Review

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The paternal age at conception effect on offspring telomere length: mechanistic, comparative and adaptive perspectives

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Telomeres are repeating DNA found at the ends of chromosomes that, in the absence of restorative processes, shorten with cell replications and are implicated as a cause of senescence. It appears that sperm telomere length (TL) increases with age in humans, and as a result offspring of older fathers inherit longer telomeres. We review possible mechanisms underlying this paternal age at conception (PAC) effect on TL, including sperm telomere extension due to telomerase activity, age-dependent changes in the spermatogonial stem cell population (possibly driven by 'selfish' spermatogonia) and non-causal confounding. In contrast to the lengthening of TL with PAC, higher maternal age at conception appears to predict shorter offspring TL in humans. We review evidence for heterogeneity across species in the PAC effect on TL, which could relate to differences in statistical power, sperm production rates or testicular telomerase activity. Finally, we review the hypothesis that the PAC effect on TL may allow a gradual multi-generational adaptive calibration of maintenance effort, and reproductive lifespan, to local demographic conditions: descendants of males who reproduced at a later age are likely to find themselves in an environment where increased maintenance effort, allowing later reproduction, represents a fitness improving resource allocation.

This article is part of the theme issue 'Understanding diversity in telomere dynamics'.

1. Introduction

Telomeres are repeating nucleotide sequences found at the ends of chromosomes that shorten in dividing cells as they proceed through the cell cycle [1,2]. As a result, telomeres decrease in length with age in most human tissues [3] and frequently in somatic tissues of metazoans [4]. This shortening can eventually place limits on further cell replication. Environmental factors, like smoking, inflammation and infection shorten telomere length (TL), but also have TL-independent effects on biology. Thus, correlations between TL and health outcomes should not be assumed to be directly causal. Still, converging evidence from molecular biology, and experimental and epidemiological studies strongly suggest that shorter TL can directly influence health, particularly by impairing immune and cardiovascular function [5–8].

In contrast to the tendency for TL to decrease in length with age in most human tissues, sperm TL shows a positive correlation with age [7,9]. In accordance with the fact that DNA carried in sperm contribute half of each offspring's autosomal genome, offspring of older fathers have longer TLs [7,10]. This putative paternal age at conception (PAC) effect on TL is intriguing because it appears to be a rare case of intergenerational genetic plasticity in which the DNA passed on to offspring is systematically changed based upon the age at reproduction of one's father. This finding, combined with evidence that the PAC effect accumulates across at least two generations of recent ancestors, has led us to hypothesize that the PAC effect on TL represents an example of adaptive intergenerational

plasticity whereby an offspring's investment in telomere-dependent maintenance effort (e.g. immunity) might be adjusted based on the average ages of reproduction of recent male ancestors [7,11,12].

In this review, we explore the mechanistic, comparative and evolutionary dimensions of the PAC effect on TL. To this end, we first examine the biology of sperm formation which may underlie the PAC effect. We then briefly consider evidence that PAC associations with TL are caused by sperm TL increasing with paternal age and whether a maternal age at conception (MAC) effect on TL exists in humans. We proceed to examine what is known about the PAC effect on TL across species. Because telomeres are a general feature of eukaryotic nuclear chromosomes [13], cross-species variability can provide insights into the evolutionary bases and possible function of TL, including the PAC effect on TL. We conclude our review by considering whether the PAC effect on TL could represent an adaptation allowing relatively rapid intergenerational adjustment of somatic maintenance effort—and perhaps even female reproductive lifespan—based upon predicted environmental and demographic conditions.

2. Mechanisms leading to PAC effect on TL in humans

Evidence that telomeres lengthen with age in human sperm, a finding that runs counter to their behaviour in most cell lines and tissues, has led to a search to explain these findings. Explanations fall into two broad and not mutually exclusive categories. First, there is some evidence that especially high levels of telomerase in testes could lead to a progressive lengthening of TL with age in sperm. Second, there may be selective loss of spermatogonial stem cells with shorter TL and gains of spermatogonial stem cells with longer TL. Below, we discuss the logic and empirical evidence for each of these scenarios to help set the stage for a broader discussion of telomeres from the perspectives of comparative and evolutionary biology.

