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Review

New surprises from an old favourite: The emergence of telomerase as a key player in the regulation of cancer stemness

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ABSTRACT

It has been well established that the upregulation/reactivation of telomerase is a prerequisite for cellular immortalisation and malignant transformation. More significantly, perhaps, telomerase stands at the crossroads of multiple signalling pathways and its upregulation/reactivation leads to the modulation of critical cellular processes, including gene expression and metabolism. In recent years, this multifaceted ribonucleoprotein particle has become increasingly associated with the cancer stem cell (CSC) phenotype in various human cancers. Cancer stemness is a major contributor to therapy resistance and hence tumour recurrence. Here, we discuss new findings about the telomere-independent tumour-promoting functions of telomerase and provide a mechanistic explanation for its regulatory role in CSC biology. It is striking that there is a positive feedback loop between a number of gene products targeting telomerase's reverse transcriptase subunit (TERT) and TERT expression itself. This plausibly amplifies the effects of central oncogenes and oncogenic pathways related to cancer stemness in a cell-autonomous fashion. A more complete elucidation of these regulatory mechanisms affords the opportunity to develop telomerase-focused therapies that differentiate or kill CSCs effectively.

Contents

Abbreviations: ABC, ATP-binding cassette; Akt, protein kinase B; ALDH1, aldehyde dehydrogenase 1; BAX, BCL-2-associated protein X; BCL, B-cell lymphoma family protein; BMI-1, B lymphoma Mo-MLV insertion region 1 homolog; BMP, bone morphogenetic protein; BRG1, Brahma-related gene 1; CD, cluster of differentiation; CHK, checkpoint kinase; COX-2, cyclooxygenase-2; CXCR4, C–X–C chemokine receptor type 4; EGFR, epidermal growth factor receptor; ERK1/2, extracellular signal-related kinase 1/2; FAK, focal adhesion kinase; GLUTs, glucose transporters; GNL3L, guanine nucleotide-binding protein-like 3-like; IL, interleukin; JAK, Janus kinase; KLF-4, Kruppel-like factor-4; MAC2BP, Mac-2-binding protein; MCL-1, myeloid cell leukaemia-1; MIC-1, macrophage inhibitory cytokine-1; MMPs, matrix metalloproteinases; MYC, v-myc avian myelocytomatosis viral oncoprotein homolog; mTOR, mammalian target of rapamycin; NANOG, Nanog homeobox transcription factor; NF-κB, nuclear factor-κB; NS, nucleostemin; OCT-3/4, octamer-binding transcription factor-3/4; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; SDF-1, stromal cell-derived factor-1; SMAD, small mother against decapentaplegic homolog; SNAI, snail family zinc-finger transcription factor; SOX-2, SRY (sex determining region Y)-box 2; STAT, signal transducer and activator of transcription; TAZ, Tafazzin; TGF-β, transforming growth factor- β; TNF-α, tumour necrosis factor-α; TWIST, twist family bHLH (basic helix-loop-helix) transcription factor; VEGF, vascular endothelial growth factor; Wnt, Wingless ligand; YAP, Yes-associated protein; ZEB, zinc-finger E-box-binding homeobox family protein.

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1. Introduction

Telomerase is a ribonucleoprotein enzyme complex consisting minimally and essentially of a protein catalytic subunit (telomerase reverse transcriptase, TERT) and a large RNA subunit (telomerase RNA, TER). This dedicated RNA-dependent DNA polymerase assists in replicating linear chromosomes through the *de novo* synthesis of telomeric repeats, thereby counteracting the progressive telomere erosion that would otherwise occur in its partial or complete absence. Although primarily localised in the cell's nucleus, telomerase can also be found in other cellular compartments, such as mitochondria [1]. Telomerase upregulation/reactivation is observed in at least 85% of human advanced tumours, strongly suggesting a crucial role during tumourigenesis [2,3]. Telomerase is upregulated/reactivated in cancer cells by a variety of mechanisms, including increased transcriptional activation of *TERT* and/or *TER*, loss of transcriptional repressors of *TERT*, mutations in the *TERT* gene promoter/enhancer region (which result in the transactivation of this gene), several kinases (which phosphorylate and thus enhance the activity of TERT), and gain of copy number of *TERT* and/or *TER* [4]. As a consequence of telomerase upregulation/reactivation, cancer cells achieve unlimited replicative potential that confer them immortal. In addition to its role in telomere length maintenance, accumulated data over the last decade support the notion that telomerase, in particular TERT, also performs telomere length-independent functions, such as modulation of gene expression. In a pathological context, telomerase's new talents are intimately related to cancer development and progression to metastatic disease. There is now emerging evidence that telomerase is a major regulator of cancer stemness, the stem-like component of human cancers. Cancer cells within an individual tumour usually exist in distinct phenotypic states which differ in functional attributes. This intratumoural heterogeneity originates from diverse cell types recruited to the tumour as well as from genetic and epigenetic differences amongst the cancer cells themselves and may lead to different responses to therapy [5]. Postulated to be the driving force behind tumour initiation and progression, cancer stem cells (CSCs) represent a unique dimension of intratumoural heterogeneity. These hypermalignant stem-like cells are believed to sustain tumour growth and dissemination as well as be responsible for treatment failure and tumour relapse. The CSC concept is of considerable clinical importance and significance because it prognosticates that successful anticancer therapy must involve strategies that will eradicate CSCs, as these cells hierarchically lie at the apex of any residual cancerous cells that survive conventional anticancer therapy. This review will highlight the recently discovered extracurricular activities of telomerase/TERT and describe how they are thought to be involved in generating and/or maintaining cancer stemness traits.

