SUPPLEMENTARY METHODS

Cell lines

Primary mixed glial cells were obtained from the cerebral cortex of 1 to 3 day old Sprague Dawley rat pups (Charles River) as described before (1). Cells cultured for 10-14 days in DMEM/F12 medium with 10% fetal bovine serum (FBS) were used in assays. C6, A10-85, and 9L rat glioma cell lines, kindly provided by Dr. Chen (University of Southern California) and R^+ and R^- cells, kindly provided by Dr. Baserga (Thomas Jefferson University), were maintained in DMEM/F12 with 10% FBS at 37^{o}C under 5% CO_2. R^+ and R^- cells are mouse embryonic fibroblast (MEF) that overexpress human IGF-IR or have IGF-IR deletion, respectively, and were generated as previously described (2). R^- cells are 3T3-like cells originating from mouse embryos with a targeted disruption of the *igf1r* genes (2). The R^+ cell line was derived from R- cells, and express the human *igf1r* cDNA under the control of the cytomegalovirus (CMV) promoter (2). Primary neurons from embryonic day 18 Sprague-Dawley rat cerebral cortices were dissociated in neurobasal medium (Invitrogen) supplemented with 0.5 mM L-glutamine, 25 µM L-glutamic acid and 2% B-27 and plated at 640 cells/mm^2 in 96-well plates which were pre-coated with 10 µg/ml poly-D-lysine dissolved in Borax buffer (0.15 M, pH 8.4). Neurons were maintained at 37°C in 5% CO_2 in neurobasal medium supplemented with B-27 and 0.5 mM L-glutamine for 4 days. PC12 rat pheochromocytoma cell line (ATCC) was maintained in F12K medium supplemented with 15% horse serum and 2.5% fetal bovine serum at 37^{o}C under 5% CO_2.

in vitro IGF-I modulation

All cells were grown to confluence prior to treatments. The inhibition of IGF-IR activation was achieved with monoclonal anti-IGF-IR antibody (αIR3, 1μg/ml; Calbiochem) in DMEM/F12 1% FBS for 24 hours. Serum restriction was performed by incubating cells in DMEM/F12 with either 10% or 1% FBS for 24 hours. IGF-I treatment was carried out by incubating cells for 48 hours in DMEM/F12 with 1% FBS and rhIGF-I (100ng/ml, ProSpec-Tany TechnoGene, Rehovot, Israel), which is shown to be within the IGF-I level range for middle age humans (3).

in vitro drug treatments

Primary glia and C6, A10-85, and 9L rat glioma cells were seeded at $2x10^4$ cells/well and incubated for 48 hours in 96 well plates prior to treatments to reach confluence and minimize differences in proliferation. Various IGF-I modulating pretreatments were followed by cyclophosphamide (CP, Sigma) treatments. Glial cells have been reported to express cytochrome P450 and thus are capable of metabolizing the prodrug CP (4, 5). CP was prepared in DMEM/F12 with 1% FBS at 40 mg/ml and was filter sterilized. The stock solution was stored at 4^oC for no longer than 2 weeks. Cells were incubated with varying concentrations of cyclophosphamide (0-15 mg/ml) for 10 hours in DMEM/F12 with 1% FBS. R^+ and R^- cells were seeded at $2x10^4$ cells/well and incubated in 96 well plates and were also grown to confluence (2 days) prior to doxorubicin (DXR) treatments. DXR was prepared at 5mg/ml in sterile saline. Cells were treated with DXR for 24 hours and 48 hours prior to survival analysis by MTT reduction. NXS2 neuroblastoma cells treated with different concentrations of etoposide (1-3 μM) in the presence or absence of octreotide (10 and 50 μM) for 72 hours were harvested by scraping, washed with complete medium, and incubated with trypan blue (0.04%;

