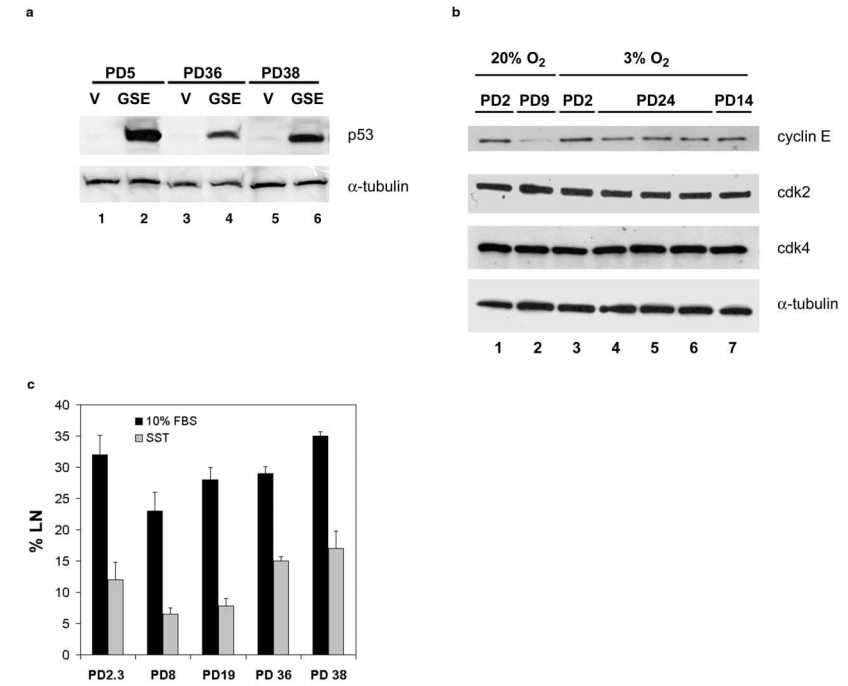


Figure S1. **Efficacy of GSE, levels of G_1 cyclin-dependent kinases, and responsiveness to serum deprivation of MEFs cultured in 3% O_2. a,** An early passage (PD5) and two late passage (PD36 and PD38) C57Bl/6 MEF cultures grown in 3% O_2 were infected with insertless (lanes 1, 3, 5) or GSE-expressing (lanes 2, 4, 6) pBABE-puro retroviruses. Proteins were prepared and assayed for p53 and α-tubulin (control) by western blotting. **b,** Proteins were prepared from C57Bl/6 MEFs proliferating in 20% (lanes 1, 2) or 3% (lanes 3-7) O_2, and analyzed by western blotting for cyclin E, Cdk2, Cdk4 and α-tubulin. Early passage (PD 2, lane 1) and senescent (PD 9, lane 2) cultures in 20% O_2, and early (PD 2, lane 3), mid- (PD 14, lane 7), and three independent later (PD 24, lanes 3-6) passage 3% O_2 cultures were analyzed. **c,** Five MEF cultures were grown for the indicated PDs in 3% O_2. The cells were shifted to 10% (10% FBS; black bars) or 0.5% (SST; gray bars) serum for 3 d before ^{3}H-thymidine was added for 1 h. The fraction of cells synthesizing DNA was determined from the %LN.