(a) Telomerase

Since males need to produce a constant supply of sperm via cell division, mechanisms must be in place to allow this production despite the shortening of TL which occurs with each round of DNA replication. Telomerase, a reverse-transcriptase enzyme that carries an RNA template molecule coding for the telomere DNA sequence, is a chief mechanism via which telomeres are lengthened. Telomerase is generally inactive in postnatal human somatic tissues, but is active across adult life at high levels in men's testes [14], and appears to be critical for continued sperm production. Spermatogonia are the diploid stem cells that give rise to a series of daughter cells, including primary spermatocytes (diploid) and secondary spermatocytes (haploid) which eventually result in terminally differentiated spermatozoa (sperm). The RNA component of telomerase is expressed at high levels in human spermatogonia [15], consistent with TLs being actively maintained via lengthening in the relevant stem cell population. The telomerase RNA template component is also highly expressed in primary and secondary spermatocytes [15] suggesting that sperm TL extension with age could be at least partially due to extension of TL not in the spermatogonia, but in differentiated spermatogonia

descendant cells. In humans, TLs increase between the spermatogonia and primary spermatocyte stage and then decrease with further differentiation towards spermatozoa [16]. However, older men show similar or slightly greater rates of TL decline between spermatogonia and differentiated spermatozoa, suggesting that the PAC effect on sperm TL is probably due to changes in spermatogonial stem cell TL [16]. If spermatogonial telomerase activity is sufficiently high it could not only maintain TL in spite of continued sperm production, but also progressively lengthen telomeres with age [14,15,17–21].

(b) Selective changes in spermatogonia

Selective survival and/or replication of spermatogonia with long telomeres is another potentially compelling explanation for the PAC effect on TL in humans—although one not necessarily mutually exclusive with that of testicular telomerase activity [22,23]. Evidence for such an effect comes from a study documenting shifts in the distribution of spermatogonial TL with age. As Kimura et al. [22] pointed out, if spermatogonia TLs were extended at a uniform rate within individuals (e.g. via telomerase) this leads to the expectation that the distribution of sperm TL will shift to the right with age while maintaining the same shape of the distribution (figure 1a—Scenario A). Instead, these authors found that older men not only have longer average sperm TL than younger men, but that they have relatively fewer short and more long telomeres in their sperm (figure 1b, consistent with figure 1a—Scenario B) [22]. One possible explanation for this change in distribution of sperm TL with age is selective changes wherein spermatogonia with shorter TL are less likely to survive or replicate to form daughter spermatogonia than spermatogonia with longer TL.

Further clues to the biology of the PAC effect may come from examinations of not just the changes in the mean TL of sperm and offspring with age, but also the changes in TL variance. While analysis suggests that sperm TL variances increase as a man ages [22,24], a twin study deploying a novel analysis suggest that the range of sperm TL transmitted to the next generation decreases with paternal age (i.e. by comparing the similarity in TLs between dizygotic twins with different aged fathers). This apparent contradiction between sperm TL and the TLs passed on by fathers to their offspring via sperm is unresolved. One possible explanation is that the increasing variance in sperm TL with age is driven by greater within-sperm (i.e. across chromosome end) variation in sperm TL, even as between sperm mean TL variation decreases with age. Alternatively, it is possible that there is a selective bias such that only a subset of the sperm with a lower variance in TL in older men are capable of fertilizing and producing viable offspring. Indeed, there is some evidence that sperm functionality varies with TL [25–29]. Regardless, future studies should be attentive not just to changes in mean TL in sperm and offspring with increasing age, but also to changes in variances and distributions of TL across chromosomes, sperm cells and offspring.

(c) Is the PAC effect on TL due to selfish spermatogonial selection?

Related to the selection scenarios outlined above, de novo germ line mutations that drive a recently described phenomenon called selfish spermatogonial selection (SSS) [30,31] could
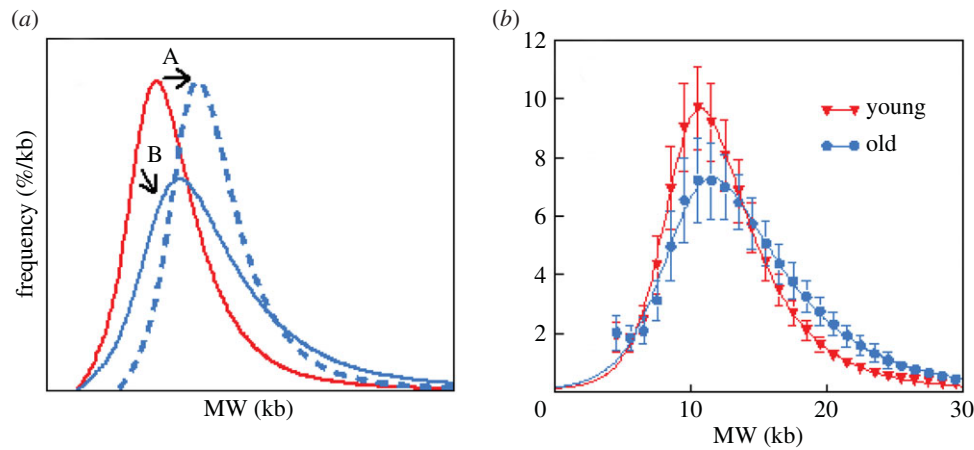
Figure 1. Hypothetical and empirical changes in distributions of sperm TL with age. (*a*) Two hypothetical scenarios for shifts in TL distributions in sperm from young and older donors. Scenario A depicts a uniform shift in the TL distribution towards longer telomeres in sperm of older men (interrupted blue line) from that of younger men (red line). Scenario B depicts a reconfiguration of the distribution, so that shorter telomeres are disproportionally 'under-represented', while longer telomeres are 'over-represented'. (*b*) Frequency distributions of TLs in sperm from eight young (18–19 years; red triangles) and eight older donors (50–59 years; blue circles) based on averaging the within-ejaculate variation in TL from southern blot telomere restriction fragment length analysis across individuals. Adapted from Kimura *et al.* [22]. (Online version in colour.)

