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Review

Telomeres and telomerase in normal and cancer stem cells

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ABSTRACT

Differences between normal adult tissue stem cells and cancer stem/initiating cells remain poorly defined. For example, it is controversial if cancer stem cells can become fully quiescent, require a stem cell niche, are better at repairing DNA damage than the bulk of the cancer cells, and if and how they regulate symmetric versus asymmetric cell divisions. This minireview will not only provide our personal views to address some of these outstanding questions, but also present evidence that an understanding of telomere dynamics and telomerase activity in normal and cancer stem cells may provide additional insights into how tumors are initiated, and how they should be monitored and treated.

1. Introduction

What do we really know about the differences between normal tissue stem cells and cancer stem (initiating) cells? While this is a complex question that covers many areas of previous and ongoing research, this review will focus on comparing and contrasting the role of telomeres and telomerase in normal and putative cancer stem (initiating) cells. Understanding the dynamics of telomeres and telomerase in normal and cancer stem cells may provide some additional insights into defining key differences between these cell types. Since the discovery of rare tumor cells with stem cell-like features, it has been proposed that these stem-like tumor cells are the primary cellular component within a tumor that drives disease progression and metastasis. The alternative to the cancer stem hypothesis is the clonal evolution hypothesis model that suggests tumor progression results from genetic variability within the original population of tumor cells that is permissive for more aggressive subtypes. While the cancer stem cell hypothesis has been difficult to prove, as it makes few predictions, there are some common elements that are generally accepted. In addition to their ability to self-renew and differentiate, cancer stem cells are also enriched in cells postulated to be resistant to conventional radiation and chemotherapy. While normal stem cells are chromosomally stable containing a normal diploid genome, cancer stem cells are almost always aneuploidy and have a significant number of chromosomal rearrangements. In addition, normal stem cells are generally quiescent or very slow growing, reside in a specific niche, and have relatively long telomeres compared to more differentiated somatic cells. In contrast, we find cancer cells expressing stem cell markers are not completely quiescent, and almost universally express cancer levels of telomerase. Importantly, we also find cancer stem/initiating cells have short telomeres (compared to normal stem cells which have relatively longer telomeres). The short telomeres in cancer stem cells may reflect the multistep nature of cancer initiation and progression. The immediate implications of this new tumor growth paradigm not only require a re-evaluation of how tumors are initiated, but also on how tumors should be monitored and treated.

2. Bypass of senescence and crisis to become a cancer initiating cell

Human telomeres consist of repetitive TTAGGG DNA sequences that associate with a series of telomere binding (shelterin) proteins [1] believed to provide genomic stability by protecting the linear chromosome ends from being recognized as DNA breaks needing repair. The inability of the DNA replication machinery to copy the extreme ends of chromosomes, often referred to as the end replication problem [2], is consistent with the observation that cells can lose telomeres without initially affecting cell function. Thus, almost all normal human cells including stem cells of renewal tissues show progressive telomere shortening with ongoing cell division until a subset of telomeres reach a critically shortened length and induce a DNA damage signal that is often referred to as replicative senescence or cell aging [3]. Thus, telomeres not only serve as chromosome 'caps' to protect chromosome ends from being recognized as DNA damage, but also serve as a gauge for

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the mitotic (replication) age of a cell. Telomerase, a RNA-containing enzyme that synthesizes DNA onto the ends of chromosomes, helps to maintain the integrity of the genome in embryonic stem cells and in proliferating progenitor cells derived from quiescent normal stem cells. Telomerase is silent in the vast majority of human tissues and is only expressed in a small number of normal cell types such as dividing male germ-line spermatocytes and a subset of proliferating somatic adult progenitor cells [4].

In 1991 we proposed a connection between telomeres, telomerase, aging and cancer [5]. The hypothesis put forth was that most normal human cells lack telomerase activity and their telomeres shorten with each cell division, until they enter replicative senescence (Fig. 1). Cells that lose critical cell cycle checkpoint functions escape this initial growth arrest (replicative senescence) and continue to divide (called extended lifespan by virologists who first identified that one of the important function of DNA tumor viruses is to bypass senescence). Cells that bypass senescence eventually enter a second growth arrest state (crisis) when many shortened chromosome ends fuse, leading to chromosome bridge-breakage-fusion cycles almost universally leading to apoptosis (Fig. 1). In human cells these two mechanisms to restrict cell growth (senescence and crisis) are at least initially potent anticancer protection mechanisms [6]. Most human cells remain in this crisis period with cell growth being balanced by cell death until a rare cell acquires a mechanism, such as telomerase expression, that can maintain or lengthen telomeres [5,6]. This rare cell that can maintain telomeres is then able to grow continuously (i.e. becomes immortal) and this is generally believed to be a critical step in cancer progression [7]. Cells that have escaped crisis generally have two defining hallmarks, telomere stability and reactivation of telomerase [8,9]. This suggests that the cancer stem (initiating) cell was likely to initially have very short telomeres and recent evidence supports this idea [10,11]. In these studies cancer cells with stem-like markers have similar or shorter telomeres compared to the bulk of the tumor [10,11]. There may thus either be an advantage and mechanism to maintain subsets of cancer cells at very short telomere lengths or the length varies with differentiation state of the tumor cells.

