SUPPLEMENTAL EXPERIMENTAL PROCEDURES

C. elegans Strains

The Bristol strain (N2) was used as the wild type strain. The following worm strains used in this study were obtained from the *Caenorhabditis* Genetics Center (CGC; Minneapolis, MN) unless otherwise noted (Baird et al., 2014; Benedetti et al., 2006; Calfon et al., 2002; Feng et al., 2001; Kimura et al., 1997; Kleine-Kohlbrecher et al., 2010; Kodoyianni et al., 1992; Libina et al., 2003; Link et al., 1999; Raizen et al., 1995; Taylor and Dillin, 2013; Vandamme et al., 2012; Yoneda et al., 2004). MQ887 (*isp-1(qm150)IV*), CB1370 (*daf-2(e1370)III*), DA1116 (*eat-2(ad1116)II)*, CF1903 (*glp-1(e2141)III*), SJ4100 (zcIs13[*hsp-6p::GFP*]), SJ4058 (zcIs9[*hsp-60p::GFP*]), SJ4005 (zcls4[*hsp-4p::GFP*]), CL2070 (dvIs[*hsp-16.2::GFP*; *pRF4(rol-6)*]), CF1553 muIs84[pAD76(sod-3::GFP)], VC936 (*jmjd-3.1(gk384)X*). Strains were backcrossed at least three times prior to experimental analysis. *F29B9.2(tm3713)IV* was a gift from A.E. Salcini (Kleine-Kohlbrecher et al., 2010). See also Table S3 for a complete list of strains generated and used in this study.

Strain generation

For generation of overexpression strains the all-tissue promoter *sur-5* (Gu et al., 1998), pan-neuronal promoter *rgef-1* (Chen et al., 2011) or intestinal promoter *gly-19* (Warren et al., 2001) were used. The *jmjd-1.2* ORF was amplified from wild-type *C. elegans* cDNA. Full length DNA plasmid constructs were injected at 50 ng/µl along with a coinjection marker (*myo-2p*::tdTomato) at 10 ng/µl to generate transgenic overexpression nematodes. Extra-chromosomal arrays were integrated by gamma irradiation and backcrossed to N2

ten times as previously described. The *jmjd-3.1* promoter and coding sequence were amplified from *C. elegans* genomic DNA. Sequences were cloned into the pPD30_38 expression vector (kind gift of Dr. Carina Holmberg) between *Pci*I and *Nhe*I restriction sites (the *unc-54* promoter and enhancer were replaced). *jmjd-3.1* overexpression plasmid was coinjected with pharyngeal CFP marker (*myo-2p::cfp*, kind gift of Dr. Carina Holmberg). Extra-chromosomal arrays were integrated using gamma irradiation and backcrossed five times to N2. Two independent lines carrying integrated transgenes were used in experiments. See also Table S3 for a complete list of strains generated and used in this study.

RNA interference

Bacterial feeding RNAi experiments were performed as described (Kamath et al., 2001) RNAi clones were used from either the Ahringer or Vidal libraries and sequence-verified. Double RNAi experiments were carried out by mixing bacterial cultures normalized to their optical densities (OD600) before seeding onto NGM plates.

UPR^{er} and HSR Stress assays

ER stress was induced in day 1 adults with 25 ng/μL tunicamycin in M9 for 4 hours on a rotating platform at 20°C. Worms were then washed with M9 and collected for further analysis. Heat shock was induced in day 1 adults by incubation in M9 submerged into 34°C water bath for 15 min. Worms were allowed to recover on solid NGM plates for 1.5 h at 20°C and collected for further analysis.

RNA-seq Analysis

Wild type N2 and transgenic overexpression strains *jmjd-3.1p::jmjd-3.1*, *sur-5p::jmjd-1.2* and *rgef-1p::jmjd-1.2* were used for the experiment. Synchronized eggs were plated on empty vector (EV) or EV + *cco-1* RNAi bacteria, grown at 20ºC and collected by washing with M9 at the L4 stage, then snap frozen in liquid nitrogen. Pellets were grinded with mortar and pestle on dry ice and the resulting powder was thawed in the presence of lysis buffer (50 mM Tris-HCl, 50 mM NaCl, 10 mM $MgCl_2$, 5 mM $CaCl_2$ 200 μg/ml cycloheximide, 200 μg/ml heparin, 1% (v/v) Triton X-100, 0.1% (w/v) sodium deoxycholate) and incubated on ice for 10 minutes prior to centrifugation at 4°C, 16,000 x g for 10 minutes. Poly-A RNA was purified from clarified lysate using olig-dT25 Dynabeads (Ambion) and Trizol-LS (Life Technologies) extraction, each according to manufacturer's instructions. Sequencing libraries were prepared using the Epicentre ScriptSeq v2 according to manufacturer's instructions. Illumina HiSeq 2500 reads were pre-processed and mapped to a set of noncoding RNAs before mapping the remaining reads to an index containing the longest single isoform ± 30nt for each gene in the *C. elegans* WS230 genome using Bowtie version 0.12.7 (Langmead et al., 2009) with the following settings: -m 1 -v 2 -a --norc --best –strata, which allows up to two mismatches and requires a single best alignment. In-house Python scripts were used to count reads mapping to each transcript and the count data were used for statistical analysis by DESeq2 (Love et al., 2014), where pairwise comparisons were evaluated by the negative binomial method. Three biological replicates of each condition were used for analysis, except for the *rgef-1p::jmjd-1.2* strain, for which one of the three replicates did not pass quality control and was removed from the analysis. Differentially expressed genes

