Role of telomerase in the tumour microenvironment

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Abstract
Telomeres are specialized genomic structures that protect chromosomal ends to maintain genomic stability. Telomeric length is primarily regulated by the telomerase complex, essentially consisting of an RNA template (TERC), an enzymatic subunit (telomerase reverse transcriptase, TERT). In humans, telomerase activity is repressed during embryonic differentiation and is absent in most somatic cells. However, it is upregulated or reactivated in 80%–90% of the primary tumours in humans. The human TERT (hTERT) plays a pivotal role in cellular immortality and tumourorigenesis. However, the molecular mechanisms of telomerase functioning in cancer have not been fully understood beyond the telomere maintenance. Several research groups, including ours, have demonstrated that hTERT possesses vital functions independent of its telomere maintenance, including angiogenesis, inflammation, cancer cell stemness, and epithelial–mesenchymal transformation (EMT). All these telomere-independent activities of hTERT may contribute to the regulation of the dynamics and homeostasis of the tumour microenvironment (TME), thereby promoting tumour growth and development. Cancer progression and metastasis largely depend upon the interactions between cancer cells and their microenvironment. In this review, the involvement of TERT in the tumour microenvironment and the underlying implications in cancer therapeutics have been summarized.

Keywords
angiogenesis, inflammation, telomerase, TERT, tumour microenvironment

1 | INTRODUCTION

The tumour mass is an organ-like structure consisting of cancer cells and their directly associated microenvironment. The tumour microenvironment (TME) is the local environment where malignant cells strive and survive, and is composed of cancers cells and their surroundings such as blood vessels, extracellular matrix (ECM), infiltrating immune cells, fibroblasts, and signalling molecules.¹,² In addition, cancer stem cells (CSCs) and endoplasmic reticulum (ER) stress influence the properties of the TME to benefit tumour cell growth.³,⁴ The cross-talk between the cancer cells and their environment involves numerous oncogenic transcription factors. These factors are aberrantly reactivated and trigger a series of cellular events such as genome instability, reprogrammed metabolism, infinite proliferation, angiogenesis, invasion and metastasis, immune cell infiltration, and enhanced inflammation, all of which have been widely recognized as the characteristics of cancer.⁵–²⁵

Telomeres consist of a non-coding DNA tandem repeat of sequence 5′-TTAGGG-3′, located at the ends of the linear eukaryotic chromosomes.²⁶,²⁷ Due to “the end replication problem”, the telomeres shorten with each round of DNA replication. Once their lengths shorten to a certain level, the cells may undergo replicative senescence.²⁶,²⁸ Telomerase is an RNA-dependent DNA polymerase that synthesizes telomeric DNA sequences and maintains the telomere length, providing the immortal cells with the molecular basis for unlimited proliferation potential. Human telomerase essentially
consists of a catalytic component TERT, telomerase template RNA component (TERC). 29 Regardless of the telomerase activity, TERC is universally expressed in cells. In contrast, the expression of TERT is the primary determinant of telomerase activity. While this activity is repressed in somatic cells, it is reactivated in 90% of human cancer cells. 30,31 It is well documented that TERT expression or telomerase activity confers the cells with unlimited proliferation capability by elongating telomere length and bypassing the senescence checkpoint. 32,33 However, accumulating evidence also reveals that TERT exhibits multiple oncogenic activities that are independent of the reverse transcriptase activity. A substantial number of clinical studies have shown a strong correlation among levels of TERT expression and tumour malignancy. 34 Consistently, it has been described that TERT can function as a transcriptional co-activator by interacting with several other important transcription factors. This enables TERT to modulate the specific gene expression profiles in favour of epithelial–mesenchymal transformation (EMT), invasion and metastasis, angiogenesis, inflammation and immunosuppression, activation of fibroblasts, and the pluripotency of CSCs. These telomere-independent activities of hTERT could greatly contribute to the dynamics and homeostasis of the TME. 35-41

In this review, we will focus on the role of TERT in TME and elucidate the underlying implications in the cancer therapeutic intervention.

