PHILOSOPHICAL TRANSACTIONS B

rstb.royalsocietypublishing.org

Introduction

Cite this article: Monaghan P, Eisenberg DTA, Harrington L, Nussey D. 2018 Understanding diversity in telomere dynamics. *Phil. Trans. R. Soc. B* **373**: 20160435.
http://dx.doi.org/10.1098/rstb.2016.0435

Accepted: 1 December 2017

One contribution of 19 to a theme issue 'Understanding diversity in telomere dynamics'.

Subject Areas:
ecology, evolution, molecular biology, physiology

Author for correspondence:
Pat Monaghan
e-mail: pat.monaghan@glasgow.ac.uk

Understanding diversity in telomere dynamics

Pat Monaghan[1], Dan T. A. Eisenberg[2], Lea Harrington[3] and Dan Nussey[4]

[1]Institute of Biodiversity, Animal Health and Comparative Medicine, College of Medical, Veterinary and Life Sciences, University of Glasgow, Graham Kerr Building, Glasgow G12 8QQ, UK
[2]Department of Anthropology, University of Washington, 314 Denny Hall, Box 353100 Seattle, WA 98195-3100, USA
[3]Départemente de Médecine, Institut de recherche en immunologie et en cancérologie, Université de Montréal, 2950 chemin de Polytechnique, Montréal, Québec, Canada H3T 1J4
[4]Institute of Evolutionary Biology, University of Edinburgh, Ashworth Labs, The King's Buildings, Charlotte Auerbach Road, Edinburgh EH9 3FL, UK

PM, 0000-0003-2430-0326; DN, 0000-0002-9985-0317

1. Introduction

Telomeres and their associated proteins constitute an ancient and highly conserved system to maintain chromosome stability and the integrity of the coding sequences in eukaryote genomes. They identify and protect the chromosome ends. While other linear chromosome-capping mechanisms also occur in nature [1], the telomeric system appears to be the most common. Many operational principles of this system are shared across a wide range of eukaryote species, indicative of its ancient origins. Telomere DNA generally comprises a string of a repeated, short, non-coding sequence, which is often G rich, such as TTAGGG [2]. The proximal end of the telomeric tract is double stranded, and the distal end terminates in a single-stranded overhang of the G-rich strand. The structure loops back on itself and the single-stranded section intrudes into the double-stranded telomeric DNA. Specific protein complexes, termed the shelterin and CST complexes, help to maintain the t-loop structure and regulate telomere access during DNA replication (e.g. for review, see [3]). Processes occur within cells not only to maintain telomere structure, but also to restore the loss of telomeric DNA that occurs as a natural consequence of the DNA replication process.

Until relatively recently, almost all of the work on telomeres was in the context of understanding how malfunctioning of this system of chromosome protection can lead to human disease. However, there has been a burgeoning of interest in looking at how the telomere system operates in different kinds of animals, and in understanding variation in telomere dynamics and in the expression of telomerase in species with different morphologies and life histories. This theme issue represents a relatively unusual coming together of scientists from different disciplinary backgrounds, including evolutionary biology, ecology, cell biology and biomedicine, to understand and elucidate the origins and diversity of telomere dynamics, and their role in driving or constraining the evolution of the key life-history traits of growth, reproduction and longevity. This endeavour, which has been greatly facilitated by an international network grant from the Leverhulme Trust, is still at a relatively early, and, therefore, very exciting, stage. There is much that we do not know about the causes and consequences of inter- and intra-specific variation in telomere length and loss. In this Introduction, we set out some of the main challenges facing the field with the aim of informing and stimulating further research into understanding the biodiversity of telomere dynamics.

2. Why did telomeres evolve?

A salient feature of the eukaryotes is that their genetic material, with the exception of that in the mitochondria, is almost always arranged into linear chromosomes contained within the nucleus of their cells [4]. By contrast, prokaryotes typically, though not exclusively [4], have circular chromosomes and smaller genomes

THE ROYAL SOCIETY PUBLISHING

than the eukaryotes [5]. The factors driving the evolution of linear chromosomes are not fully understood, but they are probably tied to the evolution of sexual reproduction. Sexual reproduction, which is nearly universal in eukaryotes [6], allows organisms to produce much more genetically diverse offspring [7]. Linear chromosomes and meiotic cell division mean that the genetic material can be shuffled across the homologous chromosomes, and that homologous chromosomes can independently segregate into the four haploid daughter cells. Telomeres appear to play an important role in meiosis, with the homologous chromosomes aligning together via tethering of the chromosome ends during the meiotic prophase [4].

