Supporting Information

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SI Materials and Methods

Cell Lines and Culture Conditions. All cell lines were routinely maintained at 37 °C under 5% (vol/vol) CO_2, in the appropriate medium containing 10% (vol/vol) FBS, 100 units/mL penicillin sodium, and 100 μg/mL streptomycin sulfate, 1 mM sodium pyruvate, and 10 mM Hepes buffer. Human colon carcinoma HCT116 and RKO cells were grown in McCoy's 5A medium, supplemented with 20 μg/mL blasticidin (Invitrogen), for the cells stably transfected with a cDNA coding for a histone 2B fused to the green fluorescent protein (H2B-GFP) from BD PharMingen. Human osteosarcoma (U2OS) cells stably expressing H2B-GFP and murine Lewis lung carcinoma (LLC) cells were cultured in Dulbecco's modified Eagle's medium (DMEM), supplemented with blasticidin for U2OS. Mouse embryonic fibroblasts (MEFs) were grown in DMEM supplemented with 1% nonessential amino acids and 2-mercaptoethanol (80 μM). Culture media and supplements for cell culture were obtained from Gibco Invitrogen. Cells were seeded in the appropriate support (6-, 12- or 96-well plates; Corning) and allowed to adapt for 24 h before experimental assessments. HCT116 $p53^{-/-}$ cells were a kind gift from Bert Volgelstein (Johns Hopkins University, Baltimore).

Generation of Tetraploid Cells. Tetraploid cells were generated from close-to-diploid parental cancer cells or diploid mouse embryonic fibroblasts with 100 nM nocodazole (Sigma-Aldrich), 1 μM dihydrocytochalasin B (DCB) (Sigma-Aldrich) or cytochalasin D (Sigma-Aldrich) for 48 h. After drug washout, cells were cultured for 2 wk, followed by cloning of clones characterized by an 8n DNA content on a FACSVantage cell sorter from BD Biosciences, as previously described (1–4).

Isolation and Culture of Mouse Mammary Gland Epithelial and Intestinal Epithelial Crypt Cells. The isolation of mouse mammary gland epithelial cells (MMECs) was performed on 7-mo-old female $Tp53^{-/-}$ C57BL/6 mice as detailed previously (3). Dissociated cells were then cultured in flasks precoated for 4 h at 37 °C with 0.1% (wt/vol in PBS) gelatin. MMECs were grown in DMEM/F12 medium supplemented with 2% FBS, 50 μg/mL gentamycin sulfate, 100 μg/mL insulin, and 5 ng/mL epithelial growth factor (EGF). mouse intestinal epithelial crypt cells (MIECs) were isolated from 11-wk-old male C57BL/6 and $Apc^{Min/+}$ mice (Charles River), as previously described (5, 6).

Chemicals. Resveratrol was purchased from Sigma-Aldrich and Selleckchem. Piceatannol, rolipram, aspirin, salicylate, 2-deoxyglucose, 3-bromopyruvate mevastatin, simvastatin, nocodazole, dihydrocytochalasin B, Checkpoint kinase 1 inhibitor (UCN-01), cisplatin (CDDP), paraquat, rotenone, quercetin, and bafilomycin A1 were obtained from Sigma-Aldrich. A-769662, AICAR, H89, etodolac, and rofecoxib were purchased from Selleckchem; MDL-12330A from Enzo Life Sciences; rapamycin and EX-527 from Tocris Bioscience; and the pan-caspase inhibitor Z-VAD-fmk from Bachem Bioscience.

RNA Interference. Diploid and tetraploid HCT116 cells preseeded in 12-well plates were transfected with siRNAs by Oligofectamine transfection reagent (Invitrogen), according to the manufacturer's instructions. The following siRNA, purchased from Sigma-Proligo, were used:

5′-GCCGGUAUGCCGGUUAAGUdTdT-3′ (siUNR),

5′-GACUCCAGUGGUAAUCUACdTdT-3′ (sip53a),

5′-GCCGGUAUGCCGGUUAAGUdTdT-3′ (sip53b),

5′-GGUGCCGGAACUGAUCAGAdTdT-3′ (siBax),

5′-GCGAAGUCUUUGCCUUCUC dTdT-3′(siBak),

5′-GCUGCACCUGACGCCCUUCdTdT-3′ (siBcl-2),

5′-GGAGAUGCAGGUAUUGGUGdTdT-3′ (siBcl-x_L),

5′-GCAUCGAACCAUUAGCAGAdTdT-3′ (siMcl-1),

5′-GGUGAUGGAGAAUAGCAGUdTdT-3′ (siAURKB).

Plasmid Transfection in Human Cell Cultures. Plasmids encoding GFP-LC3 cDNAs (Addgene) and AMP-activated protein kinase (AMPK) alpha1 subunit were obtained from Benoit Viollet (Institut Cochin, Paris) upon material transfer agreement. PcDNA3.1 was used as empty vector control. Transient plasmid cotransfections were performed by means of Lipofectamine LTX reagent (Invitrogen) and cells were analyzed by automated fluorescence microscopy 48 h after transfection or harvested for immunoblotting analyses. GFP positive cells were considered as positively transfected for each couple of plasmids.

Compound Screen. Diploid and tetraploid HCT116 and U2OS cells stably transduced with H2B-GFP, were mixed in a 1:1 ratio and seeded in 96-well black/clear imaging plates (BD Biosciences). To discriminate between diploid and tetraploid cells, only one cell type was stably expressing an H2B-GFP construct. Cells were treated for 48 h with agents from the Institute of Chemistry and Cell Biology (ICCB) Known Bioactives Library (Enzo Life Sciences), at final concentrations ranging from 5 to 12 μg/mL. Forty-eight hours after treatment, cells were fixed with 4% paraformaldehyde (PFA, wt/vol in PBS) and nuclei were stained with Hoechst 33342 (1 μg/mL in PBS, Molecular Probes; Invitrogen).

Automated Fluorescence Microscopy and Videomicroscopy. Images from plates processed as above were acquired with a BD Pathway 855 automated microscope (BD Biosciences). Four view fields per well were acquired using a Plan Apo 20× objective (Olympus). Images were segmented and the ratio between the total number of cells (stained with Hoechst 33342) and H2B-GFP–expressing cells was determined with Attovision software version 1.7 (BD Biosciences). Data were statistically evaluated using Prism GraphPad software version 5 (GraphPad Software). To take into account interplate variations, data were normalized by z scoring.

For videomicroscopy, diploid and tetraploid HCT116 WT cells or HCT116 $p53^{-/-}$ cells, stably transduced with H2B-GFP, were grown in 96-well black/clear imaging plates (BD Biosciences). The recording of the images started at the time of the treatment ($t = 0$), and pictures were taken every 16 min (Movies S1 and S2) or 20 min (Movies S3–S5) for 41 h and 72 h, respectively. Three view fields per well were acquired using a 20× objective. Both transmitted light and fluorescence imaging were used to detect the cells. Images were analyzed with the open-source software Image J.

Immunofluorescence Microscopy. For detection of apoptotic markers, cells were fixed with 4% PFA (wt/vol in PBS), permeabilized with 0.1% Triton X-100 (in PBS), and immunostained with antibodies specific for cytochrome *c* (1/100; 6H2.B4, BD Biosciences) and cleaved caspase-3 (Asp175) (1/200; 9661, Cell Signaling Technology). Revelation was performed with the appropriate Alexa Fluor conjugated secondary antibodies (Molecular

Probes; Invitrogen). Hoechst 33342 (1 μg/mL) was used for nuclear counterstaining. Images were captured with a Primo Star microscope (Carl Zeiss) equipped with an AxioCam ERc 5s camera (Carl Zeiss) and AxioVision 4.8.2 software. An oil immersion objective (63×) was used.

