Supporting Information

Molecular Responses of Human Lung Epithelial Cells to the Toxicity of Copper Oxide Nanoparticles Inferred from Whole Genome Expression Analysis

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Figure S1. Particle size distribution of CuO-NPs (25 µg/mL) in culture medium assessed by using a laser diffraction particle size analyzer.

Figure S2. Preparation and characterization of medium containing Cu ions released from CuO-NPs. (a) The culture medium with CuO-NPs (25 µg/mL) was incubated at 37°C for 24 h, and then centrifuged. The supernatant was used to estimate contribution of Cu ions released from CuO-NPs into medium to CuO-NPs toxicity. (b) Culture medium without CuO-NPs was incubated at 37°C for 24 h, and then particle size distribution was measured with a laser diffraction size analyzer. (c) CuO-NPs in water were incubated at 37°C for 24 h, and then centrifuged. No particles were detected in the supernatant.
**Figure S3.** Cell viability as indicated by staining of cells that were exposed to CuO-NPs and the supernatant for 24 h with calcein acetoxyethyl ester (Calcein-AM). A549 human lung epithelial cells were cultured in media containing 25 µg/mL CuO-NPs or the supernatant at 37°C for 24 h, and then the number of viable cells was compared to that of the control.

**Figure S4.** Damage to mitochondria by CuO-NPs. Mitochondrial damage in A549 human lung epithelial cells after exposure to H2O2 (2 mM), CuO-NPs (25 µg/mL), and CuCl2 (30 µg/mL) was measured by using 5,5′,6,6′-tetrachloro-1,1′,3,3′-tetracyethylbenzimidazolylcarbocyanine iodide (JC-1; Invitrogen). The accumulation of JC-1 in mitochondria was measured by excitation at 543 nm and detection of fluorescence at 573–607 nm. Damaged mitochondria accumulated less JC-1, and therefore, exhibited less fluorescence. The mitochondria of cells that were exposed to CuO-NPs were damaged after 4 h. Cells that were exposed to CuCl2 also were damaged after 4 h; however, the damage was not as severe as that from CuO-NPs.
Figure S5. Effect of non-toxic dummy Al2O3-NPs on supernatant toxicity. (a) Cytotoxicity of Al2O3-NPs. The primary size of Al2O3-NPs was 50 nm and the hydrodynamic size was around 160 nm. A549 cells cultured for 48 h were exposed to Al2O3-NPs at a concentration of 25 µg/ml. After 24 h, a WST assay was performed. (b) Effect of Al2O3-NPs on the supernatant toxicity. A549 cells cultured for 48 h were exposed to supernatant and supernatant with Al2O3-NPs. The supernatant contained Cu ions released from CuO-NPs. After 24 h, a WST assay was performed. Zeta potential of Al2O3-NPs was -20.37 mV. Physicochemical character of Al2O3-NPs was previously reported (Xu et al., Biomaterials 2010, 31, 8022-8031).

Figure S6. Internalized CuO-NPs observed by TEM. Yellow arrowheads indicate single or smaller (<100 nm) aggregated NPs. Red arrowheads indicate larger (> 100 nm) aggregated NPs. Cells were cultured in medium with 25 µg/mL CuO-NPs for 24 h, and then living cells were harvested.
Figure S7. Western blotting analysis to confirm the change of gene expression. A549 cells were cultured for 48 h, and then exposed to 25 µg/mL CuO-NPs, supernatant and 30 µg/mL CuCl₂ for 24 h.

Figure S8. Cell cycle arrest due to CuO-NPs. Cells that were exposed to 25 µg/mL CuO-NPs were isolated, and then seeded in fresh culture medium that did not contain CuO-NPs at a density of 5000 cells/cm². The left graph shows the number of cells after 72 h. The dotted line shows the number of cells at the time of the seeding. Cell proliferation was not observed. However, when the cells were harvested and seeded in fresh culture medium for an additional 72 h, cell proliferation resumed (right graph). Therefore, cell cycle arrest occurred after the cells were exposed to CuO-NPs.
Figure S9. Effects of SB239063 and JNK interacting protein 1 (JIP-1), which are inhibitors of p38 and JNK, respectively. Double staining with calcein acetoxymethyl ester (calcein-AM) and propidium iodide (PI). SB239063 and CuO-NPs (CuO-NPs + SB239063) decreased the number of viable cells more than CuO-NPs alone. In the presence of SB239063, many cells that were exposed to CuO-NPs detached from the culture dish.

