Figure S1. MUS81-EME2 is required for the breakage of stalled formation forks (related to Figure 2). (A) HeLa cells were transfected with siEME2 #2 for 48 hr and treated with the indicated concentrations of HU for 24 hr. Cells were collected at the indicated times and DNA breakage was analyzed by pulse field gel electrophoresis. (B) As (A) but using cisplatin instead of HU. Cells were transfected with the indicated siRNAs for 48 hr before addition of the drug. (C) Quantification of cisplatin-induced DSB formation, expressed as the ratio of broken to intact DNA. The data are presented as a mean of three experiments (± SEM). (D) As (A) except that the cells were treated with the indicated concentrations of cisplatin for 24
Figure S2. MUS81-EME2 is required for telomere maintenance in ALT cells (related to Figure 4). (A) Quantification of telomere-free chromosome ends in U2OS cells transfected with control or EME2 #2 siRNA (± SEM). Statistical significance was calculated using Pearson’s chi-squared test. *n* indicates the number of chromosome ends analyzed. (B) Histograms showing the distribution of telomere lengths (relative fluorescence units) in U2OS cells transfected with the indicated siRNAs, as determined by flow-FISH. (C) and (D) The efficiency of siRNA depletion was determined by western blotting in HeLa and U2OS cells, respectively.
Figure S3. MUS81-EME2 is not required for telomere maintenance in telomerase-positive cells (related to Figure 4). (A) Representative Q-FISH image of a metaphase spread from EME2-depleted HT1080 cells. (B) Quantification of telomere-free chromosome ends in HT1080 cells depleted using the indicated siRNAs (± SEM). Statistical significance was calculated using Pearson’s chi-squared test. $n$ indicates the number of chromosome ends analyzed.
Figure S4. EME2 is required for normal cell cycle progression in ALT cells (related to Figure 4). Telomerase-positive (HeLa, HT1080) or ALT-positive (U2OS, GM847) cell lines were transfected with the indicated siRNAs and cell cycle progression was analyzed by FACS.
**Supplementary Table 1 (related to Figure 3).** Frequency of chromosomal aberrations in RPE1-hTERT cells depleted for the indicated proteins, with or without HU treatment (1 mM HU for 24 hr).

| siRNA | Treatment        | Number of metaphases analyzed | Acentric fragments | Chromosome breaks | Chromatid breaks | Radials | Dicentrics | Rings |
|-------|------------------|-------------------------------|-------------------|------------------|------------------|---------|------------|-------|
| Control | Mock               | 50                           | 0.04              | 0                | 0.04             | 0       | 0          | 0     |
| EME1   | Mock               | 50                           | 0.08              | 0.06             | 0.08             | 0       | 0          | 0     |
| EME2   | Mock               | 50                           | 0.1               | 0.04             | 0.08             | 0.06    | 0.02       | 0.02  |
| MUS81  | Mock               | 50                           | 0.03              | 0.08             | 0.1              | 0.04    | 0          | 0     |
| Control | Hydroxyurea        | 50                           | 0.08              | 0.06             | 0.18             | 0.08    | 0.02       | 0     |
| EME1   | Hydroxyurea        | 50                           | 0.12              | 0.02             | 0.16             | 0.08    | 0          | 0     |
| EME2   | Hydroxyurea        | 50                           | 0.24              | 0.12             | 0.22             | 0.1     | 0.06       | 0.06  |
| MUS81  | Hydroxyurea        | 50                           | 0.28              | 0.1              | 0.16             | 0.08    | 0          | 0.02  |
Extended Experimental Procedures

Cell lines and cell culture

The following cell lines were cultured in Dulbecco’s Modified Eagle Media (DMEM) supplemented with 10% (v/v) FBS: Telomerase positive HeLa Kyoto and HT1080, ALT-positive U2OS and GM847, SV40 transformed Bloom’s syndrome skin fibroblast line GM08505, and the TERT-immortalized retinal pigment epithelial cell line RPE1-hTERT. All cultures were grown at 37°C in a 10% CO₂ humidified incubator.

