Body of evidence that deregulation of iron metabolism is key to cancer

- Iron is biologically important
- Too much of a good thing can be bad!
- Epidemiological, Animal and Cell based data associating iron excess with colorectal (and other) cancer

Dig Dis Sci. 2002 Jun;47(6):1266-78.

Dietary iron supplementation enhances DSS-induced colitis and associated colorectal carcinoma development in mice.

Seril DN, Liao J, Ho KL, Warsi A, Yang CS, Yang GY.

Author information

Gut. 2011 Mar;60(3):325-33. doi: 10.1136/gut.2010.216929. Epub 2010 Nov 12.

Depletion of luminal iron alters the gut microbiota and prevents Crohn's disease-like ileitis.

Werner T, Wagner SJ, Martínez I, Walter J, Chang JS, Clavel T, Kisling S, Schuemann K, Haller D.

Cancer Lett. 1988 Aug 30;41(3):251-6.

Dietary iron enhances the tumor rate in dimethylhydrazine-induced colon carcinogenesis in mice.

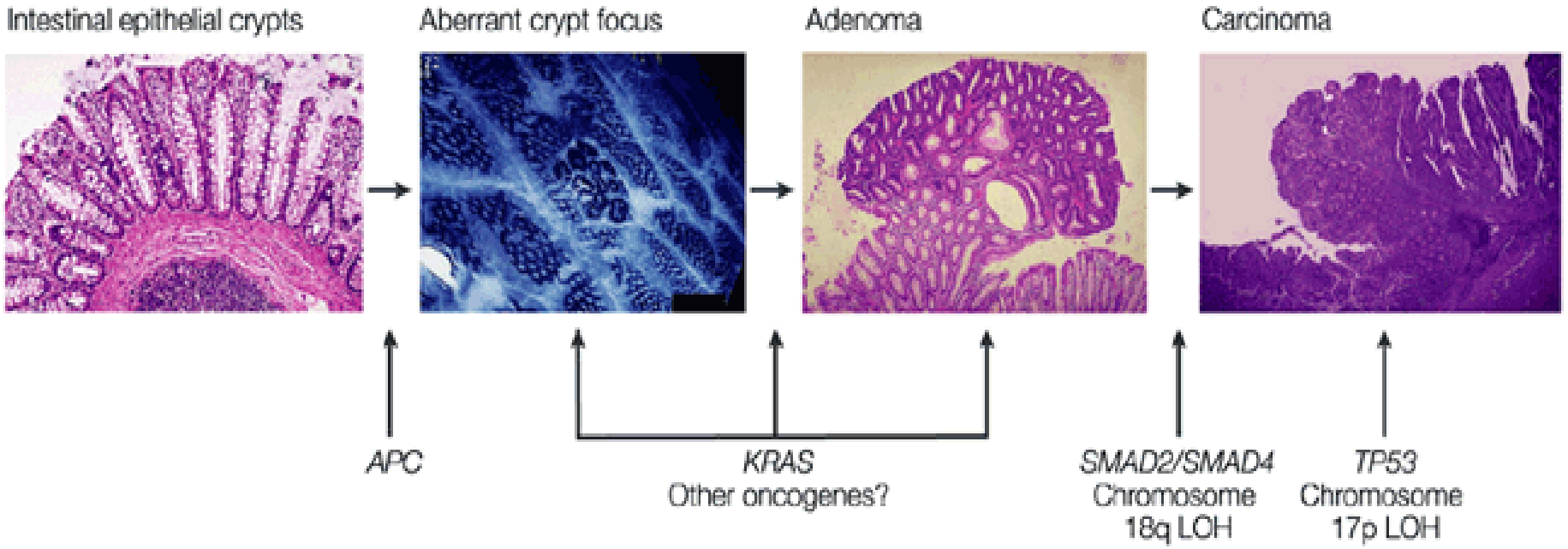
Siegers CP, Bumann D, Baretton G, Younes M.

A class of iron chelators with a wide spectrum of potent antitumor activity that overcomes resistance to chemotherapeutics

Megan Whitnall*, Jonathan Howard*, Prem Ponka†‡, and Des R. Richardson*‡

*Children's Cancer Institute Australia for Medical Research, Sydney, New South Wales 2031, Australia; and †Lady Davis Institute for Medical Research, McGill University, 3755 Cote-Ste-Catherine Road, Montreal, QC, Canada H3T 1E2

What is the profile of cellular iron transport proteins in colorectal carcinogenesis?



