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Is Telomere Erosion a Mechanism of Species Extinction?

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ABSTRACT According to the fossil record, 99.9% of all species that have ever lived on Earth have disappeared. However, only about 4% died out during the five mass extinction events, whereas it seems that the majority of species vanished without any signs of significant earthbound or extraterrestrial physical threats. Clearly, biological extinction mechanisms are by far the most important, but they are subject to serious limitations concerning the worldwide disappearance of species. In view of that, species-inherent mechanisms, which could lead to the worldwide destabilization of a population, might be worth reconsideration. Telomeres, the protective caps of chromosome ends, and the enzyme telomerase have been well preserved in plants and animals during evolution. In the absence of telomerase activity, telomeric DNA has been shown to shorten every time a cell divides. The concept of a mitotic clock based on the gradual erosion of telomeres is now generally accepted and has been confirmed in numerous plants and animals. Chromosomal rearrangements are the hallmarks of two completely different biological phenomena, cancer and speciation. In premalignant cells, gradual telomere erosion beyond a critical threshold is a well-known inducer of chromosomal instability. The species clock hypothesis, as presented here, is based on the idea of a tiny loss of mean telomere length per generation. This mechanism would not rapidly endanger the survival of a particular species. Yet, after many thousands of generations, critically short telomeres could lead to the weakening and even the extinction of old species and would simultaneously create the unstable chromosomal environment that might result in the origination of new species. *J. Exp. Zool. (Mol. Dev. Evol.) 302B: 111–120, 2004.*

INTRODUCTION

A remarkable aspect of the history of life on earth is that so many successful species have become extinct. More than ninety-nine percent of all species that have ever lived on this planet have already vanished (Raup, '91). Many of the extinctions recorded in the fossil record are of species that were ecologically tolerant and were found worldwide. Besides a steady level of background extinction, there have been five mass extinction events during the last 600 million years (Hallam and Wignall, '97). Although the 'Big Five' were important, their combined species kill accounted for only about 4% of all extinctions in the past 600 million years (Raup, '94), casting doubt upon the significance of physical threats for species extinction. Hence, biological mechanisms, such as Darwin's species interactions, are regarded as the most important causes of extinction, despite some limitations regarding the worldwide disappearance of species (Raup, '94).

In this paper, we will discuss if ever-shortening telomeres, the protective caps of chromosome ends, could function as a biological clock limiting the duration of species — affecting the whole population, worldwide.

Telomeres and the mitotic clock

More than forty years ago, Hayflick and Moorhead showed that normal human somatic cells have a limited proliferative life span (replicative senescence, Hayflick limit), related not to elapsed time but to the accumulated number of cell divisions (Shay and Wright, 2000). Hayflick's limit and its underlying mitotic clock are now generally accepted (Shay and Wright, 2000). In 1971, Olovnikov hypothesized that this phenomenon

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results from the incomplete replication at the ends of linear DNA molecules (Olovnikov, '96). According to his theory, DNA polymerases cannot copy DNA from the very beginning, due to a 'dead zone' between the front end of the enzyme and its catalytic center. It later became apparent that the 'dead zone' is the terminal RNA primer, which is essential for DNA replication and would represent the smallest possible unit of telomeric sequence loss.

The widely accepted paradigm linking telomere function to replicative senescence is based on the observation that in human somatic cells telomeres shorten with each cell division (Harley, '91). When telomere function is compromised (due to critical shortening), it can result in cell senescence and/or chromosomal instability. The latter is caused by exonucleolytic degradation and end-to-end fusion of chromosomes (Feldser et al., 2003) leading to dicentric chromosomes which themselves can initiate ongoing chromosomal instability via breakage-fusion-bridge cycles (McClintock, '39). To prevent this from occurring (or at least postpone it), eukaryotic chromosome ends are capped with up to thousands of repetitions of a short, noncoding sequence (=telomeric sequence). In germ cells and in early embryonic stem cells high levels of the enzyme telomerase, a reverse transcriptase, preserve constant telomere lengths, but in somatic cells low telomerase levels cannot prevent gradual shortening of telomeres, resulting in a limited proliferative life span of those cells. Telomerase is an universal enzyme, it has been found in most eukaryotes from single celled organisms to higher plants and animals, including humans (McEachern et al., 2000). In addition to the enzyme telomerase, several telomeric binding proteins are believed to influence telomere length (Slijepcevic, '98), yet a milestone experiment published in *Science* has clearly shown that the ectopic expression of the telomerase catalytic subunit (hTERT) alone is sufficient to extend telomere length and replicative life span of normal human fibroblasts (Bodnar et al., '98).

