

## Supplementary Information

### Supplementary Figure Legends

**Supplementary Figure 1.** Statin Response is Dose-Dependent, Independent of Mating Type and does not Induce Petite Formation. (a) A plot of optical densities after 5.5 hours of growth (following ergosterol pre-depletion, see methods) in the presence of varying concentrations of statin is shown. (b) Epistasis values are shown for zinc and copper at varying concentrations. (c) Epistasis values are shown under a variety of conditions in both yeast mating types. (d) Yeast were pretreated with statin overnight and then cultured for six hours in fresh media containing either ZnSO<sub>4</sub> (2 mM) or CuSO<sub>4</sub> (1 mM). Serial dilutions were plated on YEP-dextrose or YEP-glycerol. (e) Epistasis values are shown for yeast treated with the indicated concentration of ketoconazole as well as either ZnSO<sub>4</sub> (2 mM) or CuSO<sub>4</sub> (1 mM).

**Supplementary Figure 2.** Gene expression response to statin and metal treatment. Measurement of gene expression following treatment of yeast cultures with statin, zinc/copper or both resulted in six clusters of genes. Two of these were primarily responsive to metal treatment and four were primarily responsive to statin treatment. Yellow indicates upregulation relative to untreated cells whereas blue indicates downregulation relative to untreated cells. The scale shown is log<sub>2</sub>.

## Supplementary Tables

| Metabolite              | Solvent         | Concentration ( $\mu\text{M}$ ) | Epistasis | notes         |
|-------------------------|-----------------|---------------------------------|-----------|---------------|
| 5-hydroxytryptophan     | DMSO            | 100                             | ND        |               |
| astaxanthin             | DMSO            | 8.7                             | ND        |               |
| betaine                 | water           | 1000                            | 0.02      |               |
| biotin                  | water           | 1250                            | -0.01     |               |
| caffeine                | water           | 100                             | 0.02      |               |
| calcium chloride        | water           | 1000                            | 0.00      |               |
| $\beta$ -carotene       | chloroform      | 5.1                             | ND        |               |
|                         | 1:1 EtOH/Tween- |                                 |           |               |
| cholesterol             | 80              | 10                              | -0.03     |               |
| chromium (III) chloride | water           | 5                               | 0.07      |               |
| citrate                 | water           | 1000                            | 0.00      |               |
| coenzyme A              | water           | 13.3                            | 0.00      |               |
| coenzyme Q10            | chloroform      | 140                             | ND        |               |
| copper chloride         | water           | 3400                            | 0.39      |               |
| copper sulfate          | water           | 1000                            | 0.52      |               |
| curcumin                | DMSO            | 5                               | 0.13      |               |
| eicosapentaenoic acid   | DMSO            | 170                             | ND        |               |
| daidzein                | DMSO            | 42.4                            | -0.16     |               |
| D-pantothenic acid      | water           | 100                             | 0.08      |               |
| docosahexaenoic acid    | DMSO            | 150                             | ND        |               |
| FAD                     | water           | 9.88                            | -0.05     |               |
| folic acid              | DMSO            | 250                             | ND        |               |
| folinic acid            | water           | 10                              | 0.04      |               |
| genistein               | DMSO            | 76.97                           | -0.08     |               |
| L-glutamate             | water           | 1000                            | 0.03      |               |
| iron (II) sulfate       | water           | 50                              | 0.07      |               |
| iron (III) chloride     | water           | 500                             | 0.15      |               |
| L-arginine              | water           | 1000                            | 0.06      |               |
| L-ascorbic acid         | water           | 24.4                            | -0.02     |               |
| L-glutathione (reduced) | water           | 100                             | -0.02     | prepare daily |
| linolenic acid          | NA              | 12.9 mM                         | ND        |               |
| lithium chloride        | water           | 100                             | -0.02     |               |
| manganese (II) chloride | water           | 3000                            | 0.22      |               |
| methylcobalamin         | water           | 2                               | 0.01      |               |
| mevalonic acid          | water           | 270 mM                          | 0.67      |               |
| myoinositol             | water           | 100                             | -0.01     |               |
| sodium selenite         | water           | 5                               | 0.09      |               |
| NAD                     | water           | 7.5                             | -0.08     |               |
| nickel sulfate          | water           | 100                             | 0.05      |               |
| nicotinic acid          | water           | 100                             | -0.03     |               |
| propionic acid          | NA              | 53 mM                           | ND        |               |
| pyridoxal 5' phosphate  | water           | 10                              | -0.03     |               |
| pyruvic acid            | water           | 1000                            | -0.08     |               |
| resveratrol             | EtOH            | 100                             | -0.06     |               |

|                     |       |       |       |                  |
|---------------------|-------|-------|-------|------------------|
| riboflavin          | water | 50    | 0.03  |                  |
| taurine             | water | 461   | -0.01 |                  |
| tetrahydrobiopterin | water | 50    | -0.06 |                  |
| thiamine            |       |       |       |                  |
| pyrophosphate       | water | 23    | 0.06  |                  |
| zinc chloride       | water | 2000  | 0.18  |                  |
| zinc sulfate        | water | 2000  | 0.26  |                  |
| vitamin B12         | water | 16.84 | ND    |                  |
| hydrogen peroxide   | water | 1000  | 0.13  | prepare<br>daily |

**Supplementary Table 1. Metabolite Concentrations and Epistasis Values**

| <b>Cluster</b>   | <b>Term name<sup>§</sup></b>    | <b>% Query</b> | <b>% Total</b> | <b>P-value</b> |
|------------------|---------------------------------|----------------|----------------|----------------|
| <b>Statin #1</b> | sterol metabolic process        | 8 of 71        | 47 of 6345     | 2.08E-05       |
|                  | response to stress              | 23 of 71       | 587 of 6345    | 2.33E-05       |
|                  | lipid biosynthetic process      | 9 of 71        | 148 of 6345    | 1.98E-02       |
| <b>Statin #2</b> | no significant enrichment       |                |                |                |
| <b>Statin #3</b> | amino acid metabolic process    | 22 of 74       | 243 of 6345    | 1.26E-11       |
|                  | nucleotide metabolic process    | 11 of 74       | 145 of 6345    | 5.70E-04       |
| <b>Statin #4</b> | sterol biosynthetic process     | 5 of 26        | 36 of 6345     | 8.33E-05       |
|                  | lipid metabolic process         | 7 of 26        | 272 of 6345    | 2.51E-02       |
| <b>Metal #1</b>  | oxidative phosphorylation       | 9 of 49        | 54 of 6345     | 1.11E-07       |
|                  | amino acid biosynthetic process | 11 of 49       | 134 of 6345    | 2.17E-06       |
|                  | ion binding                     | 22 of 49       | 836 of 6345    | 2.92E-05       |
| <b>Metal #2</b>  | cation transport                | 19 of 43       | 137 of 6345    | 1.56E-18       |

## Supplementary Table 2. GO Analysis of Statin and Metal Regulated Genes

<sup>§</sup>up to three representative GO terms chosen for each cluster