Quantification of Autophagic Features by Fluorescence Microscopy. For the detection of autophagic markers, diploid and tetraploid HCT116 cells were transiently transfected with a plasmid GFP-LC3, by means of Lipofectamine 2000 (Gibco; Invitrogen) following manufacturer's recommendations. Twenty-four hours later, cells were treated with 80 μM resveratrol alone or in combination with 10 μM EX-527. Rapamycin (1 μM) was used as a positive control. Bafilomycin A1 (50 nM) was added in each condition to detect the accumulation of autophagosomes. After 6 h treatment, cells were fixed with 4% PFA and nuclei stained with 1 μg/mL Hoechst 33342. The accumulation of autophagosomes (visualized as GFP-LC3 aggregates) was examined by fluorescence microscopy, using an oil immersion objective (63×).

Cytofluorometry. For quantification of apoptotic features, living cells were costained for 30 min at 37 °C with 20 nM 3,3′dihexiloxalocarbocyanine iodide ($DioC_6(3)$, Molecular Probes; Invitrogen) or 150 nM tetramethylrhodamine methyl ester (TMRM) (Sigma-Aldrich), which measure the mitochondrial transmembrane potential ($\Delta\psi_m$), and 1 μg/mL propidium iodide (PI) (Sigma-Aldrich) or 10 μM 4′,6-diamidino-2-phenylindole (DAPI) (Molecular Probes; Invitrogen), to detect plasma membrane permeabilization. Annexin V was used to quantify phosphatidylserine exposure according to manufacturer's protocol (BD Pharmingen). Hoechst 33342 (10 μg/mL) was used to monitor DNA content.

For identification of polyploid cells from intestinal crypts, cells were extracted from the distal 5-cm small intestine. After isolation, the cells were fixed in 80% cold ethanol. To discriminate epithelial cells, cells were stained with a pan-cytokeratin antibody (1/100; C2562 Sigma-Aldrich) and counterstained with PI (50 μg/mL) according to a previously described protocol (4). The cell cycle profiles were determined upon cytoketin positive cells. All cytofluorometric determinations were conducted with a FACSCalibur, a FACScan (BD Biosciences), or a Gallios cytometer (Beckman Coulter). First line statistical analyses were performed using CellQuest software (BD Biosciences) or Kaluza software (Beckman Coulter). Single viable cells were discriminated from doublets upon gating on the events characterized by normal forward and side scatter (FSC and SSC, respectively).

Immunoblotting. Cells were washed and lysed in Nonidet P-40 lysis buffer, according to standard procedures. Thirty micrograms of protein extracts were then run on NuPAGE Novex Bis-Tris 4–12% precast gels (Invitrogen), and electrotransferred to Immobilon polyvinyldifluoride (PVDF) membranes (Bio-Rad). To block unspecific binding sites, membranes were incubated in 5% BSA (wt/vol) (Euromedex) plus 0.05% Tween (Euromedex) in 1× Tris buffered saline (TBS; Euromedex) for 1 h, before overnight incubation with appropriate primary antibody. The following antibodies were used: phospho-AMPKα (Thr172) (40H9; Cell Signaling Technology), AMPKα (23A3; Cell Signaling Technology), phospho-ACC (Ser79) (Cell Signaling Technology), and ACC (Cell Signaling Technology). Anti-β actin mouse monoclonal antibody (ab4900; Abcam) and anti-GAPDH (Millipore Chemicon International) were used to monitor equal loading of lanes. Finally, membranes were incubated with the appropriate horseradish peroxidase-labeled secondary antibodies (Southern Biotech Associates). Revelation was performed with SuperSignal West Pico chemoluminescent substrate (Thermo Scientific Pierce) and the ImageQuant LAS 4000 Biomolecular Imager (GE Healthcare Life Sciences).

Statistics. Unless otherwise specified, all experiments were carried out in duplicate parallel instances and independently repeated at least two times with multiple diploid and tetraploid clones. Data were analyzed with Microsoft Excel (Microsoft) and statistical significance was assessed by means of two-tailed unpaired Student *t* test ($^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$).

1. Castedo M, et al. (2006) Selective resistance of tetraploid cancer cells against DNA damage-induced apoptosis. *Ann N Y Acad Sci* 1090:35–49.
2. Castedo M, et al. (2006) Apoptosis regulation in tetraploid cancer cells. *EMBO J* 25(11): 2584–2595.
3. Senovilla L, et al. (2009) p53 represses the polyploidization of primary mammary epithelial cells by activating apoptosis. *Cell Cycle* 8(9):1380–1385.
4. Senovilla L, et al. (2012) An immunosurveillance mechanism controls cancer cell ploidy. *Science* 337(6102):1678–1684.
5. Sato T, et al. (2011) Long-term expansion of epithelial organoids from human colon, adenoma, adenocarcinoma, and Barrett's epithelium. *Gastroenterology* 141(5):1762–1772.
6. Sato T, et al. (2009) Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche. *Nature* 459(7244):262–265.

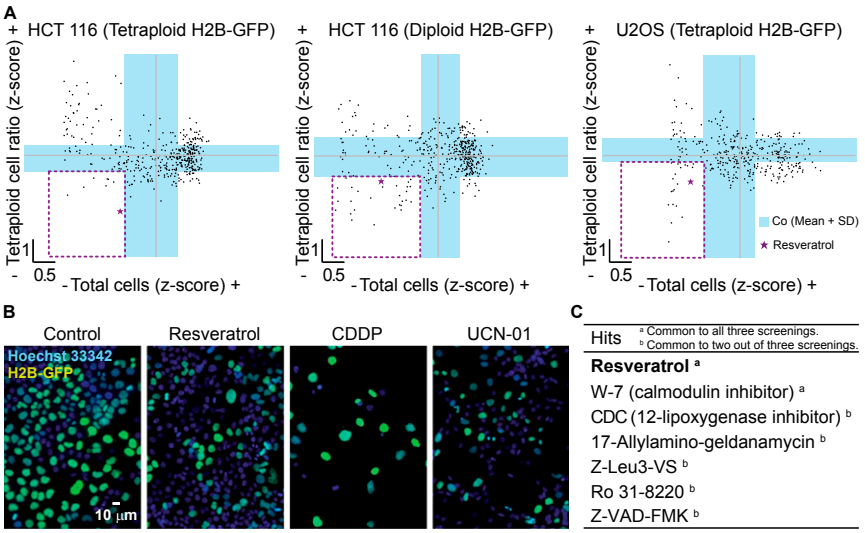


Fig. S1. Identification of resveratrol as a tetraploid-selective inhibitor. Parental and tetraploid clones from human colon carcinoma HCT116 cells or human osteosarcoma U2OS cells were cocultured at a 1:1 ration in the absence or presence of 480 compounds from the ICCB Known Bioactive Library at concentrations ranging from 5 to 12 μg/mL. Of note, only one cell type in the coculture stably expressed H2B-GFP. At 48 h, the cells were fixed and stained with 1 μg/mL Hoechst 33342 (H33342). Thereafter, the capacity of the agents to change the ratio between diploid and tetraploid cells was assessed by robotized fluorescence microscopy-mediated analysis of the H33342 and histone H2B-GFP fluorescence and reported as Z scores (*A*). Representative snapshots are shown in *B*. Cisplatin (CDDP) and UCN-01 were used as negative and positive controls, respectively. (*C*) A list of the hit compounds that preferentially impaired the proliferation of tetraploid cancer cells as identified in *A*. Please note that only two compounds, resveratrol, and the calmodulin inhibitor W7, displayed selective antitetraploid effect in all of the screenings.

