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# Cell resilience in species life spans: a link to inflammation?

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## Summary

**Species differences in life span have been attributed to cellular survival during various stressors, designated here as 'cell resilience'. In primary fibroblast cultures, cell resilience during exposure to free radicals, hypoglycemia, hyperthermia, and various toxins has shown generally consistent correlations with the species characteristic life spans of birds and mammals. However, the mechanistic links of cell resilience in fibroblast cultures to different species life spans are poorly understood. We propose that certain experimental stressors are relevant to somatic damage *in vivo* during inflammatory responses of innate immunity, particularly, resistance to reactive oxygen species (ROS), low glucose, and hyperthermia. According to this hypothesis, somatic cell resilience determines species differences in longevity during repeated infections and traumatic injuries in the natural environment. Infections and injury expose local fibroblasts and other cells to ROS generated by macrophages and to local temperature elevations. Systemically, acute phase immune reactions cause hypoglycemia and hyperthermia. We propose that cell resilience to somatic stressors incurred in inflammation is important in the evolution of longevity and that longer-lived species are specifically more resistant to immune-related stressors. This hypothesis further specifies Kirkwood's disposable soma theory. We suggest expanding the battery of stressors and markers used for comparative studies to additional cell types and additional parameters relevant to host defense and to their ecological specificities.**

**Key words: fibroblast; inflammation; lifespan; species.**

## Introduction

We propose the unifying hypothesis that species differences in fibroblast resilience to stressors are related to species life spans by mechanisms of innate immunity in host defense. Primary fibroblast cultures are widely used to evaluate correlation to species life spans for cell resilience to various stressors, including reactive oxygen species (ROS), hyperthermia, and hypoglycemia, as summarized in Table 1. These studies generally show positive correlations of species life span with short-term *in vitro* fibroblast survival and repair capacity. However, it is unclear how cell resilience to diverse stressors is related to aging and to causes of adult mortality.

The ROS stressors of Table 1 were historically guided by Harman's free-radical theory of aging that ROS damage and oxidative stress are the major causes of age-related dysfunction and disease. Clearly, the main causes of mortality during later aging in protected populations of humans and domestic animals involve oxidative damage, e.g. atherosclerosis, neoplasia, diabetes, obesity, and neurodegeneration. However, in natural populations, predation, infections, and traumatic injury are the major causes of mortality across all ages. For example, in feral chimpanzees, infections caused the majority (67%) of adult deaths (Goodall, 1986; Williams *et al.*, 2008; Finch, 2010). Until recently, infections also caused most deaths across all ages in historical European populations (Preston, 1976) and in hunter-gatherers with limited access to effective medicine (Hawkes *et al.*, 2009; Finch, 2010). Although there is little documentation of older age-specific pathology in natural populations of shorter-lived species, it seems unlikely that the majority of adults survived long enough to incur chronic arterial and brain diseases of human aging associated with inflammation and oxidative damage.

Prior work on comparative stress resistance was largely focused on the need for longer-lived animals to limit oxidative and other damage. This focus neglected the possibility that a significant portion of damage is caused by infection and infection-related tissue responses. We argue that cell responses to ROS, hyperthermia, and hypoglycemia (Table 1) are highly relevant to host somatic cell damage during acute infections and traumatic tissue injury, as well as chronic localized inflammation. Specifically, cell resilience to ROS, heat stress, and low glucose are fundamental in the acute phase inflammatory responses of innate immunity, which involves ROS production by macrophages, hyperthermia (fever), and hypoglycemia. Thus, tissue fibroblasts and other cells are exposed as bystanders to similar stressors causing oxidative damage that are used for comparative experimental gerontology. Oxidative damage during inflammation, as a generalized mechanism in aging, is also recognized

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**Table 1** Fibroblast resilience correlations with species longevity in birds and mammals (this survey was restricted to findings verified in separate reports)

