Figure S1. Stress agents often induce multiple stress responses, and often participate in multiple stress response pathways. For example, chromate can activate stress response pathways associated with genotoxicity, oxidative stress, heat shock, and metabolism.
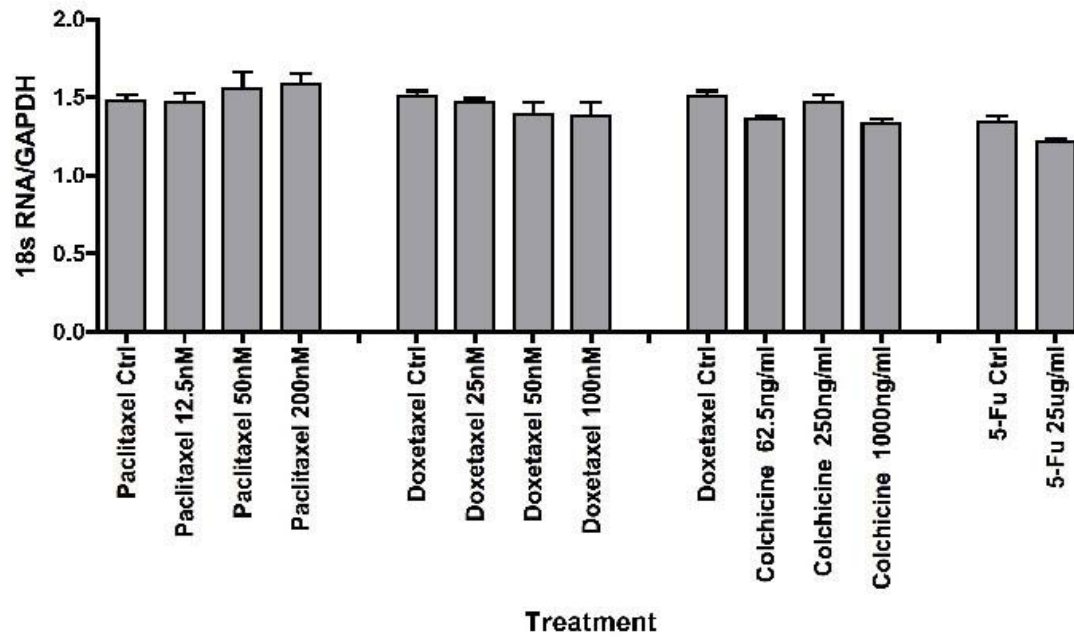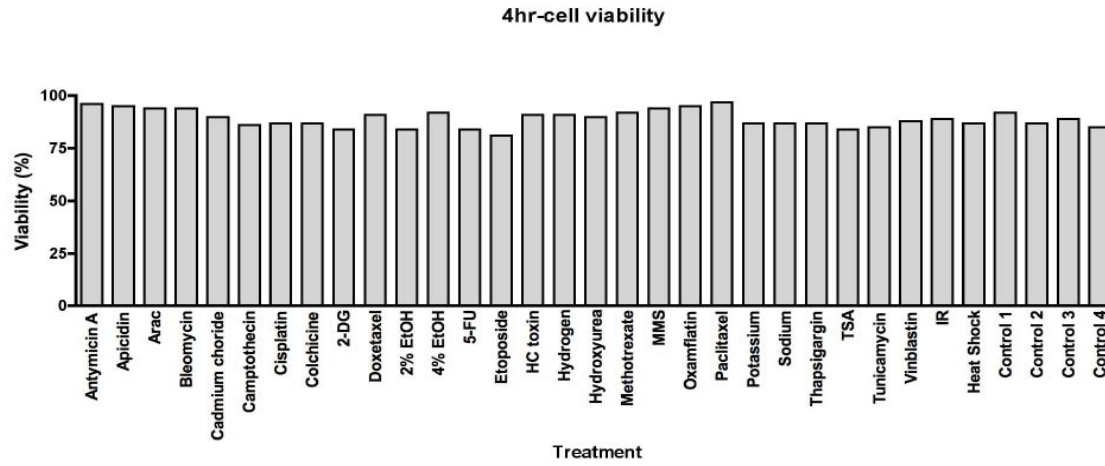
Figure S2. Examples demonstrating that the relative level of the two internal standard genes 18sRNA and GAPDH, remains consistent in treatments.