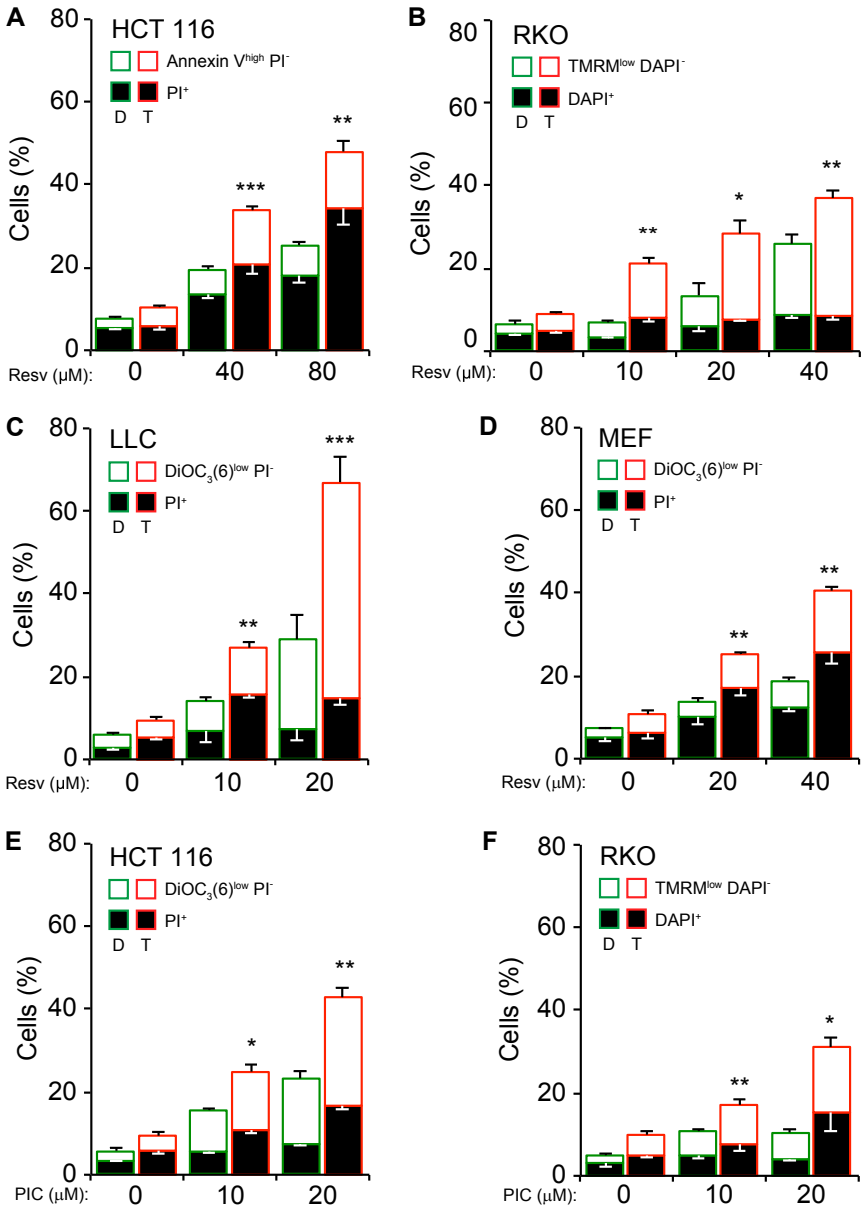


Fig. S2. Resveratrol and its metabolite piceatannol preferentially kills tetraploid cells in different cell lines. (*A–F*) Diploid and tetraploid clones (framed in green and red, respectively) from human colon carcinoma HCT116 cells (*A* and *E*), human colon carcinoma RKO cells (*B* and *F*), murine lung cancer LLC cells (*C*), and mouse embryonic fibroblasts (MEF) (*D*) were incubated with the indicated concentrations of resveratrol (Resv, for 48 h) or piceatannol (PIC, for 72 h) before cytofluorometric assessment of cell-death–related parameters (means ± SEM; two independent experiments on two diploid and two tetraploid clones per cell line). The percentage of dying cells—PI^- Annexin V^{high} (*A*), PI^- $DiOC_6(3)^{low}$ (*C–E*), $DAPI^-$ $TMRM^{low}$ (*B* and *F*), and dead cells—PI^+ or $DAPI^+$ (*A–F*) is represented by white and black columns, respectively. $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ (Student *t* test), compared with the equally treated diploid cells.

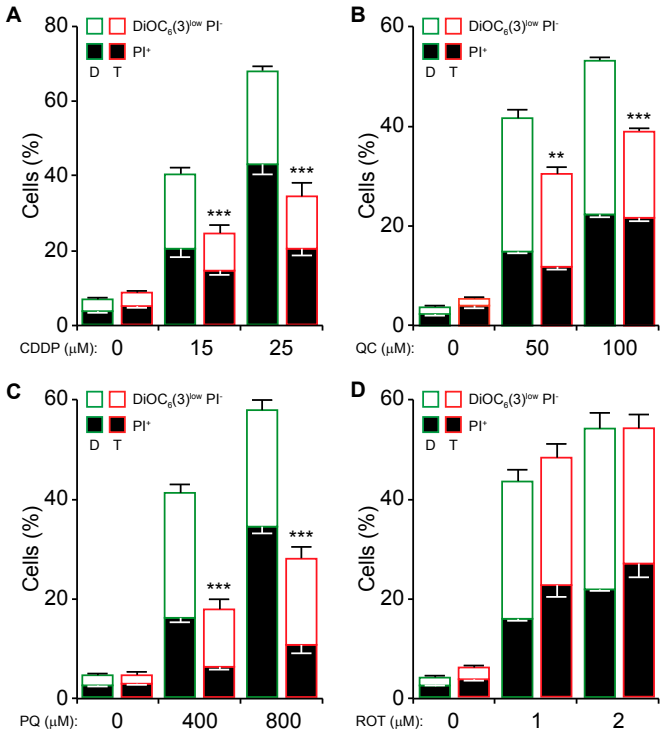


Fig. S3. Drugs that preferentially induce diploid cell death or equally kill diploid and tetraploid cells. (*A–D*) Diploid and tetraploid clones (framed in green and red, respectively) from human colon carcinoma HCT116 cells were treated for 48 h with the indicated concentrations of cisplatin (CCDP) (*A*), quercetin (QC) (*B*), paraquat (PQ) (*C*), or rotenone (ROT) (*D*), before cell death features measurement by flow cytometry (mean ± SEM; $n = 2$; two diploid and two tetraploid clones used). $^{**}P < 0.01$; $^{***}P < 0.001$ (Student *t* test), in comparison with the equally treated diploid cells.