| Endpoint | Species, ranked by life span | Life span, year | Correlation | Citation |
|---|---|---|---|---|
| ROS exposure | | | | |
| LD90:$H_2O_2$ | Hamster, rat, marmoset, rabbit, sheep, pig, cow, human | 3–100 | Positive | Kapahi *et al.* (1999) |
| LD50:$H_2O_2$ | Mouse, rat, squirrel, porcupine, beaver, bat | 3–34 | Positive | Harper *et al.* (2007) |
| LD50:$H_2O_2$, paraquat | Mouse, Snell dwarf mouse | 2–4 | | Salmon *et al.* (2005) and Leiser *et al.* (2006) |
| LD50: paraquat | Mouse, naked mole rat | 3–28 | Positive | Salmon *et al.* (2008) |
| Hyperthermia | | | | |
| LD50 | Mouse, rat, squirrel, porcupine, beaver, bat | 3–34 | Positive | Harper *et al.* (2007) |
| | Mouse, naked mole rat | 3–28 | Positive | Salmon *et al.* (2008) |
| Hypoglycemia | | | | |
| ED50 | Mouse, naked mole rat | 3–28 | Positive | Salmon *et al.* (2008) |
| | Mouse, Snell dwarf | 2–4 | Positive | Leiser *et al.* (2006) |
| | Mouse, rat, squirrel, porcupine, beaver | 3–24 | Positive | Harper *et al.* (2007) |
| $H_2O_2$ and $O_2^-$ production | | | | |
| ED50 | Mouse, rat, rabbit, pig, cow | 2–30 | Inverse | Sohal *et al.* (1989, 1990) |
| | Mouse, hamster, rat guinea pig, rabbit, pig, cow | 3–30 | Inverse | Ku *et al.* (1993) |
| | Mouse, rat, quail, guinea pig, naked mole rat, ox, pigeon, bat, baboon | 3–38 | Inverse | Lambert *et al.* (2007), Barja *et al.* (1994) and Ku & Sohal (1993) |

ROS, reactive oxygen species; Not shown: UV-induced 'long-patch DNA excision repair' in fibroblast cultures, assayed by [$^3$H]-thymidine incorporation, for which Hart & Setlow (1974) showed correlations with life span in seven species including humans. Subsequent studies gave mixed outcomes: inverse correlations with life span were also found by a BrdU photolysis assay (Francis *et al.*, 1981; Hart *et al.*, 1979), while others did not find any correlation of UV-induced DNA repair synthesis with life span (Kato *et al.*, 1980). Confounds include changes in DNA repair capacity during early-stage passage of cells, and effects of the hydroxyurea used to suppress semi-conservative DNA replication (Francis *et al.*, 1981).

in Kirkwood's disposable soma theory of aging that posits the importance of trade-offs between allocation of energy for reproduction and somatic repair of diverse molecular damage (Drenos & Kirkwood, 2005; Kirkwood, 2005). Lastly, we suggest additional stressors and measures of cell resilience and criteria for ecological relevance to species comparisons.

## Acute phase responses of innate immunity

The acute phase response of innate immunity enables short-term host defenses to transmissible pathogens and wounds. Subsequent survival is enhanced by adaptive immune responses by B and T cells to antigens of the invading pathogens. Infections and wounds produce local and systemic responses evolved for efficient tissue repair and protection from septic infections. The complex processes of inflammation are still aptly represented in Celsus' classic aphorism: *rubor et tumor cum calore et dolore* (redness and swelling with heat and pain). Many acute phase responses also persist in the chronic inflammation associated with the diseases of human aging (Finch, 2007).

## Inflammation causes oxidative stress and DNA damage

Free radicals as described in the Harman theory are also fundamental to host defense. Microbial pathogens can activate blood macrophages and neutrophils to produce the respiratory burst through NADPH oxidase, which generates superoxide ($O_2^-$) and enhances phagocytosis. In neutrophils, bacterial killing occurs intracellularly in phagocytic vacuoles through pH alterations driven by NADPH oxidase, rather than by ROS (Segal, 2005). Other ROS originating from superoxide include the hydroxyl radical (OH•) generated from $H_20_2$ and peroxynitrite ($ONOO^-$) and $O_2^-$. Tissue injury rapidly induces ROS from resident local cells and recruited leukocytes (Sen & Roy, 2008). In the zebrafish larval model of sterile wounding, $H_2O_2$ from epithelial cells recruits leukocytes to the wound margin (Niethammer *et al.*, 2009).

