Electronic Supplementary Material (ESI) for Molecular Omics.

SUPPORTING INFORMATION

Delineating Toxicity Mechanisms Associated with MRI Contrast Enhancement through a Multidimensional Toxicogenomic Profiling of Gadolinium

Roger M. Pallares,[1] Dahlia D. An,[1] Solène Hébert,[1] David Faulkner,[1] Alex Loguinov,[2] Michael Proctor,[2] Jonathan A. Villalobos,[1] Kathleen A. Bjornstad,[1] Chris J. Rosen,[1] Christopher Vulpe,[2] and Rebecca J. Abergel[1,3,]*

Affiliations:

[1]Chemical Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA, 94720, USA

[2]Center for Environmental and Human Toxicology, Department of Physiological Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL, 32611, USA

[3]Department of Nuclear Engineering, University of California, Berkeley, CA, 94720, USA

*E-mail: abergel@berkeley.edu

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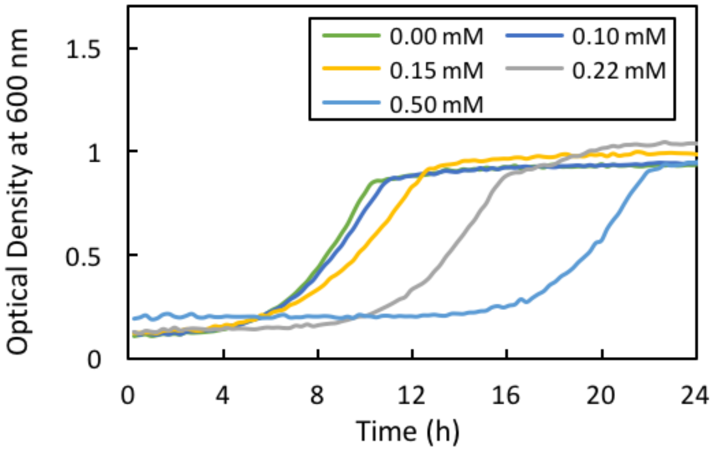
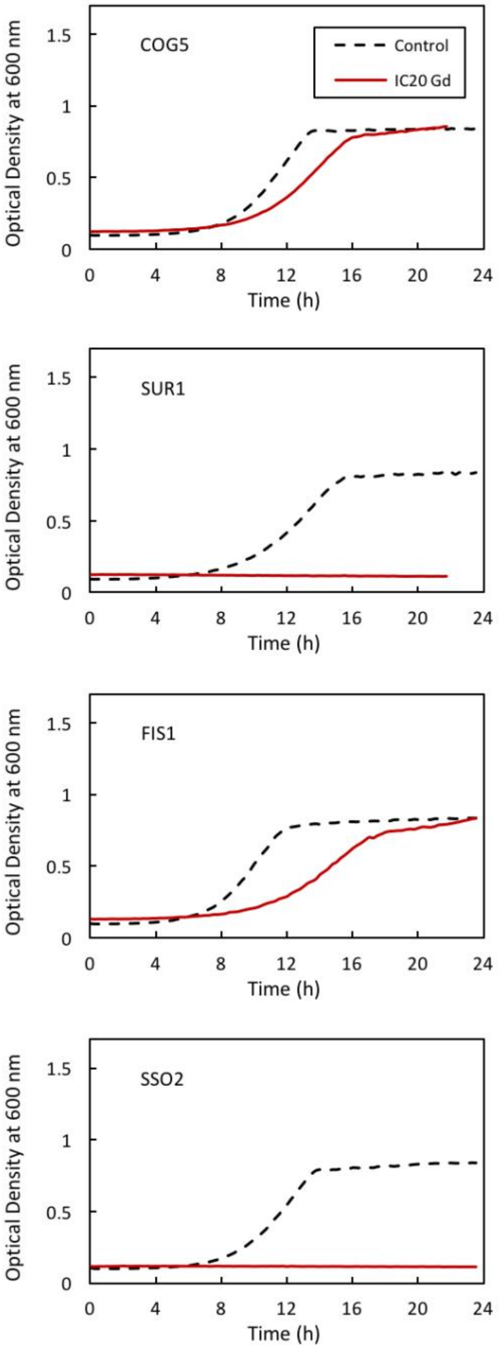


Figure S1. Growth curves of wild-type strain under different gadolinium concentrations for IC determinations. The IC_5, IC_{10} and IC_{20} were determined at 0.09, 0.12 and 0.16 mM Gd^{3+}.



