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Premature aging

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Introduction

The aging process has long been a source of fascination, not least because we are all aging throughout adult life. Several theories have been put forward to explain why we age, incorporating intrinsic, extrinsic and stochastic causes, and these are by no means mutually exclusive [1]. Animal models have been useful in identifying cellular and molecular mechanisms that underlie the aging process, with two striking examples being the roles of caloric restriction [2] and the insulin-like signalling pathway [3]. Another approach to the study of aging is to investigate the naturally occurring human syndromes that cause premature aging. These diverse conditions often illustrate an intriguing relationship between the aging process, maintenance of the genome, and the prevention of cancer [4]. Although the study of premature aging encompasses many factors, this short commentary will focus on the role of telomeres and telomere maintenance.

Telomeres, senescence and aging

To senesce is to deteriorate with age, but at the cellular level it implies a permanent end to cell division. In considering this process, it is helpful to distinguish between replicative senescence and stress-induced senescence [1]. Both result in cell cycle arrest, but while the former implies an intrinsic limit to cell proliferation, the latter is more akin to a defence mechanism whereby the cell exits the cell cycle in response to a variety of stressors, including DNA damage. Apoptosis and cell death may follow. The relative extent to which these two processes contribute to the aging of the organism is still a matter for debate [5].

Nevertheless, it is widely accepted that the main trigger of replicative senescence in human cells is the progressive shortening of the telomere with each round of cell division. Telomeres are specialised structures that cap the ends of each chromosome, consisting typically of 5–15 kb of a TTAGGG DNA repeat sequence, bound by a specific group of proteins known as the shelterin complex [6]. They terminate in a single-stranded G-rich overhang that folds back on itself, invading the double-stranded telomeric DNA to form a T-loop. However, these are clearly dynamic structures and the end in particular can be in either a capped or uncapped state [7]. Telomeres shorten with each cell division due to the inability of the DNA polymerase to fully replicate the chromosome end, known as the end replication problem [8]. This effect can be observed in tissue culture [9], and the suggestion is that telomeres act as a ‘mitotic clock’, counting and limiting the number of times a cell can divide [10]. DNA damage and the dangers of uncontrolled proliferation will accumulate with time, and so this limit to cellular lifespan can be seen as a way in which the risk of cancer is reduced.

It is important to bear in mind that oxidative damage can also be a significant cause of telomere shortening [11]. But whichever mechanism is involved, critically short telomeres will trigger a DNA damage response, not dissimilar to that involved in double-strand break repair, with telomeric damage foci being clearly visible in senescent cells [12]. In order to avoid this senescent state, most cells that undergo

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multiple rounds of cell division activate a complex called telomerase [13], which is able to maintain or lengthen telomeres by means of a reverse transcriptase (TERT) and an RNA template (hTR). Telomerase can be seen to be active in stem cells, germ cells and indeed in nearly all cancer cells [14]. TERT itself has been shown to immortalise cells in vitro [15]. In vivo experiments in mice have shown that ectopic expression of TERT leads to an increased incidence of cancer, although an increase in lifespan can be observed when these cancers are suppressed [16].

In some cases, telomere length can be maintained by a telomerase-independent mechanism, known as the alternative lengthening of telomeres (ALT) pathway [17]. Although the precise mechanism of ALT remains unknown, it is likely to involve the synthesis of telomeric DNA by recombination-mediated DNA replication, and it is often associated with heterogeneous and rapid changes in individual telomere lengths.

While telomere shortening is clearly implicated in limiting the lifespan of somatic cells, its role in aging of the organism overall is not so well established [18]. However, a suggestion that it does play a general role in organismal aging comes from the study of the rare bone marrow failure syndrome, dyskeratosis congenita, in which defective telomere maintenance gives rise to premature aging.

Dyskeratosis congenita

Dyskeratosis congenita (DC) is a multisystem disorder with a very broad range of clinical presentation. Classically, the disease is defined by a triad of mucocutaneous features: nail dystrophy, abnormal reticulate skin pigmentation and leukoplakia; the principal cause of death is bone marrow failure [19]. However, it has become clear through genetic analysis that the syndrome can also present at a very young age with life-threatening immunodeficiency and cerebral hypoplasia and failure to thrive, or much later in life, with a presentation of idiopathic aplastic anaemia or pulmonary fibrosis [20, 21]. Significant features of aging include premature greying and loss of hair, an elevated risk of cancer (notably an early presentation of epithelial tumours), nail ridging and dystrophy, and a hypocellular bone marrow.

Despite its clinical and genetic heterogeneity, the unifying feature of this disease is that all cases characterised to date are due to a primary defect in telomere maintenance. The first suggestion that telomere maintenance was the key to this disorder came from analysis of patients with the X-linked form of the disease. Cells from these patients which have mutations in the protein dyskerin, a core component H/ACA small nucleolar ribonucleoproteins [22] and of the telomerase complex [23], were shown to have reduced levels of telomerase RNA and short telomeres [24]. Subsequently, patients with autosomal dominant forms of the disease were found to have mutations either in the RNA component or the reverse transcriptase component of telomerase [25, 26]. More recently, a component of the shelterin complex (TIN2) has been found to be mutated in a severe, often sporadic form of the disease [27].