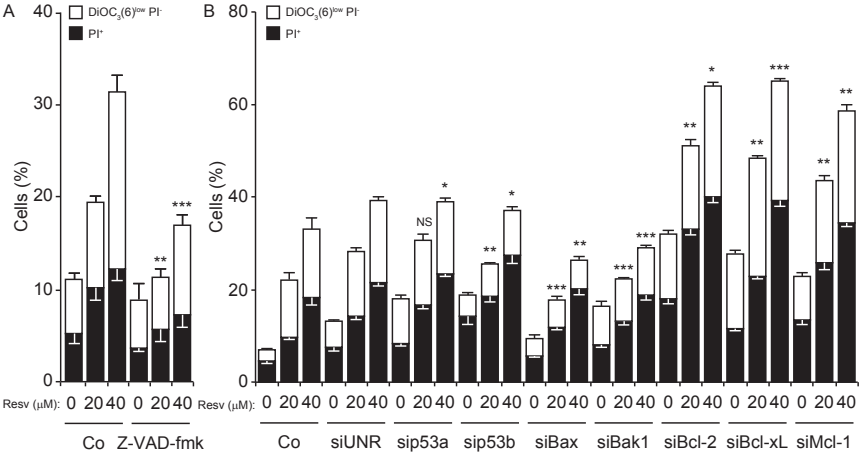


Fig. S4. Resveratrol induces a mitochondria-dependent pathway of apoptosis in HCT116 cells. (*A* and *B*) Tetraploid clones from human colon carcinoma HCT116 cells were left in control, untreated condition (Co), or incubated for 48 h with the indicated concentrations of resveratrol in combination or not with the pan-caspase inhibitor Z-VAD-fmk 50 μM (*A*), or, alternatively, left untransfected (Co) or transfected for 24 h with siRNAs targeting p53 (sip53a and sip53b), the proapoptotic Bcl-2 family members Bax and Bak1, and the antiapoptotic Bcl-2, Bcl-x_L, and Mcl-1 and treated for 48 h with resveratrol as indicated (*B*). siRNA with unrelated sequence (siUNR) was used as a control. Cell death was quantified by flow cytometry (mean ± SEM; two independent experiments with two tetraploid clones). NS, not significant; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ (Student *t* test), in comparison with the equally treated cells transfected with siUNR, after subtracting the level of basal mortality for each siRNA.

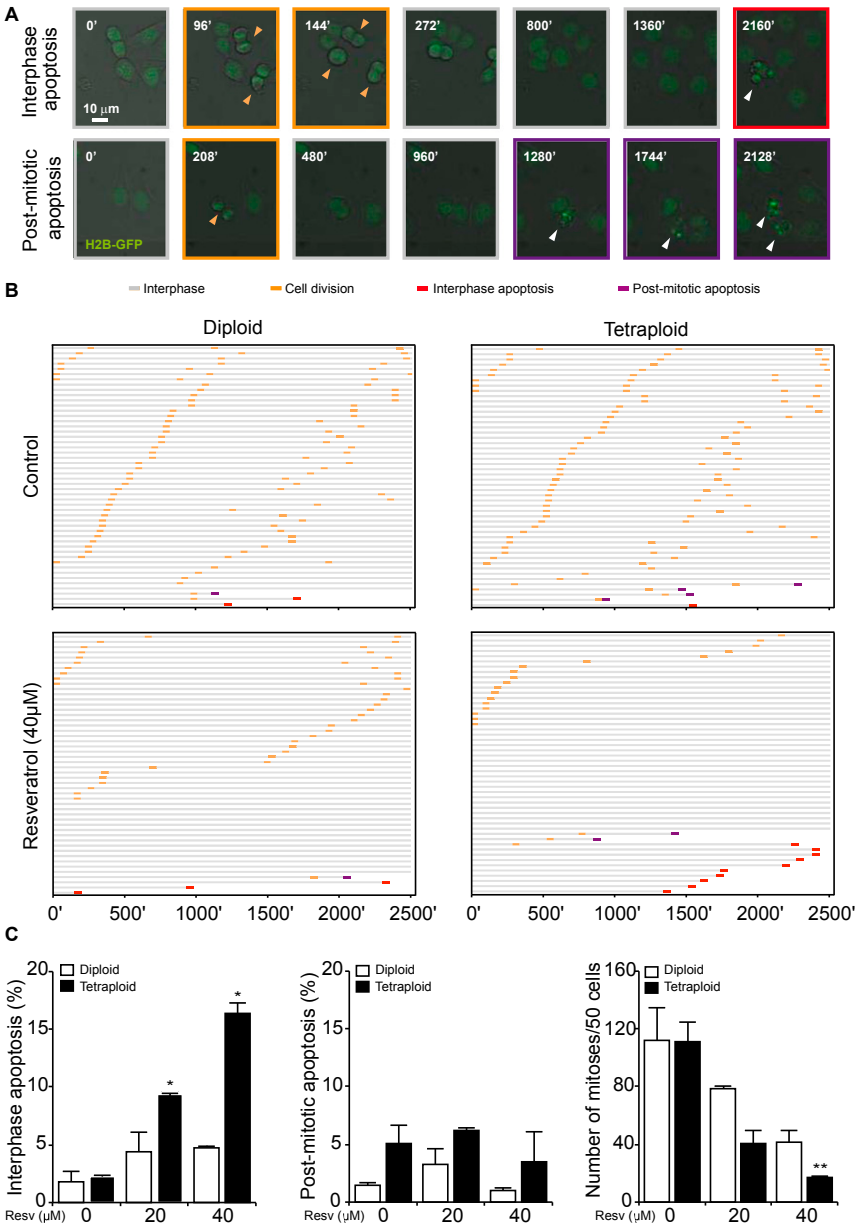


Fig. S5. Single cell fate profiling of diploid and tetraploid cells treated with resveratrol. (*A* and *B*) Diploid and tetraploid human colon carcinoma HCT116 cells stably transfected with H2B-GFP, were treated with resveratrol ($t = 0$ min) and then monitored by videomicroscopy for 41 h. In *A*, representative snapshots of cells treated with resveratrol undergoing cell division (framed in orange), interphase apoptosis (framed in red), or postmitotic apoptosis occurring shortly after mitosis (framed in purple), are shown. Interphases are framed in light gray. Arrowheads indicate relevant events. Cell fate profiles of 50 diploid and tetraploid cells untreated (control) and treated with resveratrol are depicted in *B*. Ending lines in *B* indicate deaths of the cells through the indicated mechanisms (for the code color please refer to *A*). The percentage of interphase apoptotic cells, the percentage of postmitotic apoptosis, and the number of mitoses observed over time are reported in *C* (mean ± SEM; $n = 50$ cells per data point). $^{*}P < 0.05$; $^{**}P < 0.01$ (Student t test), compared with the equally treated diploid cells.

