 2004; Merry, 2002; Monaghan et al., 2009). By suppressing growth, DR and GM channel additional energy to the maintenance pathways, thereby extending lifespan. I have recently proposed a conceptual framework as follows (Hou et al., 2011a). During growth, energy assimilated from food, *F*, (black-framed boxes in Fig. 1) is partitioned between the energy deposited in the new biomass, *S*, and three terms of metabolic energy that are dissipated as heat,

Abbreviations: DR, diet restriction; GM, genetic modification; GH, growth hormone; AL, *ad libitum*.

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namely, energy for activities, B_{act}, biosynthesis, B_{syn}, and maintaining existing biomass, B_{maint}, i.e., $F = S + B_{act} + B_{maint} + B_{syn}$ (Hou et al., 2008; West et al., 2001). The sum of B_{syn} and B_{maint} is the resting metabolic rate, B_{rest} (red-framed boxes) i.e.

$$B_{rest} = B_{syn} + B_{maint}. \quad (1)$$

So, energy from food, F, can be expressed as $F = S + B_{act} + B_{rest}$. It is important to recognize the relationship between the energy deposited in new biomass, S (green-framed boxes) and energy required for biosynthesis, B_{syn} (blue-framed boxes). The former is the deposited energy content of biomass, and the latter is the metabolic work required to synthesize biomass, which corresponds to the indirect work of biomass deposition (Brody, 1945; Hou et al., 2008). These two compartments are linearly proportional to each other (Hou et al., 2008; Moses et al., 2008).

At the beginning of DR, the energy assimilated from food, F, decreases, but in the mammals under DR the mass-specific resting metabolic rate, B_{rest}, and level of activities, B_{act}, may decrease or in some cases even increase slightly, and in general remain roughly unchanged (Hou et al., 2011c; Masoro, 2005; McCarter et al., 1985; Merry, 2002) (see detailed review in Supplementary Table S1,). Therefore the deposition in new biomass, S, must be suppressed, since $F = S + B_{act} + B_{rest}$. As emphasized above, S is proportional to B_{syn}. When there is not as much new biomass to synthesize, the animals do not have to do as much indirect work (Fig. 1B). In other words, the decreased supply of molecular building blocks (S) acquired from the food reduces the demand of work to assemble the building blocks (B_{syn}). Since mass-specific B_{rest} remains unchanged, the decreased energy require for biosynthesis results in the availability of more energy for maintenance (Eq. (1), $B_{rest} = B_{syn} + B_{maint}$, Fig. 1B). The result of enhanced maintenance is lifespan extension.

The growth of animals under DR is suppressed by an environmental factor—low food availability, whereas animals under GM do less work for biosynthesis spontaneously due to GH deficiency or GH receptor resistance. Meanwhile compared to their normal siblings, GM animals have roughly the same or slightly reduced mass-specific metabolic rate (Brown-Borg, 2003; Westbrook et al., 2009) (see detailed review in Supplementary Data). Therefore, again, a decreased energy require for biosynthesis leads to an increased availability of energy for maintenance (Fig. 1C).

I now derive a model to quantitatively estimate the extension of lifespan, based on three previously made assumptions (Hou et al., 2011b). Assumption 1: The deleterious products of oxidative metabolism, such as reactive oxygen species (ROS), cause various forms of molecular and cellular damage (Balaban et al., 2005; Barja, 2004; Bokov et al., 2004). The relationship between oxygen consumption (metabolic rate) and ROS generation is complex when comparison is made cross taxon (Barja, 2004; Perez-Campo et al., 1998), but within a taxon, especially within a species, they are shown to be proportional to each other (Heise et al., 2003; Ku et al., 1993; Mortelette et al., 2010). So I assume that the rate of damage, H (damaged mass/time), is proportional to the resting metabolic rate, B_{rest}, i.e., $H = \delta B_{rest}$, where δ is a constant within a species, indicating the amount of damaged mass associated with one unit of metabolic energy. Detailed discussion and justification of this assumption are available in Appendix I. Assumption 2: Repairing the damage requires metabolic energy. The rate of repair, R (repaired mass/time), is proportional to B_{maint}, the amount of metabolic energy available for maintenance, with a coefficient η, i.e., $R = \eta B_{maint}$, where η is also a constant, indicating the amount of mass that can be repaired by one unit of metabolic energy. Assumption 3: Repair is not perfect, so damage accumulates. When a critical fraction of body mass, C, is damaged, the organism dies, i.e., $C = \int_0^{LS}(H - R)dt/M$, where M and LS are adult body mass and lifespan respectively. C is assumed to be a constant within a species. I define an effective maintenance efficiency, $\varepsilon = \eta/\delta$, then LS can be found by solving this equation

$$D = \int_0^{LS} \frac{1}{M}(B_{rest} - \varepsilon \times B_{maint})dt \quad (2)$$

where $D = C/\delta$, a constant for a given species, is the effective mass-specific accumulated damage over a life time. Empirical measurements of the resting metabolic rate during growth show that $B_{rest} \approx B_0 m(t)^{3/4}$, where $m(t)$ is the body mass as a function of age, t, and B_0 is a normalization coefficient, which increases exponentially with body temperature (Hou et al., 2008; Moses et al., 2008; West et al., 2001; Zuo et al., 2009). The rate of energy expenditure for biosynthesis is $B_{syn} = E_m dm(t)/dt$, where $dm(t)/dt$ is the growth rate, and E_m is the energy expended to synthesize a unit of biomass, which is assumed to be a constant for a given species (Hou et al., 2008; Moses et al., 2008; West et al., 2001). Substituting these relationships together with Eq. (1) into Eq. (2) yields the effective mass-specific accumulated damage over a life time:

$$D = \int_0^{LS} \frac{1}{M}\left[B_0 m(t)^{3/4} - \varepsilon\left(B_0 m(t)^{3/4} - \frac{E_m dm}{dt}\right)\right]dt \cong (1-\varepsilon)LS \times B_0 M^{-1/4} + \varepsilon E_m\left(\frac{M - m_0}{M}\right) \quad (3)$$

where m_0 is the mass at birth (West et al., 2001). The detailed derivation of Eq. (3) is available in Section 2.

When DR or GM is applied, the adult mass reduces to $M_{D/G}$, and the body temperature decreases slightly (usually ~1 °C), so the normalization coefficient, B_0, decreases about ~8% (*SI text*). Taking these changes into account, Eq. (2) gives $D_{D/G} = (1-\varepsilon)LS_{D/G} \times B_{0,D/G} M_{D/G}^{-1/4} + \varepsilon E_m(1 - m_0/M_{D/G})$. When the lifespan is reached, both normal and DR/GM animals accumulate the same amount of damage per unit mass (Assumption 3), i.e., $D(LS) = D_{D/G}(LS_{D/G})$, which gives a simple quantitative expression of extension of the lifespan:

$$LS_{D/G} \times B_{0,D/G} M_{D/G}^{-1/4} - LS \times B_0 M^{-1/4} = \frac{\varepsilon E_m \mu}{1-\varepsilon}\left(\frac{M}{M_{D/G}} - 1\right), \quad (4)$$

where μ is the ratio of birth mass, m_0, and normal adult mass, M, i.e., $\mu = m_0/M$. This ratio is a constant for a given species. The ratio of the adult body masses of normal and DR/GM animals, $M/M_{D/G}$, indicates the degree of body mass reduction by either DR or GM. Both sides of Eq. (4) have the dimension of [energy/mass]. The detailed derivation of Eq. (4) is available in Section 2.

