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Pharmaceutical regulation of telomerase and its clinical potential

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Abstract

Telomeres serve the dual function of protecting chromosomes from genomic instability as well as protecting the ends of chromosomes from DNA damage machinery. The enzyme responsible for telomere maintenance is telomerase, an enzyme capable of reverse transcription. Telomerase activity is typically limited to specific cell types. However, telomerase activation in somatic cells serves as a key step toward cell immortalization and cancer. Targeting telomerase serves as a potential cancer treatment with significant therapeutic benefits. Beyond targeting cancers by inhibiting telomerase, manipulating the regulation of telomerase may also provide therapeutic benefit to other ailments, such as those related to aging. This review will introduce human telomeres and telomerase and discuss pharmacological regulation of telomerase, including telomerase inhibitors and activators, and their use in human diseases.

Keywords: telomerase • pharmacological activators • inhibitors • natural compounds

Introduction

Telomeres are the DNA-protein complexes of linear chromosomes that protect the ends from genomic instability caused by the loss of small portions of the chromosomes during DNA replication [1]. In humans, telomeres are comprised of a repetitive TTAGGG sequence [1, 2]. This sequence length varies greatly across species, from approximately 300 base pairs to greater than 20 kb in length, and contains a 3′ G-rich single strand overhang [2–4]. Regulation of telomere length through replication is essential to overcoming the limitations of normal cellular division [5].

Part of the role of the telomere in generating chromosome stability is in protection of chromosomes from recognition by DNA repair machinery [6, 7]. In addition to the potential loss of genetic material associated with replicating linear chromosomes, the ends of these chromosomes resemble DNA breaks [6]. Repair machinery has the potential to see these ends and attempt to repair them [8]. This can result in both end-to-end fusions and additional loss of genetic material during additional cycles of replication. The 3′ overhang is essential to the protection of the telomere from these end-to-end fusions as well as unregulated nuclease digestion. It accomplishes this by folding upon itself forming a higher order structure known as the t-loop [9, 10]. The ability of the telomere to form higher order DNA structures is due to its GC rich component and may present a significant obstacle for DNA replication machinery. Although the inherent nature of the sequence allows for higher order structures, formation of these structures including the t-loop requires additional proteins known as telomere-associated proteins [11].

Telomere-associated proteins are essential to telomere function. Telomere-associated proteins recognize and bind to the repeat sequence stabilizing it. For example, the shelterin complex binds to the telomere organizing and defining it. Shelterin is comprised of six individual proteins: TRF1 (telomere repeat binding

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factor 1), TRF2 (telomere repeat binding factor 2), RAP1 (repressor/activator protein 1), POT1 (protection of telomeres 1), TIN2 (TRF1 interacting nuclear factor 2) and TPP1 (also known as adrenocortical dysplasia homolog-mouse; TINT1, 'TIN2 interacting protein 1'/PIP1, 'POT1-Interacting Protein 1' /PTOP 1, 'POT1 and TIN2 Organizing Protein') [7, 12–14]. This simple complex has a role in many activities including regulating telomere length and forming the t-loop.

Replication of the telomere requires a specialized enzyme capable of reverse transcriptase activity called telomerase [15]. In normal, healthy cells telomerase activity is mostly limited to embryonic cells, adult male germline cells and stem cells, but is virtually absent in somatic cells [16]. In stem cells, telomerase activity serves the function of elongating telomeres thus protecting these cells from typical cellular aging and senescence [17]. The human telomerase is comprised of two major subunits, the RNA template and the catalytic enzyme [15, 18, 19]. The telomerase RNA template (hTR or hTERC) contains a complementary sequence to the human telomere that serves as the base for replication of the telomere repeat sequence [20, 21]. The extension of telomeres is completed through the catalytic enzyme, telomerase reverse transcriptase (hTERT) [19, 22]. Together this complex catalyses the addition of the six nucleotide repeat to the ends of chromosomes. Along with these two main components are additional telomere/telomerase-associated proteins. Formation of the functional holoenzyme complex requires associated proteins including the box H/ACA small nucleolar RNA proteins: dyskerin, NOP10 (NucleOlar Protein 10), NHP2 (Non-Histone Protein 2) and GAR1 (Glycine-Arginine Rich 1) [23, 24].

