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OMICS Group International is an amalgamation of Open Access publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 500 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS International also organizes 500 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

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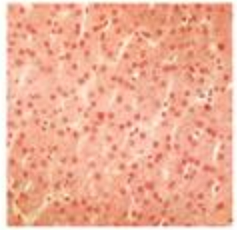
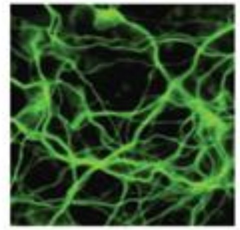
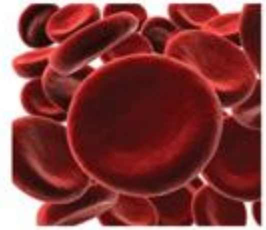
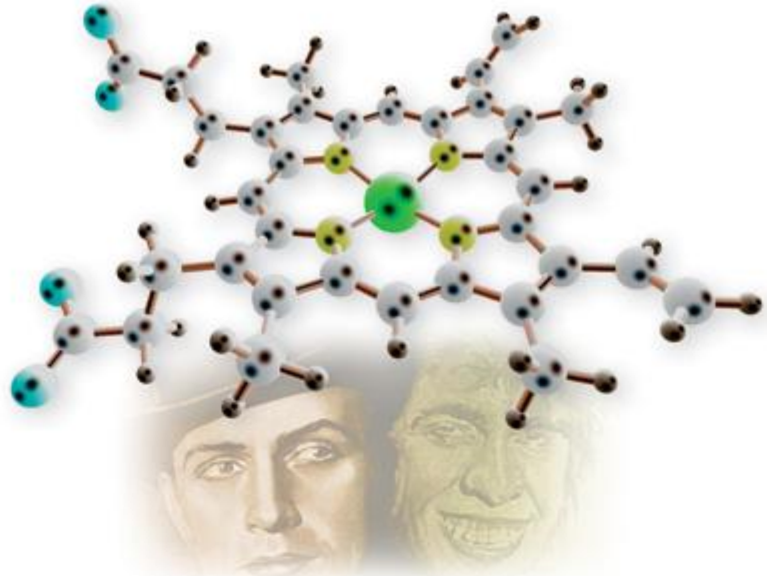
OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 300 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS International has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, SantaClara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

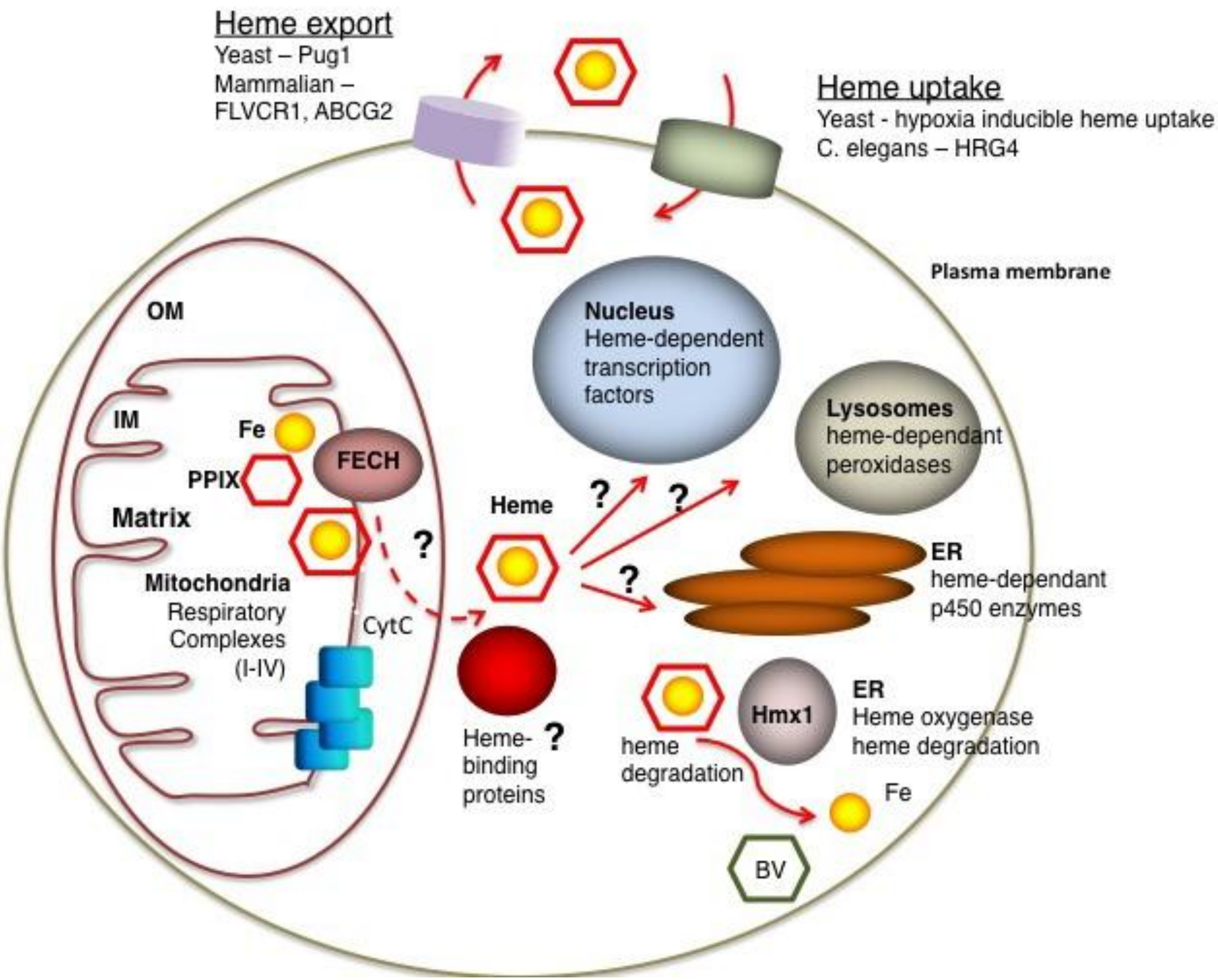
HEME BIOLOGY

The Secret Life of Heme in Regulating Diverse Biological Processes



ZHANG LI
EDITOR

World Scientific


Heme export
Yeast – Pug1
Mammalian –
FLVCR1, ABCG2
Heme uptake
Yeast - hypoxia inducible heme uptake
C. elegans – HRG4
Plasma membrane
OM
IM
Fe
FECH
PPIX
Matrix
Mitochondria
Respiratory
Complexes
(I-IV)
CytC
?
Heme
?
?
?
Nucleus
Heme-dependent
transcription
factors
Lysosomes
heme-dependant
peroxidases
ER
heme-dependant
p450 enzymes
Heme-
binding
proteins
?
heme
degradation
Hmx1
ER
Heme oxygenase
heme degradation
Fe
BV