While the evolutionary advantages of sexual reproduction are fairly clear, linear chromosomes give rise to two problems. Firstly, each chromosome has two ends, which need to be distinguished from double-stranded DNA breaks if end-to-end joining or degradation of chromosomes is to be prevented. Secondly, during DNA replication the terminus of the lagging DNA strand is not fully replicated after removal of the distal RNA primer, and there is/or due to inefficient initiation of Okazaki fragment synthesis [8]. This is referred to as the 'end replication problem'. Further nucleolytic processing also contributes to the loss of distal telomeric DNA at both the leading and lagging strands of newly replicated chromosomes [9]. Prokaryotes with linear chromosomes have solved these problems by diverse means [4]. In eukaryotes, both the identification of chromosome ends and the end-replication problem have been solved by the evolution of telomeres. Telomeres and their associated proteins shield the chromosome end from inappropriate processing by the DNA repair machinery. The loss of coding DNA is prevented by having a non-coding region at the end, whose restoration can be accomplished by processes such as that provided by the enzyme telomerase, or other less common telomere lengthening mechanisms [10,11].

However, an additional problem exists for long-lived or large-bodied species, whose cells may undergo a sufficiently large number of replications to enable them to accumulate enough mutations to cause diseases such as cancer. In these species, telomerase is often downregulated in somatic tissues, or expressed at insufficient levels to maintain telomere integrity. It has been proposed that this downregulation is one mechanism to minimize the risk of cancer development [12,13]. This so-called 'telomerase insufficiency' in somatic (or progenitor) cell types results in progressive telomere shortening with each cell division. Once telomeres become critically short, the resultant telomere dysfunction can lead to cell replicative senescence. This sets a limit on the number of times cells can divide, termed the 'Hayflick limit' [14]. A wealth of data in genetic model systems and in individuals with mutations that compromise telomere integrity or maintenance show that telomere erosion leads to an accelerated loss of cell function or viability in various stem cell types and tissues [15]. Cells with mutations that subvert the DNA damage checkpoints that would normally impose the Hayflick limit, such as pre-malignant or tumour cells, can avoid replicative senescence and carry on dividing. Hence there is a complex and intertwined relationship between telomere biology, ageing and degenerative disease.

The story, of course, is never simple. Where evolution has favoured different growth and reproductive strategies, some organisms may have evolved ways around these limitations, but others may not. Understanding this diversity in the operation of the telomeric system, and how it links to life-history evolution, is a primary focus of this theme issue. The paper by Young [16] provides an in-depth consideration of the potential role of telomeres in mediating trade-offs between current investment and future performance, and whether this role is causal. He also discusses whether the telomeric system might serve to mitigate the costs of damage accumulation, and what light this could shed on our understanding of variation in ageing trajectories. Of course our understanding of telomere diversity is very much dependent on obtaining accurate measures of telomere length and loss, and this is fraught with difficulties particularly when using non-model species [17]. The paper by Lai *et al*. [18] discusses these difficulties, and the problem introduced when examining links to disease and/or longevity when estimating average telomere length rather than the shortest telomeres.

Below we summarize the other issues covered in this theme issue, discuss key gaps in our knowledge, and also identify a number of key areas for future research.