Telomerase activity and *hTERT* expression regulation is complex. Transcriptional, post-transcriptional, post-translational, localization, subunit assembly and epigenetic regulation as well as telomeric proteins and RNAs all contribute to telomerase regulation [25, 26]. Inability to properly regulate telomerase, such as in cases of genetic dysfunction of telomerase, can lead to a variety of diseases including cancer and bone marrow disorders [27–29] (for more specific reviews on telomerase regulation and disease, the reader is invited to see references 28 and 29). For example, components of the telomerase complex are up-regulated in over 90% of human malignancies and contribute to the increased proliferation and limitless replicative potential of cancer cells [30–33]. This differential expression between normal and malignant cells makes telomerase an ideal target in cancer therapeutics [28]. Artificially regulating telomerase may be useful as a treatment not only for cancer, but also for genetic and immunodeficiency disorders involving dysregulated telomerase or telomere length. It is important to note that there is a potential for additional effects of telomerase regulation due to additional activities of telomerase related to DNA repair, cell survival and death, stem cell maintenance and the regulation of gene expression [34, 35].

The development of telomerase inhibitors for cancer treatment is a major field of study. By inhibiting telomerase, it is possible to kill cancerous cells while limiting toxicity to neighbouring normal cells. Several mechanisms of telomerase inhibition have been explored for use as therapeutic agents. For example, there have been inquiries into regulating telomerase by immunotherapy vaccines. These vaccines target the active site of telomerase, which elicits an immune response against cancer cells (see Liu *et al.* review for more detailed discussion of this topic) [36]. In addition, adenoviruses, such as telomelysin, are being developed that can selectively replicate in cancer cells by using the TERT promoter as a molecular switch; this replication causes viral toxicity that selectively kills the cancer cells (see Nemunaitis *et al.* for a review on immunotherapy) [37]. While telomerase inhibition stands as a promising neoadjuvant therapy, it is important to note that activation of telomerase in some cells may prove beneficial. Telomerase activation is currently being studied for use in immunodeficient patients to stimulate proliferation of T cells as well as in regenerative medicine and a treatment to combat the signs and symptoms of aging. This review will focus on telomerase activity and the use of pharmacological intervention to alter this activity as a treatment for diseases such as cancer.

Telomerase inhibitors

Though several synthetic compounds with telomerase inhibition properties have been developed in recent years, the majority of these compounds are highly toxic [38]. In addition, it can be difficult to determine whether these inhibitors have a direct or indirect effect on telomerase (see Fig. 1 for targets of telomerase). The compounds may themselves cause telomerase inhibition (direct effect) or it may be that the compounds cause cell death and due to apoptosis telomerase activity slows or stops (indirect effect). Various targets, such as the RNA template, TERT protein and associated proteins, are all being investigated to develop telomerase inhibitors. One clinically relevant compound, imetelstat, has been developed to date as a specific oligonucleotide competitive inhibitor of telomerase activity. Imetelstat, or GRN163L, was developed by the Geron Corporation (Menlo Park, CA, USA) to target the RNA template for TERT by binding to the catalytic site of telomerase preventing action [39]. This inhibitor has been applied to breast cancers [40, 41], prostate cancers [42], glioblastoma [43], myeloma [44] and leukaemia [39]. It has been shown to augment the effects of paclitaxel in breast cancer cells [41]. Four phase I and I/II trials were completed in 2009, and the company is planning phase II studies and combinations studies for breast and lung cancers. Throughout each of these studies, few long-term side-effects of telomerase inhibition have been reported. The lack of significant detrimental side-effects enhances the potential of telomerase inhibition to continue to be used clinically to augment current treatment protocols.

In addition to synthetic compounds, various chemical compounds that occur naturally in plants, or phytochemicals, have been suggested to inhibit telomerase activity in various cancers (Table 1). Allicin, an organophosphate derived from garlic, was shown to