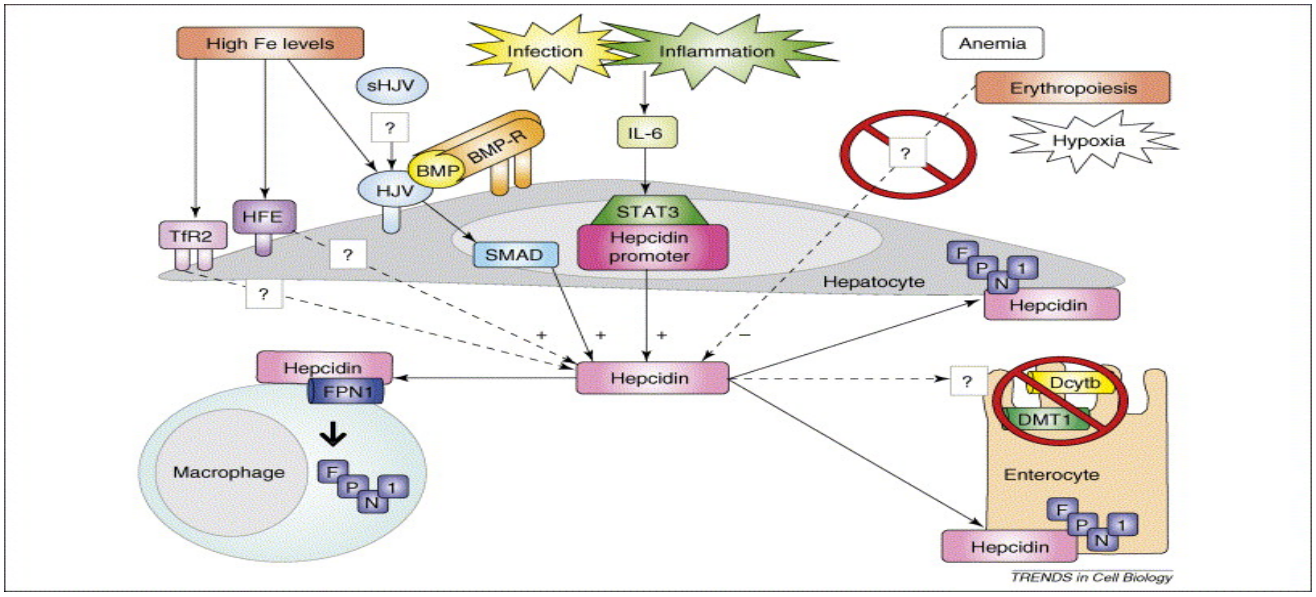
COLORECTAL CANCER

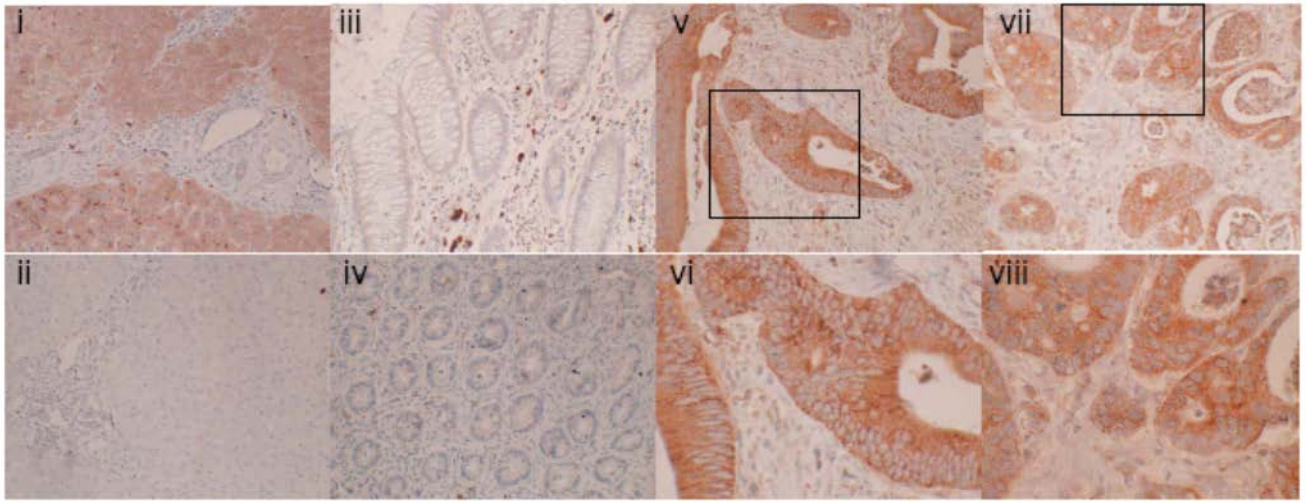
Modulation of iron transport proteins in human colorectal carcinogenesis

