Table S1 Cell lines of primary skin fibroblasts used in this study

Experiment	**Cells lines**	**Figure**
H_2O_2-hypoxia viability	*Spalax* 2013-A; Rat 2013 -A	Fig. 1
H_2O_2-hypoxia viability	*Spalax* 2013-B; Rat 2015	Fig. S3
H_2O_2-hypoxia viability (diff. settings)	*Spalax* 2013-A ; Rat 2013-A	Fig. S4
H_2O_2-hypoxia viability (diff. settings)	*Spalax* 2013-A ; Rat 2013-A	Fig. S4
Comet assay +pilot for sub lethal dose	*Spalax* 2013-A ; Rat 2013-B	Fig. 1, Fig S5
H_2O_2 staining	*Spalax* 2013-A ; Rat 2013-B	Fig. 1
Etoposide staining	*Spalax* 2013-A ; Rat 2013-B	Fig. S11
Etoposide viability	*Spalax* 2015 ; Rat 2013-B	Fig. 2
Etoposide viability	*Spalax* 2017; Rat 2015	Fig. 2
Etoposide viability	*Spalax* 2017; Rat 2013-B	Fig. 2
UV viability	*Spalax* 2017; Rat 2015	Fig. 2
UV viability	*Spalax* 2013-A; Rat 2013-B	Fig. 2
UV viability	*Spalax* 2017; Rat 2013-B	Fig. 2
Cell cycle	*Spalax* 2013-B ; Rat 2015	Fig. 1
Cell cycle	*Spalax* 2013-B; Rat 2015	Fig. 1
Cell cycle	*Spalax* 2015 ; Rat 2013-B	Fig. 1
HCR	*Spalax* 2013-A ; Rat 2013-B	Fig. 3
HCR	*Spalax* 2017-A; Rat 2015	Fig. 3
HCR	Spalax 2015; Rat 2013-A	Fig. 3
HCR	Spalax 2017-B; Rat 2017	Fig. 3

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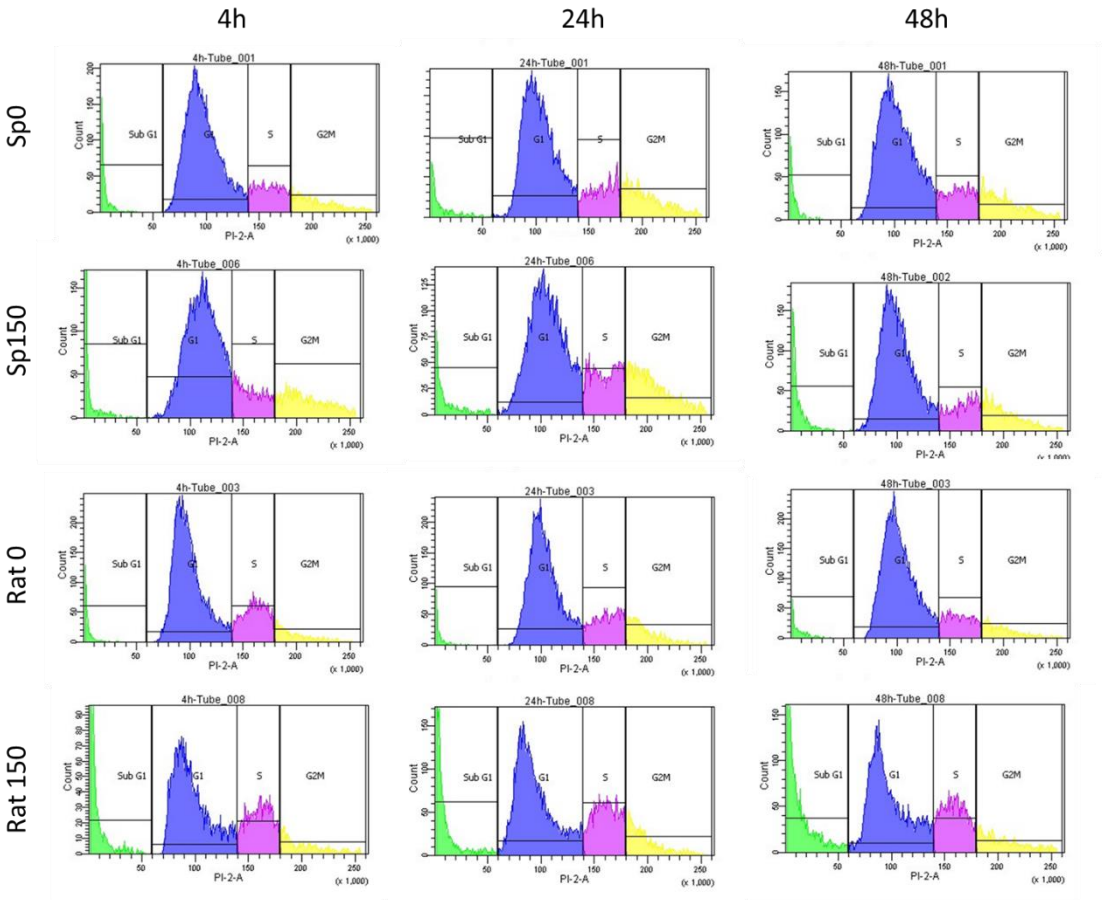

Fig. S1. **Cell Cycle distribution is presented by cell count of PI- stained nuclei.** *Spalax*/ rat cells were treated with 150 μM H_2O_2 and then subjected to cell cycle

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distributions assay 4, 24, and 48 hours following treatment. This figure describes one representative experiments out of three (see Fig. 1).