2. Methods

2.1. Derivation of Eqs. (3) and (4)

I start with Eq. (2), $D = \int_0^{LS}(B_{rest} - \varepsilon \times B_{maint})dt/M$. In this equation, $B_{rest} \approx B_0 m(t)^{3/4}$, where $m(t)$ is the body mass as a function of age, t, B_0 is a normalization coefficient, and E_m is the energy required to synthesize one unit of biomass. During growth, a portion of metabolic energy is allocated to biosynthesis, so $B_{maint} = B_{rest} - B_{syn} = B_0 m(t)^{3/4} - E_m dm(t)/dt$, where dm/dt is the growth rate. Because $\int_0^{LS} dm = M - m_0$, where m_0 and M are the birth and adult masses respectively, Eq. (2) becomes

$$D(LS) = \int_0^{LS}\left[B - \varepsilon\left(B - \frac{E_m dm}{dt}\right)\right]\frac{dt}{M} = \frac{(1-\varepsilon)B_0}{M}\int_0^{LS} m(t)^{3/4}dt + \varepsilon E_m\left(\frac{M - m_0}{M}\right) \quad (5)$$

Calculating the integral in the first term of Eq. (5) requires the analytic expression of growth curve, $m(t)$. The ontogenetic growth model (Eq. (1)) gives a growth curve, (West et al., 2001) $(m(t)/M)^{1/4} = 1 - [1 - (m_0/M)^{1/4}]e^{-B_0 t/(4E_m M^{1/4})}$. Integrating $m(t)^{3/4}$ over time gives $\int_0^t m(\tau)^{3/4}d\tau = M^{3/4}t + Term\,2 + Term\,3$, where

$$\begin{aligned} \text{Term 2} \quad &= E_m M/B_0 \times \\ &[e^{-B_0 t/(4E_m M^{1/4})}(12 - 12\mu^{1/4}) \\ &+ e^{-B_0 t/(2E_m M^{1/4})}(-6 + 12\mu^{1/4} - 6\mu^{1/2}) \\ &+ e^{-3B_0 t/(4E_m M^{1/4})}(4/3 - 4\mu^{1/4} + 4\mu^{1/2} - 4/3\mu^{3/4})] \end{aligned}$$

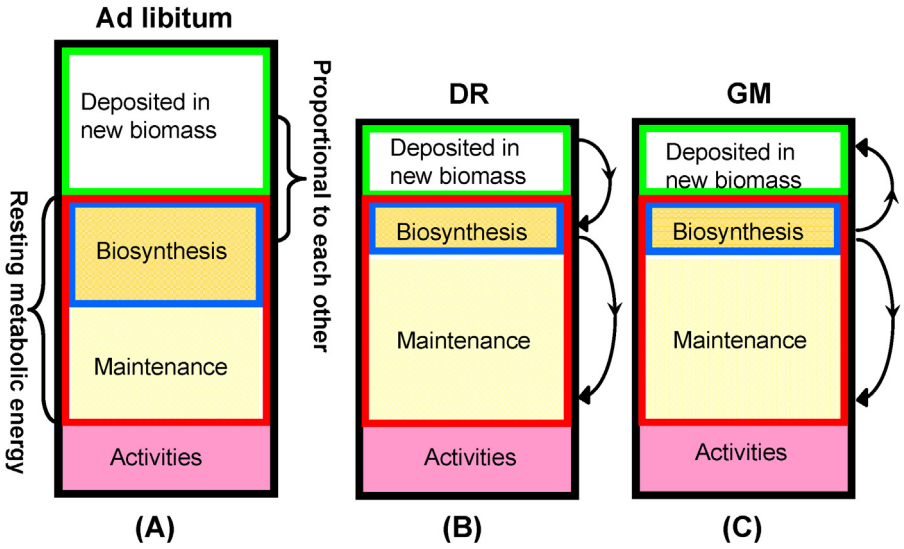

Fig. 1. Conceptual illustration of energy budget alteration under *ad libitum* condition (A), diet restriction (B), and genetic modification (C). Every quantity in this figure is mass-specific. The arrows in Fig. 1B and 1C indicate the causal relationships in the energy budget alteration. In Fig. 1B, the FR-induced decrease in deposition leads to the decrease in biosynthesis, which in turn leads to the increase in maintenance. In Fig. 1C, the GM-induced decrease in work for biosynthesis leads to the increase in both maintenance and deposition. (For interpretation of references to colour in this figure legend, the reader is referred to the web version of this article.))

Term 3 = $E_m M/B_0 \times (-22/3 + 4\mu^{1/4} + 2\mu^{1/2} + 4/3\mu^{3/4})$, and $\mu = m_0/M$ is the ratio of birth and adult mass.

When age, t, is large, Term 2, which decrease exponentially with time, becomes negligible. Term 3 is a constant over time. It is small compared to the first term $M^{3/4}t$ in the integral for a large t, e.g., 1000 days. If M = 500 gram (for a rat), Term 3 is only ~5% of the first term, and If M = 50 (for a mouse), Term 3 is ~2% of the first term. To simplify the calculations and to make the biological meaning of Eq. (4) stand out, I made the approximation: $\int_0^{LS} m(t)^{3/4}dt \approx M^{3/4}LS$. Note, Eqs (3) and (4) can be calculated without this approximation, and the slopes of the curves in Figs 1 and 2 only change negligibly. Without this approximation, the goodness of the fitting is actually improved, i.e., the R^2 values are higher, but Eq. (4) becomes more complex, and the biological meanings of it become obscured. Overall, Eq. (5) leads to Eq. (3), $D(LS) \approx (1-\varepsilon)LS \times B_0 M^{-1/4} + \varepsilon E_m(1 - m_0/M)$.

When both control and DR animals reach their lifespan, their mass-specific accumulated damage have the same level (Assumption 3), $D(LS) = D_{DR/GI}(LS_{DR/GI})$. This gives $(1-\varepsilon)LS \times B_0 M^{-1/4} + \varepsilon E_m(1 - m_0/M) = (1-\varepsilon)LS_{D/G} \times B_{0,D/G} M_{D/G}^{-1/4} + \varepsilon E_m(1 - m_0/M_{D/G})$. Since DR animals have the same birth mass, m_0, as their control siblings, it is straight forward to have Eq. (4), $LS_{D/G} \times B_{0,D/G} M_{D/G}^{-1/4} - LS \times B_0 M^{-1/4} = \frac{\varepsilon E_m \mu}{1-\varepsilon}\left(\frac{M}{M_{D/G}} - 1\right)$.

I have assumed that the damage rate is proportional to the metabolic rate. To derive Eqs. (3)–(5), I used resting MR, B_{rest}, i.e., $H = \delta B_{rest}$. Alternatively, I can use the expression of total metabolic rate, B_{total}, i.e., $H = \delta' B_{total}$, with a different coefficient, δ'. However, because B_{total} is proportional to B_{rest} with a constant factor, which averages about 2–3 (Hou et al., 2008; Moses et al., 2008; Nagy et al., 1999; Peters, 1983), and also because DR animals and free-feeding animals have the same activity level, when deriving Eqs. (3)–(5) the multiple factor between δ and δ' will be cancelled out by the multiple factor between B_{total} and B_{rest}. Thus the final result stays the same regardless of whether resting or total metabolic rate is used.