Figure S10. siRNA knockdown efficiency of GADD45B and NR4A1. (a) mRNA expression level of GADD45B. (b) Western blotting. The concentration of CuO-NPs was 25 μg/mL. GADD45B siRNA suppressed the expression at protein level. (c) mRNA expression level of NR4A1. (d) Western blotting. NR4A1 siRNA suppressed expression of NR4A1 at protein level.
Figure S11. Effect of siRNA knockdown on the expression of *GADD45B* and *NR4A1* on the cytotoxicity of CuO-NPs. Double staining with calcein-AM and PI. Knockdown of *GADD45B* and *NR4A1* decreased the number of viable cells after cells were exposed to CuO-NPs. The number of dead cells as indicated by PI staining is not accurate because it included dead cells that detached from the surface of the culture dish.

Figure S12. CuO-NPs in dead cell observed by TEM. Black dots indicate aggregates of CuO-NPs. Cells were cultured in medium with 25 μg/mL CuO-NPs for 24 h, and then dead cells detached from culture dish were harvested. Right panel is a magnified image of leaflet in left panel.
Figure S13. Cytotoxicity of CuO-NPs and Cu ions to primary human lung epithelial cells and change of gene expression. (a) Comparison of CuO-NPs toxicity between primary human epithelial cells (SAEC) and A549 cells. (b) Comparison of Cu ion toxicity between SAEC and A549 cells. (c-e) Expression level of genes in SAEC. Genes in (c) upregulated in CuO-NPs but not in 30 μg/mL CuCl2 in A549 cells. SAEC cells showed similar pattern. Genes in (d) upregulated in both CuO-NPs and 30 μg/mL CuCl2 in A549 cells. SAEC cells showed similar pattern. Genes in (e) downregulated in both CuO-NPs and 30 μg/mL CuCl2 in A549 cells. SAEC cells showed similar pattern in CCNB1, AURKA and TPX2, but not PCNA, CDC2 and AURKB. For gene expression analysis, SAEC cells were exposed to media containing 25 μg/mL CuO-NPs or 30 μg/mL CuCl2 for 24 h.
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OGT   Homo sapiens O-linked N-acetylglucosamine (GlcNAc) transferase (UDP-N-acetylglucosamine:polypeptide-N-acetylglucosaminyl transferase) (OGT), transcript variant 1, mRNA [NM_181672] 1.38
PAIP2  Homo sapiens poly(A) binding protein interacting protein 2 (PAIP2), transcript variant 1, mRNA [NM_010133112] 1.12
PAPOLA Homo sapiens poly(A) polymerase alpha (PAPOLA), mRNA [NM_032632] 1.60
PCF11  Homo sapiens PCF11, cleavage and polyadenylation factor subunit, homolog (S. cerevisiae) (PCF11), mRNA [NM_015885] 3.27
PHC3   Homo sapiens polyhomeotic homolog 3 (Drosophila) (PHC3), mRNA [NM_024947] 1.68
PHF1   Homo sapiens PHD finger protein 1 (PHF1), transcript variant 2, mRNA [NM_024165] 1.04
PHTF1  Homo sapiens putative homeodomain transcription factor 1 (PHTF1), mRNA [NM_006608] 1.39
PLRG1  Homo sapiens pleiotropic regulator 1 (PRL1 homolog, Arabidopsis) (PLRG1), mRNA [NM_002669] 1.38
PMS2L2 Homo sapiens postmeiotic segregation increased 2-like 2 pseudogene (PMS2L2), non-coding RNA [NR_003614] 1.02
PROP1  Homo sapiens PROP paired-like homeobox 1 (PROP1), mRNA [NM_006261] 1.95
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RNFL18 Homo sapiens ring finger protein 185 (RNFL185), transcript variant 1, mRNA [NM_152267] 1.07
RNMT   Homo sapiens RNA (guanine-7-) methyltransferase (RNMT), mRNA [NM_003799] 1.27
RP2    Homo sapiens retinitis pigmentosa 2 (X-linked recessive) (RP2), mRNA [NM_006915] 1.35
RPUSD4 Homo sapiens RNA pseudouridylate synthase domain containing 4 (RPUSD4), mRNA [NM_032795] 1.06
RYBP   Homo sapiens RING1 and YY1 binding protein (RYBP), mRNA [NM_012234] 1.02
SBNO1  Homo sapiens cDNA FLJ23676 fis, clone HEPO0548, highly similar to Homo sapiens mRNA for MOP-3 [AK074256] 1.19
