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REVIEW

Telomerase as a useful target in cancer fighting—the breast cancer case

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Abstract Telomerase was initially considered as a relevant factor distinguishing cancer from normal cells. During detailed studies, it appeared that its expression and activity is not only limited to cancer cells however, but in this particular cells, the telomerase is much more abundant. Thus, it has become a very promising target for an anticancer therapy. It was revealed in many studies that regulation of telomerase is a multifactorial process in mammalian cells, involving regulation of expression of telomerase subunits coding genes, post-translational protein–protein interactions, and protein phosphorylation. Numerous proto-oncogenes and tumor suppressor genes are engaged in this mechanism, and the complexity of telomerase control is studied in the context of tumor development as well as aging. Additionally, since numerous studies reveal a correlation between short telomeres and increased genome instability or cell mortality, the telomerase control appears to be one of the crucial factors to study in order to improve the cancer diagnostics and therapy or prevention. Interestingly, almost 100 % of adenocarcinoma, including breast cancer cells, expresses telomerase which makes it a good target for telomerase-related therapy. Additionally, telomerase is also supposed to be associated with drug resistance. Thus, targeting the enzyme might result in attenuation of this phenomenon. Moreover, since stem cells existence was reported, it must be considered whether targeting telomerase can bring some serious side effects and result in stem cells viability or their regenerative potential decrease. Thus, we review some molecular mechanisms engaged in therapy based on targeting telomerase in breast cancer cells.

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Introduction

Telomeres are guanine-rich repeated sequences located at the ends of chromosomes. They function as a biological clock limiting the cell proliferation potential with every next cell division (Hayflick limit) [1]. This phenomenon is accompanied by cell senescence, mitotic crisis, and/or apoptosis [2, 3]. However, most cancer cells reveal a telomere length maintenance mechanism which is responsible for telomeres renewal during cell proliferation. Majority of cancer cells utilize telomerase for this purpose, and the enzyme contains its integral RNA molecule which constitutes the template for reverse transcription of new telomeric DNA [4]. Telomerase has been recognized as a relevant factor distinguishing cancer from normal cells since it is either undetectable or has low level of activity in normal somatic cells [5]. Thus, it has become a very promising target for an anticancer therapy. It was revealed in many studies that regulation of telomerase in mammalian cells is a multifactorial process, involving expression of telomerase subunits coding genes, post-translational protein–protein interactions, and protein phosphorylation [6, 7]. Numerous proto-oncogenes and tumor suppressor genes are engaged in this mechanism. Thus the complexity of telomerase control is studied in the context of stem cell renewal, tumor development, as well as aging [8–14]. Thus, it is of great interest to identify the enzyme regulators (tumor suppressors or oncogenes, etc.) The studies across many tumor types have shown that the vast majority of tumors (~85 %) express telomerase [15, 16] and hence, are able to maintain a stable and homogenous telomere length. Consequently, they can

avoid replicative senescence. Only just about 15 % of tumors either do not maintain telomere length or activate alternative lengthening of telomeres (ALT) [17]. Interestingly, almost 100 % of adenocarcinoma, including breast cancer cells, express telomerase [18]. Till now, several strategies have been proposed to control telomerase in cancer cells: antisense technology against telomerase RNA component (TR) and telomerase reverse transcriptase (TERT), ribozymes against TERT, antiestrogens, progesterone, vitamin D, retinoic acid, quadruplex stabilizers, telomere and telomerase-targeting agents, modulation of interaction with other proteins involved in the regulation of telomerase and telomeres, etc. [19–25]. However, the transcription control of key telomerase subunits seems to play the crucial role in whole complexes activity and cancer cells immortality. Interesting results were shown by Blackburn et al. [26]. In Saccharomyces cerevisiae, the telomerase deletion response (TDR), that occurs when telomeres can no longer be maintained by telomerase, resulted in upregulation of energy production genes, accompanied by a proliferation of mitochondria. Finally, a discrete set of genes, the "telomerase deletion signature", is uniquely upregulated in the TDR but not under other conditions of stress and DNA damage. The telomerase deletion signature genes define new candidates for involvement in cellular responses to altered telomere structure or function that might mediate cell death induction. Thus, it was suggested in numerous studies, that telomerase silencing is accompanied by abundant genes expression modulation which implicates that cell death following telomerase downregulation is not always related to telomere shortening [26–28].