Table S2. C**ell count of cell cycle phases, quantified by flow cytometry of PI- stained nuclei.**

4h	**subg1**	**g1**	**s**
rat0	4.85	62.85	23.95
rat150	22.6	46.3	17.5
sp0	5.25	68.6	12.05
sp150	6.5	68.45	12.45
24h	**subg1**	**g1**	**s**
rat0	3.1	64.75	18.5
rat150	15.9	50.25	22.5
sp0	4.8	59.55	17.95
sp150	6.5	57.6	18.1
48h	**subg1**	**g1**	**s**
rat0	3.25	71.35	14.35
rat150	21.95	47.85	19.85
sp0	5.75	67.75	14.1
sp150	8.5	63.75	15.65

Spalax/ rat cells were treated with 150 µM H_2O_2 and then subjected to cell cycle distributions assay 4, 24, and 48 hours following treatment. The values represent the

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average of two duplicates in a single experiment, measuring the fraction of cells in each cell cycle phase.

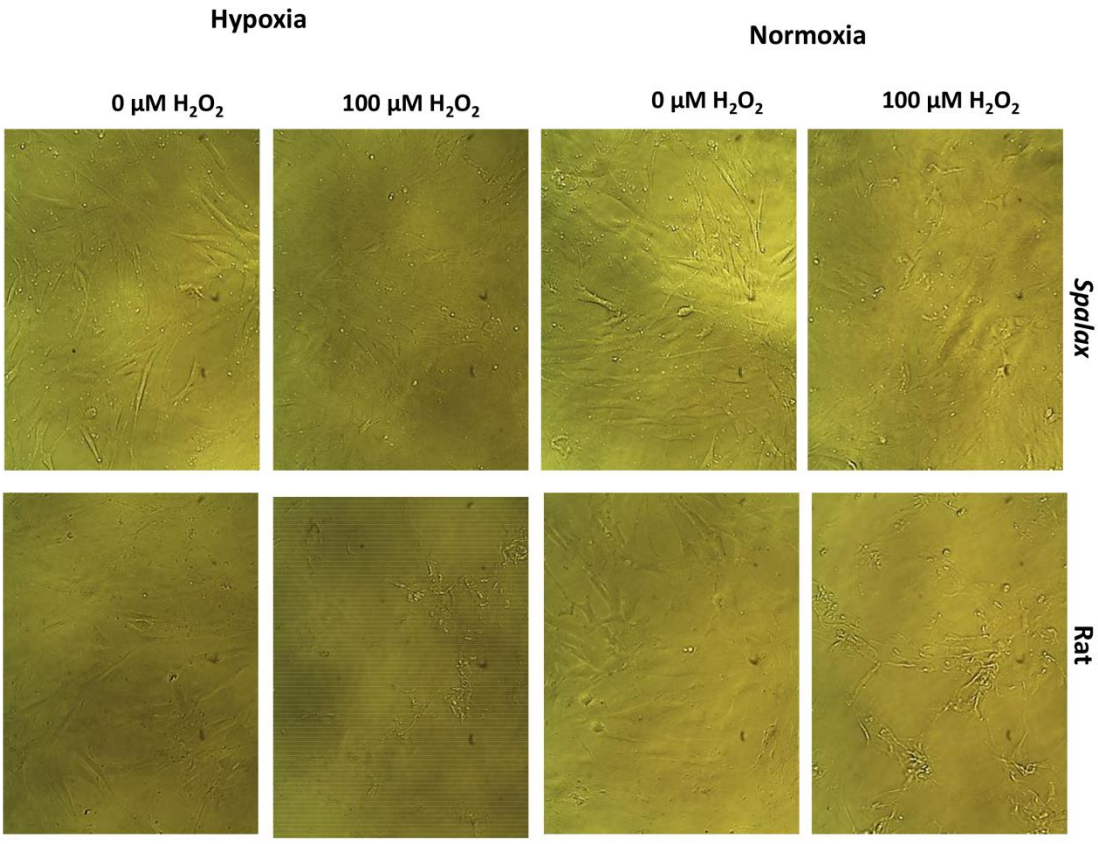

Fig. S2.*Spalax*/rat skin fibroblasts morphology following treatment with 100 µM H_2O_2 (with or without hypoxia pre-treatment). Images were taken 27 hours post hypoxia.