Sigma; St. Louis, MO) for 1 minute at 37 °C. The cells were then placed in a Burker chamber (Tecnovetro, Monza Milan, Italy) and counted with a contrast phase microscope (Olympus Optical Co LTD, Tokyo, Japan). Trypan blue-positive cells (i.e. dead cells), trypan blue-negative cells (i.e. living cells), and total cells were counted per microscope field (four fields were counted for each treatment). The proportion of dead (or living) cells was calculated by dividing the number of dead (or living) cells by the total number of cells per field. Primary rat neurons and PC12 cells were treated with IGF-I and paraquat to determine the effect of IGF-I on oxidative stress. Cortical neurons were treated for 24 hours in Eagle's minimal essential medium (Invitrogen) supplemented with 21 mM glucose and 1% horse serum. PC12 cells were plated at 5 $x10^4$ cells/well onto poly-D-lysine coated 96-well plates and were grown for 24 hours in F12K 1% HS. Both types of cells were then treated with either 100 µM of paraquat alone or followed 30 minutes later by IGF-I (100 ng/ml) or IGF-I (100 ng/ml) alone in appropriate media. Survival was determined by the MTT reduction assay and presented as percentage of treated to control.

in vitro viability assays

Cytotoxicity was measured by either lactate dehydrogenase (LDH) released using the CytoTox 96 Non-Radioactive Cytotoxicity Assay kit (Promega) or the ability to reduce methylthiazolyldiphenyl-tetrazolium bromide (MTT). MTT is reduced in the mitochondria (metabolically active cells) by mitochondrial reductase enzymes to form insoluble purple formazan crystals, which are solubilized by the addition of a detergent (*1*). Briefly, MTT was prepared at 5 mg/ml in PBS and was diluted in DMEM/F12 1% FBS media to a final

concentration of 0.5 mg/ml for assays. Following experimental treatments, media was replaced with 100 µl of MTT and cells were incubated for 3~4 hours at 37^{o}C. Formazan crystals were dissolved overnight (16hours) at 37^{o}C with 100 µl lysis buffer ((w/v) 15% SDS, (v/v) 50% dimethylformamide, pH 4.7). Survival was presented as percentage of MTT reduction level of treated cells to control cells. Absorbance was read at 570nm using a microplate reader SpectraMax 250 (Molecular Devices) and SoftMax Pro 3.0 software (Molecular Devices).

STS and IGF-I treatments in mice

Mice were fasted for 48-72 hours. Food was completely withdrawn, but water was given *ad lib*. All mice were single caged in a new clean cage to eliminate the exposure to residual food and to reduce coprophagy. Mice were monitored thrice and weighed once daily. rhIGF-I (Prospec, Rehovot, Israel) was injected intraperitoneally every 12 hours during the 48-hour STS. Control mice received bolus injections of the solvent (ddH_2O).

Comet assay protocol

Cells were diluted to 10^5/ml in culture medium (DMEM/F12 with 10% FBS), and treated with 50 µM DXR for 1 hour at 37°C. Cells were then washed once with ice cold PBS and subject to CometAssay (Trevigen, Inc, Gaithersburg, MD) according to the manufacturer's recommended procedure. Comet images were acquired with a Nikon Eclipse TE300 fluorescent microscope and analyzed with the Comet Score software (TriTek Corp., ver1.5). 100-300 cells were scored for each genotype/treatment group.

Plasma mGH, mIGF-I, and mIGFBP-1 and -3 measurements

Plasma mIGF-I and mIGFBP-1 and -3 assays were performed as previously described by in-house ELISA assay using recombinant mouse IGF-I protein and monoclonal antibodies from R&D systems (Minneapolis, MN) (6). mGH levels were measured by rat/mouse GH ELISA kit (ALPCO Diagnostics).

Blood glucose measurements

Following a 72 hour fast, mice were anesthetized with 2% inhalant isoflurane and blood was collected by left ventricular cardiac puncture. Blood glucose was measured using the Precision Xtra blood glucose monitoring system (Abbott Laboratories, USA).

STS/Octreotide treatments in mice

The murine NX3IT28 cell line was generated by hybridization of the GD2-negative C1300 murine neuroblastoma cell line (A/J background) with murine dorsal root ganglional cells from C57BL/6J mice, as previously described (7). The NXS2 subline was then created by the selection of NX3IT28 cells with high GD2 expression (8). Female A/J mice, weighing 15-18 g were purchased from Harlan Laboratories (Harlan Italy, S. Pietro al Natisone, Italy) and housed in sterile cages under specific virus and antigen-free conditions. All procedures were reviewed and approved by licensing and ethical committee of the National Cancer Research Institute, Genoa, Italy, and by the Italian Ministry of Health. A/J mice were pretreated with 1 mg/kg/day doses of octreotide (OCT, ProSpec-Tany TechnoGene, Rehovot, Israel) for 4 days given slowly through the tail vein in a volume of 100 µl. Following the 4 days of octreotide treatment, mice were intravenously injected with NXS2 cells (200,000 cells/mouse), as previously described (8). After tumor cell injection, some animals were starved for 48 hours and

then I.V. injected with 80 mg/kg of etoposide (Teva Pharma B.V., Mijdrecht, Holland), administered as a single dose. Additional daily doses of OCT were administered for 4 days after chemotherapy. Control groups without dietary intervention and OCT treatment were also investigated.