Telomerase

Human telomerase is a multisubunit ribonucleoprotein that belongs to the reverse transcriptase (RT) family containing RT-like motifs. It is composed of seven conservative motifs and telomerase-specific T motif [29, 30]. The catalytic telomerase protein subunit (TERT) is encoded by gene located on chromosome 5p15.33 [29]. A number of telomere binding proteins in human were identified [31–33] and shown to play crucial role in telomere protection. They allow to distinguish telomeres from damaged DNA by forming telomere structure with D- and T-loops and therefore prevent them from degradation and fusion. Additionally, the complex is safeguarded by shelterin that enables recognition of the natural chromosome ends from DNA breaks. It also regulates telomerase-based telomere maintenance. Shelterin, a very dynamic structure, is implicated in the generation of T-loops, and control of the telomeric DNA synthesis [34]. All six shelterin subunits (TRF1, TRF2, Rap1, TIN2, TPP1, and POT1) can be found in a single complex in fractionated nuclear extracts [35, 36]. The components specifically localize to telomeres. They are abundant at telomeres throughout the cell cycle and they do not function elsewhere in the nucleus. In addition, telomeres contain a large number of nonshelterin proteins which unlike the subunits of shelterin have other nontelomeric functions [34].

Regulation of telomerase activity and expression occurs at many levels, including transcription, alternative splicing, chaperone-mediated folding, phosphorylation, nuclear translocation of each subunit, assembly of the telomerase complex, and its accessibility to telomeres [37, 38]. However, as reported so far, increased telomerase activity is always correlated with upregulation of the *TERT* gene and an increased level of *TERT* mRNA. The Nobel Prize in Physiology or Medicine awarded in 2009 to Elizabeth H. Blackburn, Carol W. Greider, and Jack W. Szostak "for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase" highlighted the important role of telomerase and telomeres in genome stability, immortality, aging, and cancer.

Telomerase regulation in oncology

Because of significant role of telomerase in tumor development as well aging, it is of great interest to identify the enzyme expression/activity regulators. Moreover, since high telomerase expression is characteristic for stem cells but not for differentiated cells, the study of regulatory pathways that control telomerase expression may be critical for maintenance of the stem cell status. Thus, some potential side effect must be considered (Fig. 1). We do believe in significant beneficial effects of telomerase elimination in cancer cells that should be accompanied by induction of senescence, mitotic crisis, and apoptosis or autophagy. However, we are aware of the protection system of those cells which is manifested by induction of ALT.

Transactivation of telomerase, essential for cells immortalization, is supposed to be one of the reasons for cancer transformation. There are many studies describing exogenous factors influencing *TERT*, e.g., several viruses are known to be involved in tumorigenesis of infected tissues which was already widely discussed [5, 39, 40]. Thus, due to the complexity of the telomerase regulation, there is a great challenge on one hand, but on the other hand, there are a lot of potential ways to target and thus, stop the "immortality enzyme."

Regulation of telomerase transcription in breast cancer

Transcriptional mechanism of telomerase regulation (Table 1) was revealed in numerous studies and abundance of transcription factors sites in *TERT* promoter was localized [29]. For example, involvement of c-myc in telomerase regulation was widely investigated, and its role in *TERT*

