Review

Molecular Cancer Research

Understanding TERT Promoter Mutations: A Common Path to Immortality

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Abstract

Telomerase (TERT) activation is a fundamental step in tumorigenesis. By maintaining telomere length, telomerase relieves a main barrier on cellular lifespan, enabling limitless proliferation driven by oncogenes. The recently discovered, highly recurrent mutations in the promoter of *TERT* are found in over 50 cancer types, and are the most common mutation in many cancers. Transcriptional activation of *TERT*, via promoter mutation or other mechanisms, is the rate-limiting step in production of active telomerase. Although *TERT* is expressed in stem cells, it is naturally silenced upon differentiation. Thus, the presence of *TERT* promoter mutations may shed light on whether a particular tumor arose from a stem cell or more differentiated cell type. It is becoming clear that *TERT* mutations occur early during cellular transformation, and activate the *TERT* promoter by recruiting transcription factors that do not normally regulate *TERT* gene expression. This review highlights the fundamental and widespread role of *TERT* promoter mutations in tumorigenesis, including recent progress on their mechanism of transcriptional activation. These somatic promoter mutations, along with germline variation in the *TERT* locus also appear to have significant value as biomarkers of patient outcome. Understanding the precise molecular mechanism of *TERT* activation by promoter mutation and germline variation may inspire novel cancer cell-specific targeted therapies for a large number of cancer patients. *Mol Cancer Res; 14(4); 315–23. ©2016 AACR.*

Telomeres are composed of "TTAGGG" repeats at the end of chromosomes, and telomere length plays a critical role in multiple human diseases including cancer (1, 2). Telomere length is regulated by telomerase, the large multicomponent reverse transcriptase that recognizes, binds, and elongates the telomere ends using its intrinsic RNA template (3, 4). The *TERT* gene encodes the catalytic subunit of telomerase, and its transcriptional regulation is usually the limiting step in telomerase activity (5–8). Telomerase activity is silenced in the majority of normal tissues, causing telomeres to shorten with each successive round of cell division (9, 10). Eventually, a critical telomere length is reached (9, 11–13), and cells enter replicative senescence (14–16). In contrast, cells that require high rates of self-renewal such as cells in the ovary (10), intestinal epithelium (17), and hematopoietic stem cells (18) have telomerase activity and can maintain telomere length over many cell divisions. The expression of telomerase is considered a hallmark of tumorigenesis, as over 90% of human cancers express the enzyme (10, 19, 20). The cancers found to be telomerase negative use an alternative mechanism of telomere lengthening termed *ALT* (21–23). Furthermore, germline variation in genes involved in telomere regulation such as *RTEL1*, *POT1*, *TERC*, *TERT*, and genes of the CST complex underlies increased risk of glioma (24–27), melanoma (28), and cancers of the lung (29, 30), bladder (28), and pancreas (31).

In 2013, two hotspot point mutations were found in the *TERT* promoter in 71% of melanomas (32, 33). The mutations were located 124 and 146 bp upstream of the translation start site and referred to as C228T and C250T, respectively, based on their hg19 genomic coordinates. The mutations are typically heterozygous, occur in a mutually exclusive fashion, and both create an identical 11 bp sequence "CCCGGAAGGGG." The mutated sequence has an increased similarity to an ETS binding motif, leading to the hypothesis that the mutations generate a *de novo* binding site for an activating ETS family transcription factor (TF). Soon after their initial discovery, the *TERT* promoter mutations were found to be the most common point mutations in several tumor types including 83% of glioblastoma (34), 71% of melanoma (32, 33), 66% of bladder cancer (35), and 47% of hepatocellular carcinoma (HCC; refs.34, 36). To date, the hotspot mutations have been identified in over 50 distinct cancer types (Fig. 1). Both mutations activate *TERT* promoter activity and *TERT* gene transcription (32, 33). In bladder cancer, Borah and Xi and colleagues have also demonstrated that the promoter mutations are associated with increased telomerase activity and stable telomere length (37). Less commonly, *TERT* can be activated by other genetic mechanisms including rare point mutations at other promoter positions (37), rearrangements (38, 39), duplication (40), or amplification (41, 42). *TERT* promoter mutations were not detected in other common cancer types, such as breast and prostate cancer (Fig. 1).

The high frequency of *TERT* promoter mutations in just two nucleotide positions strongly implicates them as driver events, arising upon tumor initiation or potentially later in tumor evolution (43). However, recent studies suggest *TERT* promoter

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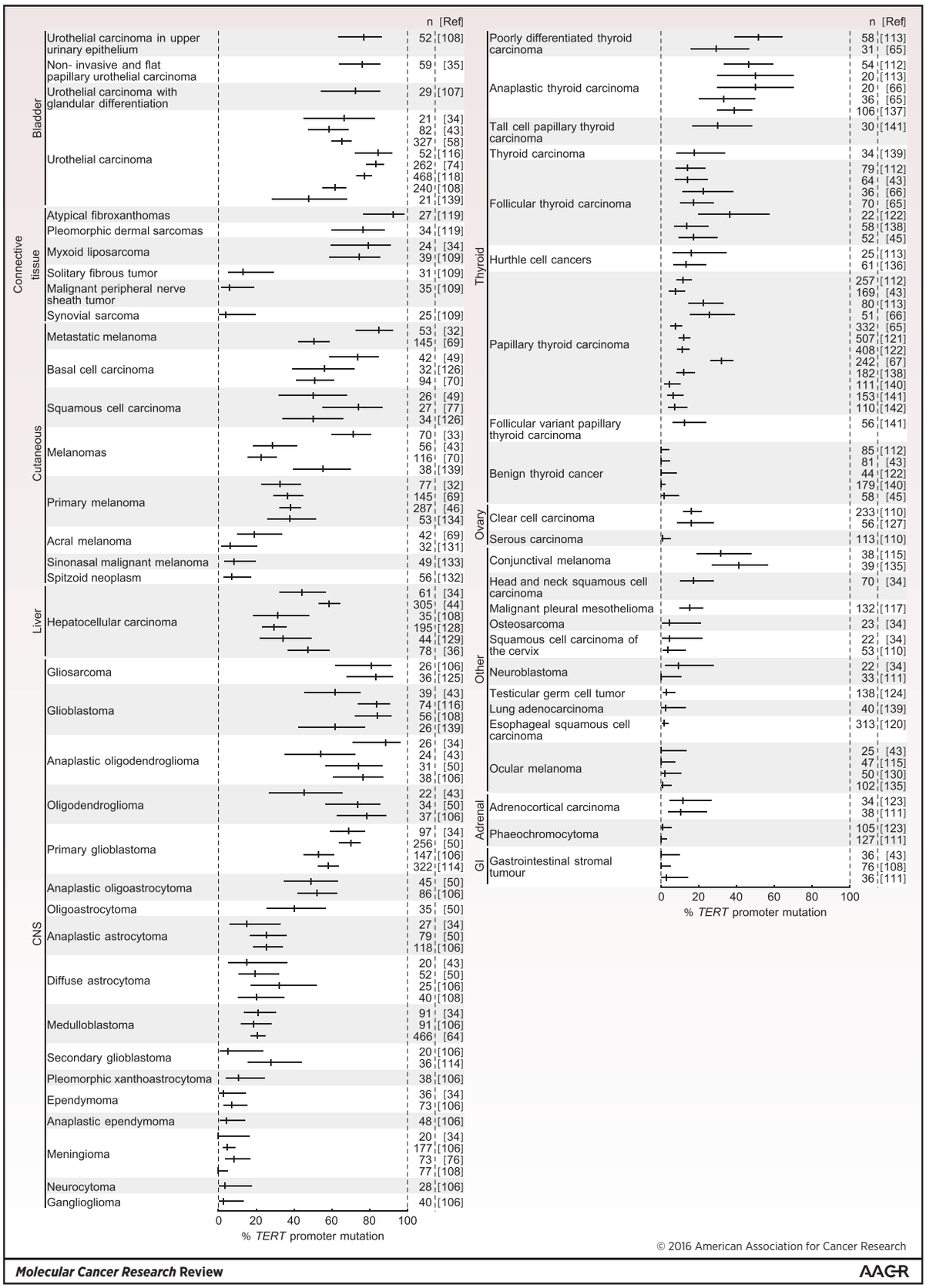

