SUPPLEMENTAL FIGURE LEGENDS

Figure S1. XPA deficiency results in mitochondria phenotype, related to Figure 2. (A) Microarray analysis in XPA-knock down vs. shRNA control fibroblast and in XPA- vs. XPA+ cells. Data show commonly upregulated (red) and downregulated (green) GO terms in both cell lines. Asterisks denote pathways associated with mitochondria as listed in Figure 2C. (B) Flow cytometry data showing changes in mitochondrial content, intracellular and mitochondrial ROS, and mitochondrial membrane potential (MMP) after knockdown of XPA with the second shRNA (means ± S.D., n=3). (C) Representative immunoblots showing knockdown efficiency of the second shRNA towards XPA. (D) Representative immunoblot of the knockdown of XPC with two different shRNAs.

Figure S2. Mitochondrial dysfunction in XPA deficient cells and XPA does not localize to mitochondria, related to Figure 2. (A) Immunoblots showing protein levels of two mitochondrial markers, COX-4 and VDAC. Quantification data (to actin) are shown on the right (means ± S.D., n=3) (B) Representative immunocytochemistry images of paraformaldehyde fixed XPA deficient and control cells stained for COX4 and DAPI. Scale bar, 15 µm. (C) SH-SH5Y neuroblastoma cells were treated with 50 µM menadione for 1h, and nuclear and mitochondrial extracts were prepared. Mitochondrial extracts were further purified using proteinase K treatment. Representative immunoblot of protein levels of lamin A/C (nuclear marker), actin (cytoplasmic marker), VDAC (mitochondrial fraction) and XPA.

Figure S3. XPA deficiency induces autophagy through mTOR inhibition. (A) Endogenous LC3, XPA and actin levels were measured by immunoblot of total cell lysates after 24h treatment with Bafilomycin A1 (100 nM Bafi. A1), chloroquine (10 µM Chloro.) and rapamycin (1 µM Rapa.). (B) Relative LC3-II levels normalized to Actin (means ± S.D., n=3). (C) Autophagosomes and autolysosomes were quantified by confocal microscopy after transient transfection with the ptfLC3 plasmid. Autolysomes are GFP-tagged (green) and combined autolysomes and autophagosomes are RFP-tagged (red). Scale bars, 15 µm. (D) Quantification of (C) (means ± S.D, n=10). (E) Micrograph of different XPA-/XPA knockdown and XPA+/wide type cells transfected with ptfLC3 for 24 h. Representative confocal microscopy images are shown. Autolysomes stain with GFP whereas RFP represents both

autolysomes and autophagosomes. Scale bars, 15 µm. (F) Representative immunoblots of autophagy-associated proteins. (G) Cells were treated with 10 µM dorsomorphin (DM), or N-acetyl-L-cysteine (NAC, 5 µM) for 1 h, and designated protein levels were detected by immunoblot.

Figure S4. Defective mitophagy in XPA deficiency, related to Figure 3. (A) Representative confocal microscopy images of 24 h rotenone (5 µM), antimycin A1 (5 µM) and FCCP (10 µM) treated XPA deficient and control cells showing LC3 and p62 staining (See Figure 3D for quantification). Scale bars, 15 µm. (B) and (D) Colocalization of p62 or Parkin with mitochondrial marker COX-4. XPA- and XPA+ cells were treated with 5 µM rotenone for 24 h followed by immufluorescence of p62 and COX-4 (see Figure 3E for quantification) or Parkin and COX-4 (see Figure 4H for quantification) (Scale bars, 15 µm). (C) Immunoblot showing protein levels of different uncoupling proteins in a purified mitochondrial fraction in XPA- and XPA+ cells. (E) ATM and control cells were transiently transfected with UCP2 or an empty vector for 2 days and designated parameters were measured by flow cytometry (means ± S.D., n=3). Dyes used were the same as mentioned in Figure S1. (F) A representative immunoblotshowing knock down efficiency of a siRNA on full length PINK1 in XPA- and XPA+ cells. (G) A representative immunoblot showing knock down efficiency of a siRNA on Parkin in XPA- and XPA+ cells.