Reactive oxygen species produced during host defense can cause oxidative damage to bystander cells and extracellular molecules. In the two-stage model of oncogenesis, chronic inflammation is considered a tumor promoter (Coussens & Werb, 2002). A leading example of ROS damage from inflammation is associated with gastric cancers, the second ranked cause of death among malignancies worldwide (Herrera *et al.*, 2005; WHO, 2009). A major cause of gastric cancer is chronic infection by *Helicobacter pylori*: about 15% of carriers develop peptic ulcers, with 1% progressing to cancer (Helicobacter and Cancer Collaborative Group, 2001). A major oncogenic pathway involves localized inflammatory cell responses to extracellular *H. pylori*. Infiltrating macrophages and neutrophils produce ROS that damages DNA in adjacent epithelial cells (8-OHdG) (Farinati *et al.*, 2003). Concurrently, shortening of telomere DNA is associated with mucosal cell proliferation (Kuniyasu *et al.*, 2003). Anti-inflammatory NSAIDs that inhibit COX-2

greatly reduced gastric cancer in human populations (Wang *et al.*, 2003). Crohn's disease and other idiopathic intestinal inflammatory disorders that are independent of *H. pylori* also increase the risk of gastric cancer (Itzkowitz & Yio, 2004). Bystander effects of inflammation causing oxidative stress and DNA damage extend to many other inflammatory conditions (Kawanishi *et al.*, 2006; Fukata & Abreu, 2008; Meira *et al.*, 2008). Thus, the comparative studies of fibroblast resilience (Table 1) may be considered as models for ROS bystander damage during inflammation.

## Selection for antimicrobial hyperthermia leads to thermotolerant fibroblasts

Fever is a key part of host defense, evolved to inhibit the growth of microbial pathogens above their optimum temperature; even poikilotherms develop fever (Nesse & Williams, 1996; Hasday *et al.*, 2000). However, hyperthermia can induce cell death (e.g. Bettaieb & Averill-Bates, 2008) through caspases-3 and 9 (Nagarsekar *et al.*, 2008). There is overlap of febrile heat-induced apoptosis with pyroptosis, a new type of cell death during inflammation that is caspase-1 dependent (Bergsbaken *et al.*, 2009).

Besides systemic hyperthermia, it is well documented, but less known, that local inflammation also increases local temperature, true to Celsus' aphorism. The best understood example is the hot spots in advanced atherosclerotic plaques, up to 3 °C above the adjacent arterial surfaces and in relation to local macrophage density (Madjid *et al.*, 2002; Toutouzas *et al.*, 2007; Tan & Lip, 2008). Local hyperthermia is produced by the induction of UCP2, which uncouples mitochondrial ATP production from respiration, thereby generating radiant energy (Van De Parre *et al.*, 2008). We suggest that local hyperthermia may be adaptive by inhibiting local bacteria that are associated with damaged vascular tissue. *Chlamydia pneumoniae*, among other common bacteria, is detected in atherosclerotic plaques and is debated as a risk indicator of vascular events (Kalayoglu *et al.*, 2000; Stassen *et al.*, 2008; Di Pietro *et al.*, 2009). These mechanisms may extend to local skin hyperthermia observed during inflammation from bone fractures in hands and feet (Huygen *et al.*, 2004). Because fibroblasts express UCP2 (Mori *et al.*, 2008), we suggest that UCP2 induction and thermogenesis be included in species comparisons. Other markers induced by hyperthermia could include the level of cell ROS (Flanagan *et al.*, 1998) and SOD1 and SOD2 activity, which is associated with cellular thermotolerance (Loven *et al.*, 1985; Yamashita *et al.*, 2000; Hoshida *et al.*, 2002).

## Hypoglycemia and cellular resistance

Hypoglycemia during the acute phase of innate immunity, e.g. 3–6 h after LPS (lipopolysaccharide, endotoxin of Gram-negative bacteria) injection in mice (Oguri *et al.*, 2002; Ali *et al.*, 2008; Cryer *et al.*, 2009) is understood as a bacteriostatic mechanism. In comparative studies (Table 1), fibroblasts from long-lived dwarf mice showed reduced effects of glucose deprivation on the levels of a metabolic marker (WST-1 reduction), which is positively correlated with resistance against cytotoxic agents, such as hydrogen peroxide (Leiser *et al.*, 2006). The level of glucose starvation in these studies (0.1–0.4 mg $ml^{-1}$) was in the low clinical range of transient hypoglycemia that disturbs human cognition and behavior (< 0.50 mg $ml^{-1}$, or < 50 mg $dL^{-1}$, Cryer, 2007; Cryer *et al.*, 2009).