Octreotide pre-treatment: 4 days 1mg/kg/day on days 1-4

NXS2: 200,000/mouse on day 4

STS: from day 4 to day 6 (after tumor cell injection)

Etoposide: 80 mg/kg on day 7

Octreotide post-treatment: days 8-11

To determine toxicity and efficacy, mice were monitored routinely for weight loss and general behavior. The animals were killed by cervical dislocation after being anesthetized with xilezine (Xilor 2%, Bio98 Srl, Milan, Italy) when they showed signs of poor health, such as adbominal dilatation, dehydration, or paraplegia.

Histology

The heart was collected for histological examinations of melanoma bearing LID and its control mice after 2 cycles of high-dose DXR. Heart failure has been documented as the major cause of acute toxicity after receiving DXR and therefore we examined the heart at the tissue level (9). The organs were collected and washed in ice cold PBS and stored in 10% neutral buffered formalin (VWR). Samples were paraffin embedded and sectioned at 5µm and H&E stained. Samples were examined and analyzed with Dr. Dubeau, professor of pathology at USC Keck School of medicine.

Bioluminescence imaging

For bioluminescence imaging (BLI), 5 mice were randomly selected from LID and control groups and followed throughout the experiment. All BLI imaging procedures were performed at the University of Southern California (USC) Small Animal Imaging core facility. Prior to imaging, mice were anesthetized using inhalant isoflurane (2%) and injected with 60 µl of 50mg/kg of the luciferase substrate luciferin (Xenogen Corp.). 10 minutes later, mice were imaged in the supine position and scanned for 2 minutes using the IVIS 200 optical imaging system (Xenogen Corp.). Signal intensity was quantified as photon count rate per unit body area per unit solid angle subtended by the detector (units of photon/s/cm^2/steridian). Images were analyzed with the IVIS 200 and LIVING IMAGE 3D (Xenogen Corp.) software.

Yeast strains

All experiments were performed with the strain DBY746 (*MATα,leu2-3,112,his3Δ1,trp1-289,ura3-52,GAL*$^+$), provided by D. Botstein, Massachusetts Institute of Technology, Cambridge, MA. The *sch9Δ* mutant has been described previously (10). All the mutant strains were originated in the DBY746 background by one-step gene replacement (11).

Yeast growth conditions

Yeast chronological life span was monitored in expired SDC medium by measuring colony forming-units (CFUs) every 48 hours. The number of CFUs at day 1 was considered to be the initial survival (100%) and was used to determine the age-dependent mortality (12). Cultures were treated once with 200 µM DXR on day 1.

Mutation frequency measurements

To characterize the type of mutations occurring in wild type and mutant strains, we measured the frequency of mutations of the *CAN1* (*YEL063*) gene (13, 14). Can^r mutations are mostly caused by point mutations as well as other DNA mutations including small insertion/deletion, complex events and gross chromosomal rearrangements (15). Cells from chronological aging cultures were plated them onto selective media every two days. The mutation frequency was calculated based on the number of viable cells as described previously (15, 16).

