

# Unravelling the secrets of ageing

Telomeres were first thought to have a role in ageing more than 30 years ago. **Susan Mayor** investigates if the theory has translated into clinical research

**E**vidence is growing that every chromosome in the body carries a marker that counts down from the day of birth to death, rather like a cellular sand clock. These biological timers are telomeres—repeat sequences of DNA that, together with associated proteins, cap the ends of chromosomes and protect them from degradation, just as the plastic coating on the ends of shoelaces stops them from fraying.

Research has shown that telomeres shorten with each cell division, gradually marking off the time to cell death.<sup>1</sup> This shortening is accelerated in diseases associated with ageing—particularly cardiovascular disease and cancers—and in the presence of risk factors for these diseases such as obesity and high blood pressure. The hope for the future is that measurements of telomere length could be used to detect early disease, allowing preventive measures to be put in place, and eventually that methods will be found to slow or even reverse the shortening.

## Telomeres and ageing

Telomeres are made up of a large number of tandem repeats of the sequence TTAGGG. The enzyme DNA polymerase cannot

fully replicate the 3' end of linear DNA, so telomeres shorten progressively with each repeated cell division. Laboratory studies have shown that the telomere length of replicating cells is inversely correlated with age.

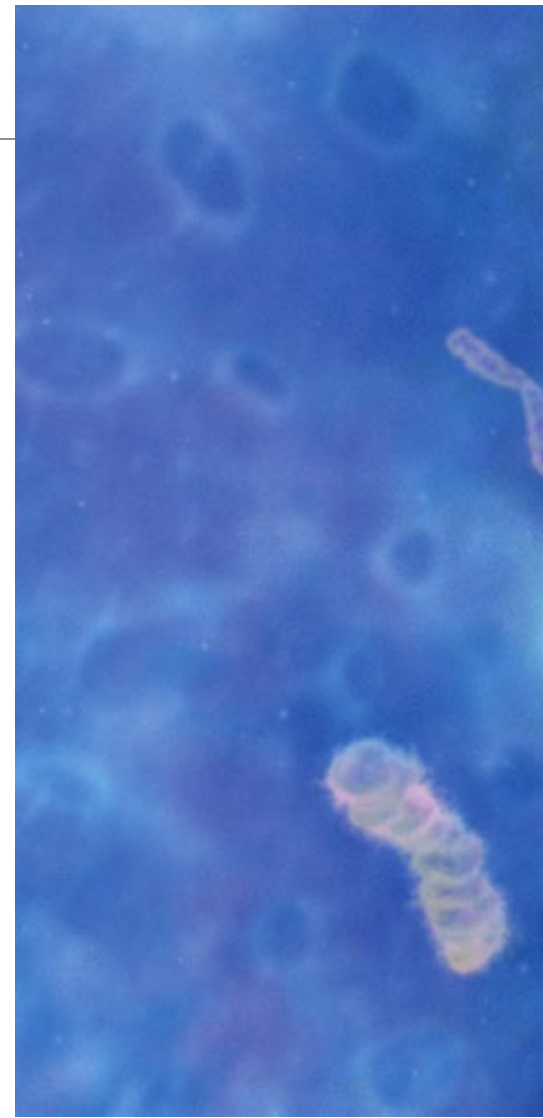
More than 30 years ago, Olovnikov proposed that this shortening could provide a mechanism for a biological clock that determines cell behaviour.<sup>2</sup> This theory—sometimes referred to as Olovnikov's clock—has subsequently been supported by in vitro and clinical research. "It sounds like science fiction, but more and more studies are showing that telomeres signal cellular ageing," explains Annette Fitzpatrick, research associate professor at the University of Washington in Seattle.

"The full extent of telomere function is not fully understood, but they are involved in some way in the maintenance of cellular stability," says Nilesh Samani, British Heart Foundation professor of cardiology at the University of Leicester and a leading researcher in the field.

Telomere length is essentially a measure of biological age, which may be more useful for understanding variations in the age of onset of disease than chronological age, he argues. This may partly explain why women live longer than men in most societies, as they generally have longer telomeres.

## Effect of disease

Studies have shown that telomere shortening is associated with several age related conditions, including cardiovascular disease, diabetes, and vascular dementia. "We know that people with specific diseases



"Telomere length is essentially a measure of biological age"

have shorter telomeres than people of the same age without that disease," explains Dr Fitzpatrick.