mutations are among the earliest genetic events in bladder cancer (35), HCC (44), thyroid carcinoma (45), cutaneous melanoma (46–48), basal cell and squamous cell carcinoma (49), and oligodendroglioma (50). *TERT* promoter mutation may be the second genetic event following the activation of an oncogenic signaling pathway, such as MAPK signaling in melanoma (46) or Wnt signaling in HCC (44). It is unclear whether reactivation of telomerase through *TERT* promoter mutation is required only for early stages of tumorigenesis or is also necessary for sustained neoplastic growth (37).

Stem cells have been proposed as the cell of origin in multiple types of cancer. Because these cells express *TERT*, tumors originating from stem cells may not require *TERT* promoter mutations to activate telomerase and maintain telomere function. Interestingly, *TERT* promoter mutations occur most frequently in cancers with low rates of self-renewal, such as cancers of the brain, liver, and melanocytes (34). In human embryonic stem cells genetically engineered to contain the hotspot mutations, there was little effect on *TERT* expression, but these cells failed to silence *TERT* upon differentiation (51). These observations raise the possibility that cells with low rates of self-renewal and lack of *TERT* expression acquire a *TERT* promoter mutation to avoid replicative senescence during early carcinogenesis. In contrast, transformation of *TERT*-expressing stem cells such as hematopoetic stem cells may not require promoter mutation to maintain *TERT* expression through tumorigenesis. As an alternative to mutation, *TERT* promoter activation may occur through an epigenetic switch (52). Stern and colleagues have additionally suggested that *TERT* promoter mutations can convert the silent *TERT* promoter into an active chromatin state (53).

Germline variation near or within the *TERT* gene is associated with telomere length in peripheral blood leukocytes and risk of *TERT* promoter mutant (25, 54) and nonmutant (55–57) cancer. Notably, the *TERT* promoter polymorphism rs2853669 modulates the prognostic value of *TERT* promoter mutations across a variety of tumor types. The rs2853669 common allele is thought to create a binding site for the ETS/TCF factor ETS2 99bp and 121bp upstream of the C250T and C228T hotspot mutations, respectively (58). In the presence of a somatic *TERT* promoter mutation in the tumor, patients with the rs2853669 common allele showed decreased overall survival and increased tumor recurrence rate in bladder cancer (58, 59) and decreased mean survival in glioma (60). In addition, gliomas bearing the common allele of rs2853669 and a hotspot promoter mutation have significantly increased *TERT* expression compared with tumors with the rs2853669 minor allele, suggesting a possible molecular link between the hotspot mutation sites and the rs2853669 site in the *TERT* promoter (61). However, other studies reported the minor allele to associate with decreased overall survival in *TERT*-mutant glioma (62) or have no prognostic effect with either allele (63). Thus, determining the precise prognostic value of rs2853669 may require larger sample sizes and cohorts with more extensive treatment information.

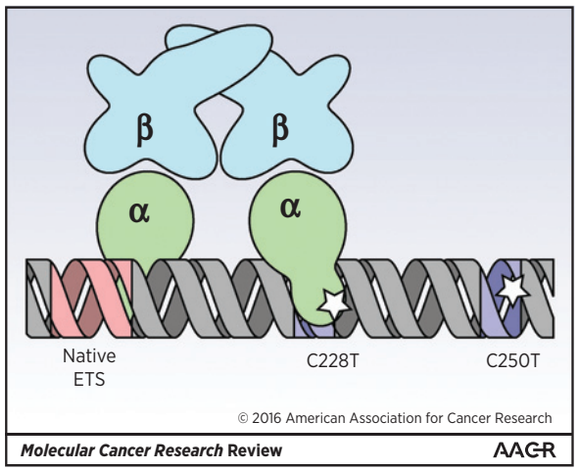

Figure 2.
A model for the activation of the mutant *TERT* promoter by GABP recruitment as a heterotetramer. The GABP heterotetramer is made up of two GABPA (green) and two GABPB (blue) subunits. GABPA is responsible for direct DNA binding, and one subunit is hypothesized to bind to the promoter mutation (stars in blue sections) whereas the other binds to a native ETS binding site further downstream (red highlighted section).

The prognostic power of *TERT* promoter mutations highlights their potential use as clinical biomarkers. In addition to bladder cancer and glioma, the presence of *TERT* promoter mutations is associated with decreased overall survival in medulloblastoma (64), thyroid cancer (65–67), urogenital cancer (58, 67), melanoma (69, 70), and laryngeal tumors (71). Furthermore, *TERT* promoter mutations may serve as biomarkers to distinguish subtypes of urologic malignancies (35, 72–74). They also predict malignant transformation of premalignant nodules in HCC (75) and meningiomas (76), and associate with the anatomic origin of squamous cell carcinomas (77). A new and powerful molecular classification of glioma subtypes is based on three common genetic alterations in the tumors, including *TERT* promoter mutations (78–80), that predicts overall survival with higher accuracy than traditional classification based on histology. The molecular classification will be useful in clinical trials to enable improved interpretation of patient response to therapy (80, 81).

On the basis of the identical 11bp DNA sequence motif created by the *TERT* promoter mutations, the mechanism of promoter activation was hypothesized to involve recruitment of an ETS

Figure 1.
Prevalence of *TERT* promoter mutations in human cancers. The frequency of *TERT* promoter mutations is plotted for all tumor types in which at least 20 samples have been tested. Horizontal lines indicate Wilson score confidence intervals. In contrast to these tumor types, no *TERT* promoter mutations were found in the following cancers: oral mucosal melanoma [$n = 39$ (105)], pilocytic astrocytoma [$n = 111$ (106)], medullary thyroid carcinoma [$n = 24$ (34), $n = 28$ (43), $n = 37$ (66)], metastatic bladder adenocarcinoma [$n = 30$ (107), colorectal adenocarcinoma [$n = 22$ (34)], gastric cancer [$n = 74$ (108)], breast carcinoma [$n = 88$ (34)], cholangiosarcoma [$n = 28$, (34)], dedifferentiated liposarcoma [$n = 61$ (109)], leiomyosarcoma [$n = 27$ (109)], undifferentiated pleomorphic sarcoma [$n = 40$ (109)],myeloid leukemia [$n = 48$ (34)], pancreatic cancer [$n = 46$ (108)], pancreatic acinar carcinoma [$n = 25$ (34)], pancreatic ductal adenocarcinoma [$n = 24$ (34)], prostate carcinoma [$n = 34$ (34)], endometrioid carcinoma [$n = 43$ (110)], leiomyosarcoma [$n = 22$ (110)], endocervical adenocarcinoma [$n = 25$ (110)], endometrial cancer [$n = 24$ (110)], intrahepatic cholangiocarcinoma [$n = 52$ (36)], thymoma [$n = 47$ (108)], head and neck paraganglioma [$n = 37$ (111)], lung squamous cell carcinoma [$n = 25$ (77)].