Today, several versions of the end replication problem exist and the story has become more complicated, mainly due to the observation that eukaryotic telomeres possess a single-stranded 3' overhang. This has shifted the focus from the end replication problem to an 'overhang generation problem.' Some researchers blame difficulties with the terminal RNA priming event on the lagging strand (Wynford-Thomas and Kipling, '97), others the inability of leading strand DNA synthesis to produce the 3' overhang for the shortening process (Lingner et al., '95). Since extensive research is on-going, and inconclusive as of yet,this paper will be based on the original model, as follows: RNA primers, which are usually about 10 nucleotides long, are needed for the replication of eukaryotic chromosomal DNA molecules. After removal of the terminal RNA primer, gaps remain at the 5' ends of the newly synthesized strands (leading and lagging strand), which cannot be filled (Dhaene et al., 2000) (Fig. 1). Hence, in the absence of telomerase activity, a particular telomere is expected to lose 10 base pairs (bp) every other S phase (Zakian, '97). Since a chromosome end is shortened by incomplete replication in only one of the daughter cells (the one acquiring the incompletely replicated strand in that telomere), the rate of telomere loss in base pairs per cell division is only half of the rate of incomplete replication. Accordingly, mean telomere length would decrease by 0.5 of a deletion event per generation, resulting in a loss of 5 bp per cell division. A comparable rate of telomere loss (about 3–4 bp per generation) has been observed in telomerase-negative yeast (Lundblad and Szostak, '89; Singer and Gottschling, '94), supporting the idea of the RNA primer being the smallest possible unit of telomere loss.

Variations in telomere length

Enormous telomere length variation has been observed between species, but significant variation has also been seen between individuals of a species, between tissues of an individual, and between chromosomes of a single cell, even between homologous chromosomes. Primarily, mean telomere length varies greatly between species, from less than 1 kbp to several 100 kbp, but seems to be relatively constant within a species (McEachern and Blackburn, '95). Nevertheless, there is some variation between human fetuses ranging from 10.6 to 11.8 kbp (Youngren et al., '98). In a human fetus mean telomere length is similar in most tissues, but synchrony is apparently lost during extrauterine life, which is consistent with different proliferative rates of different tissues with insufficient telomerase activity later in life (Youngren et al., '98). Although mean telomere length does not vary much between individuals of a species, lengths of individual telomeres are largely heterogeneous in (lab) mouse and human (Lansdorp et al., '96; Zijlmans et al., '97). Interestingly, specific chromosome arms show similar telomere lengths in

