Table S1. TERTp mutations included in this study.

TERTp mutation	Number of Cell Lines (CCLE)	Base pairs upstream from *TERT* ATG
TERT_Chr5.1295228.G.A (C228T),	61	124
TERT_Chr_5.1295250.G.A (C250T)	14	146
ERT_Chr5.1295242-1295243.GG.AA (CC242-243TT)	5	138-139
TERT_Chr5.1295161.T.G (A161C)	2	57
TERT_Chr5.1295228-1295229.GG.AA	1	124-125
All Lines	83	

Extended methods

Gene Set Enrichment Analysis (GSEA) and Matching Gene Sets to Mutation Status Phenotypes

The gene set enrichment analysis profiles displayed in Figs 1A, 1C and S2, and the phenotype in Fig S2, were obtained using single-sample Gene Set Enrichment Analysis[1] (ssGSEA) and gene sets from the *Molecular Signatures Database MSigDB* [2,3]. The matching of the gene sets profiles in those figures, and published transcriptional components[4] in Fig 1B, against the mutations status of *TERT* (TERT_pg_any genotype) were computed using the Information Coefficient (IC), labeled as "Score" in the Figures) which is an Information Theoretic measure of association[4] similar to the correlation coefficient. The numbers in parenthesis after the "Score" in the figures are bootstrap estimates of the variability of the Information Coefficient. The p-values and False Discover Rates (FDR), also displayed in the figures, were computed using an empirical permutation test. This association metric was also used in Fig 2 to match the *TERT* promoter mutation signatures against the TERT transcriptional signature (Fig S2, top) and to estimate the degree of association between the *TERT* promoter mutation and transcriptional signatures with respect to each other (Fig S2, bottom). For Fig 2D, we performed RNAseq experiments on SV40 T antigen expressing BJ fibroblasts obtained from a previous study[5]. RNA was extracted from cells with *vs* without TERT expression using RNeasy (Qiagen) and libraries were prepared and sequenced at the Dana Farber Cancer Institute Molecular Biology Core Facility on a Nextseq 500 as previously described[6]. The RNA-Seq files were processed using the Picard and Firehose pipelines at the Broad Institute[7] (http://broadinstitute.github.io/picard/). The BJ sample was compared against the control and a differential expression score was obtained by subtracting the control from the BJ sample. The top/bottom 100 genes with higher/lower scores were used to produce the TERT transcriptional signature UP and DOWN gene sets. Finally, single-sample GSEA[1] (ssGSEA) was used to produce ssGSEA TERT signature scores (ssGSEA score UP - score DOWN) for the Cancer Cell Line Encyclopedia samples and used in Figs 2D and S2.

Cell Culture

SNU-423, SNU-475, SNU-398, HEK293T, and DAOY were obtained from the American Type Culture Collection. U87MG, SCaBER, and MDA-MB-231 were obtained from the University of Colorado, Anschutz, Tissue Culture Shared Resource. HaCaT cells were a gift from X. Liu. Mel3249, Mel3616, and Mel1692 were gifts from K. Couts at the University of Colorado, Anschutz Medical Campus[8,9]. Cancer cell lines and HaCaT cells were cultured in DMEM (VWR Scientific) with 2 mM GlutaminePlus (Atlanta Biologicals), 10% FBS (Thermo Fisher), 2 mM GlutaMAX-I (Gibco), 100 units/ml penicillin and 100 mg/ml streptomycin (Gibco) and 1mM sodium pyruvate (Gibco). All cell lines were regularly tested for mycoplasma contamination by PCR at the University of Colorado, Boulder Biofrontiers Core Tissue Culture Facility and were used for experiments within 10 weeks of resuscitation. Human mesenchymal progenitor cells were grown from human bone marrow[10] obtained from Lonza and supplemented with 1 ng/mL FGF, and were used at passage three for experiments. MPC grown in DMEM display mesenchymal progenitor markers $CD73^+$, $CD90^+$, $CD105^+$, $CD34^+$. hMPC and osteocytes were a gift from H. Ma and K. Anseth (University of Colorado Boulder). Differentiation of osteocytes[10] was carried out by growing 4.2×10^5 hMPCs onto each 150mm tissue culture treated plastic dish with normal growth medium (DMEM low glucose supplemented with 10% FBS + plus FGF). Media was changed every other day until hMSCs grew to ~70% confluent. Cells were then switched to osteogenic differentiation medium (high glucose DMEM (Thermo Fisher 11965-092), Pen/strep, fungizone, dexamethasone (100 nM), L-ascorbic acid (50 ug/mL), β-glycerophosphate (10 mM), and 10% FBS) and kept culture for 3 weeks with medium change every the other day. iPSCs were maintained in Essential 8 Flex medium (Thermo Fisher A2858501) using vitronectin coated plates (Thermo Fisher A14700). The medium was changed every other day. For passaging, iPSCs were washed twice in PBS without calcium followed by 4 min incubation with 0.5 mM EDTA in PBS at 37°C. Cells were then detached and split at a ratio of 1 in 4 to

1 in 6 into new culture dishes coated with vitronectin. For long-term storage, cells were stored in the gas phase of liquid nitrogen in Essential 8 Flex medium (serum free) with 10% DMSO.

Supplementary References

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