3. Is telomere length or loss predictive of longevity?

A key question of interest to scientists across many disciplines is whether telomere length is predictive of mortality risk within species, and of average lifespan across species. In recent years, a considerable, and still rapidly growing, literature has emerged measuring telomere length in a range of bird species in both captivity and the wild. Birds are an interesting taxon in this regard because good individual longevity data are available from bird ringing studies in the wild and from populations kept in captivity. Also, there is considerable variation in lifespan among species, with some exhibiting maximum lifespans in excess of 50 years (many seabirds and parrots for example). Two papers in this issue harness these emerging data on avian telomeres to provide important new insights into the relationship between telomere length and longevity. Tricola *et al.* [19] compare average telomere length and rates of change in telomere length with age across 19 species of birds. They show that species with longer maximum lifespans have slower rates of telomere loss with age than species with shorter lifespans. Wilbourn *et al.* [20] have conducted the first formal meta-analysis of the link between within-species variation in telomere length and subsequent mortality risk in non-human vertebrates. They found that, across 27 studies, there was a significant overall tendency for individuals with shorter average telomere length to show increased subsequent mortality risk, providing overarching support for a correlative link between telomere length and lifespan within species. However, the vast majority (21 of 27) of these studies came from birds and, while the meta-analysis reveals an intriguing hint that there may be a different relationship between telomere length and mortality in reptiles, there are insufficient studies to substantiate this trend.

Clearly, more studies of non-avian species are needed. Indeed, the range of taxa for which telomere data are available in healthy individuals remains very limited, and is biased towards the endothermic vertebrates, the birds and mammals. The paper by Olsson *et al.* [21] draws attention to this shortcoming in the literature and points out how much we have to gain from studies of ectotherms, both in deepening our knowledge of diversity in telomere dynamics, and in the context of understanding the costs and benefits of telomere restoration in tissue regeneration and disease prevention.

They discuss the evidence in support of an intriguing hypothesis predicting that ectothermic vertebrates should have lower rates of tumour formation. While much of this theme issue is particularly focused on vertebrate telomeres, being where most data are currently available with respect to links to organismal life, they also provide a useful overview of the literature on plant telomeres.

Most data obtained from non-model systems, like those in the papers above, are correlational. There have been relatively few studies in which telomere length has been experimentally manipulated and the organismal level outcomes investigated. Criscuolo *et al*. [22] discuss this issue and examine a number of studies in which telomere length was manipulated by experimentally changing telomerase activity. They provide an important critical evaluation of the utility of this approach, and also review the role of telomerase in health and disease beyond that of telomere maintenance. Bateson & Nettle [23] provide a critique of the difficulties in establishing the direction of causality in correlational studies, using as an example the correlational link between smoking and shorter telomere length in humans. They consider the possibility that the direction of causality is different from that usually supposed. That is, rather than smoking causing telomere loss, individuals with high telomere loss are more likely to adopt particular behaviours, in this case smoking. This could occur, for example, if poorer early life environments cause increased telomere loss and such individuals engage in more risky behaviours. This tendency could be part of a suite of behaviours that have evolved to improve reproductive success when the prospects for long-term health and survival are compromised.

4. Telomere length, body size and disease risk

The relationships between telomere length, body size and cancer risk are also of great interest across disciplines. Risques & Promislow [24] present a simple model to help frame our current understanding of these relationships and explore the costs and benefits of long and short telomeres in terms of cancer prevention and replicative senescence. They provide a general conceptual framework for considering the role of body size in the evolution of tumour suppression mechanisms. Aviv and Shay [25] also consider the costs and benefits of short and long telomeres in shaping optimal telomere length in humans, with relatively long telomeres proving potential protection against cardiovascular disease, but increasing the risk of tumour formation. There is recent empirical evidence in support of this [26]. Tian *et al.* [27] further consider telomerase expression, body size and cancer risk by examining the relationship between the propensity of fibroblasts to form tumours in 18 rodent species varying in body size and maximal lifespan. They propose that two different strategies of tumour prevention have evolved in small- and large-bodied species.

5. Telomere structure and genomic evolution

Baird provides an overview of the dynamic nature of telomere regions and possible functions of this variation in the context of genetic diversity and genomic evolution. Short telomeres, and the genome instability they induce, can also influence genome integrity in other less obvious ways. Harrington reviews recent literature on how genome-wide telomere-induced perturbations of the genome can have substantial consequences for cell functions, by influencing, for example, DNA methylation and histone modifications. These papers emphasize that telomeres are highly dynamic structures that have wide-ranging impacts beyond the telomeres themselves.

