Supplementary Figure Legends

Figure S1. Gene expression analyses of CS-iPSCs and gene-corrected CS-iPSCs and their adult stem cell derivatives.

(A) Scatter plots showing the correlation between two replicates for the indicated cell samples. Ctrl: untreated; UV: treatment with UV irradiation; RS: under RS stress; rep: replicate.

(B) Heatmaps showing the pairwise Euclidian distance among the indicated cell samples. Ctrl: untreated; UV: treatment with UV irradiation; RS: under RS stress.

(C) Heatmaps showing the numbers of differentially expressed genes between CS-iPSCs and GC-iPSCs, between CS-MSCs and GC-MSCs, and between CS-NSCs and GC-NSCs. Ctrl: untreated; UV: treatment with UV irradiation; RS: under RS stress. Red represents upregulated genes, and blue represents downregulated genes. “GC” stands for GC cells, and “mut” stands for CS cells.

(D) Principal component analysis (PCA) of the RNA profiles of CS-MSCs and GC-MSCs in the absence or presence of UV irradiation (Ctrl or UV), as well as under RS stress (RS). Each point represents a sample. Data points were computed based on $\text{Log}_2(\text{FPKM} + 1)$.

(E) Volcano plots showing the differentially expressed genes between UV-treated and untreated MSCs (UV vs. Ctrl, left panel), between MSCs in the presence and MSCs in the absence of RS stress (RS vs. Ctrl, middle panel), and between UV-treated and untreated NSCs (UV vs. Ctrl, right panel). Red represents upregulated genes, and blue represents downregulated genes.

Figure S2. Transcriptome analysis of stress-induced genes in CS and gene-corrected CS adult stem cell derivatives.

(A) Heatmaps showing the upregulated/downregulated genes in CS-MSCs but not in GC-MSCs upon UV treatment (UV vs. Ctrl, left panel) or under RS stress (RS vs. Ctrl, middle panel). Heatmaps in the right panel showing the upregulated/downregulated genes in CS-NSCs but not in GC-NSCs upon UV treatment (UV vs. Ctrl).

(B) Venn diagrams showing the number of overlapping downregulated genes in CS-cells but not in GC-cells. Gene set A indicated the overlapping downregulated genes in CS-cells but not in GC-cells both upon UV irradiation and under RS stress. Gene set B indicated the overlapping downregulated genes in both CS-MSCs and CS-NSCs but not in GC-cells upon UV irradiation.

(C-D) Gene Ontology Biological Process (GO-BP) enrichment analysis of overlapping downregulated genes from gene set A (C) or gene set B (D). The network showing the relationship between different terms is visualized using Cytoscape. Each node represents an enriched term, each color indicates a cluster consisting of similar terms, and each line represents the correlation between two clusters/terms. The larger the node, the more terms are associated with it. The thicker the line is, the closer relationship between the two clusters/terms.

(E) An interaction network of overlapping genes was constructed using the STRING database. Red represents the overlapping genes from set A and the aging database, blue represents the overlapping genes from set B and the aging database. The solid line represents the interaction between genes from the same gene set, and the dotted line represents the interaction between genes from the different gene sets. The larger the node is, the more genes interact with it.

Figure S3. Analysis of ROS level in iPSCs and evaluation of tri-lineage differentiation potential of MSCs obtained under a cGMP-compliant condition.