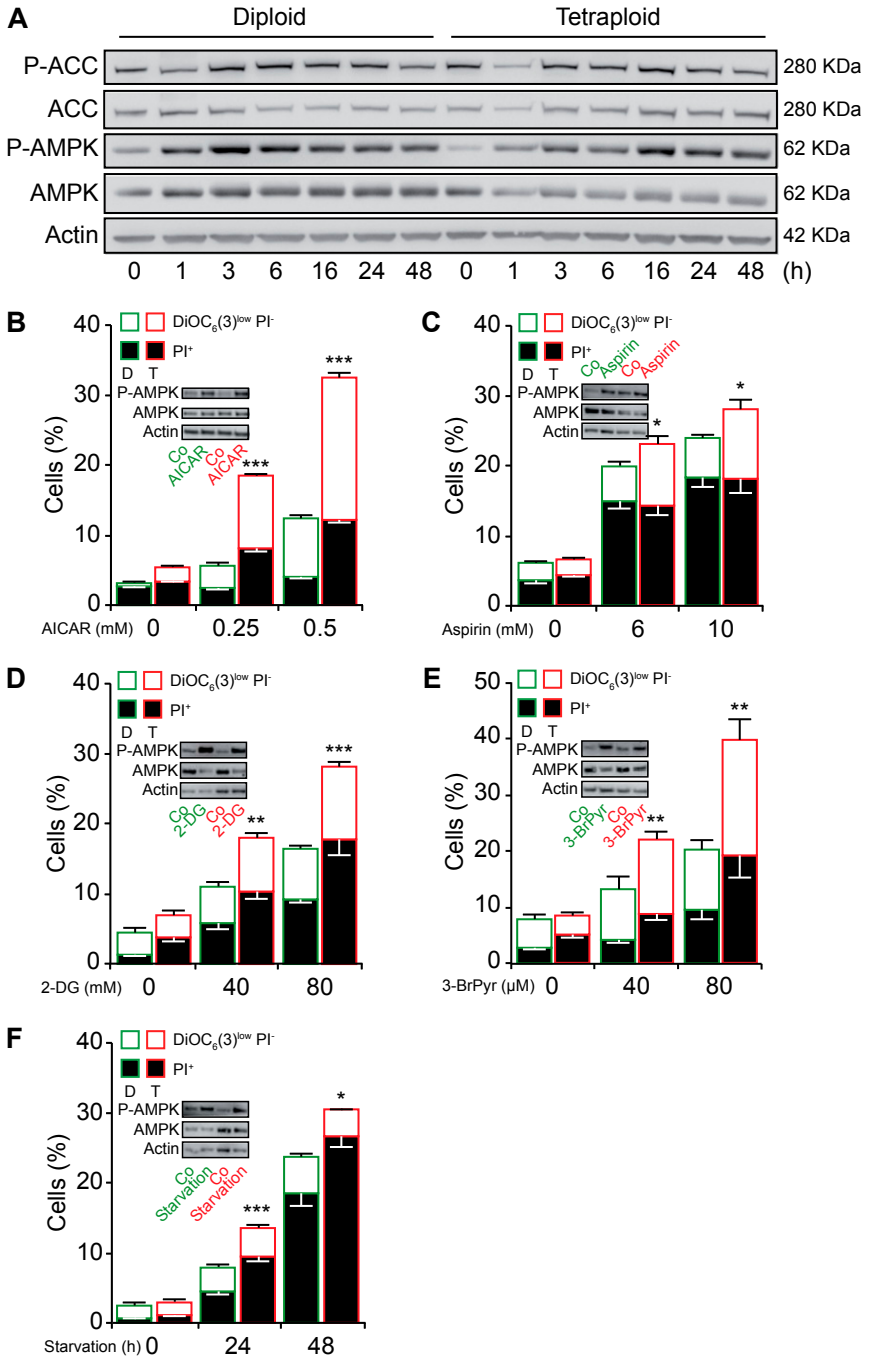


Fig. S6. Activation of AMPK preferentially promotes tetraploid cell death. (*A*) Immunoblot measurements of AMPK activation. Diploid and tetraploid clones from human colon carcinoma HCT116 cells were incubated with 40 μM resveratrol (Resv) for the indicated time, followed by Western blot analysis of the level of AMPK, AMPK phosphorylation (on Thr172), acetyl-CoA carboxylase (ACC, an AMPK substrate), and ACC phosphorylation (on Ser79) with suitable antibodies. Actin was used as a loading control. (*B–F*) Functional impact of AMPK activation. AMPK was induced by culture of the cells in standard media supplemented with the indicated concentrations of AICAR (*B*), aspirin (*C*), 2-deoxyglucose (2-DG) (*D*), or 3-bromopyruvate (3-BrPyr) (*E*) for 48 h, or by culture of the cells in nutrient-free Earl's balanced salt solution for the indicated time (*F*). The frequency of dead and dying cells was determined by staining with PI plus $DiOC_6(3)$ and cytofluorometric analysis. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ (Student *t* test), compared with the equally treated diploid cells.

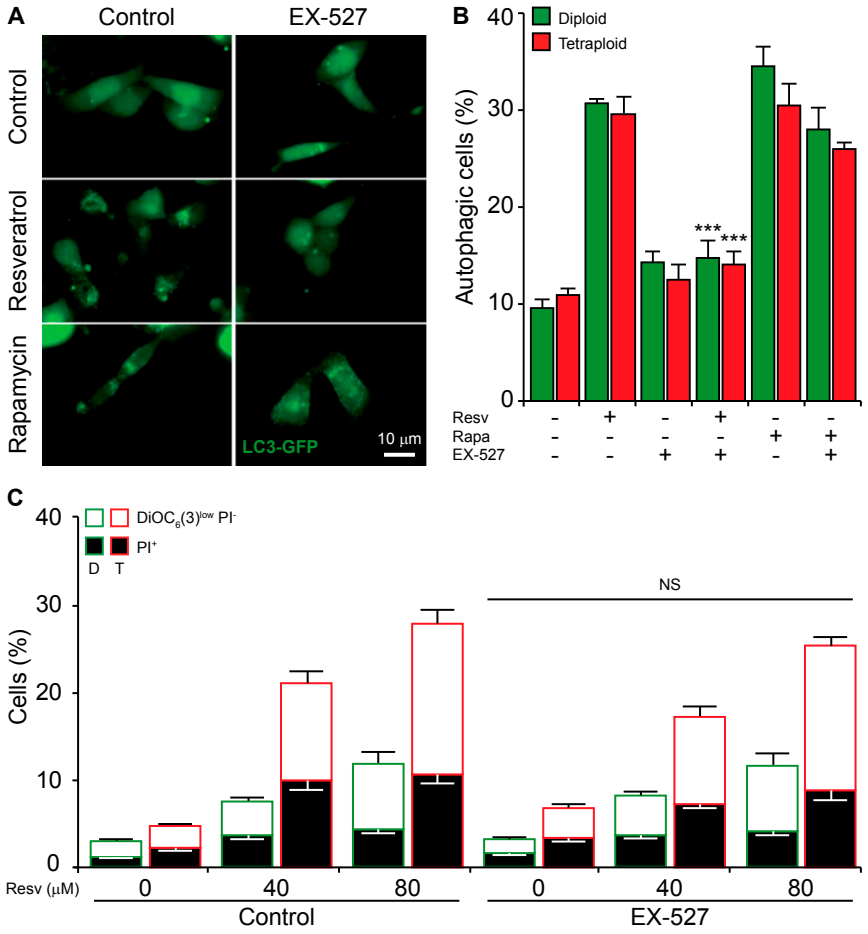


Fig. S7. Resveratrol-mediated HCT116 cell death is autophagy independent. (*A* and *B*) Diploid and tetraploid clones from human colon carcinoma HCT116 cells were transiently transfected with an GFP-LC3 construct and left untreated (control) or exposed for 6 h to 80 μM resveratrol or 1 μM rapamycin, combined or not with 10 μM EX-527, a sirtuin-1 inhibitor. Representative images (*A*) and quantification (mean ± SEM; $n = 500$ cells) of autophagic cells—defined as cells with more than 30 cytoplasmic GFP-LC3$^+$ dots (*B*)—are reported. ***$P < 0.001$ (Student *t* test), in comparison with cells treated with the same drug but not exposed to EX-527. (*C*) Diploid and tetraploid HCT116 clones were treated with the indicated concentrations of resveratrol, alone or in combination with 10 μM EX-527. Cell death was assessed after 48 h treatment by flow cytometry (mean ± SEM; two independent experiments on two diploid and two tetraploid clones). NS, not significant (Student *t* test).