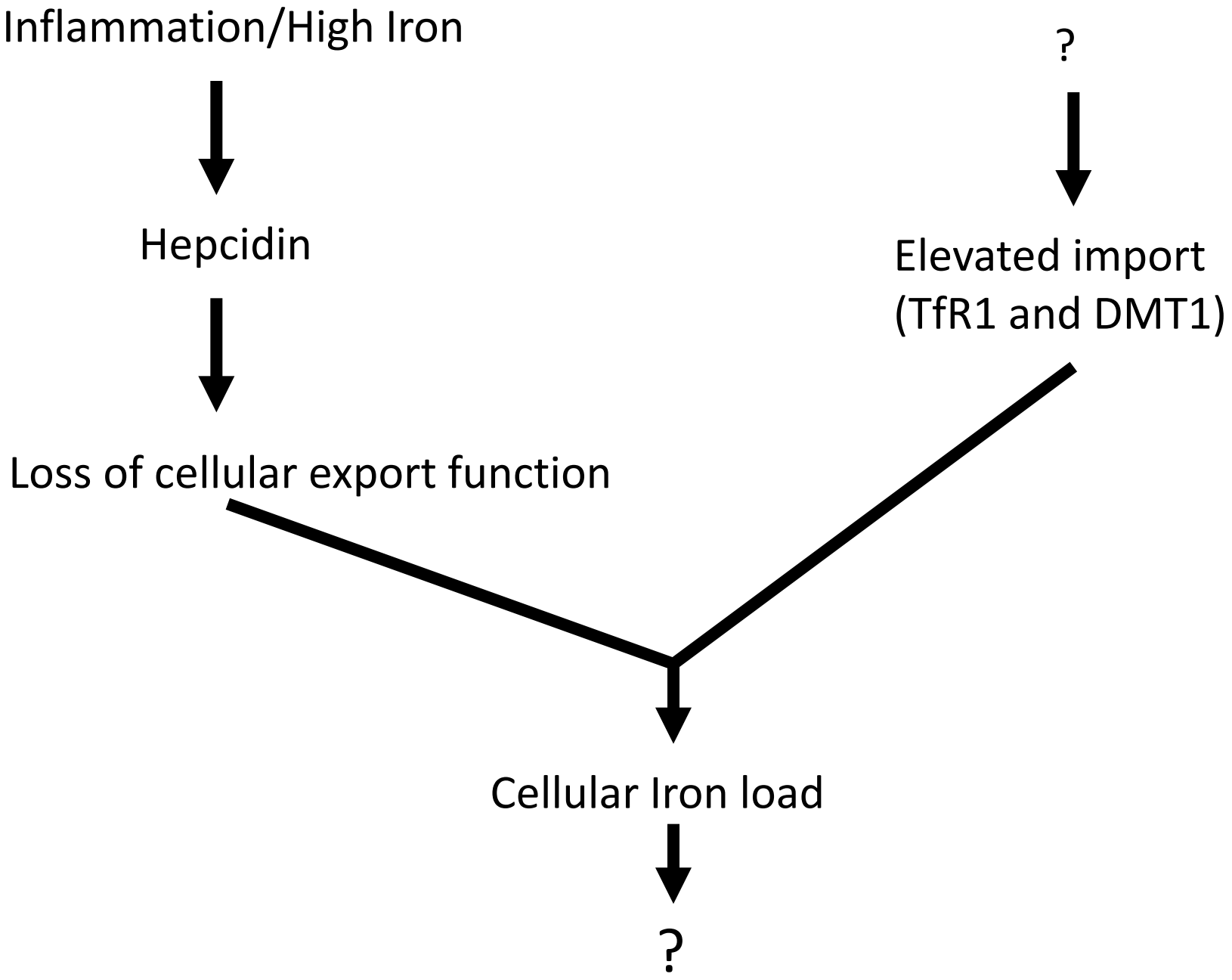
M J Brookes, S Hughes, F E Turner, G Reynolds, N Sharma, T Ismail, G Berx, A T McKie, N Hotchin, G J Anderson, T Iqbal, C Tselepis