6. Factors influencing within-species variation in telomere length

It is well established that early life conditions have long-term consequences for health and longevity. Growing evidence suggests that early life development may represent a particularly sensitive period for processes affected by telomere integrity, suggesting that changes in telomere length may underlie some early life effects. In addition, there are clearly inherited determinants of telomere length, and inherited telomere length may have effects on health even in early life. Better understanding of these inherited and environmentally mediated determinants of inter-individual telomere length variation is a key aspect of telomere research. Dugdale & Richardson [28] provide an overview and critical evaluation of what we know about telomere length inheritance, emphasising both the importance of, and challenges associated with, the separation of environmental and genetic components of variation. Their review covers the extensive literature on the heritability of telomere length in humans and the rapidly emerging literature on the same subject in birds. They provide important guidance on how the separation of environmental and genetic effects can best be achieved. Early-life environment and parental effects represent salient examples of such environment effects. Entringer *et al.* [29] discuss the effects of prenatal conditions on telomere length, particularly in mammals, and outline a number of routes whereby intra-uterine conditions can affect the initial 'setting' of telomere length and telomerase expression. Monaghan & Ozanne [30] examine the relationship between telomere dynamics and somatic growth in endothermic vertebrates, and the extent to which relatively fast growth is associated with reduced longevity. They evaluate the routes whereby such effects could occur, oxidative stress in particular, and the evidence that growth and telomere length are negatively related.

In studies of telomere length, variation in telomerase activity remains the elephant in the room. This has been studied very little outside of the rodents, in part because of the difficulties in obtaining quantitative, non-destructive measures of telomerase activity. The paper by de Punder *et al.* [31] presents the results of a study that aimed to develop and validate a measure of maximal telomerase activity which was based on stimulation of telomerase activity in leucocyte samples. The study was conducted using white blood cells collected from young adult humans whose stress levels and stress sensitivity were also assessed. Their results suggest that this method shows considerable promise and could open the way to more widespread studies of variation in telomerase activity.

That paternal age has a positive association with offspring telomere length in humans has attracted considerable interest, because this association appears to go in the opposite direction to that which might have been predicted. This is discussed in detail in the paper by Eisenberg & Kuzawa [32]. They review evidence for considerable variability in paternal age associations with offspring telomere lengths across species, and the converging evidence that the human association is mediated via increases in telomere length in sperm as men become

older. They also speculate that the paternal age effect may represent a means of adaptive calibration of offspring telomeres, and thereby maintenance effort, based on the reproductive ages of male ancestors. As pointed out by Aviv [33], who also considers the paternal age effect, we lack longitudinal studies of sperm telomere length within males; these are needed to exclude the possibility that males with longer telomeres are more likely to survive, or remain reproductively active, into old age. The paper by Aviv puts forward a new idea as to how the sperm of older men might come to have longer telomeres. He postulates that this could be linked to age-related deterioration in mitochondrial function and the possibility that oxidative damage imposes a selection for sperm with long telomeres in older men.

7. Future research

As is evident from the above, there are many questions concerning telomere function and diversity that remain to be answered. What role do telomeres have in normal ageing and does this differ across taxa? We need more research on telomere length changes across the life course, and in telomere maintenance or absence of, in a greater diversity of organisms. This will enable us to deepen our understanding of why this diversity occurs and how the life-history traits that are linked to it might be influenced by environmental change. Such studies may also uncover some clever solutions that organisms have evolved to circumvent the conflict between restricting cell replicative potential and maximizing longevity and/or tissue regenerative potential. These solutions might help us in dealing with degenerative disease in our own species. Although detailed longitudinal studies of telomere dynamics are emerging, the vast majority of studies to date have been cross-sectional. Papers throughout this issue highlight the importance of long-term longitudinal studies for the furthering of our understanding of the causes of variation in telomere dynamics among and within species. Given that telomere length may influence survival, age-related studies can suffer from important biases that could exaggerate or mask relationships. But longitudinal studies are difficult, especially in long-lived species. The comparative analysis of Tricola *et al*. [19] and the meta-analysis of Wilbourn *et al*. [20] are both limited to using cross-sectional data. For this reason, their conclusions regarding the importance of initial telomere length, and the rate of telomere loss over different time scales, for lifespan remain tentative. Only with longitudinal data can we address the degree to which telomere length variation is driven by initial differences set early in development or rates of telomere attrition. We also need more studies of environmental effects on telomere dynamics and of the routes whereby these effects occur. More data are needed on the 'setting' of so-called 'initial' telomere length and on parental effects, both maternal and paternal. There is considerable scope for experimental and longitudinal work in this area.