2 | TERT PROMOTES TUMOUR ANGIOGENESIS

Angiogenesis is an extremely complex process involving the proliferation, migration, and lumen formation of endothelial cells. In most malignant tumours, angiogenesis is dense and occurs rapidly. New blood vessels not only provide nutrients and oxygen for tumour cell growth but also furnishes a metastatic environment that supports tumourigenesis. 42 Pallini et al revealed a direct correlation between the mRNA expression of TERT in neovascular endothelial cells and the histological grade of human tumours. 43 In a mouse model of angiogenesis, the TERT knockdown in endothelial cells reduced the formation of microvessels. On the contrary, the microvessel formation was highly enhanced upon upregulation of TERT expression. 44 Ectopic TERT expression has specifically been shown to improve the formation of persistent microvascular structures in human dermal microvascular endothelial cells, in addition to the proliferation, migration, and survival of endothelial progenitor cells in immunodeficient mice. 45 Conversely, inhibition of telomerase activity in the human umbilical vein endothelial cells (HUVECs) of glioblastoma xenografts, either by siRNA or by a dominant-negative (DN) allele of hTERT, has been reported to disrupt tumour angiogenesis significantly in the tumour environment. 44 Furthermore, treatment with IFN-γ and knockdown of the TERT gene in human glioblastoma cells can reduce the production of pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). Subsequently, there was a reduction in the extent of microvascular formation, thereby effectively inhibiting angiogenesis and tumorigenesis. 46 A previous report by our group demonstrated that hTERT could facilitate tumour angiogenesis by upregulating VEGF expression through direct interactions with the Vegf gene and the Sp1 transcription factor. Conversely, deletion of the mTert gene in the first generation of Tert null mice compromised tumour growth, with lowered VEGF expression and CD31-positive tumour-associated microvessel formation. 28 Intriguingly, the angiogenic factors such as VEGF and bFGF have been identified to upregulate TERT expression by activating its promoter via PI3K/Akt, nitric oxide, and ERK 1/2 pathways. 47,48 Thus, this kind of autocrine feedback loop may possibly enable TERT to contribute to angiogenesis and tumour progression. Nonetheless, tumour angiogenesis is a complex process regulated by multiple factors, and the specific molecular mechanism beneath TERT-mediated regulation of tumour angiogenesis needs further investigation.

3 | TERT CONTRIBUTES TO SHAPING OF THE INFLAMMATION AND IMMUNOSUPPRESSIVE ENVIRONMENT

Inflammation can upregulate growth factors, survival factors, promote angiogenesis, and induce EMT, all of which contribute to the tumour progression. 24,49-55 The key inflammatory cytokines, such as IL-6, IL-8, and TNF-α, that activate the NF-κB pathway, have also been shown to be positively regulated by TERT through the NF-κB pathway. 26 It has been proven that IL-6 is essential in creating a “chemo-resistant niche” and in promoting cancer progression. 56 Besides, IL-8 and TNF-α were also revealed to be involved in the proliferation, invasion, metastasis, and inhibition of apoptosis in cervical and breast cancers. 57-59 A few studies, including ours, found that TERT could interact with RelA/p65 as a transcriptional co-activator to activate the NF-κB target genes such as interleukins IL-6, IL-8, and TNF-α, which are critical for inflammation and cancer progression. 36,37 Interestingly, NF-κB has been experimentally demonstrated as an activator of TERT expression, potentially amplifying the TERT-dependent carcinogenic effects. 36,60 These findings suggest that the feedback loop between the NF-κB pathway and TERT may reinforce the inflammatory signalling, leading to the development of inflammation in the TME.

The TME usually showcases its immunosuppressive features in the presence of the tumour and immune cells, allowing immune evasion and tumour progression. 61,62 Chronic inflammation and myeloid-derived suppressor cells (MDSCs) together conduct to constitute an immunosuppressive environment in the TME. 63 In fact, IL-6 has been confirmed as a key inflammatory cytokine that creates an immunosuppressive TME. 63,64 In breast cancer, IL-6 has been demonstrated to contribute to the immunosuppressive TME by activating the STAT3/NF-κB/IDO pathways in MDSCs. 65,66 Additional studies reveal that IL-6 inclines the TME towards immunosuppression largely by stimulating the infiltrations of MDSCs. Clearly, an interaction between IL-6 and MDSCs contributes to the formation
of the immunosuppressive TME. It has been noted that MDSCs negatively affect immune responses via inhibiting T-cell activity and upregulating immunosuppressive cells and cytokines. Apart from exerting an immunosuppressive effect, MDSCs also promote tumour angiogenesis, invasion, and metastasis via production of matrix metalloproteinase-9 (MMP9), VEGF, and bFGF proteins, all of which are direct targets of TERT. Schupp et al found that VEGF, released by cancer cells induces the production of MDSCs in the bone marrow. All the studies suggest that TERT might directly and indirectly regulate the inflammation and immunosuppression within the TME.