Associations with telomere length have been reported for several disease risk factors, including hypertension, insulin resistance, obesity, and atherosclerosis. Shorter telomeres have also been found in women under chronic, severe stress.

Blood samples collected during major epidemiological and clinical trials are proving a rich hunting ground for information on telomeres and disease risk. Telomeres isolated from leucocytes are measured and the length compared between disease cases and controls.

Professor Samani's group has shown that average telomere length is shorter in people who have had a myocardial infarction before the age of 50 years than in controls matched for age and sex. Telomeres are also shorter in patients with severe triple vessel coronary artery disease than in people with angiographically normal coronary arteries.

## KEY TERMS

**DNA polymerase**—The enzyme that replicates DNA

**3' end of linear DNA**—The two ends of a single strand of DNA are called 3' (prime) and 5'. DNA is synthesised from the 5' to 3' direction

**Oxidative stress**—The level of oxidative damage in a cell caused by reactive oxygen species such as free radicals



Many of these data are from cross sectional studies so shorter telomere length could be a consequence of coronary heart disease, rather than being a primary abnormality. However, a recent prospective study also showed a link. The West of Scotland Primary Prevention Study analysed telomere length in blood samples taken from 484 middle aged men at high risk of coronary heart disease who were randomised to a statin or placebo.<sup>3</sup> Mean telomere length decreased by 9% per decade in men who had coronary events and in those who did not, confirming telomere shortening with ageing. But men with shorter telomeres at baseline had a higher risk of events than those with longer telomeres. In the placebo group, the risk of coronary heart disease was almost double in the lower two tertiles of telomere length compared with those in the highest tertile.

“Our findings support the hypothesis that differences in biological ageing might contribute to the risk—and variability in age of onset—of coronary heart disease,” Professor Samani said. He noted that the risk of coronary heart disease associated with shorter

telomeres was at least comparable to, if not greater than, that associated with established risk factors. At recruitment, men who developed coronary heart disease had leucocyte telomeres that on average were of similar length to those of men without disease who were six years older, despite the narrow age range (45-64 years) of participants.

The findings suggest that the association of shorter telomeres with coronary heart disease is not simply a consequence of the disease. “Our view is that telomere length might bring together several different factors that impact on disease, acting as a unifying marker. In the future, we may be able to use telomere length as an integrated marker for different risk factors for coronary heart disease,” Professor Samani predicted.

The study also showed that the increased risk associated with shorter telomeres was substantially attenuated in patients treated

with a statin. The mechanism of this effect was independent of effects on lipid levels or markers of inflammation. In future, he

**“In the future, we may be able to use telomere length as an integrated marker for different risk factors for coronary heart disease”**

suggested that measuring leucocyte telomere length could identify people who would benefit most from statins.

Research has also shown that telomere instability may be important in cancer.

A recent study found significantly shorter telomeres in breast cancer tissue than in adjacent tissue from women with breast cancer.<sup>4</sup> Telomere shortening was greater in more aggressive tumours. A further study found that telomeres were significantly shorter in people with bladder, head and neck, lung, and renal cell cancers compared with healthy controls.<sup>5</sup>

#### **Inflammation**

The biological mechanisms underlying telomere shortening are generally thought to be oxidative stress and inflammation.

Increased oxidative stress has been shown to increase rates of telomere shortening in vitro. Using this theory to explain the results his group saw in the west of Scotland study, Professor Samani noted that coronary heart disease is a chronic inflammatory process, with oxidative stress contributing to atherosclerosis. “The risk associated with conventional risk factors for coronary artery disease, such as hypertension, smoking, and diabetes, could also be partly mediated through increased telomere attrition from oxidative stress.”

A study of older people participating in the US Cardiovascular Health Study supports this hypothesis.<sup>6</sup> Results showed that shorter telomere length was associated with diabetes, blood glucose and insulin concentrations, diastolic blood pressure, thickness of the carotid intima-media, and interleukin-6 concentrations.

**Slowing down the rate of shortening**

The holy grail in telomere research is determining whether modifying the rate of shortening could slow, or even reverse, ageing. Even lifestyle factors may influence the rate of telomere shortening. A recent study of more than 2000 twins from the UK Adult Twin Registry found those who were physically active during their leisure time had longer telomeres than their sedentary peers (P<0.001).<sup>7</sup>

Results showed that, on average, telomeres lost 21 nucleotides every year. But the average telomere length in people who took the least amount of exercise—16 minutes of physical activity a week—was 200 nucleotides shorter than in those who took the most exer-

cise—just over three hours of physical activity a week. The most physically active people had telomeres the same length as those of inactive people who were up to 10 years younger.