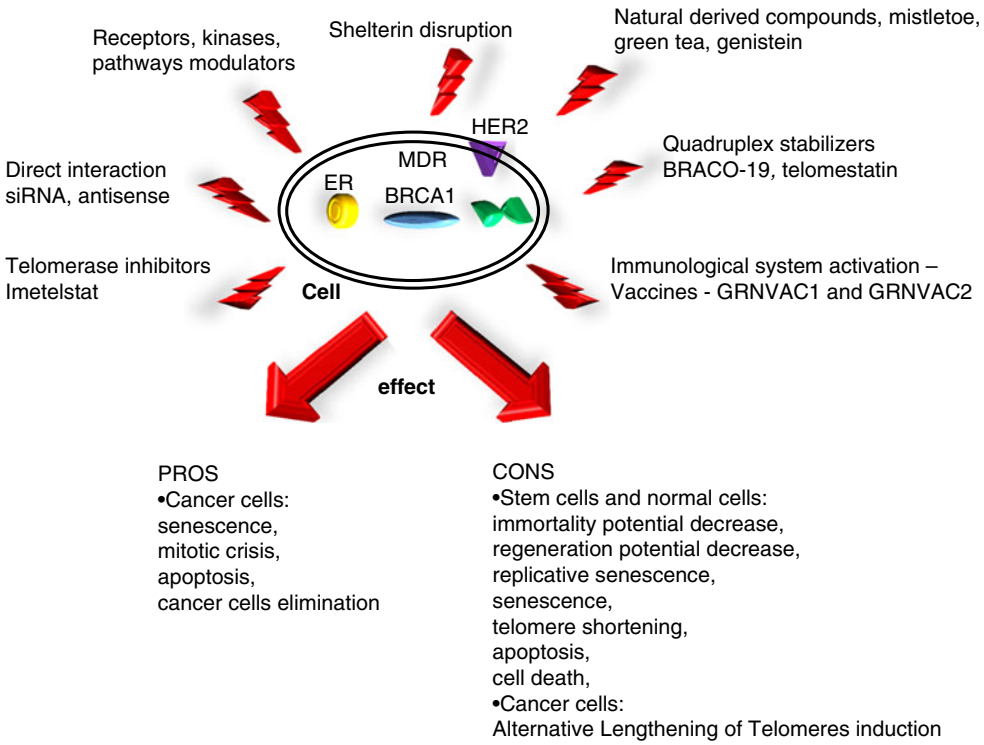

Fig. 1 Possible telomerase modulation effects. Numerous strategies against telomerase were developed that are supposed to work at different levels and specificity. However, all potential telomerase-targeting agents must be considered in the context of potential side effects

gene expression induction was confirmed in many studies [12, 41, 42]. Additionally, both, human epidermal growth factor-2 (Her2) and ER81 (transcription factor involved in ontogenesis and breast tumor formation) [43], have been suggested to cause a synergistic increase in the transcriptional induction of *TERT* in breast cancer patients [44]. It was suggested that *TERT* gene expression could be induced by activating mutations of oncogenes such as HER2/Neu, Ras, and Raf [45]. Consequently, it was shown that HER2/Neu might become another target for a combined anticancer therapy in the context of telomerase elimination. Among other factors that contribute to telomerase expression induction, leptin (significant breast cancer risk factor) [46], epidermal growth factor receptor (EGFR) [47], and estrogen receptors ERa and ERb [48] were found. These receptors are ligand-dependent transcription factors capable of direct interaction between the hormone–receptor complex and estrogen responsive elements [49]. Their status significantly contributes to breast cancer development, diagnosis, and prognosis [50]. Estrogens were shown to activate telomerase via direct and indirect effects on the *TERT* promoter and suggested hormonal control of telomerase activity, cellular senescence and aging as well as estrogen-induced carcinogenesis [51]. Additionally, latest reports show that anticarcinogenic plant compound, indole-3-carbinol, that can modulate steroid hormone-mediated processes, can also trigger *TERT* downregulation in breast cancer MCF7 cells [52]. As suggested, this compound might induce *TERT* inhibition-related cell cycle arrest.