Gut 2006;**55**:1449–1460. doi: 10.1136/gut.2006.094060

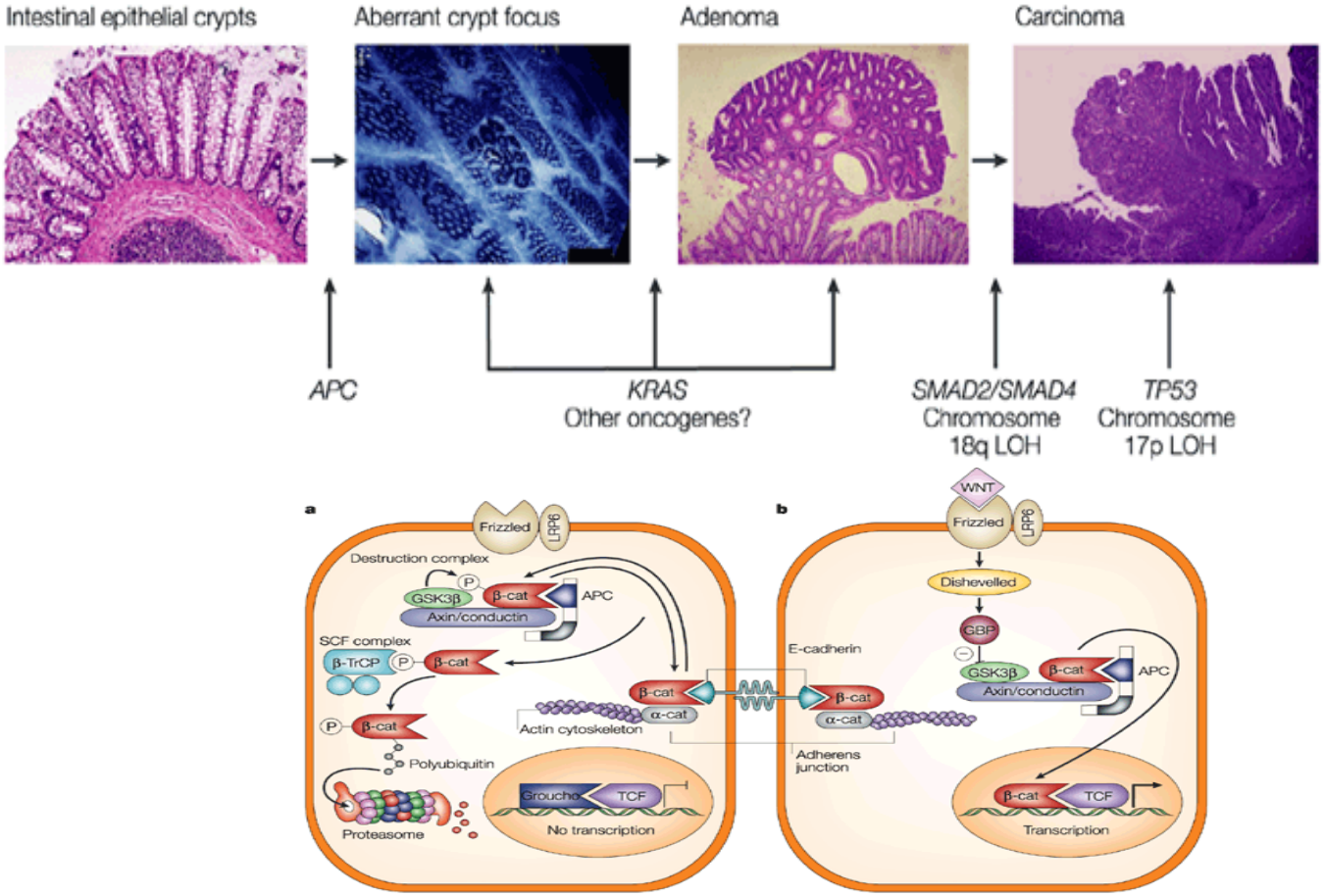
What is mediating the relocalisation of ferroportin?






Inflammation/High Iron
Hepcidin
Loss of cellular export function
?
Elevated import
(TfR1 and DMT1)
Cellular Iron load
?

Iron amplifies Wnt signalling?



Oncogene (2008) 27, 966–975

www.nature.com/onc

ORIGINAL ARTICLE

A role for iron in Wnt signalling

MJ Brookes[1,2], J Boult[1], K Roberts[1], BT Cooper[2], NA Hotchin[3], G Matthews[4], T Iqbal[1,5] and C Tselepis[1,5]