theoretically also contribute to a progressive lengthening of average sperm TL with age. SSS is a phenomenon wherein some spermatogonial stem cells acquire mutations that affect the phenotype of the spermatogonia in a way that increases their rate of division to form daughter spermatogonia. Mutations which cause SSS seem to be in pathways regulating self-renewal and differentiation of spermatogonial stem cells [30] and have shared signatures with preneoplastic somatic mutations [31,32]. SSS explains some autosomal-dominant disorders that increase in prevalence with PAC [31,32].

Spermatogonial stem cells which are capable of expanding in a pattern consistent with SSS seem to gain their selective advantage via signalling pathways including PI3 K (phosphatidylinositol-3 kinase)/AKT, and STAT3 (signal transducer and activator of transcription 3) [33,34]. These same pathways also play a role in regulating telomerase activity [35–37], hinting at the potential for shared biology between SSS and the PAC on TL—and possibly even that *de novo* mutations that drive SSS could increase telomerase activity. Because these highly proliferative cell lines become numerically dominant with time, any tendency for these cells to express telomerase at higher levels, and increase sperm TL, could cause average sperm TL to increase with age.

Despite these shared molecular pathways between SSS and the PAC effect on TL, it is presently unclear if SSS contribute to the PAC effect on TL. Available data provide mixed support for such a role. On the one hand, and as noted above, age-related shifts in the distribution of sperm TL suggest that the PAC effect on TL is at least partially driven by selective losses of spermatogonia with shorter TL and gains in spermatogonia with longer TL. These findings are potentially consistent with the selective expansion of long TL spermatogonia described in the SSS model. However, the SSS model also leads to the expectation that SSS mutations increase exponentially in frequency with age (see [38]). In contrast, this expectation is not confirmed for the PAC effect on TL. Instead in humans both sperm and offspring TL appear to increase linearly, not exponentially, with advancing PAC. In contrast to the nonlinear changes in SSS, telomerase activity extends telomeres during the DNA replicative phase (S phase) of the cell cycle in humans [39], such that a slight but persistent overshooting of

expression of testicular telomerase is expected to lead to a linear increase in sperm TL with age, which is consistent with the character of the PAC–TL association as documented thus far in humans.

This line of investigation suggests multiple areas for future research. First, while the PAC effect on TL has been observed to be linear, large and well-powered studies should continue to examine whether exponential models are a better fit for the influence of male age on sperm and offspring TL, which would be consistent with a role for SSS. Second, important evidence for SSS has been demonstrated via examination of the clustering of mutations within the testes [40]. SSS leads to the expectation that spermatogonia with SSS mutations will tend to cluster together as some spermatogonia symmetrically divide and take over a region of testes [30]. If SSS is driving the PAC effect on TL we should find that long TL in spermatogonia also tends to cluster together. Since mutations which cause SSS are in pathways which also regulate telomerase activity, it is possible that these SSS mutations tend to cause increased telomerase activity and thereby longer telomeres. If *de novo* mutations that drive SSS also cause higher telomerase activity and longer TL then clusters of spermatogonia with these mutations should also tend to have higher telomerase activity and longer TL.