There are also some other factors that may repress telomerase in breast cancer cells. *BRCA1*, playing a role in maintaining genomic stability and acting as a tumor suppressor, was found to interact with c-myc (TERT inducer). It was indicated that overexpression of the *BRCA1* gene inhibits *TERT* expression and telomerase enzymatic activity in various cell types via the inhibition of c-myc-mediated transactivation of the *TERT* promoter [53, 54]. Furthermore, it is suggested that *BRCA1* and Nmi (N-myc and c-myc interacting protein) can form a complex with c-myc in vitro and in vivo [55]. *BRCA1* is also involved in telomere shortening independently of telomerase [54, 56]. BRCA1 interacts with TRF1 and TRF2, and it is suggested that it regulates the length of the 3′ G-rich overhang by being recruited to the telomere in a Rad50-dependent manner [56]. It was demonstrated that p53 repressed telomerase activity through downregulation of *TERT* transcription and that interaction of p53 with Sp1 or other transcription factors may be involved in this regulation [57, 58]. The p73 protein, structural and functional homologue of p53, encoded by *TP73* gene was also suggested to contribute to cell cycle regulation, apoptosis, and *TERT* promoter repression [59, 60]. Additionally, dexamethasone was reported to inhibit telomerase expression similarly to a "stress hormone"—cortisol [61]. Similarly, genistein (phytoestrogen) was shown to cause similar effect [62]. Among other factors that contribute to telomerase downregulation in breast cancer, raloxifene [63] and melatonin [64] were found.

Table 1 Human telomerase regulation

Telomerase inducers	
Leptin [45]	HBZ (HTLV1 bZIP factor) [92]
EGFR [46]	LANA (latency-associated nuclear antigen) [93]
Survivin* [94]	Her2/Neu/Ras/Raf [44]
Sp1 [95]	ΔNp73 [96]
Mad1/c-Myc [97, 98]	Ets2 [99]
HBX protein (X protein of HBV) [100]	STAT3 [101]
HPV16 E6 [102]	Estrogen receptors (ERs) ERα and ERβ [47]
ERK/ER81 [28, 44, 103, 104]	17β - estradiol (E2) [47, 50]
Telomerase repressors	
Dexamethasone (Dex) [60]	Egr-1(early growth response 1) transcription factor [105]
Gefitinib* [64]	TGFβ [106]
Genistein (phytoestrogen)* [61]	PTEN [107]
Upstream stimulatory factor (USF) 1 and 2 [108]	IP6* [109]
WT1 (Wilm's tumor 1 suppressor gene product) [110]	Imatinib mesylate* [111]
MZF-2 [112, 113]	Indole-3-carbinol (I3C)[51]
p53-Sp1 complex [114]	*BRCA1* gene [52, 53]
p53/p21/Rb/E2F [95]	Nmi (N-myc and c-myc interacting protein)[54]
p73 [115]	Rad50 [55]
NFX1-91 [116]	Raloxifene [62]
Interferon-γ [117]	Melatonin [63]
CTCF [118, 119]	Butein (3,4,2′,4′-tetrahydroxychalcone) [64]
PPARγ (peroxisome proliferator-activated receptor γ) [120]	Pectenotoxin-2 (PTX2) [65]
PPAR α (peroxisome proliferator-activated receptor α) [121]	Imetelsat sodium (GRN163L) [68]
Menin [106]	ATRA (all-*trans* retinoic acid) [71]
TR antisense oligonucleotides [77]	Sulforaphane (SFN) [72]
BIBR1532 [80]	

Telomerase and cancer treatment at the molecular level

It is suggested that the loss of proliferative potential observed in human cells lacking telomerase may be considered as a potential mechanism helping to avoid cancer. This is hypothesized since cancer arises after multiple genetic mutations that altogether cause the cell escape from replication, migration, and growth control. Thus, a lack of telomerase would limit the growth of tumors by causing continually dividing cells to shorten their telomeres and to die before starting to spread. This is why telomerase inhibitors seem to be promising factors eliminating cancer cells (Fig. 2).

Recently, several natural-derived compounds were found to exhibit antitumor activity in the context of telomerase regulation. One of them is butein (3,4,2′,4′-tetrahydroxychalcone), a polyphenolic compound causing downregulation of telomerase through suppression of *TERT* gene expression. Moreover, it was demonstrated that this suppression is c-myc-dependent, because butein prevents c-myc binding to *TERT* promoter [65] which is followed by *TERT* expression decrease. Comparing telomerase-positive and ALT cells, it was found that c-myc activity was lower in ALT cells but there was no difference in the gene expression. Interestingly, it was demonstrated that leptin activated telomerase in a dose-dependent manner, upregulated the expression of *TERT* at mRNA and protein levels. On the other hand, the blockade of signal transducer and activator of transcription 3 (STAT3) phosphorylation significantly counteracted leptin-induced *TERT* transcription and protein expression. Thus, a new mechanism of the proliferative effect of leptin on breast cancer cells was suggested, and a new explanation of obesity-related breast cancer was hypothesized [46].