Figure S5. Increased PARylation in XPA deficiency, related to Figure 5. (A) Representative immunoblot of UCP2 levels in XPA- and XPA+ after siRNA knockdown of UCP2. (B) XPA- and XPA+ cells were transfected with siRNA on SIRT1 or control siRNA for two days, and then treated with 1 µM rotenone or vehicle for 24 h, followed by immunoblotting for designated proteins. (C) Representative immunoblot of PAR in CSB-, CSB+, ATM- and ATM+ cells. (D) Representative immunoblot of PAR in XPC knockdown and control cells (Knockdown efficiency shown in Fig. S1D). (E) XPA- and XPA+ cells were treated with the PARP inhibitor 3AB (1 mM) for 24 h, and changes in PAR levels were determined by confocal microscopy. Scale bars, 15 µm.

Clinical trait	XPA	CS	ATM
Ataxia	+	+	+
Cerebellar atrophy	+	+	+
Peripheral neuropathy	+	+	+
Short stature	+	+	+
Cancer	+		+
Chorea	+		+
Dysarthria	+		+
Cerebral atrophy	+	+	
Developmental delay	+	+	
Sensorineural hearing loss	+	+	
Sun sensitivity	+	+	
Mental retardation	+		
Microcephaly	+	+	
Areflexia		+	+
Demyelination		+	+
Nystagmus		+	+
Weight loss		+	+
Athetosis			+
Dystonia			+
Immune deficiency			+
Increased blood α-foeto protein			+
Oculomotor apraxia			+
Strabismus			+
Telangiectasia			+
Basal ganglia pathology	+	+	
Cataracts		+	
Contractures		+	
Dental caries		+	
Hyperactive reflexes		+	
Hypertension		+	
Kyphosis		+	
Lactic acidosis in the CNS		+	
Leukodystrophy		+	
Optic atrophy		+	
Pruritus		+	
Retinitis pigmentosa		+	
Seizures		+	

Tremor	+
Vomiting	+
Xerophthalmus	+

Table S1. XPA, CS and AT are phenotypically similar to mitochondrial diseases, related to Figure 1. Red color represents a symptom commonly observed in mitochondrial diseases. + represents that this symptom is often observed in the designated disease. For references see www.mitodb.com.

EXPERIMENTAL PROCEDURES

Database. Prediction of mitochondrial pathology of XPA was generated using the on-line database www.mitodb.com. A number of qualitative and quantitative measures were calculated as previously reported (Scheibye-Knudsen et al., 2013).

Animals. Mice carrying WT, *Xpa*$^{-/-}$, *Csa*$^{-/-}$ or CX (*Csa*$^{-/-}$/*Xpa*$^{-/-}$) alleles in a C57BL/6 background (Brace et al., 2013; de Vries et al., 1995) were maintained under standard laboratory conditions at Harvard School of Public Health and allowed free access to water and control casein pelleted diet (Research Diets D12450B). Male homozygous *Csb* $^{m/m}$ mice and sex- and age-matched wide type C57BL/6 mice were maintained at the National Institute on Aging under standard conditions and fed standard animal chow. All animal experiments were performed with the approval of the appropriate institutional animal care and use committee. WT Bristol N2 and RB864 *xpa-1*(ok698) nematodes were purchased from the Caenorhabditis genetics Centre at the University of Minnesota. RB864 *xpa-1*(ok698) was backcrossed five times into the N2 (WT) reference strain and cultured at 20 °C on solid Nematode Growth Medium (NGM) agar plates (Arczewska et al., 2013).