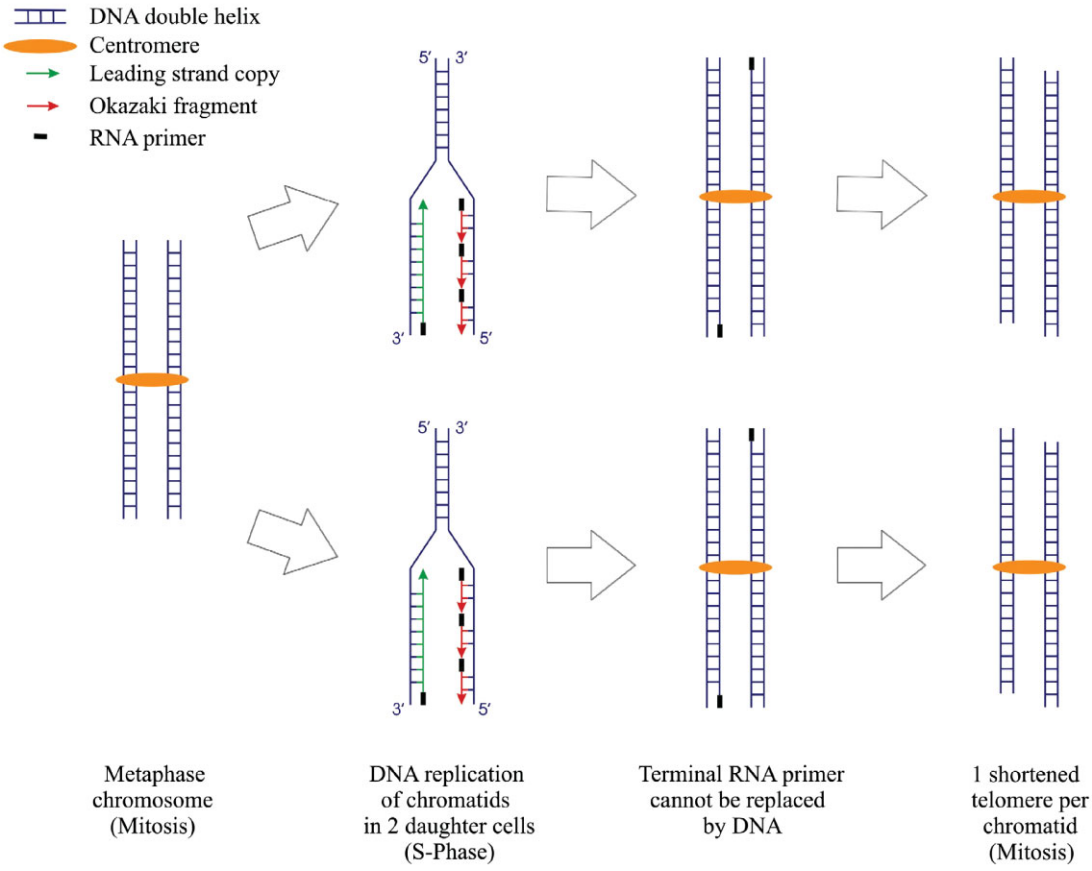

Fig. 1. The original model of the end replication problem: During DNA replication the gap at the 5′ end caused by the terminal RNA primer (~10 nucleotides) cannot be filled. Hence in the absence of a special compensation mechanism, linear DNA molecules shorten each cell cycle by at least 10 base pairs in eukaryotes. Supposing that the RNA primer does not bind to the single-stranded overhang (not shown in this graph) and that the creation (extension) of the overhang does not require telomerase activity (demonstrated in yeast [Dionne and Wellinger, '96]). Extensive research over the last two decades has lead to a more complicated picture (McEachern et al., 2000), but has not clearly identified the exact mechanism of telomere shortening.

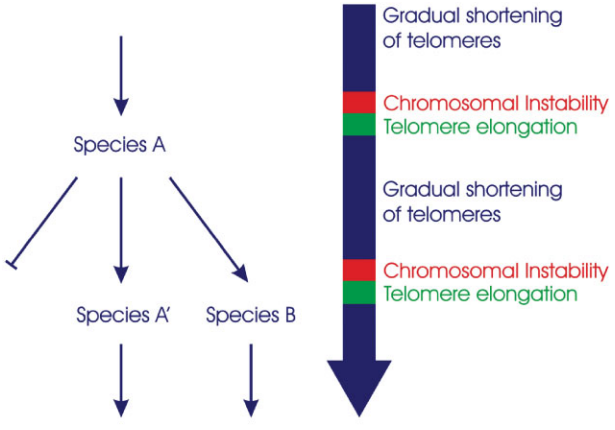

Fig. 2. The species clock hypothesis: Gradual telomere shortening to a critical threshold leads to populationwide chromosomal instability and the sporadic creation of new stable karyotypes in the offspring due to chromosome healing and telomere elongation. Depending on the telomere stabilizing mechanisms in the new species, three scenarios are possible: a) Telomere stabilizing mechanisms are not capable of capping all chromosome ends. In this case a particular branch of the evolutionary tree would come to an end; b) All telomeres are stabilized before chromosomal rearrangements occur, which would result in the preservation of the old phenotype. The population experiences mass mortality during the instability phase, but the species would survive (species A′); c) Pairs of identically rearranged homologous chromosomes in a few individuals and extensive telomere elongation set the stage for a new species (species B).

different tissues of individual (lab) mice (Zijlmans et al., '97) and specific chromosome arms appear to have relatively short telomeres in certain (lab) mouse strains (Hande et al., '99). Humans, too, have a common telomere profile which is conserved during life (Graakjaer et al., 2003). Telomeres on the short arm of human chromosome 17 have been found to be consistently shorter than median human telomere length (Martens et al., '98). The latter is astounding, since loss of 17p alleles, including the tumor suppressor *p53*, is very common in human cancers.