Worldwide Prevalence of Anemia, by severity

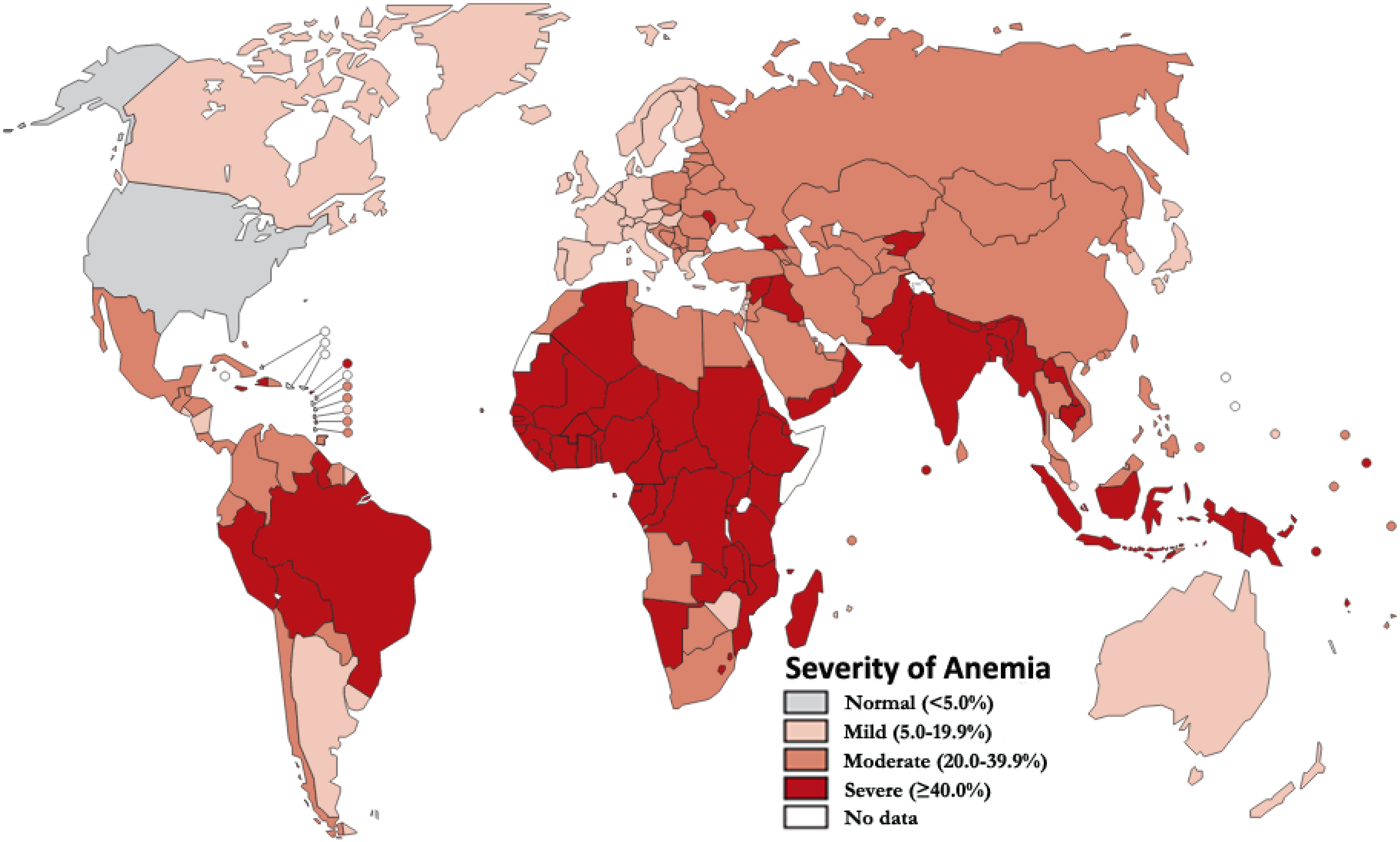
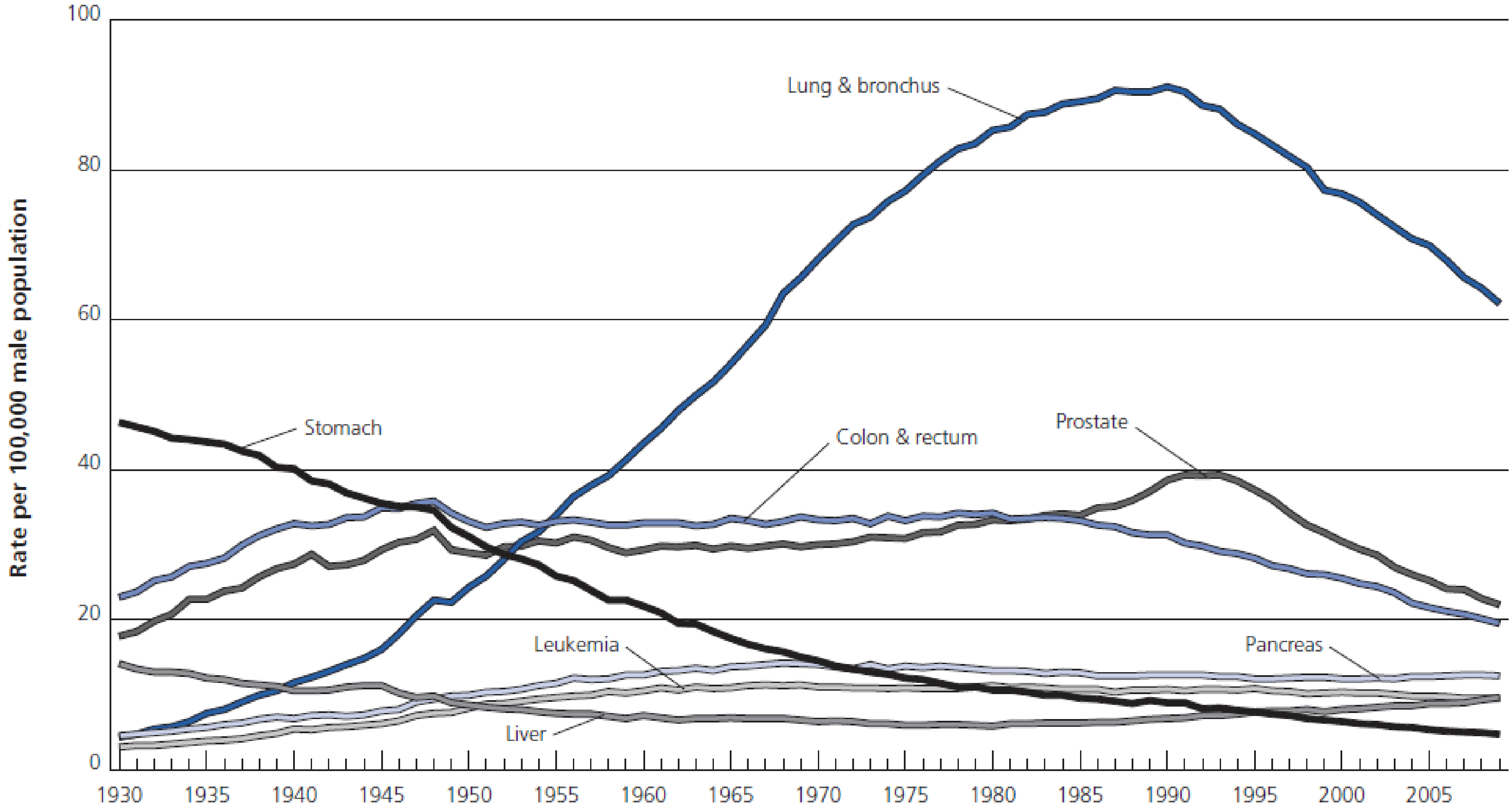


Table 1. Summary of epidemiological studies investigating the association between dietary intake of heme iron and/or red meat w various diseases.

Disease	Diet Intake	HR/OR/RR (95% CI) Highest *vs.* Lowest	Reported Association	Number of Pzarticipants	Age (Years)	Years of Follow Up	Diet Assessment Method
Colorectal cancer	Red Meat	HR = 1.24 (1.12–1.36)	+	567,169	50–71	8.2	124-item FFQ
Colon cancer	High heme and low chlorophyll	RR = 1.58 (0.99–2.54)	+	58,279 Men	55–69	9.3	150-item semi quantitative FFQ
Colorectal cancer with KRAS mutation	Heme Iron	HR = 1.71 (1.15–2.57)	+	4026	55–69	7.3	150-item FFQ
Esophageal squamous cell carcinoma	Red Meat	HR = 1.79 (1.07–3.01)	+	494,979	50–71	10	124-item FFQ
	Heme Iron	HR = 1.47 (0.99–2.20)					
Esophageal cancer	Red Meat	HR = 1.51 (1.09–2.08)	+	567,169	50–71	8.2	124-item FFQ
	Heme Iron	OR = 3.04 (1.20–7.72)	+	124 esophageal, 154 stomach cancer and [illegible]	≥21		100-item Short health habit and history [illegible]
Lung cancer	Red Meat	HR_{Men} = 1.11 (0.79–1.56)	No Association	99,579	55–74	8	124-item FFQ
		HR_{Women} = 1.30 (0.87–1.95)					
	Red Meat	HR = 1.2 (1.10–1.31)	+	567,169		8.2	124-item FFQ
	Red Meat	HR_{Men} = 1.22 (1.09–1.38)	+	278,380 men and 189,596 women	50–71	8	124-item FFQ
		HR_{Women} = 1.13 (0.97–1.32)					
	Heme Iron	HR_{Men} = 1.25 (1.07–1.45)					
		HR_{Women} = 1.18 (0.99–1.42)					
Type 2 Diabetes	Red Meat	RR = 1.44 (0.92–2.24)	moderate, non-significant	91,246 U.S women	26–46	8	133-item semiquantitative FFQ
	Red Meat	RR = 1.63 (1.26–2.10)	+	38,394 Men	40–75	12	131-item semiquantitative FFQ
	Heme Iron	RR = 1.28 (1.04–1.58)	+	35,698 postmenopausal women	55–69	11	127-item FFQ
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	131-item expanded