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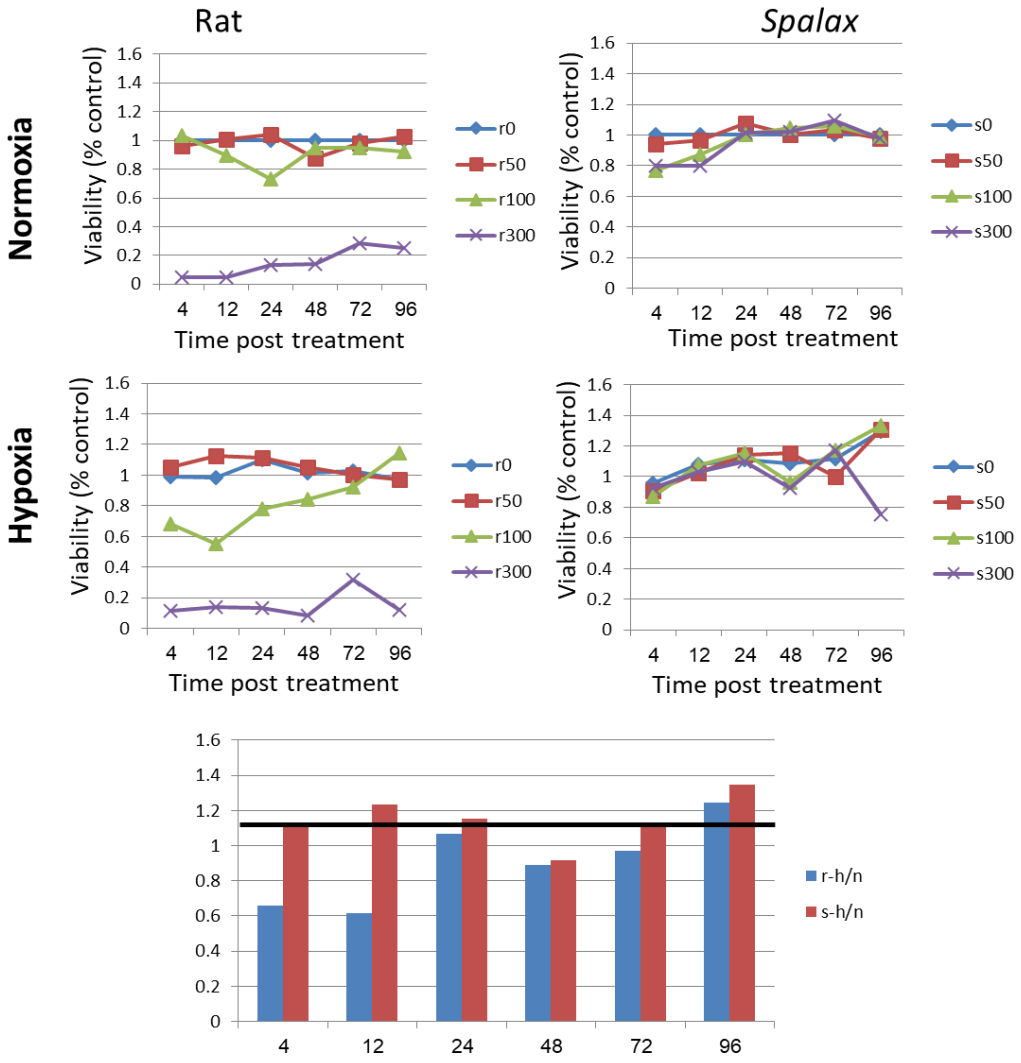

Fig. S3. **Viability of cells following peroxide treatment**: Biological repeat of the experiment presented in Fig. 1. Rat ("r) and *Spalax* ("s") skin fibroblasts' cell lines were isolated from different rat and *Spalax* individuals (see Table S1). Cells were then either incubated in hypoxic or in normoxic conditions and treated with different concentrations of peroxide. Viability rates were measured in different incubation periods post treatments.