When telomerase is upregulated or reactivated in cells escaping crisis many outcomes are possible. For example, there can be too little telomerase expressed and these cells may not be able to divide long-term and they are unlikely to become robust cancer cells. If telomerase is made in excess then telomeres would be predicted to grow rapidly leading to long telomeres, but this is only rarely observed (less than 10% of primary cancers). Thus, there may be no selective advantage for cancer cells having more telomerase than is needed to maintain telomeres longer than that which provides protection against DNA-damage signaling/end-fusion. What is observed is that the vast majority of human cancer cells have telomeres generally the same or shorter than adjacent normal tissues.

It is believed that greatly shortened telomeres in initiated but still preneoplastic cells (while initially a potent anti-cancer protection mechanism) may also promote genomic instability and lead to the development of advanced disease. It is widely accepted that genetic instability drives malignant transformation. With only a few cellular alterations, the DNA damage signals from telomere shortening (telomere uncapping) would be predicted to be a very potent tumor suppressor pathway, since the "damage" could not be repaired in the absence of telomerase. Thus, replicative senescence is likely to initially stop cells from proliferating and progressing to cancer. This would certainly have an advantage in large long-lived species such as humans but may be less important in short-lived animals (such as mice). Proof that telomeres shortening and cellular aging are causally and not just correlatively related was provided in 1998 when Bodnar and co-workers [12] showed that introduction of telomerase into normal telomerase silent cells was sufficient to bypass senescence, activate telomerase activity, and lead to cell immortalization. It was further shown that ectopic

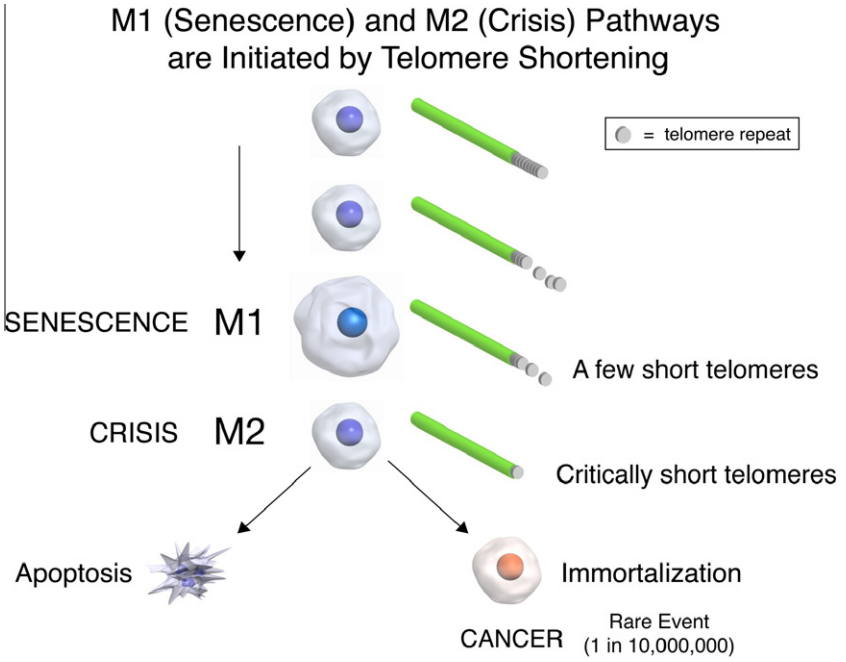

Fig. 1. The M1 and M2 model of senescence and crisis. All normal human somatic cells have progressive shortening of telomeres with each cell division. This is also true in proliferative (transit amplifying) adult stem cells. When a few telomeres in a cell reach a shortened state, a DNA damage signal is initiated. This DNA damage signal indicates that the shortened telomeres is being sensed as uncapped or broken DNA. In cells that have bypassed the M1 senescent state by inactivation of important cell cycle checkpoint genes (e.g. TP53 and/or pRB), cells ignore the ongoing DNA damage signal and continue to divide until many telomeres are critically shortened. During this extended lifespan period, end associations occur eventually leading to breakage-fusion-bridge cycles resulting in M2 or a state of crisis. During crisis apoptotic cell death almost universally occurs. However, in a rare human cell (based on fluctuation analyses calculated to be about one in ten million cells) an immortalization event occurs. This cell has two characteristics, expression of telomerase and stabilization of telomeres.