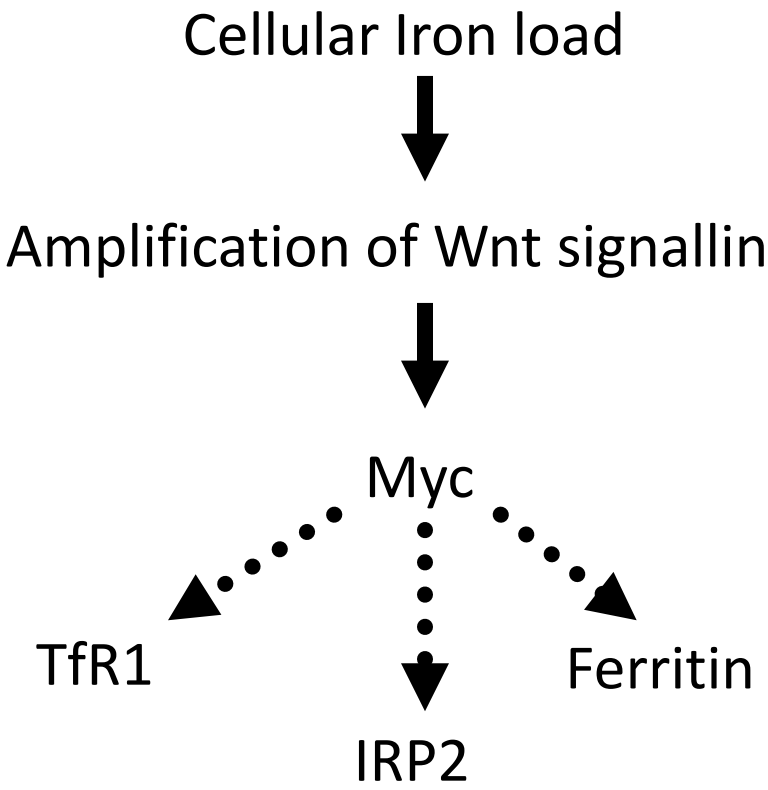
Gene	Organism/system	Direct/Indirect	up/down	Ref.
Â c-myc	human colon cancer	yes	up	He 1998
Â Cyclin D	human colon cancer	yes	up	Tetsu 1999 Shtutman 1999 Disputed by Sansom, 2005
Tcf-1	human colon cancer	yes	up	Roose 1999
LEF1	human colon cancer	yes	up	Hovanes, 2001 Filali 2002
PPARdelta	human colon cancer	yes	up	He TC, et al 1999
c-jun	human colon cancer	yes	up	Mann B, 1999
fra-1	human colon cancer	yes	up	Mann B, 1999
uPAR	human colon cancer	?	up	Mann B, 1999
matrix metalloproteinase MMP-7	human colon cancer	yes	up	Brabletz 1999 Crawford 1999
Axin-2	human colon cancer	yes	up	Yan, 2001 Lustig, 2002 Jho, 2002
Nr-CAM	human colon cancer	yes	up	Conacci-Sorrell 2002
ITF-2	human colon cancer	yes	up	Kolligs, 2002
Gastrin	human colon cancer	?	up	Koh, 2000
Â CD44	human colon cancer	?	up	Wielenga 1999
EphB/ephrin-B	human colon cancer	?	up/down	Batlle, 2002
BMP4	human colon cancer	?	up	Kim 2002
claudin-1	human colon cancer	yes	up	Miwa 2002
Survivin	human colon cancer		up	Zhang, 2001
VEGF	human colon cancer	yes	up	Zhang, 2001
FGF18	human colon cancer	yes	up	Shimokawa 2003
Hath1	human colon cancer		down	Leow 2004
Met	human colon cancer		up	Boon 2002
endothelin-1	human colon cancer		up	Kim 2004
c-myc binding protein	human colon cancer	yes	up	Jung 2005
L1 neural adhesion	human colon cancer		up	Gavert 2005
Id2	human colon cancer	yes	up	Rockman 2001 Willert 2002
Tiam1	Colon tumors			Malliri 2005
Nitric Oxide Synthase 2	Hepg2 cells		up	Du, 2006
Dickkopf	Various cells, tumors		up	Niida, 2004 Gonzalez-Sancho 2004 Chamorro 2004
FGF9	ovarian endometrioid adenocarcinoma		up	Hendrix, 2006
FGF20	Various cells, tumors			Chamorro 2004
LGR5/GPR49	Intestine	yes	up	Barker, 2007
Sox9	Intestine		up	Blache 2004
Sox9	mesenchyme		down	Hill, 2005 Day 2005 Yano, 2005
Runx2	chondrocytes		up	Dong 2006
Gremlin	fibroblasts		up	Klapholz-Brown 2007
SALL4				Bohm, 2006
RANK ligand	Osteoblasts		down	Spencer 2006
CCN1/Cyr61	Osteoblasts		up	Si, 2006
Sox2	Xenopus retina		up	Van Raay, 2005
Pituitary tumor transforming gene	esophageal squamous cell			Zhou 2004