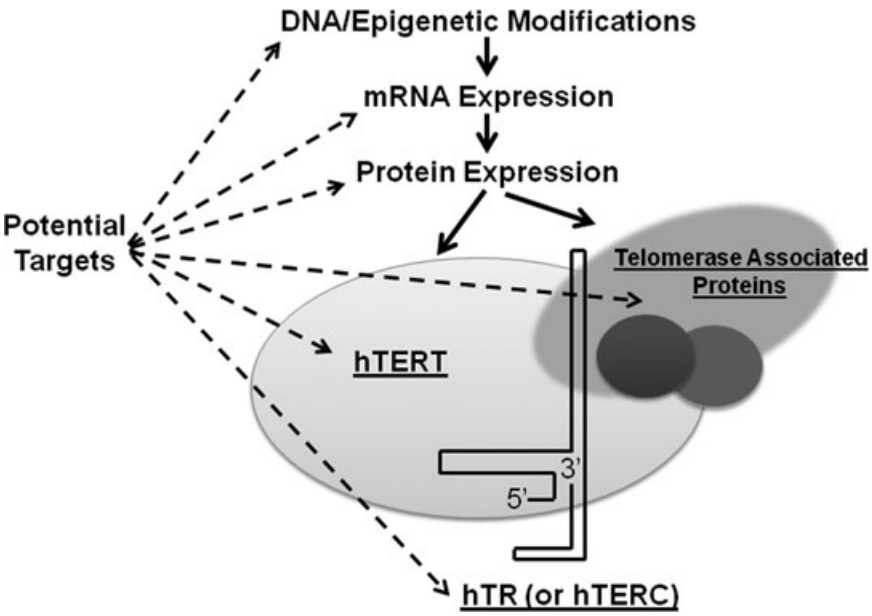

Fig. 1. Targets of telomerase activity. Targets of telomerase and its activity are represented [29]. The pharmaceutical agents and phytochemicals discussed in this paper have been suggested to affect expression or epigenetic regulation of telomerase. More investigation into the specific anti-telomerase activities of these chemicals is necessary to define their mechanisms.

decrease telomerase activity and increase apoptosis in gastric adenocarcinoma cells though the mechanism is undetermined [47]. Curcumin, a phenol present in turmeric, has been shown to decrease telomerase activity in several cancer types [38, 48–53]. This inhibition has been shown to be due to the inhibition of translocation of TERT to the nucleus [38] by dissociating Hsp-90 co-chaperone p23 from TERT [50] as well as the reduction of TERT expression [48, 49]. A flavonolignan found in milk thistle, silbinin, has been shown to decrease TERT expression as well as telomerase activity [54]. The organosulfur derived from cruciferous vegetables, sulforaphane, has been shown to cause epigenetic regulation resulting in a decrease of TERT expression as well as the phosphorylation of TERT which prevents translocation to the nucleus. Epigallocatechin gallate (EGCG), a catechin in green tea, has shown to inhibit TERT expression [55], which may be largely due to epigenetic regulation of the TERT promoter [56]. Furthermore, EGCG showed inhibition of telomerase in several cervical cancer cell lines only with concurrent retinoic acid treatment. This effect was associated with a decrease in hTERT expression [45]. Several of these chemicals have been tested on normal, non-malignant, as well as cancerous cells. Curcumin [48], genistein [57], EGCG [26] and sulforaphane [58] were all tested on breast cancer cells and the non-malignant breast cell line MCF10A; curcumin [48] and sulforaphane [58] had no effect on normal cells whereas genistein was shown to inhibit telomerase in these MCF10A cells as well as the cancer cells [57]. It is important to note, not all studies on these chemicals are in agreement. Several compounds have been shown to act as both inhibitors and activators of telomerase though this may be due to treatment concentration or cell type differences. For example, resveratrol has been shown to inhibit telomerase activity in cancer cells [59] and activate telomerase in epithelial [60] and endothelial progenitor cells [61]. In addition to this, a study about genistein (soybean) suggests it may activate telomerase activity at low concentrations and inhibit telomerase activity at higher treatment concentrations (see 'Telomerase Activators' and Table 1) [46]. These studies suggest that more research needs to be done on these phytochemicals to ascertain their specificity for their potential development as effective telomerase inhibitors that could be utilized for clinical applications.

Telomerase activators

As telomere length is associated with cellular aging, there have been interesting inquiries into the development of telomerase activators to reverse normal cellular aging and treat symptoms of aging. Geron Corp. and TA Therapeutics developed a single molecule telomerase activator, TAT2 (cycloastragenol). This small molecule has been shown to transiently activate telomerase in T lymphocytes that were no longer proliferating [62]. With continuous treatment, this agent could be useful for patients with HIV/AIDS and immunodeficiency. In addition, this molecule is being used to develop nutraceuticals and cosmeceuticals to enhance immune function and skin condition. However, more work needs to be done to determine mechanism of action and safety of these products.