When deriving Eqs (3)–(5), I followed the previous works (Hou et al., 2008; Moses et al., 2008; Ricklefs, 1974; Withers, 1992; Zuo et al., 2009), and assume that E_m, the energy required to synthesize one unit of biomass, is a constant for a given species over ontogeny, regardless of whether animals are under AL or DR. However, if body compositions, e.g., the fractions of fat and protein, change over ontogeny, and differ in free-fed and DR animals, then E_m would be a function of age and body compositions. In Appendix II, I discuss the variable E_m, and provide justifications for the assumption of a constant E_m.

2.2. Data collection

Supplementary Tables S2–S4 contain the data on body mass change and lifespan extension from 73 empirical studies of DR and GM on small rodents. I have excluded the studies in the following categories when making Figs. 2 and 3. (1) Studies that involve cold stress and heat stress, because these factors induce metabolism alterations that are not considered in the model; (2) studies that only reported lifespan, but no body mass data. Some studies have several experimental groups, but only reported the body mass data on one group. In these cases, I only included data from the group with body mass data; (3) studies that involve vitamin-restriction, because death caused by vitamin-restriction cannot be explained by the model based on energy conservation; and (4) studies that involve extremely severe diet restriction, for example, 12% of what *ad libitum* fed animal have, because the extremely severe diet restriction causes substantial abnormal death early in life.

Some studies did not report the mean lifespan, but gave mortality curves. In those cases, mean lifespan was calculated from the mortality curve. The numbers in the column of "DR methods" in the tables indicate the percentage of food that DR animals were fed, comparing to the control animals. Some studies conducted DR protocols that cannot be summarized by a simple percentage. The DR methods in those cases were briefly described in the column.

3. Results and discussion

3.1. Trade-off between growth and longevity in diet restricted and genetically modified rodents

Eq. (4) has three species-specific parameters: μ indicates a base line of body mass reduction; E_m indicates how much energy can be saved for maintenance by body mass reduction; and ε indicates how efficiently the energy can be used for maintenance. For a given species, since μ, E_m, and ε are constants, Eq. (4) predicts that the normalized lifespan extension, $LS_{D/G} \bullet B_{0,D/G}/M_{D/G}^{1/4} - LS \bullet B_0/M^{1/4}$, is proportional to the normalized adult mass reduction, $M/M_{D/G} - 1$, with the slope, $E_m\varepsilon\mu/(1-\varepsilon)$. I collected empirical data from DR studies on mice and rats to test this prediction (Section 2 and Supplementary Table S2, S3). Fig. 2 shows that the prediction is well supported by data, for the body mass reduction explains 82% of the lifespan extension in mice (Fig. 2A), and 87% in rats (Fig. 2B). I need to emphasize that E_m, and ε, the parameters determining the slope of Eq. (4), can be estimated independently from first principles of biochemistry, and therefore can be used to verify the slopes obtained in Fig. 2. Previous studies have estimated E_m values for mammals averages of about 4–5000 J/g (Hou et al., 2008; Moses et al., 2008). The ratios of birth mass and adult mass for mice and rats, μ_{mice} and μ_{rats}, are about 0.1 and 0.01 respectively. Substituting E_m and μ into the slopes obtained in Fig. 2A and B yields estimates of the effective maintenance efficiency, ε, 0.998 and 0.999 for mice and rats respectively. These values are very close to the range of ε, 0.964–0.999, estimated based on the bioenergetics of breaking and repairing polymer linkages (Supplementary Data).

Eq. (4) makes the same prediction for lifespan extension in GM animals. More importantly, Eq. (4) predicts that, because animals within the same species have the same μ, E_m, and ε, the lifespan

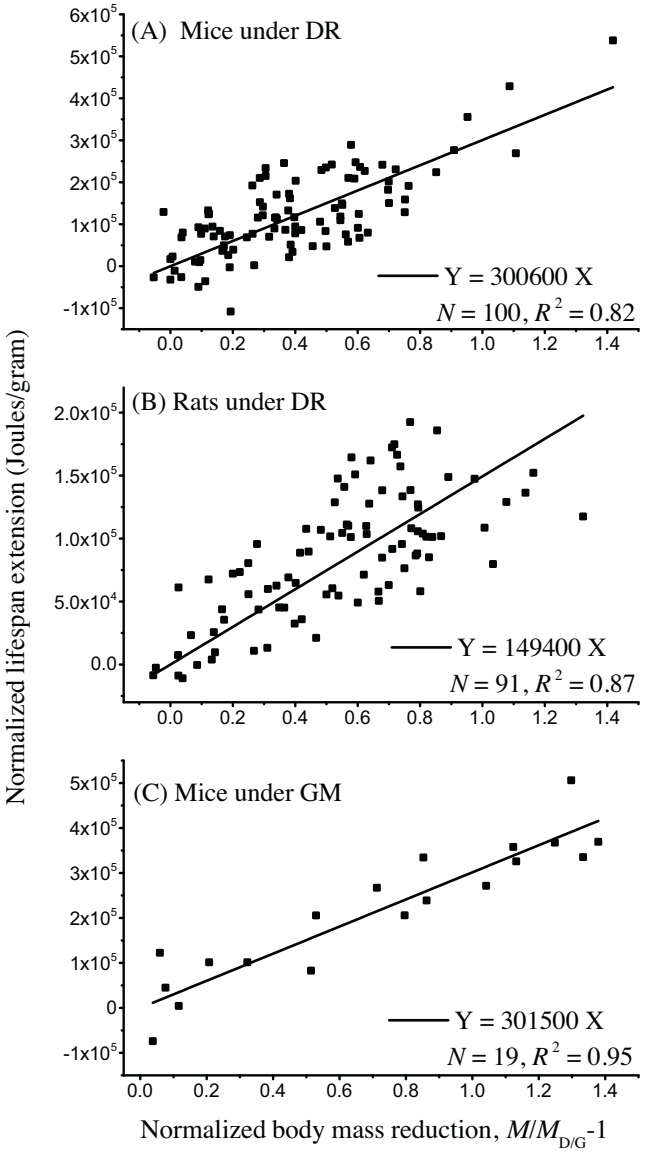

Fig. 2. Normalized lifespan extension versus normalized adult body mass reduction: (A) mice under DR. A linear regression yields $y = 300{,}600x$ ($N = 100$, $R^2 = 0.82$), (B) rats under DR, $y = 149{,}400x$ ($N = 91$, $R^2 = 0.87$) and (C) mice under GM, $y = 301{,}500x$ ($N = 19$, $R^2 = 0.95$). Detailed data collection is available in Section 2 and Supplementary Data.