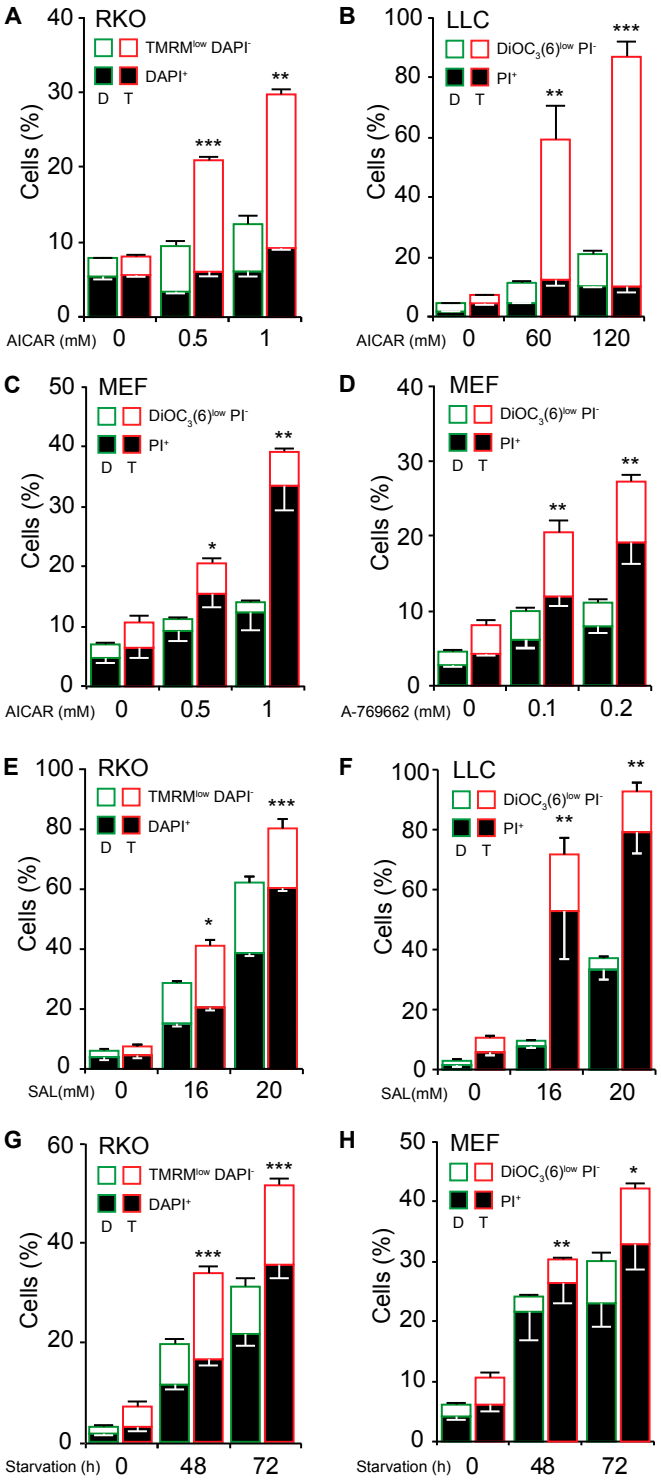


Fig. S8. AMPK activators preferentially induce tetraploid cell death in various cell lines. (*A–H*) Diploid and tetraploid clones (depicted in green and red, respectively) from human colon carcinoma RKO cells (*A*, *E*, and *G*), murine lung cancer LLC cells (*B* and *F*), and mouse embryonic fibroblasts (MEFs) (*C*, *D*, and *H*), were treated for 48 h with the indicated concentrations of AICAR (*A–C*), A769662 (*D*), or salicylate (*E* and *F*), or starved for the indicated time (*G* and *H*), before cytofluorometric analysis of cell-death–associated parameters (mean ± SEM; $n = 3$; two diploid and two tetraploid clones per cell line). $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ (Student *t* test), in comparison with the equally treated diploid cells.

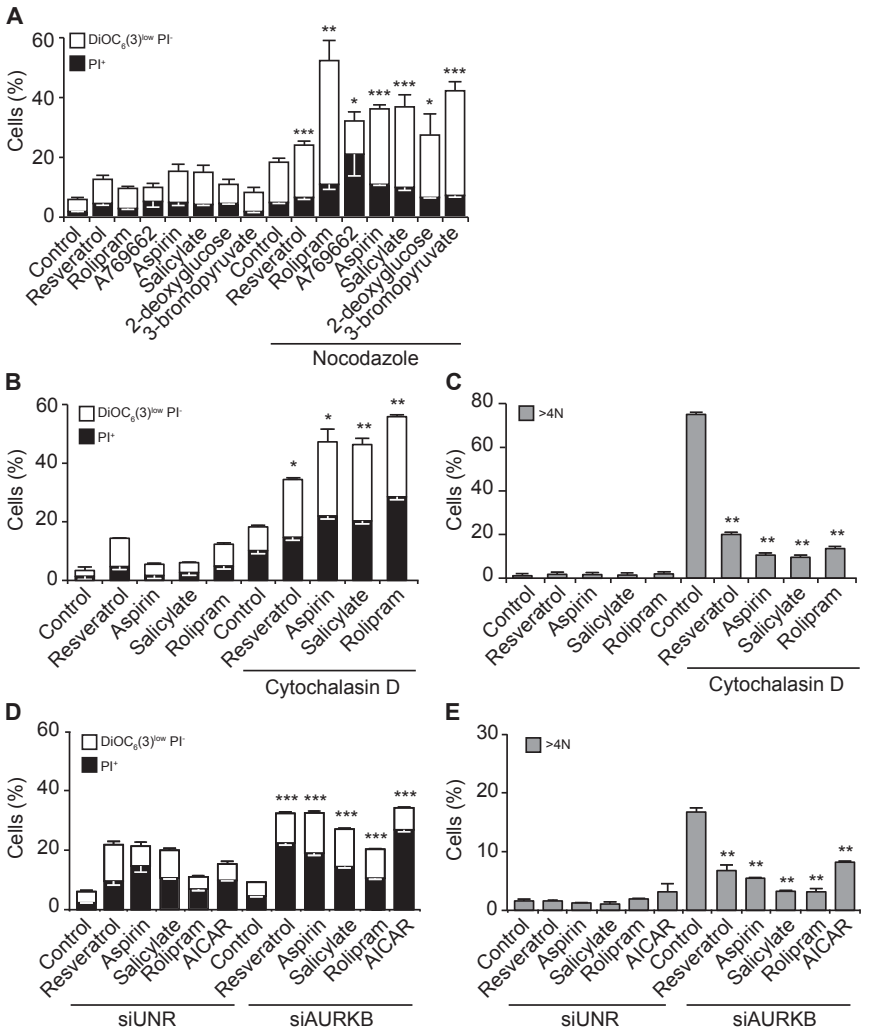


Fig. S9. Resveratrol and AMPK activators induce HCT116 cell death during polyploidization (related to Fig. 3). (*A*) Polyploidy induction by nocodazole. p53-deficient human colon carcinoma HCT116 cells incubated for 48 h with the indicated drugs in combination or not with the polyploidizing agent nocodazole 100 nM. The following concentrations were used: resveratrol (40 μM), rolipram (0.8 mM), A-769662 (0.4 mM), aspirin (10 mM), salicylate (10 mM), 2-deoxyglucose (40 mM), and 3-bromopyruvate (80 μM). At the end of the incubation, apoptotic features were assessed by cytofluorometry upon $DiOC_6(3)$/PI costaining, respectively. Note that the ploidy determinations of the same experiments are shown in Fig. 3*A*. (*B* and *C*) Polyploidy induction by cytochalasin D. Cells were cultured as in *A*, with the difference that nocodazole was replaced by cytochalasin D (1 μM). (*D* and *E*) Polyploidy induction by depletion of Aurora kinase B (AURKB). Polyploidy induction by cytochalasin D. Cells were cultured as in *A*, with the difference that cells were either transfected with an unrelated siRNA (siUNR) or with a siRNA targeting AURKB 24 h before addition of the pharmacological agents. The results are reported as mean ± SEM ($n = 3$). $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ (Student *t* test), compared with the cells treated with the same drug but not incubated with the polyploidizing agent.