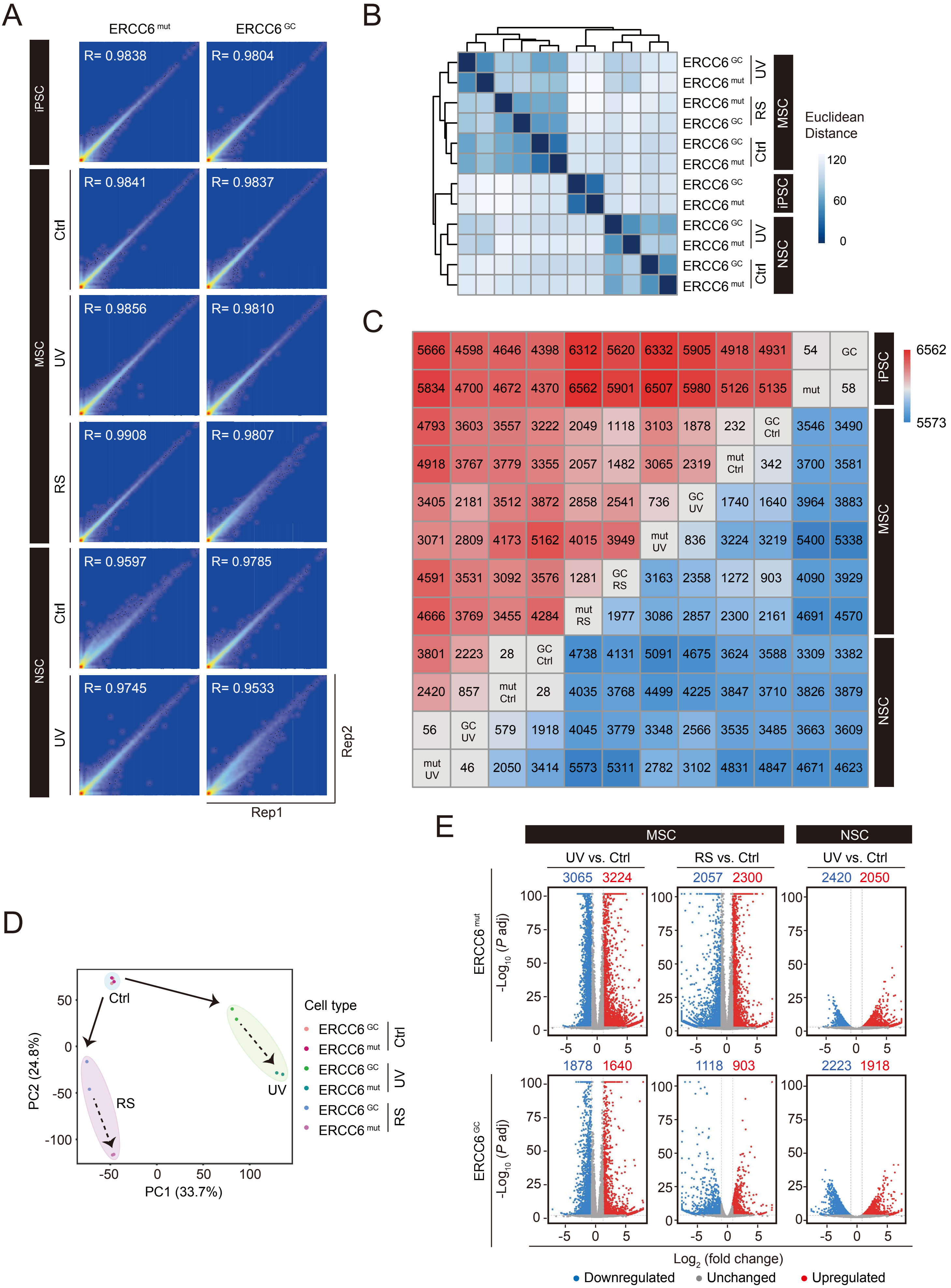
(A) Cellular ROS levels of CS-iPSCs and GC-iPSCs were determined by staining with H2DCFDA probe and measured with FACS.

(B) Heatmap showing the expression of genes involved in oxidative stress response in the CS-iPSCs and GC-iPSCs by RT-qPCR. The transcript levels were normalized to CS-iPSCs.

(C) Comparative analysis of the osteogenic, chondrogenic and adipogenic differentiation potential of CS-MSCs and GC-MSCs generated under a cGMP-compliant condition. Von Kossa, Alcian blue, and oil red O staining were used to characterize osteoblasts, chondrocytes, and adipocytes, respectively. Scale bar, 50 μm.

(D) The intensity of von Kossa staining was calculated by ImageJ and compared in the left panel. Data are presented as the mean ± SEM, *n* = 3, * *P* <0.05. The cross-sectional area of chondrocyte spheres was compared in the middle panel. Data are presented as the mean ± SD, *n* = 15, ** *P* <0.01. The relative intensity of oil red O was measured and compared in the right panel. Data are presented as the mean ± SEM, *n* = 3, *** *P* <0.001.

Figure S1



5666	4598	4646	4398	6312	5620	6332	5905	4918	4931	54	GC
5834	4700	4672	4370	6562	5901	6507	5980	5126	5135	mut	58
4793	3603	3557	3222	2049	1118	3103	1878	232	GC Ctrl	3546	3490
4918	3767	3779	3355	2057	1482	3065	2319	mut Ctrl	342	3700	3581
3405	2181	3512	3872	2858	2541	736	GC UV	1740	1640	3964	3883
3071	2809	4173	5162	4015	3949	mut UV	836	3224	3219	5400	5338
4591	3531	3092	3576	1281	GC RS	3163	2358	1272	903	4090	3929
4666	3769	3455	4284	mut RS	1977	3086	2857	2300	2161	4691	4570
3801	2223	28	GC Ctrl	4738	4131	5091	4675	3624	3588	3309	3382
2420	857	mut Ctrl	28	4035	3768	4499	4225	3847	3710	3826	3879
56	GC UV	579	1918	4045	3779	3348	2566	3535	3485	3663	3609
mut UV	46	2050	3414	5573	5311	2782	3102	4831	4847	4671	4623