Antibodies and Reagents. Antibodies against Lamin A/C (H-110) (#sc-20681), SIRT1 (sc-74465), PGC-1α (#sc-13067), COX-4 (#SC-69362), and p53 (#sc-71818) were from Santz Cruz. Antibodies against LC3 (#NB 100-2220), Sir2.1 (#NB100-1923), and atg5-atg12 (#NB 110-53818) were from Novus. Anti-β-actin (#ab6276), anti-XPA (#ab151508), anti-VDAC/porin (#ab34726), anti-p62 (#ab56416), anti-Parkin (#ab15954), anti-PINK1 (#ab23707), and anti-mitofusion 1 (#ab107129) were purchased from abcam. Antibodies against UCP2 (#Ab-LS-B3249) and UCP4 (#Ab-LS-C148475) were provided by Lifespan company. Antibody against Poly (ADP-ribose) (#551813) was from BD pharmingen. Antibodies against UCP1 (#662045) and UCP3 (#662048) were from Calbiochem. Anti-p70S6 kinase(#9202), anti-phospho-p70S6 kinase (#9205), anti-Bak (#6947), anti-Bax (#2772), anti-PARP-1 (#9542), anti-Caspase-3 (#9662), anti-Caspase-9 (#9502), anti-Caspase 8 (#9746), anti-mitofusion 2 (#9482), anti-DRP1 (D8H5, #5391), anti-phospho-DRP1 (ser616, #3455), anti-NF-κB p65 (L8F6, #6956), anti-acetyl NF-κB p65 (Lys310, #3045), and acetyl p53 (Lys379, #2570) were from Cell Signaling. Antibody against Beclin-1 (#PRS3613) was purchased

from Sigma-Aldrich. Second antibodies including anti-mouse IgG (#NA931V) and anti-rabbit IgG (NA934V) were from GE Healthcare, and anti-goat IgG were from Sigma-aldrich (#A8919). All reagents including rapamycin (#R0395), bafilomycin A1 (#B1793), chloroquine (#C6628), rotenone (#R8875), antimycin A1 (#A8674), and FCCP (#C2920) were provided by Sigma-Aldrich unless otherwise stated. Nicotinamide riboside (Niagen) was generously provided by ChromaDex, and nicotinamide mononucleotide was from Sigma. Olaparib (AZD 2281, #S1060) was from Selleckchem.

Cell Culture. All cell lines were purchased from American Type Culture Collection or Coriell Cell Repository. XPA-deficient (GM04312C) and the matched complemented (GM15876A) cells, as well as the human neuroblastoma cell line SH-SY5Y were maintained in Gibco DMEM medium supplemented with 10% FBS with 1% penicillin-streptomycin (P&S). Primary fibroblasts from XPA patients including GM2009, GM2010, GM04314, as well as their gender and age matched controls GM1652, GM5565, GM969, respectively, were cultured in Gibco MEM medium mixed with 15% FBS, 1% P&S, and 1 X Glutamin. CSB-deficient (CS1AN-v) and its CSB corrected (CS1AN-CSB) were cultured in Gibco DME medium supplemented with 10% FBS, 1% P&S and 400 µg/ml geneticin. The ATM cell (GM5849) and the control (GM637) were maintained in Gibco DME medium supplemented with 10% FBS, 1% P&S, 1 X Glutamin, and 1 X nonessential amino acids. Dissociated cerebral cortical neurons were prepared from embryonic rat (Sprague Dawley) using standard procedures and cultured in neurobasal medium (Gibco) with 1% P&S, 1 X Glutamin, and B27 (Invitrogen) (Liu et al., 2009). All cells were grown in 20% O_2/5% CO_2 at 37°C.

Detection of Autophagy and Mitophagy. Monitoring autophagy/mitophagy was carried out by detecting LC3-II/actin ratio, protein levels of different autophagy-associated proteins, and numbers of autophagic elements (Klionsky et al., 2012). Autophagic flux was measuring using two autophagy inhibitors bafilomycin A1 (100 nM) and chloroquine (10 µM). After 4 h treatment, cells were harvested and prepared for western blotting. Autophagic elements were detected by transient transfection of cells with ptfLC3 plasmid (Addgene, ID 21074, deposited by Tamotsu Yoshimori) and images by confocal microscopy (Eclipse TE-2000e, Nikon). Mitophagy was induced with

three mitochondrial toxins: rotenone, Antimycin A1, and FCCP. After treatment with indicated doses for 24 h, cells were harvested and prepared for western blotting.

