High telomerase expression is a hallmark of most types of cancer, and, therefore, strategies to inhibit telomerase as an anticancer treatment have been pursued for many years. In contrast to cancer, short telomeres and lack of telomerase are associated with aging and age-related disease, including heart disease. Consequently, pharmacological telomerase activation can delay aging and also provides cardioprotection. In this viewpoint, we briefly summarized the 2 faces of telomerase in cancer and during aging. We discuss why we see the therapeutic future in telomerase activation rather than its inhibition, for the treatment of cardiac disease and possibly even in the context of cancer.

Cardiovascular disease is a worldwide epidemic and represents the most common cause of morbidity and mortality in the western world. Significant advances in health care have led to a steadily rising life expectancy and consequently to a dramatically increased incidence of age-related diseases, such as cancer and heart disease. One of the main reasons for the high incidence of heart failure (HF) is an extremely low regeneration capacity of mammalian cardiomyocytes. Hence, the only effective way to replace lost cardiomyocytes in humans to date, for instance after myocardial infarction, is heart transplantation, which emphasizes the need for novel intervention and prevention strategies.

Intensive research provided insights into the cellular and molecular mechanisms of aging. Among others (eg, cellular senescence, genomic instability, stem cell exhaustion, mitochondrial dysfunction, and epigenetic alterations), telomere attrition, in particular, has emerged as a main driver of aging and age-related diseases, such as HF.1

Telomeres are dynamic nucleoprotein structures which form a protective cap to conceal the ends of chromosomes from the DNA repair machinery, thus providing chromosomal and cellular integrity.2 However, telomeres are sensitive to aging because telomerase (TERT [telomere reverse transcriptase]), the enzyme that maintains telomere length, is repressed in most adult human tissues, including heart, which results in a lifelong loss of telomeric sequence. After reaching a critically short length, telomeres are detected as DNA damage eliciting a persistent DNA damage response at telomeres leading to the induction of cellular senescence or apoptosis.3 Accordingly, mice with genetically engineered short telomeres develop cardiomyopathy characterized by impaired cell division, enhanced cardiomyocyte death, and cellular hypertrophy.4 In addition to cell division, oxidative stress also contributes to telomere shortening and cellular senescence.5 Cardiomyocytes with high energy consumption rates and a very dense content of mitochondria are exposed to increasing amounts of DNA damaging reactive oxygen species (ROS) with age. Indeed, telomeres are preferential targets for a persistent DNA damage response in stress-induced senescence and during aging. Stress-induced DNA damage accumulates over time independent of telomere length.6 Thus, the association of dysfunctional telomeres with cardiac decline might be cumulative; that is, replicative senescence in actively proliferating cardiac stem cells synergizes with stress-induced senescence in postmitotic cardiomyocytes, both contributing to age-related heart disease.

Thus, telomere biology plays a central role also in cardiac aging and disease, and, therefore, telomeres and TERT represent potential therapeutic targets.

Dual Functions of Telomerase
The extension of telomeres to provide youth, chromosomal stability, and virtually unlimited proliferation potential describes the canonical function of TERT. In addition to this nuclear role, namely telomere preservation, several noncanonical functions have been described. Intriguingly, TERT was found to translocate from the nucleus to mitochondria where it may regulate mitochondrial ROS. This is particularly important in the context of the aging or diseased heart where TERT, if expressed, may detoxify ROS in turn protecting from DNA damage, senescence, and subsequently the loss of cardiac cells. Pharmacological stimulation of TERT protects from apoptosis and DNA damages induced by H2O2, whereas the lack of TERT results in higher levels of mitochondrial ROS.7 Cardiomyocyte-specific transgenic overexpression of TERT is proproliferative in neonatal mouse cardiomyocytes and also protects from apoptosis in vitro and in vivo.6 In addition to cardiomyocytes, TERT is important for maintaining endothelial cell homeostasis through repression of inflammation, ROS, and senescence.8 In line, there is a critical role for TERT in the protection against mitochondrial ROS in endothelial cells and was shown to re-establish physiological vasodilation in arterioles from patients with coronary artery disease.9

