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OPINION

Do the fastest concepti have a shorter life span?

Juan J.Tarín

Department of Molecular, Cellular and Developmental Biology, University of Colorado at Boulder, Boulder, Colorado, USA

Present address and address for correspondence: Department of Paediatrics, Obstetrics and Gynaecology, Faculty of Medicine, University of Valencia, Avda. Blasco Ibañez 17, 46010 Valencia, Spain

An evolutionary hypothesis based on an 'antagonist pleiotropy' or 'disposable soma' mechanism is put forward to explain differences in longevity between species, strains, and sexes. Data from several congenic mouse strains and mammalian species suggest that there may be an association between cleavage rate of concepti and longevity, in such a way that concepti from species, strains or the sex (male) with the fastest cleavage rates have shorter life spans. The major histocompatibility complex (MHC) and, in particular, the conceptus development gene (*Ped*) together with several Y-linked genes that are expressed during the preimplantation stages of development may play an important role in determining or modulating longevity in mammals. Notwithstanding, effects of other loci as well as environmental factors on conceptus development and longevity cannot be ignored.

Key words: conceptus development/gender gap/longevity/major histocompatibility complex/maximum life span

Introduction

Maximum life span is a characteristic of each species, influenced by genetic and environmental factors and subject to evolution (Hart and Turturro, 1987; Hayflick, 1987). The evolution of longevity has taken place despite the fact that the strength of natural selection declines with age after sexual maturity and rearing of progeny (Hayflick, 1987). This paradox can be explained by the 'mutation-accumulation' (Medawar, 1957) and the 'antagonist pleiotropy' (Williams, 1957) theories which were put forward originally to explain the evolution of senescence. The 'mutation-accumulation' theory states that deleterious mutations, accumulated by mutation pressure, with effects only at older ages are maintained in populations because natural selection is extremely weak at post-reproductive ages. The 'antagonist pleiotropy' theory, on the other hand, says that alleles with early beneficial effects on survivorship or fecundity are selectively favoured despite the fact that they may have deleterious effects at older ages. This idea is justified by the fact that changes early in life have a greater effect on fitness than changes later in life. A convergent and complementary theory of the 'antagonist pleiotropy' is the 'disposable soma' theory which explains the evolution of senescence in terms of a trade-off between the investment of metabolic resources into reproduction and into the repair/maintenance of the soma (Kirkwood and Rose, 1991). Although, at present, a role for a 'mutation-accumulation' mechanism cannot be ruled out (Partridge and Barton, 1993), the fact that longer-lived species appear to be in general less fecund, require more time to reach maturity, and have longer gestation periods, lower infant mortality rates, smaller litters, and a longer period for the raising of young than shorter-lived species (Smith, 1995), strongly supports the intervention of an 'antagonist pleiotropy' or 'disposable soma' mechanism on the evolution of longevity.

The major histocompatibility complex (MHC, called H-2 in mice and HLA in humans) is one of only a few gene systems which are known to affect mammalian maximum life span and reproductive fitness [see Walford (1990); Crew (1993) and Yunis and Salazar (1993) for reviews]. Table I shows longevity and fecundity data from two classical studies by Smith and Walford (1977) and Lerner *et al.* (1988). Smith and Walford (1977), using congenic mice (inbred strains that theoretically differ from each other only at the H-2 complex) with three different strain backgrounds, demonstrated background-dependent differences in longevity when the H-2 haplotype was the same (a haplotype is a collection of all the MHC genes on a single chromosome, in the case of the mouse on chromosome 17), and also gender and H-2 haplotype-dependent differences when analysing the same background genome [data shown in Table I are only from congenic mice with the C57Bl/10 (B10) background]. Lerner *et al.* (1988) showed that reproductive senescence of female mice was correlated with the tenth decile of survivorship (mean life span of the last 10% of the survivors), e.g. females from the strain C57BL/10SnJ, which had the shortest life span, exhibited an earlier outset of age-associated infertility, a lower number of litters/female and of total number of pups/female than females from the longest-lived strains B10.BR/SgSnJ and B10.RIII/SgDv. The original point in the analysis of these data that is emphasized here, however, is the fact that the cleavage rate *in vivo* of concepti from the longest-lived strains B10.BR/SgSnJ and B10.RIII/SgDv is typically slower than that of concepti from the other B10 congenic strains. These results support the hypothesis first formulated by Mittwoch (1993) of an association between developmental rate of concepti/embryos/fetuses and longevity.

