

## SUPPLEMENTAL TABLE AND FIGURE LEGENDS

**Supplemental Table 1. Genes expression clusters.** Table listing the genes in each of the 14 expression clusters in Figure 1A.

**Supplemental Table 2. Putative transcription factors regulating genes in each cluster.** For each cluster, the top enriched transcription factors, source of ChIP-seq data [1-3], and enrichment statistics as calculated by Enrichr [4] are provided.

**Supplemental Table 3. Highly connected nodes within Cluster 1 network.** The top 5 nodes based on network centrality (betweenness) as calculated by esyN [5].

**Supplemental Table 4. Putative NRF2 target genes in Cluster 1.** NRF2 target genes in Cluster 1, as called by Enrichr [4].

**Supplemental Figure S1. TBOOH treatment increases *HIF1A* mRNA expression in multiple cell types.** (A) *HIF1A* expression in HepG2 cells treated for 8 hours with vehicle control or TBOOH. Gene expression values were measured by quantitative reverse transcription PCR, and normalized relative to *ACTB* expression. (B) Same as (A) only for MCF7 breast cancer cell. (C) Same as (A) only for MDA-MB-231 breast cancer cells. Gene expression changes were measured after 8 hours of TBOOH exposure and, to avoid confounding cell death gene expression signatures, TBOOH treatments for each cell line were based on a concentration that resulted in 80% cell viability after 24 hours (24hr EC<sub>80</sub>). The 24hr EC<sub>80</sub> for HepG2 was 300μM, for MCF7 was 80μM, and for MDA-MB-231 was 100μM. Asterisks represent p-values for TBOOH versus vehicle for each cell type (\*\*p ≤ 0.001; \*p ≤ 0.01; \*p ≤ 0.05, Welch's t-test).

**Supplemental Figure S2. An NRF2 binding site at the *HIF1A* locus.** (A) An NRF2 ChIP-seq peak at the human *HIF1A* locus. ChIP-seq data are the same as described in Figure 3A, only zoomed out to show more of the genomic region around *HIF1A*. The center column represents compiled topologically associated domain (TAD) boundaries from high-throughput chromosome conformation capture (Hi-C) datasets [6, 7]. A region that is called as a TAD in eight out of eight profiled cell types is highlighted with a box. Overall, four genes have transcription start sites that fall within this TAD: *HIF1A* and three noncoding RNAs (*FLJ22447* and the *HIF1A* antisense RNAs *HIF1A-AS1* and *HIF1A-AS2*). (B) Zoomed in ChIP-seq data from A, equivalent to region presented in Figure 3A. The "Chromatin State" track summarizes chromatin state calls across 127 human tissues and cell types by the Roadmap Epigenomics Project [8]. The height of the color is proportional to the number of cell/tissue types where given chromatin state is called; for example, the prominent red peak near the start of the *HIF1A* gene represents a region that is called as an active transcription start site (TSS) in almost all cells or tissues. The NRF2 ChIP-seq peak overlaps a prominent enhancer (yellow) region at this locus.

**Supplemental Figure S3. Inducible ARE binding at the *HIF1A* locus.** (A) NRF2 ChIP-seq fold enrichment values for the ARE-containing peak at the human *HIF1A* locus. Fold enrichment values from vehicle/control treated lymphoblastoid cells (DMSO; DMSO = dimethylsulfoxide) and from sulforaphane treated lymphoblastoid cells. As in Figure 3A, data are from Chorley et al. ChIP-seq fold enrichment values are calculated relative to negative controls (merged mock and input samples) from the same cells. Fold enrichment values were calculated using MACS2. (B) Same as (A), only for ChIP-seq enrichment significance [-log<sub>10</sub>(q-value)] as calculated by

MACS2. **(C)** Electrophoretic mobility shift assay (EMSA) using either the ARE from the *NQO1* promoter or the ARE from the *HIF1A* enhancer as a labeled probe, as indicated. Each labeled probe was incubated with increasing amounts of nuclear protein lysate from MCF7 cells that had either been treated with 0.1% ethanol (EtOH; vehicle/control treatment) or with 10 $\mu$ M menadione for 8 hours. Lanes marked with “ $\emptyset$ ” contain no protein (labeled probe only) and all other lanes have increasing amounts (0.5  $\mu$ g, 1  $\mu$ g, or 2  $\mu$ g) of the indicated lysate. Binding levels at the uppermost band (Band 1) for each probe are increased approximately 1.5-fold for both the *NQO1* and *HIF1A* probe ( $1.49 \pm 0.25$ , and  $1.57 \pm 0.10$ , respectively). Binding levels do not increase for Band 2, so Band 1 is the ROS-responsive band in MCF7 lysates. Probe sequences are the same as in Figure 3C, however, an IRDye labeled *HIF1A* ARE probe was used in this experiment. **(D)** Quantitation of binding levels from (C). For each lane, Band 1 levels were normalized relative to Band 2, and MCF7+menadione binding signals were compared to MCF7+EtOH binding signals for the corresponding lysate concentration. The bar graph represents average of these comparisons for each probe ( $\pm$  standard deviation); values over 1 represent a stronger binding signal in lysates from menadione treated cells.