SCML1  Homo sapiens sex comb on midleg-like 1 (Drosophila) (SCML1), transcript variant 1, mRNA [NM_001037540] 2.00
SIN3B  Homo sapiens SIN3 homolog B, transcription regulator (yeast), mRNA (cDNA clone IMAGE:3923074), partial cds. [BC025026] 1.28
SIRT6  Homo sapiens sirtuin (silent mating type information regulation 2 homolog) 6 (S. cerevisiae) (SIRT6), mRNA [NM_016539] 1.68
SLC25A44 Homo sapiens solute carrier family 25, member 44 (SLC25A44), transcript variant 1, mRNA [NM_014655] 1.12
SLU7   Homo sapiens SLU7 splicing factor homolog (S. cerevisiae) (SLU7), mRNA [NM_006425] 1.93
SNAI1  Homo sapiens snail homolog 1 (Drosophila) (SNAI1), mRNA [NM_005985] 3.18
SNIP1  Homo sapiens Smad nuclear interacting protein 1 (SNIP1), mRNA [NM_024700] 3.07
SOX8   Homo sapiens SRY (sex determining region Y)-box 8 (SOX8), mRNA [NM_014587] 1.93
SP1    Homo sapiens Sp1 transcription factor (SP1), transcript variant 1, mRNA [NM_138473] 2.03
SRBFB2 Homo sapiens steroid regulatory element binding transcription factor 2 (SRBFB2), mRNA [NM_004599] 1.32
SUPT4H1 Homo sapiens suppressor of Ty 4 homolog 1 (S. cerevisiae) (SUPT4H1), mRNA [NM_003168] 1.23
TAF13  Homo sapiens TAF13 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 18kDa (TAF13), mRNA [NM_005645] 1.98
TAF7   Homo sapiens TAF7 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 55kDa (TAF7), mRNA [NM_005642] 1.41
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<th>Description</th>
<th>Expression Level</th>
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<td>TAF8</td>
<td>Homo sapiens TAF8 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 43kDa, mRNA (cDNA clone IMAGE:5166848), with apparent retained intron. [BC033728]</td>
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<td>Homo sapiens thymine-DNA glycosylase (TDG), mRNA [NM_003211]</td>
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<td>TEAD1</td>
<td>Homo sapiens TEA domain family member 1 (SV40 transcriptional enhancer factor) (TEAD1), mRNA [NM_021961]</td>
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<td>TTF1</td>
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<td>UHMK1</td>
<td>Homo sapiens U2AF homology motif (UHM) kinase 1 (UHMK1), mRNA [NM_175866]</td>
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<td>USP15</td>
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<td>USP32</td>
<td>Homo sapiens ubiquitin specific peptidase 32 (USP32), mRNA [NM_032582]</td>
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<td>UTP11L</td>
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<td>ZNF143</td>
<td>Homo sapiens zinc finger protein 143 (ZNF143), mRNA [NM_003442]</td>
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<td>Homo sapiens cDNA FLJ78762 complete cds, highly similar to Homo sapiens zinc finger protein 224, mRNA. [AK292500]</td>
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<td>Homo sapiens zinc finger protein 256 (ZNF256), mRNA [NM_005773]</td>
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<td>ZNF780B</td>
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<td>ZNF8</td>
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<td>ZRANB2</td>
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<td>ZRSR2</td>
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<td>ZSCAN2</td>
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<td>ZSCAN20</td>
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Table S2. List of genes upregulated by CuO-NPs classified into the GO category of “response to stress”. Fold-change is represented by logarithmic ratio (log_ratio) to expression level in control.