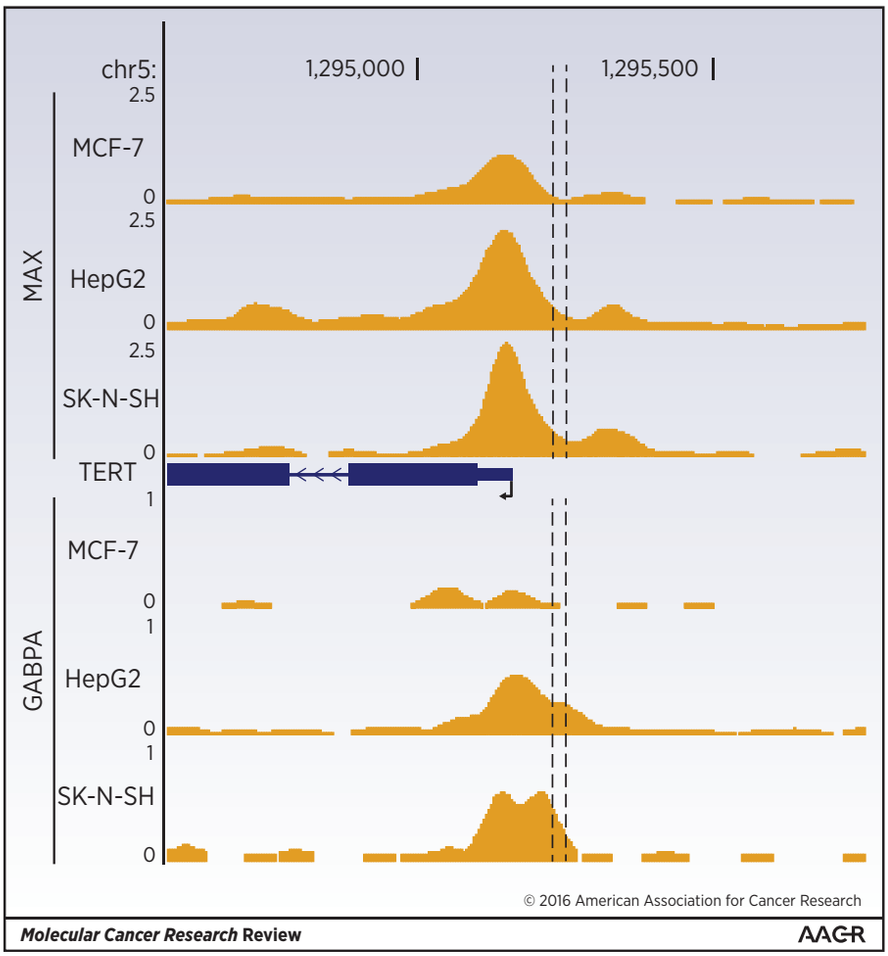

Figure 3.
GABPA and MAX binding at the *TERT* promoter in ENCODE cell lines. ChIP-seq coverage for GABPA and MAX is displayed at the *TERT* promoter for MCF-7 (WT), HepG2 (C228T), and SK-N-SH (C228T) cells, respectively. MAX binding is observed in all three cell lines whereas GABPA binding is specifically associated with *TERT* promoter mutation status.

family TF. Indeed, site-directed mutagenesis of the hotspot positions in a promoter–reporter plasmid revealed the generated ETS motif was necessary for promoter activation (40). There are 27 ETS factors, however, and most bind a very similar DNA sequence *in vitro*, suggesting extensive redundancy (82). It was therefore surprising that GABPA but no other ETS factors were identified to be the TF responsible for mutant *TERT* activation (40). GABPA is the only ETS factor of those expressed in *GBM* to selectively regulate the mutant *TERT* promoter without affecting wild-type promoter activity. Single-molecule binding assays, chromatin immunoprecipitation and sequencing (ChIP-seq), and ChIP-qPCR analysis revealed that GABPA is exclusively recruited to the mutant allele *in vitro* and *in vivo*. GABPA binding to the mutant *TERT* promoter was conserved across cell lines from multiple cancer types including GBM, melanoma, HCC, and neuroblastoma. This finding was later corroborated in bladder cancer (53). Although the other ETS factors are active as a monomer GABPA is unique in that it can only function as a heterodimer or heterotetramer with GABPB (83–85). Analysis of the sequence content of GABPA binding sites at the *TERT* promoter and genomewide from GABPA ChIP-seq data, suggested that the promoter mutations create the second in a pair of binding motifs that are optimally spaced to recruit the heterotetramer complex (Fig. 2). This work begins to explain how the mutant *TERT* promoter is activated, though factors binding to the sequences upstream and downstream of the mutation sites may cooperate (Fig. 3). This study also provided supporting evidence as to why GABPA is a key, mutation-selective activating factor across multiple cancer types. It also raised a new, testable hypothesis as to why the mutations occur in the same two nucleotides in nearly all TERT-mutant tumors.

Li and colleagues have suggested that the C228T and C250T mutations may be subject to differential regulatory mechanisms in glioma (86). Utilizing a cell culture system of noncanonical NF-κB activation, p52 is recruited to the C250T mutation but not to C228T. Furthermore, p52 cooperated with ETS1/2 to induce *TERT* expression specifically in the context of C250T. That C228T and C250T are not functionally identical is independently supported by the fact that the two mutations do not occur at equal frequency within a given tumor type. For example, in one study of glioma, although 48% of patients were found to harbor the C228T mutation, only 22% contained the C250T mutation (50; Fig. 4). Whether these biases in mutation prevalence reflect differences in upstream regulatory factors or significant differential effects on downstream *TERT* expression remains to be determined.

The mechanism of mutant *TERT* promoter activation has just begun to be revealed. It will be critical to elucidate the similarities and differences of all the proteins bound to the mutant promoter compared with the active wild-type *TERT*

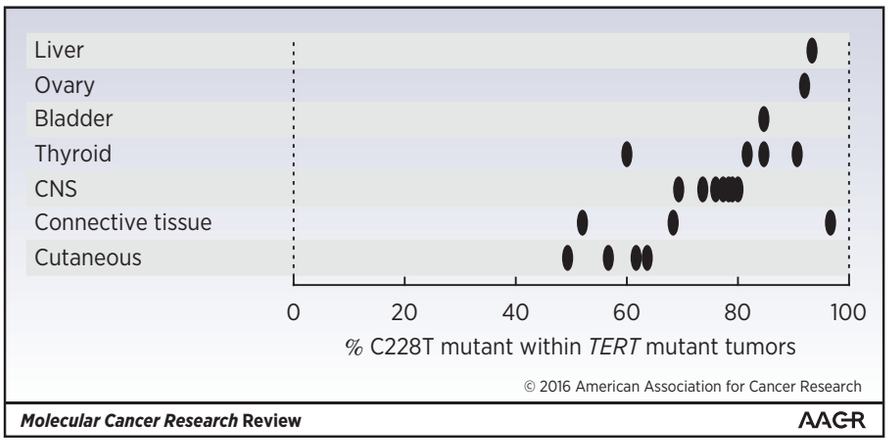

Figure 4.
Percentage of C228T mutations within tumor types harboring high *TERT* promoter mutation frequency. Each oval indicates the percentage of C228T mutations observed within *TERT* mutant tumors (aggregated across studies) for a specific cancer type. A value of 50% means there is equal occurrence of C228T and C250T within that cancer type. Only studies with 20 or more samples and only cancer types with 20 or more observed mutations were included. The cancers types were grouped as in Fig. 1.