A recent study showed that even between homologous human chromosomes, significant differences in telomere length are frequently observed (Londono-Vallejo et al., 2001). Those differences appear to be stable in vivo, but disappear after prolonged proliferation in vitro. These findings suggest the existence of mechanisms that maintain differences in telomere length between chromosomes in vivo. The authors speculated that those differences are already present in the zygote and are simply perpetuated through uniform telomere shortening and very tight regulation of telomerase activity (Londono-Vallejo et al., 2001).

Formulating the hypothesis

To cap chromosome ends, a short piece of telomeric DNA, just long enough to form the t loop (=functional structure of telomeres), would be sufficient. So, why does mean telomere length differ to such an extent between species, from less than 1 kbp to several 100 kbp? Could it be that telomeres of a particular species get longer or shorter over time? If mean telomere length of an established species changes gradually over many generations, the most realistic option seems to be that telomeres start out long and get shorter.

We have already discussed why telomeres shorten in somatic cells, but in the germ cell line it is generally assumed that high levels of the enzyme telomerase prevent telomeric erosion, stabilizing telomere length of a particular species. However, evidence that telomerase levels might be extremely low in mature germ cells and in fertilized ova support the idea of a temporary end replication problem in the germ cell line. It has been shown for rat, bovine, and human that telomerase is not or is barely active in mature germ cells, although its activity increases dramatically very early during embryonic development (Wright et al., '96; Eisenhauer et al., '97; Betts and King, '99). In rats, the level of telomerase activity is significantly lower (50–fold) in ovulated oocytes than in those of immature follicles (Eisenhauer et al., '97). A loss of telomerase activity during male germ cell differentiation has also been reported for rats (Ravindranath et al., '97). In plants, little or no telomerase activity can be found in seeds, whereas appreciable activity is present in growing root tips of germinating seedlings (Osborne and Boubriak, 2002). Since transcription does not start previous to the first cell division of the fertilized ovum, it is reasonable to assume that telomerase levels cannot be up-regulated during the first S-phase, resulting in a transient end replication problem.

If telomeres become eroded over thousands of generations of a species, what could lead to healing of telomeres? Barbara McClintock has shown in a number of elegant experiments that chromosomal instability, caused by ruptured chromosome ends, persists during meiosis but disappears in the fertilized egg and developing embryo of maize (McClintock, '39; McClintock, '84). Similar results have been reported for wheat, where chromosome healing is probably intrinsic to replication during gametogenesis or early zygote development (Werner et al., '92; Melek and Shippen, '96; Friebe et al., 2001). Consequently, ruptured chromosome ends seem to be capable of activating telomere healing mechanisms during early developmental stages.

Nevertheless, in addition to the healing process, is there any evidence for extensive telomere elongation? The existence of extremely long telomeres (up to 1 Mega base pairs in some birds [Lejnine et al., '95; Delany et al., 2000]) implies that there must be a mechanism which can produce them. Although it is a common feature of plant tissue culture (Osborne and Boubriak, 2002), extensive telomere elongation has not been observed in vivo yet (this is compatible with the rarity of telomere elongation). Indirect evidence for extensive telomere elongation in vivo comes from lab mice. In 1990, when hypervariable ultralong telomeres were discovered in established strains of lab mice, it was assumed that this is a general feature of *Mus musculus* (Kipling and Cooke, '90). Ten years later, it was shown that inbred strains recently derived from wild mice have short telomeres (Hemann and Greider, 2000). To be specific, established inbred and outbred strains of lab mice have exceptionally long telomeres in the range of 30–150 kbp, in contrast to short telomeres of 8–10 kbp seen in

wild mice (Hemann and Greider, 2000). Hence, despite their progenitors' (*Mus m. musculus* and *Mus m. domesticus*) short telomeres, laboratory mice somehow multiplied telomere length (Hemann and Greider, 2000). Since mean telomere length differs greatly between closely related strains (subspecies), those differences must have originated after the split of two species. Hemann and Greider suggested that telomere elongation in established strains of lab mice might have resulted from extensive breeding of an isolated colony. In a more recent paper, Manning and colleagues go even further by claiming that inbreeding, through unknown mechanisms, results in the elongation of telomeres (Manning et al., 2002). This would be in agreement with the current view of how new species emerge. Accordingly, the creation of lab mouse strains over the past 100 years might shed some light on the creation of species in general.

