Human telomerase reverse transcriptase as a major therapeutic target in different cancer types

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Abstract

Telomerase is a known global therapeutic target in cancer cells. Human telomerase reverse transcriptase (hTERT) is a catalytic subunit of the telomerase enzyme. hTERT is usually silenced in almost all somatic cells but it is significantly expressed in ~90 % of human cancers. Many cancer suppressing genes produce factors that hinder hTERT activity. Here, in this review paper, an attempt has been made to emphasize the role of hTERT in different cancer types. Various recent therapeutic studies involving hTERT suppression have also been discussed. Serum hTERT mRNA levels have been found to reflect the tumour burden and the clinical status of the patient. Nano-formulations like nano-curcumin and nano-chrysin have also been shown to significantly decrease hTERT gene expression in SW480 cells. High frequency of hTERT-promoting mutations and increased expression of hTERT mRNA makes it a suitable target in different cancer types.

Introduction

Telomerase reverse transcriptase (TERT) is a catalytic subunit of the telomerase enzyme and is abbreviated as hTERT in case of humans. Telomerase is known as a global therapeutic target in cancer cells due to its main role in tumorigenesis [1]. Cancer cells achieve proliferative immortality by activating or upregulating the normally silent human TERT gene (hTERT) that encodes telomerase [2]. It has been proved that hTERT is aberrantly methylated in tumour tissue versus healthy counterparts [3]. The degradation of chromosomal ends is prevented by the addition of repetitive DNA sequences. The enzyme telomerase helps to lengthen the telomeres in DNA strands. TERT is liable for catalysing the nucleotide addition in a “TTAGGG” sequence to the ends of chromosomal telomeres. hTERT gene is located on chromosome 5 that consists 16 exons and 15 introns spanning 35 kb. Cri du chat is a rare genetic disorder reported due to absence of hTERT or deletion on chromosome 5. This disorder is also known as chromosome 5p-syndrome or Lejeune's syndrome.

Promoter of hTERT is GC-rich and deficient in TATA and CAAT boxes. Recent reports have implicated two cancer-specific hTERT promoter mutations (mainly C-T transitions) in the activation of telomerase in cancer cells [4]. These mutations, which are located either −124 base pairs (bp) or −146 bp upstream from the TERT translation start site have been found to be associated with increased telomerase activity [5]. High frequency of hTERT-promoting mutations and increased expression of hTERT mRNA in anaplastic thyroid cancer (ATC) make TERT a suitable molecular target for its treatment [6]. There are transcription factors that can initiate hTERT which includes many oncogenes and many cancer suppressing genes including p53 and WT1 have been reported to produce factors that hinder hTERT activity. hTERT plays an important role in colorectal cancer growth [7]. Although hTERT is usually silenced in almost all somatic cells but is significantly expressed in ~90 % of human cancers [2] thus confirming that over-expression of hTERT is associated with cancers and tumour formations.

hTERT in different cancer types

A number of studies were found targeting hTERT in different cancer types. Function and underlying molecular mechanism of MicroRNA -138 in cervical cancer was investigated and was found that MicroRNA -138 inhibits proliferation, migration and invasion through targeting hTERT in cervical cancer [8]. Nano-formulations have also been investigated for their efficacy to regulate hTERT expressions. Drug release study was performed using dialysis method and the cytotoxic and inhibitory effects of individual and combined drugs on expression level of hTERT in T47D breast cell line were evaluated using MTT assay and qPCR, respectively. Real-time PCR results revealed that Metformin (Met), Curcumin (Cur) and combination of Met-Cur in free and nano-encapsulated forms inhibited hTERT gene expression [9]. Similarly, a study revealed that Curcumin (Cur) and Chrysin (Chr) and combination of Cur-Chr in free and encapsulated forms inhibited hTERT gene expression [10]. Free and nano-encapsulated Chrysini-Curcumin has also been investigated for inhibition of hTERT gene expression in SW480 colorectal cancer cell line. A significant decrease in hTERT gene expression in SW480 cells that were treated with nano-curcumin and nano-chrysin as compared to untreated cells [11]. Silibinin-loaded magnetic nanoparticles have also been reported to inhibit hTERT gene expression and proliferation of lung cancer cells [12]. hTERT expression seems to promote invasiveness of cancer cells [13]. Resveratrol attenuates norepinephrine-induced ovarian cancer invasiveness through downregulating hTERT expression [14]. Table 1 summarizes various studies reporting the association of hTERT and different cancer types [15-41].

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Table 1. Studies reporting the association of hTERT with different cancer types