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<th>Gene name</th>
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<th>Fold-change (log_ratio)</th>
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<td>ATF1</td>
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<td>CDKL3</td>
<td>Homo sapiens cyclin-dependent kinase-like 3 (CDKL3), transcript variant 2, mRNA [NM_016508]</td>
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<td>CLK1</td>
<td>Homo sapiens CDC-like kinase 1 (CLK1), mRNA [NM_004071]</td>
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<td>CREM</td>
<td>Homo sapiens cAMP responsive element modulator (CREM), transcript variant 19, mRNA [NM_183013]</td>
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<td>CRYAB</td>
<td>Homo sapiens crystallin, alpha B (CRYAB), mRNA [NM_001885]</td>
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<td>DNAJA1</td>
<td>Homo sapiens DnaJ (Hsp40) homolog, subfamily A, member 1 (DNAJA1), mRNA [NM_001539]</td>
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<td>DNAJA4</td>
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<td>DNAJB1</td>
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<td>DNAJB6</td>
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<td>DNAJB9</td>
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<td>DNAJC3</td>
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<td>FOS</td>
<td>Homo sapiens v-fos FBJ murine osteosarcoma viral oncogene homolog (FOS), mRNA [NM_005252]</td>
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<td>FOSB</td>
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<td>FSD1L</td>
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<td>GADD45B</td>
<td>Homo sapiens growth arrest and DNA-damage-inducible, beta (GADD45B), mRNA [NM_015675]</td>
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<td>GADD45G</td>
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<td>HSP90AA1</td>
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<td>NR4A1</td>
<td>Homo sapiens nuclear receptor subfamily 4, group A, member 1 (NR4A1), transcript variant 1, mRNA [NM_002135]</td>
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<td>TTC1</td>
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<td>VEGFA</td>
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Table S3. List of genes downregulated by CuO-NPs classified into the GO category of “cell cycle”. Fold-change is represented by logarithmic ratio (log ratio) to expression level in control. *, also classified into the category of “mitosis”.

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<th>Gene name</th>
<th>Description</th>
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<td>ACTR3B*</td>
<td>Homo sapiens ARP3 actin-related protein 3 homolog B (yeast) (ACTR3B), transcript variant 2, mRNA [NM_001040135]</td>
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<td>Homo sapiens aurora kinase A (AURKA), transcript variant 1, mRNA [NM_198433]</td>
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<td>CCNA2*</td>
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<td>CCNB1*</td>
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<td>DIS3L*</td>
<td>Homo sapiens DIS3 mitotic control homolog (S. cerevisiae)-like (DIS3L), transcript variant 2, mRNA [NM_133375]</td>
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<td>DNAJC5</td>
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<td>Homo sapiens cDNA: FLJ21489 f1s, clone COL05450. [AK025142]</td>
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Table S5. List of genes downregulated by CuO-NPs classified into the GO category of “chromosome segregation”. Fold-change is represented by logarithmic ratio (log; ratio) to expression level in control.

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Table S7. List of shared genes whose expressions were upregulated in cells exposed to both CuO-NPs and released Cu ions. Fold-change is represented by logarithmic ratio (log₂ ratio) to expression level in control.

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<th>Gene name</th>
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<th>Cu ions</th>
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<tbody>
<tr>
<td>MT1F</td>
<td>Homo sapiens metallothionein 1F (MT1F), mRNA [NM_005949]</td>
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<td>Homo sapiens cDNA FLJ37158 fis, clone BRACE2026293, [AK094477]</td>
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<td>Jkx3a</td>
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## Table S8. List of shared genes whose expressions were downregulated in cells exposed to both CuO-NPs and released Cu ions.
Fold-change is represented by logarithmic ratio (log₂ ratio) to expression level in control.

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<th>Cu ions</th>
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<td>KIF20A</td>
<td>Homo sapiens kinesin family member 20A (KIF20A), mRNA [NM_005733]</td>
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<td>MYBL1</td>
<td>Homo sapiens v-myb myeloblastosis viral oncogene homolog (avian)-like 1 (MYBL1), mRNA [NM_001080416]</td>
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Table S9. Shared downregulated genes by CuO-NPs and released Cu ions, which fall into the categories of “mitosis”, chromosome segregation”, and “cell cycle”.

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**cell cycle**
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