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☐ Initial submission ☐ Revised version ☒ Final submission

Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

Experimental design

1. Sample size

Describe how sample size was determined.

STATISTICA software, ver. 12 (StatSoft Inc., USA) was used to estimate the sample size. For the power of 80%, the level of significance set at 5%, 4 groups and RMSSE = 0.8, 7 mice in each group was estimated. For usage of non-parametrical statistical methods, the number of 8 (and 10) mice in each group was finally planned.

2. Data exclusions

Describe any data exclusions.

No data were excluded.

3. Replication

Describe whether the experimental findings were reliably reproduced.

All experiments were reproduced to reliably support conclusions stated in the manuscript.

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

Animals were randomly divided into experimental groups.

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

Administration of compounds was carried out as a blinded experiment (all information about the expected outputs and the nature of used compounds were kept from the animal-technicians).

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒	A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	A statement indicating how many times each experiment was replicated
☒	☐	The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
☒	☐	A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒	The test results (e.g. *P* values) given as exact values whenever possible and with confidence intervals noted
☐	☒	A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒	Clearly defined error bars

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.	The data were anlyzed using Microsoft Excel 2016, STATISTICA 12, Graphpad Prism 4, PeakView 1.2, Image Lab 4.1, Carl Zeiss Zen 2011 SP6 (black), Nano Analyze Software 2.3.6, Olympus ScanR Analysis 1.3.0.3.

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.	All materials used is fully available from commercial sources with the exception of LAPC4 cell line, that we obtained from Zoran Culig, University of Innsbruck.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	anti-ubiquitin (Cell Signaling, cat.n.:3933; lot 4), anti-H2A, acidic patch (Merck Millipore, cat. n.: 07-146; lot 2880748), anti-monoubiquityl-H2A (Merck Millipore, clone E6C5; lot 2239798), anti-IκBα (Santa Cruz Biotechnology, cat. n.: sc-371), anti-phospho(Ser32/36)-IκBα (Cell Signaling, clone 5A5), anti-p53 (1:500; Santa Cruz Biotechnology, clone DO-1; D0915), anti-HIF1α (BD Biosciences, cat. n.: 610958; lot 47858), anti-Cdc25A (Santa Cruz Biotechnology, clone DCS-120; our own clone comercially available by Santa Cruz), anti-NRF1 (Cell Signaling, clone D5B10; lot 1), anti-VCP (Abcam, cat. n.: ab11433; lot GR298429-3), anti-VCP (Novus Bio, cat. n.: NBP100-1557; lot A1), anti-NPLOC4 (Novus Bio, cat. n.: NBP1-82166; lot A96635), anti-ubiquitin lys48-specific (Merck Millipore, clone Apu2; lot 2724416), anti-β-actin (Santa Cruz Biotechnology, cat. n.: sc-1616; lot B2206),anti-β-actin (Santa Cruz Biotechnology,C4, cat. n.: sc-47778; lot C0916), anti-GAPDH (GeneTex, clone 1D4; lot 821603479), anti-Lamin B (Santa Cruz Biotechnology, M20, cat. n.: sc-6217; lot J2313), anti-calnexin (Santa Cruz Biotechnology, H70, cat. n.: sc-11397; lot C1214), anti-α-Tubulin (Santa Cruz Biotechnology,B7, cat. n.: sc-5286; lot C1313), anti-Xbp1 (Santa Cruz Biotechnology, M-186, cat. n.: sc-7160; lot A2314), CHOP (Cell Signaling, L63F7, cat. n.: 2895; lot 10), Ufd1 (Abcam, cat. n.: ab155003; lot GR119674-2), cleaved PARP1 (Cell Signaling, cat. n.: 9544; lot 4), p-eIF2a (Cell Signaling, cat. n.: 3597; lot 9), ATF4 (Merck Millipore, cat. n.: ABE387 lot 2736396), HSP90 (Enzo, cat. n.: ADI-SPA-810; lot 05051501), TDP-43 (Proteintech, cat. n.: 10782-2-AP; lot number not provided by manufacturer), HSP70 (Enzo, cat. n.: ADI-SPA-830; lot 05021648), HSF1(Cell Signaling, cat. n.: 4356; lot 2, pHSP27 (Abcam, cat. n.: 155987; lot GR117377), HSP27 (Abcam, cat. n.: 109376; lot GR61497-8). FK2 antibody (Enzo, cat. n.: BML-PW8810), Sumo2/3 (Abcam, cat. n.: ab3742; lot GR8249-1), Cytochrome c Alexa Fluor 555 conjugated (BD Pharmingen, cat. n.: 558700). Secondary antibodies: goat-anti mouse IgG-HRP (GE Healthcare), goat-anti rabbit (GE Healthcare), donkey-anti goat IgG-HRP (Santa Cruz Biotechnology, sc-2020), Alexa Fluor 488 and Alexa Fluor 568 (Invitrogen, 1:1000). Antibodies critical for novel conclusions were validated by elimination of signals upon KD experiments and/or by functional assays. All antibodies were used in the system under study (assay and species) according to the profile of manufacturer.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.