Lentivirus Generation and Infection, and RNA Interference. The two shRNA vectors against XPA were from Sigma-Aldrich including TRCN0000083193 NM (clone ID: 000380.2-1087s1c1; sequence: CCGGGCACAA TGTCATGTCT GTGATCTCGA GATCACAGAC ATGACATTGT GCTTTTTG) and TRCN0000083194 NM (clone ID: 000380.2-660s1c1; sequence: CCGGGCATTA GAAGAAGCAA AGGAACTCGA GTTCCTTTGC TTCTTCTAAT GCTTTTTG). Lentiviral production was performed by co-transfection of packing plasmid pCMV-dr8.2 DVPR (Addgene plasmid 8455) , envelope vector pCMV-VSV-G (Addgene 8454) (Stewart et al., 2003), and the abovementioned XPA shRNA plasmid or scrambled plasmid (Addgene 1864) (Sarbassov et al., 2005) into 293T cells using X-tremeGENE transfection reagents (Roche). For infection, the virus was incubated with cells plus 4 µg/ml Polybrene for 2 days followed by 24 ~ 48 h puromycin (4 µg/ml for SH-SY5Y, others using 2 µg/ml) selection. SIRT1Trilencer-27 siRNA, UCP2 siRNA, PINK1 siRNA, and Parkin siRNA were all purchased from Origene. In brief siRNAs were incubated in Optimem with 4 µL RNA Interferin (siRNA transfection reagent, Polyplus) per 1 ng RNA for 15 minutes and added to complete media for a final concentration of 10 nM siRNA. After 2-day incubation, cells were applied for further experiments.

Microarray. Total RNA extraction was applied using a TRIzol Plus RNA purification kit as per manufacturer's protocol and the quality was assessed by a NanoDrop ND-1000 spectrophotometer. The microarray was performed by the Gene Expression and Genomics Unit (NIA) and then analyzed using DIANE 1.0 software (see http://www.grc.nia.nih.gov/branches/rrb/?dna/diane_software.pdf for information). Raw microarray data were log transformed to yield z-scores. The z-ratio was calculated as the difference between the observed gene z-scores for the experimental and the control comparisons, and dividing by the standard deviation associated with the distribution of these differences. Z-ratio values of ± 1.5 were chosen as cut-off values and calculated using a 5% false discovery rate (FDR) threshold. A complete set of 522 cellular pathways was obtained from the Molecular Signatures Database (MSigDB, Broad Institute, Massachusetts Institute of Technology, Massachusetts, USA). The complete set was tested for Geneset enrichment using Parametric analysis of Gene set enrichment (Schurman et

al., 2009). For each pathway z-score, a p-value was computed using JMP 6.0 software to test for the significance of the z-score obtained. Submission of microarray data to the Gene Expression Omnibus (GEO) is in process.

Mitochondrial Parameters. Mitochondrial membrane potential (MMP), mitochondrial content and ROS at both cellular and mitochondrial levels were measured by a BD Accuri™ C6 flow cytometer as previously described (Scheibye-Knudsen et al., 2012). Briefly, cells were plated in 6-well plate at a confluence of 10^5/well followed by different treatment for designated intervals. Cells were then harvested by trypsin, washed with PBS, and resuspended in DME without phenol indicator (Invitrogen). After incubation with different dyes (all from Life technologies™), including TMRM (40 nM for 15 min) to detect MMP, MitoTracker Green (50 nm for 30 min) for mitochondrial content, dihydroethidium (DHE, 3 µM for 30 min) to detect cellular ROS, and mitoSOX (3 µM for 30 min) for mitochondrial ROS, fluorescence was determined with flow cytometry by counting $1X10^4$ cells. Data were analyzed using FCS Express 4 software.

ATP and NAD^+/NADH Quantitation. ATP concentration was detected using an ATPlite™ Luminescence Assay System (PerkinElmer) as per manufacturer's instruction. Briefly, cells were plated in a 96-well plate (10^5 cells in 100 µL/well) for 24 h before the ATP consumption assay. At time 0, ATP inhibitor cocktail (100 mM 2-deoxyglucose with 1 µM oligomycin) was added, followed by adding 50 µL lysis buffer at a serial time points. After adding substrate to all the wells, luminescence was measured on the 1450 MicroBeta TriLux Microplate Scintillation and Luminescence Counter (PerkinElmer). Measurement of NAD^+/NADH was performed by using a commercial NAD/NADH assay kit (#ab65348) by following the provided protocol. The NAD Cycling Enzyme Mix in the kit recognizes NADH and NAD, but not NADP or NADPH, in an enzyme cycling reaction.