Figure S2

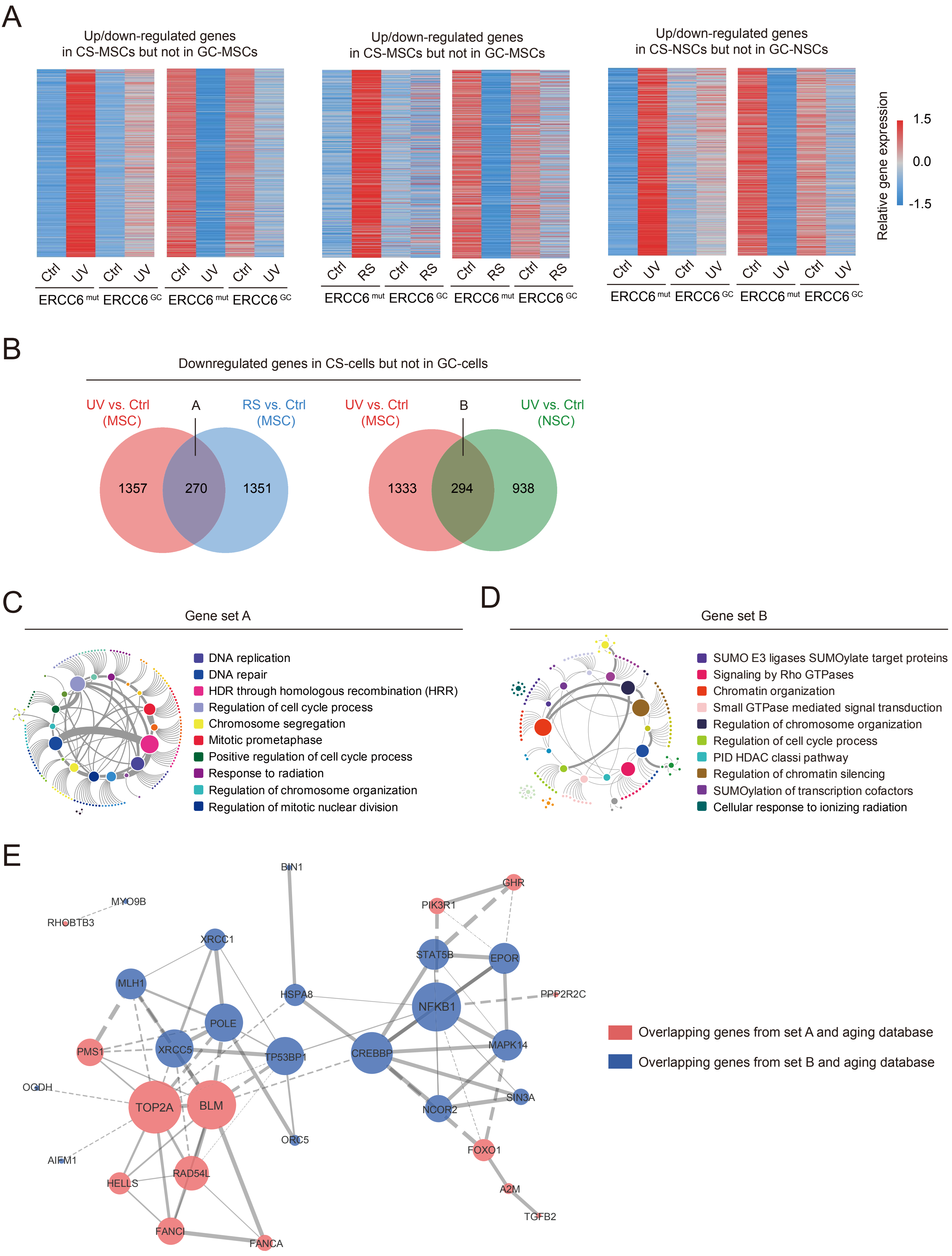
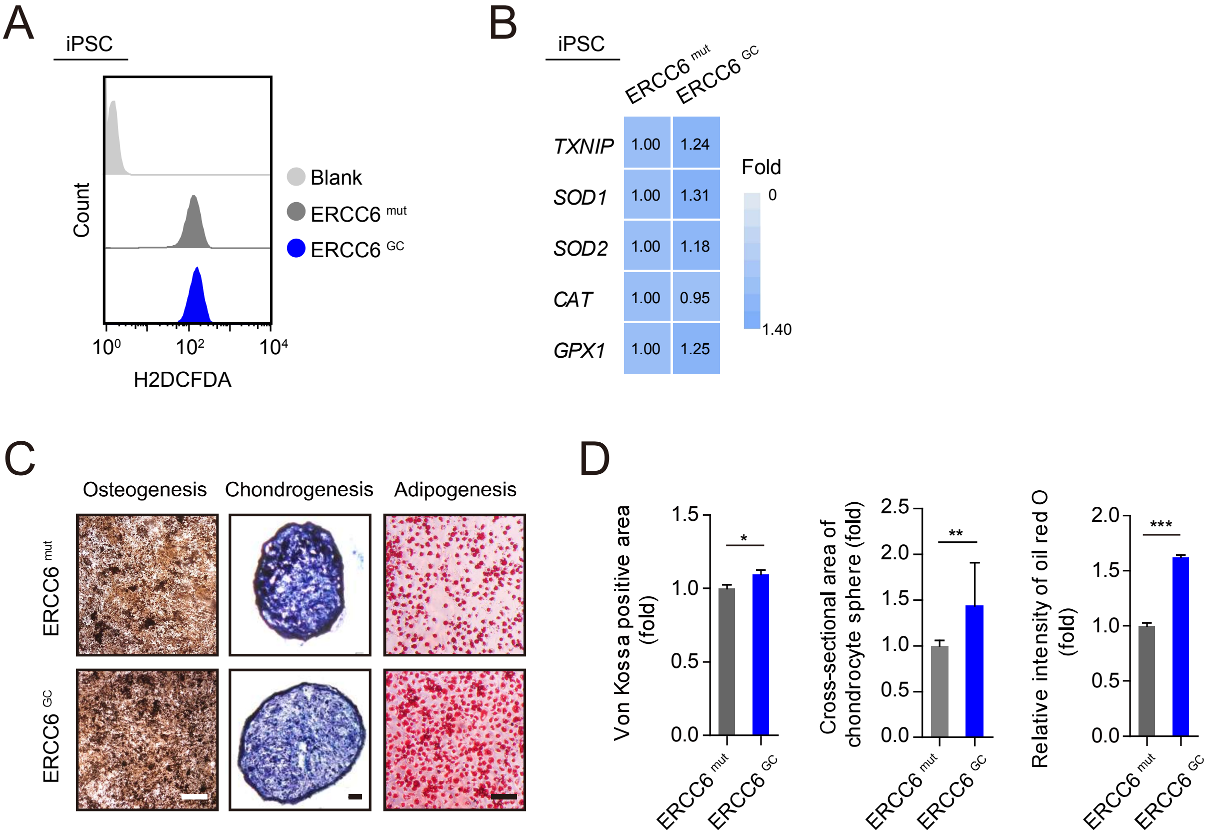