The researchers acknowledged the paradox that exercise increases oxidative damage but suggested that physical activity might protect by up-regulating anti-inflammatory processes.

In an accompanying editorial, Jack Guralnik, from the US National Institute on Aging, cautioned that more work was needed to show a direct relationship between ageing and physical activity.<sup>8</sup> “A great deal of research has been done on telomere length in the past few years, and exactly what it tells us is still being argued.”

He pointed out that people who exercise regularly may be different from those who are sedentary in many ways, although the twin study controlled for some of these variables, including body mass index and smoking. “Nevertheless, this research serves as one of many pieces of evidence that telomere length might be targeted in studying ageing outcomes,” he said.

Drug companies and other research organisations are already working on a wide range of compounds with the aim of developing drugs that can slow telomere shortening. The enzyme telomerase is able to repair and extend telomeres, representing a good target for extending biological age.

There is cautious optimism that telomere length and rates of shortening provide useful markers of biological ageing. “Age adjusted telomere length is highly variable, highly

heritable, longer in women than men, and shorter in people who harbour a host of age related disorders, whose common denominators may prove to be increased oxidative stress and inflammation,” noted Abraham Aviv, from the Cardiovascular Research Institute at the University of Medicine and Dentistry of New Jersey.<sup>9</sup> However, he concluded, “It is unsettled whether human telomere dynamics is only a proxy for fundamental mechanisms that govern the course of aging or a key determinant in its progression.”

Susan Mayor is a freelance journalist, London  
susanmayor@mac.com

Competing interests: None declared.

- 1 Allsopp RC, Chang E, Kashefi-Aazam M, Rogaev EI, Platyszek MA, Shay JW, et al. Telomere shortening is associated with cell division in vitro and in vivo. *Exp Cell Res* 1995;220:194-200.
- 2 Olovnikov AM. A theory of marginotomy. *J Theor Biol* 1973;41:181-90.
- 3 Brouillette SW, Moore JS, McMahon AD, Thompson JR, Ford I, Shepherd J, et al. Telomere length, risk of coronary heart disease, and statin treatment in the west of Scotland primary prevention study: a nested case-control study. *Lancet* 2007;369:107-14.
- 4 Poonepalli A, Benerjee B, Ramnarayanan K, Palanisamy N, Choudary Putti T, Hande MP. Telomere-mediated genomic instability and the clinico-pathological parameters in breast cancer. *Genes Chromosomes Cancer* 2008;47:1098-109.
- 5 Wu X, Amos CI, Zhu Y, Zhao H, Grossman BH, Shay JW, et al. Telomere dysfunction: a potential cancer predisposition factor. *J Natl Cancer Inst* 2003;95:1211-8.
- 6 Fitzpatrick AL, Kronmal RA, Gardner JP, Psaty BM, Jenny NS, Tracy RP, et al. Leukocyte telomere length and cardiovascular disease in the cardiovascular health study. *Am J Epidemiol* 2007;165:14-21.
- 7 Cherkas LF, Hunkin JL, Kato BS, Richards JB, Gardner JP, Surdulescu GL, et al. The association between physical activity in leisure time and leukocyte telomere length. *Arch Intern Med* 2008;168:154-8.
- 8 Guralnik JM. Successful aging. Is it in our future? *Arch Intern Med* 2008;168:131-2.
- 9 Abraham A. Telomeres and human aging: facts and fibs. *Sci Aging Know Environ* 2004;51:43.

Cite this as: *BMJ* 2009;338:a3024

## BMJ/MSF Christmas appeal

Last year the *BMJ* launched its first Christmas appeal and is calling on readers to support our chosen charity, Médecins Sans Frontières. MSF seemed the obvious choice for our first Christmas appeal. We hear—and indeed report—ever more tragic stories of people around the world caught up in conflict and political unrest, including Zimbabwe and the Democratic Republic of the Congo (right). It’s important to know that MSF is there, delivering medical care and expertise to people in direst need in some of the toughest places on earth. MSF’s staff and volunteers deal daily with extraordinary personal risks and practical clinical challenges. I hope readers will feel inspired to support this unique charity in whatever way they can.

Fiona Godlee, editor, *BMJ*



To donate, please visit [www.msf.org.uk/bmjappeal](http://www.msf.org.uk/bmjappeal)



KAREN PRINSCLOPPA