SUPPLEMENTARY FIGURES

Figure S1

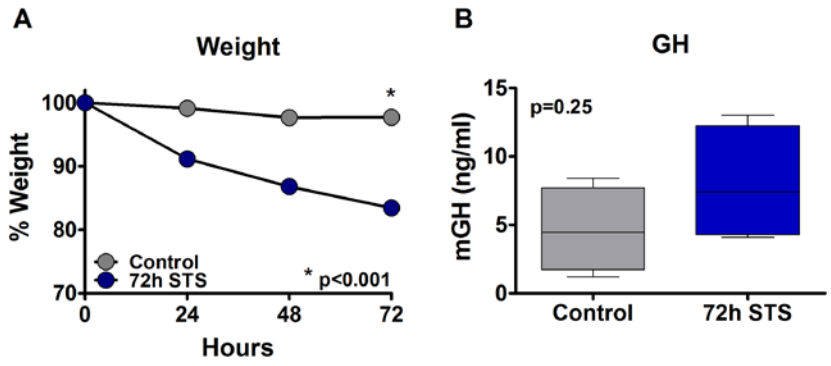
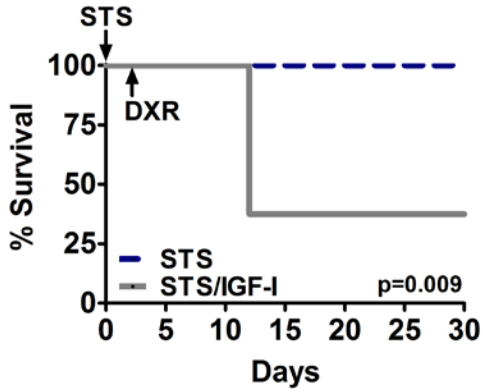