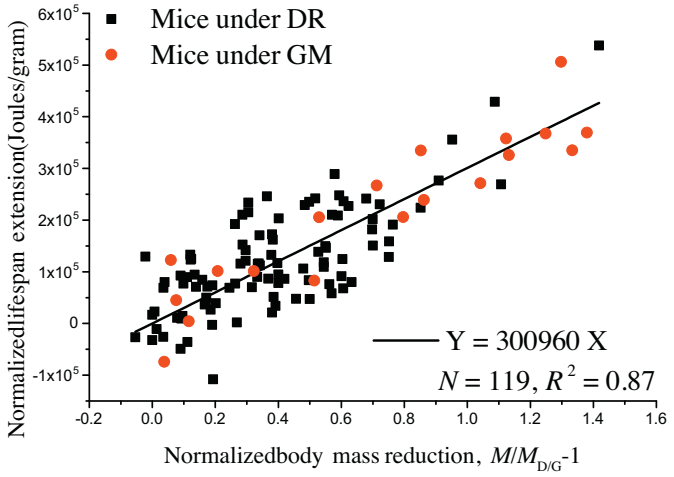

Fig. 3. Overlap of lifespan extension in mice by DR (black square dots) and GM (red round dots). Normalized lifespan extension versus normalized adult body mass reduction in mice by DR (black square dots) and GM (red round dots). A linear regression yields $y = 300{,}960x$ ($N = 119$, $R^2 = 0.87$). (For interpretation of references to colour in this figure legend, the reader is referred to the web version of this article.)

extension curve for GM animals should have the same slope as the one for DR animals. I collected data from genetic manipulation studies on lifespan extension in mice to test these predictions. The studies include mutant mice with growth hormone deficiency, and growth hormone receptor knock-out mice with growth hormone resistance (Supplementary Table S4). The empirical data strongly support the predictions (Fig. 2C). Body mass reduction explains 95% of the lifespan extension in GM mice. More importantly, the slope for GM mice, 301,500 J/g (Fig. 2C), is nearly identical to the one for DR mice, 300,600 J/g (Fig. 2B).

In Fig. 3, I combine the data from DR and GM mice to show the complete overlap of these two interventions. The identical slopes of the curves reveal an important result. Although DR and GM suppress growth in different ways, environmentally and genetically, the mechanisms underlying their lifespan extension effects are the same from an energetic viewpoint. Because animals within the same species have the same μ and E_m, DR and GM channel the same amount energy to the somatic maintenance pathways if they retard same amount of biosynthesis, and with the same maintenance efficiency, ε, they lead to the same lifespan extension.

Table 1
List of experiments, in which different treatments failed to induce differences in final body mass, and therefore failed to extend lifespan. M1 and M2 are final body masses, and LS1 and LS2 are lifespans in treatment 1 and 2 respectively.

Species	Treatment 1	Treatment 2	M1 (g)	M2 (g)	LS1 (days)	LS2 (days)	References
Balb/C mice	DR started at 22-day old	DR started at 120-day old	29.3	29.2	641	647	Stoltzner (1977)
B/W mice	Free fed; 49% protein in diet; same calorie as treatment 2	Free fed; 15% protein in diet; same calorie as treatment 1	38	38.6	280	295	Gajjar et al. (1987)
C57BL/6 mice	Add Alpha lipoic acid to diet	add Coenzyme Q10 to diet	44	44	939	926	Lee et al. (2004)
Wistar rats	DR started after weaning	DR started at 80-day old; switched to 40% casein at 430-day old; stopped at 600-day old	320	320	1019	1020	Fujita et al. (1984)
Long-Evan rats	Sedentary; body mass kept at 330 grams	Forced to exercise; 70% DR	330	333	1051	1058	Holloszy (1997)
Fischer 340 rats	Reduced fat in diet; same calorie as treatment 2	Reduced mineral in diet; same calorie as treatment 1	498	502	763	764	Iwasaki et al. (1988)
Donryu rats	10% casein in diet	27% casein in diet	297	306	543	569	Nakagawa et al. (1974)
Donryu rats	10% casein in diet	18% casein in diet	297	287	543	545	Nakagawa et al. (1974)

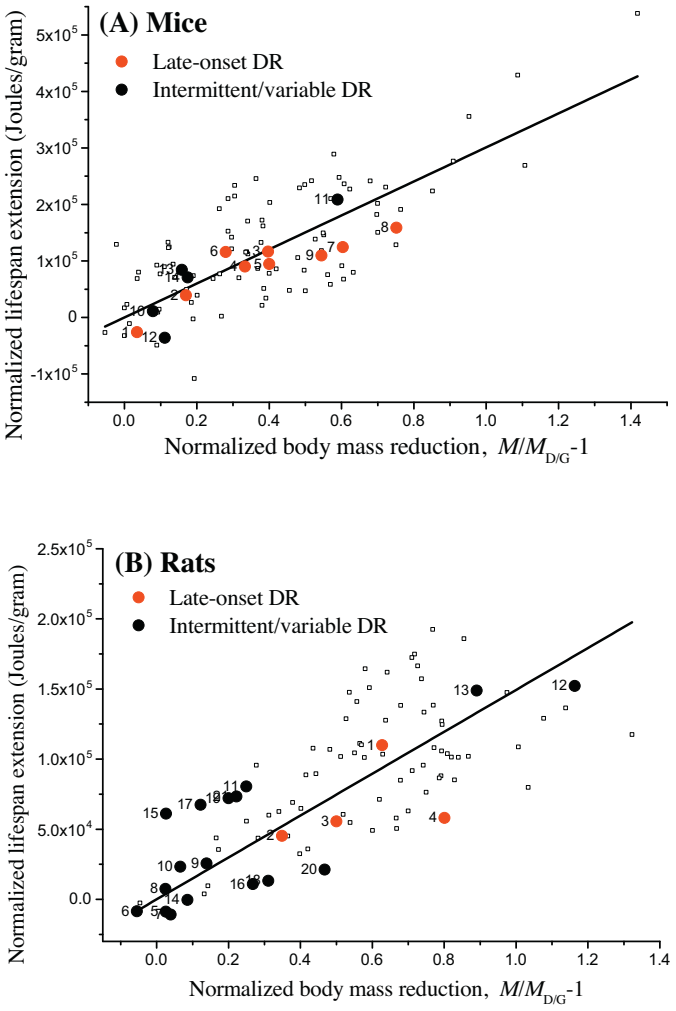

Fig. 4. Lifespan extension in late-onset (solid red dots) and intermittent/variable DR (solid black dots). (A) Mice. The numbers to the left of the dots indicate the following. 1–3: DR started at 6-month old; 4–6: DR started at one year old; 7–9: DR started older than 61 weeks. 10: DR started at 6-wk old, and stopped at 12-wk old; 11: Lifelong DR started before weaning; 12: DR started before weaning, and stopped after weaning; 13: DR started after weaning, and stopped at 61-wk old; 14: DR started before weaning, and stopped at 61-wk old. (B) Rats. The numbers to the left of the dots indicate the following. 1: DR started at 6-month old; 2–4: DR started older than 300 days; 5–8: DR started at 3-wk old, and stopped at 12-wk old; 9: DR started at 1-month old, and stopped at 1-year old; 10: DR started at 6-wk old, and stopped at 20-wk old; 11–12: DR started at 4-wk old, and stopped at 600-day; 13: DR started at 80-day old, and stopped at 350-day old; 14–21: DR started when animals were 50 grams, and stopped at 300-day old. The different nutrients added to diet include starch (14, 15), sugar (16, 17), meat (18, 19), and milk (20, 21). The empty squares in both (A) and (B) are from studies, in which a constant and life-long DR started when animals were younger than 6 months. (For interpretation of references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. The effects of late-onset DR and intermittent diet restriction on lifespan extension

Eq. (4) predicts that lifespan extension by diet restriction (DR) is proportional to the body mass reduction, regardless of how DR was implemented. The data in Fig. 2A and B were collected from studies with a broad variation of DR protocols, including different severities of restriction, diet compositions, ages of DR onset, and lengths of DR period (Supplementary Table S2, S3). The results of these different DR designs fall on the same pattern shown in Fig. 2, and therefore confirm the prediction. Below I discuss two types of DR studies, namely, "late-onset DR," in which restriction initiates after adult mass has been reached, and "intermittent/variable DR," in which DR is switched on and off, or its severity and/or diet composition vary during the DR course. Late-onset DR usually causes "negative growth," i.e., body mass reduction after adult mass is reached, whereas intermittent/variable DR causes variations in growth, such as catch-up growth or compensatory growth, which often take place when free-feeding is resumed after a period of DR. In a previous paper (Hou et al., 2011c), I have used an early version of this energy budget model to predict the negative growth induced by late-onset DR and the variation in growth induced by the intermittent/variable DR. The predictions are well supported by the data (Hou et al., 2011c). The extended energy model presented in this paper predicts that no matter how late DR is initiated, and no matter how complex the DR protocol is, the extension of lifespan depends on the amount of body mass reduction, and if DR fails to induce body mass reduction, then it will fail to extend lifespan.