3. Is the PAC association with TL causal in humans?

Despite the plausibility of the above scenarios linking advancing paternal age with sperm telomere lengthening, it remains possible that the PAC association with TL in humans is not causal. The most obvious non-causal scenario is one in which men who inherited longer TLs at birth tend to live healthier and/or longer lives. Even if sperm TL did not change at all with male age, we might then see that healthier men with longer TL are more likely to reproduce at later ages and more likely to volunteer to donate sperm (used in telomere studies) at later ages. Because mortality is low in early adulthood and high in late adulthood, this non-causal scenario leads to the expectation that the PAC effect should be most apparent, or
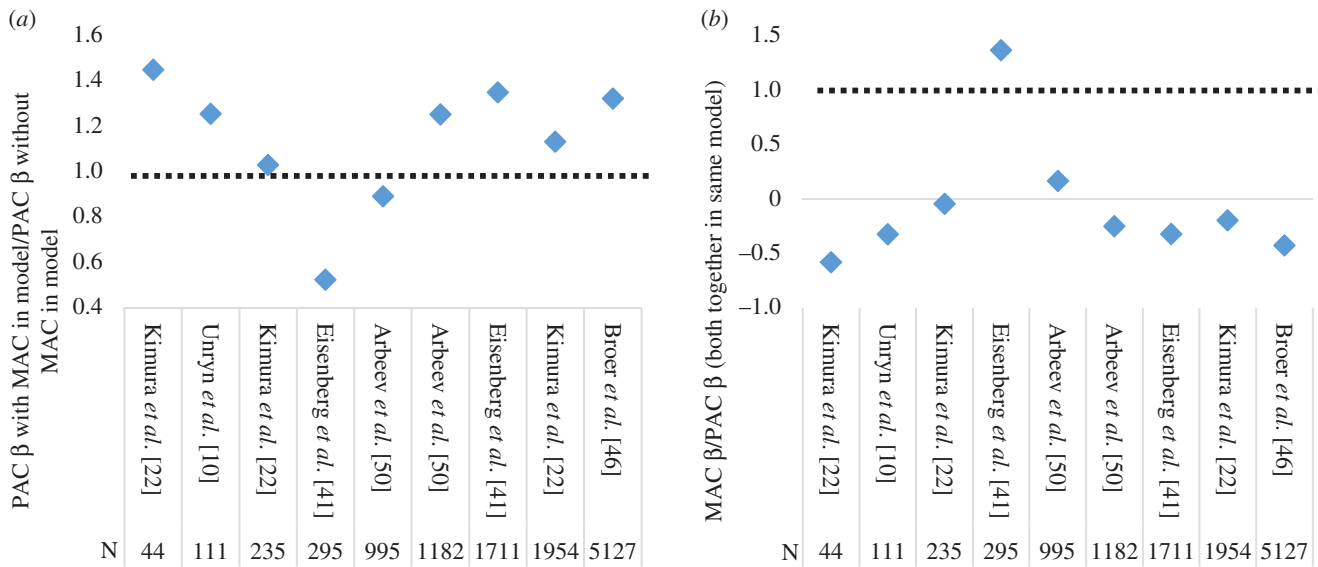
Figure 2. Comparing the relative strength of the PAC and MAC effects on offspring TL in human studies: (a) assesses how the PAC effect on offspring TL changes after controlling for the MAC effect. Calculated by examining PAC effect in a regression model including MAC and one not including MAC and then dividing PAC effect in first model by PAC effect in second. Values greater than 1 indicate that PAC effect increases when controlling for MAC, suggesting that PAC effect is not driven by MAC. (b) Assesses direction and relative magnitude of MAC effect compared to PAC effect (the ratio of MAC effect/PAC effect). Values greater than 1 indicate a greater positive MAC effect than PAC effect. Values less than zero indicate MAC effects in opposite direction of PAC effects (i.e. shorter offspring TL with older MAC). Statistics from Eisenberg et al. [41] has been updated from the original publication based on measurement improvements in the same dataset [49]. Studies with multiple entries include separate estimates for independent cohorts. (Online version in colour.)

perhaps only apparent, among offspring born to fathers of advanced age. Contrary to this expectation, past studies point to a PAC effect on sperm and offspring TL that is linear and apparent even when fathers are young [22,41]. If men with longer TL were more likely to donate sperm samples with advancing age, than we would expect these donors to not only have longer sperm TL, but also longer blood TL. Contrary to this, within the same men, sperm TL shows a cross-sectional increase with age while blood TL shows a cross-sectional decrease [42]. Thus, although selection of men with longer TL is a theoretically possible explanation for the PAC effect on TL, multiple lines of evidence argue against this explanation.

Factors such as birth order or socio-economic status (SES) might also be correlated with PAC but affect offspring TL via pathways independent of changes in sperm TL with paternal age. For example, older fathers could have higher SES and being raised in a higher SES household could promote increased TL in their offspring. If the PAC–TL association were due to factors such as health, SES, or birth order we would expect the PAC effect to be attenuated after statistical adjustment for these factors, and to change across ecological and cultural contexts where these factors and their inter-correlations vary. Contrary to this, the PAC association with offspring TL is reported in all human populations studied, including in the US, Canada, UK, Denmark and the Philippines [10,22,41,43]. The PAC effect has been found to not be attenuated appreciably by adjustment for SES, birth order or other factors [41,44]. Similarly, there is no evidence that the human PAC effect varies with offspring age [10,22,41,43,45,46] (electronic supplementary material, table S1) [41], as might be expected if age-related changes in paternal provisioning ability led to variable rates of postnatal TL attrition across individuals born to fathers varying in age (see evidence for this in European shag: [47]). Finally, our closest living relatives, chimpanzees, show a similar PAC–TL association despite having very different mating, rearing (e.g. no paternal care) and

social systems than humans [48]. Collectively, these findings suggest that these other sources of confounding are unlikely to account for the PAC–TL association.