Figure S2



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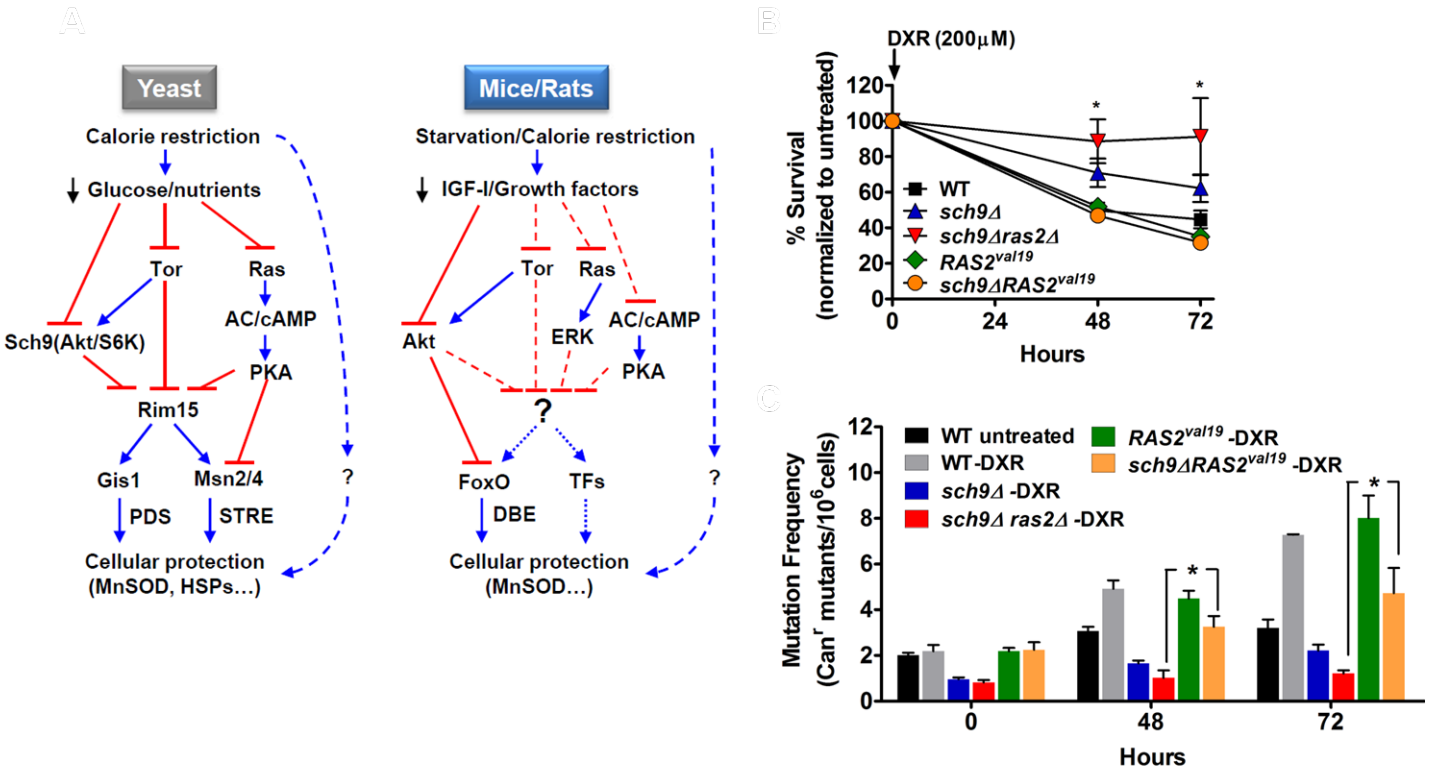
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Yeast
Calorie restriction
Glucose/nutrients
Tor
Ras
Sch9(Akt/S6K)
AC/cAMP
PKA
Rim15
Gis1
Msn2/4
PDS
STRE
Cellular protection
(MnSOD, HSPs…)
?
Mice/Rats
Starvation/Calorie restriction
IGF-I/Growth factors
Tor
Ras
Akt
ERK
AC/cAMP
PKA
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FoxO
TFs
DBE
Cellular protection
(MnSOD…)
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B
DXR (200μM)
% Survival
(normalized to untreated)
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RAS2val19
sch9ΔRAS2val19
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RAS2val19 -DXR
sch9ΔRAS2val19 -DXR
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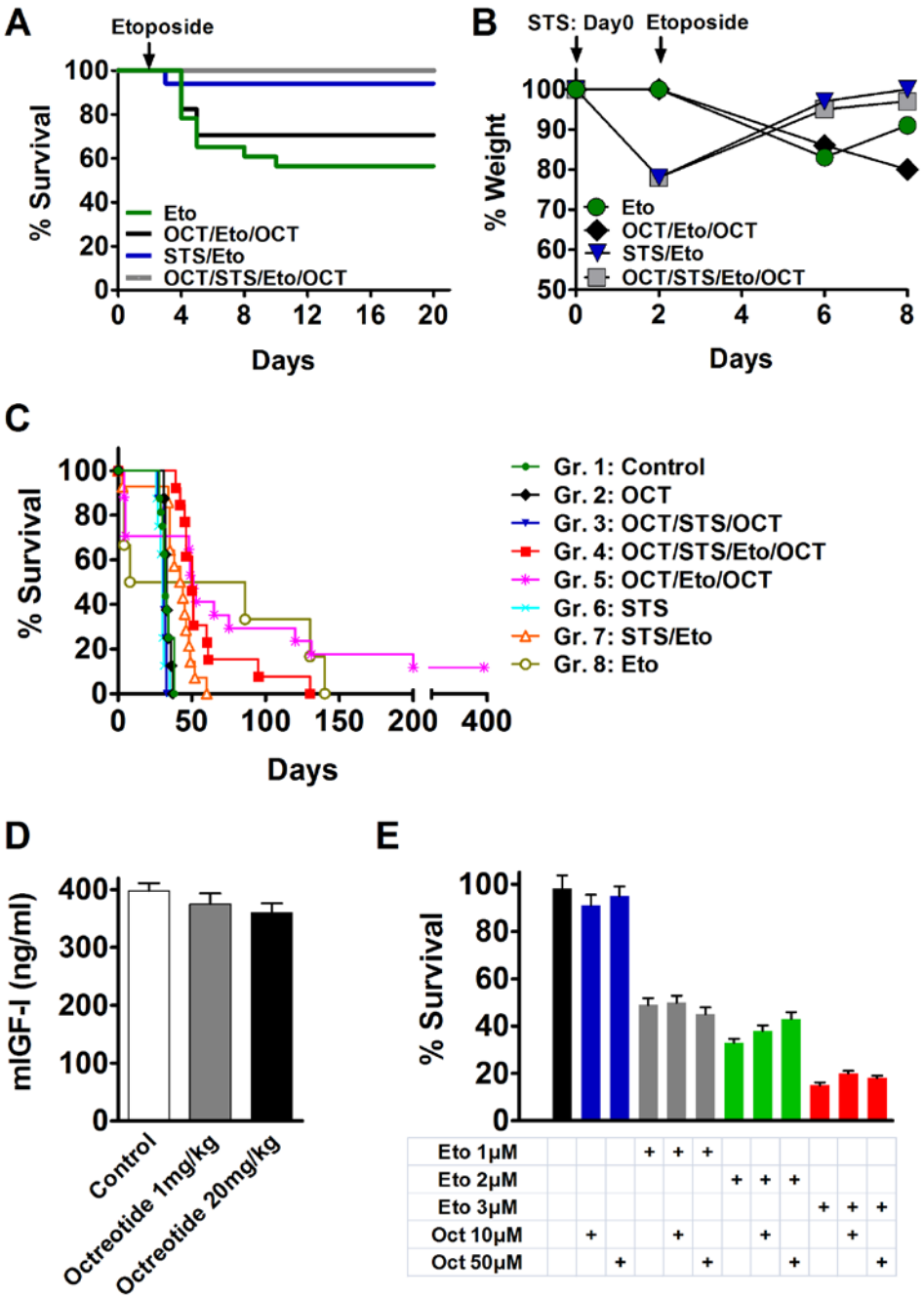
48
72
Hours