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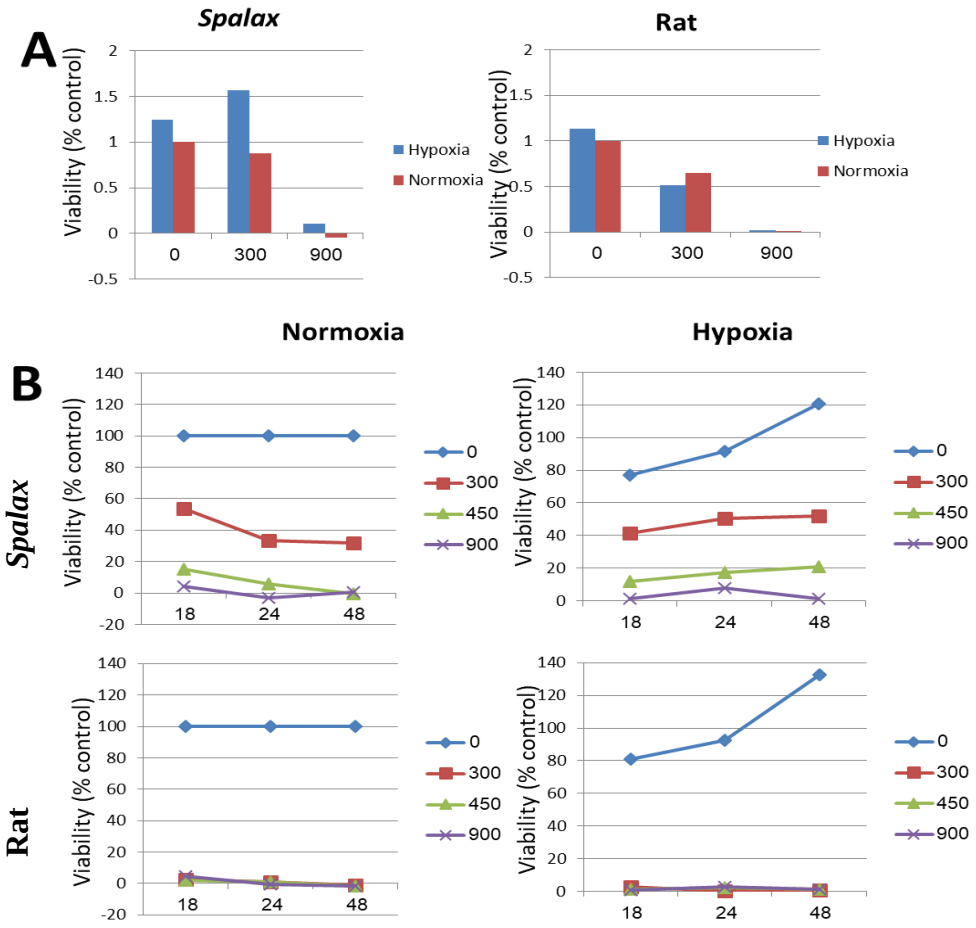

Fig. S4. Viability rates of *Spalax* and rat skin fibroblasts are presented as percentages from normoxic control. Cells were either incubated under hypoxic or normoxic conditions and then treated with H_2O_2 (see Table S3 for specific experimental settings).

Table S3. Experimental settings for testing resistance to oxidative stress in combination with hypoxia in *Spalax* and rat skin fibroblasts

Modified settings	**Fig. 2**	**Fig. S4**
H_2O_2 incubation conditions	30 minutes, on ice	1 hour, room temperature
H_2O_2 doses	300 µM H_2O_2 and below	300 µM H_2O_2 and above
Hypoxia duration	10 hours	4 hours
O_2 percent	0.5%	1%
Time point	4-96 hours post H_2O_2 treatment	**Fig. S4A** - 3 hours post H_2O_2 treatment **Fig S4B**- 18-48 hours post H_2O_2 treatment

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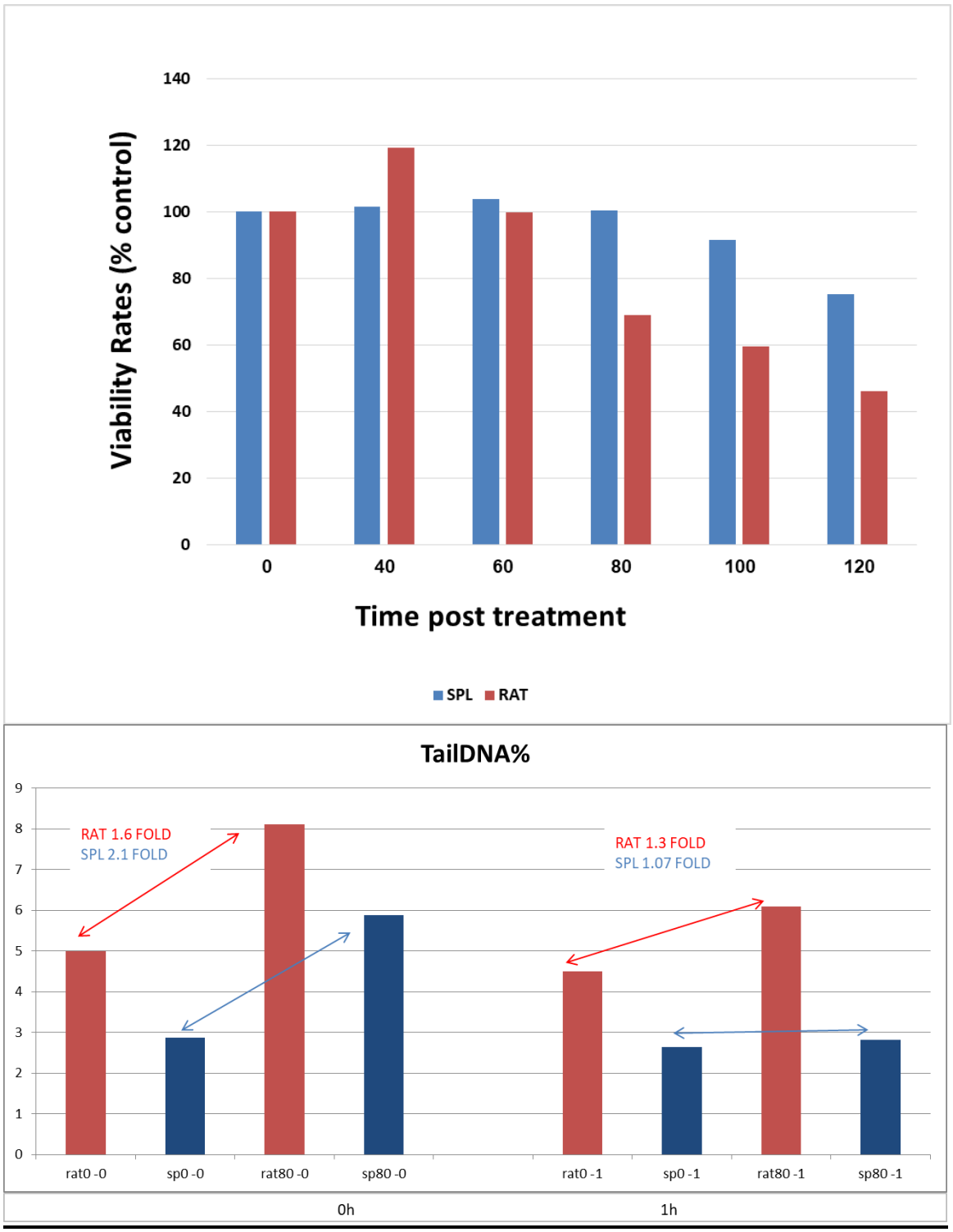