## Acute phase resilience hypothesis and relevance of fibroblasts

We propose that cell resilience to oxidative damage from immune-related stressors is a critical component of longevity systems. Infections occur from ingestion and inhalation of transmissible viral and bacterial pathogens and ectoparasites. The importance of the infectious inflammatory load to life span is shown by the increased life spans of laboratory rodents from husbandry improvements that minimized chronic lung diseases, ectoparasites, and other endemic infections: for C57BL/6J mice at Jackson Labs, life spans increased > 50% from 1957 (17 months) to 1970 (28 months) (Finch, 2007, p. 137). Fibroblasts, as the main test cell in species comparisons (Table 1), are relevant to the importance of the skin in the Darwinian world. Skin fibroblasts are ubiquitously subject to chronic inflammation from ectoparasites and microbial fauna, and from wounds incurred during fighting or from aggressive social grooming (Takahashi & Lore, 1982; Litvin *et al.*, 2007). The very long-lived naked mole rat incurs deep bites during intracolony aggression that pierce internal organs and are occasionally fatal (Lacey *et al.*, 1991; Clarke & Faulkes, 2001; Chris Clarke, pers. comm.). Abscesses associated with bite wounds contain *Pasteurella* sp. and *Haemophilus* sp. (Artwohl *et al.*, 2002). The resilience of long-lived naked mole rats to repeated wounding supports the disposable soma hypothesis (Kirkwood, 2005) that selection for somatic cell resilience can retard aging.

Skin wounding–stimulated responses remove necrotic debris and protect against infection that employ many innate immune system genes; fibroblasts may be stimulated to proliferate as well as undergo apoptosis (Santiago *et al.*, 2004; Fujiwara *et al.*, 2007). Wounding induces $H_2O_2$ production by epithelial cells that appear to guide the influx of leukocytes (Niethammer *et al.*, 2009), as noted above. The induction of SOD-1 and 2 and catalase (Steiling *et al.*, 1999; Schäfer & Werner, 2008) is associated with the clearance of $H_2O_2$ and other ROS, which can impair wound repair (Wilgus *et al.*, 2005; Wasserbauer *et al.*, 2008). Although fibroblast monolayers can be used as a wounding model, we are not aware of comparative studies related to species life spans.

Other cells besides fibroblasts show inverse relationships of damage to life span. Aortic endothelial cells exposed to oxidant stress (hyperglycemia) showed more inflammatory gene induction in laboratory mice (C57BL/6) than the longer-lived deermouse (*Peromyscus leucopus*) (Labinskyy *et al.*, 2009). Similarly, less mitochondrial ROS was generated by *P. leucopus* aortic cells

than by those from laboratory mice, consistent with other comparisons (Table 1). These findings of inverse relationships of species life spans with both mitochondrial ROS and cell vulnerability to ROS in arterial tissues are consistent with fibroblast comparisons and give a basis for expanding the range of somatic cell types in comparative studies. Mucosal epithelial cells merit consideration in future species comparisons for their critical role in enteric and oral defenses.

## Genomic comparisons of immune and cell death gene sequences

There is a major gap in understanding how the species differences in fibroblast phenotypes are related to genomic differences in terms of DNA sequence and gene expression. At the level of coding sequence, immune response genes show many relevant species differences; there are indications of lineage-specific innovation in mammals that would attenuate innate immune responses in longer-lived species (Wang *et al.*, 2006). Positive selection is well documented for immune response genes from codon ratio statistics for synonymous vs. nonsynonymous mutations (Nielsen *et al.*, 2005). Species differences in genes related to apoptosis comprise a considerable fraction of genes under positive selection as humans diverged from chimpanzees (Nielsen *et al.*, 2005).

Besides codon changes, there are many species differences in gene deletions and changes in expression profiles. The human and chimpanzee genomes show extensive gene deletions (Olson, 1999; Wang *et al.*, 2006), many of which are associated with inflammatory responses, illustrated by examples relevant to immune function. Chimpanzees have deletions of *ICEBERG*, *IL1F7*, and *IL1F8*, which are on a pathway inhibiting expression of caspase-1 (Chimpanzee Sequencing and Analysis Consortium, 2005; Kersse *et al.* 2007); these deletions could increase responses to LPS-induced IL-1 (Humke *et al.*, 2000). Humans differ from great apes in the absence of *N*-glycolylneuraminic acid (Neu5Gc) (Varki, 2009) because of the inactivation of cytidine monosphosphate-N-acetylneuraminic acid hydroxylase (CMAH), which enzymatically converts Neu5Ac to Neu5Gc. The inactivation of CMAH before 0.5 million years ago has implications for human-specific pathogens that target Neu5Ac: the chimpanzee malarial parasite binds Neu5Gc during erythrocyte invasion, while the human *Plasmodium falciparum* binds Neu5Ac. A comparison of humans and chimpanzees showed that genes associated with inflammatory responses and cell proliferation are more likely to show gene loss or gain, e.g. *APOL1,* which is only present in humans and mediates trypanosome resistance (Perry *et al.*, 2008).