Figure S4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STS/Eto
OCT/STS/Eto/OCT
C
% Survival
Days
Gr. 1: Control
Gr. 2: OCT
Gr. 3: OCT/STS/OCT
Gr. 4: OCT/STS/Eto/OCT
Gr. 5: OCT/Eto/OCT
Gr. 6: STS
Gr. 7: STS/Eto
Gr. 8: Eto
D
mIGF-I (ng/ml)
Control
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Octreotide 20mg/kg
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% Survival
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Eto 2μM
Eto 3μM
Oct 10μM
Oct 50μM

Figure S5

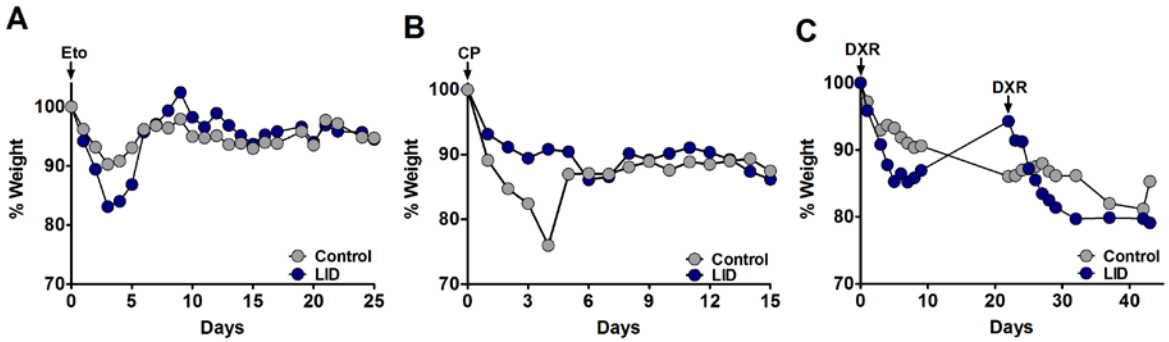
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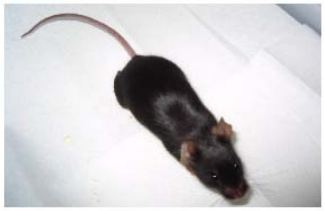
Figure S6

A

B



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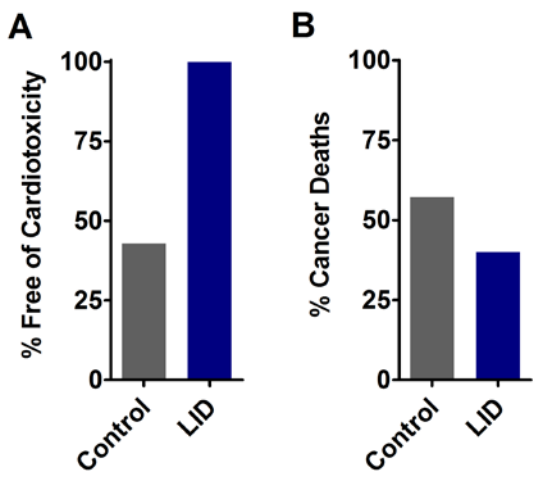