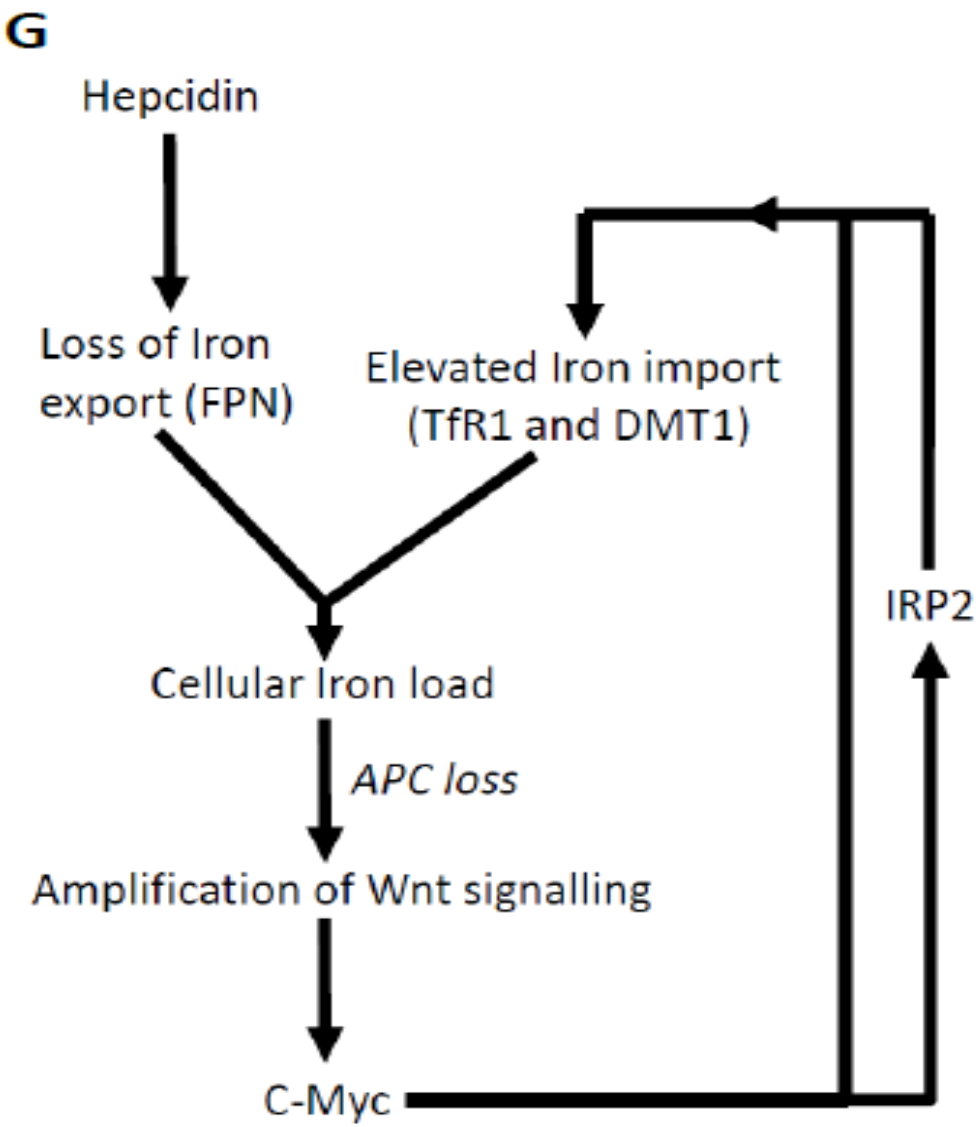
nature Vol 446|5 April 2007|doi:10.1038/nature05674