Age-adjusted Cancer Death Rates*, Males by Site, US, 1930-2009

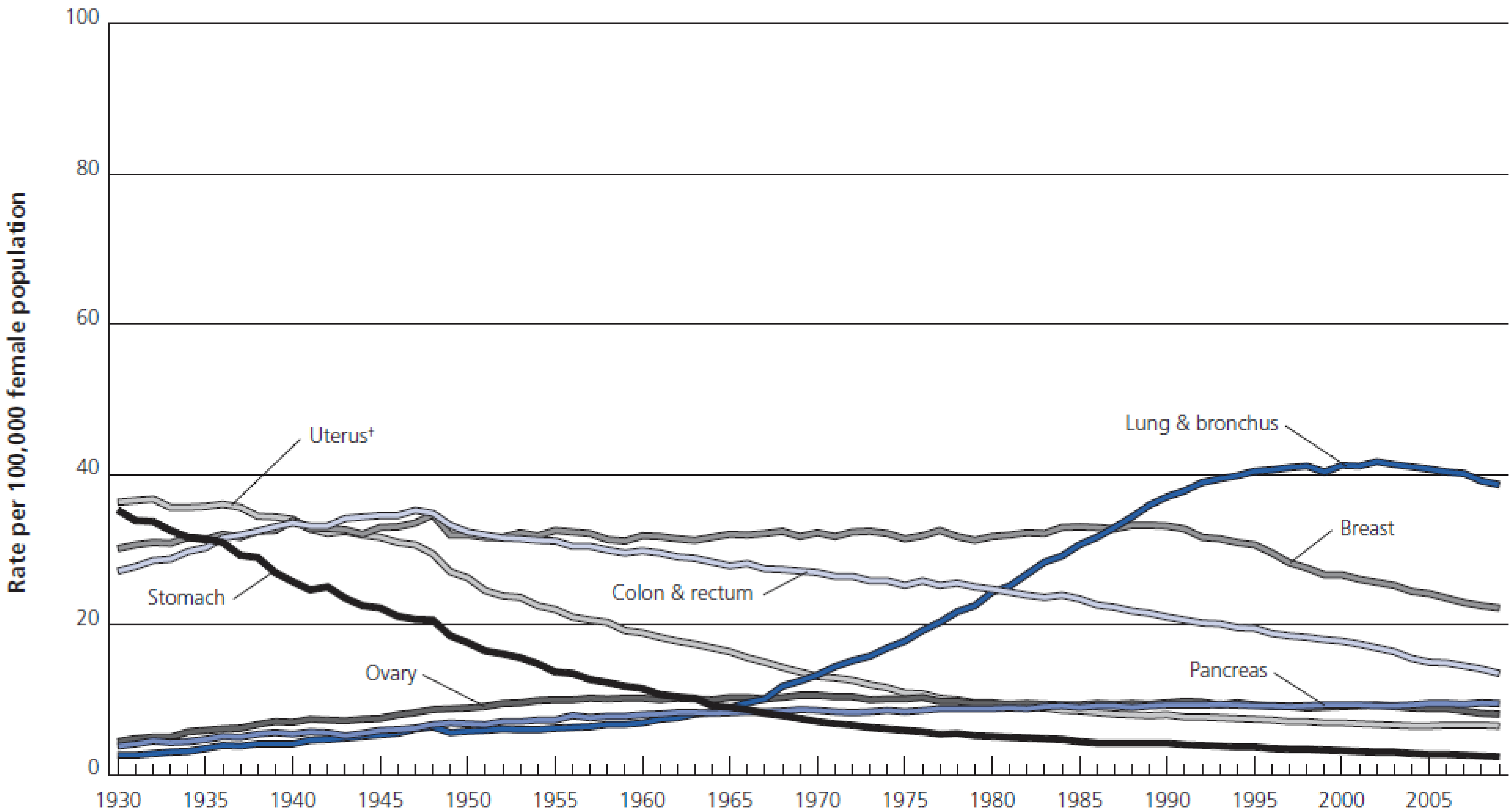


*Per 100,000, age adjusted to the 2000 US standard population.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2009, National Center for Health Statistics, Centers for Disease Control and Prevention.

Age-adjusted Cancer Death Rates*, Females by Site, US, 1930-2009



*Per 100,000, age adjusted to the 2000 US standard population. †Uterus refers to uterine cervix and uterine corpus combined.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the lung and bronchus, colon and rectum, and ovary are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2009, National Center for Health Statistics, Centers for Disease Control and Prevention.

Lung Cancer

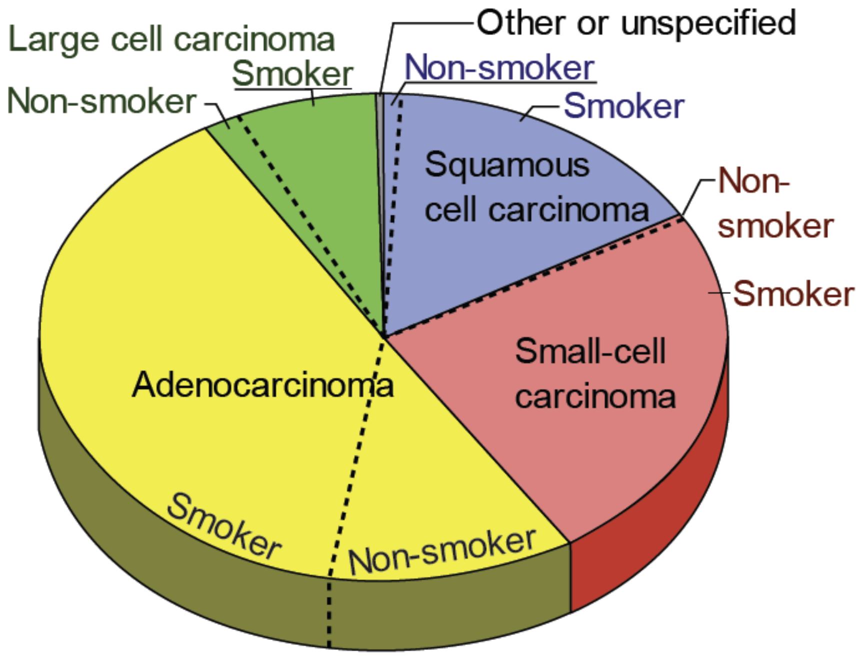
Non-small cell lung cancer (NSCLC, 85%)

Adenocarcinoma

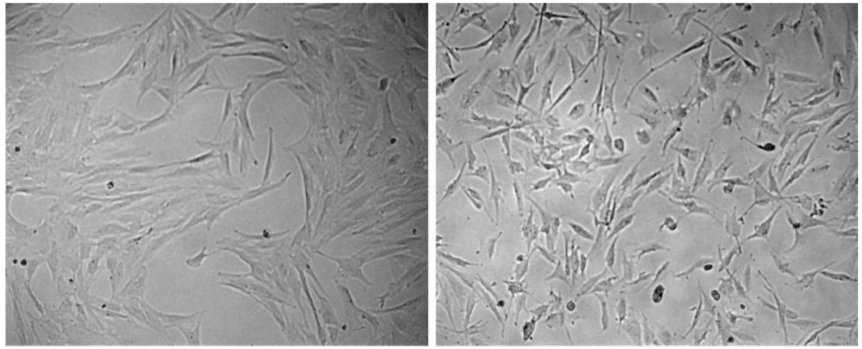
Squamous cell carcinoma

Large cell carcinomas

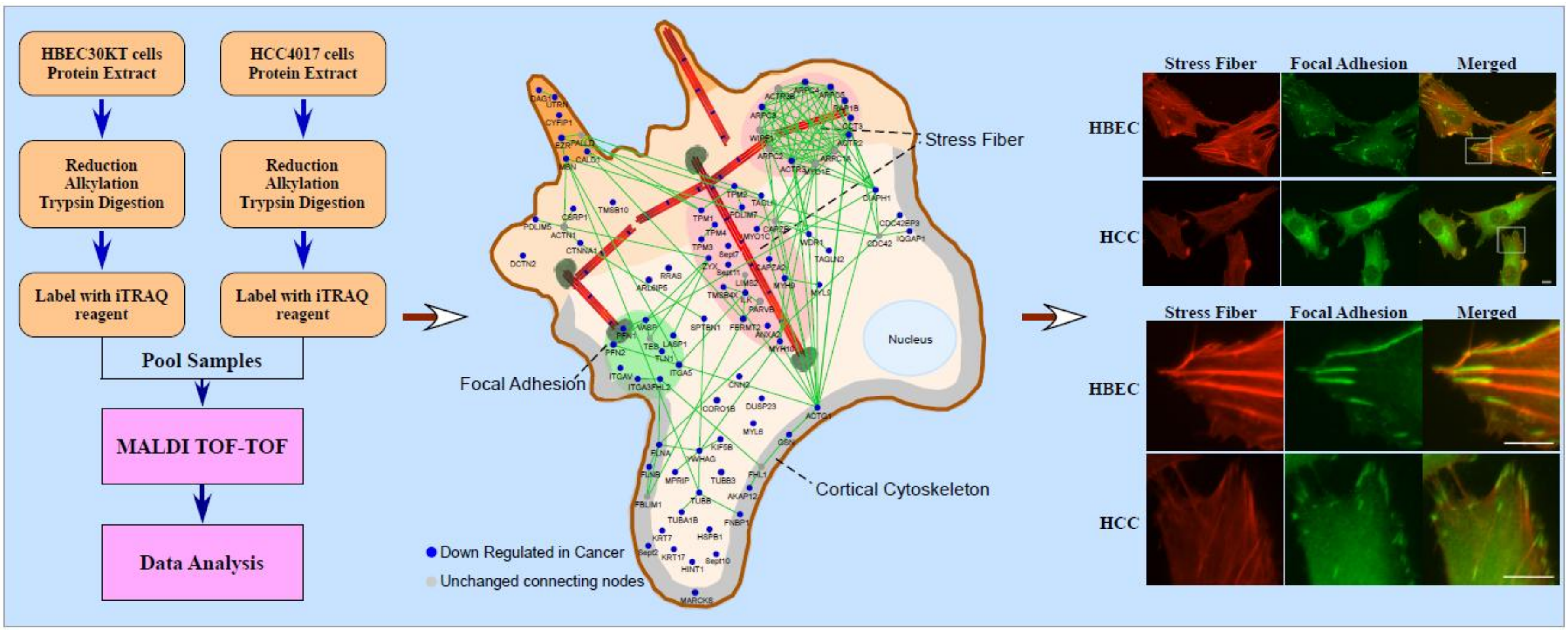
Small Cell Lung Cancer (15%)



Normal **NSCLC**



HBEC30KT HCC4017



Proteomic data indicate that hemoproteins are increased in lung cancer cells

A List of Mitochondrial Proteins Upregulated in NSCLC Cells

Protein ID	Gene Symbol	Description	Fold	p-value
NP_001203	C1QBP	complement 1 Q subcomponent-binding protein	1.5	3.27E-02
NP_001907	CYC1	cytochrome c1, heme protein	4.3	3.61E-02
NP_002147	HSPD1	60 kDa heat shock protein	3.3	5.19E-16
NP_573566	LRPPRC	leucine-rich PPR motif-containing protein	3.9	4.71E-14
NP_006285	UQCRB	cytochrome b-c1 complex subunit 7	6.1	1.68E-02

SnapShot: Cancer Metabolism Pathways

Cell Metabolism

Lydia W. S. Finley, Ji Zhang, Jiangbin Ye, Patrick S. Ward, and Craig B. Thompson
Cancer Biology and Genetics Program, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA

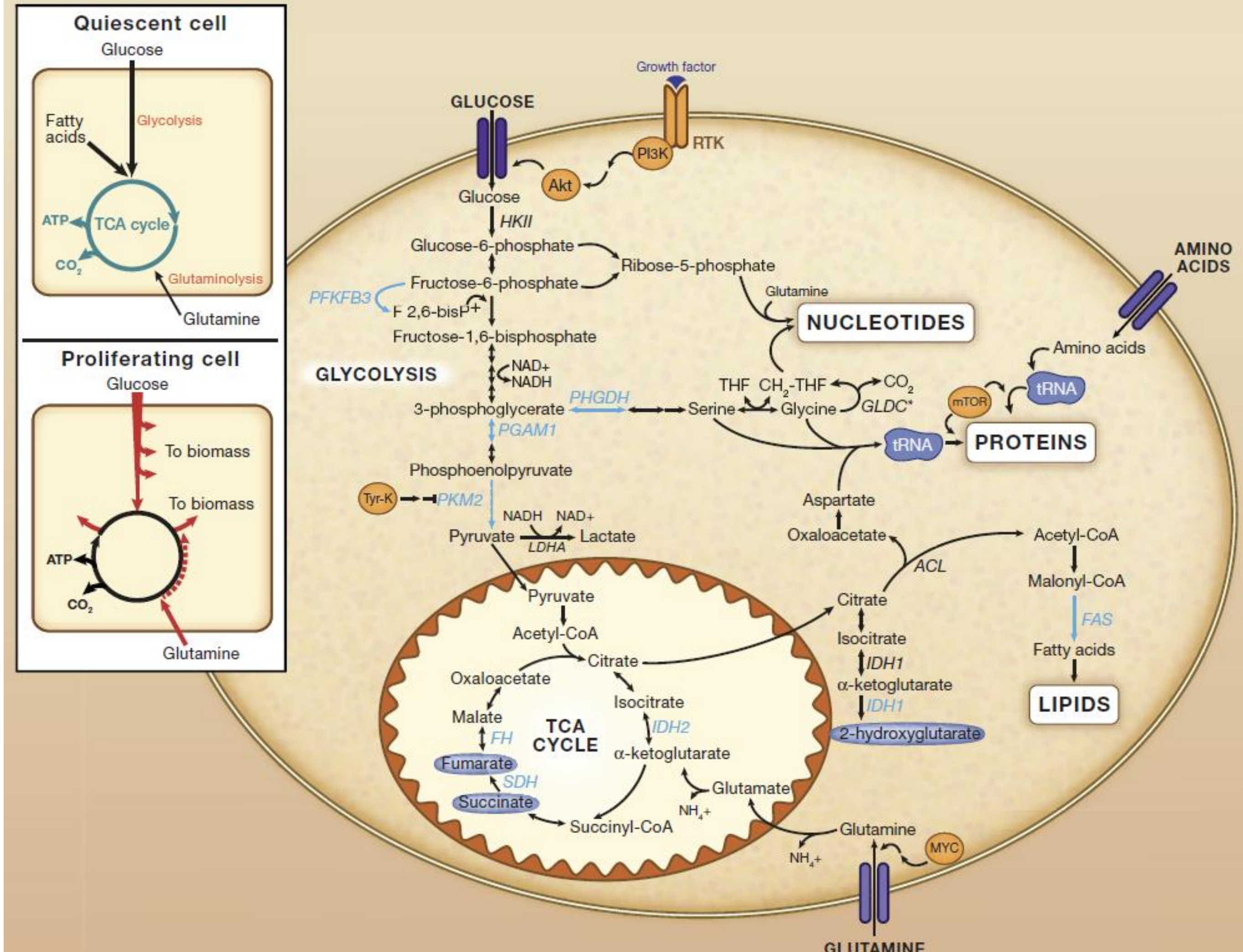


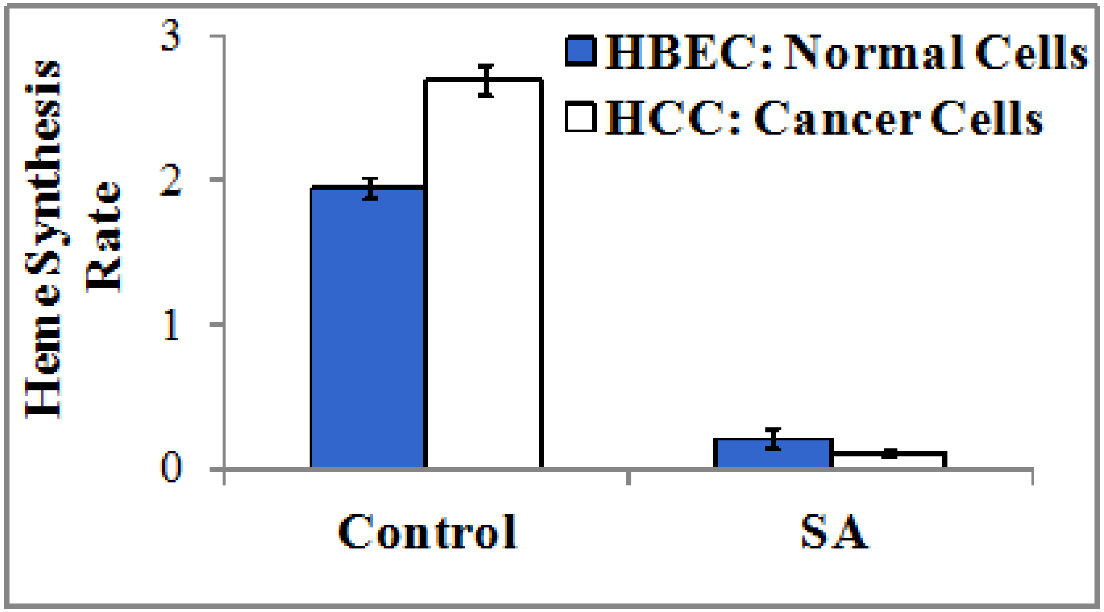
Table 1. Cancer Cells Substantially Increase the Rates of Glucose and Oxygen Consumption*.

Cell Line	Glu	O_2	mtDNA
HBEC30KT	10.9±0.6	1.07±0.18	0.63±0.02
HCC4017	15.1±1.0	2.47±0.15	0.61±0.02

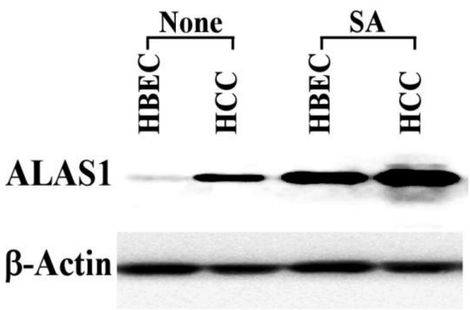
*The rates of glucose uptake and oxygen consumption are shown in nmol/min/10^6 cells, while the mitochondrial DNA level (mtDNA) is shown as the ratio of threshold cycle number of mitochondrial DNA vs. nuclear DNA, measured by real-time PCR.

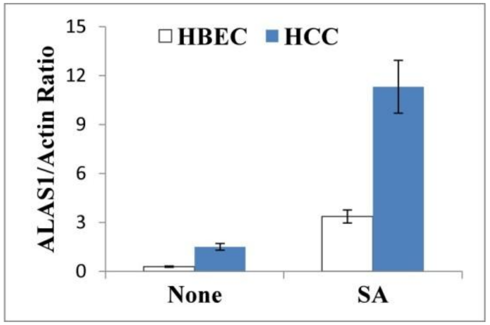
doi:10.1371/journal.pone.0063402.t001

Heme synthesis is significantly enhanced in cancer cells compared to the normal cells

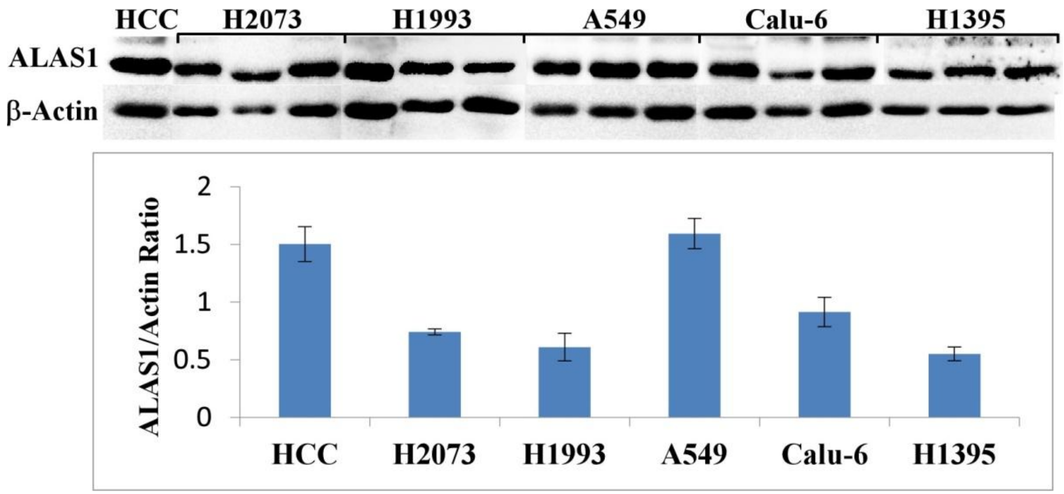


The level of the rate-limiting heme biosynthetic enzyme ALAS1 is dramatically enhanced in NSCLC cells