4. Is there a maternal age effect on TL in humans?

Because oocytes are all produced prenatally, while sperm are continually produced throughout life, it is thought that there is more potential for TL plasticity with age in sperm than in oocytes. Nonetheless, studies in humans tend to show a positive correlation between MAC and offspring TL. One challenge in assessing a MAC effect on offspring TL comes from the typically strong age correlation between reproductive partners in humans. That is, offspring of older mothers may have longer TL simply because the offspring's fathers are also older.

Supporting the hypothesis that PAC is of primary importance in determining offspring TL in humans, controlling for MAC in regression models tends to lead to a larger PAC effect than when not controlling for MAC (figure 2a—most values greater than 1). Comparing the PAC and MAC effects included together in the same regression model, most human studies show evidence for a negative association between MAC and offspring TL (figure 2b—most values less than 0). Both of these patterns are particularly apparent in larger studies (farther to the right in both figures), which due to their greater statistical power are likely to have more reliable estimates. The Eisenberg et al. [41] study of 295 Filipino women stands out as an outlier among the studies investigated. Of note, that study focused on a small subset of the sample (16% of a larger sample) for which data on PAC and MAC were opportunistically available. In contrast, another cohort from the same population (the offspring of these women) with more complete MAC and PAC data (Eisenberg et al. [41], N = 1711) shows results more consistent with other

Table 1. Paternal age effect on offspring TL across species. Bold values indicate $p < 0.05$.

genus species	common name	N	PAC s.d. (years)	r^a	p	relative testis size[b]	refs
Lacerta agilis	**sand lizard**	**12**	**1.38**[c]	**−0.59**	**0.041**		[56]
Phalacrocorax aristotelis	European shag	204	4.38	+	0.43		[47]
Acrocephalus arundinaceus	great reed warbler	154		+	0.7		[57]
Mus musculus	**mouse**	**12**[c]	**0.39**	**−**	**≤0.05**	0.5	[58]
Ovis aries	Soay sheep	318	2.17	0.066	0.238	4.9/1.2[d]	[59][c]
Macaca fascicularis[e]	long-tailed macaque	9	~7.8	+	NS	2.3	[21]
Homo sapiens	**Human**	**144**	8.2	**0.15**	**0.03**	0.5	[48]
Pan troglodytes	**chimpanzee**	**40**	6.4	**0.42**	**0.009**	1.5	[48]

[a]Correlation values if reported, otherwise '+' indicates positive association and '−' negative association.
[b]Ratio of observed mass of testis to that predicted by body mass from [60].
[c]Personal communication.
[d]Breeding season/non-breeding season calculated from [61].
[f]Testicular TL instead of offspring TL.

studies. We speculate that biases introduced by opportunistic sampling might account for the outlier results among the older cohort in this study.

The tendency towards a negative association between MAC and offspring TL (figure 2b) might be explained if oocytes that had fewer mitotic divisions tend to be ovulated earlier in the lifecycle than those ovulated later—although it is not clear if this occurs in humans [51]. In cows, it has been shown that TLs in immature oocytes are shorter in older cows than in younger ones, providing some support for this notion [52]. However, in cows TLs elongate during embryo development up until the blastocyst stage and TL has not been shown to differ between young and old cows at the blastocyst stage [52], suggesting that initial differences in oocyte TL may be obscured or eliminated through TL changes over the course of development. Because telomere and telomerase biology vary markedly across species [53,54], it may be that more of the initial oocyte differences in TL with MAC are retained with age in humans compared to other species.

Together, available evidence suggests that, at least in humans, older PAC probably acts to extend offspring TL while older MAC may slightly decrease offspring TL. This apparent negative MAC effect on TL could result if oocytes formed after more mitotic divisions, which will tend to decrease TL, tend to be ovulated later in life. Evidence in other species, among which parental ages are less strongly correlated and can be experimentally manipulated, may provide more definitive answers.

5. Cross-species evidence

Because telomeres are general features of eukaryotic nuclear chromosomes [13], additional insights into their function, and the extent of variability and possible function of the PAC effect on TL, may be gained by looking at these processes across species differing in life-history and reproductive strategies. Non-human studies also sometimes have the advantage of allowing the use of experimental approaches (e.g. selecting the age of mating), low correlations between parental ages, and more invasive and precise tissue sampling. High testicular

telomerase levels are probably a general feature of mammals; indeed, high telomerase activity has been found in testes in all mammalian species in which it has been examined, including 15 rodent species spanning from the small, short-lived mouse to the long-lived naked mole-rat and large capybara [54], cats, dogs [55], long-tailed macaques [21] and humans [14].