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.
From the Institute of Molecular and Translational Therapeutic Strategies, Hannover Medical School, Germany.
Correspondence to Thomas Thum, MD, PhD, Hannover Medical School, Institute of Molecular and Translational Therapeutic Strategies, Strategies, OE8886, Carl-Neuberg-St 1, Hannover 30625, Germany, E-mail thum.thomas@mh-hannover.de
(Circ Res. 2017;120:1393-1395.
DOI: 10.1161/CIRCRESAHA.116.310316.)
© 2017 American Heart Association, Inc.
Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/CIRCRESAHA.116.310316
**TERT Therapeutic Strategies in Cancer: Inhibition**

High levels of TERT are a hallmark of most cancers, thus therapies aiming at the inactivation of TERT are not far-fetched. Because most somatic cells possess very little TERT activity, inhibitory strategies are fairly cancer cell specific. Accordingly, approaches to block TERT have been pursued. One prominent example is Geron specifically modified oligonucleotide chemistry Imetelstat (GRN163L) which is complementary to TERC (the RNA component of the telomerase holoenzyme) and, thus, able to bind to the catalytic center of TERT thereby inhibiting its function. Imetelstat is under investigation in clinical trials for the treatment of hematologic myeloid malignancies, whereas other previous phase I/II studies of solid tumors were discontinued due to disappointing results.

Other studies investigated the use of small natural and synthetic molecules as telomerase inhibitors, for example, the compounds EGCG and BIBR1532. However, without knowing their precise mode of action and potential off-target effects, many of such compounds are currently restricted to in vitro and preclinical studies.

In contrast to direct TERT blockade, immunotherapeutic approaches use TERT-derived peptides to develop vaccines that would activate the immune system to specifically target cancer cells with high TERT expression. GV1001 is such a peptide vaccine that is currently under investigation in a substantial number of clinical trials. However, results published to date show modest or no efficacy presumably owing to the development of immune tolerance against the TERT self-antigens.

A fourth approach may be the use of suicide constructs which express a cytotoxic gene under the control of the (cancer cell specific) TERT promoter, thus specifically killing cancer cells.

**TERT Therapeutic Strategies in Aging and Disease: Activation**

In contrast to inhibition, (re)activation of TERT may seem a plausible strategy for cell, tissue, and even organismal rejuvenation and age-related diseases. Various preclinical studies demonstrated remarkable results with regards to life span and health span extension in wild-type mice and significant improvements of disease phenotypes in mouse models that recapitulate telomere syndromes. In the past, TERT activation was achieved through delivery of the TERT sequence by either viral gene therapy or by delivery of the TERT mRNA. For example, applying a TERT gene therapy (using AAV9 vectors) in adult and even aged mice was shown to significantly delay aging and associated pathologies, including heart disease.

Further strategies aim at liberating the silenced TERT gene or at enhancing residual TERT activity, for example, through treatment with sex hormones. About the latter, androgen therapy has proven successful in a mouse model of aplastic anemia caused by short telomeres. Sex hormone–dependent TERT activation compensates for replication-mediated telomere attrition in hematopoietic stem and progenitor cells and prevented the development of aplastic anemia. A recently published phase I/II prospective study demonstrated that treatment with the synthetic sex hormone danazol led to telomere elongation in patients with telomere diseases.

In the cardiovascular system, the role of TERT seems to be more diverse than simply replenishing telomeres; noncanonical TERT functions are required to maintain homeostasis and prevent cardiovascular senescence and disease. In cardiomyocytes, TERT is beneficial to repress inflammation, oxidative stress, senescence, and to promote survival, whereas in endothelial cells, additional proangiogenic effects are described. The other way around, low or no levels of TERT are associated with a senescence phenotype in endothelial cells in atherosclerotic plaques and coronary artery disease. Along these lines, TERT activation by means of cardiotropic AAV9 gene therapy in a mouse model of myocardial infarction resulted in improved cardiac function parameters, reduced fibrosis, and infarct sizes. Another feasible strategy is a TERT-mediated ex vivo rejuvenation in cell therapies, for example, in patients with severe heart failure. In a mouse model of hindlimb ischemia, such an approach was shown to promote revascularization and tissue repair (Figure).