## SUPPLEMENTAL REFERENCES

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**Supplemental Table 2**

<b>Cluster</b>	<b>Transcription Factor</b>	<b>Source</b>	<b>P-value</b>	<b>Adj P-value</b>	<b>Z-score</b>	<b>Combined score</b>
1	NFE2L2	CHEA	3.15E-11	3.22E-09	-1.64	39.62
	ZBTB7A	ENCODE	2.89E-08	1.47E-06	-1.62	28.16
	UBTF	ENCODE	1.18E-07	4.03E-06	-1.6	25.5
2	RUNX1	CHEA	7.09E-06	0.00053	-1.67	19.78
	E2F6	ENCODE	1.15E-05	0.00053	-1.63	18.51
	NFE2L2	CHEA	1.53E-05	0.00053	-1.57	17.37
3	--	--	--	--	--	--
4	UBTF	ENCODE	1.77E-10	1.70E-08	-1.67	37.55
5	--	--	--	--	--	--
6	E2F4	ENCODE	8.97E-31	8.88E-29	-1.77	122.45
	SIN3A	ENCODE	1.90E-07	7.02E-06	-1.73	26.78
	NFYB	ENCODE	2.13E-07	7.02E-06	-1.62	24.87
7	--	--	--	--	--	--
8	--	--	--	--	--	--
9	TP53	CHEA	1.27E-05	0.000701	-1.68	18.92
10	HNF4A	ENCODE	9.05E-29	9.42E-27	-1.73	111.52
	E2F4	ENCODE	1.63E-17	8.48E-16	-1.73	67
	FOXM1	ENCODE	1.36E-15	4.70E-14	-1.79	61.39
11	CEBPD	ENCODE	9.36E-06	0.000852	-1.73	20.06
12	TCF3	ENCODE	1.5E-06	0.000138	-1.63	21.91
13	--	--	--	--	--	--
14	E2F4	ENCODE	3.85E-06	0.000358	-1.77	22.07

**Supplemental Table 3**

<b>Gene</b>	<b>Node Betweenness Score</b>
SQSTM1	1
UBE2D1	0.91
CBL	0.68
TRIM21	0.66
HIF1A	0.53

**Supplemental Table 4**

<b>Putative NRF2 Targets in Cluster 1</b>					
<i>ABCC5</i>	<i>GCLC</i>	<i>KLF5</i>	<i>OSGIN1</i>	<i>SLC25A30</i>	<i>TMEFF1</i>
<i>ASF1A</i>	<i>GCLM</i>	<i>KLHL21</i>	<i>PAWR</i>	<i>SLC40A1</i>	<i>TMEM159</i>
<i>C16ORF72</i>	<i>GPCPD1</i>	<i>KRAS</i>	<i>PDLIM3</i>	<i>SLC7A11</i>	<i>TNFRSF1A</i>
<i>C5ORF30</i>	<i>GRB10</i>	<i>LMCD1</i>	<i>PIK3CD</i>	<i>SQSTM1</i>	<i>TRIB1</i>
<i>DLX2</i>	<i>GRK5</i>	<i>LRP8</i>	<i>PXDC1</i>	<i>SRXN1</i>	<i>TSKU</i>
<i>DUSP4</i>	<i>HMOX1</i>	<i>MAFF</i>	<i>RGMB</i>	<i>ST3GAL4</i>	<i>TUBE1</i>
<i>F3</i>	<i>IGFBP3</i>	<i>MAFG</i>	<i>RGS10</i>	<i>STC2</i>	<i>ZNF330</i>
<i>FBLIM1</i>	<i>JAG1</i>	<i>MEGF9</i>	<i>RICTOR</i>	<i>STIM2</i>	<i>ZYX</i>
<i>FOPNL</i>	<i>KLF4</i>	<i>MSANTD3</i>	<i>SGK223</i>	<i>TMC7</i>	