Another compound, pectenotoxin-2 (PTX2), most toxic compound from the group of pectenotoxins (found in marine sponges and shellfish) was shown to downregulate telomerase activity through suppression of *TERT* gene expression at the transcriptional level. It was shown that PTX2-dependent attenuation of *TERT* expression was mediated through suppression of c-myc- and Sp1-binding on the regulatory regions of *TERT* [66]. Both factors influenced telomerase also on posttranscriptional level by attenuation of Akt phosphorylation, thereby reducing the phosphorylation and nuclear translocation of *TERT* [65, 66]. The investigation of the effects of PTX on human breast cancer cells (MDA-MB-231 and MCF7) revealed a significant suppression of cell proliferation and induction of G2/M phase arrest through downregulation of cyclin B1 and cdc2 expression, as well as through phosphorylation of cdc25C. The increased phosphorylation of ATM and Chk1/2 in a PTX2 dose-dependent manner was also found. Furthermore, treatment with PTX2 increased H_2O_2 generation with correlated G2/M arrest revealing that PTX2-induced cell cycle arrest was not restricted to p53 status in human breast cancer cells [67]. As demonstrated by Heaphy et al. [68], telomeres were shorter in more aggressive subtypes, such as luminal B, HER-2-positive and triple-negative tumors, suggesting that tumor telomere length may have utility as a prognostic and/or risk marker for breast cancer. Joseph et al. [69] revealed that when breast and pancreatic cancer cell lines were treated with potent telomerase inhibitor, imetelstat (oligonucleotide, direct enzyme inhibitor) in vitro, telomerase activity in the bulk tumor cells and cancer stem cells subpopulations was inhibited. In vitro treatment with imetelstat, but not control oligonucleotides, also reduced the proliferation and self-renewal potential of MCF7 mammospheres and resulted in cell death after <4 weeks of treatment.

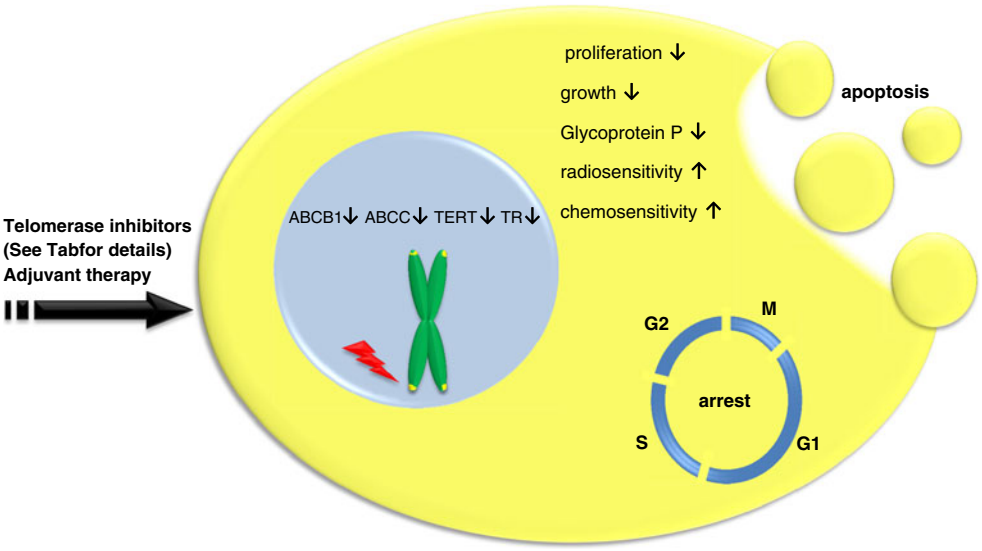

Fig. 2 Potential advantages of telomerase downregulation. Traditional chemotherapeutic drugs combined with telomerase-targeting agents may result in higher efficiency and attenuated side effects

