Supplemental Methods: Microarray Analysis (1)

All microarrays in this study were normalized together using GCRMA[1,2]. Log fold changes between conditions and the statistical significance of these fold changes were determined using contrasts in Linear Models for MicroArrays (LIMMA)[3]. Both GCRMA and LIMMA are implemented in Bioconductor[4] which runs under R[5]. Thee data been deposited in the gene expression omnibus GEO[6], series accession number GSE22873. A cutoff of a Benjamini-Hochberg false discovery rate (PBH) <0.05 was used[7,8].

The KEGG Pathways[9] associated with differential expression between conditions were identified with Pathway Express[10] which identifies the pathways associated with differential expression in a way that takes pathway structure into account. Pathways with a gamma p-value calculated using the hypergeometric distribution and corrected for false discoveries of ≤0.05 are taken to be statistically significantly associated with differential expression of a given contrast.

Perturbation factors, as referred to in the manuscript text, are defined and discussed in detail by Draghici and collegues[10] are effective $\log_2$ fold changes which take into account both any actual change in the expression of the gene and the effect of those genes in the pathway upstream from it upon the pathway at the protein level.

The perturbation factor, PF(*g*), of a gene product, g, in a pathway is defined by Draghici et al.[10] as follows:

$$PF(g) = \log_2 FC + \sum \beta_{ug} \frac{PF(u)}{N_{ds}(u)}$$

Where is the base 2 logarithm of the fold-change of the gene. The second term is a sum over all of the genes, u, whose products are upstream in the pathway from gene g. $PF(u)$ is the perturbation factor of gene product u. β_{ug} is positive if gene product u is an activator in the pathway, and negative if it is an inhibitor. $N_{ds}(u)$ is the number of gene products downstream from gene u. For a thorough discussion of the implications of this equation, see the original paper by Draghici et. al.[10]

Supplemental Methods: Microarray Analysis Literature Citations (2)

1. Wu, Z., and Irizarry, R.A. (2005) Stochastic models inspired by hybridization theory for short oligonucleotide arrays. *J Comput Biol* **12**, 882-893
2. Wu, Z., Irizarry, R.A., Gentleman, R., Murillo, F.M., and Spencer, F. (2004) A model based background adjustment for oligonucleotide expression. *J. Am. Stat. Assoc.* **99**, 909-917
3. Smyth, G.K. (2004) Linear models and empirical Bayes methods for assessing differential expression in microarray experiments. *Statistical Applications in Genetics and Molecular Biology*. **3**:Article 3, http://www.bepress.com/sagmb/vol3/iss1/art3/
4. Gentleman, R.C., Carey, V.J., Bates, D.M., Bolstad, B., Dettling, M., Dudoit, S., Ellis, B., Gautier, L., Ge, Y., Gentry, J., Hornik, K., Hothorn, T., Huber, W., Iacus, S., Irizarry, R., Leisch, F., Li, C., Maechler, M., Rossini, A.J., Sawitzki, G., Smith, C., Smyth, G., Tierney, L., Yang, J.Y., and Zhang, J. (2004) Bioconductor: open software development for computational biology and bioinformatics. *Genome Biol.* **5**, R80
5. Ihaka, R., and Gentleman, R.R. (1996) A language for data analysis and graphics. *Journal of Computational and Graphical Statistics*. **5**, 299-314
6. Barrett, T., Suzek, T.O., Troup, D.B., Wilhite, S.E., Ngau, W.C., Ledoux, P., Rudnev, D., Lash, A.E., Fujibuchi, W., and Edgar, R. (2005) NCBI GEO: mining millions of expression profiles—database and tools. *Nucleic Acids Res* **33**,D562-566
7. Benjamini, Y. and Hochberg, Y. (1995) Controllling the false discovery rate; a practical and powerful approach to multiple testing. *J. Roy. Stat. Ser. B.* **57**, 289-300
8. Reiner, A., Yekutieli, D., and Benhamini, Y. (2003) Identifying differentially expressed genes using false discovery rate controlling procedures. *Bioinformatics* **19**, 68-375
9. Kanehisa, M., Goto, S., Kawashima, S., Okuno, Y., and Hattori, M. (2004) The KEGG resource for deciphering the genome. *Nucleic Acids Res* **32**, D277-280
10. Draghici, S., Khatri, P., Tarca, A.L., Amin, K., Done, A., Voichita, C., Georgescu, C., and Romero, R. (2007) A systems biology approach for pathway level analysis. *Genome Res* **17**, 1537-1545