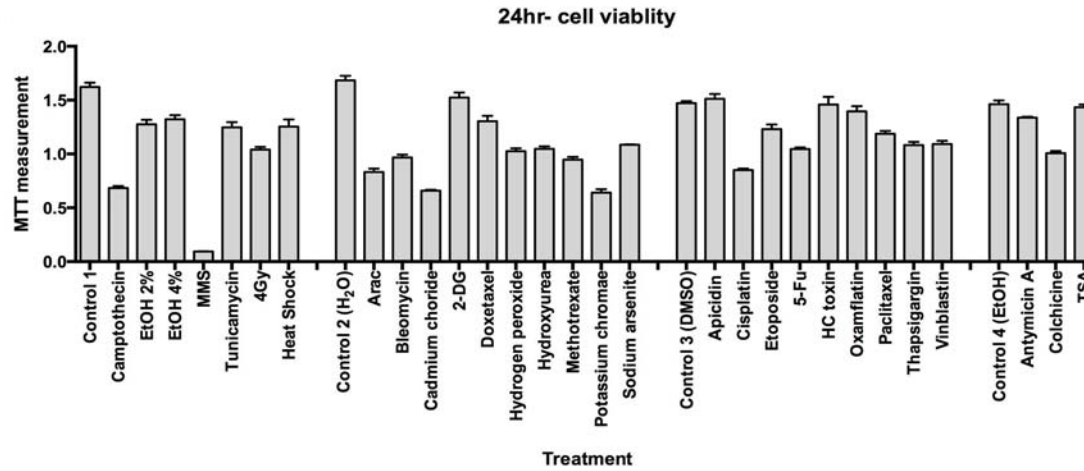
Figure S3. Cell viability results of treatments with the agents at the dose for microarray. (A) Trypan blue exclusion test at 4 hours of treatment. (B) MTT assay at 24 hours of treatment; y-axis represents arbitrary scale of readout.
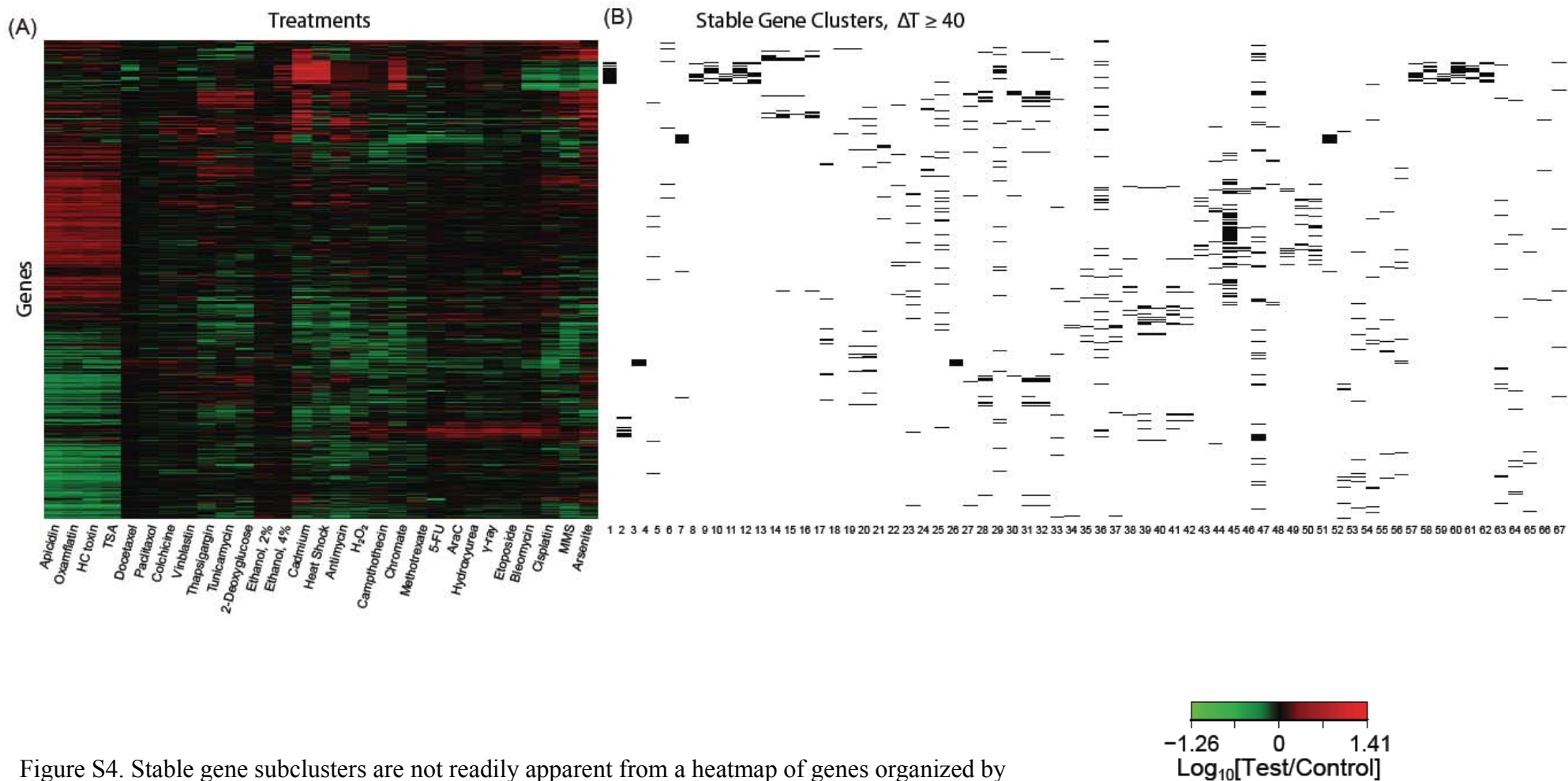
Figure S4. Stable gene subclusters are not readily apparent from a heatmap of genes organized by hierarchical clustering. (A) The heatmap contains 1682 genes that were significantly (p< 0.01, t-test) perturbed at least 1.7-fold, relative to the control, by one or more stress agents. The genes in the heatmap were organized by hierarchically clustering with complete linkage based on their error-weighted Pearson distances. (B) Stable gene subclusters ($\Delta T \geq 40$) were identified from the 1682 genes using coupled two-way clustering (CTWC) with superparamagnetic clustering. The columns represent gene subclusters and the rows represent genes that are ordered to match (A). Minimum gene subcluster size was set to 15 and CTWC was run with a gene depth of 5 and sample depth of 1.