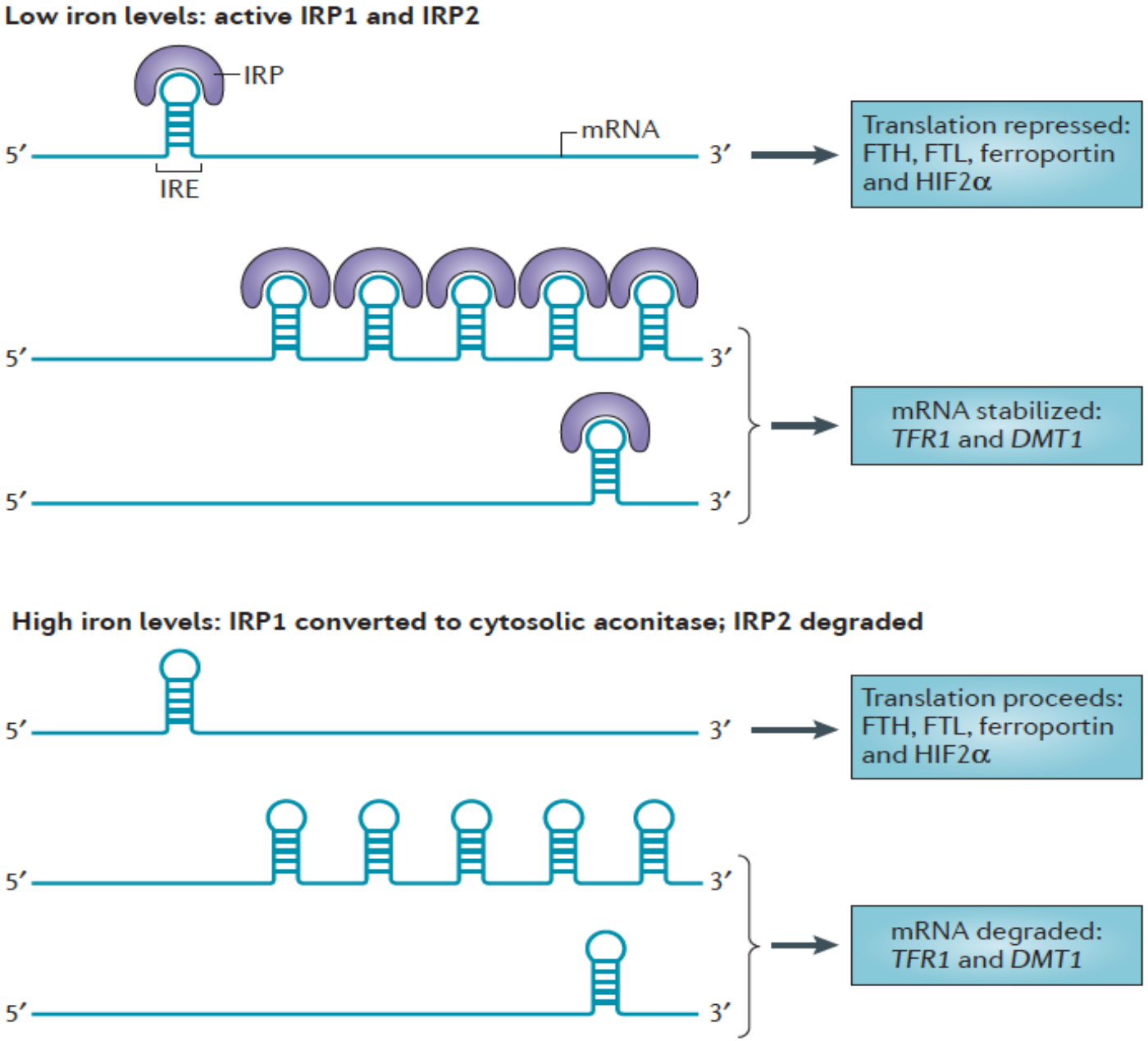
LETTERS

Myc deletion rescues Apc deficiency in the small intestine

Owen J. Sansom[1], Valerie S. Meniel[2], Vanesa Muncan[3], Toby J. Phesse[2], Julie A. Wilkins[1], Karen R. Reed[2], J. Keith Vass[1], Dimitris Athineos[1], Hans Clevers[3] & Alan R. Clarke[2]