Non-competitive assay
$\text{Log}_2 = -3.53$

Competitive assay
$\text{Log}_2 = -2.72$

Non-competitive assay
$\text{Log}_2 = -6.17$

Competitive assay
$\text{Log}_2 = -6.61$

Non-competitive assay
$\text{Log}_2 = -4.62$

Competitive assay
$\text{Log}_2 = -2.85$

Non-competitive assay
$\text{Log}_2 = -6.25$

Competitive assay
$\text{Log}_2 = -5.65$

Figure S2. Non-competitive growth of representative strains in absence and presence of IC_{20} concentrations of gadolinium. The inhibition growth values after IC_{20} gadolinium treatments in $\log_2$ scale under non-competitive conditions (black) are compared to the values obtained under competitive conditions (grey). The full list of strains and their inhibition growth values under competitive conditions are presented in Dataset S1.

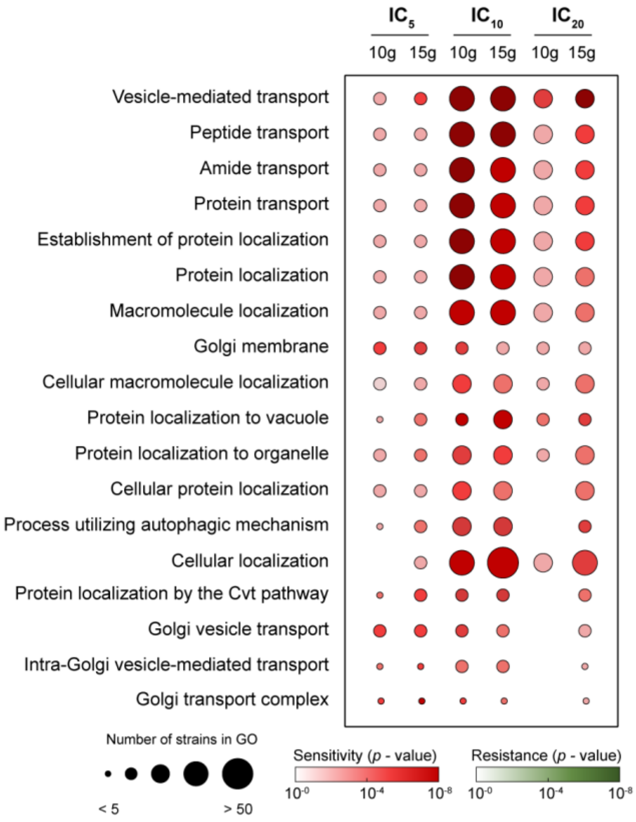


Figure S3. Top 18 overrepresented GO terms under the different gadolinium treatments.