The new hypothesis, as presented here, is based on the assumption that telomeres shorten due to a shortage of telomerase during the first cell cycle of the fertilized ovum in animals and plants (evidence was presented above that this might be so). This mechanism would limit the duration of a species and consequently will be named the 'species clock.' For every generation a supposed shortage of telomerase during the first S-phase may result in a slight decrease of mean telomere length.

Extremely long telomeres (100 kbp and more) have been observed in such distinct species as lab mice, mud puppies, and some birds (Lejnine et al., '95; Hemann and Greider, 2000; Delany et al., 2000). A minimal telomere length of 50 kbp in a new species is feasible, because of interchromosomal telomere length variation and because the shortest, not the longest, telomere is the limiting factor (Hemann et al., 2001). In this hypothetical setting the supposed minimal loss per generation due to a transient end replication problem would not endanger the survival of a species for thousands of years.

Assuming a minimal telomere length of 50 kbp, a telomere loss of 5 bp per generation in humans, and a generation time of 15 years, our species could have survived for 120,000 years without critical shortening of telomeres (10 kbp left). In contrast, a short-lived mammal like *Mus musculus domesticus* with a generation time of only four months (Wilson et al., '77) would remain phenotypically stable for at least 2,670 years (10 kbp left). This is in accordance with the observation that chromosomal speciation proceeds at an extraordinarily high speed in house mice (Nachman et al., '94; Britton-Davidian et al., 2000), although *M. musculus domesticus* seems to be special in this regard (Nachman and Searle, '95; Gazave et al., 2003). Of course, all these rates and numbers are speculative, and future experiments might lead to major adaptations, but the aim of these calculations is to show the impressive potential of this new theoretical model.

However, is the species clock model compatible with the observed telomere length variation between individuals and between chromosomes of an individual? Depending on the initial process of telomere elongation, there are three imaginable sources of variation:

a) If telomere elongation is a result of (in)breeding of an isolated colony (Hemann and Greider, 2000, Manning et al., 2002), it would produce rather uniform telomere lengths in all individuals. Later on, length variation would be the consequence of the species clock operating on the basis of telomere shortening over many generations. Since individuals may have different generation histories (some may have had ancestors who, on average, produced offspring later in life, giving birth to fewer generations over a certain time span) and chromosomes are randomly distributed during Meiosis, some chromosomes would develop significantly shorter telomeres than others after hundreds of generations. The variation produced by this model might be relatively modest, as long as the mechanism is completely random.

b) If telomere elongation is an individual process, subsequent to chromosome healing (McClintock, '39) and not triggered and synchronized by an inbreeding environment, it would result in extensive variation of telomere length between the founder individuals. There would be no length variation between chromosomes of an individual though. Yet, massive telomere length variation between homologous chromosomes would occur in the second generation. Due to the random nature of chromosome distribution in Meiosis, interchromosomal variation would increase for several generations, eventually reaching a plateau. While hypervariable ultra-long telomeres seen in lab mice (=young species) seem to support this model, it is important to keep in mind that contamination may have been a significant factor earlier in the development of established strains of lab mice, when quality control procedures were less refined (Fitch and Atchley, '85). In a small population, just one mouse (with short telomeres) could have gener-

ated extensive telomere length variation. So, someone has to be careful in drawing any hasty conclusions.

c) If the initial telomere elongation process in the founder individuals cannot completely equalize telomeric variation accumulated in the ancestral species, telomere length heterogeneity would be a prerequisite of the new species.

The species clock at work

Over the past 100 years geographic isolation has been considered by far the most common requirement for speciation (=allopatric model). The foundation of this model is reproductive isolation, initially achieved by geographic isolation of a small group of individuals followed by the fixation of genetic and/or chromosomal differences over time, creating independent species. Prevention of gene flow between daughter and parent population is critical. However, even within a small colony, chromosomal (and genetic) mutations without a pronounced heterozygote advantage would occur as temporary polymorphisms only, and would not be able to achieve a homozygous state in a significant number of individuals without intensive inbreeding.

Recent theoretical and experimental work suggests that chromosomal speciation does not rely on geographic isolation (Levin, 2002; Wolfe, 2003; Navarro and Barton, 2003; Rieseberg and Livingstone, 2003), highlighting the importance of chromosomal change for evolution. However, the creation of homozygotes for the new chromosomal rearrangements is essential for the origination of new species. Until now, no compelling model of how pairs of identical rearranged homologous chromosomes occur without intensive inbreeding has been presented.