Fig. S5. Upper panel- Viability assay used as a pilot experiment to determine the sub-lethal peroxide dose in *Spalax* and rat skin fibroblast to be thereafter used for the comet assay. **Lower panel-** Additional Comet assay experiment. Cells where treated with 80µM H_2O_2 for 20 minutes on ice and then recovered for 0/1 hours. Cells where thereafter subjected to the comet assay. Median values of % DNA in the tail are presented.

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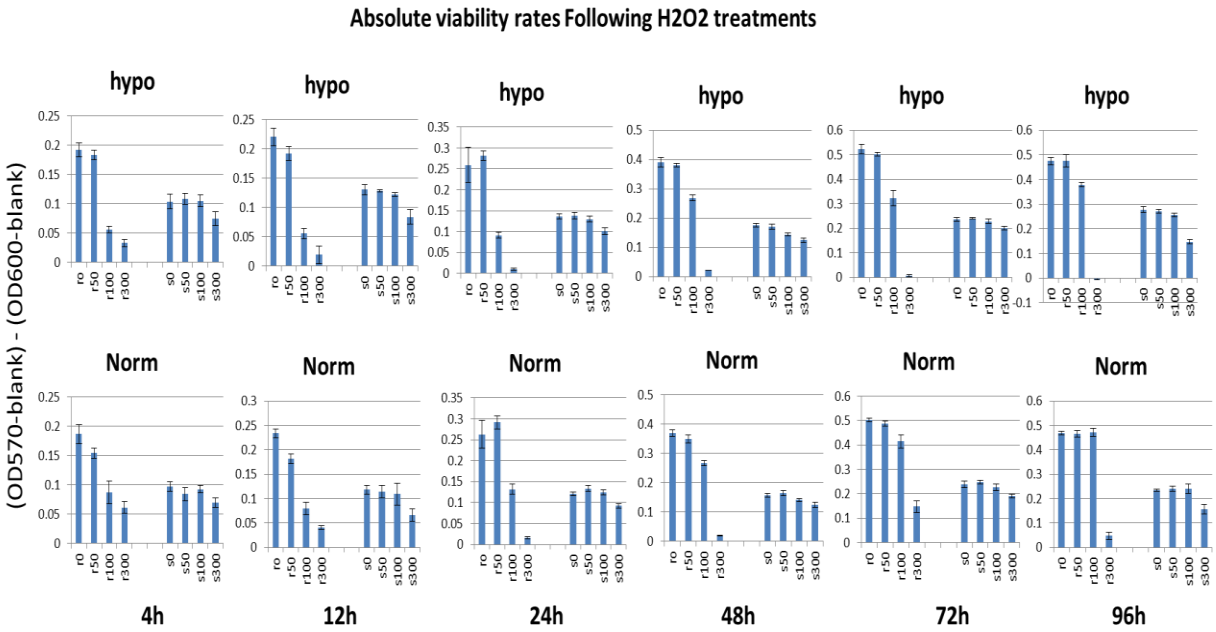

Fig. S6 Absolute viability rates of *Spalax* ("s") vs. rat ("r") cells treated with peroxide following hypoxia/normoxia. Cells where either treated with hypoxia or incubated in ambient air. Then cells where treated with different doses of peroxide (50, 100, 300 µM). PrestoBlue© reagent was used to asses cells' viability 4-96 hours post

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treatments. This figure describes one representative experiments out of two (see Fig. 1). Error bars denotes SD of technical replicates.

