Short telomere syndromes, premature ageing syndromes, and biological ageing

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A new family of premature ageing syndromes has been identified and described in recent years and collectively referred to as short telomere syndromes (STS).[1] These syndromes are the result of mutations affecting a set of genes involved in the synthesis and maintenance of telomeres. Defects in one or more of these genes can cause accelerated telomere shortening and result in dysfunction of multiple organs. Patients affected by these syndromes present with premature greying of the hair, idiopathic interstitial pneumonia, bone marrow failure, cryptogenic cirrhosis of the liver, nodular regenerative hyperplasia with portal hypertension, and immune dysfunction. Dyskeratosis congenita is an inherited disorder seen in paediatric patients that represents one variant of STS, and is characterised by abnormal skin pigmentation, nail dystrophy, oral leukoplakia, and progressive bone marrow failure.[1] Short telomere syndromes are probably the most prevalent among the various premature ageing syndromes, and are probably underdiagnosed at present. One important point that is emerging from the study of premature ageing syndromes is that mutation in genes that impact DNA replication and repair leads to syndromes that mimic, but only partially, the process of "normal" ageing. This is true for mutations in genes that regulate telomeric mechanics and cause STS, as described by the work of Mangaonkar et al[1] and also for Werner syndrome (where the mutations affect a DNA helicase involved in DNA replication and repair[2]) and for progeroid syndromes such as Hutchinson-Guilford syndrome[3] (where the mutations affect the Lamin A gene, coding for a structural protein that is nevertheless important for the replication mechanics of the cell). All these syndromes display gene mutations that affect different parts of the replicative mechanisms of the eukaryotic cell, and yet they all lead to a clinical effect of pathologies suggesting accelerated ageing. Taken together these data strongly suggest that the process of "normal" biological ageing must be strongly influenced by dysfunction in the process of DNA replication and cell division. This, however, has nothing to do with replicative senescence and the Hayflick limit, which was described by Leonard Hayflick[4] when he observed that WI-38 (the human fibroblast cell line used for the study of cellular senescence) have a finite replicative capacity during cell culture in vitro. Hayflick's observation did not take into account the existence of stem cells (and did not account for their own replicative potential) but only considered the replicative potential of fully differentiated somatic cells, such as fibroblasts.[4] Because of this, the Hayflick limit is not very meaningful in terms of the ageing process of the entire organism: it does tell us that the differentiated somatic cells are mortal but does not tell us anything about the lifespan of somatic stem cells. In turn, these stem cells can give rise to newer generations of differentiated somatic cells when they replicate, and each of these "new" differentiated cells can potentially divide up to about 56 times, as predicted by the Hayflick limit.[4]

However, the mutations that cause premature ageing syndrome suggest that somatic stem cells are themselves not immortal (ie, their DNA replication and repair mechanisms may be different from those of the stem cells of the germline, which are obviously immortal, since they are able to regenerate a new organism after reproduction has taken place). Premature ageing syndromes demonstrate that, when somatic stem cells cannot adequately replace the differentiated cells of the tissues and maintain homeostasis, then a process closely resembling premature ageing occurs. It is therefore plausible that during normal physiological ageing, somatic stem cells drive the development of the organism to a certain adult size, but once this is attained, the stem cells become gradually less able to repopulate the tissues with fresh differentiated cells to replenish the losses caused through wear and tear and may eventually become quiescent or dormant and only reactivate in case of a wound or injury that needs to be repaired. Thus, the organism as a whole would gradually lose the ability to maintain homeostasis in its tissues, as described by Sharpless and DePinho[5] in more detail. As an example, it is now well known that the cellularity of the human bone marrow decreases markedly with age,[6] with adipose tissue tending to replace stem cells as the individual ages. It is still debated, however, if clinical dysfunction results from this decrease in the bone marrow complement of stem cells.[6] Anaemia is certainly very common among older adults,[7] but it is not clear if this correlates with the decrease in the cellularity of the bone marrow. Many animals that exhibit negligible

senescence keep growing throughout their life,[8] showing that for continued homeostasis, the stem cells need to continue to drive the growth of the organism without arresting when a certain adult size is reached. The clinical significance of STS is that these conditions can explain at least a proportion of cases of idiopathic interstitial pneumonia and also can account for some cases of immunodeficiency which were hitherto unexplained.[1] In conclusion, STS represent a new family of premature ageing syndromes which is currently underdiagnosed, and which can help us unravel the molecular mechanisms that underpin normal biological ageing.

Author contributions

The author contributed to the concept of the study, acquisition and analysis of the data, drafting of the article, and critical revision for important intellectual content. The author had full access to the data, contributed to the study, approved the final version for publication, and takes responsibility for its accuracy and integrity.

Conflicts of interest

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