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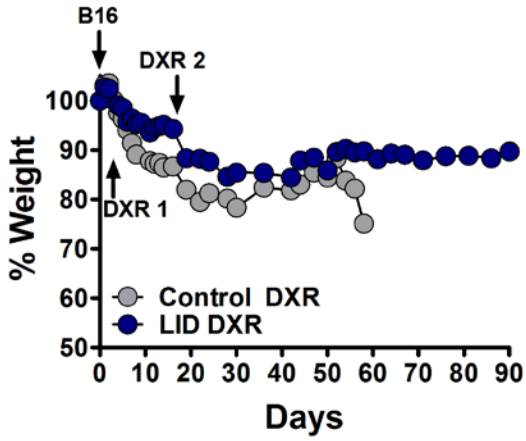

SUPPLEMENTARY FIGURE LEGENDS

Figure S1

The effect of 72 hour fasting on body weight and GH levels. 30 week old CD-1 mice were fasted for 72 hours and sacrificed. Blood was collected via cardiac puncture under deep anesthesia. Plasma GH levels were measured by a mouse-specific in-house ELISA. All *P* values were calculated by Student's t-test.

Figure S2

IGF-I restoration during STS reverses STS-dependent protection. 16-20 week-old female CD-1 mice were fasted for 48-hours (STS). During STS, IGF-I (200 µg/kg) was intraperitoneally injected every 12 hours to restore IGF-I levels. Immediately following STS/IGF-I treatment, all mice were intravenously injected with 16 mg/kg DXR. For STS/IGF-I treatments, mice were transferred to clean new cages to eliminate residual food pellets and excretion (reduce coprophagy). Food was withheld completely during STS (48 hours), but water was given *ad lib.*

Figure S3

(**A**) The conserved regulatory pathways of stress resistance in response to starvation/calorie restriction. In yeast, nutrient-sensing pathways controlled by Sch9, Tor, and Ras converge on the protein kinase Rim15. In turn, the stress response transcription factors Msn2, Msn4, and Gis1 transactivate stress response genes and enhance cellular protection, which leads to life span extension. In mice and humans,

short-term starvation leads to a significant reduction in circulating IGF-I levels. The partially conserved IGF-I signaling pathways negatively regulate the FoxO family transcription factors through Akt. Ras and Tor also function downstream of IGF-I, although their roles in the regulation of stress resistance and aging are poorly understood. Mice deficient in type 5 adenylyl cyclase (AC) are stress resistant, analogous to the adenylate cyclase deficient yeast. Notably, oncogenic mutations that cause the hyperactivation of IGF-I, Akt, Ras, Tor and PKA are among the most common in human cancers (17). (**B-C**) The effect of Sch9-/Ras2-deficiencies on DSR against DXR in *S. cerevisiae*. (**B**) Wild type (DBY746), *sch9Δ, sch9Δras2Δ, RAS2*^{val19}, and *sch9ΔRAS2*^{val19} strains were inoculated at OD_{600} = 0.1, grown separately in glucose media, and treated with DXR (200μM) 24 hours after initial inoculation. Viability was measured as colony forming units (CFU) onto appropriate selective media. Data from 3 independent experiments are shown as mean ± SE. * P <0.05 by Student's t test, *sch9Δras2Δ vs. sch9ΔRAS2*^{val19}. (**C**) Mutation frequency over time, measured as Can^{r} mutants/10^{6} cells. Strains shown are wild type (WT), cells lacking Sch9 and/or Ras2, and cells overexpressing constitutively active *Ras2*^{val19}. Data represent the mean ± SEM (n= 3-5 experiments). Cells were treated with DXR (200μM) on day 1. Mutation frequency of wild type untreated cells was reported as control. * P < 0.05 by Student's t test, *sch9Δras2Δ vs. sch9ΔRAS2*^{val19}.

Figure S4

The effect of Octreotide (OCT) on short-term starvation (STS) based DSR against etoposide (Eto). (**A**) Stress resistance in A/J mice after a 48 hours STS and 4 days of