I quantitatively highlight these predictions in Fig. 4 and Table 1. In Fig. 4A (mice) and 4B (rats), the solid red dots are from the experiments that initiated DR when animals were at middle age (6 months and older than 1 year) after the adult mass has been reached, and the solid black dots are from the intermittent/variable DR experiments. In these DR studies the amount of body mass reduction varies, depending on the strain of animals and detailed designs of DR. As predicted by the model, lifespan extension varies accordingly with the slopes that are insignificantly different from the ones obtained in Fig. 2 (ANCOVA, $P = 0.693$ and 0.853 for mice and rats respectively). Table 1 lists a few DR experiments that support the prediction of "no body mass reduction, no lifespan extension." In these experiments, the different treatments, including different ages of DR initiation, different diet compositions, and sedentary versus forced exercise, fail to induce significant difference in body mass, and therefore fail to induce alteration in energy budget. Thus, as predicted by the model, there was no significant difference in lifespan between the treatment groups.

4. Conclusion

I have derived a quantitative and predictive model for the effects of DR and GM on lifespan extension. The model offers a mechanistic foundation and a more general version for the long standing "rate of living theory". This theory hypothesizes that the lifespan of organisms, *LS*, is inversely proportional to their mass-specific metabolic rate, B/M (McCoy and Gillooly, 2008; Pearl, 1928). This is because, according to the free radical theory of aging, higher B/M leads to higher production rate of ROS, and thus a higher rate of molecular damage (Barja, 2004; Brys et al., 2007; Merry, 2002; Stuart and Brown, 2006). However, it has been shown that DR and GM animals have similar mass-specific metabolic rate to their normal counterparts, yet live much longer. This apparent conflict, which has been a puzzle (Balaban et al., 2005; Brys et al., 2007; Merry, 2002; Stuart and Brown, 2006), can be explained by the detailed energy trade-off revealed here, i.e., Eq. (4). Without growth suppression, i.e., $M/M_{D/G} - 1 = 0$, the mass-specific lifetime energy usage, $LS \times B/M = LS \times B_0 M^{-1/4}$, is a constant between animals (Eq. (4)), consistent with the rate of living theory suggestion. In the case of DR and GM, similar mass-specific metabolic rates cause similar rates of total damage, but due to the suppression of growth, i.e., $M/M_{D/G} > 1$, more energy is allocated to the repair mechanisms, so that the net damage rate is lowered. The result of the reduced net damage rate is the lifespan extension.

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Appendix A. Appendix I. The proportionality between the rates of damage/ROS generation and oxygen consumption

In the model, I assumed that the rates of ROS generation and damage, H, is proportional to the metabolic rate (or rate of oxygen consumption), B, i.e., $H = \delta B$, where δ is a constant within a species. This assumption is based on the oxidative stress theory, which suggests that the dissipative mechanisms of oxidative metabolism and their subsequent deleterious productions (e.g. ROS) cause various forms of molecular and cellular damages associated with the process of aging (Balaban et al., 2005; Barja, 2004; Hulbert et al., 2007; Lombard et al., 2005; Sohal and Weindruch, 1996). Below I review some empirical evidence supporting this assumption. After that I address the evidence that appears to counter this assumption.

Because mitochondria consumes 80% of the oxygen used by the cells, and produce 90% of the ROS in cells (Balaban et al., 2005; Monaghan et al., 2009), most direct measurements of ROS generation were conducted on mitochondria from both ectotherms and endotherms. Heise et al. (2003) found that in mitochondria from Antarctic polar bivalve, ROS generation rate is "correlated significantly with oxygen consumption" within a temperature range from 1 to 12 °C. Cross species but within a taxon, it was found that the ratio of ROS generation and oxygen consumption is a constant in the mitochondria from Antarctic polar bivalve and soft shell clam (Abele et al., 2002; Heise et al., 2003). Similarly, Mortelette et al. (2010) "confirms the existence of a positive ROS generation/metabolic rate relationship in fish muscle" (trout and eel); moreover the authors found that the ratio of ROS generation and oxygen consumption rate is the same in the mitochondria from trout and eel. The constant ratios between ROS generation and oxygen consumption reflect the proportionality between these two rates within a taxon.

In endotherms, it was found that in the mitochondria from both rat liver and pigeon heart, an increase in oxygen partial pressure, which is positively correlated to the cellular oxygen consumption, increases the generation rate of H_2O_2 (Boveris and Chance, 1973). More importantly, in a study on the heart and kidney of seven different mammalian species, including mouse, hamster, rat, guinea pig, rabbit, pig, and cow, Ku et al. (1993) found positive correlations between ROS generation and mitochondrial oxygen consumption, and between mitochondrial oxygen radical generation and metabolic rate. Several researchers have taken the results from Ku et al. (1993) as a strong empirical evidence for the positive relationship between ROS generation and oxygen consumption in mammals (Mortelette et al., 2010; Perez-Campo et al., 1998; Sohal and Weindruch, 1996).

At the whole organismal level, the indirect evidence for this assumption comes from the reconciliation of the oxidative stress theory and the rate of living theory. On one hand, the rate of living theory identifies that metabolic rate (oxygen consumption rate) is inversely correlated to lifespan of animals within a taxon (Beckman and Ames, 1998; Lints, 1989; Pearl, 1928; Sohal, 1986); on the other hand oxidative stress theory links ROS generation to aging (and therefore lifespan). Although there are exceptions against the rate of living theory (for example, (Brys et al., 2007; Hulbert et al., 2004); I am going to address these exceptions below), the general negative correlation between metabolic rate and lifespan still holds when broad comparisons are made cross species *within* a taxon for example, (Calder, 1984; Economos, 1982; Hulbert et al., 2007; Ku et al., 1993; McCoy and Gillooly, 2008; Schmidt-Nielsen, 1984).

Nonetheless, there exists some evidence that seemingly opposes this assumption. Some researchers have summarized that ROS generation is not proportional to oxygen consumption in five situations (Hulbert et al., 2007) and Barja (2007), namely, (1) between different states of mitochondrial respiration; (2) under diet restriction; (3) in comparison cross taxon; (4) between different exercise status; and (5) between different tissues.

The assumption made in this study is within a taxon (as opposed to bird-mammal comparison), is lifelong normal status (as opposed to short term exercise status), and is at the whole organismal level (as opposed to tissue-specific). So the situations (3)–(5) are excluded here. Below I will address the first two situations.