As reported by Moon et al. [65], gefitinib downregulated the activation of Akt and subsequent TERT phosphorylation and translocation into the nucleus in MDA-MB-231 cells. These results indicate that gefitinib induces loss of telomerase activity through dephosphorylation of EGFR in MDA-MB-231 cells showing high expression of *EGFR*. Similarly, Papanikolaou et al. [70] showed that silencing of *TERT* and *HER2* achieved by small interfering RNA technology increased radiosensitivity of cells. Knockdown of *HER2* also led to increased radiosensitivity and downregulation of *TERT*/telomerase. It was confirmed that c-myc and mad1 regulated *TERT* expression in all irradiated breast cancer cells. Additionally, it was shown that circulating *TERT* DNA had a better diagnostic value than carbohydrate antigen CA 15.3 in early breast cancer disease and could be a possible candidate as a tumor marker in patients with infiltrating ductal carcinoma positive to steroid hormonal receptor and with amplification of *HER-2/Neu* [71]. Another natural compound, genistein, was reported as one of the most promising natural compounds targeting telomerase. This natural isoflavone found in soybean products has been reported to downregulate telomerase activity, to prevent cancer and to contribute to the apoptosis of cancer cells. It was shown that genistein inhibited the transcription of *TERT* in breast MCF10AT benign and MCF7 cancer cells in a time- and dose-dependent manner. Three major DNA methyltransferases (DNMTs; 1, 3a, and 3b) were decreased in genistein-treated breast cancer cells, suggesting that this compound might repress *TERT* by impacting epigenetic pathways. Thus, it was concluded that genistein might work, at least in part, through epigenetic mechanisms of telomerase inhibition and might facilitate approaches to breast cancer prevention and treatment in a combined therapy. Another compound showing potent telomerase inhibition is all-*trans* retinoic acid (ATRA) which was reported to have significant effect on the morphology and proliferation rate of the breast cancer SK-BR-3 cells [72]. It was shown to decrease the cancer cell growth and lower telomerase activity which was associated with a rapid decrease in histone H3-lysine 9 acetylation (H3-K9-Ac) of the *TERT* promoter. Further ATRA treatment was shown to induce apoptosis in estrogen receptor-negative breast cancer cells [72]. Another telomerase-inhibiting natural compound, sulforaphane (SFN), an isothiocyanate found in cruciferous vegetables is a common dietary component that reveals histone deacetylase inhibition activity and significant potential in cancer prevention. The mechanism of action is supposed to act through the decrease of DNMTs, especially DNMT1 and DNMT3a, suggesting that SFN may repress *TERT* by impacting epigenetic pathways [73]. Similarly, trichostatin A, an inhibitor of histone deacetylase, is a well-known antitumor agent that effectively and selectively induces tumor growth arrest and apoptosis.

Telomerase, drug resistance, and therapy

Resistance to chemotherapy is one of the principal causes of cancer mortality and generally appears in a late tumor progression process. Cellular models of drug resistance have been useful in identifying the molecular mechanism of this phenomenon and most of them are derived from a late stage of cancer. As suggested, the ability to acquire multidrug resistance (MDR) can arise before the malignant transformation stage and is preceded by expression of telomerase and inactivation of p53 and pRb. Thus, the pathways inactivated during tumorigenesis confer the ability to acquire drug resistance [74]. Telomerase catalytic subunit expression shows correlations with MDR- and apoptosis-related genes and is of prognostic significance [75, 76]. The contribution of telomerase to multidrug resistance was suggested to result from increased chromosome stability

and a strong expression of both *ABCB1* and *ABCC* genes [77]. As reported by Ji et al. [78], TR antisense oligonucleotides could downregulate the telomerase activity, increase radiation-induced DNA damage, and reduce the subsequent repair. Furthermore, it could inhibit the proliferation and increase cancer cell radiosensitivity; however, without telomere shortening. Similarly, Cerone et al. [18] demonstrated that mutated *TR* coding subunit resulted in an increased sensitivity of breast cancer cells to anticancer drugs. It was shown in cells with different initial telomere lengths and different mechanisms of telomere maintenance. Authors suggested that dysfunctional TR coding gene affects the binding of the shelterin complex, disturbs telomere capping, and induces a DNA damage response. It has been proposed that the mutant TR might interfere with alternative functions of telomerase [79] especially since the ability to synthesize new telomeric repeats is essential for the mutant TR-dependent effects.