As telomeres are studied in more detail and in more diverse organisms, it is clear that they serve a number of functions other than those considered here, functions that are only just being elucidated. Future research may change our perspectives on telomere evolution. One such example may be telomere position effects on gene transcription. Genes positioned near the chromosome ends might be silenced by functional telomeres, but expressed as telomeres shorten [34]; this could conceivably contribute to age-related changes in gene expression. Another example relates to the fact that telomere sequences do not only occur at the chromosome ends. They also occur within the chromosomes. Such interstitial chromosome repeats have often been treated as a nuisance that interferes with our measurements of the 'true' telomeres. The occurrence of these interstitial repeats varies among chromosomes, individuals and species. Furthermore, we assume that the level of these repeats is stable within individuals, but this may not always be so. We are only beginning to appreciate the diversity in the occurrence of these interstitial repeats of the telomere sequence and to understand their potential functionality [35–37]. This is likely to represent an important area of future research.

As is evident from the papers in this issue, telomeres and their diversity in length, loss and maintenance provide a fertile area for cross disciplinary research, and there remains much that is still to be uncovered about their role in diverse, important topics such as variation in rates of ageing, in maximal life span and in the evolution of life histories.

Data accessibility. This article has no additional data.

Authors' contributions. All four editors contributed to the writing of this paper.

Competing interests. We declare we have no competing interests.

Funding. We received no funding for this study.

Acknowledgements. The editors and authors wish to thank to the Leverhulme Trust for funding an International Network on Diversity in Telomere Dynamics which greatly facilitated the interdisciplinary collaborations and discussions that laid the foundations for this theme issue. We also thank all the contributors for their interesting and thoughtful papers, and for maintaining as much as possible the interdisciplinary perspective that we feel to be an important aspect. We also thank the Senior Commissioning Editor at *Philosophical Transactions B*, Helen Eaton, and all the reviewers, for all their help in putting this issue together.

Author biographies

Pat Monaghan is the Regius Professor of Zoology at the University of Glasgow, UK. Her work is focused on how environmental conditions shape individual life histories and the link between early life circumstances and later life health and longevity. This encompasses evolutionary and behavioural ecology, physiology and molecular biology. She is particularly interested in whether and how telomere dynamics play a role in long-term effects observed at the individual level. Her group work with a range of taxa in the laboratory and in the field.

Dan Eisenberg is an Associate Professor of Anthropology at the University of Washington, USA. His work focuses on human evolutionary biology, life-history theory and recent human adaptations. He particularly focuses on studying the evolutionary fitness costs and benefits of telomeres in humans and intergenerational dynamics of telomere length transmission. Much of his work is with the Cebu Longitudinal Health and Nutrition Survey in the Philippines and the Tsimane', a group of indigenous Amazonian forager-horticulturalists.

Lea Harrington is a Professor in the Department of Medicine at the University of Montreal, and a Visiting Professor and former Chair of Telomere Biology at the University of Edinburgh. She studies the mechanisms by which telomeres are elongated and protected by the RNA-dependent telomerase reverse transcriptase. Her laboratory employs genetic model systems, from yeast to mammals, with a particular interest in how subtle changes in telomerase dosage affect genome stability and other cell processes in ageing, cancer and stem cells.

Dan Nussey is a Professor in Evolutionary Ecology at the University of Edinburgh, UK. His work focuses on the causes and consequences of variation in the ageing process in wild animals. He is particularly interested in what telomere length as a biomarker can tell us about among- and within-individual variation in health and fitness in both free-living and domestic mammals.