The disproportionality between mitochondrial ROS generation and oxygen consumption occurs under state 4 conditions, when ATP synthesis is low. In this case, oxygen consumption is low, proton-motive force is high, and ROS generation is highest (Harper et al., 2004). When the mitochondrial respiration is under state 3 conditions, and ADP phosphorylation is high, ROS generation reduces rapidly (Boveris and Chance, 1973; Boveris et al., 1972; Loschen et al., 1971). In general, mitochondria in intact cells normally operate in the states between states 3 and 4, indicating that ROS generation is neither extremely high nor low (Barja, 1999; Harper et al., 2004). This, combined with the positive evidence I reviewed above, suggests that the proportionality holds under the normal and general conditions.

Diet restriction (DR) has often been taken as a counter example to question the rate of living theory (Balaban et al., 2005; Brys et al., 2007; Stuart and Brown, 2006) and the assumption on the proportionality. At the first glance, this questioning is reasonable because the rate of living theory suggests that extended lifespan is attributable to a reduced metabolic rate, whereas DR does not reduce metabolic rate, but extends lifespan. However, aging is not only associated with damage, but also associated with repair and maintenance. It is a product of the processes of oxidant generation (damage) and oxidant scavenging, damage repair and other maintenance mechanisms (Beckman and Ames, 1998; Merry, 2004; Monaghan et al., 2009). As emphasized in the conclusion of this paper, DR extends lifespan, *not* because it reduces metabolic rate (and presumably reduces the damage rate), but because it alters the energy allocation strategy, and channels extra energy to maintenance by suppressing biosynthesis. Metabolic rate (and damage rate) may not be reduced in DR animals, but the net accumulated damage is reduced due to the enhanced repairing.

Several studies showed that DR decreases the ROS generation in isolated mitochondria from brain, heart, and liver in small rodents (Barja, 2007; Faulks et al., 2006; Gredilla and Barja, 2005). However, there exist important enzymes in the mitochondria that rapidly scavenge the ROS (Taylor et al., 2003). It was suggested that "(due to these highly efficient scavenging systems), any measured release of ROS from mitochondria may represent only a small fraction of the total ROS generated" (Balaban et al., 2005). Scavenging ROS is a type of protection mechanism that belongs to maintenance. So, it is not surprising that the *measured* ROS generation is lower in DR animals, because, as said above, DR enhances the maintenance efforts.

There is another possible explanation within the framework of this model for the reduced ROS generation in DR animals. It has been hypothesized that under normal conditions, mitochondrial integrity declines as a function of age (Richter et al., 1988; Shigenaga et al., 1994), and old mitochondria produces more ROS due to the morphological alteration and/or mutation in mtDNA (Balaban et al., 2005; Golden and Melov, 2001; Raha and Robinson,

2000; Wallace, 1997, 1999). Here I hypothesize that DR, by enhancing the maintenance and repairing efforts, retards the aging of mitochondria, and therefore reduces the mitochondrial ROS generation.

This hypothesis is indirectly supported by the observations that short-term DR, usually shorter than 6 months, does not reduce the mitochondrial ROS generation (Faulks et al., 2006; Gredilla and Barja, 2005). If this hypothesis is valid, then the observations can be explained as the following. When DR is initiated at a young age, the mitochondria in both DR and control animals function equally well. Moreover, when DR is implemented for a short period, it is not as effective for enhancing maintenance, so the reduction in ROS generation in DR animals is not detectable. In contrast, in the case of long-term DR, usually longer than one year, the control animals are relatively less healthy, whereas the DR animals maintain a relatively youthful stage. So, compared to the control animals, the integrity of mitochondria in DR animals is better maintained, and therefore the difference in mitochondrial ROS generation between control and DR becomes significant. I call for more direct empirical evidence to test this hypothesis.

Both explanations above—scavenging ROS and maintaining the integrity of mitochondria—attribute the DR-induced low ROS generation to the effects of DR on enhancing the maintenance effort. Thus, they are consistent with the model proposed in this paper. Mathematically, after the effects of scavenging and maintenance on ROS generation being taken into account, the ratio of the ROS generation coefficient and repairing coefficient, $\varepsilon = \delta/\eta$, for DR animals does not change, therefore the final equation (Eq. (4)) does not change.

Appendix B. Appendix II. The variable body compositions

When deriving Eq. (4), I followed the previous works (Hou et al., 2008; Moses et al., 2008; Ricklefs, 1974; Withers, 1992; Zuo et al., 2009), and treated E_m, the energy required to synthesize one unit of biomass, as a constant for a given species over ontogeny, regardless of whether animals are ad libitum (AL) or under DR. However, AL and DR animals often have different body compositions, e.g., different fractions of fat and protein. If it requires different amounts of energy to synthesize different body components, then AL and DR animals would have different values of E_m, which would be a function of age and body compositions. Rigorously, instead of having a constant parameter, E_m, Eqs (3)–(5) should have two variables, $E_{m,AL}(t, \sum_i m_i \times E_{m,i}/\sum_i m_i)$ for AL animals, and $E_{m,DR}(t, \sum_i m_i \times E_{m,i}/\sum_i m_i)$ for DR animal, where m_i is the ith body component, such as fat or protein, $E_{m,i}$ is the energy required to synthesis the ith body component, and t is the age of the animal; the subscripts AL and DR stand for ad libitum and diet restriction.

For the following reasons, I took the approximation, $E_m \approx E_{m,AL}(t, \sum_i m_i \times E_{m,i}/\sum_i m_i) \approx E_{m,DR}(t, \sum_i m_i \times E_{m,i}/\sum_i m_i)$ in this study.

1. Constant values of E_m are sufficient to describe the growth trajectories accurately under both conditions of ad libitum (AL) and diet restriction. West et al. (2001) has used constant values of E_m to accurately predict the growth trajectories for a broad diversity of AL organisms. In a previous paper of mine (Hou et al., 2011c), I made accurate predictions on growth trajectories of different organisms under complex diet restriction protocols (different diet composition, different DR starting age, intermittent DR, etc.), assuming AL and DR animals have the same constant value of E_m for a given species.
2. As far as I am concerned, the exact expression of $E_m(t, \sum_i m_i \times E_{m,i}/\sum_i m_i)0$, as a function of age and body composition, is not available for either ad libitum or diet restricted animals. No empirical study has given data with high resolution for estimating it.
3. Most diet restriction and lifespan studies, which contribute data points to this study, did not report the quantitative body compositions in ad libitum or DR animals. So, even if we know the exact expression, $E_m(t, \sum_i m_i \times E_{m,i}/\sum_i m_i)$, we do not have empirical data on body compositions to calculate it, and use it in Eq (4) to estimate lifespan extension.
4. Finally, although the combustion energy contents in fat and protein are largely different, the energy required to synthesize them ($E_{m,fat}$ and $E_{m,protein}$) may be close. It was estimated that the free energy of hydrolysis of the peptide bond and of an ester are 12.6 and 10.5 kilojoules per mole respectively (Krebs and Kornberg, 1957; Morowitz, 1978). When estimating the energy for synthesis of polymeric linkages, Calow (1977) also did not differentiate fat and protein. If the values of E_m are close for different components, then the difference in body composition between ad libitum and DR animals may not largely influence the overall average values of E_m.

Appendix C. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.mad.2013.07.001.