4 | ROLE OF TERT IN ACTIVATION OF FIBROBLASTS

Telomerase reverse transcriptase promotes cell proliferation by modulating the expression of growth-controlling genes. Human immortalized fibroblasts can be generated by overexpression of hTERT. Compared with normal fibroblasts, the expressions of 172 genes were found to be altered, including that of epiregulin, a growth factor belonging to the epidermal growth factor (EGF) family. Gorbunova et al found that hTERT-expressing fibroblasts were able to avoid apoptosis and necrosis induced by physicochemical factors. It is also shown that TGF-β plays a chief role in the transformation of fibroblasts into cancer-associated fibroblasts (CAFs). In mouse embryonic fibroblasts (MEFs), ectopic expression of TERT could antagonize the TGF-β-dependent growth inhibition, elevating the proliferative potential of these cells.

The CAFs are activated fibroblasts found in numerous types of solid cancers and are characterized by expression of activation markers such as FAP, α-SMA, and multiple secretory factors. Being highly abundant in the TME, CAFs not only promote tumour initiation, progression, and recurrence, but also participate in the microenvironment remodelling processes such as angiogenesis, ECM degradation, cancer-associated inflammation, and metabolic reprogramming. Studies show that there is a cross-talk between TLR4/NF-κB signalling and fibroblast activation. The LPS-stimulated fibroblast activation is executed cumulatively by induced expression of FAP, secretion of collagen I and TGF-β, and activation of TLR4/NF-kB signalling of the uterine fibroid fibroblasts. Furthermore, Dickkopf1 (Dkk1), an antagonist of Wnt signalling that reduces the accumulation of β-catenin, was injected into the mouse model of renal fibrosis. Consequently, a decrease in the α-SMA protein levels was observed, indicating that Wnt/β-catenin pathway influences α-SMA expression levels.
has now been demonstrated that TERT can activate NF-κB and Wnt/β-catenin pathways, and thereby increase the expression of its downstream target genes. Therefore, it is postulated that TERT is likely involved in regulating the expressions of α-SMA and FAP through activation of NF-κB and Wnt/β-catenin signalling pathways, which ultimately lead to the activation of CAFs. Taken together, studies suggest that it might play an imperative role in regulating fibroblast proliferation and survival. Nevertheless, considerable efforts are still needed to investigate the role and the specific mechanisms by which TERT regulates the activation of CAFs in the TME.

5 | ROLE OF TERT IN CANCER STEM CELLS

Cancer stem cells are a subset of tumour cells that are able to self-renew, proliferate, and differentiate similar to the normal stem cells. CSCs have been shown to possess a tumour-initiating capacity, closely interacting with the TME. Both these elements rely on each other, subsequently favouring tumour promotion. Increasing evidence reveals that CSCs can not only adapt to alterations in the TME but also affect the TME. Moreover, various factors derived from the tumour microenvironment work in synergistically to promote self-renewal and prevent differentiation of CSCs. Recently, studies demonstrated that CSCs express higher levels of TERT, which can regulate various CSCs-associated cellular behaviours such as pluripotency, proliferation, gene expression, and therapeutic resistance. For instance, while hTERT overexpression can promote stemness of gastric CSCs, its inhibition can suppress the stemness by regulating the expression of the CSC marker CD44. The siRNA-mediated silencing of hTERT in gastric CSCs can also inhibit the production of a well-known stem cell marker OCT-4, suggesting that TERT has the potential to maintain the pluripotency in CSCs. Zhang et al further demonstrated that hTERT-mediated CSC properties were at least partly dependent on β-catenin signalling in prostate CSCs. It is also known that most CSCs require EGFR signalling to maintain their stemness.
Reports have revealed that TERT promotes stem cell-like features in glioma cells and maintains glioma stem cell properties by inducing EGFR expression, which is independent of its telomerase activity. Conversely, lower TERT expression in turn leads to a reduced expression of EGFR and bFGF, promoting loss of glioma stem cell properties. However, the specific molecular mechanism of TERT regulation in maintaining the stemness of CSCs remain unclear and prompt for further investigations.