promoter. For example, MYC (87), SP1 (88), USF1/2 (89), ID2 (90), and ETS2 (91) have all been reported to regulate *TERT* promoter activity. Analysis of ENCODE ChIP-seq in HepG2 and SK-N-SH cells shows binding of the MAX TF downstream of GABPA in the *TERT* promoter. However, this is also observed in the MCF7 breast cancer cell line that is wild type at the *TERT* promoter, implying that MAX could be involved in regulation from the mutant and wild-type *TERT* promoter (Fig. 3).

It remains unclear how GABPA is regulated by upstream signaling pathways within the context of *TERT* promoter mutant cancer cells. GABPA function is primarily regulated by its transport to the nucleus. Both the MAPK and Hippo signaling pathways modulate GABPA activity through posttranslational modification and nuclear localization in different cell contexts (92, 93). *EGFR* amplification and $BRAF^{V600E}$ mutation, both MAPK-activating events, significantly cooccur with *TERT* promoter mutations in GBM and melanoma, respectively (32, 34).

An increased mechanistic understanding of both germline variation and somatic mutation at the *TERT* promoter could help inform newer strategies to therapeutically target telomerase. Several attempts have been made to block telomerase activity in cancer patients, but thus far none are standard of care. Past strategies have included the use of small molecules, immunotherapy, gene therapy, and G-quadruplex stabilizers (94). One promising approach is the antisense oligonucleotide therapy GRN163L (Imetelstat) from Geron. By hybridizing and inhibiting the RNA template of telomerase, GRN163L reduced tumor growth in preclinical models of breast cancer (95, 96), GBM (97, 98), and pancreatic (99) and liver cancer (100). The preclinical success has not translated to clinical benefit in cancer patients, as trials in breast, lung, and pediatric CNS cancers were discontinued (101–103). In each trial, frequent grade III/IV hematopoietic toxicities were observed, potentially resulting from telomerase inhibition in healthy hematopoietic stem cells. As a result, trials with GRN163L have been restricted to myeloproliferative diseases. Promising results have been reported in myelofibrosis patients treated with GRN163L (104). Determining whether *TERT* promoter mutations can act as a biomarker to predict patient response to existing telomerase inhibitor trials, or foster the creation of new telomerase inhibitors will be an exciting area of research in the future.

Disclosure of Potential Conflicts of Interest

RJAB is co-founder of Telo Therapeutics Inc. J.F. Costello has ownership interest (including patents) in Telo Therapeutics and is a consultant/advisory board member for Telo Therapeutics. No potential conflicts of interest were disclosed.

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References

1. Moyzis RK, Buckingham JM, Cram LS, Dani M, Deaven LL, Jones MD, et al. A highly conserved repetitive DNA sequence, (TTAGGG)n, present at the telomeres of human chromosomes. Proc Natl Acad Sci U S A 1988; 85:6622–26.
2. Blasco MA.Telomeres and human disease: ageing, cancer and beyond. Nat Rev Genet 2005;6:611–22.
3. Bryan TM, Cech TR. Telomerase and the maintenance of chromosome ends. Curr Opin Cell Biol 1999;11:318–24.
4. Greider CW, Blackburn EH. Identification of a specific telomere terminal transferase activity in tetrahymena extracts. Cell 1985;43:405–13.
5. Weinrich SLS, Pruzan RR, Ma LL, Ouellette MM, Tesmer VMV, Holt SES, et al. Reconstitution of human telomerase with the template RNA component hTR and the catalytic protein subunit hTRT. Nat Genet 1997; 17:498–502.
6. Nakamura TM, Morin GB, Chapman KB, Weinrich SL, Andrews WH, Lingner J, et al. Telomerase catalytic subunit homologs from fission yeast and human. Science 1997;277:955–9.
7. Meyerson M, Counter CM, Eaton EN, Ellisen LW, Steiner P, Caddle SD, et al. hEST2, the putative human telomerase catalytic subunit gene, is up-regulated in tumor cells and during immortalization. Cell 1997;90:785–95.