References

Abele, D., Heise, K., Pörtner, H.-O., Puntarulo, S., 2002. Temperature-dependence of mitochondrial function and production of reactive oxygen species in the intertidal mud clam Mya arenaria. Journal of Experimental Biology 205, 1831–1841.

Balaban, R., Nemoto, S., Finkel, T., 2005. Mitochondria, Oxidants, and Aging. Cell 120, 483–495.

Barja, G., 1999. Mitochondrial oxygen radical generation and leak: sites of production in states 4 and 3, organ specificity, and relation to aging and longevity. Journal of Bioenergetics and Biomembranes 31, 347–366.

Barja, G., 2004. Free radicals and aging. Trends in Neurosciences 27, 595–600.

Barja, G., 2007. Mitochondrial oxygen consumption and reactive oxygen species production are independently modulated: implications for aging studies. Rejuvenation Research 10, 215–224.

Bartke, A., 2005. Role of the growth hormone/insulin-like growth factor system in mammalian aging. Endocrinology 146, 3718–3723.

Beckman, K.B., Ames, B.N., 1998. The free radical theory of aging matures. Physiological Reviews 78, 547–581.

Bokov, A., Chaudhuri, A., Richardson, A., 2004. The role of oxidative damage and stress in aging. Mechanisms of Ageing and Development 125, 811–826.

Boveris, A., Chance, B., 1973. The mitochondrial generation of hydrogen peroxide. General properties and effect of hyperbaric oxygen. Biochemical Journal 134, 707.

Boveris, A., Oshino, N., Chance, B., 1972. The cellular production of hydrogen peroxide. Biochemical Journal 128, 617.

Brody, S., 1945. Bioenergetics and Growth. Reinhold, New York.

Brown-Borg, H.M., 2003. Hormonal regulation of aging and life span. Trends in Endocrinology and Metabolism 14, 151–153.

Brown-Borg, H.M., Borg, K.E., Meliska, C.J., Bartke, A., 1996. Dwarf mice and the ageing process. Nature 384 , pp. 33–33.

Brys, K., Vanfleteren, J.R., Braeckman, B.P., 2007. Testing the rate-of-living/oxidative damage theory of aging in the nematode model *Caenorhabditis elegans*. Experimental Gerontology 42, 845–851.

Calder, W.A., 1984. Size, Function, and Life History. Harvard University Press, Cambridge, MA.

Calow, P., 1977. Conversion efficiencies in heterotrophic organisms. Biological Reviews 52, 385–409.

Economos, A.C., 1982. Mammalian design and rate of living. Experimental Gerontology 17, 145–152.

Faulks, S.C., Turner, N., Else, P.L., Hulbert, A.J., 2006. Calorie restriction in mice: effects on body composition, daily activity, metabolic rate, mitochondrial reactive oxygen species production, and membrane fatty acid composition. Journals of Gerontology Series A: Biological Sciences and Medical Sciences 61, 781–794.

Fujita, Y., Ichikawa, M., Kurimoto, F., Rikimaru, T., 1984. Effects of feed restriction and switching the diet on proteinuria in male wistar rats. Journal of Gerontology 39, 531–537.

Gajjar, A., Kubo, C., Johnson, B., Good, R., 1987. Influence of extremes of protein and energy intake on survival of B/W mice. Journal of Nutrition 117, 1136–1140.

