Supplementary Materials and Methods

Translocation PCR. The following thermocyling conditions were used: First round was 96C for 5 min followed by 25 cycles of 94°C, 15 s; 62°C, 15 s; and 68°C, 7 min with 20 s of additional extension time per cycle. Second round was 25 cycles with 4 min of elongation time extended for 20 s per cycle. The following primers were used: derivative chromosome 12 translocations first round, 5′-TGA GGA CCA GAG AGG GAT AAA AGA GAA-3′ and 5′-GGG GAG GGG GTG TCA AAT AAT AAG A-3′; derivative chromosome 12 translocations second round, 5′-CAC CCT GCT ATT TCC TTG TTG CTA C-3′ and 5′-GAC ACC TCC CTT CTA CAC TCT AAA CCG-3′; derivative chromosome 15 translocations first round, 5′-ACT ATG CTA TGG ACT ACT GGG GTC AAG-3′ and 5′-GTG AAA ACC GAC TGT GGC CCT GGA A-3′; and derivative chromosome 15 translocations second round 5′-CCT CAG TCA CCG TCT CCT CAG GTA-3′ and 5′-GTG GAG GTG TAT GGG GTG TAG AC-3′. Myc loading control primers were 5′-GGG GAG GGG GTG TCA AAT AAT AAG A-3′ and 5′-GTG AAA ACC GAC TGT GGC CCT GGA A-3′. PCR products were purified, cloned (TOPO-TA, Invitrogen), and sequenced.

For the DR-GFP:Chr 2 translocation PCR, cells were infected with adeno-I-Sce1 with an MOI 500:1 at 50% confluency. 72 hours later the cells were harvested and genomic DNA was prepared using DNeasy Blood and Tissue Kit (Qiagen). First round was 96°C for 5 min followed by 30 cycles of 94°C, 15 s; 55°C, 45 s; and 72°C, 1.5 min. Second round was 96°C for 5 min followed by 30 cycles of 94°C, 15 s; 55°C, 45 s; and 72°C, 1.5 min. Primers used were *MMP2-4* 5'- GGT CAC TAA CTC ATG CCC CAC C -3'and *DR-GFP-400* 5'- GGT TCG GCT TCT GGC GTG -3' for the first round and *MMP2-5* 5'- GAG GAG ACG GAA GTG AAG CTC TG -3'and *DR GFP* 5'- GGT AGC GGC TGA AGC ACT GC -3'for the second round.

Immortalization of primary MEFs with c-Myc. Primary MEFs were generated from mouse embryos of the desired genotypes (E13.5), and the genotypes were verified via a PCR based strategy, as previously described (1). The cells were plated at passage 3 (P3) into a 6 well dish at 1.5 x 10^5 cells per well and cultured overnight at 37°C. 50μL of pLenti-Myc T58A or a pLenti-empty control (generous gifts from David Lombard) were introduced to the cells with a 1:4000 dilution of polybrene (Santa Cruz) in DMEM without serum or antibiotics. After 24 hours, retrovirus was removed and cells were washed twice with PBS. 24 hours later, cells were split 1:3 with medium containing 2μg/mL puromycin. After 5 days in selection media, 100% of the cells that were introduced with the control empty vectors were dead.

Southern Blot Analysis. Genomic DNA (gDNA) from control tissues and thymic or lymph node tumor masses were enzymatically digested with *Eco*RI and hybridized with the following radiolabeled probes within the J_H, Cμ, HS3a regions and N-Myc and c-Myc loci, as described previously (2-5). Bands were visualized by autoradiography and using a phosphorimager (STORM, Molecular Dynamics), signals were normalized to a non-lymphoid locus (LR8) and fold induction was determined compared to kidney gDNA controls.

Senescence Staining. Primary MEFs were treated with adeno-cre or adeno-empty as described above. 5 days after second adenovirus infection, cells were plated at a low density (1 x 10^5 cells per well in a 6 well dish) until reaching 50-75% confluency (2-3 days). Cells were stained for senescence using the Senescence β- Galactosidase Staining Kit (Cell Signaling) and the percentage of senescent cells were counted using a Leica DMIL phase contrast microscope.

Western Blotting. B lymphocytes, MEFs or tumor cells were lysed with RIPA buffer with protease inhibitors (Roche). Immunoblotting was performed as previously described (6). Using the following antibodies from Cell Signaling: Mre11 (#4895S), and GAPDH (#2118L). Membranes were imaged using Li-Cor Odyssey Imaging System and software.

Immunofluorescence Microscopy. U2OS cells were originally obtained from the ATCC and tested for mycoplasma using the MycoAlert Mycoplasma detection kit (Lonza) and a PCR detection method in 2015. The cells were transduced with pBABE or pBABE-cMycER retroviruses and selected in puromycin, as described in Materials and Methods. Upon treatment with U2OS-pBABE and U2OS-cMycER cells were fixed with ice cold 3.7% paraformaldehyde, 2% sucrose (γ H2AX, Nbs1), 3.7% paraformaldehyde, 2% sucrose, 0.5% Triton-X (FANCD2, BRCA1, RPA), or methanol (c-MYC) for 20 min and washed 3x with PBS. For γ H2AX, FANCD2, and BRCA1 foci, cells were then incubated with ice cold buffer (20mM HEPES, 50mM NaCl, 3mM $MgCl_2$, 0.5% TX-100, 300mM sucrose) for 4 min. For RPA and BRCA1 foci, cells were incubated with ice cold buffer (10mM HEPES, 50mM NaCl, 3mM $MgCl_2$, 0.5% TX-100, 200mM sucrose) for 5 min. For Nbs1 foci, cells were incubated with 0.2% Triton-X for 10 min.

Mouse models. Gene targeted Artemis null, Mre11 conditional, and $Mre11^{H129N}$ (129Svev/C57Bl6 background) mice have been previously described (1, 7). p53 ($Trp53^{tm1Tyj}$) mutant mice in a 129Sv background were obtained from Jackson labs and intercrossed into the Artemis and Mre11 gene targeted mice. All mice were housed in a specific pathogen free facility. All experiments complied with regulations and ethics guidelines of the National

Institute of Health and were approved by the Institutional Animal Care and Use Committee of the University of Michigan (PRO00006263).

References

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