**Activation Versus Inhibition**

Due to its high expression, TERT represents a marker for cancer cells, but the success of TERT inhibition as anticancer treatment has been modest. In our view, immunotherapeutic and cytotoxic gene therapy are the most promising strategies, but major hurdles, such as immune tolerance, gene delivery, and cancer cell specificity, remain. Critical considerations when directly targeting TERT are also that cells have a telomere reserve which allows proliferation for some time even in the absence of TERT. Furthermore, critically shortened telomeres not only elicit cellular senescence but are also a source for chromosomal instability, hence inhibiting TERT may increase the probability for secondary cancers. Finally, systemic TERT inhibition also affects high turnover tissue and stem cell niches in particular. This notion is of critical importance especially in the case of pediatric patients with a lifelong proliferation history still ahead. Indeed, it is a well-known fact that chemotherapy treatments may impose severe early- and late-onset complications, for example, aplastic anemia and heart failure, respectively. Although this remains to be addressed, we predict that concomitant TERT inhibition would augment side effects of chemotherapy, whereas TERT inhibition alone is not sufficient to kill cancer as evidenced by several clinical studies.

In this viewpoint, we would like to go 1 step further and provoke with the hypothesis that TERT activation may be beneficial even in the context of cancer, or more precisely, in the prevention of complications that may arise from anticancer therapies. As an example, treatment success of malignancies, such as acute myeloid leukemia during childhood, has increased significantly over the past 2 decades. However, chemotherapy agents (especially anthracyclines) are very toxic for cardiomyocytes too, leading to cardiovascular complications and heart failure in a significant number of cancer survivors even decades after the treatment. If TERT is activated before or during cancer treatment, this may have little effect on the cancer cell itself as it already has endogenously activated TERT.
In contrast, activation may preserve other cells, including cardiomyocytes, because of the ROS detoxifying and anti-apoptotic traits of TERT. Moreover, the proangiogenic function of TERT may be an additional advantage with regards to cardioprotection.

Another interesting question in the context of cardiac regenerative medicine is whether active TERT can improve the outcome of stem cell–based therapy, for example, for myocardial infarction. We propose that canonical and non-canonical function of TERT may give treatment an edge over other treatments that target only single pathways. Specifically, active TERT would allow for enhanced and prolonged proliferation through maintaining telomeres, whereas limiting ROS and the activation of antiapoptotic and prosurvival pathways would prevent massive stem cell death in ischemic tissue, which represents a major limitation in cardio reparative treatments. We acknowledge that reflexive safety concerns are common to all TERT activation strategies because of the prominent role of TERT in cancer. Admittedly, at the first glance, TERT activation in the context of cancer seems counterintuitive. Nevertheless, we put the question forward that what would it do to cancer cells that already highly express TERT? Moreover, although it is true that most cancers require TERT to maintain their immortal state, TERT overexpression in human cell is insufficient to induce transformation and tumorigenesis,9 which in the context of regenerative strategies is of utmost importance.

Conclusions

TERT expression poses a dilemma, too little of it can kill you but too much of it can kill you too. The crucial question is when to block and when to activate it. In our opinion, TERT inhibition in the cancer setting is the less promising therapeutic strategy due to several pitfalls outlined above. TERT activation for treatment of multiple age-related diseases on the other hand seems more technically feasible. However, despite remarkable results in animal models of aging and disease, safety concerns and technical challenges remain to be addressed before such approaches become reality in the clinic.

Sources of Funding

We acknowledge funding of this viewpoint article from the European Research Council (Project Longheart) and the Hannover Medical School REBIRTH-Excellence Cluster and Deutsche Forschungsgemeinschaft (BA5631/2-1).

Disclosures

None.

References

Changing Direction: From Therapeutic Telomerase Inhibition to Activation?
Christian Bär and Thomas Thum

_Circ Res._ 2017;120:1393-1395
doi: 10.1161/CIRCRESAHA.116.310316

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/120/9/1393

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org//subscriptions/