Immunoprecipitation

To follow the synchronous release of G1/S-arrested cells into mitosis, HeLa Kyoto cells expressing MUS81FLAP at endogenous levels (Matos et al., 2011) were synchronized with a double thymidine block (2.5 mM thymidine, 16 hr each) and released for 6 hr, at which time nocodazole (100 ng/ml) was added and incubation continued. At various times after release from the block, cells were washed with PBS, treated with trypsin and harvested. Cell pellets were washed with PBS and resuspended in 500 µl of lysis buffer (TBS supplemented with 1x phosphatase inhibitor cocktail 2 (Sigma), 1x phosphatase inhibitor cocktail 3 (Sigma), 1x protease inhibitor cocktail (Roche) and 0.5% (v/v) NP-40). The DNA was sheared using a 1 ml syringe with a 0.8 mm x 40 mm needle (20 strokes on ice). Samples were incubated on ice for 30 min and then centrifuged for 30 min at 14000 rpm at 4°C. Cleared lysates were transferred to a fresh Eppendorf tube and protein concentrations were determined using a Bio-Rad Dc protein assay kit. The volumes and concentrations of each samples was normalized and 15 µl of GFP-TRAP® packed beads were added to each. Prior to addition, the GFP-TRAP® beads (Chromotek) were washed four times in lysis buffer and incubated in lysis buffer + 1 mg/ml BSA for 30 min on a rotating wheel at 4°C. The lysate/bead mixtures were incubated for 1.5 hr on a rotating wheel at 4°C, washed 4x with IP buffer (TBS supplemented with 0.5% (v/v) NP-40) and boiled in 25 µl of 1x protein loading buffer (NuPAGE® LDS loading buffer
supplemented with 10% (v/v) β-mercaptoethanol) for 5 min. The resulting MUS81FLAP immunoprecipitates were analyzed by loading 20 µl of the protein sample on NuPAGE® 7% Tris-Acetate gels (Life technologies) and by western blotting. The antibodies used for western blotting were: mouse anti-MUS81 (ab14387, Abcam, 1:500), mouse anti-EME1 (clone MTA31 7H2, Santa Cruz, 1:500), rabbit anti-EME2 (APEP13, Cancer Research UK) and sheep anti-SLX4 (a gift from Prof. John Rouse). Mouse anti-β-Actin (ab8226, Abcam, 1:10000) was used to monitor protein loading.

**siRNA transfection and western blotting**

The siRNAs used in this study were purchased from Eurofins. EME2 siRNAs were designed using Sfold (http://sfold.wadsworth.org/cgi-bin/index.pl). The siRNAs sequences (5' to 3') were as follows:

Luciferase (control) GL2: CGTACGCGGAATACTTCGA

EME1: GCCUAAGCAGUGAAAGUGAA (Naim et al., 2013)

EME2: GCGAGCCAGUGGCAAGAGA (Pepe and West, 2014)

EME2 #2: UGGAGCCCGAGGAGUUUCU

MUS81: CAGCCCGUGGUGGGAUCGAUA (Wechsler et al., 2011)

One day before transfection, 3 - 7 x 10^5 or 7 x 10^5 cells were seeded in 6 cm or 10 cm cell culture plates, respectively. EME1 (40 nM), EME2 (80 nM), EME2 #2 (80 nM) or MUS81 (60 nM) siRNAs were transfected using Lipofectamine RNAiMAX. Cells were transfected with MUS81 siRNA 2x within 24 hr, whereas all other transfections were performed once. The control siRNA, Luciferase GL2, was used at comparable amounts. Cells were collected 72 hr after the first transfection, unless stated otherwise.
Pulse field gel electrophoresis