Barbara McClintock speculated in 'The Significance of Responses of the Genome to Challenge' that some specific genome shock is responsible for origins of new species. ''Our present knowledge would suggest that these reorganizations originated from some shock that forced the genome to restructure itself in order to overcome a threat to its survival'' (McClintock, '84).

The species clock hypothesis predicts critical shortening of telomeres after thousands of years depending on the generation time and the initial telomere length of a species. It is well known that replication-dependent shortening of telomeres beyond a critical threshold induces chromosomal instability. If proliferating cells bypass the Hayflick limit, short and sticky telomeres can lead to numerical and structural chromosome aberrations by forming telomere associations, fusions, and dicentric chromosomes (Artandi et al., 2000, Gisselsson et al., 2001). High mortality in the population induced by chromosomal instability would automatically generate isolated groups; each of them could give rise to a new species.

As mentioned earlier, a common telomere profile has been discovered in humans (Graakjaer et al., 2003) and telomeres on specific chromosome arms tend to be the shortest in all individuals of a species (Slijepcevic, '98; Martens et al., '98; Graakjaer et al., 2003). Accordingly, chromosomal instability would be limited to just a few chromosomes, producing similar or identical aberrations in the germ cells of many individuals simultaneously. The most intriguing example from the cancer field is the frequent involvement of the p-arm of human chromosome 17 in chromosomal aberrations in cancer cells, and the discovery of the p-arm of chromosome 17 having one of the shortest telomeres in normal human cells (Martens et al., '98). The accumulation of identical chromosomal rearrangements in the germ cells of several individuals, due to chromosome-specific short telomeres in a population (Martens et al., '98; Hande et al., '99), would facilitate the combination of identically rearranged homologous chromosomes in the offspring. Supposing that chromosome healing mechanisms can stop the state of chromosomal instability in the gametocytes or early zygotes by stabilizing all telomeres. For long term survival of the species, an initial phase of extensive telomere elongation would be required, which seems to be triggered by some degree of inbreeding, as has been postulated for lab mice (Manning et al., 2002).

Most notably, the species clock model would circumvent the problem of underdominance (=heterozygous disadvantage for a certain chromosomal rearrangement), a part of currently favored models of chromosomal speciation. Those standard models predict that novel chromosomal arrangements must be at a selective disadvantage, when they first appear in a population. The new model, unlike all other speciation models, does not suffer from the problem of competition, because viability of the old species would be diminished due to chromosomal instability.

Depending on the type of chromosomal rearrangement and the telomere stabilizing mechanisms in the new species, three scenarios are possible (Fig. 2):

a) Telomere stabilizing mechanisms are not capable of capping all chromosome ends. In this case a particular branch of the evolutionary tree would come to an end.

b) All telomeres are stabilized (elongated) in a small number of individuals before chromosomal rearrangements occur. This would result in the preservation of the old phenotype. The population experiences mass mortality during the instability phase, but the species would survive.

c) Chromosomal rearrangements create a new phenotype and a new species. In case of a widespread species, where instability-induced mass mortality might generate many isolated groups, the simultaneous creation of several new (sub)-species is feasible.

Clearly, chromosome healing and telomere elongation would be crucial mechanisms for the survival of new species.

Concluding thoughts

In humans, it has been shown that telomere erosion in somatic tissues contributes to numerous forms of age-related pathology, such as impaired wound healing, immunosenescence, cancer, and vascular disease (Kim et al., 2002; Cawthon et al., 2003). Initial telomere shortening followed by chromosomal instability, and finally activation of telomere stabilizing mechanisms, are the hallmarks of cancer cells (DePinho, 2000). Hence a totally destructive and most feared disease such as cancer might be a side effect of a highly creative mechanism of evolution.

It is a major weakness of the mitotic clock model that telomere erosion seems to trigger age-associated diseases in humans, but not in the (lab) mice used in most experiments in cancer research. The common theory is that (lab) mice do not experience any adverse effects from replicative senescence, due to the considerable amounts of telomerase expressed in most somatic tissues, and the extreme length of the telomeres (Artandi et al., 2000). To overcome this obstacle, telomerase knockout mice were created (Blasco et al., '97). Starting at the sixth generation telomeres in these mice become critically short and these animals suffer from age-related diseases, similar to those seen in humans (Rudolph et al., '99; Artandi et al., 2000). This begs the question: Is the only purpose of such a sophisticated biological clock to adversely affect the regeneration potential of tissues in just a few species? The most probable explanation is that this mitotic clock is part of a universal mechanism operating in (the germ cell line of) most species, but the adverse effects of the limited replication potential of somatic cells might occur in 'old species' with short telomeres only.