(A) Chromate/Genotoxic Agents

(B) Chromate/Cadmium/Heat Shock

Network Shapes

- ☐ Cytokine
- ⬚ Growth Factor
- ⬭ Chemical / Drug/ Toxicant
- ◇ Enzyme
- ▯ G-protein Coupled Receptor
- ⬚ Ion Channel
- ▽ Kinase
- ▭ Ligand-dependent Nuclear Receptor
- ◇ Peptidase
- △ Phosphatase
- ⬭ Transcription Regulator
- ⬡ Translation Regulator
- ⬭ Transmembrane Receptor
- ⏢ Transporter
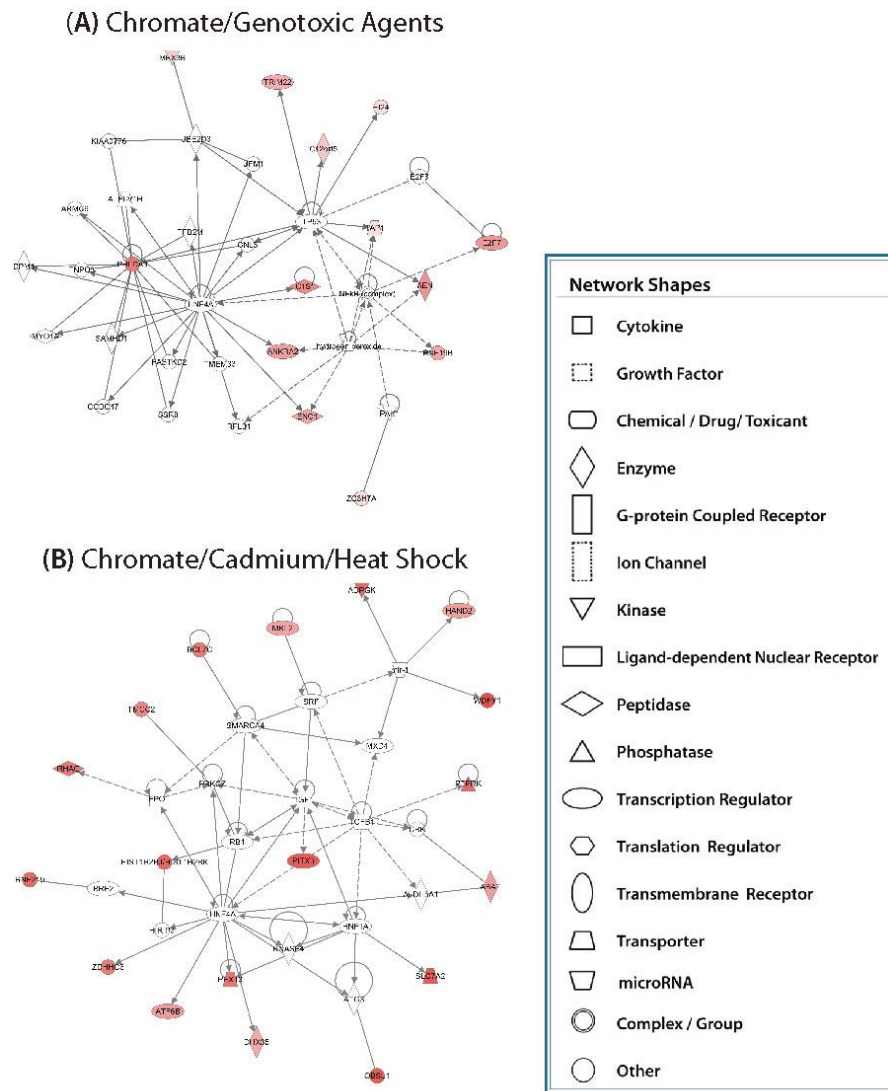- ▽ microRNA
- ◎ Complex / Group
- ○ Other

Figure S5. Chromate induces pleiotropic stress response that involved in genotoxic and non-genotoxic modes (Figure 3). Ingenuity Pathway Analysis was applied to the (A) genotoxic subcluster and the (B) subcluster that was up-regulated in response to chromate, cadmium, and heat shock but are either repressed or not perturbed by other genotoxic agents. Nodes corresponding to genes in the subclusters that were up-regulated are colored pink or red representing low or high induction, respectively. Empty nodes indicate not in the subclusters. Solid lines denote a direct interaction, and dashed lines denote an indirect interaction.