Also, certain phytochemicals have been shown to activate telomerase (Table 1). Resveratrol has been shown to activate telomerase in human mammary epithelial [60] and endothelial progenitor cells [61]. It has been suggested that this may be due

Table 1 Phytochemicals shown to have telomerase regulation properties

	Phytochemical	Cancer type	Cell lines	Mechanism of regulation
Inhibitor	Allicin (Garlic)	Gastric	SGC-7901 [47]	ND
	Curcumin (Turmeric)	Breast	MCF-7 [48]	• Transcriptional [48] • Translational [49] • Post-translational – Nuclear Localization [38, 50]
		Cervical	HeLa, SiHa, Ca Ski [51]	
		Gastric	SGC-7901 [52]	
		Leukaemia	HL60 [52, 53], K-562 [38]	
		Liver	Bel7402 [52]	
		Lung	H1299 [50], A549 [49]	
	Epigallocatechin Gallate (Green Tea)	Brain	U87-MG, 1321N1 [65]	• Transcriptional – Epigenetics [56] • Translational [55]
		Breast	MCF-7 [26, 55, 56], MDA-MB-231 [26]	
		Cervical	OMC-4, TMCC-1 [66]	
		Head and Neck	Hep-2 [67]	
		Leukaemia	HL60 [56]	
		Lung	H69, H69VP [68]	
	Genistein (Soybean)	Breast	MCF-7 [57]	• Transcriptional [69, 70] • Post-translational – Nuclear Localization [70]
		Ovarian	SKOV-3 [46]	
		Prostate	LNCaP [69], PC-3 [66], DU-145 [70]	
	Resveratrol (Red Grape)	Breast	MCF-7 [59]	• Post-translational – Nuclear Localization [59]
		Colon	HT-29, WiDr [71]	
	Silibinin (Milk Thistle)	Prostate	LNCaP [54]	ND
	Sulforaphane (Cruciferous Vegetables)	Breast	MCF-7, MDA-MB-231 [72]	• Transcriptional [58] – Epigenetics [72] • Post-translational [58]
		Liver	Hep3B [58]	
Activator	Resveratrol (Red Grapes)	-	Epithelial cells [60], Endothelial progenitor cells [61]	• Post-translational [60]
	Genistein (Soybean)	Breast	MCF-7 [46]	• Transcriptional [46]
		Ovarian	SKOV-3 [46]	
		Prostate	DU-145, LNCaP [46]	

ND: not determined.

to the up-regulation of SIRT1 [63]. As discussed above, one study showed that the phytochemical genistein caused an activation of telomerase in DU-145 and LNCaP prostate cancer cells as well as MCF-7 breast cancer cells and SKOV-3 ovarian cancer cells at low (0.5–1 μM) treatment concentrations. No activation was seen in normal human prostate, PrEC, cells which are telomerase-negative. However, telomerase inhibition was seen at higher (50 μM) concentrations with all lines and this result suggests that genistein has a bilateral effect on telomerase activity in cancer cells [46]. Further screening of phytochemicals should be conducted to determine other telomerase activators, and more studies are needed to determine the effectiveness of these chemicals as telomerase activators.

Furthermore, additional studies need to be conducted on the safety of activating telomerase. There is little information to address the possible over-activation of telomerase due to pharmaceuticals that could lead to uncontrolled cell growth. Examples of this can be seen among non-pharmaceutical chemicals. For instance, a major component of cigarettes, cotinine, has been shown to activate telomerase causing abnormal proliferation [64]. In addition, it is possible that activation of telomerase could reactivate the proliferative capability of benign tumours.

Conclusions and perspectives

The potential benefits of regulating telomerase activity are clear. Pharmaceutically inhibiting telomerase may prove an important option in cancer therapy in conjunction with traditional chemotherapeutics. Conversely, the activation of telomerase could be useful to treat age-related diseases and HIV/AIDS patients where lymphocytes have stopped proliferating. However, the long-term effects of regulating telomerase either positively or negatively are unclear. It is possible that inhibition of telomerase could have adverse side effects on normal stem cell function and immune response as stem and immune cells have increased telomerase activity to accommodate frequent proliferation. Understanding of telomerase regulation in normal cells is crucial for the development of telomerase inhibitors and activators. The regulation of telomerase is complex. This complexity may make pharmaceutical regulation difficult due to compensation by other regulatory pathways. However, phytochemicals that seem to regulate telomerase provide a starting place. These chemicals can be used as lead compounds to develop drugs that may be able to be used in the clinic.

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Conflict of interest

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