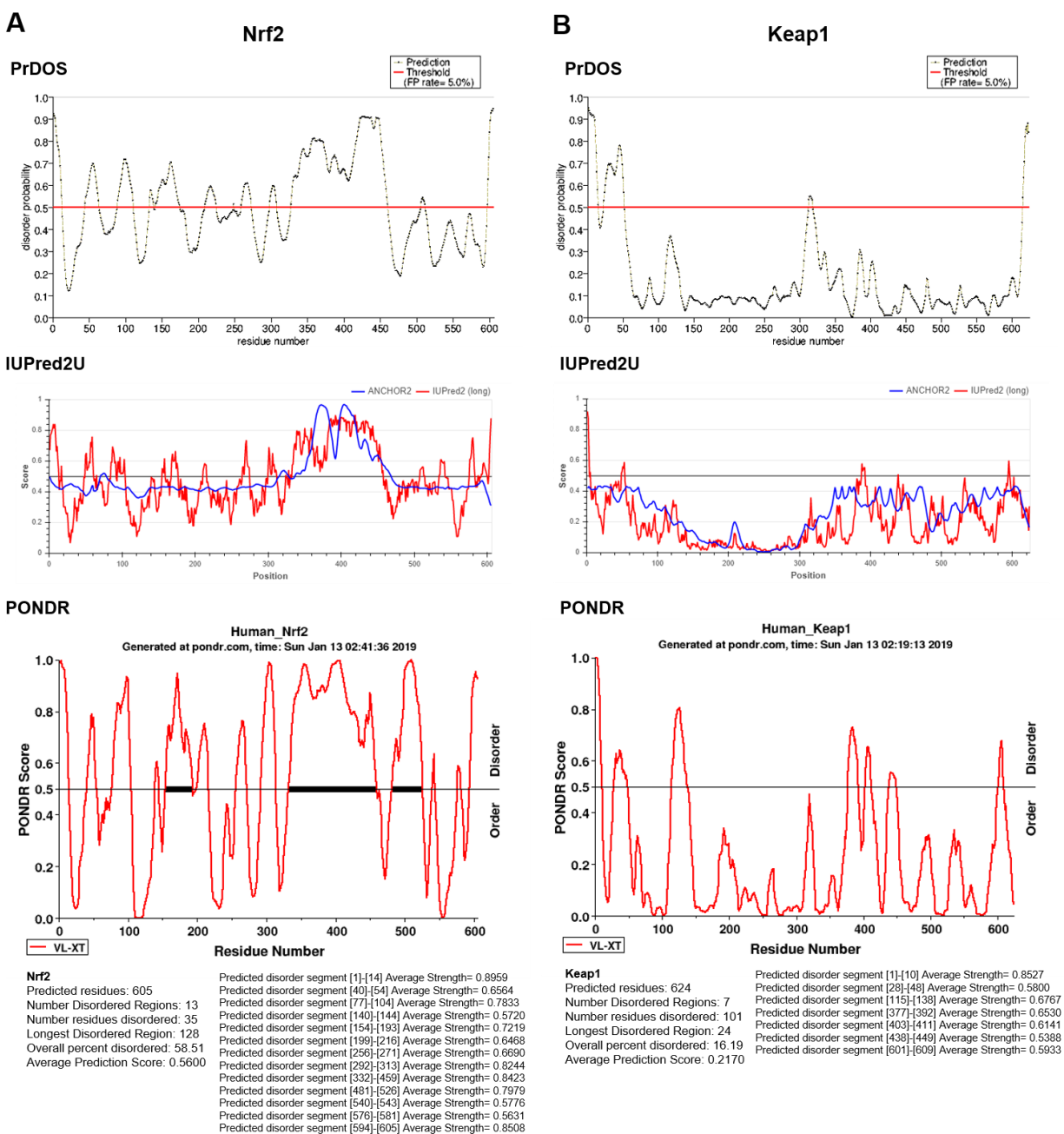
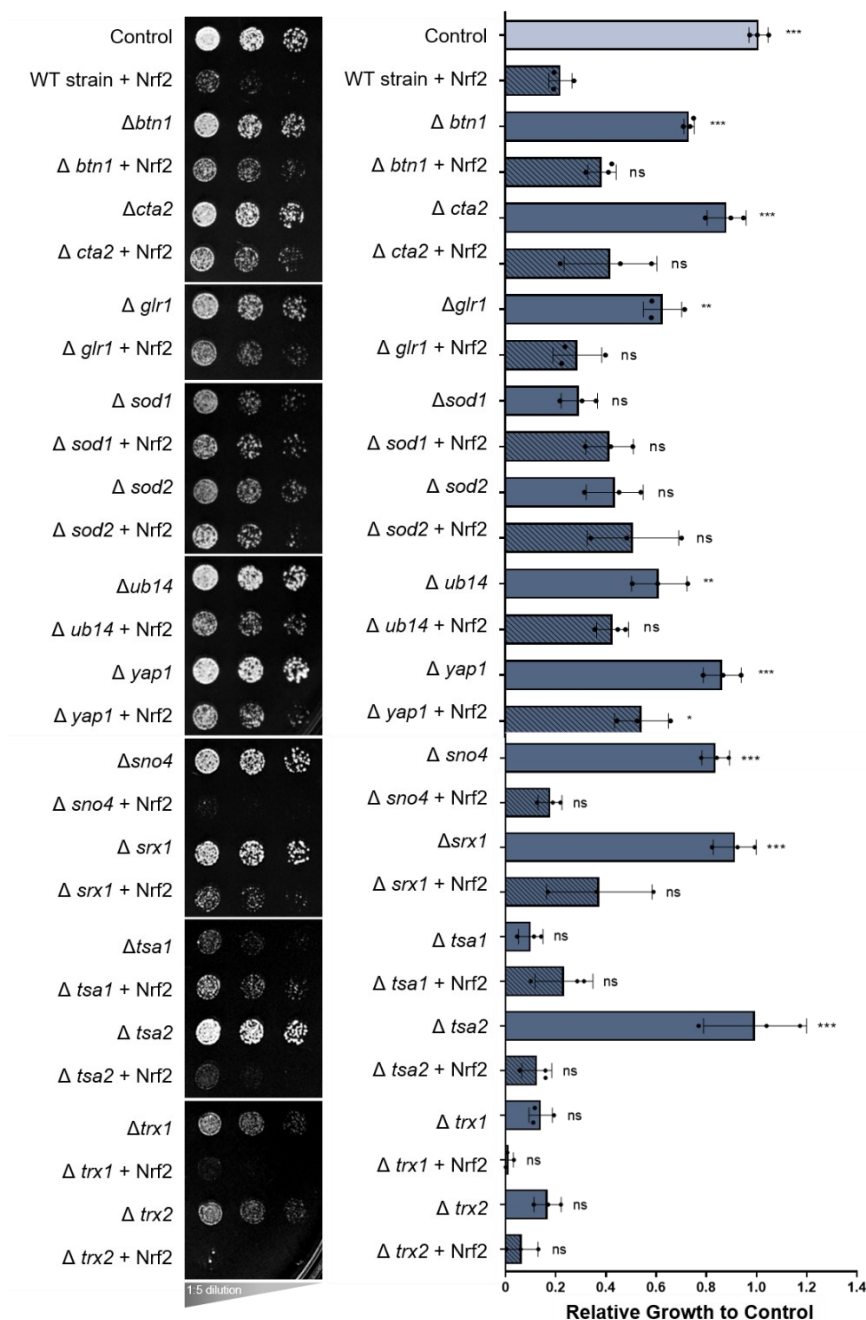


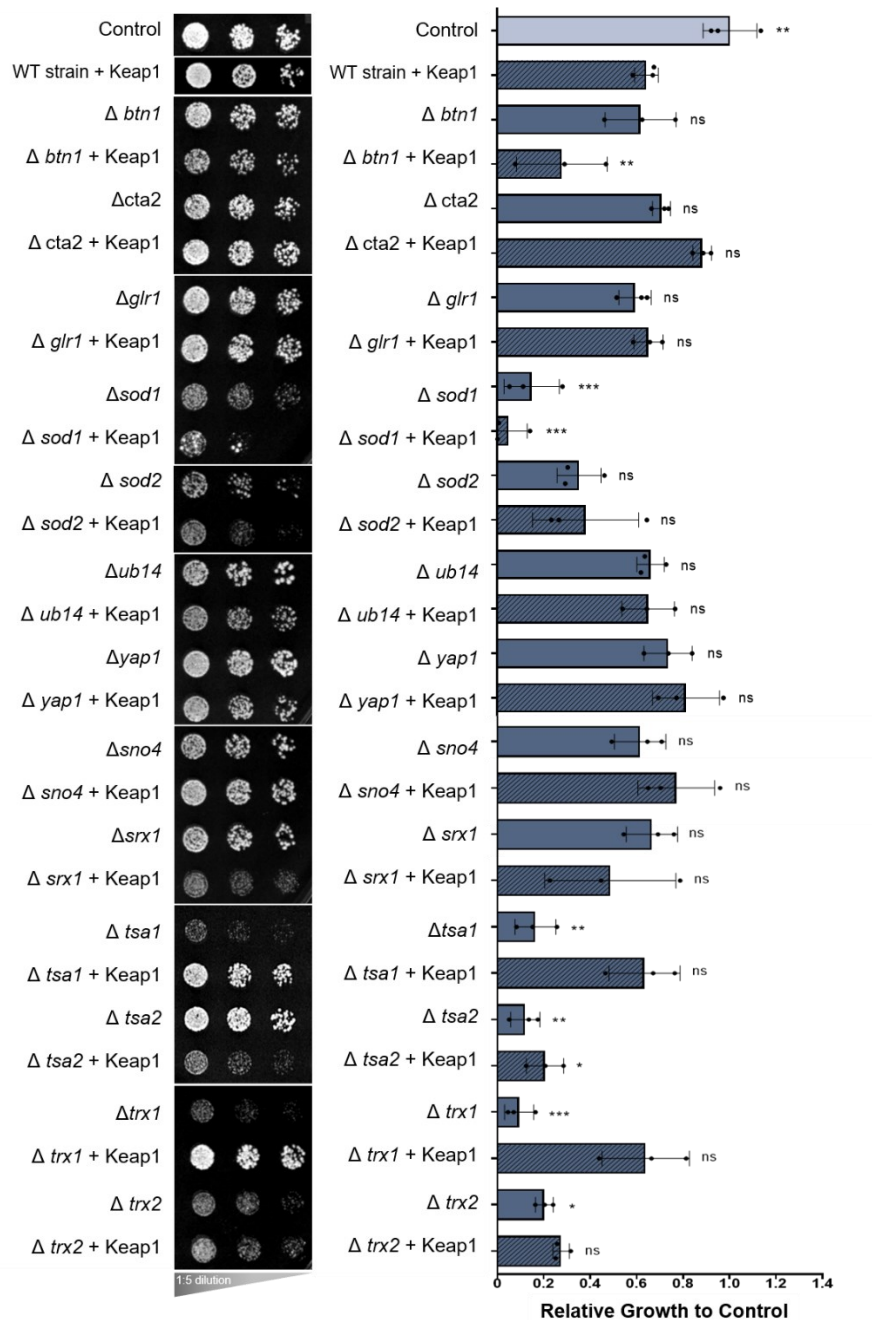