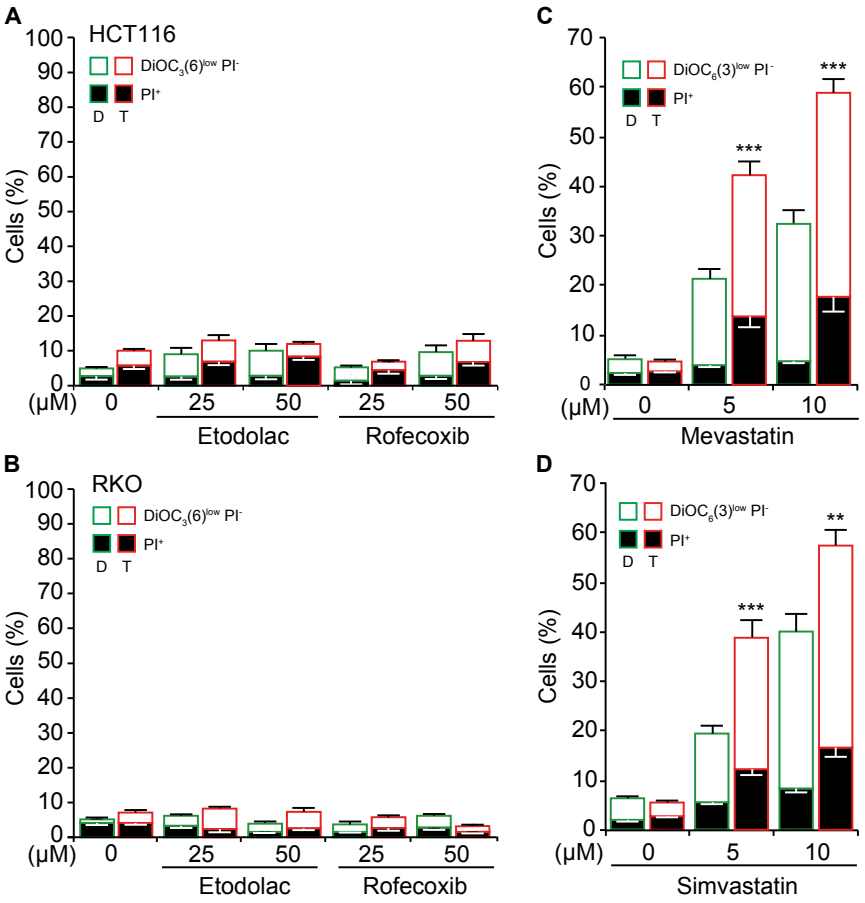
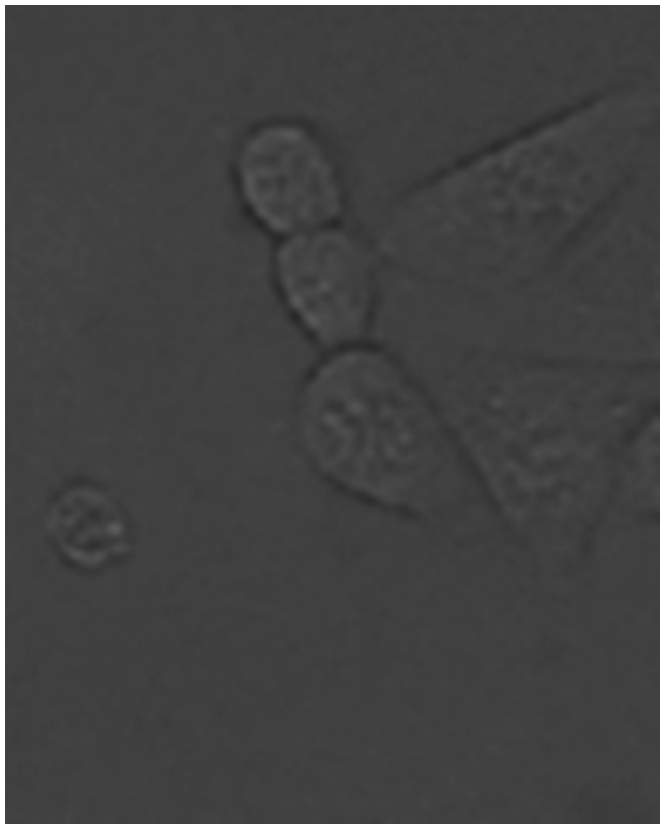


Fig. S10. Proapoptotic effects of cyclooxygenase-2 inhibitors and statins on the survival of diploid and tetraploid cells. (*A* and *B*) Effects of cyclooxygenase-2 inhibitors. Diploid and tetraploid cell clones (framed in green and red, respectively) from human colon carcinoma HCT116 (*A*) or RKO cells (*B*) were exposed for 48 h to the indicated concentrations of etodolac and rofecoxib before the evaluation of the cell-death–associated parameters by staining with the vital dye iodure propidium (PI) and the mitochondrial membrane potential ($\Delta\psi_m$)-sensing dye $DiOC_6(3)$, followed by cytofluorometric analyses. (*C* and *D*) Effects of statins. Diploid and tetraploid cell clones (framed in green and red, respectively) from human colon carcinoma HCT116 cells were treated for 48 h with the indicated concentrations of mevastatin (*C*) or simvastatin (*D*), before cytofluorometric analysis of apoptotic features (mean ± SEM; $n = 3$; three diploid and three tetraploid clones). $^{**}P < 0.01$; $^{***}P < 0.001$ (Student *t* test), in comparison with the equally treated diploid cells.