Expression profiling of fibroblasts from different species is relatively undeveloped. We propose that gene expression comparisons across species with diverse life spans may reveal genes involved in aging-related phenotypes. Species-specific cellular responses to stress and inflammation, in particular, may contribute to the evolution of longevity. Next-generation sequencing technologies that allow deep RNA sequencing that is more sensitive for expression profiling than traditional microarrays should be used (de Magalhães *et al.*, 2010). Gene expression profiling of these cellular responses across rodents may identify genes and pathways that evolved unique roles in long-lived rodents and may contribute to their longevity. For example, rodent–human comparisons show differences in a DNA repair gene of relevance to ROS in the fibroblast model: the UV-damage DNA-binding protein (UV-DDB). Its much lower expression in mouse and hamster epidermal cells is consistent with deficits in global genome repair, relative to humans. Ectopic expression of DDB2 increased DNA repair in mouse fibroblasts and reduced UV-induced skin cancer *in vivo* (Alekseev *et al.*, 2005). We anticipate future studies to reveal additional species-specific differences in gene expression patterns that associate with longevity using new transcriptional profiling technologies.

For human–primate comparisons, the most detailed study may be the comparison of fibroblasts from adult human, bonobo, chimpanzee, and gorilla by Affymetrix GENECHIP 5.0, with confirmation of select changes by Northern blots (Karaman *et al.*, 2003): of the 10 000 genes discriminated, about 1% showed ≥ 2-fold species differences including various associations with host defense: humans had higher expression of HLA-E, MICA, SDF1, and TGFβ1, but much lower expression of glypican 3, a heparin-sulfate proteoglycan. Another gene with direct links to immune function is the very low expression of the glycoprotein siglec-5 in human T cells, which is a factor in the much greater immune reactivity of human vs. chimpanzee CD4 T cells, as shown by expression manipulation (Nguyen *et al.*, 2006). Of relevance to the evolution of cancer, the *erbB* proto-oncogene had higher expression in humans and two great apes vs. several shorter-lived primates, while *myc*, *ras-K* and *src* did not differ (Nakamura & Hart, 1987).

None of these genes have been considered in the context of fibroblast resilience in species comparisons. These differences suggest a major evolutionary change in immune responses that are part of the biology of human longevity. It seems clear that no single assay can address the multiple facets of species differences, irrespective of microevolution of immune responses.

Somatic damage from inflammation is relevant to the disposable soma theory of aging according to which longevity is determined by the rate of accumulating somatic cell damage, which is offset by the level of energy allocation for repair and regeneration (Kirkwood, 2005). Thus, a short-lived mouse with ten progeny per mating will invest less in repair to oxidative damage than a long-lived chimpanzee with singleton births at 5 or more year intervals. This can be easily observed in unicellular organisms such as bacteria or yeast, which are much more resistant to multiple stresses after entering a nonreproductive phase (post-diauxid and stationary phases). The genomic basis of these species differences could be resolved by RNA profiling and DNA sequence comparisons. We anticipate that species differences in genes that protect against inflammatory damage and mediate repair will provide clues about repair and regeneration mechanisms in long-lived species that may explain the evolution of longevity.

## Phylogenetic and ecological issues

The study of Kapahi *et al.* (1999) was a benchmark by its inclusion of mammalian species from four taxonomic orders including humans. Studies of rodents with eight species have generally confirmed the cell resilience-life span relationships (Harper *et al.*, 2007). Recent studies of species for *in vitro* comparisons have expanded the range of life spans represented within a taxon. Inclusion of the extraordinarily long-lived naked mole rat (*Heterocephalus glaber*, life span > 28 years) now gives a sevenfold range of life spans, relative to laboratory rodents (Buffenstein, 2008; Gorbunova *et al.*, 2008). Except for *H. glaber*, the other species of this study are terrestrial. The inclusion of mole rats raises new issues about the ecological relevance of experimental stressors: UV irradiation would not seem relevant to mole rats that have avoided sunlight for millions of years. Other ecophysiological adaptations may be important to experimental design. *Heterocephalus glaber* lives entirely in long underground burrows, a niche occupied with other bathyergids for at least 20 million years (Early Miocene) (Nevo *et al.*, 1999). *Heterocephalus glaber* has a low core temperature < 34 °C and is considered close to poikilothermic (Buffenstein & Yahav, 1991). Nonetheless, fever with elevated core temperature can arise during innate immune activation (R. Buffenstein, pers. comm.). The low core temperature introduces a species-specific factor in culture conditions.