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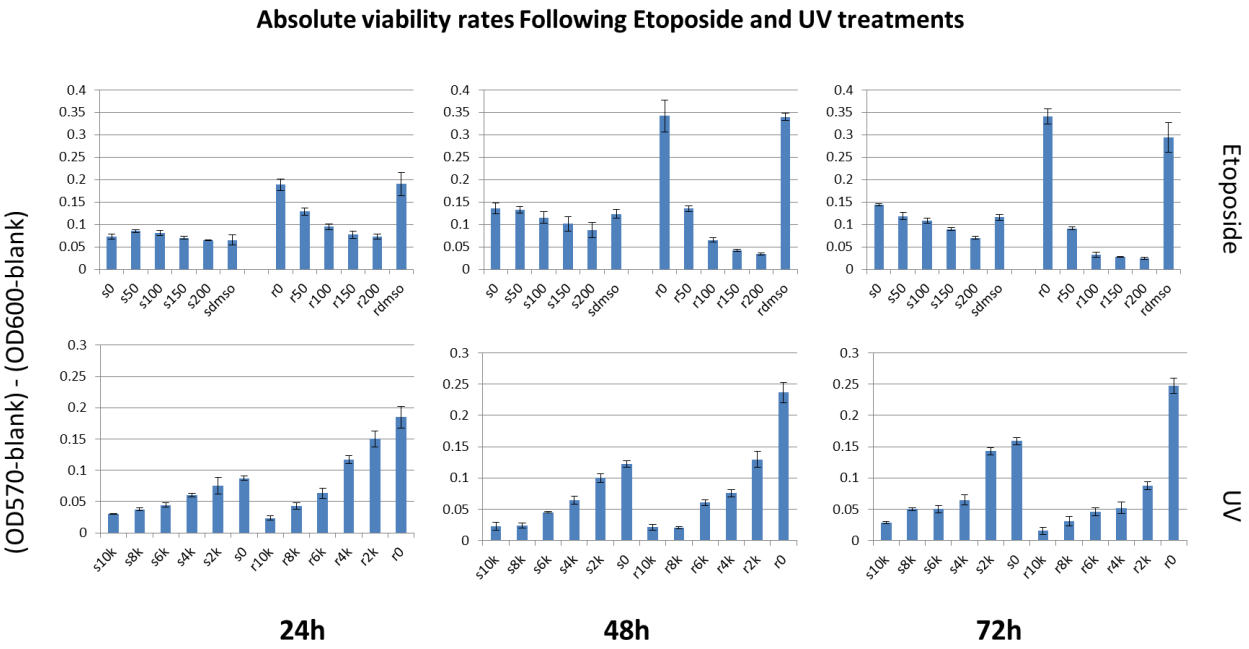

Fig. S7. Absolute viability rates of *Spalax* ("s") vs. rat ("r") cells treated with etoposide and UVC. Cells where treated with etoposide and UVC in different doses. PrestoBlue© reagent was used to asses cells' viability 24-72 hours post treatments. This

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figure describes one representative experiments out of three (see Fig. 3). Error bars denotes SD of technical replicates.

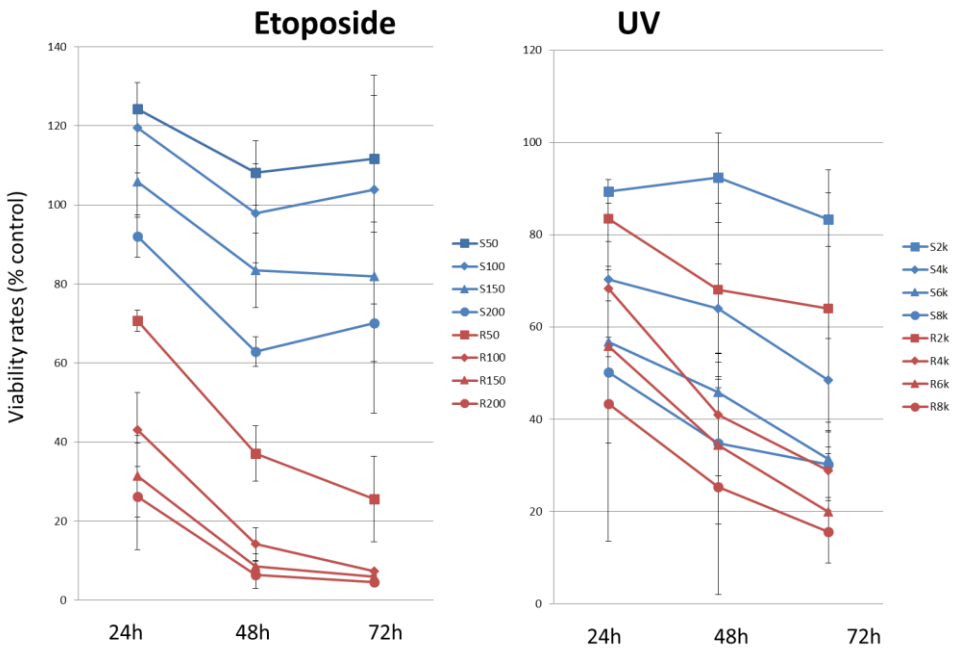

Fig. S8. Viability rates (%control) following UV and etoposide treatments in *Spalax* ("S") and rat ("R") cells, which are presented in several panels in Fig. 2, are presented here in the same graph.