## Supplementary Figures



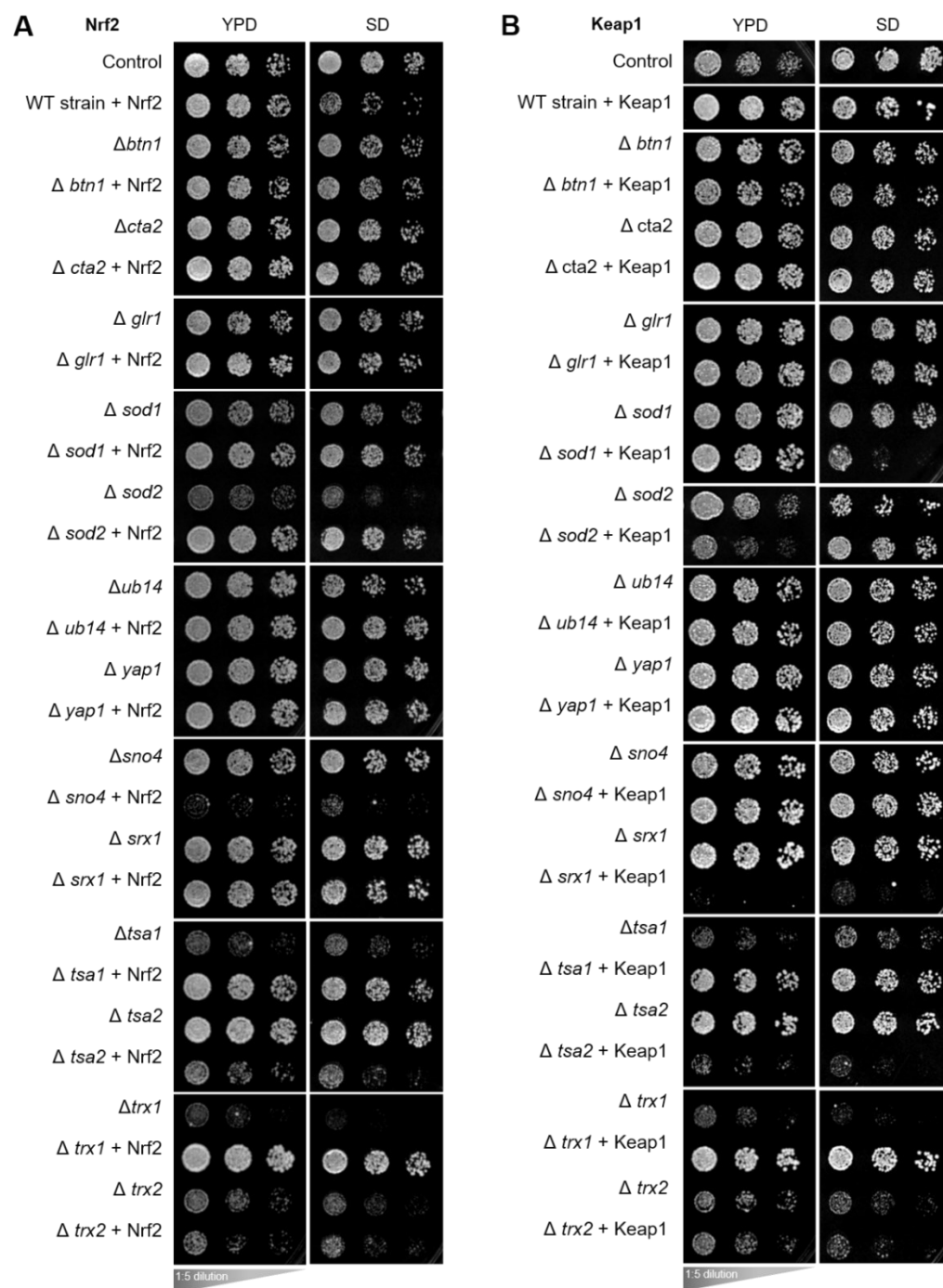
**Figure S1: Individual disordered profile plots for PrDOS, IUPred2U, and PONDR.** Disorder probability prediction graphs for Nrf2 and Keap1 are shown for all three prediction algorithms. A score of >0.5 predicts disorder and a score of <0.5 predicts order.