Furthermore, Massard et al. [80] demonstrated that *TERT* repression may constitute a promising strategy for facilitating the induction of the mitochondrial pathway of apoptosis. Other researchers showed that BIBR1532 (2-[(*E*)-3-naphtalen-2-yl-but-2-enoylamino]-benzoic acid)-treated cells show progressive telomere shortening, decreased proliferative capacity, and sensitization to chemotherapeutic treatment [81]. It was postulated to be provoked by potent, selective, and reversible inhibitory action on human telomerase activity. This suggested that pharmacological telomerase inhibition in combination therapy may be a valid strategy for the treatment of both drug-sensitive and drug-resistant breast cancers. Interestingly, the combined effect of low-dose doxorubicin and siRNA inhibition of telomerase on breast cancer cells caused a rapid and potent apoptosis induction in breast cancer cells. The effect of doxorubicin was potentiated by the RNA interference directed against telomerase subunits [82]. Although numerous telomerase inhibition strategies cause cancer cells to undergo apoptosis or senescence, there is often a lag period between the beginning of the treatment regimen and a biological effect. Thus, much better perspectives are expected when applying effective telomerase inhibitors together with standard chemotherapeutic agents, Doxorubicin/Adriamycin or Taxol. Such attitude is supposed to provoke an increased sensitization and efficacy for triggering senescence and/or apoptosis in cultures of breast cancer cells while reducing toxicity [83].

First trials with oligonucleotides against telomerase showed that methoxyethyl oligomers (2′-*O*-methoxyethyl oligonucleotide) directed against the template region of telomerase are potent agents and that significant antiproliferative effects can be observed after 2–3 weeks of treatment. Reduced cell proliferation and tumor growth support the hypothesis that telomerase inhibition can make a useful contribution to chemotherapy and should encourage broad testing of telomerase inhibitors [84]. One of the most advanced telomerase-targeting strategies against cancer are represented by Geron (Menlo Park, Ca, USA). The technology being at the clinical trials at the moment is based on the oligonucleotides, called imetelstat sodium (originally known as GRN163L). GRN163L, a telomerase template antagonist, was effective in inhibiting telomerase activity and shortening telomeres in HER2-positive breast cancer cells [85]. It acts synergistically with trastuzumab in inhibiting HER2-positive MDA-MB-231 breast cancer cell growth. More importantly, it was shown that GRN163L can restore the sensitivity of therapy-resistant breast cancer cells to trastuzumab. These findings implicate that telomerase template antagonists might have a potential use in the treatment of cancers that have developed resistance to traditional cancer therapy [86]. It was also reported that breast cancer cells treated with GRN163L exhibited significantly diminished invasive potential [87]. As shown, long-term continuous treatment of cells with GRN163L results in progressive telomere shortening. It demonstrated that transient inhibition of telomerase activity by the specific inhibitor, GRN163L, increased the cytotoxicity of some, but not all, DNA-damaging agents. These results suggest that the protective role of telomerase in cell cycle-restricted DNA damage repair could be exploited for combined anticancer chemotherapy [88]. Recently, it was reported that Phase I clinical trials in breast cancer patients treated with GRN163L were successfully completed and the agent was selected for Phase II clinical trials. As it was demonstrated, the compound is characterized by promising bioavailability and pharmacokinetics. Phase II tests are currently ongoing and Imetelstat is tested in a combination with standard chemotherapeutic drugs (bevacizumab and paclitaxel) in a group of patients with locally relapsing or metastatic breast cancer [89].

