

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 \pm 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 \pm 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 \pm SEM, $n = 3$, *** $P < 0.001$.