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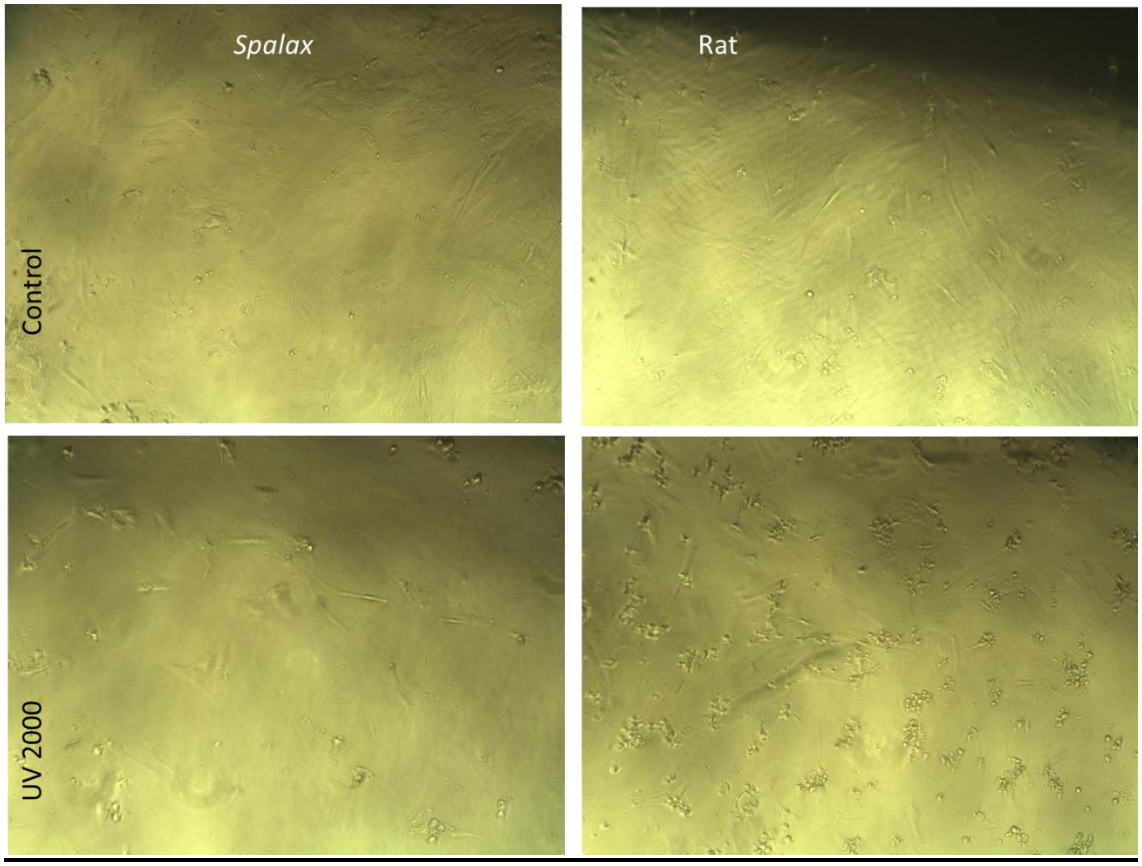

Fig. S9 Morphology of rat and *Spalax* skin fibroblasts that were treated with 2000 J/m^2 UVC. Images were taken 54 hours post treatment

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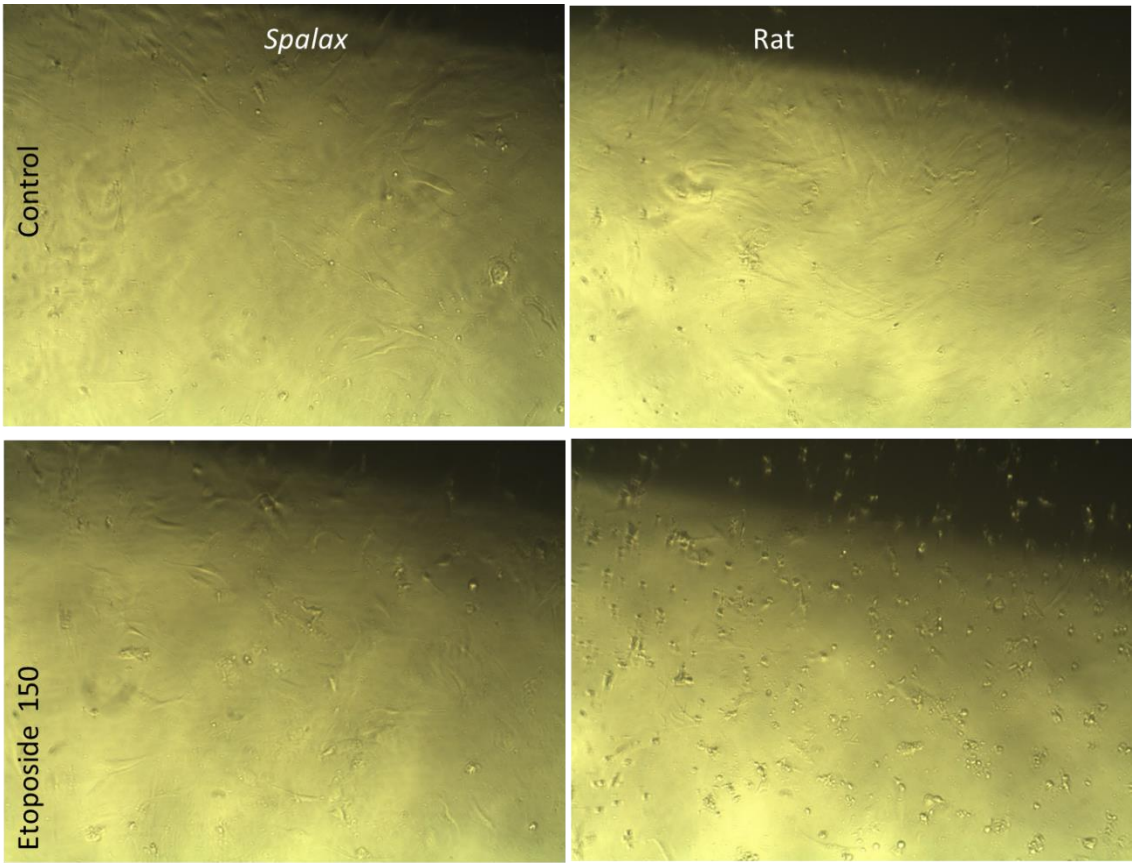