References

1. Fulcher N, Derboven E, Valuchova S, Riha K. 2014 If the cap fits, wear it: an overview of telomeric structures over evolution. *Cell. Mol. Life Sci.* **71**, 847–865. (doi:10.1007/s00018-013-1469-z)
2. Gomes NMV, Shay JW, Wright WE. 2010 Telomeres and telomerase. In *The comparative biology of aging* (ed. NS Wolf), pp. 227–258. New York, NY: Springer.
3. Price CM, Boltz KA, Chaiken MF, Stewart JA, Beilstein MA, Shippen DE. 2010 Evolution of CST function in telomere maintenance. *Cell Cycle* **9**, 3157–3165. (doi:10.4161/cc.9.16.12547)
4. Ishikawa F, Naito T. 1999 Why do we have linear chromosomes? A matter of Adam and Eve. *Mutat. Res. DNA Repair* **434**, 99–107. (doi:10.1016/s0921-8777(99)00017-8)
5. de Lange T. 2015 A loopy view of telomere evolution. *Front. Genet.* **6**. (doi:10.3389/fgene.2015.00321)
6. Goodenough U, Heitman J. 2014 Origins of eukaryotic sexual reproduction. *Cold Spring Harb. Perspect. Biol.* **6**. (doi:10.1101/cshperspect.a016154)
7. Barton NH, Charlesworth B. 1998 Why sex and recombination? *Science* **281**, 1986–1990. (doi:10.1126/science.281.5385.1986)
8. Ohki R, Tsurimoto T, Ishikawa F. 2001 In vitro reconstitution of the end replication problem. *Mol. Cell. Biol.* **21**, 5753–5766. (doi:10.1128/mcb.21.17.5753-5766.2001)
9. Bonetti D, Martina M, Falcettoni M, Longhese MP. 2013 Telomere-end processing: mechanisms and regulation. *Chromosoma.* **123**, 57–66. (doi:10.1007/s00412-013-0440-y)
10. Pickett HA, Reddel RR. 2015 Molecular mechanisms of activity and derepression of alternative lengthening of telomeres. *Nat. Struct. Mol. Biol.* **22**, 875–880. (doi:10.1038/nsmb.3106)
11. Casacuberta E. 2017 *Drosophila*: retrotransposons making up telomeres. *Viruses* **9**. (doi:10.3390/v9070192)
12. Hackett JA, Greider CW. 2002 Balancing instability: dual roles for telomerase and telomere dysfunction in tumorigenesis. *Oncogene* **21**, 619–626. (doi:10.1038/sj.onc.1205061)
13. Gorbunova V, Seluanov A. 2009 Coevolution of telomerase activity and body mass in mammals: from mice to beavers. *Mech. Ageing Dev.* **130**, 3–9. (doi:10.1016/j.mad.2008.02.008)
14. Hayflick L, Moorhead PS. 1961 Serial cultivation of human diploid cell strains. *Exp. Cell Res.* **25**, 585–621. (doi:10.1016/0014-4827(61)90192-6)
15. Harrington L. 2012 Haplo insufficiency and telomere length homeostasis. *Mutat. Res. Fundam. Mol. Mech. Mutagen.* **730**, 37–42. (doi:10.1016/j.mrfmmm.2011.11.004)
16. Young AJ. 2018 The role of telomeres in the mechanisms and evolution of life-history trade-offs and ageing. *Phil. Trans. R. Soc. B* **373**, 20160452. (doi:10.1098/rstb.2016.0452)
17. Nussey DH *et al.* 2014 Measuring telomere length and telomere dynamics in evolutionary biology and ecology. *Methods Ecol. Evol.* **5**, 299–310. (doi:10.1111/2041-210x.12161)