Golden, T.R., Melov, S., 2001. Mitochondrial DNA mutations, oxidative stress, and aging. Mechanisms of Ageing and Development 122, 1577–1589.
Gredilla, R., Barja, G., 2005. The role of oxidative stress in relation to caloric restriction and longevity. Endocrinology 146, 3713–3717.
Harper, M.E., Bevilacqua, L., Hagopian, K., Weindruch, R., Ramsey, J.J., 2004. Ageing, oxidative stress, and mitochondrial uncoupling. Acta Physiologica Scandinavica 182, 321–331.
Heise, K., Puntarulo, S., Pörtner, H.O., Abele, D., 2003. Production of reactive oxygen species by isolated mitochondria of the Antarctic bivalve *Laternula elliptica* (King and Broderip) under heat stress. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology 134, 79–90.
Holloszy, J.O., 1997. Mortality rate and longevity of food-restricted exercising male rats: a revaluation. Journal of Applied Physiology 82, 399–403.
Hou, C., Bolt, K., Bergman, A., 2011a. A general life history theory for effects of caloric restriction on health maintenance. BMC Systems Biology 5, 78–90.
Hou, C., Bolt, K.M., Bergman, A., 2011b. Energetic basis of correlation between catch-up growth, health maintenance, and aging. Journals of Gerontology Series A: Biological Sciences and Medical Sciences 66A, 627–638.
Hou, C., Bolt, K.M., Bergman, A., 2011c. A general model for ontogenetic growth under food restriction. Proceedings of the Royal Society B: Biological Sciences 278, 2881–2890.
Hou, C., Zuo, W.Y., Moses, M.E., Woodruff, W.H., Brown, J.H., West, G.B., 2008. Energy uptake and allocation during ontogeny. Science 322, 736–739.
Hulbert, A.J., Clancy, D.J., Mair, W., Braeckman, B.P., Gems, D., Partridge, L., 2004. Metabolic rate is not reduced by dietary-restriction or by lowered insulin/IGF-1 signalling and is not correlated with individual lifespan in *Drosophila melanogaster*. Experimental Gerontology 39, 1137–1143.
Hulbert, A.J., Pamplona, R., Buffenstein, R., Buttemer, W.A., 2007. Life and death: metabolic rate, membrane composition, and life span of animals. Physiological Reviews 87, 1175–1213.
Iwasaki, K., Gleiser, C.A., Masoro, E.J., McMahan, C.A., Seo, E.-j., Yu, B.P., 1988. Influence of the restriction of individual dietary components on longevity and age-related disease of fischer rats: the fat component and the mineral component. Journal of Gerontology 43, B13–B21.
Kapahi, P., 2010. Protein synthesis and the antagonistic pleiotropy hypothesis of aging. In: Tavernarakis, N. (Ed.), Protein Metabolism and Homeostasis in Aging. Springer, US, pp. 30–37.
Krebs, H.A., Kornberg, H., 1957. Energy Transformations in Living Matter. Springer, Berlin, Germany.
Ku, H.H., Brunk, U.T., Sohal, R.S., 1993. Relationship between mitochondrial superoxide and hydrogen peroxide production and longevity of mammalian species. Free Radical Biology & Medicine 15, 621–627.
Lee, C.-K., Pugh, T.D., Klopp, R.G., Edwards, J., Allison, D.B., Weindruch, R., Prolla, T.A., 2004. The impact of α-lipoic acid, coenzyme Q10 and caloric restriction on life span and gene expression patterns in mice. Free Radical Biology & Medicine 36, 1043–1057.
Lints, F.A., 1989. The rate of living theory revisited. Gerontology 35, 36–57.
Lombard, D., Chua, K., Mostoslavsky, R., Franco, S., Gostissa, M., Alt, F., 2005. DNA repair, genome stability, and aging. Cell 120, 497–512.
Loschen, G., Flohe, L., Chance, B., 1971. Respiratory chain linked H_2O_2 production in pigeon heart mitochondria. FEBS Letters 18, 261.
Mair, W., Dillin, A., 2008. Aging and survival: the genetics of life span extension by dietary restriction. Annual Review of Biochemistry 77, 727–754.
Masoro, E., 2005. Overview of caloric restriction and ageing. Mechanisms of Ageing and Development 126, 913–922.
McCarter, R., Masoro, E.J., Yu, B.P., 1985. Does food restriction retard aging by reducing the metabolic-rate. American Journal of Physiology – Endocrinology and Metabolism 248, E488–E490.
McCay, C.M., Crowell, M.F., Maynard, L.A., 1935. The effects of retarded growth upon the length of life span and upon the ultimate body size. Journal of Nutrition 10, 63–79.
McCoy, M.W., Gillooly, J.F., 2008. Predicting natural mortality rates of plants and animals. Ecology Letters 11, 710–716.
Merry, B.J., 2002. Molecular mechanisms linking calorie restriction and longevity. International Journal of Biochemistry and Cell Biology 34, 1340–1354.
Merry, B.J., 2004. Oxidative stress and mitochondrial function with aging – the effects of calorie restriction. Aging Cell 3, 7–12.
Metcalfe, N.B., Monaghan, P., 2001. Compensation for a bad start: grow now, pay later? Trends in Ecology & Evolution 16, 254–260.
Monaghan, P., Metcalfe, N.B., Torres, R., 2009. Oxidative stress as a mediator of life history trade-offs: mechanisms, measurements and interpretation. Ecology Letters 12, 75–92.
Morowitz, H.J., 1978. Foundations of Bioenergetics. Academic Press, New York.
Mortelette, H., Moisan, C., Sébert, P., Belhomme, M., Amérand, A., 2010. Fish as a model in investigations about the relationship between oxygen consumption and hydroxyl radical production in permeabilized muscle fibers. Mitochondrion 10, 555–558.
Moses, Melanie E., Hou, C., Woodruff, William H., West, Geoffrey B., Nekola, Jeffery C., Zuo, W., Brown, James H., 2008. Revisiting a model of ontogenetic growth: estimating model parameters from theory and data. American Naturalist 171, 632–645.
Nagy, K.A., Girard, I.A., Brown, T.K., 1999. Energetics of free-ranging mammals reptiles and birds. Annual Review of Nutrition 19, 247–277.
Nakagawa, I., Sasaki, A., Kajimoto, M., Fukuyama, T., Suzuki, T., Yamada, E., 1974. Effect of protein nutrition on growth, longevity and incidence of lesions in the rat. Journal of Nutrition 104, 1576–1583.
Pearl, R., 1928. The Rate of Living. University of London, London.
Perez-Campo, R., Lopez-Torres, M., Cadenas, S., Rojas, C., Barja, G., 1998. The rate of free radical production as a determinant of the rate of aging: evidence from the comparative approach. J Comp Physiol B-Bioch Syst Environ Physiol 168, 149–158.
Peters, R.H., 1983. The Ecological Implications of Body Size. Cambridge University Press, Cambridge, UK.
Raha, S., Robinson, B.H., 2000. Mitochondria, oxygen free radicals, disease and ageing. Trends in Biochemical Sciences 25, 502–508.
Richter, C., Park, J.-W., Ames, B.N., 1988. Normal oxidative damage to mitochondrial and nuclear DNA is extensive. Proc Natl Acad Sci U. S. A. 85, 6465–6467.
Ricklefs, R.E., 1974. Energetics of reproduction in birds. In: Paynter, R.A.J. (Ed.), Avian Energetics. Nuttall Ornithol Club 15, Cambridge, MA.
Ricklefs, R.E., 2006. Embryo development and ageing in birds and mammals. Proceedings of the Royal Society B: Biological Sciences 273, 2077–2082.
Rollo, C.D., 2002. Growth negatively impacts the life span of mammals. Evolution and Development 4, 55–61.
Ross, M.H., Lustbader, E., Bras, G., 1976. Dietary practices and growth responses as predictors of longevity. Nature 262, 548–553.
Schmidt-Nielsen, K., 1984. Scaling: why is animal size so important? Cambridge University Press.
Shigenaga, M.K., Hagen, T.M., Ames, B.N., 1994. Oxidative Damage and Mitochondrial Decay in Aging. Proc Natl Acad Sci U. S. A. 91, 10771–10778.
Sibly, R.M., Calow, P., 1986. Physiological Ecology of Animals: An Evolutionary Approach. Blackwell Scientific publications, Palo Alto, U. S. A.
Sinclair, D., 2005. Toward a unified theory of caloric restriction and longevity regulation. Mechanisms of Ageing and Development 126, 987–1002.
Sohal, R.S., 1986. The rate of living theory: a contemporary interpretation. In: Collatz, K.G., Sohal, R.S. (Eds.), Insect aging: strategies and mechanisms. Springer-Verlag, Berlin, pp. 23–44.
Sohal, R.S., Weindruch, R., 1996. Oxidative stress, caloric restriction, and aging. Science 273, 59–63.
Stearns, S.C., 1992. The evolution of life histories. Oxford University Press, Oxford, UK.
Stoltzner, G., 1977. Effects of life-long dietary protein restriction on mortality, growth, organ weights, blood counts, liver aldolase and kidney catalase in Balb/C mice. Growth 41, 337.
Stuart, J., Brown, M., 2006. Energy, quiescence and the cellular basis of animal life spans. Comp. Biochem. Physiol. A. Mol. Integr. Physiol. 143, 12–23.
Taylor, S.W., Fahy, E., Zhang, B., Glenn, G.M., Warnock, D.E., Wiley, S., Murphy, A.N., Gaucher, S.P., Capaldi, R.A., Gibson, B.W., 2003. Characterization of the human heart mitochondrial proteome. Nature Biotechnology 21, 281–286.
Turturro, A., Blank, K., Murasko, D., Hart, R.W., 1994. Mechanisms of Caloric Restriction Affecting Aging and Disease. Annals of the New York Academy of Sciences 719, 159–170.
Wallace, D., 1997. Mitochondrial DNA mutations and bioenergetic defects in aging and degenerative diseases. In: Rosenberg, R., Prusiner, S., DiMauro, S., Barchi, R. (Eds.), The molecular and genetic basis of neurological disease. Butterworth Heinemann, Boston, pp. 237–269.
Wallace, D.C., 1999. Mitochondrial diseases in man and mouse. Science 283, 1482–1488.
Weindruch, R., Walford, R.L., 1988. The Retardation of Aging and Disease by Dietary Restriction. Thomas, Springfield, IL.
West, G.B., Brown, J.H., Enquist, B.J., 2001. A general model for ontogenetic growth. Nature 413, 628–631.
Westbrook, R., Bonkowski, M.S., Strader, A.D., Bartke, A., 2009. Alterations in Oxygen Consumption, Respiratory Quotient, and Heat Production in Long-Lived GHRKO and Ames Dwarf Mice, and Short-Lived bGH Transgenic Mice. Journals of Gerontology Series A: Biological Sciences and Medical Sciences 64A, 443–451.
Withers, P.C., 1992. Comparative Animal Physiology. Saunders College Pub., Fort Worth.
Zera, A.J., Harshman, L.G., 2001. The physiology of life history trade-offs in animals. Annual Review of Ecology, Evolution, and Systematics 32, 95–126.
Zuo, W.Y., Moses, M.E., Hou, C., Woodruff, W.H., West, G.B., Brown, J.H., 2009. Response to Comments on "energy uptake and allocation during ontogeny". Science 325, 1206–1210.