Fig. S10 Morphology of rat and *Spalax* skin fibroblasts that were treated with 150 µM etoposide. Images were taken 30 hours post treatment

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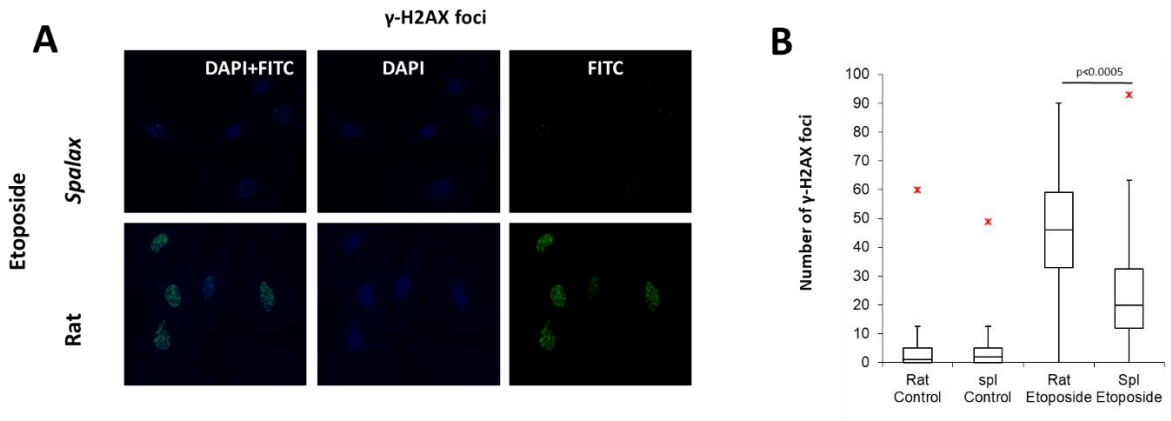

Fig. S11. Immunofluorescent staining of γ-H2AX foci in rat and *Spalax* skin fibroblasts following etoposide treatment of 50 µM, for 24 hours. Cells were fixated 60 minutes after treatment. **A.** Representative images of rat and *Spalax* skin fibroblasts' nuclei γ-H2AX foci and DAPI stating are presented. **B.** The number of γ-H2AX foci, quantified by FociCounter software, represents the number of DSBs formed 60 minutes following 50µM etoposide treatment. At least 55 nuclei were analyzed for γ-H2AX foci is each sample.

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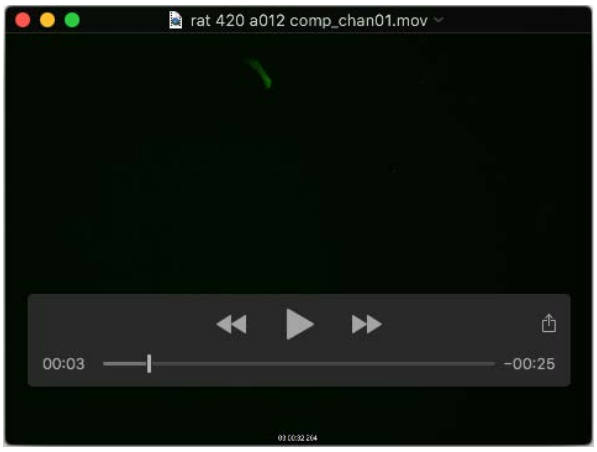
Movie 1

Spalax skin fibroblasts 24-48 hours following transfection with GFP plasmid that was treated with 420 J/m^2 UVC radiation. The overlay between FICT and DIC channels is presented in Fig. 3 for 24, 36, and 48 hours post transfection.



Movie 2

Rat skin fibroblasts 24-48 hours following transfection with GFP plasmid that was treated with 420 J/m2 UVC radiation. The overlay between FICT and DIC channels is presented in Fig. 3 for 24, 36, and 48 hours post transfection.

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