18. Lai T-P, Wright WE, Shay JW. 2018 Comparison of telomere length measurement methods. *Phil. Trans. R. Soc. B* **373**, 20160451. (doi:10.1098/rstb.2016.0451)
19. Tricola GM *et al.* 2018 The rate of telomere loss is related to maximum lifespan in birds. *Phil. Trans. R. Soc. B* **373**, 20160445. (doi:10.1098/rstb.2016.0445)
20. Wilbourn RV, Moatt JP, Froy H, Walling CA, Nussey DH, Boonekamp JJ. 2018 The relationship between telomere length and mortality risk in non-model vertebrate systems: a meta-analysis. *Phil. Trans. R. Soc. B* **373**, 20160447. (doi:10.1098/rstb.2016.0447)
21. Olsson M, Wapstra E, Friesen C. 2018 Ectothermic telomeres: it's time they came in from the cold. *Phil. Trans. R. Soc. B* **373**, 20160449. (doi:10.1098/rstb.2016.0449)
22. Criscuolo F, Smith S, Zahn S, Heidinger BJ, Haussmann MF. 2018 Experimental manipulation of telomere length: does it reveal a cornerstone role for telomerase in the natural variability of individual fitness? *Phil. Trans. R. Soc. B* **373**, 20160440. (doi:10.1098/rstb.2016.0440)
23. Bateson M, Nettle D. 2018 Why are there associations between telomere length and behaviour? *Phil. Trans. R. Soc. B* **373**, 20160438. (doi:10.1098/rstb.2016.0438)
24. Risques RA, Promislow DEL. 2018 All's well that ends well: why large species have short telomeres. *Phil. Trans. R. Soc. B* **373**, 20160448. (doi:10.1098/rstb.2016.0448)
25. Aviv A, Shay JW. 2018 Reflections on telomere dynamics and ageing-related diseases in humans. *Phil. Trans. R. Soc. B* **373**, 20160436. (doi:10.1098/rstb.2016.0436)
26. Haycock PC *et al.* 2017 Association between telomere length and risk of cancer and non-neoplastic diseases: a Mendelian randomization study. *JAMA Oncol.* **3**, 636–651. (doi:10.1001/jamaoncol.2016.5945)
27. Tian X, Doerig K, Park R, Can Ran Qin A, Hwang C, Neary A, Gilbert M, Seluanov A, Gorbunova V. 2018 Evolution of telomere maintenance and tumour suppressor mechanisms across mammals. *Phil. Trans. R. Soc. B* **373**, 20160443. (doi:10.1098/rstb.2016.0443)
28. Dugdale HL, Richardson DS. 2018 Heritability of telomere variation: it is all about the environment! *Phil. Trans. R. Soc. B* **373**, 20160450. (doi:10.1098/rstb.2016.0450)
29. Entringer S, de Punder K, Buss C, Wadhwa PD. 2018 The fetal programming of telomere biology hypothesis: an update. *Phil. Trans. R. Soc. B* **373**, 20170151. (doi:10.1098/rstb.2017.0151)
30. Monaghan P, Ozanne SE. 2018 Somatic growth and telomere dynamics in vertebrates: relationships, mechanisms and consequences. *Phil. Trans. R. Soc. B* **373**, 20160446. (doi:10.1098/rstb.2016.0446)
31. de Punder K, Heim C, Przesdzing I, Wadhwa PD, Entringer S. 2018 Characterization in humans of *in vitro* leucocyte maximal telomerase activity capacity and association with stress. *Phil. Trans. R. Soc. B* **373**, 20160441. (doi:10.1098/rstb.2016.0441)
32. Eisenberg DTA, Kuzawa CW. 2018 The paternal age at conception effect on offspring telomere length: mechanistic, comparative and adaptive perspectives. *Phil. Trans. R. Soc. B* **373**, 20160442. (doi:10.1098/rstb.2016.0442)
33. Aviv A. 2018 The mitochondrial genome, paternal age and telomere length in humans. *Phil. Trans. R. Soc. B* **373**, 20170210. (doi:10.1098/rstb.2017.0210)
34. Robin JD, Ludlow AT, Batten K, Magdinier F, Stadler G, Wagner KR, Shay JW, Wright WE. 2014 Telomere position effect: regulation of gene expression with progressive telomere shortening over long distances. *Genes Dev.* **28**, 2464–2476. (doi:10.1101/gad.251041.114)
35. Lin KW, Yan J. 2008 Endings in the middle: current knowledge of interstitial telomeric sequences. *Mutat. Res. Rev. Mutat. Res.* **658**, 95–110. (doi:10.1016/j.mrrev.2007.08.006)
36. Wood AM, Laster K, Rice EL, Kosak ST. 2015 A beginning of the end: new insights into the functional organization of telomeres. *Nucleus* **6**, 172–178. (doi:10.1080/19491034.2015.1048407)
37. Bolzan AD. 2017 Interstitial telomeric sequences in vertebrate chromosomes: origin, function, instability and evolution. *Mutat. Res. Rev. Mutat. Res.* **773**, 51–65. (doi:10.1016/j.mrrev.2017.04.002)