8. Kilian A, Bowtell DD, Abud HE, Hime GR, Venter DJ, Keese PK, et al. Isolation of a candidate human telomerase catalytic subunit gene, which reveals complex splicing patterns in different cell types. Hum Mol Genet 1997;6:2011–9.
9. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. Exp Cell Res 1961;25:585–621.
10. Kim NW, Piatyszek MA, Prowse KR, Harley CB, West MD, Ho PLC, et al. Specific association of human telomerase activity with immortal cells and cancer. Science 1994;266:2011–5.
11. Shay JW, Wright WE. Hayflick, his limit, and cellular ageing. Nat Rev Mol Cell Biol 2000;1:72–6.
12. Cong Y-S, Wright WE, Shay JW. Human telomerase and its regulation. Microbiol Mol Biol Rev 2002;66:407–25.
13. Nandakumar J, Cech TR. Finding the end: recruitment of telomerase to telomeres. Nat Rev Mol Cell Biol 2013;14:69–82.
14. Huschtscha LI, Holliday R. Limited and unlimited growth of SV40-transformed cells from human diploid MRC-5 fibroblasts. J Cell Sci 1983;63:77–99.
15. Wright WE, Pereira-Smith OM, Shay JW. Reversible cellular senescence: implications for immortalization of normal human diploid fibroblasts. Mol Cell Bio 1989;9:3088–92.
16. Counter CM, Avilion AA, LeFeuvre CE, Stewart NG, Greider CW, Harley CB, et al. Telomere shortening associated with chromosome instability is arrested in immortal cells which express telomerase activity. EMBO J 1992;11:1921–9.
17. Hiyama E, Tatsumoto N, Kodama T, Hiyama K, Shay J, Yokoyama T. Telomerase activity in human intestine. Int J Oncol 1996;9: 453–8.
18. Yui J, Chiu CP, Lansdorp PM. Telomerase activity in candidate stem cells from fetal liver and adult bone marrow. Blood 1998;91:3255–62.
19. Castelo-Branco P, Choufani S, Mack S, Gallagher D, Zhang C, Lipman T, et al. Methylation of the TERT promoter and risk stratification of childhood brain tumours: an integrative genomic and molecular study. Lancet Oncol 2013;14:534–42.
20. Shay JW, Bacchetti S. A survey of telomerase activity in human cancer. Eur J Cancer 1997;33:787–91.
21. Murnane JP, Sabatier L, Marder BA, Morgan WF. Telomere dynamics in an immortal human cell line. EMBO J 1994;13:4953–62.
22. Bryan TM, Englezou A, Gupta J, Bacchetti S, Reddel RR. Telomere elongation in immortal human cells without detectable telomerase activity. EMBO J 1995;14:4240–8.
23. Bryan TM, Englezou A, Dalla-Pozza L, Dunham MA, Reddel RR. Evidence for an alternative mechanism for maintaining telomere length in human tumors and tumor-derived cell lines. Nat Med 1997;3:1271–4.
24. Walsh KM, Wiencke JK, Lachance DH, Wiemels JL, Molinaro AM, Eckel-Passow JE, et al. Telomere maintenance and the etiology of adult glioma. Neuro Oncol 2015;17:1445–52.
25. Walsh KM, Codd V, Smirnov IV, Rice T, Decker PA, Hansen HM, et al. Variants near TERT and TERC influencing telomere length are associated with high-grade glioma risk. Nat Genet 2014;46:731–5.
26. Wrensch M, Jenkins RB, Chang JS, Yeh R-F, Xiao Y, Decker PA, et al. Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility. Nat Genet 2009;41:905–8.
27. Walsh KM, Codd V, Rice T, Nelson CP, Smirnov IV, Mccoy LS, et al. Longer genotypically-estimated leukocyte telomere length is associated with increased adult glioma risk. Oncotarget 2015;6:42468–77.
28. Rafnar T, Sulem P, Stacey SN, Geller F, Gudmundsson J, Sigurdsson A, et al. Sequence variants at the TERT-CLPTM1L locus associate with many cancer types. Nat Genet 2009;41:221–7.
29. McKay JD, Hung RJ, Gaborieau V, Boffetta P, Chabrier A, Byrnes G, et al. Lung cancer susceptibility locus at 5p15.33. Nat Genet 2008; 40:1404–6.
30. Wang Y, Broderick P, Webb E, Wu X, Vijayakrishnan J, Matakidou A, et al. Common 5p15.33 and 6p21.33 variants influence lung cancer risk. Nat Genet 2008;40:1407–9.
31. Petersen GM, Amundadottir L, Fuchs CS, Kraft P, Stolzenberg-Solomon RZ, Jacobs KB, et al. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. Nat Genet 2010;42:224–8.
32. Horn S, Figl A, Rachakonda PS, Fischer C, Sucker A, Gast A, et al. TERT promoter mutations in familial and sporadic melanoma. Science 2013; 339:959–61.
33. Huang FW, Hodis E, Xu MJ, Kryukov GV, Chin L, Garraway LA. Highly recurrent TERT promoter mutations in human melanoma. Science 2013; 339:957–9.
34. Killela PJ, Reitman ZJ, Jiao Y, Bettegowda C, Agrawal N, Diaz LA, et al. TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. Proc Natl Acad Sci U S A 2013;110:6021–6.
35. Kinde I, Munari E, Faraj SF, Hruban RH, Schoenberg M, Bivalacqua T, et al. TERT promoter mutations occur early in urothelial neoplasia and are biomarkers of early disease and disease recurrence in urine. Cancer Res 2013;73:1–18.
36. Quaas A, Oldopp T, Tharun L, Klingenfeld C, Krech T, Sauter G, et al. Frequency of TERT promoter mutations in primary tumors of the liver. Virchows Arch 2014;465:673–7.
37. Borah S, Xi L, Zaug AJ, Powell NM, Dancik GM, Cohen SB, et al. Cancer. TERT promoter mutations and telomerase reactivation in urothelial cancer. Science 2015;347:1006–10.
38. Valentijn LJ, Koster J, Zwijnenburg DA, Hasselt NE, van Sluis P, Volckmann R, et al. TERT rearrangements are frequent in neuroblastoma and identify aggressive tumors. Nat Genet 2015;47:1411–4.
39. Peifer M, Hertwig F, Roels F, Dreidax D, Gartlgruber M, Menon R, et al. Telomerase activation by genomic rearrangements in high-risk neuroblastoma. Nature 2015;526:700–4.
40. Bell RJA, Rube HT, Kreig A, Mancini A, Fouse SD, Nagarajan RP, et al. Cancer. The transcription factor GABP selectively binds and activates the mutant TERT promoter in cancer. Science 2015;348:1036–9.
41. Zhu C-Q, Cutz J-C, Liu N, Lau D, Shepherd FA, Squire JA, et al. Amplification of telomerase (hTERT) gene is a poor prognostic marker in non-small-cell lung cancer. Br J Cancer 2006;94:1452–9.
42. Kang JU, Koo SH, Kwon KC, Park JW, Kim JM. Gain at chromosomal region 5p15.33, containing TERT, is the most frequent genetic event in early stages of non-small cell lung cancer. Cancer Genet Cytogenet 2008;182:1–11.
43. Vinagre J, Almeida A, Pópulo H, Batista R, Lyra J, Pinto V, et al. Frequency of TERT promoter mutations in human cancers. Nat Commun 2013; 4:2185–5.
44. Nault JC, Mallet M, Pilati C, Calderaro J, Bioulac-Sage P, Laurent C, et al. High frequency of telomerase reverse-transcriptase promoter somatic mutations in hepatocellular carcinoma and preneoplastic lesions. Nat Commun 2013;4:2218.
45. Wang N, Liu T, Sofiadis A, Juhlin CC, Zedenius J, Höög A, et al. TERT promoter mutation as an early genetic event activating telomerase in follicular thyroid adenoma (FTA) and atypical FTA. Cancer 2014;120: 2965–79.
46. Heidenreich B, Nagore E, Rachakonda PS, Garcia-Casado Z, Requena C, Traves V, et al. Telomerase reverse transcriptase promoter mutations in primary cutaneous melanoma. Nat Commun 2014;5:3401.
47. Hosler GA, Davoli T, Mender I, Litzner B, Choi J, Kapur P, et al. A primary melanoma and its asynchronous metastasis highlight the role of BRAF, CDKN2A, and TERT. J Cutan Pathol 2015;42:108–17.
48. Shain AH, Yeh I, Kovalyshyn I, Sriharan A, Talevich E, Gagnon A, et al. The genetic evolution of melanoma from precursor lesions. N Engl J Med 2015;373:1926–36.
49. Scott GA, Laughlin TS, Rothberg PG. Mutations of the TERT promoter are common in basal cell carcinoma and squamous cell carcinoma. Mod Pathol 2014;27:516–23.
50. Arita H, Narita Y, Fukushima S, Tateishi K, Matsushita Y, Yoshida A, et al. Upregulating mutations in the TERT promoter commonly occur in adult malignant gliomas and are strongly associated with total 1p19q loss. Acta Neuropathol 2013;126:267–76.
51. Chiba K, Johnson JZ, Vogan JM, Wagner T, Boyle JM. Cancer-associated TERT promoter mutations abrogate telomerase silencing. Elife 2015:1–20.
52. Azouz A, Wu Y-L, Hillion J, Tarkanyi I, Karniguian A, Aradi J, et al. Epigenetic plasticity of hTERT gene promoter determines retinoid capacity to repress telomerase in maturation-resistant acute promyelocytic leukemia cells. Leukemia 2010;24:613–22.

