Editorial Foreword

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The impact of telomeres and telomerase in cellular biology and medicine: it's not the *end* of the story

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In 2009, Elizabeth H. Blackburn, Carol W. Greider and Jack W. Szostak were jointly awarded the 100th Nobel Prize in Medicine or Physiology for their discovery of 'how chromosomes are protected by telomeres and the enzyme telomerase' [1]. This prize appropriately recognized the substantial merits of the vast array of research and discoveries produced by these investigators and their predecessors (including several Nobel Laureates) who set out to understand the function of telomeres, their maintenance and their role in cellular and organismal processes. Indeed, the recent findings by Ronald DePinho and colleagues on the effects of reversing the degenerative signs of aging in mice by reactivating telomerase further highlight the impact of telomeres and telomerase in health and medicine [2].

The chronicles of telomeres and telomerase began with investigations into how cellular lifespan is controlled. In the early 1900s, Alexis Carrel (awarded the Nobel Prize in 1912) observed the continuous growth of mammalian cells in culture and suggested that aging is 'an attribute of the multicellular body as a whole' [3]. In 1961, Hayflick and colleagues observed that normal diploid cells have a finite replicative capacity (termed Hayflick limit) and further showed in 1975 that the control centre for mitosis is located within the nucleus of the cell [reviewed in 4]. But the nature of the replication clock remained a puzzle.

In the 1930s, Hermann Muller (Nobel Prize in 1946) and Barbara McClintock (Nobel Prize in 1983) made the astute observations that the ends of chromosomes protected the chromosomes from fusing together [3, 4]. Muller coined the term 'telomeres' (from the Greek *telos* for end and *meros* for part) to described the ends of the chromosomes [1]. In 1972, James D. Watson (Nobel Prize in 1962) poised the 'end replication problem' in which the 3′ ends of linear duplex DNA cannot be completely replicated by DNA polymerase machinery. Around the same time, Alexy Olovnikov made the connection between the end replication problem and Hayflick's limit. Olovnikov predicted that cells have a special mechanism to permit maintenance of chromosome ends which prevented the end replication problem (and cellular aging) [4]. Finally, the advent of modern molecular and cellular biology techniques allowed the connection between Muller's and McClintock's findings and Watson's and Olovnikov's ideas to be understood at the molecular level. These new findings ultimately defined the importance of telomeres in cellular lifespan, and perhaps also in whole organismal health.

In the late 1970s and 1980s, Elizabeth Blackburn mapped the repetitive DNA sequences at the ends of chromosomes (telomeres) of simple organisms [1, 3, 4]. The repetitiveness of these sequences were later shown to be not only evolutionary conserved across multiple organisms, but that they were essential for relevant for chromosome integrity. Blackburn collaborated with Jack Szostak to show that these telomeric sequences from one organism (*Tetrahymena*) protected linear DNA molecules from degrading when introduced into cells of another organism (yeast). We now understand that telomeres are protected by multiple associated proteins and in mammals this complex has been termed shelterin [5]. Furthermore, the newly seeded telomeres in yeast built on the *Tetrahymena* repeat templates were longer. This led to the hypothesis that a telomere-synthesizing enzyme (*i.e.* telomerase) existed.

Since the cloning of one component of telomerase (*i.e.* its RNA template used for new repeat addition) in 1985 by Elizabeth Blackburn and her then graduate student Carol Greider, the field of telomere biology has vastly expanded [1, 3, 4]. Tom Cech (Nobel Prize 1989) cloned the catalytic component of the enzyme telomerase and others have shown that telomerase is a complex consisting of many other proteins regulating it structure and function. With the discovery of their sequences, telomere length and telomerase expression or activity can now be measured and these measurements can be used as tools for diagnostics and physiological association studies. For example, there is now strong evidence of the association of telomere shortening or dysfunction, replication potential of cells, and increased risk of several age-related diseases [2, 6, 7]. Moreover, the evidence for a link between telomeres and cellular lifespan was obtained when the catalytic component of

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telomerase was introduced into normal human cells that ordinarily lack telomerase and these cells bypassed the Hayflick limit of cellular aging [8]. Ever since McClintock's ground-breaking discoveries in maize, further investigations into telomere function in plants and other model organisms continue to aid in our basic understanding of how telomeres function in cells [9].

For modern medicine another key discovery has been the finding that telomeres are maintained in cancer cells which facilitates their immortal status [reviewed in 1]. This has led to investigations into how telomerase is normally active only in germ cells and stem-like cells yet repressed in most of our somatic cells. The possibility that the telomere maintenance pathway could be a target in cancer has also been investigated by multiple laboratories.

The impact of these discoveries on modern medicine is becoming better understood. Given the accumulating new evidence on the role of telomeres in cellular biology and human health, it is timely to conduct a review series on telomeres and telomerase hosted by the *Journal of Cellular and Molecular Medicine*. In this review series, several researchers assess the current status and future perspectives of the field, ranging from telomere replication, diagnostics, molecular genetics, genetic diseases associated with dysfunctional telomerase and therapeutic targeting of telomeres and telomerase for age-related diseases such as cancer. Even though telomeres and telomerase have been studied for decades, the field is continually producing novel breakthroughs that have significant potential to influence human health and treatment. Therefore, we have not seen the *end* of the telomere and how it can have an effect on biology and medicine.

Conflict of interest

The author confirms that there are no conflicts of interest.

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