These major ecological differences from terrestrial rodents could be a factor in several anomalies. *Heterocephalus glaber* fibroblasts are more sensitive to $H_2O_2$, UV, rotenone, and low glucose, while mice did not differ from two mole rats in ROS production by heart mitochondria (Lambert *et al.*, 2007) or levels of hepatic antioxidants SOD, catalase, and glutathione (Andziak & Buffenstein, 2006). Moreover, *in vivo*, the *H. glaber* had a higher load of oxidized lipids and proteins than mouse (Andziak *et al.*, 2006). The greater sensitivity of *Heterocephalus* lipids to oxidative damage $H_2O_2$ was considered '…provocative, because it does not support most models of oxidative stress and longevity' (Salmon *et al.*, 2008). However, *H. glaber* has a very different habitat than the other rodents: the gas composition in its long narrow tunnels has very low $pO_2$ (6%, hypoxia) and high $pCO_2$ (10%, hypercapnia), which would kill most rodents (van Aardt *et al.*, 2007). Corresponding adaptations include hemoglobin with higher oxygen affinity and altered acid–base regulation (greater Bohr effect) (Johansen *et al.*, 1976; van Aardt *et al.*, 2007), which we suggest may extend to redox sensitivity of other biochemical systems mediating stress responses. Other rodents with life spans of 20 years include beavers, porcupines, and squirrels (Gorbunova *et al.*, 2008; Austad, 2009); other mole rats may be shorter lived (Ansell's mole rat, 21 years; Cape mole rat, 11 years), but the small numbers observed preclude firm conclusions (http://genomics.senescence.info/species/).

## Suggestions for future studies

Because the acute phase response exposes cells to both hyperthermia and hypoglycemia, future comparisons could consider heat shock responses (e.g. HSP70-1,2), the mitochondrial UCP2, which generates local hyperthermia, and glucose regulatory and transport proteins (e.g. Grp58, GLUT-4). Combinations of heat and low glucose should be examined by deep RNA profiling. We postulate that life spans will scale with somatic cell resilience to combinations of stressors experienced during host defense. Bacterial endotoxins will also be useful as probes. The LPS endotoxin of common Gram-negative infections induces inflammatory gene induction in fibroblasts (Perfetto *et al.*, 2003; Warner *et al.*, 2004). The LPS induction of SOD-2 mRNA (Visner *et al.*, 1990) enhances resistance to $H_2O_2$ (Rohl *et al.*, 2008). Further insights are anticipated from deep RNA profiling in basal and stressed cells. In parallel with ongoing rodent studies, we encourage further comparison of human cells with great apes and other anthropoids for which expression data are very limited.

Another consideration is allelic variation in the human cells used for comparisons, which so far as we know have not been considered in species comparisons. For example, caspase 12 varies between human populations in the level of a pseudogene that increases resistance to sepsis (Wang *et al.*, 2006); the active allele (Casp12-L), while rare (< 1%) in most Asian and European populations, is common in sub-Saharan Africa, up to 60% (Kachapati *et al.*, 2006); chimpanzees and other mammals have active Casp12. Besides association with infections, caspase12 is also associated with amyloid-induced neuronal apoptosis, which may be relevant to the apparent absence of Alzheimer's disease in chimpanzees and other great apes (Chimpanzee Sequencing and Analysis Consortium 2005; Finch, 2010). Another relevant allele system is apoE, which influences cytokine secretions (Vitek *et al.*, 2009), as well as life span, Alzheimer's and heart disease (Finch, 2007). The main histocompatibility gene complex (Mhc) also has allelic variations relevant to somatic cell resilience.

## Concluding remarks

The link between *in vitro* cell resilience and species life span is a fascinating and important paradigm in the biology of aging. We have argued that the evolutionary selection for resistance to multiple types of inflammatory events underpins the general observation that cells in culture from long-lived species are stress resistant. This hypothesis further specifies aspects of Kirkwood's disposable soma theory that relate to inflammation (2005). We predict that longer-lived species are specifically more resistant to particular immune-related stressors and propose future studies based on this hypothesis.

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