As summarized in table 1, the PAC effect on TL has only been studied in eight species. Findings are highly variable across species, hinting at rapid evolution of telomere/sperm production biology. Only half of the studied species show statistically significant associations between PAC and offspring/sperm TL—two of these associations are negative and two are positive. Although the remaining null findings could reflect the true nature of the biology of these species, it is important to also consider the effect of statistical power as a limitation. All else equal, the greater the range of variation in PAC, the greater the statistical power to detect relationships. As illustrated in supplementary figure 1, assuming the yearly PAC effect size observed in humans, PAC effects in species with limited variation of PAC require large sample sizes to detect an association. For example, samples greater than 1000 and 4000, respectively, would be needed to reliably detect a PAC of human magnitude in European shags and Soay sheep. In contrast, assuming the much greater PAC effect found in chimpanzees, the more manageable sample sizes of 80 and 346 would be sufficient. Conversely, the significant negative PAC effects found in mice and sand lizards, despite limited power, imply a very large magnitude effect on TL in order to be detected in these species (table 1). The negative PAC effects on TL in mice shows that even high testicular telomerase activity, as has been documented in this species [54], may not be sufficient to increase sperm TL with age, or that testicular telomerase activity is by itself insufficient to explain the PAC effect.

Building on the idea that the continual need for production of sperm is a key driver of the PAC effect on TL, Eisenberg et al. [48] predicted that the PAC effect should be larger in species with greater sperm production rates. This prediction gains only limited support in the sparse available data. The chimpanzee–human comparison is particularly informative given the close phylogenetic relationship between the two species. Chimpanzees experience sperm competition secondary to

their promiscuous mating system, which has led to a higher rate of sperm production compared to humans [62,63]. Consistent with an effect of sperm production rate on the magnitude of the PAC effect on TL, chimpanzees show increases in TL with each year of delayed paternal conception that are an estimated six-fold greater than in humans ($p = 0.026$) [48]. In contrast, Soay sheep, which have a much larger relative testes size (and probably, sperm productive rates) even than chimpanzees, lack a discernible PAC effect on TL (table 1). Possibly explaining this, Soay sheep are seasonal breeders whose relative testes size reduces considerably in the off season (table 1), which probably reflects an attenuated sperm production rate [64]. Additionally, as noted above, statistical power to detect a PAC effect on TL may be low in this species.

In sum, while all 19 measured mammalian species show evidence for high testicular telomerase activity, evidence of PAC associations with offspring TL show little consistency across species. Depending on the species, PAC has been shown to relate to offspring TL in positive or negative directions, while in others there is no evidence for an association. Some of the null findings might be a result of low statistical power. The most consistent pattern is a tendency for catarrhine primates to have positive PAC effects—as evident from significant positive relationships between PAC and offspring TL in humans and chimpanzees and suggestive evidence for a similar relationship in a small sample of long-tailed macaques.

6. Does the PAC effect on TL allow adaptive transmission of plasticity-generated genetic information across generations?

Thus, evidence for relationships between PAC and offspring TL are most consistently observed in humans and their close primate kin. Although it is presently uncertain if there is a direct causal relationship between PAC and offspring TL in humans, such an effect is a likely explanation in our view, in light of the converging evidence reviewed above (§3). Irrespective of the specific underlying mechanisms, an effect of PAC on offspring TL would represent an unusual form of intergenerational genetic plasticity in which the DNA passed on to offspring varies systematically based on the father's age at reproduction. Age at reproduction is an event that is of fundamental importance from an evolutionary perspective. Organisms have limited energy and other substrate that can be devoted to growth, reproduction, maintenance, activity or storage [65]. According to some models of aging [66], the optimal allocation of resources varies primarily based on unavoidable mortality and other environmental circumstances. When the likelihood of living and reproducing into the future are high, intensive investment in maintenance effort at the expense of reduced immediate reproductive expenditure can be a good fitness strategy. Conversely, when extrinsic mortality risks are high, optimism about the future is reduced, shifting the balance in favour of current reproductive expenditure and at a cost to maintenance functions. This evolutionary life-history perspective has lead us to suggest that the PAC effect on TL may represent an adaptation whereby TLs passed on to offspring are systematically altered to improve the fit to the environmental and demographic setting he or she is likely to encounter across the life course [7]. That is, males with the ability to adjust the TL of their offspring in

response to their own age of reproduction may have had offspring with higher average fitness—thus selecting for this capability to adjust sperm TL with age.