Table I. Relationship among conceptus development (*Ped*) gene phenotype, mean life span of the last 10% of survivors, and reproductive ageing in several B10 congenic mouse strains

Strain	H-2 haplotype[a]	Qa-2 protein[a]	*Ped* gene phenotype[a]	No. of cells/ conceptus at 89 h post-HCG[a]	Tenth decile of survivorship (weeks)[b]		Age at last litter (days)[c]	No. of litters/female[c]	Total no. of pups/female[c]	No. of pups/litter[c]
					Females	Males				
C57BL/10SnJ	b	Yes	Fast	33.1 ± 2.1[d]	148 ± 1.2	155 ± 0.4	260 ± 17	5.4 ± 0.5	34 ± 3	6.4 ± 0.3
B10.PL/J	u	Yes	Fast	30.4 ± 1.7	145 ± 1.7	153 ± 1.7				
B10.A/SgSnJ	a	Yes	Fast	32.0 ± 1.1	164 ± 2.9	154 ± 0.4				
B10.D2n/nSnJ	d	Yes	Fast	39.1 ± 1.5	154 ± 0.8	155 ± 0.5				
B10.BR/SgSnJ	k	No	Slow	22.8 ± 1.3	161 ± 2.1[e]	149 ± 1.1[g]	311 ± 15[h]	7.5 ± 0.5[h]	43 ± 3[h]	5.8 ± 0.3
B10.RIII/SgDv	r	No	Slow	25.4 ± 0.9	165 ± 1.0[f]	170 ± 0.8[f]	317 ± 16[h]	7.8 ± 0.5[h]	50 ± 3[h]	6.7 ± 0.3

[a,b,c]Data from [a]Warner *et al.* (1988); [b]Smith and Walford (1977) and [c]Lerner *et al.* (1988).
[d]Values are means ± SE.
[e]Value significantly different from all the congenic strains except B10.A/SgSnJ strain ($P \leqslant 0.05$).
[f]Value significantly different from all the other congenic strains ($P \leqslant 0.05$).
[g]Value significantly different from all the other congenic strains except B10.PL/J ($P \leqslant 0.05$).
[h]Value significantly different from C57BL/10SnJ strain ($P \leqslant 0.05$).
HCG = human chorionic gonadotrophin.

The existence of a relationship between the speed of conceptus development and longevity is further supported by data from different mammalian species. Table II shows a significant ($P \leqslant 0.013$) positive correlation between cleavage rate of the first conceptus-regulated cell division and maximum life span of five mammalian species, including human beings. Extrapolating from data obtained in *Rana pipiens* (Sze, 1953), the cleavage rate at which concepti develop before gastrulation is extraordinarily rapid (at a rate not seen elsewhere, even in tumour cells) and likely to be constant within species, strains, and sexes. Therefore, this parameter can be used to perform comparative analyses. Special care was taken, however, to choose the first conceptus-regulated division in each species since cleavage rates before activation of conceptus genome may be controlled by maternally inherited products (Goddard and Pratt, 1983). In addition, no further divisions, e.g. until the blastocyst stage, were taken into account for calculating cleavage rates of concepti because of possible differences between species in levels of programmed cell death within the pluriblast and/or trophoblast lineages (Hardy *et al.*, 1989).

Evidence of a correlation between the rate of cell division of concepti and reproductive fitness, as predicted if we assume the existence of an 'antagonist pleiotropy' relationship between cleavage rate of concepti and longevity, is also revealed by studies using two congenic mouse strains, B6.K1 and B6.K2, differing only at the Q region of the mouse MHC (Warner *et al.*, 1991, 1993). Table III shows that mice from the B6.K1 strain, which have a slower cleavage rate of concepti, exhibit a longer duration of gestation and a smaller litter size than mice from the faster-cleaving strain B6.K2. Birthweight of B6.K1 pups is also lower than pups from the B6.K2 strain.

The 'gender gap' in longevity

Although there are exceptions to the rule (Smith, 1989), it can be said that the 'gender gap', or bias in the expectation of life between males and females in favour of females, is a general phenomenon observed in the animal kingdom. In humans, for instance, females live ~6 years longer than males (WHO, 1982). Although several hypotheses have been formulated, none of them appears to give a definitive and clear answer to the question of why there is a 'gender gap' in favour of females. It has been suggested, for instance, that the greater longevity of women when compared to men may be due to the fact that men live more risky lives than women. It appears that men are more likely to be involved in alcohol and drug addiction than women. Furthermore, it seems that women take more specific preventive measures and use health services for established diseases more regularly than men (Silman, 1987). It has also been suggested that the longer life span of women is due to gender differences in atherogenesis, which in turn would be caused, at least in part, by gender-specific differences in sex steroids (Hospital Practice, 1988). Notwithstanding these ideas, it appears that the 'gender gap' would not be eliminated even after the hypothetical elimination of major causes of death in the USA, including all cardiovascular diseases, ischaemic heart disease, diabetes, and cancer (Olshansky *et al.*, 1990).