(DEGs) relative to the N2 EV condition were defined by a Benjamini-Hochberg adjusted p-value of less than 0.05. Venn diagrams were generated with InteractiVenn (Heberle et al., 2015). GO terms of overlapping genes were determined with DAVID (Huang et al., 2009a, 2009b), using Bonferroni and Benjamini-Hochberg adjusted p value < 0.05. DESeq2-determined normalized count values were used for generating gene expression bar graphs and heatmaps. Fold change was calculated by dividing to average of normalized count values for N2 EV condition. Heatmaps were generated using heatmap.2 function from the gplots R package or GENE-E (Broad Institute). The set of 470 mitochondrial genes used in Figure 5F was retrieved from GO:0005739. The set of 111 OXPHOS genes in Figure 5G was retrieved from GO:0006119 and manual annotation. For mitochondria and OXPHOS heatmaps, genes with 0 counts in at least one condition were removed. RNA-sequencing data described in this study have been deposited in the Gene Expression Omnibus (GEO) database (Edgar et al., 2002) under accession number GSE78990. See also Table S2 for complete list of DEGs.

ChIP-qPCR Analysis

Chromatin immunprecipitation (ChIP) assays were performed essentially as described (Mukhopadhyay et al., 2008) with minor modifications. Briefly, wild type N2 worms were synchronized by bleaching and grown on solid NGM plates at 20°C until L3 stage, exposed to either empty vector or *cco-1* RNAi. Crosslinking was performed by treatment with 1% (w/v) formaldehyde for 20 min at room temperature. Worms were then lysed and sonicated with Bioruptor (Diagenode) to obtain 500–1,000 bp DNA fragments. H3K27me3 was then immunoprecipitated from 500 µg lysate using rabbit H3K27me3

ChIP-grade (07-449, Abcam) or rabbit IgG (sc2027, Santa Cruz) antibodies and protein A sepharose beads (sc2003, Santa Cruz). Crosslinks were reversed by 4h incubation at 65°C. DNA fragments were extracted with phenol-chlorophorm-isoamylalcohol and precipitated with ethanol. Standard quantitative RT-PCR experiments were performed as described above. Primers used for qRT-PCR were *hsp-6* (fw, gccagaaagggacttcagac, rv, cttttgggcccatagtgaca), *clpp-1* (fw, tctccgcagagaagtgtgaa, rv, cccaaagcgagaatcatacc) and *atfs-1* (fw, agcttacaggaccagcttcg, rv, gttccagctcgtctgatggt).

Bioinformatics Analyses

All BXD transcriptome data sets for bioinformatic analyses were downloaded from GeneNetwork (http://www.genenetwork.org) and performed as described in previous studies (Andreux et al., 2012; Lagouge et al., 2006; Wu et al., 2014). BXD transcriptome datasets used to establish genetic correlations were INIA Hypothalamus Affy MoGene 1.0 ST (Nov10) Male, INIA Amygdala Affy MoGene 1.0 ST (Nov10) RMA Male, UTHSC Affy MoGene 1.0 ST Spleen (Dec10) RMA Males, INIA Adrenal Affy MoGene 1.0ST (Jun12) RMA Males, INIA Pituitary Affy MoGene 1.0ST (Jun12) RMA and EPFL/LISP BXD CD Liver Affy Mouse Gene 1.0 ST (Apr13) RMA, Lifespan datasets ID 10148 and 12564. The correlations are Pearson's *r* or Spearman's *rho*, depending on the distribution of data. The correlation matrix was constructed using corrgram package in R. Publicly available microarray, RNA-seq and ChIP-seq data were retrieved from the GEO database (http://www.ncbi.nlm.nih.gov/geo). H3K27me3 ChIP-seq raw data (GSE56696) were re-analyzed using Galaxy (Goecks et al., 2010) with the same parameters as previously described (Ntziachristos et al., 2014). PHF8 ChIP-Seq data was

obtained from GSE20725 (Fortschegger et al., 2010). Binding of UPR^{mt} genes were explored using IGV (Thorvaldsdóttir et al., 2013). Heatmaps of UPR^{mt} genes from *Jmjd3*-knockout embryos (GSE40332) and human T-cell lymphoblastic leukemia cell lines CUTLL1 and CEM (GSE56696) (Ntziachristos et al., 2014) were made using heatmap.2 function from the gplots R package.

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