6 | TERT PROMOTES TUMOUR INVASION AND METASTASIS

Invasion and metastasis are complex processes that are regulated by several components of the TME. The ECM is a key non-cellular component of TME and acts as a barrier to tumourigenesis. The EMT is an indispensable biological process in cancer progression by which the epithelial-derived malignant cells acquire the ability to migrate and invade. The degradation of ECM and induction of EMT are necessary for tumour invasion and metastasis. The tumour invasion and metastasis in the TME have also been demonstrated to be facilitated by MMPs, which are zinc-containing endopeptidases that cleave the ECM and destruct the basement membrane structure. Ding et al showed that TERT could increase the expressions of MMP1, MMP3, MMP9, and MMP10 proteins of the MMP family to promote tumour invasion independent of telomerase activity. This was executed by TERT-mediated enhancement of the NF-κB pathway, which is a critical pathway for EMT. Overexpressed TERT also activates the Wnt/β-catenin signalling pathway by binding to β-catenin directly as a transcriptional co-activator and upregulating the downstream target genes such as Snail-1 and vimentin, along with facilitating EMT. Similarly, TERT can also synergize with transforming growth factor β (TGFβ) and β-catenin to promote EMT in gastric cancer cells. Additional studies have shown that hTERT could facilitate cellular metastasis in HCT116 and SW480 cells by forming a complex with ZEB1 that directly binds to the E-cadherin promoter and inhibits the expression of E-cadherin. Besides, other components of the TME such as angiogenesis, inflammatory environment, and CAFs provide a metastatic environment for tumours and promote tumour invasion and metastasis. As mentioned previously, TERT can contribute to angiogenesis, inflammation, and the activation of CAFs by regulating several cytokines and growth factors. Collectively, these findings indicate that TERT directly regulates tumour invasion and metastasis during cancer development and/ or progression.

7 | CONCLUSIONS AND PERSPECTIVES

Credible evidence indicates that hTERT plays a pleiotropic role independent of telomere maintenance in many aspects of the TME. We speculate that TERT can act as a co-activator to excite multiple signalling pathways for regulating various features of the TME such as angiogenesis, inflammation and immunosuppression, fibroblast activation, and maintenance of CSCs pluripotency. This contributes to the TME for promoting tumour invasion and metastasis (Table 1). Interestingly, most of the genes regulated by TERT are known activators of TERT expression, that can up-regulate transcription of TERT and enhance the telomerase activity (Figure 1). Therefore, it is debatable whether TERT may be involved in the dynamics and homeostasis of the TME by amplifying transcriptional outputs through such feedback loops. It is well recognized that NF-κB, Wnt/β-catenin, and PI3K/Akt pathways can also cross-talk with other oncogenic pathways such as the Notch, STAT3, MEK/ERK, and MAPK pathways. Thus, the effects of TERT on these pathways may potentially have multiple indirect oncogenic effects. However, there are many other unresolved questions regarding the effects of TERT on TME, and the genetic mechanisms involved in its regulation, which demand further evaluation. In addition, recent study demonstrates that telomerase can contribute to telomere shortening by stabilizing stalled replication forks at telomeres in certain genetic context, which compromises replication and leads to telomere dysfunction. The detailed mechanistic action of telomerase within and beyond telomeres clearly merits future investigation.

Since tumour development is highly dependent on the specific TME, a huge effort has been made to develop new therapeutic strategies targeting TME components such as blood, ECM, immune cells, and fibroblasts, to enable a more efficient targeting of TME. However, the TME of solid tumour is highly heterogeneous and complex. The development of effective anti-cancer therapies has been challenged by the overall complexity of tumours. Due to the roles of TERT in regulating the components of TME, developing the therapeutic approaches targeting of TERT in TME may increase the effectiveness of cancer therapy. While targeting TERT in the TME, multiple features of the TME may be targeted simultaneously, avoiding the menace of multidrug resistance and presenting lower toxicity. Thus, a precise understanding of the contribution of TERT in the different components of the TME in specific cancer types is a prerequisite to designing better therapeutic agents. Since TERT is also a determinant of telomerase activity, targeting TERT can simultaneously limit the proliferation potential of cancer cells by hindering the telomerase activity. It would also restrict invasion and metastasis by interfering with the TME.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.
AUTHORS CONTRIBUTIONS
All authors were participated in manuscript writing. All authors read and approved the final manuscript.

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