Together, these studies indicate that abnormal telomere homeostasis can lead to symptoms of premature aging. It is noticeable that the tissues that bear the brunt of the pathology in DC are those that are turning over the most rapidly. This is consistent with the idea that erosion of telomeres has its greatest effect in the stem cell pool, and that telomere-dependent replicative senescence can contribute to tissue and organismic aging.

Telomere length defects in other progeroid syndromes

Although DC displays several features of premature aging, they are not as dramatic as those observed in other more classical progeroid syndromes such as Werner syndrome (WS) and Hutchinson–Gilford progeria syndrome (HGPS). These diseases are often referred to as segmental progeroid syndromes, as each one will display some but not all of the features of normal aging [28]. In WS, clinical features are usually first recognised around adolescence and include scleroderma-like skin changes, predisposition to diabetes and cancer and premature arteriosclerosis; a bird-like face with a beaked nose is characteristic. The gene mutated in WS encodes a protein that is a member of the RecQ family of helicases and which has both helicase and exonuclease activity [29]. It is involved in DNA metabolism and repair, in particular homology-dependent recombinational repair as well as telomere maintenance. Accelerated telomere shortening has been observed in WS [30] possibly due to a role of the WRN protein in making telomeres accessible for replication and/or repair [31]. In mouse models of WS, telomere attrition has been directly implicated in the pathogenesis of the disease [32].

HGPS is the most severe progeroid syndrome, and although affected individuals appear normal at birth, the median age of death is about 13 [33]. Features of the disease include alopecia, atherosclerosis, scleoderma, nail atrophy and skin hyperpigmentation [28]. The disease is most frequently caused by aberrant splicing of the *LMNA* gene that encodes A-type nuclear lamin [34, 35]. In addition to maintaining the nuclear envelope, lamins are involved in the regulation of transcription and cell-cycle control, and cells from HGPS patients show signs of activated DNA-damage response. Telomeres are short in fibroblasts from HGPS patients [10]; reasons for this are not well established, although recent studies indicate that the mutant lamin is directly involved [36].

In two other progerias that display shortened telomeres, ataxia telangiectasia (AT) and the Nijmegen breakage syndrome (NBS), the primary defects lie in a failure of DNA repair. However, the NBS DNA repair complex has also been shown to localise to telomere ends where it may play a role in T-loop formation [37], and it has been suggested that NBS is a required accessory protein for the extension of telomeres [38]. But, as in AT, an increased chromosome instability resulting from ineffective repair of double-strand DNA breaks can eventually lead to shortened telomeres through repetitive chromosome fusion and breakage [39].

What is striking about these disorders is that the recurring theme of shortened telomeres is associated with shared progeroid phenotypes [40]. However, the extent to which these mimic the normal aging process remains a debateable issue. Two important differences need to be noted: firstly that the symptoms in the progerias are usually more severe, and secondly that they do not necessarily appear in the same order [40].

The majority of the work described in this short review focuses on the role of telomere shortening in inducing cellular senescence, and how abnormally fast telomere shortening can lead to premature aging. But it is also important to consider how the progressive accumulation of senescent cells contributes to the aging of the tissues in which they reside and the aging of the organism as a whole. We can envisage two distinct mechanisms [41]: firstly that aging results simply from a loss of proliferative capacity, and secondly that the accumulation of senescent cells, with their specific changes in function, morphology and gene expression, alters the tissue microenvironment in a way that promotes aging. In a model in which human skin is reconstituted, it has been shown that an increased proportion of senescent dermal fibroblasts caused an increase in fragility and subepidermal blistering, reminiscent of skin in the elderly [42]. In another study, the senescence of vascular smooth muscle cells was induced in rat carotid arteries [43]. This resulted in vascular inflammation and features of atheroma in the affected arteries, and therefore demonstrates a link between senescence and one of the hallmarks of aging.

Concluding remarks

The aging process is clearly linked to the consequences of wear and tear and our ability to deal with them. It is not surprising therefore that a common theme among premature aging syndromes is that they are caused by defects in the pathways involved in genome maintenance. And one important aspect of this is the maintenance of telomeres. The fact that telomere length is a major factor in determining cellular lifespan is widely accepted, but in the lifespan of the organism the role is less clear. It has been suggested that anticipation of symptoms in dyskeratosis congenita is associated with progressive telomere shortening through the generations. This is consistent with mouse models of telomerase deficiency and could result from an impaired ability to reset telomere lengths in the germ line. It would also imply that the inherited telomere length might be a contributing factor in determining the rate of onset of age-related symptoms. However, it is also clear that the aging process is a complex one, and telomere maintenance is likely to be one of many interacting genetic and environmental factors. Despite this complexity, the examples discussed above show that our level of understanding of the processes involved in aging is increasing so rapidly that it is not unreasonable to speculate that we will one day be able to use this knowledge to intervene and prolong human life.

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