One obvious limitation to the utility of the PAC effect on TL as a reliable signal of the expected age at reproduction is the noise introduced by stochastic processes, such as the effect of birth order. A father may sire multiple children at different ages, thus potentially sending different age signals to offspring facing the same environment. This problem led Eisenberg [7] to suggest that TL might not only reflect the father's age at conception, but could, by virtue of the high fidelity of DNA replication, also reflect the conception ages of multiple generations of paternal ancestors going back in time. In this scenario, the TL that an individual receives would reflect not just one's own father's age, but also that of the grandfather and other more distant male ancestors, thereby providing a rolling average age of recent reproductive timing in the lineage (for a related example, see [67]). Consistent with this prediction, a subsequent study showed that the paternal grandfather's age at conception of the father predicted the grandchild's TL, independent of and additive to, the effect of the father's age at conception [41]. Studies of socio-economic status across many generations show high levels of continuity within families across multiple countries around the world [68], suggesting a level of consistency that could make the PAC effect on TL a good adaptive signal of local conditions. We also recognize, however, that this same stability in socio-economic status may complicate efforts to distinguish a direct PAC effect on offspring TL from other processes like niche construction, genetic, epigenetic and cultural transmission.

It is important to note that, older fathers transmitting longer telomeres to their offspring than younger fathers do not imply that TLs increase with each generation. The testes are formed from the intermediate mesoderm early in pre-natal development [69]. Sperm production in the testis begins at puberty, but adult-like sperm concentration, morphology and motility are not evident until some years later [69,70]. This developmental sequence involves many cell divisions, which probably allow opportunities for TL shortening due to cell replication and DNA damage, prior to the onset of any mechanisms that cause lengthening of TL in spermatogonia with age. It is presently not clear at what age (if any) a man would need to reproduce in order to transmit longer telomeres to his offspring than he himself received. However, all else equal, intergenerational lengthening of sperm TL is made more likely as the conception ages of one's father, and his recent paternal ancestors, is delayed.

(a) What are the potential benefits of inheriting long telomeres from late-reproducing male ancestors?

If the PAC effect on TL does provide a reliable cue of local demographic conditions, as we hypothesize, it is of interest to consider the biological changes that might be calibrated in response to this information, and the trade-offs probably involved. As alluded to above, because TL provides a limit on how many times a cell can replicate, longer TL is expected to enhance cell proliferation-dependent functions. Because mounting an immune response often involves cell proliferation-dependent processes, this leads to the expectation that longer TL should manifest as more robust cell-proliferation-dependent components of immunity, and possibly a slowing of the pace of immune senescence with advancing age.

Indeed, experimental and longitudinal observational evidence *in vitro*, in mice, and in humans suggests that longer TL promotes resistance to infection, and that these effects are evident in young adulthood and possibly infancy [7,71–74]. Longer TL are also likely to reduce the likelihood of atherosclerosis by improving vascular maintenance and reducing the build-up of senescent cells in atherosclerotic plaques [75,76]. Additionally long TLs probably improve wound healing, which also relies upon cellular proliferation [77].

Another biological function that depends upon cell proliferation is gamete formation. As discussed above, in females the pool of oocytes is established in its entirety during fetal life, and menopause occurs when the pool of follicles is depleted. It has been hypothesized that TL could influence the pace of female reproductive senescence, including late-life fecundity, by influencing the pool of initial oocytes formed, and their viability as a woman ages [78,79]. There is evidence that TL measured in blood cells is shorter in women who experience menopause at an earlier age—although this finding has not been replicated across all ethnic groups [78–80]. While links between TL and female reproduction await additional validation in humans, they add to the list of candidate cell replication-dependent processes in offspring that might benefit as a result of inheriting longer TL from older fathers.

(b) The potential costs of inheriting long telomeres

Given that longer telomeres very probably improve functions that require cell proliferation, it also seems likely that long telomeres will carry costs. Otherwise we would expect the rapid evolution and fixation of inherited (i.e. germ line) long telomeres to avoid any functional constraints imposed by short telomeres, and thus no association between TL and fitness relevant phenotypes in the general population. The most commonly cited fitness cost associated with inheriting long TL is an increased risk of cancer. The theoretical reasons to expect a link between longer telomeres and cancer risk are clear: because accumulation of oncogenic mutations is dependent on cell replication, a cell lineage with shorter TL is less likely to gain the necessary mutations for cancer development before cell proliferation stops due to critically short TL [76]. However, there are also pathways via which longer TL could promote cancer protection. Short TLs are known to cause chromosomal instability and fusions which can promote cancer, although it has been argued that this only occurs in rare pathological conditions and is of limited relevance to the general population [76]. Longer TL also promotes improved immune function [7,71–73], which plays a key role in combating cancer-inducing pathogens and parasites (e.g. human papillomavirus and *Helicobacter pylori*), as well as fighting off cancers once they begin to develop [7,81].

Empirical results have not yet given a clear resolution to the TL-cancer question. Although telomerase shows high activity in the vast majority of cancers and the activation of telomere maintenance pathways in somatic tissues is likely to be critical for cancer development, it is less clear what role inheriting longer telomeres—germ line TL—plays in cancer risk [7]. Results from prospective human studies tend to show that longer somatic TL is associated with decreased cancer risk or has no association with cancer at all [82–85]. In contrast, genetic polymorphisms associated with longer TL tend to predict increased cancer risk—particularly for rarer cancers [6,84,86,87]. These contrasting results could be due to the fact

that measured somatic TL are confounded by environmental variables that shorten TLs and increase cancer risks via other pathways (e.g. smoking), or pleiotropic effects of TL-associated genetic polymorphisms that increase cancer risk via germ line TL-independent pathways [84,88,89].

