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Editorial

Stem Cell Maintenance and the Imperative to Understand Telomerase Regulation

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Telomerase is an essential component of reproduction, development, and maintenance of genomic stability in organisms with linear chromosomes. Since the discovery of telomerase 30 years ago, research dedicated to understanding the roles of this ribonuclear enzyme from the molecular level to its impact on lifespan has grown into a thriving global community.

Telomerase-dependant telomere extension has been extensively explored, and the importance of telomerase in the maintenance of self-renewal capacity in embryonic and adult stem cells is so well appreciated that no respectable modern publication claiming to demonstrate the discovery of a novel stem cell is complete without evidence of telomerase activity. However the regulation of telomerase, and particularly the activity-limiting component TERT, has yet to be worked out in detail.

Current understanding of hTERT transcription was recently reviewed by Daniel and colleagues [1]. The regulation of hTERT is governed by multiple factors through trans-activation mediated by the zinc-finger transcription factors GC-box binding Sp1, and CCCTC-binding factor CTCF, in general for up- and down-regulation respectively. These factors bind the promoter region of hTERT and modify local chromatin structure by histone acetylation and methylation leadings to changes in TERT expression, and subsequently, telomerase activity. In addition, a number of oncogenic transcription factors have been associated with increases in hTERT expression, and conversely tumor suppressor transcription factors with a decrease i.e. the c-Myc [2] and TGF-β [3] pathways respectively. The elevated telomerase activity common to the majority of human cancers fueled studies that led to these findings, and thus the relationship of these classes of transcription factors with telomerase is not surprising. However, cancer is by nature abnormal. Therefore whilst the genomic sites and mechanisms of regulation of TERT elucidated by the study of carcinoma-derived cells are instructive, it does not necessarily inform us about factors involved in homeostatic TERT transcriptional control. An apt demonstration of this is repression in cancer cells and promotion in normal somatic cells of hTERT by the same members of the E2F transcription factor family [4].

Little published work has explored the factors and functions of TERT regulators in healthy models for development and homeostasis, especially in stem cells. Previously we demonstrated that the low oxygen tension responsive protein hypoxia inducible factor 1 alpha (HIF1α) is a regulator of the telomerase catalytic subunit gene TERT in murine embryonic stem cells (ESC) [5]. This interaction was discovered using a knockdown screening approach that monitored for changes in the expression of TERT and activity of telomerase. Hif1α had previously been shown to have a role in the upregulation of hTERT [6], but since it also stabilizes the TERT repressor p53 [7] the relationship between Hif1α expression and TERT regulation is by no means clear. Since the inner cellular mass of the blastocyst from which ESC are derived receive oxygen by diffusion, it is assumed to be a relatively hypoxic environment, and Hif1α expression could be reasonably anticipated. Following implantation, extensive vascular networks are formed within the embryo, and the most critical period of telomerase-dependant telomere extension has passed. Leading to the question, does Hif1α have a relevant role to play in telomerase regulation later in development, and in adult stem cells? There is a large body of evidence supporting adult stem cell niches having low oxygen partial pressures [8], and reduction in oxygen tension reduces the differentiation capacity and extends the self-renewal of mesenchymal stem cells [9] and hematopoietic stem cells [10]. This suggests that the interaction of TERT and Hif1α extends well beyond the embryonic stage of development and may have an important part in adult stem cell self-renewal that could have implications for healthy aging.

It is imperative that we elucidate the mechanisms of telomerase regulation throughout all stages of development, especially in the homeostatic maintenance of adult stem cell self-renewal. Gaining insights in the network of normal telomerase regulation would enable research and therapies that address organ-specific morbidities and human aging.

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