Another group of telomerase-targeting drugs demonstrated by Geron are telomerase cancer vaccines—GRNVAC1 and GRNVAC2. They are autologous products consisting of mature dendritic cells (antigen-presenting cells) pulsed with RNA for the protein component of human telomerase (TERT) and a portion of a lysosomal targeting signal (LAMP). GRNVAC1 is injected into the patient's skin. From there, the dendritic cells travel to the lymph nodes and instruct cytotoxic T cells to kill tumor cells that express telomerase. Alternatively, Geron proposed another solution (GRN1005) based on peptide technology to facilitate the transfer of anticancer compounds across the blood–brain barrier (BBB) to enable the treatment of primary brain cancers and cancers that have metastasized to the brain. It is not connected with telomerase directly; however, due to the connection of telomerase with multidrug resistance, this mechanism of action cannot be totally excluded [85]. It is known that telomerase can function in a number of alternative signaling mechanisms and some of them could be involved in chemotherapeutic resistance, including DNA damage response, and DNA repair [90]. Thus, it is suggested that

upregulation of telomerase itself, independent of its role in telomere maintenance, is capable of providing an alternative pathway to drug resistance that does not require elongating telomere lengths [83]. In the light of carcinogenesis complexity and the contribution of mutations in many genes to the breast cancer development [91], it should be emphasized that monofunctional-targeted drugs will not cure most of the patients with common carcinomas. Thus, the multifunctional drugs or alternative treatment regimens are needed. Possibly telomerase inhibitors could be administered as adjuvant therapy in combination with conventional drugs to improve the efficiency of chemotherapeutic agents used in the low doses.

Summary and conclusions—prospects for cancer therapy

The expression of telomerase in various human cancers and its diminished expression in most normal cells suggest that the enzyme might serve as a good target for anticancer drugs. Due to telomerase inhibition, activity, or expression, these drugs might kill tumor cells by allowing telomeres to shrink or by provoking apoptosis. First of all, this process might have a chance to be cell-specific without serious side effects (Fig. 1). In contrast, most existing anticancer therapies disturb normal cells as well as malignant ones and often show some serious toxicity. Since telomerase seems to be a universal cancer marker, the agents targeting the enzyme might work against a broad spectrum of tumors. Nevertheless, a number of questions must be answered. For instance, researchers need to determine which normal cells (beyond the few already identified) reveal telomerase expression/activity and in what extent. They also need to assess the importance of the enzyme to those cells. Telomerase-inhibiting agents might cause cancer cells to lose their telomeres and die well before normal cells, with their much longer telomeres, lose enough of their telomeres to suffer any ill effects. It should be unquestionably demonstrated that inhibition of telomerase can destroy telomerase-producing tumors as expected. Another problem might be the delivery of telomerase-targeting agents in a way that would provide high efficiency and specificity. Therapeutic potential of vaccination has been explored in many clinical trials involving patients with breast cancer. A large variety of cancer immunogens have been tested. The majority of clinical vaccination studies have been carried out in patients with metastatic breast cancer, characterized by extremely aggressive malignant tumors, resistant to all standard cytotoxic treatments, and with longest-lasting disease. However, it is unclear whether therapeutic vaccines for cancer prolong survival. Data of clinical activity have been observed by using vaccines targeting HER-2/neu protein, human telomerase reverse transcriptase, carcinoembryonic antigen, and carbohydrate antigen given after stem cell rescue [92].

Intensive studies of telomerase functioning in human cells gave new perspectives on the mechanism of senescence, stem cells, and cancer therapy. The studies show that numerous enzymes are required for telomerase functioning that facilitate new approaches for inhibiting telomerase in treating cancer. Probably there are still numerous unrevealed proteins that contribute to regulation of such a dynamic complex. Anyway, it is still supposed to use both, activity and expression regulation methods, as adjuvant therapies similarly to G-quadruplex stabilization. Understanding of telomerase activity may then bring a new insight into many serious clinical problems that we have to face in aging societies especially since telomerase might be also considered as a predictive marker maybe even in malignant transformation. It is still unclear whether telomerase inhibitors will become a treatment option against cancer. There is concern about the alternative mechanisms of telomere maintenance and whether there will be side effects on normal, hematopoietic, and germline cells. These questions, however, can be only answered if those drugs are moved into animal and human clinical trials.

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Conflict of interest None

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