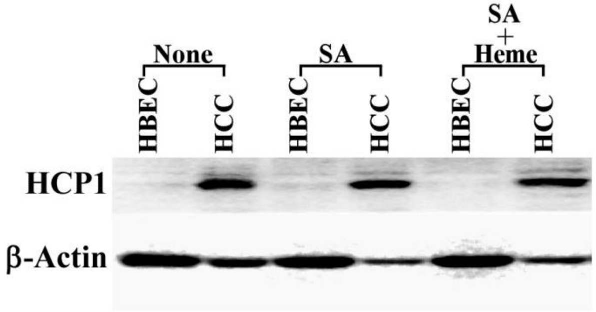


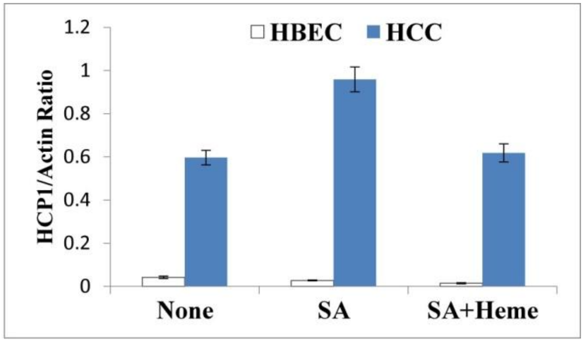


and in mouse xenograft tumors



The level of heme-transporting HCP1 is dramatically enhanced in NSCLC cells





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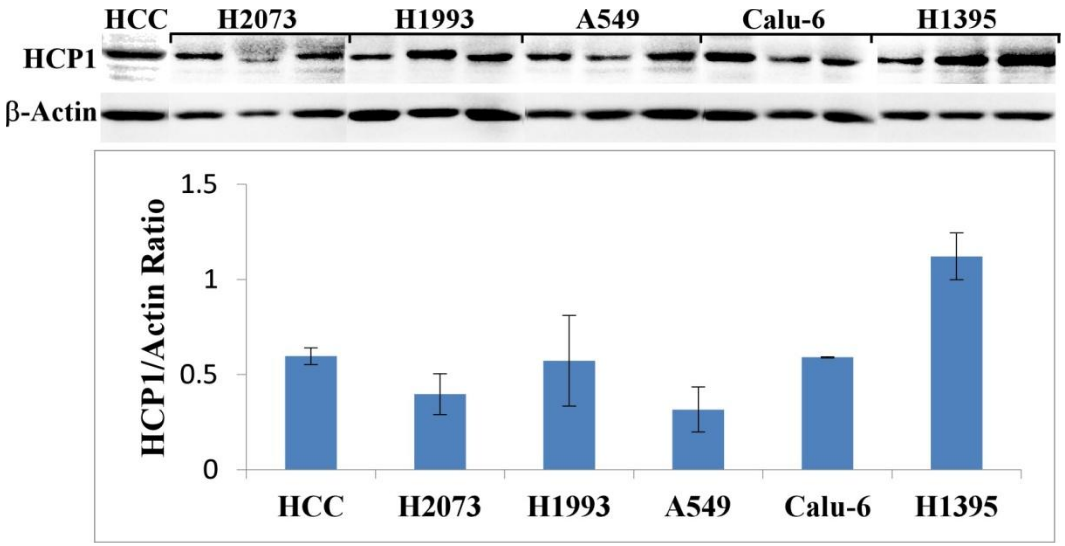
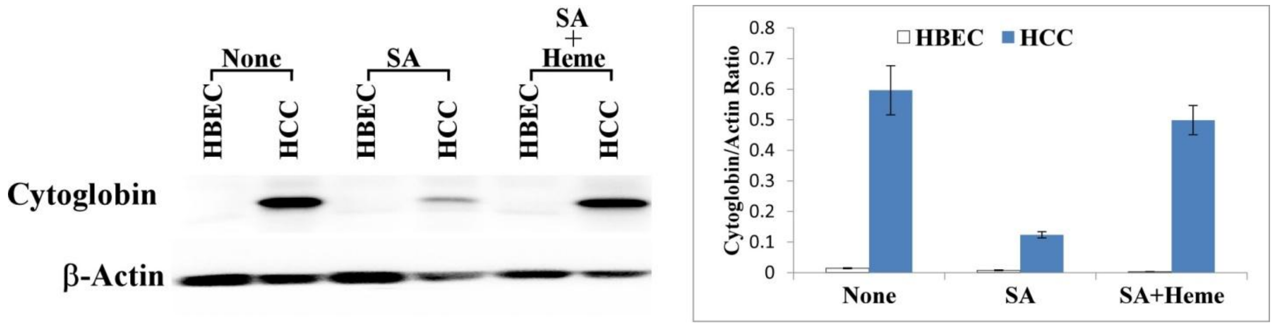
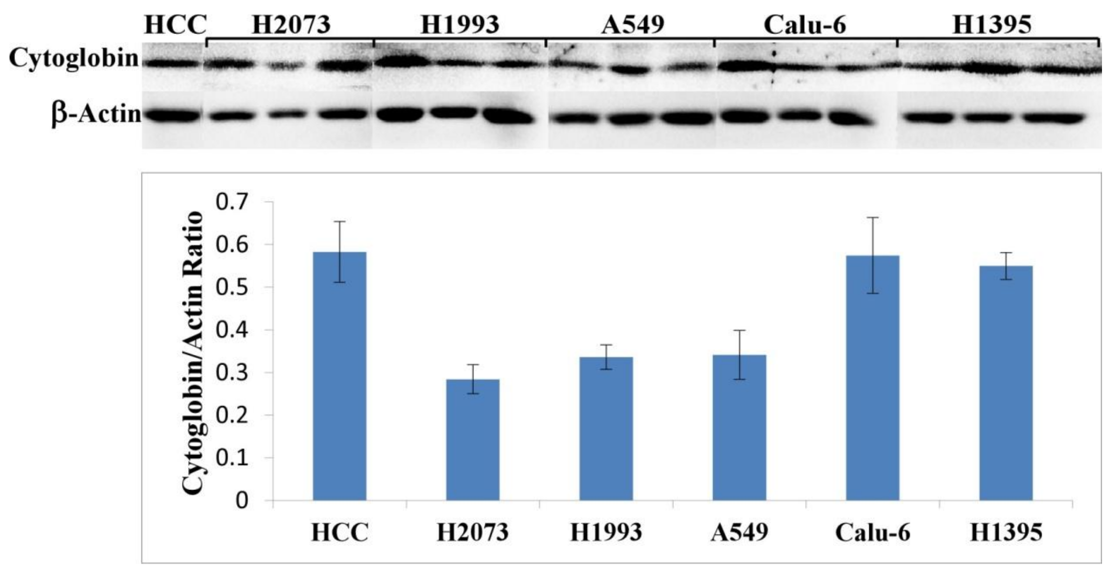
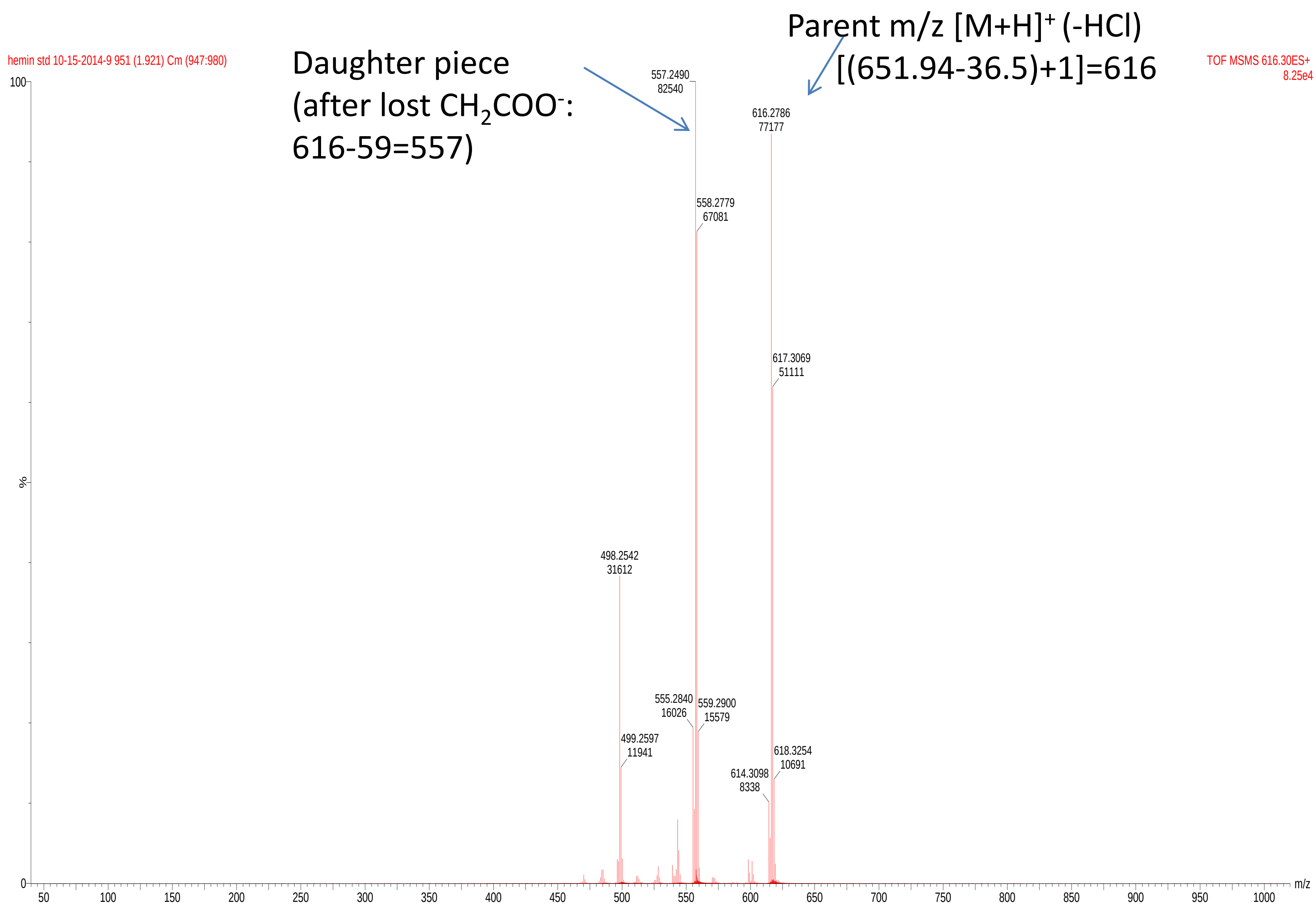