53. Stern JL, Theodorescu D, Vogelstein B, Papadopoulos N, Cech TR. Mutation of the TERT promoter, switch to active chromatin, and monoallelic TERTexpression in multiple cancers. Genome Res 2015; 29:2219–24.
54. Mosrati MA, Malmström A, Lysiak M, Krysztofiak A, Hallbeck M, Milos P, et al. TERT promoter mutations and polymorphisms as prognostic factors in primary glioblastoma. Oncotarget 2015;6:16663–73.
55. Beesley J, Pickett HA, Johnatty SE, Dunning AM, Chen X, Li J, et al. Functional polymorphisms in the TERT promoter are associated with risk of serous epithelial ovarian and breast cancers. PLoS One 2011;6: e24987–7.
56. Bojesen SE, Pooley KA, Johnatty SE, Beesley J, Michailidou K, Tyrer JP, et al. Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer. Nat Genet 2013;45:371–2.
57. Yoo SS, Do SK, Choi JE, Lee SY, Lee J, Cha SI, et al. TERT polymorphism rs2853669 influences on lung cancer risk in the Korean population. J Korean Med Sci 2015;30:1423–8.
58. Rachakonda PS, Hosen I, de Verdier PJ, Fallah M, Heidenreich B, Ryk C, et al. TERT promoter mutations in bladder cancer affect patient survival and disease recurrence through modification by a common polymorphism. Proc Natl Acad Sci U S A 2013;110:17426–31.
59. Hosen I, Rachakonda PS, Heidenreich B, de Verdier PJ, Ryk C, Steineck G, et al. Mutations in TERT promoter and FGFR3 and telomere length in bladder cancer. Int J Cancer 2015;137:1621–9.
60. Spiegl-Kreinecker S, Lotsch D, Ghanim B, Pirker C, Mohr T, Laaber M, et al. Prognostic quality of activating TERT promoter mutations in glioblastoma: interaction with the rs2853669 polymorphism and patient age at diagnosis. Neuro Oncol 2015;17:1231–40.
61. Labussière M, Di Stefano AL, Gleize V, Boisselier B, Giry M, Mangesius S, et al. TERT promoter mutations in gliomas, genetic associations and clinico-pathological correlations. Br J Cancer 2014;111:2024–32.
62. Mosrati MA, Malmström A, Lysiak M, Krysztofiak A, Hallbeck M, Milos P, et al. TERT promoter mutations and polymorphisms as prognostic factors in primary glioblastoma. Oncotarget 2015;6:16663–73.
63. Nencha U, Rahimian A, Giry M, Sechi A, Mokhtari K, Polivka M, et al. TERT promoter mutations and rs2853669 polymorphism: prognostic impact and interactions with common alterations in glioblastomas. J Neurooncol 2016:126:441–6.
64. Remke M, Ramaswamy V, Peacock J, Shih DJH, Koelsche C, Northcott PA, et al. TERT promoter mutations are highly recurrent in SHH subgroup medulloblastoma. Acta Neuropathol 2013;126:917–29.
65. Melo M, da Rocha AG, Vinagre J, Batista R, Peixoto J, Tavares C, et al. TERT promoter mutations are a major indicator of poor outcome in differentiated thyroid carcinomas. J Clin Endocrinol Metab 2014;99:E754–65.
66. Liu T, Wang N, Cao J, Sofiadis A, Dinets A, Zedenius J, et al. The age- and shorter telomere-dependent TERT promoter mutation in follicular thyroid cell-derived carcinomas. Oncogene 2014;33:4978–84.
67. George JR, Henderson YC, Williams MD, Roberts DB, Hei H, Lai SY, et al. Association of TERT promoter mutation, but not BRAF mutation, with increased mortality in PTC. J Clin Endocrinol Metab 2015;100: E1550–9.
68. Wu S, Huang P, Li C, Huang Y, Li X, Wang Y, et al. Telomerase reverse transcriptase gene promoter mutations help discern the origin of urogenital tumors: a genomic and molecular study. Eur Urol 2014;65:274–7.
69. Griewank KG, Murali R, Puig-Butille JA, Schilling B, Livingstone E, Potrony M, et al. TERT promoter mutation status as an independent prognostic factor in cutaneous melanoma. J Natl Cancer Inst 2014;106: dju246.
70. Pópulo H, Boaventura P, Vinagre J, Batista R, Mendes A, Caldas R, et al. TERT promoter mutations in skin cancer: the effects of sun exposure and X-irradiation. J Invest Dermatol 2014;134:2251–7.
71. Qu Y, Dang S, Wu K, Shao Y, Yang Q, Ji M, et al. TERT promoter mutations predict worse survival in laryngeal cancer patients. Int J Cancer 2014; 135:1008–10.
72. Wang K, Liu T, Liu C, Meng Y, Yuan X, Liu L, et al. TERT promoter mutations and TERT mRNA but not FGFR3 mutations are urinary biomarkers in Han Chinese patients with urothelial bladder cancer. Oncologist 2015;20:263–9.
73. Wang K, Liu T, Ge N, Liu L, Yuan X, Liu J, et al. TERT promoter mutations are associated with distant metastases in upper tract urothelial carcinomas and serve as urinary biomarkers detected by a sensitive castPCR. Oncotarget 2014;5:12428–39.
74. Hurst CD, Platt FM, Knowles MA. Comprehensive mutation analysis of the TERT promoter in bladder cancer and detection of mutations in voided urine. Eur Urol 2014;65:367–9.
75. Nault JC, Calderaro J, Di Tommaso L, Balabaud C, Zafrani ES, Bioulac-Sage P, et al. Telomerase reverse transcriptase promoter mutation is an early somatic genetic alteration in the transformation of premalignant nodules in hepatocellular carcinoma on cirrhosis. Hepatology 2014;60: 1983–92.
76. Goutagny S, Nault JC, Mallet M, Henin D, Rossi JZ, Kalamarides M. High incidence of activating TERT promoter mutations in meningiomas undergoing malignant progression. Brain Pathol 2014;24:184–9.
77. Cheng KA, Kurtis B, Babayeva S, Zhuge J, Tantchou I, Cai D, et al. Heterogeneity of TERT promoter mutations status in squamous cell carcinomas of different anatomical sites. Ann Diagn Pathol 2015;19:146–8.
78. Killela PJ, Pirozzi CJ, Healy P, Reitman ZJ, Lipp E, Rasheed BA, et al. Mutations in IDH1, IDH2, and in the TERT promoter define clinically distinct subgroups of adult malignant gliomas. Oncotarget 2014;5: 1515–25.
79. Labussière M, Boisselier B, Mokhtari K, Di Stefano A-L, Rahimian A, Rossetto M, et al. Combined analysis of TERT, EGFR, and IDH status defines distinct prognostic glioblastoma classes. Neurology 2014;83: 1200–6.
80. Eckel-Passow JE, Lachance DH, Molinaro AM, Walsh KM, Decker PA, Sicotte H, et al. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. N Engl J Med 2015;372:2499–508.
81. The Cancer Genome Atlas Research Network. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med 2015; 372:2481–98.
82. Wei G-H, Badis G, Berger MF, Kivioja T, Palin K, Enge M, et al. Genome-wide analysis of ETS-family DNA-binding *in vitro* and *in vivo*. The EMBO Journal 2010;29:2147–60.
83. Thompson CC, Brown TA, Mcknight SL. Convergence of Ets- and notch-related structural motifs in a heteromeric DNA binding complex. Science 1991;253:762–8.
84. Oikawa T, Yamada T. Molecular biology of the Ets family of transcription factors. Gene 2003;303:11–34.
85. LaMarco K, Thompson CC, Byers BP, Walton EM, Mcknight SL. Identification of Ets- and notch-related subunits in GA binding protein. Science 1991;253:789–92.
86. Li Y, Zhou Q-L, Sun W, Chandrasekharan P, Cheng HS, Ying Z, et al. Non-canonical NF-κB signalling and ETS1/2 cooperatively drive C250T mutant TERT promoter activation. Nat Cell Biol 2015;17:1327–38.
87. Wu KJ, Grandori C, Amacker M, Simon-Vermot N, Polack A, Lingner J, et al. Direct activation of TERT transcription by c-MYC. Nat Genet 1999;21:220–4.
88. Kyo S, Takakura M, Taira T, Kanaya T, Itoh H, Yutsudo M, et al. Sp1 cooperates with c-Myc to activate transcription of the human telomerase reverse transcriptase gene (hTERT). Nucleic Acids Res 2000;28: 669–77.
89. Goueli BS, Janknecht R. Regulation of telomerase reverse transcriptase gene activity by upstream stimulatory factor. Oncogene 2003;22: 8042–7.
90. Xiao X, Athanasiou M, Sidorov IA, Horikawa I, Cremona G, Blair D, et al. Role of Ets/Id proteins for telomerase regulation in human cancer cells. Exp Mol Pathol 2003;75:238–47.
91. Xu D, Dwyer J, Li H, Duan W, Liu J-P. Ets2 maintains hTERT gene expression and breast cancer cell proliferation by interacting with c-Myc. J Biol Chem 2008;283:23567–80.
92. Wu H, Xiao Y, Zhang S, Ji S, Wei L, Fan F, et al. The Ets transcription factor GABP is a component of the hippo pathway essential for growth and antioxidant defense. Cell Rep 2013;3:1663–77.
93. Flory E, Hoffmeyer A, Smola U, Rapp UR, Bruder JT. Raf-1 kinase targets GA-binding protein in transcriptional regulation of the human immunodeficiency virus type 1 promoter. J Virol 1996;70: 2260–8.
94. Ruden M, Puri N. Novel anticancer therapeutics targeting telomerase. Cancer Treat. Rev 2013;39:444–56.
95. Hochreiter AE, Xiao H, Goldblatt EM, Gryaznov SM, Miller KD, Badve S, et al. Telomerase template antagonist GRN163L disrupts telomere