| Cancer type            | Authors                  | Year | Reference |
|------------------------|--------------------------|------|-----------|
| Breast cancer          | Chatran et al.           | 2018 | [15]      |
| Breast cancer          | Daniel and Tollefsbol    | 2018 | [16]      |
| Breast cancer          | Rasouli and Zarghami     | 2018 | [17]      |
| Breast cancer          | Jahanban-Esfahlan et al. | 2017 | [18]      |
| Breast cancer          | Thiriveni et al.         | 2018 | [19]      |
| Breast cancer          | Farajzadeh et al.        | 2018 | [9]       |
| Breast cancer          | Feng et al.              | 2017 | [20]      |
| Breast cancer          | Dinami et al.            | 2017 | [21]      |
| Breast cancer          | Ebrahimi-Nezhad et al.   | 2018 | [22]      |
| Breast cancer          | Yu et al.                | 2018 | [23]      |
| Breast cancer          | Aydin et al.             | 2018 | [24]      |
| Cervical cancer        | Zhou et al.              | 2016 | [8]       |
| Cervical cancer        | Molano et al.            | 2016 | [25]      |
| Cervical cancer        | Yang et al.              | 2017 | [26]      |
| Gastric cancer         | Zhang et al.             | 2017 | [27]      |
| Gastric cancer         | Zhang et al.             | 2018 | [28]      |
| Gastric cancer         | Mahfouz et al.           | 2017 | [29]      |
| Lung cancer            | Ludlow et al.            | 2018 | [30]      |
| Lung cancer            | Yang et al.              | 2017 | [31]      |
| Lung cancer            | Amirnasab et al.         | 2017 | [12]      |
| Lung cancer            | Sadeghzadeh et al.       | 2017 | [32]      |
| Lung cancer            | Chen et al.              | 2017 | [33]      |
| Lung cancer            | Jahanban-Esfahlan et al. | 2017 | [18]      |
| Lung cancer            | Lin et al.               | 2018 | [34]      |
| Lung cancer            | Zalewska-Ziob et al.     | 2017 | [35]      |
| Head and neck cancer   | Barczak, Sobeka et al.   | 2018 | [36]      |
| Head and neck cancer   | Sobeka et al.            | 2018 | [3]       |
| Head and neck cancer   | Barczak, Suchorska et al.| 2017 | [37]      |
| Colon cancer           | Martin, Kala and Tollefsbol | 2018 | [38]    |
| Bladder cancer         | Marsh-Villalba et al.    | 2018 | [39]      |
| Bladder cancer         | Huang et al.             | 2017 | [40]      |
| Non-small-cell lung cancer | Ludlow et al.            | 2018 | [30]      |
| Non-small-cell lung cancer | Lin et al.               | 2018 | [34]      |
| Non-small-cell lung cancer | Zalewska-Ziob et al.     | 2017 | [35]      |
| Non-small-cell lung cancer | Chen et al.              | 2017 | [33]      |
| Thyroid cancer         | Lombardo et al.          | 2018 | [6]       |

Bufalin can induce apoptosis in certain human cancer cell lines. Zhang et al. [7] investigated the role and interactions of bufalin, CPSF4 and hTERT and the effects of bufalin in human colorectal cancer. The results revealed that CPSF4 acts as an hTERT promoter-binding protein in colorectal cancer cells. Alternative splicing is dysregulated in cancer and the reactivation of telomerase involves the splicing of TERT transcripts to produce full-length (FL) TERT. A study by Ludlow et al. [30] identified splicing factors that reduced telomerase activity and shortened telomeres. NOVA1, when knocked down resulted in a shift in hTERT splicing to non-catalytic isoforms, reduced telomerase activity, and progressive telomere shortening. Similarly, ZEB1 stimulates the growth and was found to be positively correlated with hTERT expression in breast invasive ductal carcinoma samples at both the mRNA and protein levels [23]. This study revealed a new ZEB1- hTERT signalling pathway involved in regulation of cell proliferation in breast cancer. Melissa officinalis extract (MOE) elicits potent anti-proliferative effects on different human cancer cells. MOE has been reported to result in a significant downregulation of hTERT (0.023 fold) compared to the untreated control [18]. It was further suggested that the potent anti-proliferative activity of the hydro-alcoholic extract of Melissa officinalis is somehow explainable by its high potency to inhibit expression of the prominent oncopgenes Bcl2, Her2, VEGF-A and hTERT in prostate cancer.

Likewise, the mechanistic investigation showed that the tumour-promoting role of Bromodomain PHD finger transcription factor (BPTF) in hepatocellular carcinoma (HCC) was realized by transcriptionally regulating the expression of hTERT. Furthermore, it was found that patients with high BPTF expression displayed high hTERT expression. High BPTF or hTERT expression levels were positively correlated with advanced malignancy and poor prognosis in HCC patients [42]. Another research study explored the relationship between quantitative mRNA determination (hTERT) in patients with bladder tumour, history of bladder tumour, and in subjects without a history of this neoplasia. Differences were observed in mean hTERTN levels in each of the groups: tumour presence 21.33±40.66, tumour history 2.16±2.67 and controls 0.9±1.75 (p<0.001). In patients with tumour, there was no difference in mean hTERTN levels between the different grades and stages. Thus, hTERTN mRNA levels in urine were higher in patients with bladder tumours compared to patients with a history of bladder tumour and with negative cystoscopy, as well as in the control group presenting hTERTN as a useful biomarker in bladder tumours [39]. Serum hTERT mRNA levels may reflect the tumour burden and the clinical status of the patient. A study evaluated the feasibility of the detection of hTERT transcripts in serum. hTERT mRNA levels were determined in serum and serum-derived exosomes from 133 patients with different malignancies and 45 healthy controls.
hTERT transcript was absent in all controls and was variably detected in 67.5% of patients with all cancer types. A correlation between hTERT transcript levels and the clinical course was found in several cases evidencing that mRNA levels may reflect the tumour burden [43].

Conclusion

Human telomerase reverse transcriptase (hTERT), a catalytic subunit of the telomerase enzyme and is significantly expressed in ~90% of human cancers. In the present review paper, a number of studies were found reporting the association of hTERT with different cancer types. A large number of studies were found reporting the role of hTERT in breast and lung cancers. Now a days, hTERT has been taken as a useful therapeutic target in different studies to cope up with the menace of cancer. Many studies were found putting up different moieties to significantly decrease hTERT gene expression including MicroRNA-138, metformin, curcumin, chrysin and extracts of Melissa officinalis extracts and Silibinin-loaded magnetic nanoparticles. Conclusively, downregulation of hTERT expression should be the prime focus of the future studies so as to put forward new strategies to control tumorigenesis.

Conflicts of interest
None declared.

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