The levels of hemoproteins, such as the oxygen-binding cytoglobin, are dramatically enhanced in NSCLC cells



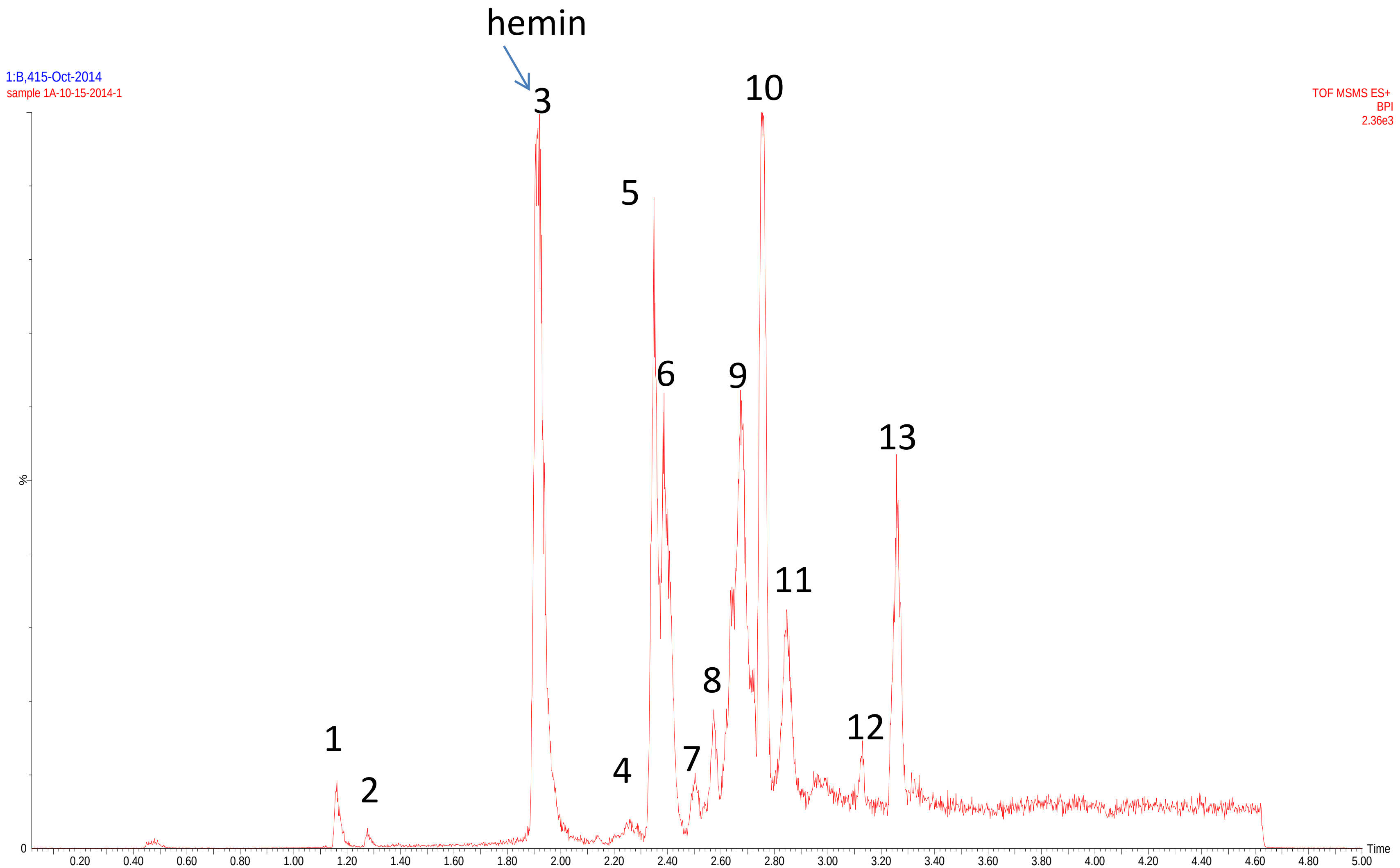
and in mouse xenograft tumors





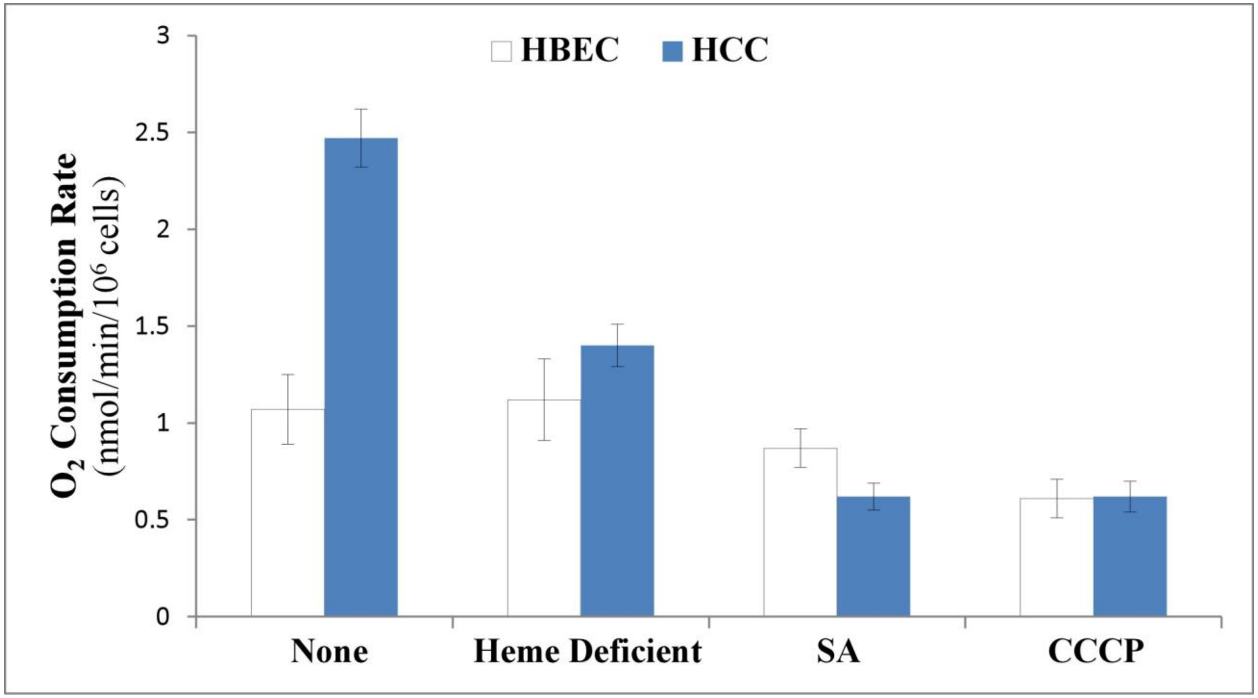
hemin std 10-15-2014-9 951 (1.921) Cm (947:980)
TOF MSMS 616.30ES+
8.25e4
Daughter piece
(after lost CH_2COO^-:
616-59=557)
Parent m/z $[M+H]^+$ (-HCl)
[(651.94-36.5)+1]=616
557.2490
82540
616.2786
77177
558.2779
67081
617.3069
51111
498.2542
31612
555.2840
16026
559.2900
15579
499.2597
11941
618.3254
10691
614.3098
8338
100
%
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
1000
m/z

Sample 1A

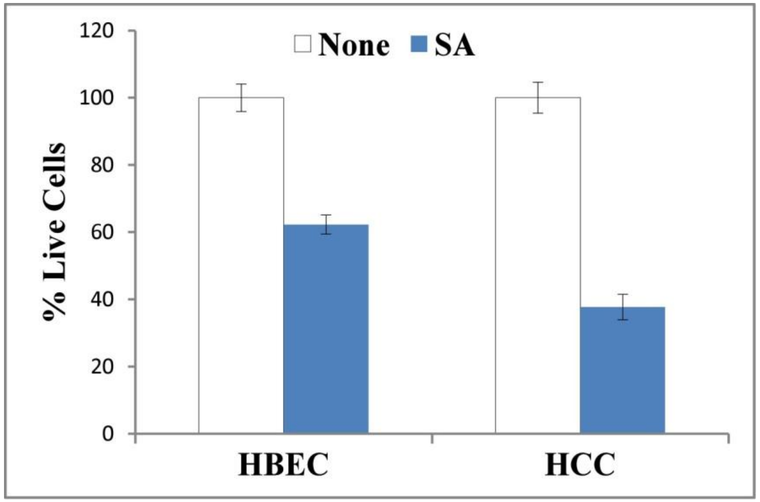


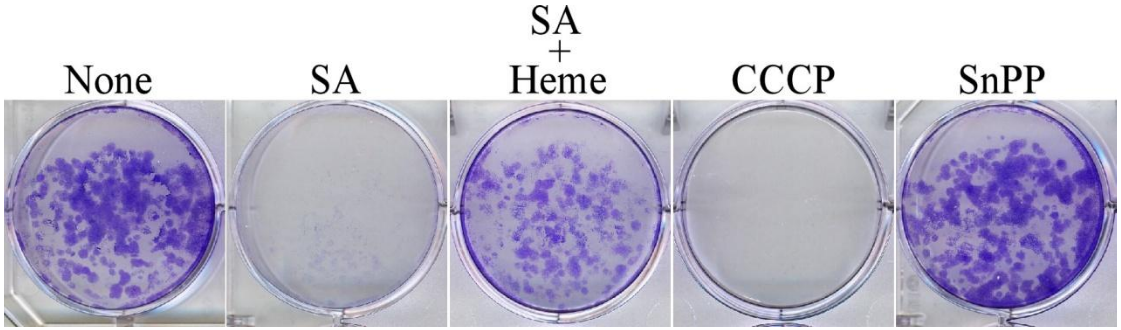
hemin
1:B,415-Oct-2014
sample 1A-10-15-2014-1
TOF MSMS ES+
BPI
2.36e3
1
2
3
4
5
6
7
8
9
10
11
12
13
%
0
0.20
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00
3.20
3.40
3.60
3.80
4.00
4.20
4.40
4.60
4.80
5.00
Time