PFGE was performed essentially as described (Hanada et al., 2007). In brief, HeLa cells were transfected with siRNAs targeting Luciferase, EME1, EME2 or MUS81. Hydroxyurea was added 48 hr post-transfection, and after 24 hr the cells were collected, and washed in PBS. Approximately $1 \times 10^6$ cells were used to make low melting point agarose plugs using CHEF Mapper® XA system plug molds (Bio-Rad). To do this, the cells were centrifuged, resuspended in 50 µl of washing buffer (10 mM Tris-HCl pH 8.0, 100 mM EDTA) and mixed with 50 µl 1% (w/v) low melting point agarose in water. The agarose plugs were allowed to polymerize for 30 - 40 min at 4°C and then lysed at 37°C in 10 mM Tris-HCl pH 8.0, 100 mM EDTA, 1% (w/v) sodium lauryl sarcosine, 0.2% (w/v) sodium deoxycholate and 1 mg/ml proteinase K. After 48 hr, the plugs were washed 2x in washing buffer and incubated overnight in RNase buffer (10 mM Tris-HCl pH 8.0, 10 mM EDTA, 1 mg/ml RNase A). The next day, the plugs were washed in 10 mM Tris-HCl pH 8.0 and 100 mM EDTA, and loaded on a 1% (w/v) agarose gel in 0.5% (v/v) TBE. After the plugs were positioned, the gel was sealed with 0.5% (w/v) low melting point agarose in 0.5% (v/v) TBE and run for 23 hr at 13°C in a Gene Navigator PFGE apparatus (Amersham Biosciences) using the following parameters: voltage 180–120 V log; angle from 1201 to 1101 linear; interval 30 s to 5 s log. Gels were stained with 1.25 µg/ml ethidium bromide in 0.5% (v/v) TBE for 1 hr and visualized using the Molecular Imager GelDoc XR+ (Bio-Rad). Data analysis was performed using ImageLab software.

Analysis of metaphase chromosomes

SCEs analyses were carried out essentially as described (Bayani and Squire, 2005). Briefly, cells were incubated with 100 µM BrdU for 72 hr and colcemid (0.2 µg/ml) was added for the last 1.5 hr of BrdU incubation. Cells were collected by mitotic shake-off, washed in PBS and swollen in 5 ml of 750 mM KCl for 30 min at 37°C. Ice-cold methanol / acetic acid (3:1, 5 ml) was added on top of the swelling buffer and the cells were centrifuged for 5 min at 1200
rpm at RT. The two-layered solution was removed from the bottom to the top and the cells were resuspended in an additional 5 ml of ice-cold methanol/acetic acid (3:1). Fixation was performed for 15 min on ice. Metaphase cells were then spread on Superfrost Microscope slides (Thermo Scientific) and air-dried overnight at RT. Slides were stained for 30 min in 50 ml Soerensen buffer pH 6.8 (38% (v/v) 133 mM Na₂HPO₄, 62% (v/v) 133 mM KH₂PO₄) containing 100 µg/ml Hoechst 33258 (Sigma). After washing with a further 50 ml of Soerensen buffer, the slides were placed in a shallow container, covered with Soerensen buffer and exposed to 254 nm UV light (Stratalinker 2400) for 45 min. The slides were then covered with 2x SSC buffer (300 mM sodium citrate pH 7.0, 30 mM NaCl), incubated at 60°C for 1 hr and stained in 50 ml 7% (v/v) GIEMSA solution at room temperature for 7 min. After washing three to four times with 50 ml water, the coverslips were mounted on the slides using 80 µl DPX mounting medium (Fisher BioReagents). Images were acquired with a Zeiss Axio Imager M1 microscope using a Plan-Neofluar x60, 0.4 numerical aperture oil objective lens, and captured using an ORCA-ER camera (Hamamatsu) controlled by Volocity 6.0.1 software (Improvision).

To visualize chromosomal aberrations, the same procedure was followed with the exception of the BrdU incubation. siRNA-transfected RPE-1 hTERT cells were either left untreated or treated with 150 nM aphidicolin (16 hr) or with 1 mM hydroxyurea (24 hr). Cells treated with HU were washed and incubated with fresh media for 24 hr before analysis. Metaphase spreads were stained with 50 ml 7% GIEMSA for 7 minutes immediately after spreading and drying.