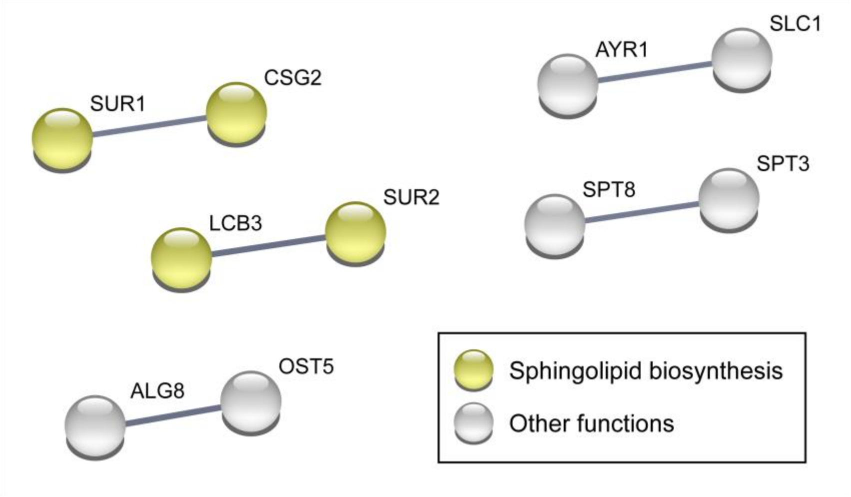


Figure S4. Protein-protein interaction network analysis identified key protein pairs involved in yeast response to gadolinium. Network of proteins coded by genes whose deletion promoted sensitivity to gadolinium. All genes affected by at least 3 gadolinium treatments were considered (*n* = 63). Proteins with more than one connection were displayed in Figure 5a. Proteins without connections were not displayed for clarity. The network analysis was performed with STRING and a cutoff for confidence interactions of 0.90 (highest confidence).