Table S1. Nuclear diameter of cells from the intestine of $Apc^{Min/+}$ mice

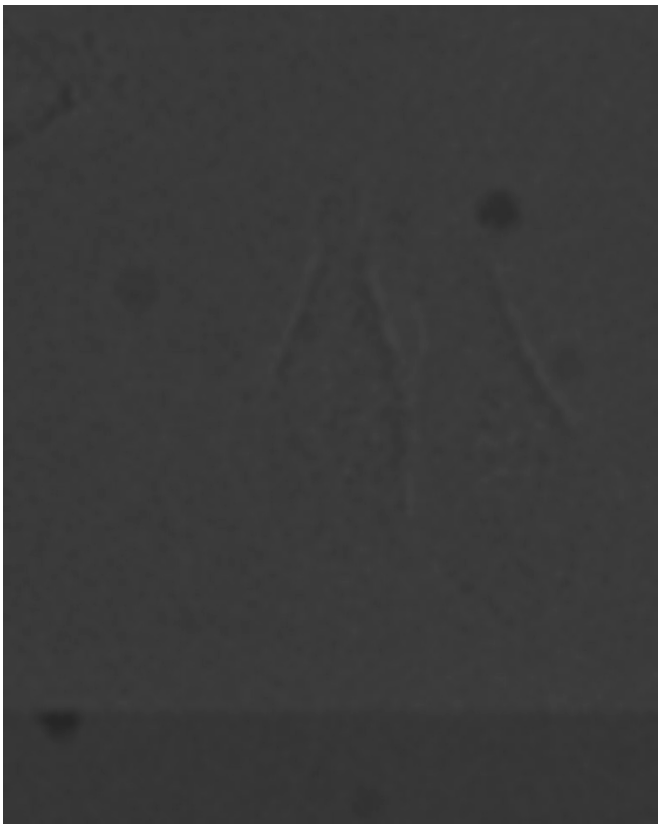
Ploidy	*n* cells	Nuclear ∅, μm (mean ± SEM)
Diploid	100	6.7 ± 0.19
Triploid	40	9.4 ± 0.04***
Tetraploid	46	10.7 ± 0.02***,#

Paraffin-embedded intestinal tissues from 10-wk-old $Apc^{Min/+}$ mice were stained for FISH detection with DAPI and analyzed for nuclear diameter upon FISH staining for the visualization of chromosomes 8 and 15 (as in Fig. 5) and counterstaining of chromatin with DAPI. The mean nuclear diameter was determined for cells bearing two, three, or four sets of both chromosomes (labeled as diploid, triploid, or tetraploid, respectively). $^{***}P < 0.001$ (Student *t* test) in comparison with diploid cells; $^{\#}P < 0.05$ compared with triploid cells.



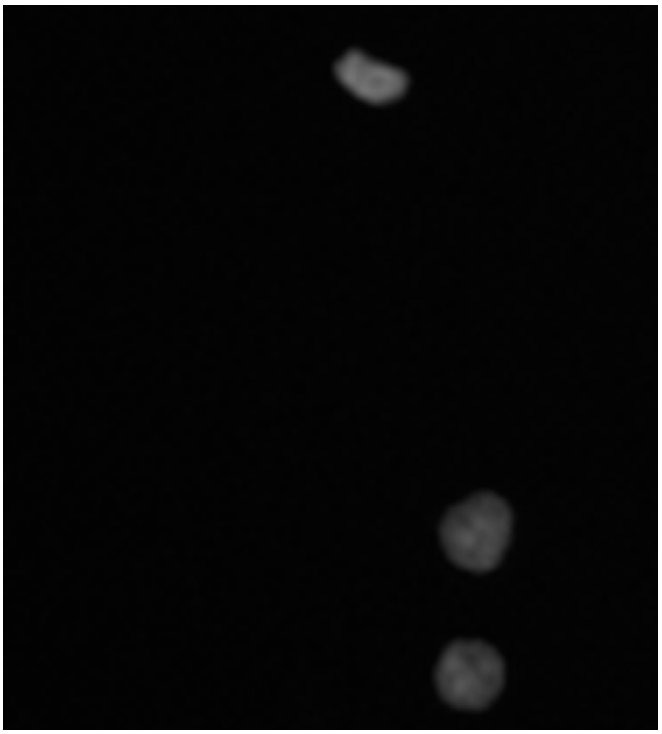
Movie S1. Interphase apoptosis of HCT116 tetraploid cells treated with resveratrol. Human colon carcinoma HCT116 tetraploid cells, stably expressing H2B-GFP, were treated with 40 μM resveratrol for 41 h.

Movie S1



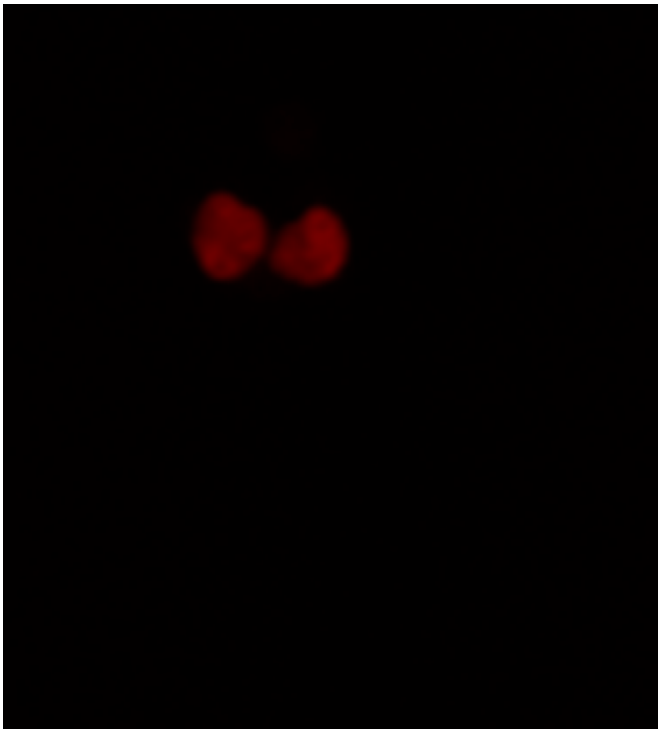
Movie S2. Postmitotic apoptosis of HCT116 tetraploid cells treated with resveratrol. Human colon carcinoma HCT116 tetraploid cells, stably expressing H2B-GFP, were treated with 40 μM resveratrol for 41 h.

Movie S2



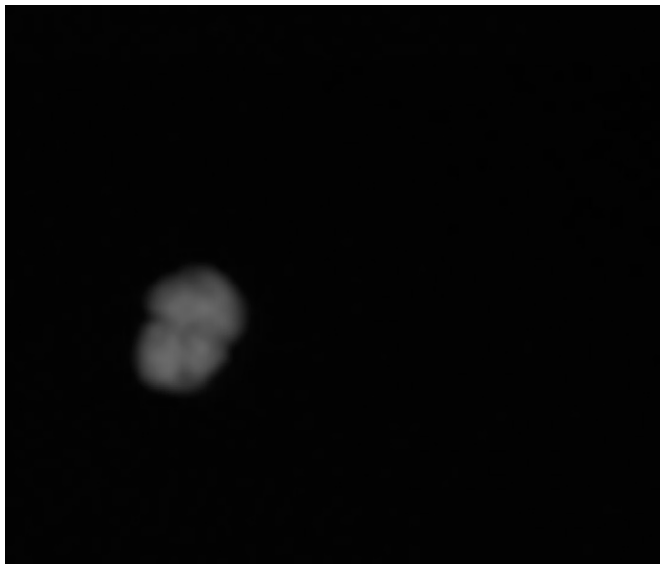
Movie S3. Polyploidization of $p53^{-/-}$ HCT116 cells treated with nocodazole. Human colon carcinoma $p53^{-/-}$ HCT116 cells, stably expressing H2B-GFP, were treated with nocodazole for 72 h.

Movie S3



Movie S4. Interphase apoptosis of $p53^{-/-}$ HCT116 cells treated with nocodazole and resveratrol. Human colon carcinoma $p53^{-/-}$ HCT116 cells, stably expressing H2B-GFP, were treated with nocodazole in combination with 40 μM resveratrol for 72 h.

Movie S4



Movie S5. Mitotic apoptosis of $p53^{-/-}$ HCT116 cells treated with nocodazole and resveratrol. Human colon carcinoma $p53^{-/-}$ HCT116 cells, stably expressing H2B-GFP, were treated with nocodazole in combination with 40 μM resveratrol for 72 h.

Movie S5