**Telomeric quantitative-FISH (Q-FISH)**

Q-FISH was performed essentially as described (Blasco et al., 1997; Zijlmans et al., 1997). Briefly, following metaphase spreading, as described above, the slides were re-hydrated in 50 ml PBS for 5 min, fixed with 100 µl of 4% (v/v) paraformaldehyde for 2 min and treated with 100 µl of 1 mg/ml pepsin for 10 min at 37°C. Slides were washed in 50 ml PBS, fixed again with 100 µl of 4%
paraformaldehyde and dehydrated using a series of ethanol washes (5 min in 70% (v/v), 5 min in 95% (v/v) and 5 min in 100%). Hybridizing solution (80 µl, 10 mM Tris-HCl pH 7.2, 70% (v/v) deionized formamide, 0.5% (w/v) Roche FISH blocking solution) containing 110 nM FITC-TelC probes (bioSYNTHESES) was added to the slides and denaturation was performed on a 70°C hot plate for 7 min. Slides were incubated in a humid chamber for 2 hr at RT or overnight at 4°C, washed 2x with 50 ml of 10 mM Tris-HCl pH 7.2, 70% (v/v) formamide for 15 min and 3x with 50 ml of 100 mM Tris-HCl pH 7.2, 150 mM NaCl, 0.08% (v/v) Tween-20 for 5 min (160 ng/ml DAPI was added to the second wash) in Coplin jars. Slides were dehydrated using a series of ethanol washes (5 min in 70% (v/v), 5 min in 95% (v/v) and 5 min in 100%), air-dried and mounted using ProLong Gold Antifade Reagent (Life technologies). Images were acquired with a Zeiss Axio Imager M1 microscope using a Plan-Neofluar x60, 0.4 numerical aperture oil objective lens, and captured using an ORCA-ER camera (Hamamatsu) controlled by Volocity 6.0.1 software (Improvision).

**Telomeric chromosome orientation-FISH (CO-FISH)**

U2OS cells (7 x 10^5 cells) were seeded on 10 cm plates and 24 hrs later were transfected with siRNA. Twenty hours before harvesting, 10 µM BrdU was added to the cells and metaphase spreads were prepared as described above. CO-FISH was performed as described (Bailey et al., 2004; Bechter et al., 2004; Londono-Vallejo et al., 2004). Briefly, slides were re-hydrated for 5 min in PBS, treated with 0.5 mg/ml RNase A (Qiagen) for 10 min at 37°C and stained with 0.5 µg/ml Hoechst 33258 in 2x SSC (300 mM sodium citrate pH 7.0, 30 mM NaCl) for 15 min at RT. Slides were placed in a shallow container, covered with 2x SSC buffer and exposed to 365 nm UV light (Stratalinker 1800) at RT for 30 min. The BrdU-substituted DNA strands were digested by treatment with 80 µl of 10 U/ml of Exonuclease III (Promega) at RT for 10 min. Slides were washed with 50 ml of PBS, dehydrated using a series of ethanol washes (5 min in 70% (v/v), 5 min in 95% (v/v) and 5 min in 100%) and air-dried at RT. The first hybridization was performed by adding 80 µl of
hybridizing solution (80 μl, 10 mM Tris-HCl pH 7.2, 70% (v/v) deionized formamide, 0.5% (w/v) Roche FISH blocking solution) containing 10 nM TelG-TMR probe onto the slides and incubating for 2 hr at RT in a humidified chamber. Slides were rinsed in 50 ml of 10 mM Tris-HCl pH 7.2, 70% (v/v) formamide for 5 s. The second hybridization was performed by adding 80 μl of hybridizing solution containing 110 nM FITC TelC probe onto the slides and incubating for 2 hr at RT in a humidified chamber. Slides were washed 2x with 50 ml of 10 mM Tris-HCl pH 7.2, 70% (v/v) formamide for 5 min each, 3x with 50 ml of 100 mM Tris-HCl pH 7.2, 150 mM NaCl, 0.08% (v/v) Tween-20 for 5 min (160 ng/ml DAPI was added to the second wash) in Coplin jars, dehydrated using a series of ethanol washes (5 min in 70% (v/v), 5 min in 95% (v/v) and 5 min in 100%) and air-dried at RT. Coverslips were mounted onto the slides using ProLong Gold Antifade Reagent (Life technologies). Images were acquired with a Zeiss Axio Imager M1 microscope using a Plan-Neofluar x60, 0.4 numerical aperture oil objective lens, and captured using an ORCA-ER camera (Hamamatsu) controlled by Volocity 6.0.1 software (Improvision).