The publication of an unusual phenomenon observed on a small island off the coast of Great Britain might give us a hint of the species clock at work. In 1987, Parker and Wilby conducted chromosome analyses of 227 plants of the dioecious species (*Rumex acetosa*) collected on Skomer Island and detected extreme chromosomal heterogeneity. They found fourteen different chromosomal polymorphisms; the great majority of these were detected in 67 plants found in a small area (Parker and Wilby, '89), that had experienced a population crash in 1977. This is in stark contrast to the three common chromosomal rearrangements seen on the mainland, although it has to be mentioned that *Rumex acetosa* is known for its cytological heterogeneity, typically involving the Y-chromosome. Fourteen years after the publication of their paper, it would be very interesting to do a chromosomal reanalysis and to measure telomere length in these plants. It might well be that one of these chromosomal variants has taken over and is now dominating on Skomer Island.

When it comes to chromosomal polymorphisms, one of the best studied animals is the house mouse, *M. m. domesticus*. The ancestral karyotype consists of 40 acrocentric chromosomes. Over the last several thousand years, it has undergone major chromosomal changes resulting in over 40 distinct chromosomal races (Nachman and Searle, '95). The new races are mainly a result of robertsonian fusion of two acrocentrics forming a metacentric chromosome. Intriguingly, telomeres on the p-arms (getting lost during fusion) appear shorter than telomeres on the long arms of mouse chromosomes (Slijepcevic, 98). Numerous chromosomal analyses in a large number of individuals would be required to study the degree of chromosomal polymorphisms and the occurrence of chromosomal instability in many species. Unfortunately, cytogeneticists are a dying species (not related to telomeres, of course), since current science has entirely focused on DNA sequence and genes.

A well-known downside of the gradualistic model of slow, steady change by natural selection acting on genetic variation is that it cannot account for rapid transitions, catastrophic extinctions and spectacular radiations. Consequentially, these observations had long been attributed to the

imperfection of the fossil record (Gould and Eldredge, '93). In 1972, Eldredge and Gould offered an alternative interpretation for the mysterious paleontological observations. In their view, evolution proceeds through periods of stasis followed by periods of rapid evolution (punctuated equilibrium) (Gould and Eldredge, '93). Accordingly, species are rapidly established in periods of instability and resistant to essential changes thereafter (Gould, '82). Since gradualists have always had a hard time explaining long-term phenotypic stability, Gould suggested that the answer to stasis could come from internal genetic regulatory mechanisms (Gould, '82).

As long ago as 1897, the great paleontologist Alpheus Hyatt claimed that evolutionary lineages had periods of rise (epacme), expansion (acme), contraction, and extinction (paracme), comparable to an individual's passage through the cycles of youth, maturity, old age, and death. He was convinced that decline and extinction are programmed into the history of species (Hyatt, 1897). Gradual telomere shortening to a critical threshold followed by populationwide chromosomal instability, and the sporadic creation of new stable karyotypes in the offspring due to chromosome healing may be the internal (genetic) regulatory mechanisms Gould and Hyatt were looking for.

Numerous chromosomal rearrangements have been observed between closely related eukaryotic species (O'Brien et al., '99; Eichler and Sankoff, 2003), all these various types of aberrations can theoretically be caused by dysfunctional telomeres (Feldser et al., 2003). Emerging evidence suggests that evolutionary diversity arises mainly from changes in gene expression (Levine and Tjian, 2003). Accordingly, chromosomal aberrations modify the expression rates of numerous genes instantaneously (Phillips et al., 2001), and provide an ideal mechanism for a significant phenotypic change, which would otherwise require the occurrence of many mutations. Indeed, the species clock model can explain the punctuated patterns of speciation seen in the fossil record of higher organisms, but it would be fatal to disregard the gradualistic model of speciation. Certain microfossil groups (unicellular eukaryotes like radiolaria, diatoms, and foraminifera) frequently show gradualistic patterns of speciation (Benton and Pearson, 2001), yet, future research may show that most of these organisms have circular chromosomes, without telomeres.

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