**Figure S1**

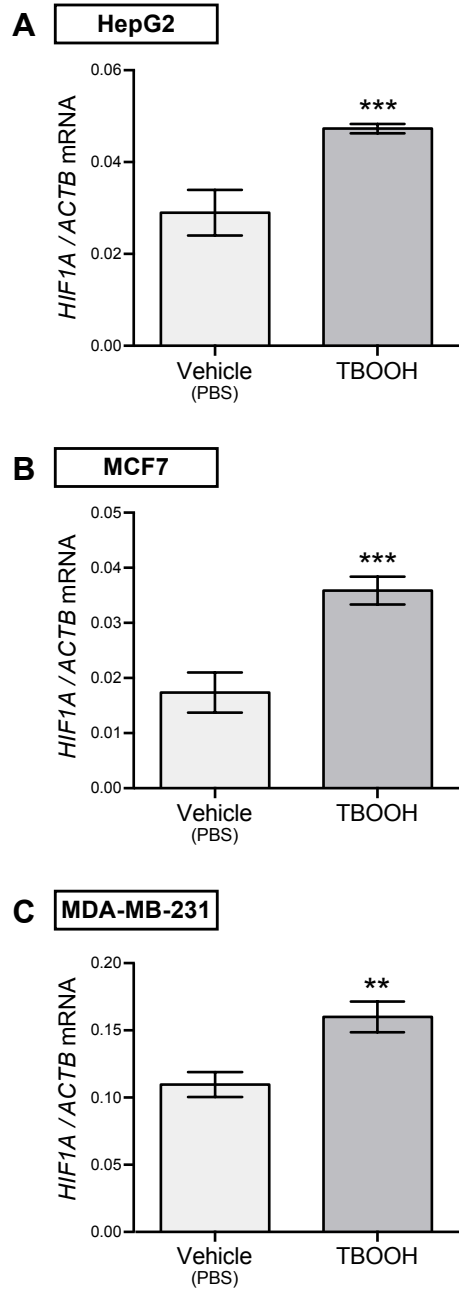
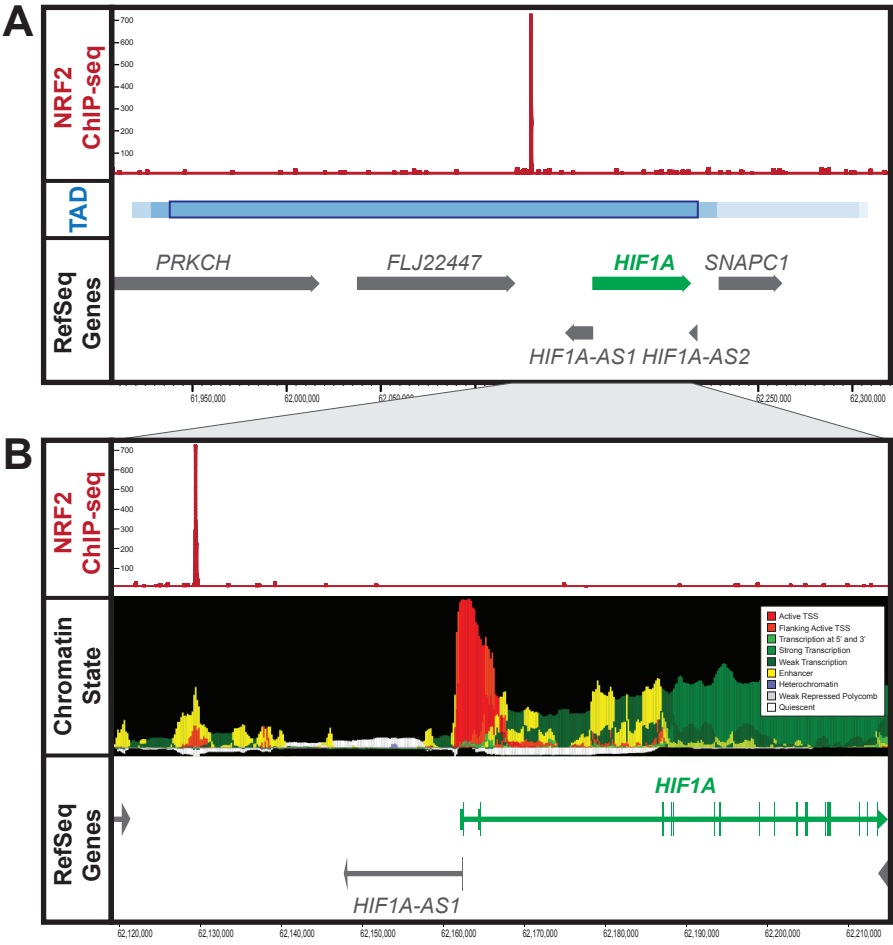


Figure S2



**Figure S3**