Immunofluorescence (IF) and IF-FISH

Immunofluorescence was carried out as described (Perez-Burgos et al., 2004) with some variations. Briefly, cells were seeded in 6 cm plates containing two 22 mm x 22 mm coverslips. The coverslips were transferred into 6-well plates, washed with 2 ml PBS and incubated with 2 ml pre-extraction buffer (PBS supplemented with 0.1% Triton X-100) for 4 min at RT. Cells were fixed with 2 ml of 4% paraformaldehyde for 10 min, washed 2x in PBS and permeabilized in 2 ml 0.1% (w/v) sodium citrate and 0.1% Triton X-100 for 5 min at RT. The coverslips were washed 2x with PBS (2 ml, 5 min each) and then 2x in IF washing solution (PBS supplemented with 0.25% BSA and 0.1% Tween-20, 2ml, 5 min each) before incubating with 2 ml of IF blocking solution (PBS supplemented with 2.65% BSA, 0.1% Tween-20 and 10% FBS) for 30 min at RT. Mouse anti-MUS81 (ab14387, Abcam), mouse anti-PML (ab50637, PML-97, Abcam) and rabbit anti-FLAG (F7425, Sigma) antibodies were diluted
1:500 in IF blocking solution and 40 µl drops were placed on parafilm. The coverslips were positioned on the primary antibody solution drops and incubated in a humid chamber for 2 hr at RT or overnight at 4°C. After washing the coverslips 3x with 2 ml of IF washing solution (10 min each), secondary antibodies (Alexa Fluor 488 goat anti-mouse IgG (H+L), Alexa Fluor 488 F(ab’)2 fragment of goat anti-rabbit IgG (H+L), Molecular probes) were diluted in IF blocking buffer and applied to the coverslips as described above. Excess secondary antibody was washed out with 2 ml of IF washing solution (three washes, 10 min each). Finally, the coverslips were air-dried and mounted using ProLong Gold Antifade Reagent with DAPI (Life technologies).

To perform IF-FISH, the same procedure was followed. Then, after incubation with the secondary antibody, cells were washed 3x with 2 ml PBS (5 min each) and fixed for 2 min with 2 ml of 4% paraformaldehyde. Coverslips were washed with 2 ml of PBS, dehydrated using a series of ethanol washes (5 min in 70%, 5 min in 95% and 5 min in 100%) and air-dried for 30 min at RT. FISH was performed as described above. Images were acquired with a Zeiss Axio Imager M1 microscope using a Plan-Neofluar x60, 0.4 numerical aperture oil objective lens, and captured using an ORCA-ER camera (Hamamatsu) controlled by Volocity 6.0.1 software (Improvision).

**Analysis of DAPI-positive anaphase bridges**

One day before siRNA transfection, cells were seeded in 6 cm plates containing two 22 mm x 22 mm coverslips. Forty-eight hours after transfection, cells were treated with 150 nM aphidicolin for 16 hr or with 1 mM HU for 24 hr. Cells treated with HU were washed and incubated with fresh media for 24 hr before analysis. On the day of the experiment, coverslips were transferred into 6-well plates, washed with 2 ml PBS and fixed for 10 min with 2 ml of 4% paraformaldehyde. After washing 2x with PBS, cells were permeabilized with 2 ml of permeabilization buffer (0.1% sodium citrate, 0.1% Triton X-100) for 5 min at RT, washed 2x with PBS and mounted on glass
slides using ProLong® Gold Antifade Reagent with DAPI (Life technologies). Images were acquired with a Zeiss Axio Imager M1 microscope using a Plan-Neofluar x60, 0.4 numerical aperture oil objective lens, and captured using an ORCA-ER camera (Hamamatsu) controlled by Volocity 6.0.1 software (Improvision).

**Flow cytometry**

Following siRNA transfection, cells were washed with PBS, treated with trypsin and harvested in their own media. Pellets were washed with PBS and fixed with 70% ethanol for at least 30 min on ice. Ethanol was removed by washing the cell pellets 2x with 5 ml of PBS. Cells were treated with 50 µl of 100 µg/ml RNase A (Qiagen) and stained with 200 µl of 50 µg/ml propidium iodide (Sigma). DNA content was analyzed on a FACSCalibur flow cytometer (BD Biosciences) and FACS data were analyzed using FlowJo 10.1 software.