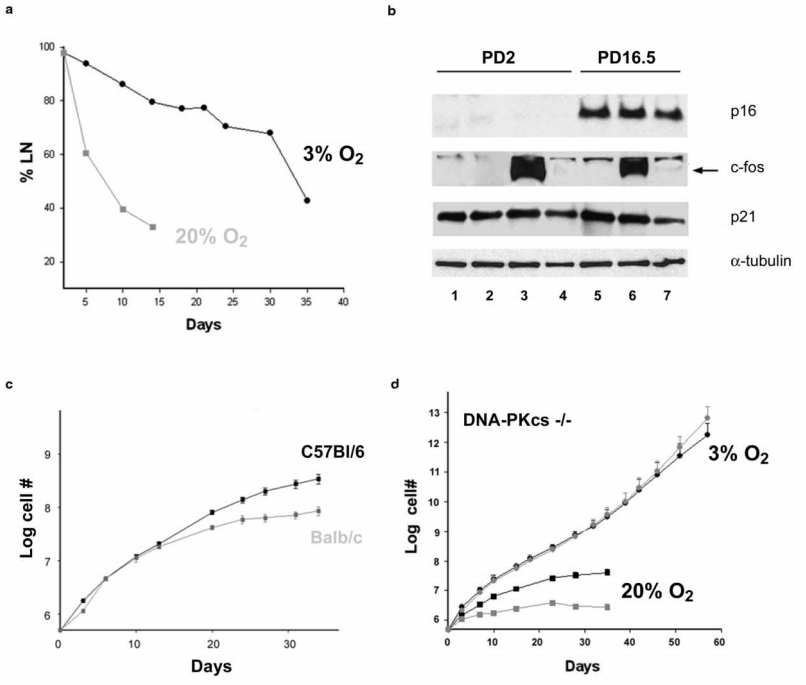
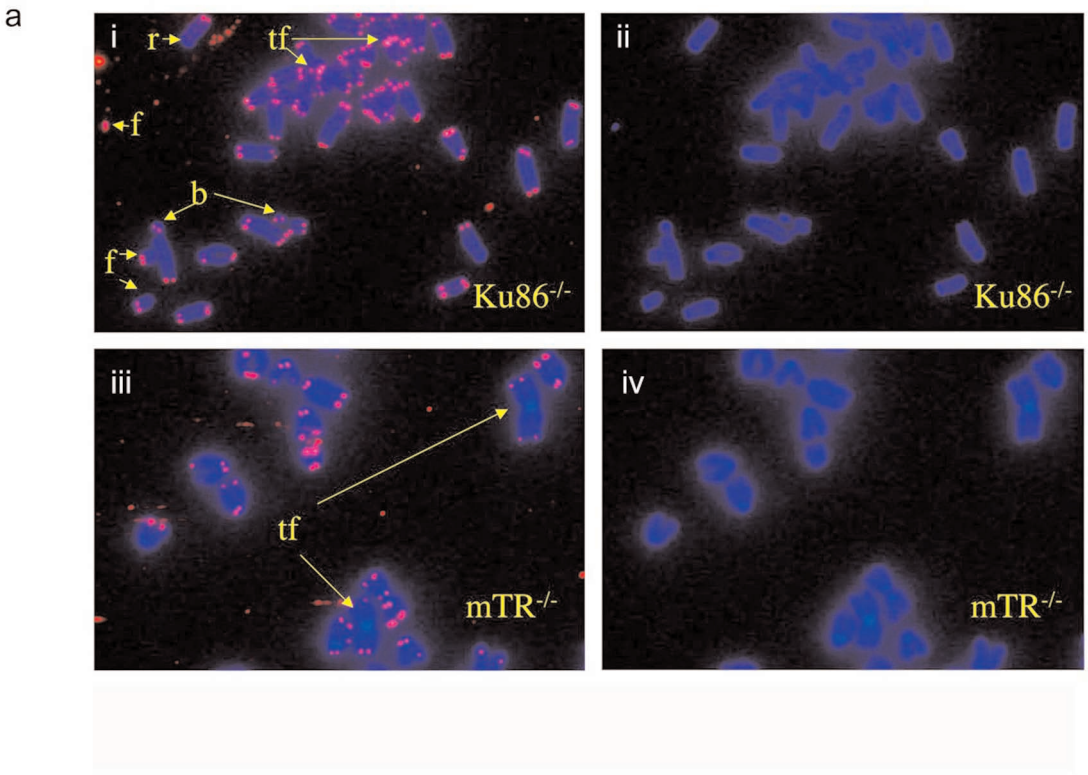


Figure S2. **Senescence of Balb/c and DNA-PKcs -/- MEFs in low oxygen. a,** The labeling index (% LN) was determined at every passage for representative Balb/c cultures grown in 20% (gray) or 3% (black) O_2. **b**, Early passage (PD 2, lanes 1-4) and senescent (PD 16.5, lanes 5-7) Balb/c MEF cultures grown in 3% O_2 were analyzed for C-FOS, p16, p21 and α-tubulin by western blotting. Proteins were prepared from exponentially growing (lane 1) and serum-deprived (lanes 2 and 5) cultures, or cultures that were serum deprived and then serum-stimulated for 1.5 h. (lanes 3, 6) or 6 h (lanes 4, 7). **c**, The lifespan of three C57Bl/6 (black) and three Balb/c (gray) MEFcultures, derived and grown in 20% O_2, was determined. **d,** The replicative life span of DNA-PKcs -/- MEFs in 3% or 20% O_2 is shown. Four DNA-PKcs (gray) and three wild-type littermate (black) cultures were derived and grown in 3% or 20% O_2.



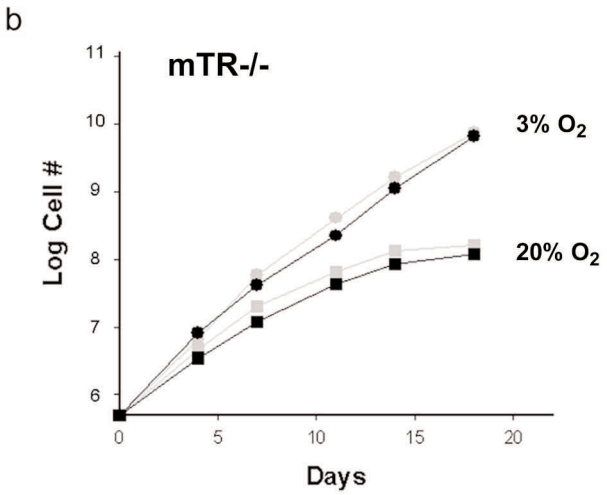


Figure S3. **Telomere-FISH and growth of telomerase-deficient MEFs in 3% and 20% O_2. a**, Representative metaphase spreads of early passage *ku80-/-* and fourth generation *mTR-/-* MEFs before (ii and iv) and after (i and iii) fluorescence *in situ* hybridization (FISH) with a telomere probe. Arrows denote breaks (b), fragments (f), rings (r) and telomeric fusions (tf). **b**, Replicative life spans of a representative fourth generation *mTR-/-* (gray) and wild-type littermate (black) MEF culture in 3% O_2 (circles) and 20% (squares) O_2 are shown. Duplicate cultures were grown in parallel. Similar results were obtained with an independent *mTR-/-* MEF culture.