Western Blotting. Briefly, cells were harvested, dissolved with RIPA buffer (Cell Signaling) and sonicated. After centrifugation at 14,000 RPM for 30 min at 4 °C, 50 µg supernatant was denatured at 95 °C for 5 min, and then loaded on an NuPage 4-12% Bis-Tris Gel and running at 200 V for 1h. Proteins were transferred to a PVDF

membrane (Bio-Rad), sequentially incubated with first and second antibodies. Images were examined using a ChemiDoc^{TM} MP system (Bio-Rad) and analyzed with Image Lab^{TM} software.

Mitochondria purification for cellular localization studies of XPA. Mitochondrial fractions were prepared for detecting UCPs protein members and investigation of the mitochondrial localization of XPA, using either a commercial kit as per manufacturer's instructions (ab110171, abcam) or by differential centrifugation. For differential centrifugation, cells were suspended in 70 mM sucrose, 210 mM mannitol, 10 mM HEPES, 1 mM EGTA (MSHE) buffer and homogenized in a glass-glass homogenizer. Nuclei and intact cells were precipitated by centrifugation at 1.000 g, 4 C°, 10 min. The supernatant containing mitochondria were precipitated in a second spin 6.000 g, 4 C°, 10 min. The mitochondrial precipitate was washed and resuspended in MSHE. A second spin 6.000 g, 4 C°, 10 min was performed and the resulting mitochondrial pellet was layered on top of a percol-gradient and spun at 30.000 g, 4 C°, 10 min. The mitochondrial band was extracted and resuspended in MSHE and spun at 6.000 g, 4 C°, 10 min. Half of the resulting mitochondrial pellet was treated with proteinase K (1 ug/mL, 20 min on ice) and the other half was not. Purified mitochondria were stored in -80 C° for further experiments.

Cellular Oxygen Consumption. Cellular oxygen consumption and extracellular acidification rates were measured using the Seahorse XF-24 instrument (Seahorse Biosciences) as previously described (Scheibye-Knudsen et al., 2012). In brief, cells (7×10^4/well) were cultured with DMEM medium in a Seahorse tissue culture plate overnight, and before experiments was changed to working medium (unbuffered XF assay medium with 25 mM glucose, 1 mM sodium-pyruvate, and 1 mM glutamax, pH 7.4), and incubated in a non-CO2 incubator for 1 h. Respiration was subsequently measured in the seahorse XF-24 instrument (Seahorse Biosciences). After the experiment, the cell number in each well was measured by trypsinization and counting on a coulter counter and the results was applied for final normalization. The data represents the mean of at least 3 separate experiments with at least three wells per cell line in each experiment.

Confocal and Electron Microscopy. Protein colocalization was determined by immunocytochemistry using a confocal microscope (Eclipse TE-2000e, Nikon). Cells were first seeded in 4-well chamber slide (5×10^4/well) overnight and treated with different reagents for specified time intervals. Cells were then washed in cold PBS and fixed with 3.7% paraformaldehyde in PBS for 10 min on ice, and subsequently washed with PBS and permeabilized in 0.25% Triton X-100 for 10 min on ice. Cells were then blocked in 5% FBS in PBS overnight at 4°C and probed with the indicated primary antibodies (1:100 ~ 1:500 dilution) at 37°C for 1 h. Cells were washed with PBS x 3 times and probed with fluorescent secondary antibodies (1:1000 dilution) for 1 h at 37°C before finally washes with PBS x 6 times. Cells were mounted in prolong gold anti-fade with DAPI (Invitrogen) and images were taken at 60 × magnification on a Nikon Eclipse TE-2000e confocal microscope (Nikon, Tokyo, Japan). The Volocity software was used to quantitatively analyze the unbiased global Pearson's coefficients in at least 10 random images of total 50 cells. Electron microscopy was done by Electron Microscopy Bioservices. Briefly, cells were washed in cold PBS, fixed in EM fixative buffer for 10 min, and subsequently scraped with a cell lifter. Cells were immediately centrifuged into a tight pellet at 2000 RPM for 10 min, and placed in 4 °C for an additional 3-h fixation. Fixative buffer was removed and cell pellet was carefully rinsed with Millonig's buffer in triplicate. The cell pellet was then minced post-fixed in 1.0% OsO_4, en bloc stained with 2.0% aqueous uranyl acetate, embedded in Spurr's plastic resin. Ultra-thin section analysis was performed on an electron microscope (Tecnai Spirit Twin Transmission; FEI) at 80 kV. Percentage of damaged mitochondria was counted in 14 random shoot images, and mitochondrial length and diameter was carried out with ImageJ (n>150).