HCT116 (ATCC), DU145 (ECACC), PC3 (ECACC), T47D (NCI60), HS578T (NCI60), MCF7 (ECACC), MDA-MB-231 (ATCC), U-2-OS (ECACC), HeLa (ATCC), NIH-3T3 (ATCC), CAPAN-1 (ATCC), A253 (ATCC), FaDu (ATCC), , h-TERT-RPE1 (ATCC), NCI-H358 (ATCC), NCI-H52 (ATCC), HCT-15 (ATCC), AMO-1 (ATCC), MM-1S (ATCC), ARH77 (ATCC), RPMI8226 (ATCC), OVCAR-3 (NCI60), CCRF-CEM (ATCC), K562 (ATCC), 786-0 (NCI60), U87-MG (ATCC), SiHA (ATCC), A549 (ATCC), HT29 (ATCC), LAPC4 (kindly provided by prof. Zoran Culig, University of Innsbruck). RWPE-1 (ATCC)

b. Describe the method of cell line authentication used.

All cell lines authenticated by STR method.

c. Report whether the cell lines were tested for mycoplasma contamination.

All cell lines were tested for mycoplasma contamination.

d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.

None of the used cell lines is listed in ICLAC database.

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.

In this study were used athymic nu/nu female mice (AnLab Ltd.) median age 13 weeks (+/- 1 week) and SCID female mice (ENVIGO, NL) median age 10 weeks (+/- 2 weeks).

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

Human participants were 4 males (age of 34, 38, 41, 60 years) and 5 females (age of 37, 56, 46, 59, 63 years). All freshly diagnosed for alcohol use disorder and dedicated for Antabuse therapy. Blood samples were collected before and after first application of Antabuse.

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Flow Cytometry Reporting Summary

Form fields will expand as needed. Please do not leave fields blank.

Data presentation

For all flow cytometry data, confirm that:

☒ 1. The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ 2. The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ 3. All plots are contour plots with outliers or pseudocolor plots.

☒ 4. A numerical value for number of cells or percentage (with statistics) is provided.

Methodological details

5. Describe the sample preparation.	Cell cultures were treated as indicated and harvested by trypsinization. Initial culture medium and wash buffer were collected to include detached cells. Cells were centrifuged (250g, 5min) and resuspended in staining buffer (140 mM NaCl, 4 mM KCl, 0.75 mM MgCl2, 10 mM HEPES). Then cell number was determined and after centrifugation, cells were resuspended in appropriate amount of staining buffer to get concentration of 1million cells per 900 microliters. For annexinV analysis, 1x10 5 cells was incubated in 100 microliters of staining buffer containing 2.5 mM CaCl2, Annexin V-APC (1:20, BD Biosciences) and 2.5 µg/ml 7-AAD (BD Biosciences) for 15 minutes on ice in the dark. For caspases 3/7 activity assay 1x10 5 cells was incubated in 100 microliters of staining buffer supplemented with 2% FBS, 0.5 µM CellEvent™ Caspase-3/7 Green Detection Reagent (ThermoFisher Scientific) for 45 minutes at room temperature in the dark. Subsequently, 0.5 µg/mL DAPI was added before analysis by flow cytometry. Samples were analyzed by flow cytometry using BD FACSVerse (BD Biosciences), at least 10.000 events were acquired per sample . Collected data were processed by BD FACSSuite (BD Biosciences).
6. Identify the instrument used for data collection.	BD FACSVerse (BD Biosciences) equipped with 405nm,488nm and 640nm lasers, manufactured in october 2012.
7. Describe the software used to collect and analyze the flow cytometry data.	BD FACSSuite (BD Biosciences)
8. Describe the abundance of the relevant cell populations within post-sort fractions.	cell sorting not employed
9. Describe the gating strategy used.	Using the FSC/SSC gating, debris was removed by gating on the main cell population. Positivity threshold for each cell line was defined on the basis of mock-treated (DMSO) sample. Identical positivity threshold was applied to all samples within cell line.

Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information. ☒