Oxygen consumption is intensified in NSCLC cells, and inhibition of heme uptake and biosynthesis suppresses it

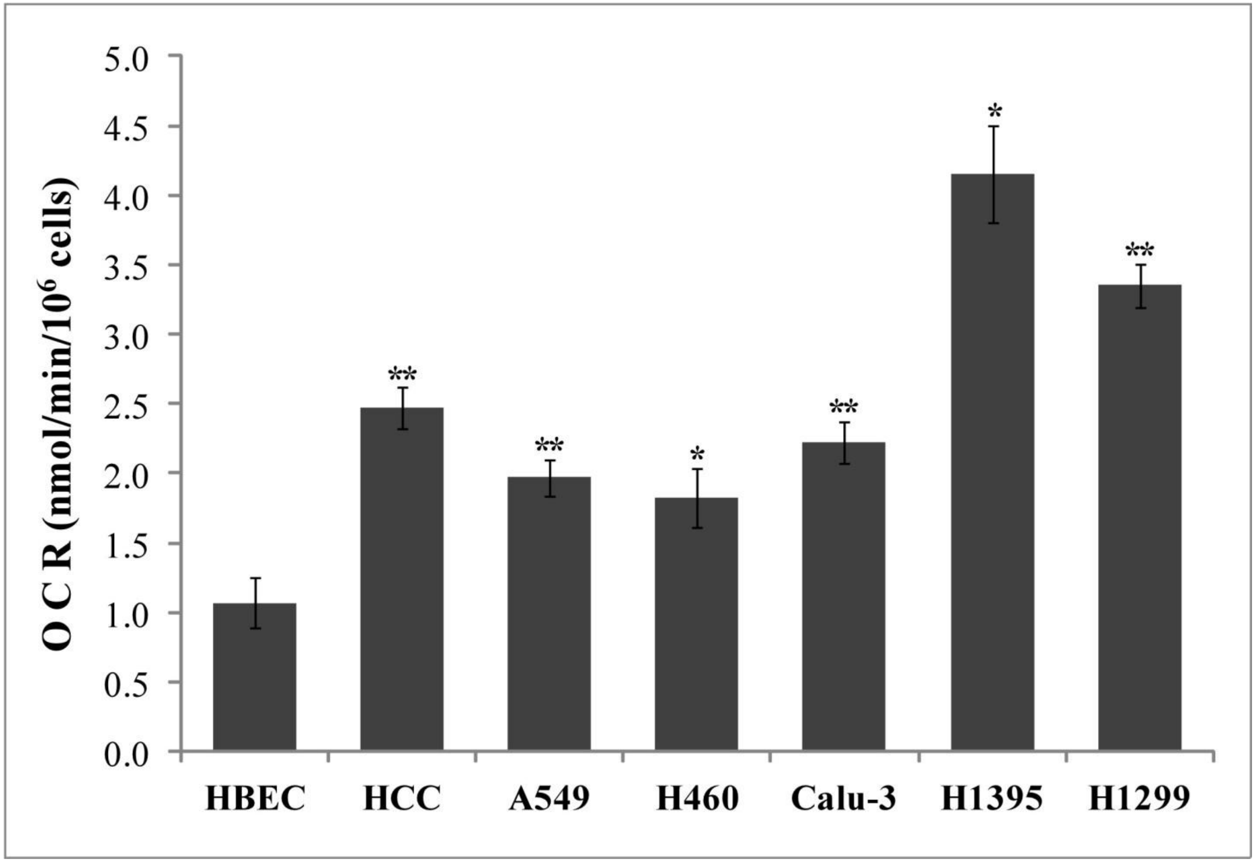


Reduction of intracellular heme level inhibits NSCLC cell proliferation and colony formation

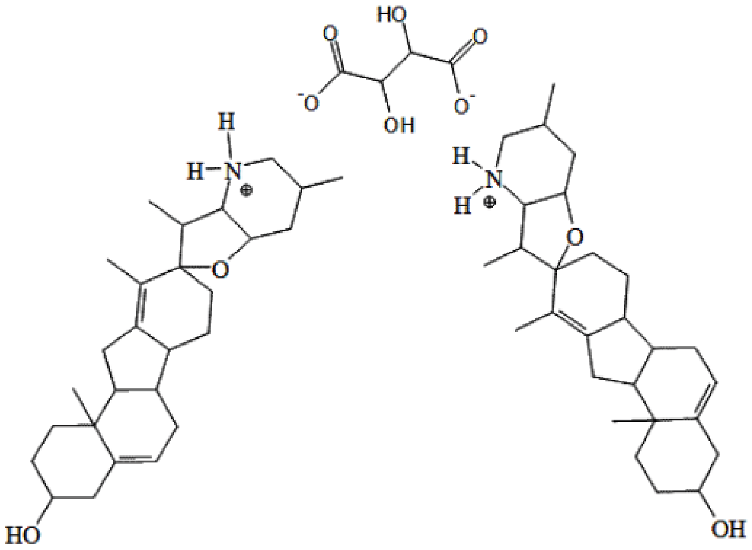


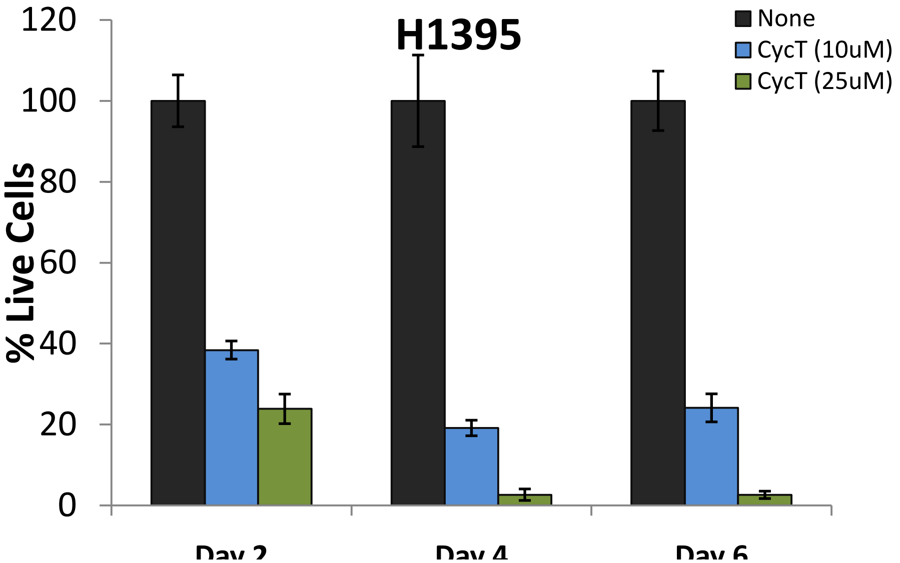


Most NSCLC Cell Lines Exhibit Intensified Oxygen Consumption

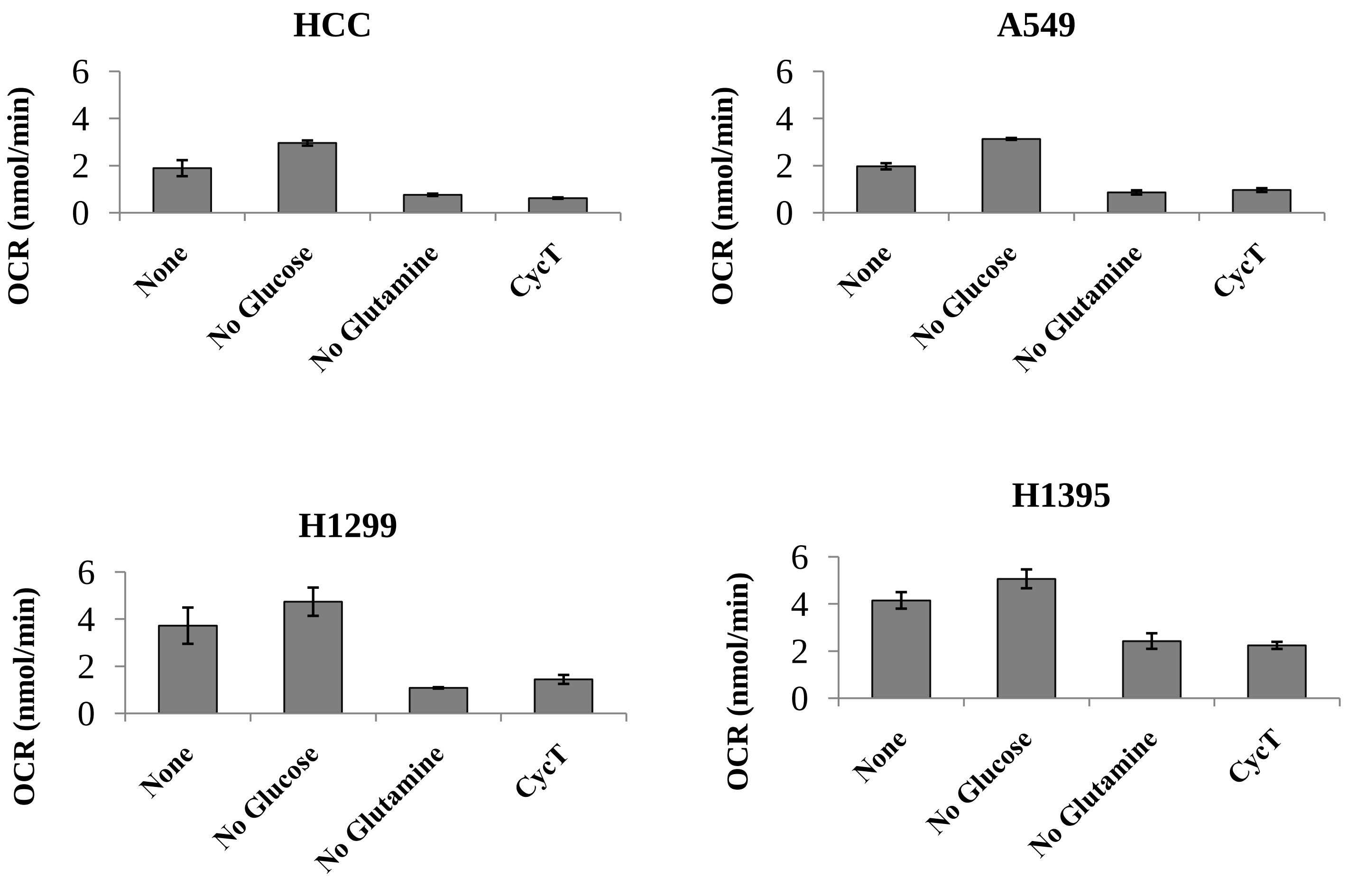


Cyclopamine Tartrate (CycT), an Inhibitor of Hedgehog Signaling, Strongly Inhibits Lung Cancer Cell Proliferation