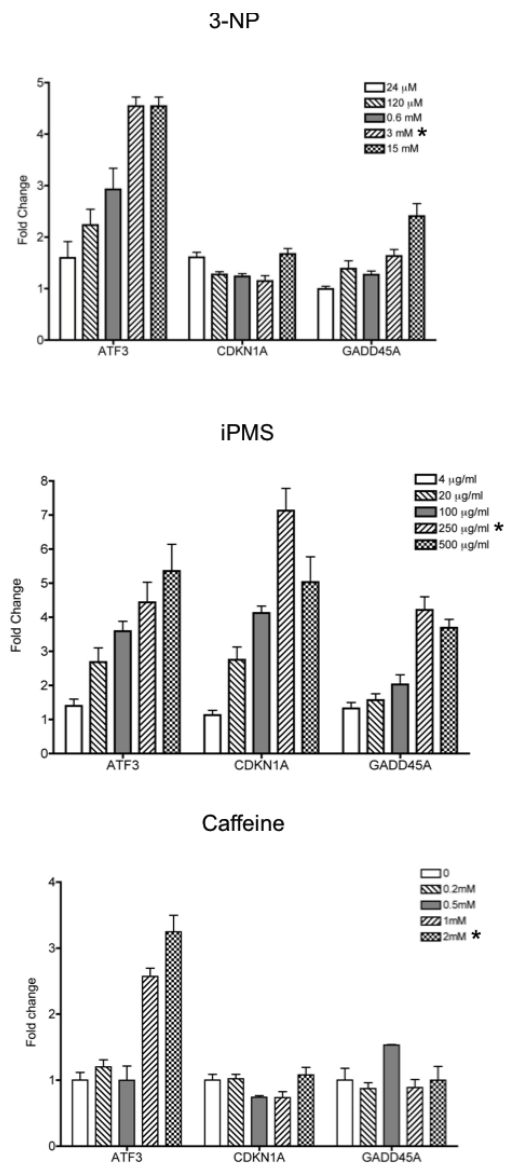
Figure S6. Workflow for identifying stress response gene subclusters and hypotheses regarding pathways with the subclusters. Transcriptome measurements are performed for a diverse array of stress agents (Table 1). Then coupled two-way clustering with superparamagnetic clustering (CTWC/SPC) is used to identify stable subclusters of genes. The subclusters are then visualized and subjected to Ingenuity Pathway Analysis to identify potential associations between the subclusters and known stress response

Figure S7. Quantitative RT-PCR measurements for a panel of known stress response genes (*ATF3, CDKN1, GADD45A*) for dose response profiles of testing agents. The doses that showed the most robust induction of one or more genes out of these three stress response genes were selected for subsequent microarray analyses. The selected doses are indicated with asterisks (3 mM for 3-NP, 250 µg/ml for iPMS, and 2 mM for caffeine).