A
Up/down-regulated genes in CS-MSCs but not in GC-MSCs
Ctrl UV Ctrl UV Ctrl UV Ctrl UV
ERCC6 mut ERCC6 GC ERCC6 mut ERCC6 GC
Up/down-regulated genes in CS-MSCs but not in GC-MSCs
Ctrl RS Ctrl RS Ctrl RS Ctrl RS
ERCC6 mut ERCC6 GC ERCC6 mut ERCC6 GC
Up/down-regulated genes in CS-NSCs but not in GC-NSCs
Ctrl UV Ctrl UV Ctrl UV Ctrl UV
ERCC6 mut ERCC6 GC ERCC6 mut ERCC6 GC
Relative gene expression
1.5
0.0
-1.5
B
Downregulated genes in CS-cells but not in GC-cells
UV vs. Ctrl (MSC)
A
RS vs. Ctrl (MSC)
1357
270
1351
UV vs. Ctrl (MSC)
B
UV vs. Ctrl (NSC)
1333
294
938
C
Gene set A
DNA replication
DNA repair
HDR through homologous recombination (HRR)
Regulation of cell cycle process
Chromosome segregation
Mitotic prometaphase
Positive regulation of cell cycle process
Response to radiation
Regulation of chromosome organization
Regulation of mitotic nuclear division
D
Gene set B
SUMO E3 ligases SUMOylate target proteins
Signaling by Rho GTPases
Chromatin organization
Small GTPase mediated signal transduction
Regulation of chromosome organization
Regulation of cell cycle process
PID HDAC classi pathway
Regulation of chromatin silencing
SUMOylation of transcription cofactors
Cellular response to ionizing radiation
E
BIN1
GHR
MYO9B
PIK3R1
RHOBTB3
XRCC1
STAT5B
EPOR
MLH1
HSPA8
PPP2R2C
NFKB1
POLE
PMS1
XRCC5
TP53BP1
CREBBP
MAPK14
OGDH
SIN3A
TOP2A
BLM
NCOR2
ORC5
FOXO1
AIFM1
RAD54L
HELLS
A2M
TGFB2
FANCI
FANCA
Overlapping genes from set A and aging database
Overlapping genes from set B and aging database

Figure S3



	ERCC6 ^{mut}	ERCC6 ^{GC}
TXNIP	1.00	1.24
SOD1	1.00	1.31
SOD2	1.00	1.18
CAT	1.00	0.95
GPX1	1.00	1.25