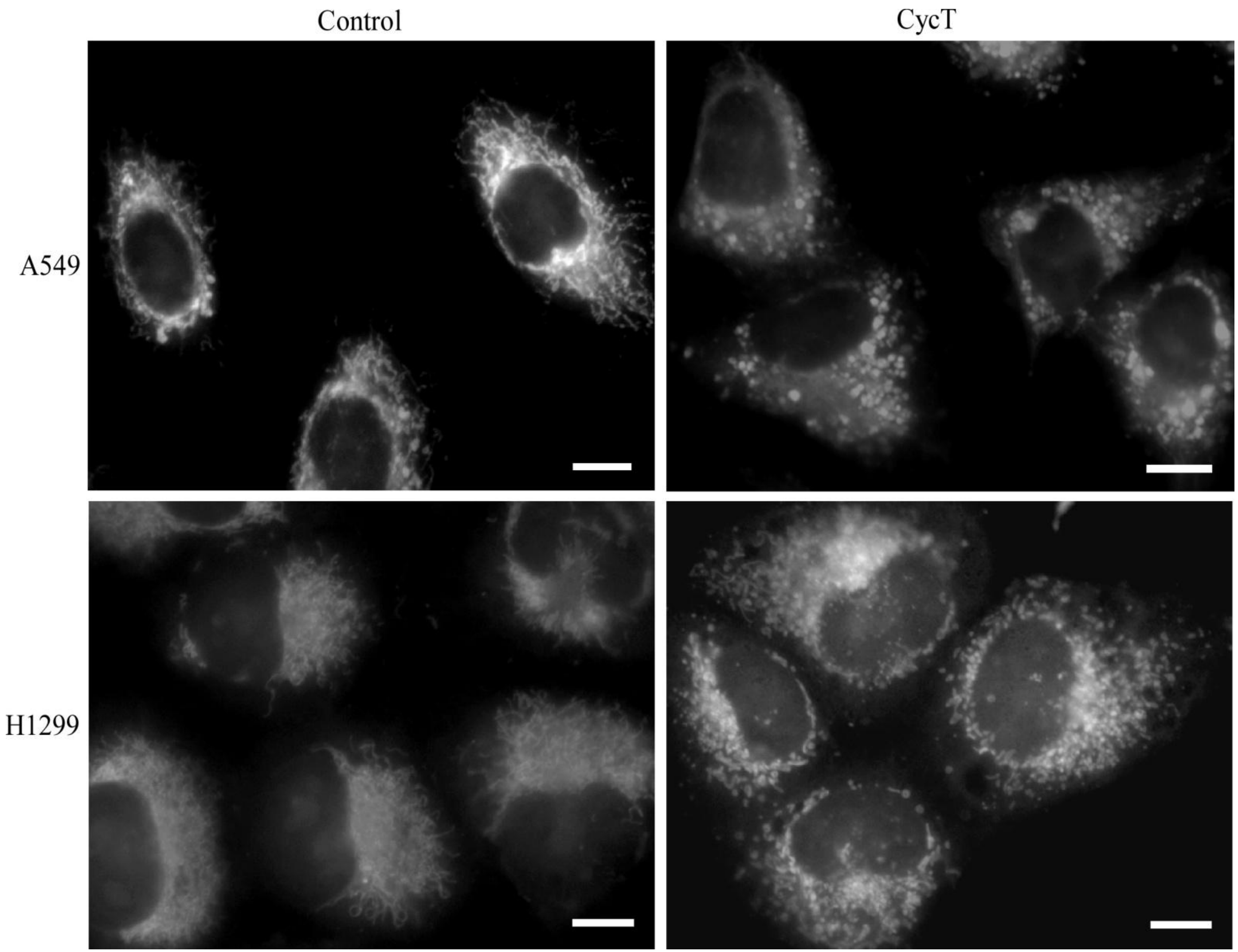


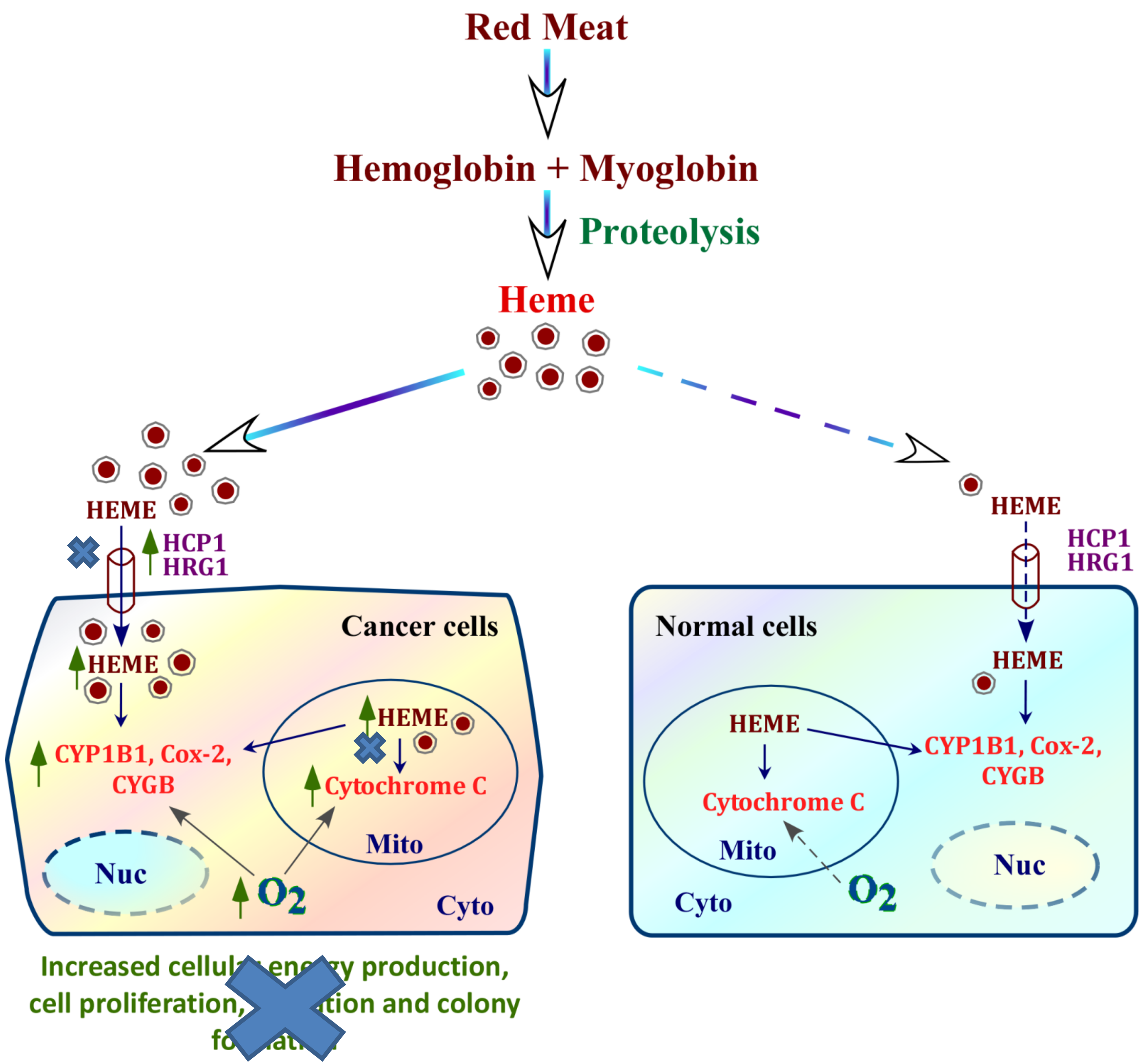


Glucose, Glutamine and Cyclopamine Tartrate Strongly Impact the Rate of Oxygen Consumption in NSCLC cells



Cyclopamine Tartrate Causes Mitochondrial Fragmentation




Red Meat
Hemoglobin + Myoglobin
Proteolysis
Heme
HEME
HCP1
HRG1
Cancer cells
HEME
HEME
CYP1B1, Cox-2,
CYGB
Cytochrome C
Mito
Nuc
O_2
Cyto
HEME
HCP1
HRG1
Normal cells
HEME
HEME
CYP1B1, Cox-2,
CYGB
Cytochrome C
Mito
Nuc
O_2
Cyto
Increased cellul
y production,
cell proliferation,
tion and colony

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