octreotide treatment prior to and 4 days following Eto injection. All mice received an I.V. injection of 80 mg/kg Eto on day 7. The different groups were treated as follows: (Eto) treatment with 80 mg/kg Eto on day 7 (n=23); (OCT/Eto/OCT) pre-treatment with 1 mg/kg/day octreotide for 4 days + treatment with 80 mg/kg Eto on day 7 + post-treatment with 1 mg/kg/day octreotide on days 8-11 (n=17); (STS/Eto) 48-hour STS on days 4-6 + treatment with 80 mg/kg Eto on day 7 (n=16); (OCT/STS/Eto/OCT) pre-treatment with 1 mg/kg/day octreotide for 4 days + 48-hour STS (day 4-6) + treatment with 80 mg/kg Eto on day 7 + post-treatment with 1 mg/kg/day octreotide on days 8-11 (n=35). *P* =0.0002 by Peto's log rank test. (**B**) The weight profile of A/J mice after high-dose etoposide (80mg/kg) injection is shown. (**C**) Survival rate of neuroblastoma (NXS2) bearing mice after a single high-dose Eto (80 mg/kg) treatment. All mice were inoculated intravenously with 200,000 NXS2 cells/mouse on day 4. Octreotide was administered for 4 days prior to tumor inoculation and 4 days following chemotherapy. Survival of mice was monitored daily. The different groups were treated as following: (Gr. 1) Control - I.V. inoculation with NSX2 tumor cells on day 4 (n=16); (Gr. 2) OCT - pre-treatment with 1 mg/kg/day octreotide for 4 days before and after tumor inoculum (n=8); (Gr. 3) OCT/STS/OCT - pre-treatment with 1 mg/kg/day OCT before tumor cell inoculum + 48-hour STS on days 4-6 + post-treatment with 1 mg/kg/day OCT on days 8-11 (n=8); (Gr. 4) OCT/STS/Eto/OCT - pre-treatment with 1 mg/kg/day OCT for 4 days before tumor cell inoculum + 48-hour STS on day 4-6 + I.V. injection of 80 mg/kg Eto on day 7 + post-treatment with 1 mg/kg/day OCT on days 8-11 (n=13); (Gr. 5) OCT/Eto/OCT - pre-treatment with 1 mg/kg/day OCT for 4 days before tumor cell inoculum + I.V. injection of 80 mg/kg Eto on day 7 + post-treatment with 1 mg/kg/day

OCT on days 8-11 (n=17); (Gr. 6) STS - 48-hour STS on days 4-6 (n=8); (Gr. 7) STS/Eto - 48-hour STS on days 4-6 + I.V. injection of 80 mg/kg Eto on day 7 (n=15); (Gr. 8) Eto - I.V. injection of 80 mg/kg Eto on day 7 (n=6). Statistics: *P* Gr. 4 vs. Gr.1 < 0.0001, *P* Gr.5 vs. Gr.1 < 0.005, *P* Gr.7 vs. Gr.1 = 0.001, *P* Gr.6 vs. Gr.1 > 0.999, *P* Gr.4 vs. Gr.5 = 0.34, *P* Gr.4 vs. Gr.7 = 0.009, *P* Gr.5 vs. Gr.8 = 0.46, *P* Gr.7 vs. Gr.8 = 0.8. *P* values by Peto's log rank test. (**D**) IGF-I levels were measured by a mouse-specific ELISA from mice treated I.P. with 1 mg/kg/day or 20 mg/kg/day octreotide for 7 days. (**E**) NXS2 cells were incubated with different concentrations of Eto (1-3 μM) ± octreotide (10 and 50 μM) for 72 hours. Cell viability was determined by trypan blue exclusion. Data shown as percentage of dead cells (i.e. trypan blue positive), mean ± SE (n= 3 independent experiments). The effect of OCT/STS/OCT on etoposide toxicity.

Figure S5

Weight loss after high-dose chemotherapy in LID mice. LID and its control mice received a single high-dose injection of either (**A**) etoposide (Eto,100 mg/kg) or (**B**) cyclophosphamide (CP, 500 mg/kg). (**C**) Doxorubicin (DXR) was given twice, first on day 0 at 20 mg/kg, and the second on day 22 at 28 mg/kg.

Figure S6

LID mice show no signs of cyclophosphamide-dependent toxicity. (**A**) A mouse from the control group and (**B**) Liver *igf1* gene deleted (LID) group shown after high-dose cyclophosphamide (500mg/kg) treatment.

Figure S7

(**A**) LID mice are protected against DXR toxicity and (**B**) show slightly reduced metastasis related deaths. Survival recorded at Day 90 following cancer inoculation.

Figure S8

Weight of LID and control mice. B16Fluc cells were injected intravenously on Day 0. DXR injections were intravenously given on Days 3 and 17.

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