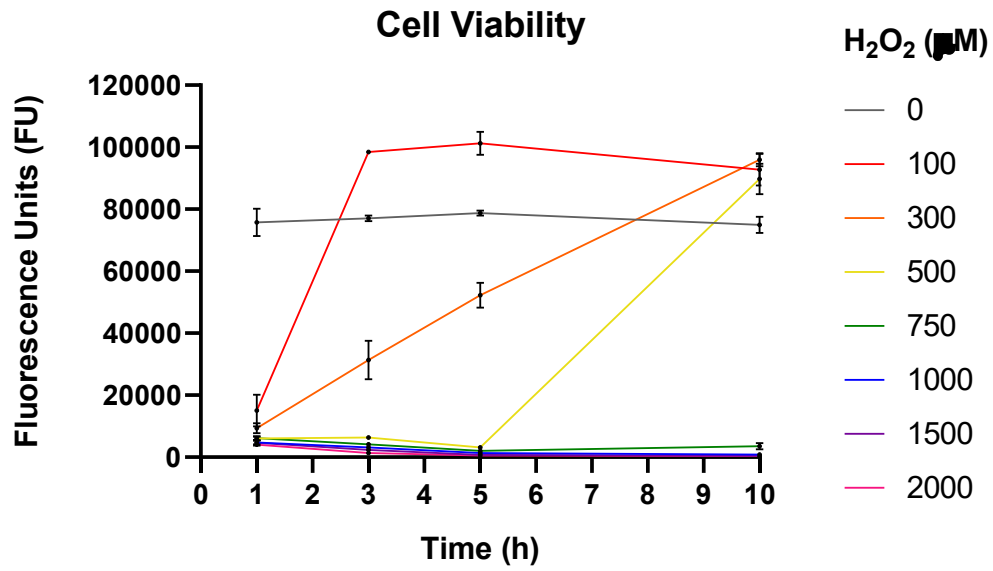
**Figure S2: Full panel of growth assays for Nrf2 expression in yeast oxidative stress deletion strains.** Growth was quantified relative to control. Means derived from three biological replicates were used during analysis. Means were analyzed using one-way ANOVA followed by Tukey's post hoc test. Data are expressed as mean ± SD.  $p < 0.05$  was considered statistically significant; \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ .



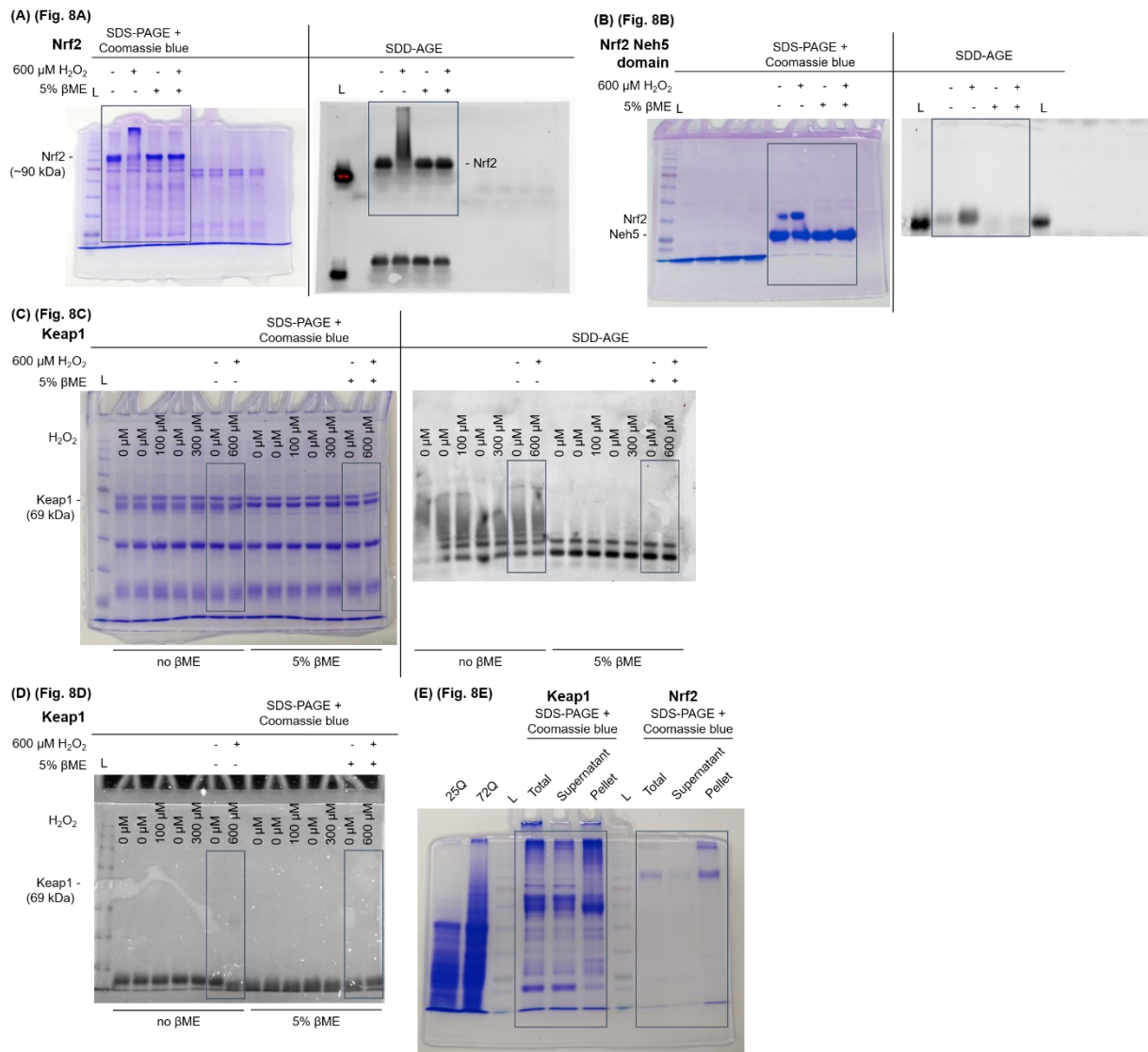
**Figure S3: Full panel of growth assays for Keap1 expression in yeast oxidative stress deletion strains.** Growth was quantified relative to control. Means derived from three biological replicates were used during analysis. Means were analyzed using one-way ANOVA followed by Tukey's post hoc test. Data are expressed as mean  $\pm$  SD.  $p < 0.05$  was considered statistically significant; \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ .



**Figure S4: Growth assay control plates for all yeast oxidative stress deletion studies.** Yeast- extract-peptone-dextrose (YPD) and selective dextrose (SD) control plates are shown for **(A)** Nrf2 and **(B)** Keap1 experiments. Note that some deletions strains harbour an inherent toxic growth phenotype observed even on control media.



**Figure S5: Optimization of hydrogen peroxide treatment concentration and duration.** Non-transfected HeLa cells were treated with various concentrations of hydrogen peroxide for 1, 3, 5, and 10 h and cell viability was assessed (measured by ATP levels which indicates the presence of metabolically active cells).