Another factor that reduces the likelihood that cancer has been a key factor shaping within-species variation in TL in humans is the fact that in human cancer mortality is very rare until middle age and mostly occurs in the elderly [7]. Additionally, human cancer is thought to have been much less prevalent before recent changes coincident with the demographic transition and industrialization [7]. While humans engage in extensive intergenerational transfers of resources that allow us to continue to contribute to inclusive fitness late in life, the force of selection still declines with age in humans—such that late-life traits are less shaped by natural selection than those earlier in life [7]. The presence of a PAC effect on TL in chimpanzees, among whom many of these factors do not apply, suggests that the PAC effect on TL that is documented in human populations very probably predates the human–chimpanzee split. Given this, other TL-influenced (i.e. cell proliferation dependent) phenotypes which influence health earlier in life, such as immunity and wound healing ability, may be more likely to shape optimal TL.

In the absence of clear costs to longer telomeres, or of benefits of having shorter TL, Eisenberg proposed the *thrifty telomere hypothesis* [7]. The thrifty telomere hypothesis suggests that longer telomeres promote increased maintenance effort and thereby health and longevity—but that this comes at energetic costs. Increased investments in long-term maintenance mean less energy available for current reproductive investments, a strategy that could reduce fitness in environments with high extrinsic mortality risks. By the reasoning of this model then, in low mortality environments, offspring inherit longer telomeres from multiple recent generations of male ancestors, who reproduced on average at later ages. This signal of late-life survival and reproduction in turn facilitates a shift in resource allocation away from immediate reproduction and in favour of enhanced maintenance effort and lifespan extension—via boosted immunity, wound repair, and perhaps even oocyte number and longevity. This model leads to several testable predictions, including that individuals who inherit longer TL will exhibit evidence for greater maintenance expenditures at an expense to reproduction, and that, controlling for potential confounders, secular trends in PAC will predict improved immune function in progeny.

7. Conclusion

The putative PAC effect on TL represents a novel type of intergenerational plasticity. We are not aware of any other such systematic alteration to DNA sequences that are transmitted to offspring. As we have reviewed, there is convergent evidence that this PAC effect on TL is due to progressive lengthening of sperm TL as human males age (as we note, it is at present less clear how widespread this phenomena is in other species). The biological mechanisms underlying these increases in sperm TL are less certain, but could include some combination of high testicular telomerase activity, selective loss of spermatogonia with short TL and/or increased proliferation of spermatogonia with long TL. We also reviewed parallels between selfish spermatogonial selection and the PAC

8

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effect on TL which might reflect shared biology. Unlike the plasticity created by continued sperm production with age, oocytes are produced prenatally and correspondingly there is limited evidence for a MAC effect on offspring TL. If a MAC effect exists, it is likely to be negative rather than positive.

The PAC effect on TL has only been studied across eight species and shows considerable variation, with chimpanzees showing a positive six-fold greater PAC effect than humans, other species showing negative PAC effects and several showing no associations at all. We note that statistical power to detect PAC effects will be limited by a combination of variation in PAC within a species and study sample size, and that some past studies are thus underpowered to detect human-sized PAC effects. In the future, appropriately powered comparative studies will help clarify the extent, and possible function, of PAC–TL associations across a wider range of species.

We have suggested that the PAC effect on TL could represent an adaptive intergenerational signalling mechanism. Specifically, age at reproduction is a key factor shaping life-history strategies and having had multiple generations of recent male ancestors who reproduced at later ages may indicate that similar demographic conditions are likely to be experienced in the near future. Longer TLs are postulated to promote increased maintenance effort, particularly via improved immune function and wound healing. Maintenance effort is energetically costly and has a greater fitness payoff in contexts of lower extrinsic mortality and delayed reproduction. In addition, there is emerging evidence that inheriting longer telomeres could also allow increased proliferation of follicles in female offspring, which might delay the timing of menopause and cessation of reproductive senescence when recent male ancestors have delayed reproduction themselves.

Other similar adaptive intergenerational signalling mechanisms have been suggested [12] but it remains unclear how common or adaptive such phenomena are [90–92]. The PAC effect on TL is noteworthy, and distinct from many examples of maternal-offspring signalling, for being multi-generational [41] which may allow for the communication of an integrated signal reflecting average age at conception among multiple recent generations of paternal ancestors [12]. Further, the PAC effect on TL is based in changes to DNA sequences and thus provides an intergenerational signalling pathway that is mechanistically well-established and of high fidelity.

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