maintenance, tumor growth, and metastasis of breast cancer. Clin Cancer Res 2006;12:3184–92.
96. Goldblatt EM, Gentry ER, Fox MJ, Gryaznov SM, Shen C, Herbert B-S. The telomerase template antagonist GRN163L alters MDA-MB-231 breast cancer cell morphology, inhibits growth, and augments the effects of paclitaxel. Mol Cancer Ther 2009;8:2027–35.
97. Hashizume R, Ozawa T, Gryaznov SM, Bollen AW, Lamborn KR, Frey WH, et al. New therapeutic approach for brain tumors: intranasal delivery of telomerase inhibitor GRN163. Neuro Oncol 2008;10: 112–20.
98. Marian CO, Cho SK, McEllin BM, Maher EA, Hatanpaa KJ, Madden CJ, et al. The telomerase antagonist, imetelstat, efficiently targets glioblastoma tumor-initiating cells leading to decreased proliferation and tumor growth. Clin Cancer Res 2010;16:154–63.
99. Joseph I, Tressler R, Bassett E, Harley C, Buseman CM, Pattamatta P, et al. The telomerase inhibitor imetelstat depletes cancer stem cells in breast and pancreatic cancer cell lines. Cancer Res 2010;70:9494–504.
100. Djojosubroto MW, Chin AC, Go N, Schaetzlein S, Manns MP, Gryaznov S, et al. Telomerase antagonists GRN163 and GRN163L inhibit tumor growth and increase chemosensitivity of human hepatoma. Hepatology 2005;42:1127–36.
101. Kozloff M, Sledge GW, Benedetti FM, Starr A. Phase I study of imetelstat (GRN163L) in combination with paclitaxel (P) and bevacizumab (B) in patients (pts) with locally recurrent or metastatic breast cancer (MBC). J Clin Oncol 2010.
102. Chiappori AA, Kolevska T, Spigel DR, Hager S, Rarick M, Gadgeel S, et al. A randomized phase II study of the telomerase inhibitor imetelstat as maintenance therapy for advanced non-small-cell lung cancer. Ann Oncol 2015;26:354–62.
103. Salloum R, Hummel T, Kumar SS, Dorris K, Li S, Lin T, et al. TR-11. A molecular biology and phase II study of imetelstat (GRN163L) in children with recurrent or refractory central nervous system (CNS) malignancies: a pediatric brain tumor consortium study. Neuro Oncol 2015;17:iii39–9.
104. Tefferi A, Lasho TL, Begna KH, Patnaik MM, Zblewski DL, Finke CM, et al. A pilot study of the telomerase inhibitor imetelstat for myelofibrosis. N Engl J Med 2015;373:908–19.
105. Miao Y, Wang R, Ju H, Ren G, Guo W, Lyu J. TERT promoter mutation is absent in oral mucosal melanoma. Oral Oncol 2015;51:e65–6.
106. Koelsche C, Sahm F, Capper D, Reuss D, Sturm D, Jones DTW, et al. Distribution of TERT promoter mutations in pediatric and adult tumors of the nervous system. Acta Neuropathol 2013;126:907–15.
107. Vail E, Zheng X, Zhou M, Yang X, Fallon JT, Epstein JI, et al. Telomerase reverse transcriptase promoter mutations in glandular lesions of the urinary bladder. Ann Diagn Pathol 2015;19:301–5.
108. Huang D-S, Wang Z, He X-J, Diplas BH, Yang R, Killela PJ, et al. Recurrent TERT promoter mutations identified in a large-scale study of multiple tumour types are associated with increased TERT expression and telomerase activation. Eur J Cancer 2015;51:969–76.
109. Koelsche C, Renner M, Hartmann W, Brandt R, Lehner B, Waldburger N, et al. TERT promoter hotspot mutations are recurrent in myxoid liposarcomas but rare in other soft tissue sarcoma entities. J Exp Clin Cancer Res 2014;33:33.
110. Wu R-C, Ayhan A, Maeda D, Kim K-R, Clarke BA, Shaw P, et al. Frequent somatic mutations of the telomerase reverse transcriptase promoter in ovarian clear cell carcinoma but not in other major types of gynaecological malignancy. J Pathol 2014;232:473–81.
111. Papathomas TG, Oudijk L, Zwarthoff EC, Post E, Duijkers FA, van Noesel MM, et al. Telomerase reverse transcriptase promoter mutations in tumors originating from the adrenal gland and extra-adrenal paraganglia. Endocr Relat Cancer 2014;21:653–61.
112. Liu X, Bishop J, Shan Y, Pai S, Liu D, Murugan AK, et al. Highly prevalent TERT promoter mutations in aggressive thyroid cancers. Endocr Relat Cancer 2013;20:603–10.
113. Landa I, Ganly I, Chan TA, Mitsutake N, Matsuse M, Ibrahimpasic T, et al. Frequent somatic TERT promoter mutations in thyroid cancer: higher prevalence in advanced forms of the disease. J Clin Endocrinol Metab 2013:1–5.
114. Nonoguchi N, Ohta T, Oh J-E, Kim Y-H, Kleihues P, Ohgaki H. TERT promoter mutations in primary and secondary glioblastomas. Acta Neuropathol 2013;126:931–7.
115. Griewank KG, Murali R, Schilling B, Scholz S, Sucker A, Song M, et al. TERT promoter mutations in ocular melanoma distinguish between conjunctival and uveal tumours. Br J Cancer 2013;109:497–501.
116. Liu X, Wu G, Shan Y, Hartmann C, Deimling von A, Xing M. Highly prevalent TERT promoter mutations in bladder cancer and glioblastoma. Cell Cycle 2013;12:1637–8.
117. Tallet A, Nault J-C, Renier A, Hysi I, Galateau-Sallé F, Cazes A, et al. Overexpression and promoter mutation of the TERT gene in malignant pleural mesothelioma. Oncogene 2014;33:3748–52.
118. Allory Y, Beukers W, Sagrera A, Flández M, Marqués M. Telomerase reverse transcriptase promoter mutations in bladder cancer: high frequency across stages, detection in urine, and lack of association with outcome. Eur Urol 2014;65:360–6.
119. Griewank KG, Schilling B, Murali R, Bielefeld N, Schwamborn M, Sucker A, et al. TERT promoter mutations are frequent in atypical fibroxanthomas and pleomorphic dermal sarcomas. Mod Pathol 2014;27:502–8.
120. Zhao Y, Gao Y, Chen Z, Hu X, Zhou F, He J. Low frequency of TERT promoter somatic mutation in 313 sporadic esophageal squamous cell carcinomas. Int J Cancer 2014;134:493–4.
121. Xing M, Liu R, Liu X, Murugan AK, Zhu G. BRAF V600E and TERT promoter mutations cooperatively identify the most aggressive papillary thyroid cancer with highest recurrence. J Clin Oncol 2014;32: 2718–26.
122. Liu X, Qu S, Liu R, Sheng C, Shi X, Zhu G, et al. TERT promoter mutations and their association with BRAF V600E mutation and aggressive clinicopathological characteristics of thyroid cancer. J Clin Endocrinol Metab 2014;99:E1130–6.
123. Liu T, Brown TC, Juhlin CC, Andreasson A, Wang N, Bäckdahl M, et al. The activating TERT promoter mutation C228T is recurrent in subsets of adrenal tumors. Endocr Relat Cancer 2014;21:427–34.
124. Cárcano FM, Vidal DO, van Helvoort Lengert A, Neto CS, Queiroz L, Marques H, et al. Hotspot TERT promoter mutations are rare events in testicular germ cell tumors. Tumour Biol. 2015 Nov 3. [Epub ahead of print].
125. Oh J-E, Ohta T, Nonoguchi N, Satomi K, Capper D, Pierscianek D, et al. Genetic alterations in gliosarcoma and giant cell glioblastoma. Brain Pathol 2015 Oct 7. [Epub ahead of print].
126. Griewank KG, Murali R, Schilling B, Schimming T, Möller I, Moll I, et al. TERT promoter mutations are frequent in cutaneous basal cell carcinoma and squamous cell carcinoma. PLoS One 2013;8:e80354–4.
127. Huang H-N, Chiang Y-C, Cheng W-F, Chen C-A, Lin M-CKuo K-T. Molecular alterations in endometrial and ovarian clear cell carcinomas: clinical impacts of telomerase reverse transcriptase promoter mutation. Mod Pathol 2015;28:303–11.
128. Chen YL, Jeng YM, Chang CN, Lee HJ, Hsu HC, Lai PL, et al. TERT promoter mutation in resectable hepatocellular carcinomas: a strong association with hepatitis C infection and absence of hepatitis B infection. Int J Surg 2014;12:659–65.
129. Cevik D, Yildiz G, Ozturk M. Common telomerase reverse transcriptase promoter mutations in hepatocellular carcinomas from different geographical locations. World J Gastroenterol 2015;21:311–7.
130. Dono M, Angelini G, Cecconi M, Amaro A, Esposito AI, Mirisola V, et al. Mutation frequencies of GNAQ, GNA11, BAP1, SF3B1, EIF1AX and TERT in uveal melanoma: detection of an activating mutation in the TERT gene promoter in a single case of uveal melanoma. Br J Cancer 2014;110:1058–65.
131. Liau JY, Tsai JH, Jeng YM, Chu CY, Kuo KT, Liang CW. TERT promoter mutation is uncommon in acral lentiginous melanoma. J Cutan Pathol 2014;41:504–8.
132. Lee S, Barnhill RL, Dummer R, Dalton J, Wu J, Pappo A, et al. TERT promoter mutations are predictive of aggressive clinical behavior in patients with spitzoid melanocytic neoplasms. Sci Rep 2015;5:11200.
133. Jangard M, Zebary A, Ragnarsson-Olding B, Hansson J. TERT promoter mutations in sinonasal malignant melanoma: a study of 49 cases. Melanoma Res 2015;25:185–8.
134. Macerola E, Loggini B, Giannini R, Garavello G, Giordano M, Proietti A, et al. Coexistence of TERT promoter and BRAF mutations in cutaneous melanoma is associated with more clinicopathological features of aggressiveness. Virchows Arch 2015;467:177–84.
135. Koopmans AE, Ober K, Dubbink HJ, Paridaens D, Naus NC, Belunek S, et al. Prevalence and implications of TERT promoter mutation in uveal