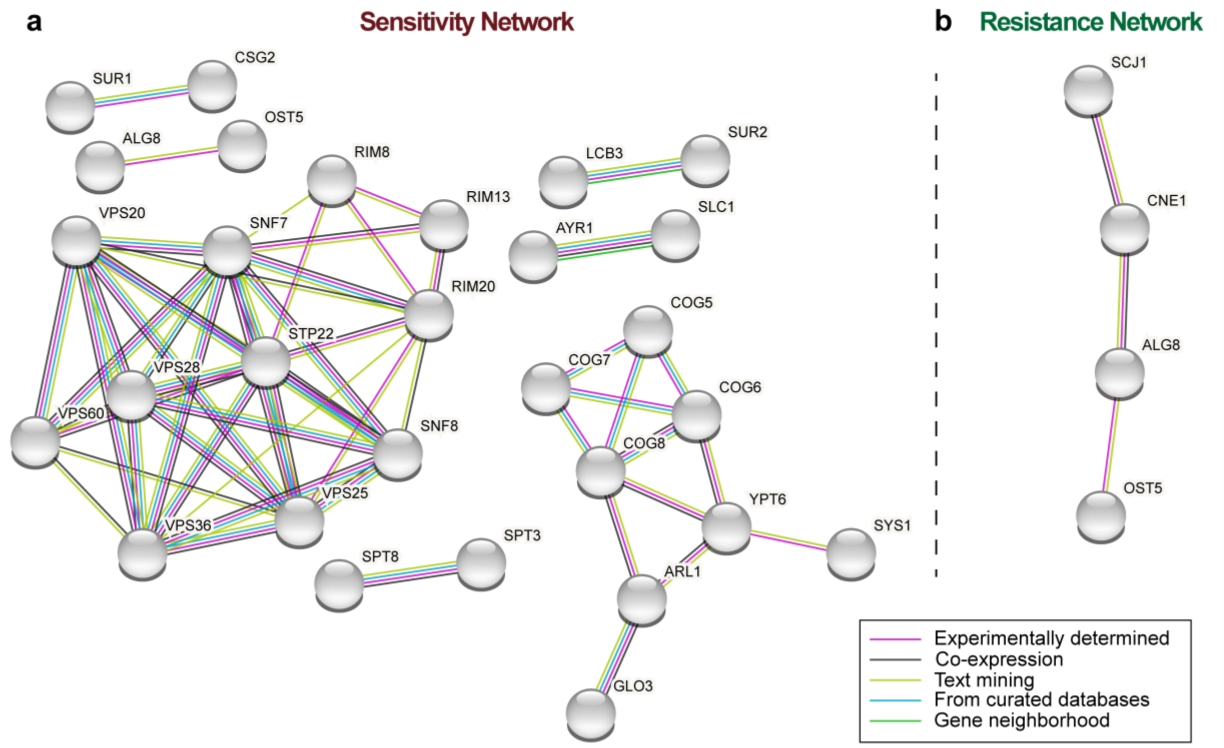


Figure S5. Protein-protein interaction network analysis with protein-protein associations. (**a**) Network of proteins coded by genes whose deletion promoted sensitivity to gadolinium. All genes affected in at least 3 experimental conditions were considered (*n* = 63). (**b**) Network of proteins coded by genes whose deletion promoted resistance to gadolinium. All genes affected in at least 2 experimental conditions were considered (*n* = 30). Proteins without connections were not displayed for clarity. The network analysis was performed with STRING and a cutoff for confidence interactions of 0.90 (highest confidence).

Table S1. Parameters of protein-protein interaction network analysis

	Sensitive Network	**Resistant Network**
Number of edges	56	3
Average node degree	1.84	0.207
Average local clustering coefficient	0.415	0.069
PPI enrichment p-value	$< 10^{-16}$	0.000935

Table S2. Human orthologues of genes associated with gadolinium toxicity in yeast

Yeast gene	Human gene ortholog	Human protein	Pathologies
SCJ1	DNAJB11	DnaJ heat shock protein family member B11	Kidney disease that results on interstitial fibrosis[1]
CNE1	CALR	Calreticulin	Myelofibrosis[2]
CNE1	CLGN	Calmegin	Kidney fibrosis through MAPK signaling pathway[3]
CNE1	CANX	Calnexin	
ALG8	ALG8	ALG8 alpha-1,3-glucosyltransferase	
APS1	AP1S1	Adaptor related protein complex 1 subunit sigma 1	MEDNIK syndrome and hepatic fibrosis[4]
APS1	AP1S2	Adaptor related protein complex 1 subunit sigma 2	
APS1	AP1S3	Adaptor related protein complex 1 subunit sigma 3	Skin autoimmune disorder[5]
APL6	AP3B1	Adaptor related protein complex 3 subunit beta 1	Pulmonary fibrosis[6,7]
APL6	AP3B	Adaptor related protein complex 3 subunit beta 2	Pulmonary fibrosis[6]
YPL191C	MINDY1	MINDY lysine 48 deubiquitinase 1	Acute respiratory distress syndrome and pulmonary fibrosis[8]
YPL191C	MINDY1	MINDY lysine 48 deubiquitinase 1	Acute respiratory distress syndrome and pulmonary fibrosis[8]
UBP15	USP7	Ubiquitin specific peptidase 7	Cardiac fibrosis[9]
TOR1	mTOR	Mechanistic target of rapamycin kinase	Pulmonary and cardiac fibroses[10,11]
YDR018C	LCLAT1	Lysocardiolipin acyltransferase 1	Pulmonary fibrosis[12]
YDR018C	AGPAT3	1-acylglycerol-3-phosphate O-acyltransferase 3	
YDR018C	AGPAT4	1-acylglycerol-3-phosphate O-acyltransferase 4	
YDR018C	AGPAT5	1-acylglycerol-3-phosphate O-acyltransferase 5	
CAT1	CAT	Catalase	
GLO2	HAGH	Hydroxyacylglutathione hydrolase	
GLO2	HAGHL	Hydroxyacylglutathione hydrolase like	
GLO2	PNKD	PNKD metallo-beta-lactamase domain containing	
UNG1	UNG	Uracil DNA glycosylase	
PHM7	TMEM63A	Transmembrane protein 63A	
PHM7	TMEM63B	Transmembrane protein 63B	
MOH1	YPEL1	Yippee like 1	
MOH1	YPEL2	Yippee like 2	
MOH1	YPEL3	Yippee like 3	
MOH1	YPEL4	Yippee like 4	Pulmonary fibrosis[13]
MOH1	YPEL5	Yippee like 5	
CEX	SCYL1	SCY1 like pseudokinase 1	
CEX	SCYL3	SCY1 like pseudokinase 3	

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