Flow-FISH was performed essentially as described (Rufer et al., 1998). Briefly, siRNA-transfected cells were washed with PBS, treated with trypsin and harvested in their own media. 3 x 10^5 cells per sample were counted and resuspended in PBS + 0.1% (w/v) BSA. Cells were centrifuged at 13000 rpm for 15 sec, the supernatant was removed and the pellet was resuspended in 300 µl of hybridization mixture containing 70% deionized formamide, 20 mM Tris-HCl pH 7.0, 1% (w/v) BSA and 0.3 µg/ml FITC TelC probe. Samples were subjected to heat denaturation of DNA for 10 min at 80°C in a thermomixer and hybridization was allowed to occur for 2 hr at RT. Cells were centrifuged for 7 min at 3000 rpm and the supernatant removed. Pellets were washed 2x with 1 ml of 70% deionized formamide, 10 mM Tris pH 7.0, 0.1% BSA and 0.1% Tween 20 and once with 1 ml of PBS supplemented with 0.1% BSA and 0.1% Tween 20. Samples were centrifuged at 2000 rpm for 5 min and cell pellets were resuspended in PBS + 0.1% BSA containing 10 µg/ml RNAse A (Qiagen). Cells were then transferred to a FACS tube and the fluorescence signal was analyzed on a FACSCalibur flow cytometer (BD Biosciences). FACS data were analyzed using FlowJo 10.1 software.
DNA combing was performed essentially as described (Michalet et al., 1997). Briefly, siRNA-transfected HeLa cells were treated with 1 mM HU and labeled with 20 µM IdU for 24 hr. Cells were then washed 3x with PBS and pulse-labeled with 200 µM CldU for 30 min. After washing 2x with PBS, cells were treated with trypsin, harvested and 400,000 cells/sample were used to make low melting point agarose plugs using CHEF Mapper® XA system plug molds (Bio-Rad). Protein lysis was performed in proteinase K buffer (10 mM Tris-HCl pH 7.5, 50 mM EDTA, 1% (w/v) sarkosyl, 2 mg/ml proteinase K) at 50°C for 8 hr. The buffer was then changed and incubation was continued overnight. Next day, the plugs were incubated with fresh proteinase K buffer for further 8 hr before incubation with 2 U of β-agarase (NEB, 1000 U/ml) at 42°C overnight. DNA fibers were stretched on silanized coverslips using the molecular combing system (Genomic vision) and slides were incubated at 65°C for a minimum of 2 hr. For immunodetection, DNA was denatured with 50% formamide, 2X SSC at 75°C for 2 min. The slides were then dehydrated using a series of ethanol washes (5 min in 70%, 5 min in 95% and 5 min in 100%) and blocked using 1% Roche blocking reagent at 37°C for 1 hr. CldU was detected with rat anti-BrdU antibody (BU1/75, AbCys; 1:20, 45 min, 37°C), followed by goat anti-rat coupled to Alexa 594 (A11007, Molecular Probes; 1:50, 30 min, 37°C) and finally by chicken anti-goat coupled to Alexa 594 (A21468, Molecular Probes; 1:50, 30 min, 37°C). IdU was detected with mouse anti-BrdU coupled to FITC antibody (BD44, Becton Dickinson; 1:20, 45 min, 37°C), followed by rabbit anti-mouse coupled to Alexa 488 (A11059, Molecular probes; 1:50, 30 min, 37°C) and finally by donkey anti-rabbit antibody coupled to Alexa 488 (A21206, Molecular Probes; 1:50, 30 min, 37°C). Between each antibody incubation, the slides were washed 3x with 4X SSC, 0.05% (v/v) Tween-20 for 5 min. Slides were mounted using Vectashield mounting media. Images were acquired with a Zeiss Axio Imager M1 microscope using a Plan-Neofluar x60, 0.4 numerical aperture oil objective lens.
lens, and captured using an ORCA-ER camera (Hamamatsu) controlled by Volocity 6.0.1 software (Improvision).

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