and conjunctival melanoma and in benign and premalignant conjunctival melanocytic lesions. Invest Ophthalmol Vis Sci 2014;55:6024–30.
136. Chindris A-M, Casler JD, Bernet VJ, Rivera M, Thomas C, Kachergus JM, et al. Clinical and molecular features of Hürthle cell carcinoma of the thyroid. J Clin Endocrinol Metab 2015;100:55–62.
137. Shi X, Liu R, Qu S, Zhu G, Bishop J, Liu X, et al. Association of TERT promoter mutation 1,295,228 C>T with BRAF V600E mutation, older patient age, and distant metastasis in anaplastic thyroid cancer. J Clin Endocrinol Metab 2015;100:E632–7.
138. Muzza M, Colombo C, Rossi S, Tosi D, Cirello V, Perrino M, et al. Telomerase in differentiated thyroid cancer: promoter mutations, expression and localization. Mol Cell Endocrinol 2015;399:288–95.
139. Fredriksson NJ, Ny L, Nilsson JA, Larsson E. Systematic analysis of noncoding somatic mutations and gene expression alterations across 14 tumor types. Nat Genet 2014;46:1258–63.
140. Liu R, Xing M. Diagnostic and prognostic TERT promoter mutations in thyroid fine-needle aspiration biopsy. Endocr Relat Cancer 2014;21:825–30.
141. Qasem E, Murugan AK, Al-Hindi H, Xing M, Almohanna M, Alswailem M, et al. TERT promoter mutations in thyroid cancer: a report from a Middle Eastern population. Endocr Relat Cancer 2015;22:901–8.
142. Dettmer MS, Schmitt A, Steinert H, Capper D, Moch H, Komminoth P, et al. Tall cell papillary thyroid carcinoma: new diagnostic criteria and mutations in BRAF and TERT. Endocr Relat Cancer 2015;22:419–29.