Apoptosis. Cell apoptosis was determined with both flow cytometry and western blotting (Fang et al., 2012; Klionsky et al., 2012). Cells were treated with rotenone (5 µM), Antimycin A1 (5 µM), and FCCP (10 µM) for 24 h. Apoptotic cells were detected using a dead cell apoptosis kit with Annexin V Alexa Fluor® 488 and propidium iodide (Invitrogen) and analyzed in a BD Accuri™ C6 flow cytometer. Data were analyzed using FCS Express 4 software.

Worm studies. Lifespan analysis was performed at 20 °C for Bristol N2 and xpa-1 (opk698) mutants grown on classical NGM plates, or NGM plates supplemented with 500 µM NR, 500 µM NMN, or 100 nM Olaparib (AZD2281) seeded with *E. coli* OP50 as food source (Fensgard et al., 2010). 20-25 L4 stage worms (Day 0) were transferred to 10-13 plates, to give synchronous populations of at least 200 animals per condition. Animals were scored as dead or alive and transferred every day to fresh plates seeded with *E. coli* OP50 during the fertile period, and then every other day or every 3 days until death. Worms were considered dead when they stopped pharyngeal pumping and were unresponsive to touch. Worms that died because of internal bagging, desiccation due to crawling on the edge of the plates, or gonad extrusion were scored as censored. These animals were included in life-span analyses up to the point of censorship and were weighted by half in mortality calculations. We calculated mean, standard deviation of the mean, and P value using the log-rank test, from pooled population of animals. Figures display Kaplan Meier survival curves of pooled populations utilized for statistical analysis. For western blotting, whole cell lysis was prepared with a standard method as we mentioned previously (Arczewska et al., 2013).

Nicotinamide riboside supplementation on CX (*Csa*$^{-/-}$/*Xpa*$^{-/-}$) mice. CX and WT (C57BL/6) mice of 3 months of age were given subcutaneous interscapular injections of 500 mg NR/kg body weight/day or the equivalent volume of saline for a consecutive of 14 days at 4:00 pm (Gomes et al., 2013). On day 15, mice were sacrificed and half of a cerebellum was harvested for purification of mitochondria, with the left half snap-frozen, homogenized, and aliquoted for western blotting, microarray, and detection of ATP and NAD^+. To purify fresh mitochondria, half of a cerebellum were homogenized in MAS-buffer (70 mM sucrose, 220 mM mannitol, 10 mM KH2PO4, 5 mM MgCl2, 2 mM HEPES, 1 mM EGTA and 0.2% (w/v) fatty acid-free BSA, pH 7.2 at 37°C) using a glass-teflon homogenizer and nuclei/debris was precipitated by a 1.000 g centrifugation for 10 minutes, 4°C. Supernatants were transferred to new tubes and mitochondria were precipitated by a 6.000 g centrifugation for 7 minutes, 4°C. The mitochondria were washed in MAS buffer and precipitated by a 6.000 g centrifugation for 7 minutes, 4°C. Mitochondria were resuspended in 500 µL MAS, followed by FACS. Detection of other parameters was done as above-mentioned.

Quantifications and Statistics

Comparison between two groups was analyzed by nonparametrical two-tailed Student's *t* test. One-way ANOVA was performed to analyze statistical significance for multiple groups. For lifespan studies, we calculated mean, standard deviation of the mean, and P value using the log-rank test, from pooled population of animals.

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