**Figure S6: Full uncropped and unadjusted blots for all Coomassie blue and SDD-AGE experiments in Figure 8. (A-E) Nrf2 or Keap1 purified protein or protein domains were treated with  $H_2O_2 \pm \beta$ ME for 30 mins.**

	Species	Specific Name	UniProt Code
<b>Nrf2</b>	Human	<i>Homo sapiens</i>	Q16236
	Chimpanzee	<i>Pan troglodytes</i>	H2RAX5
	Orangutan	<i>Pongo abelii</i>	H2P7Y6
	Rhesus macaque	<i>Macaca mulatta</i>	F7GPD8
	Marmoset	<i>Callithrix jacchus</i>	F7CLI8
	Galago	<i>Otolemur garnettii</i>	H0Y129
	Mouse	<i>Mus musculus</i>	Q60795
	Rat	<i>Rattus norvegicus</i>	O54968
	Golden hamster	<i>Mesocricetus auratus</i>	A0A1U7QFW3
	Rabbit	<i>Oryctolagus cuniculus</i>	G1SEJ1
	Cow	<i>Bos taurus</i>	Q5NUA6
	Bat	<i>Myotis lucifugus</i>	G1P184
	Elephant	<i>Loxodonta africana</i>	G3TGN3
	Chicken	<i>Gallus gallus</i>	F1P315
	Zebrafish	<i>Danio rerio</i>	Q7ZVI2
<b>Keap1</b>	Human	<i>Homo sapiens</i>	Q14145
	Chimpanzee	<i>Pan troglodytes</i>	H2QFB9
	Orangutan	<i>Pongo abelii</i>	Q5R774
	Rhesus macaque	<i>Macaca mulatta</i>	G7NL03
	Marmoset	<i>Callithrix jacchus</i>	F7HDW0
	Galago	<i>Otolemur garnettii</i>	H0X799
	Mouse	<i>Mus musculus</i>	Q9Z2X8
	Golden hamster	<i>Mesocricetus auratus</i>	A0A1U7R3C2
	Rat	<i>Rattus norvegicus</i>	P57790
	Rabbit	<i>Oryctolagus cuniculus</i>	G1SFF4
	Cow	<i>Bos taurus</i>	A7MBG4
	Bat	<i>Myotis lucifugus</i>	G1PRL8
	Elephant	<i>Loxodonta africana</i>	G3TJS6
	Chicken	<i>Gallus gallus</i>	Q5ZL67
	Zebrafish	<i>Danio rerio</i>	E7FB56

**Table S1: The 15 species observed in cysteine analysis studies.** The species name, specific name, and UniProt code are shown.

<b>Gene</b>	<b>Protein</b>	<b>Function (UniProt Consortium)</b>	<b>UniProt Code</b>
<i>BTN2</i>	Protein BTN2	V-SNARE binding protein that facilitates specific protein retrieval from a late endosome to the Golgi. Modulates the rate of arginine uptake. Involved in pH homeostasis.	P53286
<i>CTA1</i>	Peroxisomal catalase A	Occurs in almost all aerobically respiring organisms and serves to protect cells from the toxic effects of hydrogen peroxide.	P15202
<i>GLR1</i>	Glutathione reductase	Maintains high levels of reduced glutathione in the cytosol.	P41921
<i>SOD1</i>	Superoxide dismutase	Destroys radicals that are normally produced within the cells and which are toxic to biological systems.	P00445
<i>SOD2</i>	Superoxide dismutase		S4VPL7
<i>UBI4</i>	Polyubiquitin	Becomes conjugated to proteins, marking them for selective degradation via the ubiquitin-26S proteasome system.	P0CG63
<i>YAP1</i>	AP-1-like transcription factor YAP1	Transcription activator involved in oxidative stress response and redox homeostasis. Regulates the transcription of genes encoding antioxidant enzymes and components of thiol-reducing pathways.	P19880
<i>SNO4</i>	Probable glutathione-independent glyoxalase SNO4	Catalyzes the conversion of methylglyoxal (MG) to D-lactate in a single glutathione (GSH)-independent step. May play a role in detoxifying endogenously produced glyoxals. Involved in protection against reactive oxygen species (ROS).	Q04902
<i>SRX1</i>	Sulfiredoxin	Contributes to oxidative stress resistance by reducing cysteine-sulfinic acid formed under exposure to oxidants in the peroxiredoxin TSA1. May catalyze the reduction in a multi-step process by acting both as a specific phosphotransferase and as thioltransferase.	P36077
<i>TSA1</i>	Peroxiredoxin TSA1	Thiol-specific peroxidase catalyzing the reduction of hydrogen peroxide and organic hydroperoxides to water and alcohols, respectively.	P34760
<i>TSA2</i>	Peroxiredoxin TSA2		Q04120
<i>TRX1</i>	Thioredoxin-1	Participates as a hydrogen donor in redox reactions through the reversible oxidation of its active center dithiol to a disulfide, accompanied by the transfer of 2 electrons and 2 protons.	P22217
<i>TRX2</i>	Thioredoxin-2		P22803

**Table S2: Yeast oxidative stress gene deletion strains used in this study.** The gene name, protein name, function (obtained from UniProt), and UniProt code are shown.