Another hypothesis put forward to explain the 'gender gap' in humans is based on the endowment of a second functioning female X chromosome before the random inactivation of one X chromosome at the blastocyst stage and/or after reactivation of X-linked genes by ageing. This would allow female concepti and/or ageing women to have twice as much activity for an X-linked enzyme as male concepti and/or ageing men who have only one X chromosome. It has been suggested, for instance, that the presence on the X chromosome of the gene coding for one of the enzymes that binds ubiquitin to cyclin could bestow a replicative advantage for females if this gene were reactivated by ageing (the transition from metaphase to anaphase is induced by cyclin degradation by the ubiquitin-dependent proteolytic system) (Magnani and Accorsi, 1993). However, this hypothesis is weakened by the fact that differences in cleavage rates between human female and male concepti occur as early as fertilization, or during the first or second cleavage division. From this point of development until the blastocyst stage, differences between sexes are maintained but not increased (Ray *et al.*, 1995). In other words, the

Table II. Relationship between cleavage rate of the first conceptus-genome-regulated cell division and maximum life span (MLS) in several mammalian species

	Human	Pig	Rat	Hamster	Mouse
Embryo stage at which RNA synthesis from conceptus genome is initiated[a]	4 cells	4–8 cells	2 cells	2 cells	1–2 cells
Conceptus stage at which major changes in qualitative pattern of protein synthesis occur[a]	4–8 cells	4–8 cells	2–4 cells	1–4 cells	2–4 cells
Cleavage rate of the first conceptus-genome-regulated cell division	~24 h[b] (8–16 cells)	~18 h[c] (8–16 cells)	~13 h[d] (4–8 cells)	~10 h[e] (4–8 cells)	~10 h[f] (4–8 cells)
MLS (years)[g]	120	27	4.7	4.0	3.5

Pearson correlation coefficient (r) between cleavage rate of the first conceptus-genome-regulated cell division and MLS = 0.9233 (one-tailed test, $P \leqslant 0.013$).
[a,b,c,d,e,f,g]Data from [a]Schultz and Heyner (1992); [b]Hardy *et al.* (1989); [c]Hunter (1973); [d]Dalcq (1957); [e]Bavister *et al.* (1983); [f]Harlow and Quinn (1982) and [g]Rockstein *et al.* (1977) and Allard (1993).

Table III. Relationship between conceptus development (*Ped*) gene phenotype and reproductive performance in two congenic mouse strains that differ at only the Q subregion of the major histocompatibility complex (H-2)

Strain	H-2 haplotype[a]	Qa-2 protein[a]	*Ped* gene phenotype[a]	No. of cells/conceptus at 89 h post-HCG[a]	Duration of gestation (h)[b]	No. of pups/litter[b]
B6.K2	b	Yes	Fast	31.0 ± 1.4[c]	476 ± 2.4	8.1 ± 1.3
B6.K1	b	No	Slow	20.4 ± 1.1	490 ± 3.9[d]	5.4 ± 0.3[e]

[a,b]Data from [a]Warner *et al.* (1988) and [b]Warner *et al.* (1993).
[c]Values are means ± SE.
[d,e]Value significantly different from B6.K2 strain ([d]$P \leqslant 0.01$; [e]$P \leqslant 0.001$).
HCG = human chorionic gonadotrophin.

cleavage rate of female concepti does not appear to increase between the genomic activation of concepti at the 4–8-cell stage and the blastocyst stage, a period during which female concepti have two functioning X chromosomes.

It has also been proposed that the presence on the X chromosome of the gene coding for glucose 6-phosphate dehydrogenase (G6PDH) may confer on females a better protection against oxidative stress during both the development of concepti, which as mentioned above is characterized by an unusually high mitotic rate, and senescence, after reactivation of X-linked genes by ageing (Magnani and Accorsi, 1993). The presence on the X chromosome of the gene coding for hypoxanthine phosphoribosyl transferase (HPRT) may contribute further to protect women against oxidative damage. The rationale of this hypothesis is based on the fact that G6PDH is a key enzyme in the production of NADPH which, in turn, keeps cellular glutathione in its reduced form (GSH). GSH is a free radical reaction inhibitor and a substrate for glutathione peroxidase, keeping the cellular concentration of H_2O_2 and organic hydroperoxides low. HPRT, on the other hand, is an enzyme involved in the salvage of purine nucleotides. It catalyses the conversion of hypoxanthine to inosine monophosphate (IMP). This reaction decreases the intracellular concentration of hypoxanthine which is catabolized by xanthine oxidase, the enzyme that produces superoxide radicals during the conversion of hypoxanthine to xanthine and of xanthine to uric acid. This hypothesis is flawed, however, by the fact that, in the mouse, G6PDH (De Schepper *et al.*, 1993) and HPRT (Harper and Monk, 1983) activities are maternally controlled (oocyte-encoded) during the early stages of preimplantation development, postponing to later stages [the morula stage in the case of HPRT (Monk and Handyside, 1988)] the appearance of quantitative differences in enzyme activities between sexes. This effect is further reinforced by the decreased expression of the paternal HPRT allele when compared to its maternal counterpart (Moore and Whittingham, 1992). Furthermore, age-related reactivation is not a feature of all X-linked loci. In fact, ageing does not affect the frequency of reactivation of the X-linked HPRT locus in human skin fibroblast clones (Migeon *et al.*, 1988).