For our systemic analysis, we first focus on the extratelomeric cancer-promoting effects of manipulating telomerase/TERT expression or function in well-defined cancer cells, including CSCs, as well as in stem/progenitor and mature cells, all of which may serve as potential targets for oncogenic transformation and cellular reprogrammimg. We then extrapolate the results of these studies to the operation of CSCs within a tumour. Although some of the observed cellular/microenvironmental changes may require a catalytically active enzyme, there are several examples of oncogenic alterations brought about by catalytically inactive telomerase, as in the case of alternatively spliced (AS) TERT variants.

2. The definition and determinants of cancer stemness

Accumulating evidence suggests that CSCs are important players in most, if not all, types of human cancers, including sarcomas [6], melanomas [7,8], lymphomas [9], leukaemias [10–12], and various carcinomas, such as brain [13], skin [14], head and neck [15], lung [16,17], liver [18], gastric [19], colorectal [20,21], bladder [22], pancreatic [23,24], prostate [25], breast [26] and ovarian [27] cancers. This often-rare subpopulation of phenotypically distinct cancer cells has critical roles in tumour formation, maintenance and aggressiveness, spreading, treatment resistance, and recurrence, all of which lead to poor prognosis. The three noticeable features that contribute to the above-mentioned critical roles of CSCs in cancer, also referred to herein as cancer stemness traits, are their unlimited capacity for self-renewal, their aberrant potential for differentiation into extremely heterogeneous populations of neoplastic cells and their high ability to shift from a proliferative to a quiescent or dormant state. Although these peculiar functional characteristics are shared by both CSCs and physiological stem cells, only CSCs are associated with multiple malignant phenotypes, including resistance to cell death and activation of invasion and metastasis. Furthermore, CSCs are distinguished from bulk cancer cells by their expression of a selected repertoire of stem cell-surface markers, their ability to form spheres when grown in stem cell media under nonadherent culture conditions and their propensity to seed tumours when transplanted into immunodeficient mice [28]. Regardless of how it is assayed, cancer stemness stresses the ways in which CSCs differ from bulk cancer cells as well as from physiological stem cells.

Recent studies have revealed that cancer stemness is governed by genetic changes (*e.g.*, oncogene activation and oncosuppressor gene inactivation) and epigenetic changes (*e.g.*, miRNA targeting and promoter DNA hypomethylation/hypermethylation) concomitant with changes in the tumour microenvironment (especially the CSC niche). These changes are required for the oncogenic transformation and cellular reprogramming of non-CSCs to CSCs and result in the inactivation of certain oncosuppressor proteins, upregulation/reactivation of telomerase, reactivation of the epithelial-to-mesenchymal transition (EMT) programme, modulation of energy metabolism, stimulation of varied embryonic/oncogenic signalling pathways, and differential expression of several microRNAs (miRNAs).

An early molecular event accompanying the emergence of cancer stemness traits is disruption of a number of oncosuppressor proteins with antiproliferative, prodifferentiative and/or proapoptotic effects. $p16^{INK4A}$, pRB, p53, and PTEN are among the most frequently inactivated oncosuppressor proteins in human cancers [29]. Their inactivation allows premalignant cells to bypass senescence and escape apoptotic cell death, thereby continuing to divide and accumulating further tumourigenic changes such as chromosomal instability resulting from telomere erosion [30]. The