Clarke and Mittwoch (1994, 1995) have suggested a negative relationship between basal metabolic rate and longevity to explain the greater longevity of women when compared to men. We should bear in mind, however, that although basal metabolic rates may play an important role in determining or modulating longevity, the relationship between longevity and basal metabolic rate is uncertain, at least among species (Austad and Fischer, 1991). Therefore, other cellular, physiological and/or environmental factors must also be taken into account to explain the 'gender gap' in longevity.

The weakness of the aforementioned hormonal–enzymatic–metabolic hypotheses is overcome, at least to a certain degree, by adopting an evolutionary point of view. Rossler *et al.* (1995) utilized a mathematical model that, in humans and

sperm whales, showed that the shorter life expectancy of males can be explained by the higher fecundity of males. This would be attributed to the long gestation period and even longer period of suckling-induced amenorrhoea in females, and to the promiscuity of males (in the case of the human, this would be applicable under archaic conditions). However, returning to the 'antagonist pleiotropy' and 'disposable soma' theories, it is possible to link the shorter longevity of males with their higher reproductive fitness and this, in turn, with their higher developmental rates. It is well known that, in general, mammalian male concepti/embryos/fetuses, and in particular human male concepti/embryos/fetuses, cleave and/or develop faster, have shorter gestation periods, and are heavier at birth than female concepti/embryos/fetuses (Mittwoch, 1993; James, 1994; Tarín *et al.*, 1995).

Although the adoption of an evolutionary point of view may explain the 'gender gap' in longevity in humans as well as in other animal species, it does not give a direct answer to which factors modulate or determine sex differences in longevity. The answer, however, is still in the realm of speculation due to the limited knowledge gathered in this field. The genetics influencing life span seem to be complex, involving interactions among loci and allelic interactions during life which may be changed by environmental factors such as exposure to Sendai virus infection [see Yunis and Salazar (1993) for review]. The MHC and, in particular, the *Ped* gene may play an important role in determining or modulating life span, with the 'slow' phenotype being associated with a reduced reproductive fitness and greater longevity. Data from Burgoyne (1993) suggest also an effect of Y-linked genes on developmental rate of concepti. This effect would be superimposed by an X-chromosomal effect at post-implantation stages (prior to gonadal differentiation) (Thornill and Burgoyne, 1993). If the hypothesis of an association between rate of cell division of concepti and longevity is correct, allelic differences in Y-linked genes between strains may explain the spectrum of variable effects of sex on mouse longevity, up to strains where the male has a longer life span (Smith, 1989). In Table I, it can be observed that males from the 'slow' strain B10.BR/SgSnJ have a decreased survival when compared to both the remaining congenic strains and females of their own strain. On the other hand, the longevity of males from the other 'slow' strain, B10.RIII/SgDv, is greater than that shown by corresponding females and by the remaining congenic strains. The Y-linked gene *Zfy*, which encodes a zinc finger protein, may play an important role in the interaction between sex and the *Ped* gene phenotype. Another factor with a potential role within this system would be the autosomal serologically detected male antigen (SDMA) whose expression requires a gene located on the short arm of the Y chromosome [reviewed by Burgoyne (1993)]. These two genes have the common denominator of being expressed during preimplantation stages (Shelton and Goldberg, 1984; Ao *et al.*, 1994) and, therefore, may affect cleavage rates of concepti during their preimplantation development. It is unlikely that the Y-linked gene *Sry*, which encodes the testes-determining factor (TDF), makes a major contribution to the preimplantation difference in cleavage rate between female and male concepti. It has been shown that deletion of *Sry* does not hamper the faster developmental growth of mouse male concepti (Burgoyne *et al.*, 1995). Furthermore, ovine male concepti develop faster than female concepti during preimplantation development despite the fact that ovine concepti do not express the *Sry* gene (Bernardi *et al.*, 1996).

In conclusion, a great deal of effort should be dedicated in the future to uncover the genetic and environmental factors that play an important role in determining or modulating conceptus growth rates and life span of species, strains and sexes. Here, I have provided insights to the potential participation of just a few genetic loci and allelic interactions. Progress in this area will allow us to ascertain whether the hypothesis of an association between rates of cell division during preimplantation stages and longevity is true and, if so, which loci and allelic interactions have a real effect on the beginning and end of life.

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