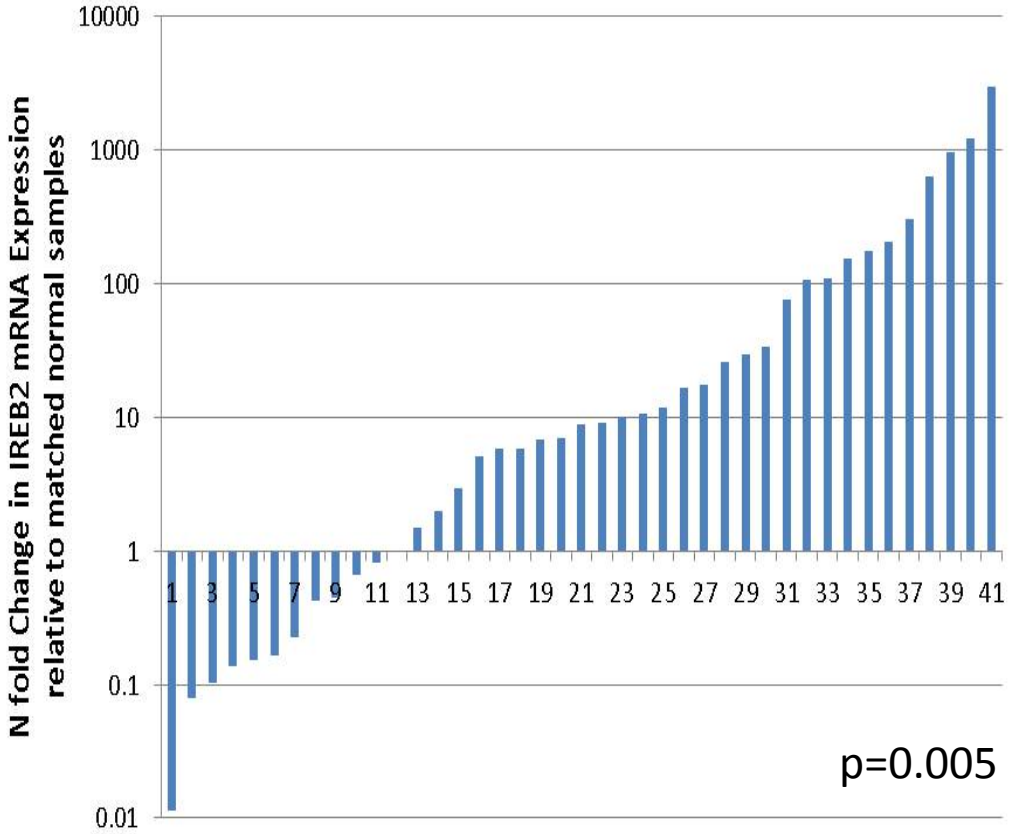


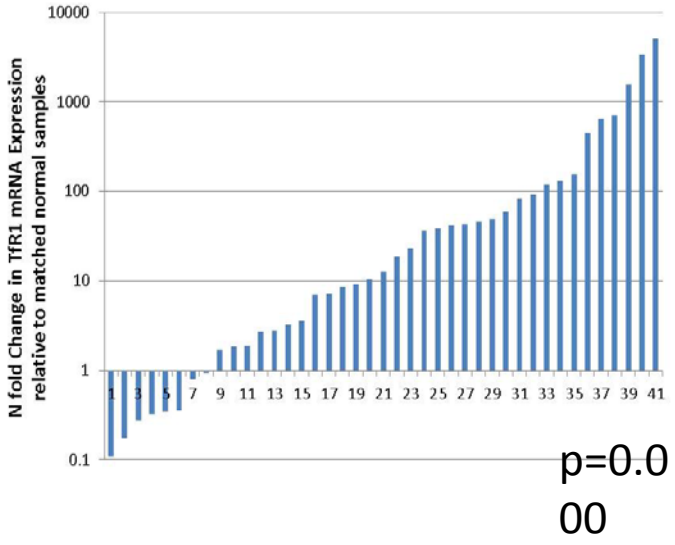

G
Hepcidin
Loss of Iron export (FPN)
Elevated Iron import (TfR1 and DMT1)
IRP2
Cellular Iron load
APC loss
Amplification of Wnt signalling
C-Myc

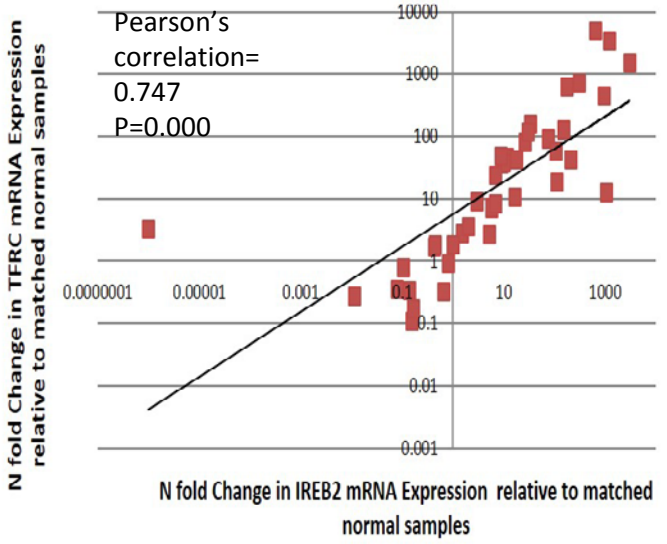


Torti SV, Torti FM, Nature.Rev 2013;13:342-355

IRP2 mRNA is Upregulated in Adenocarcinomas Relative to Normal Controls

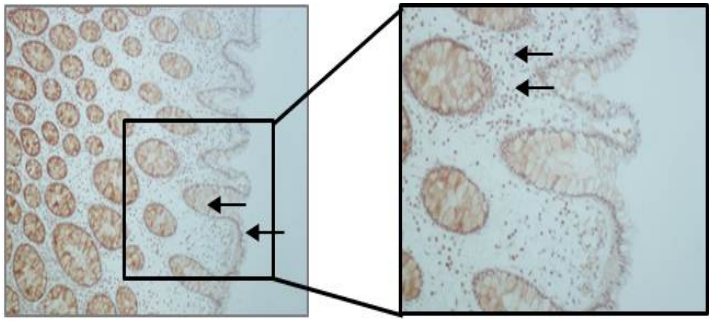




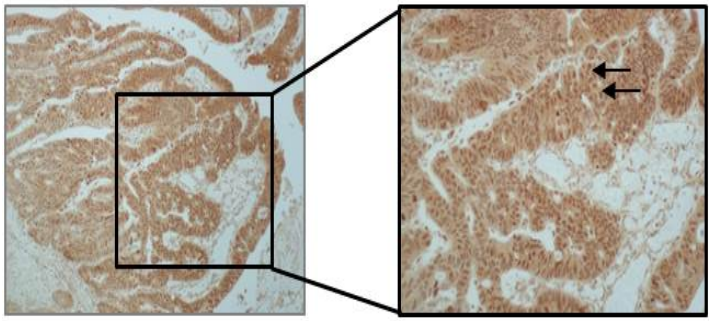


IRP2 Protein is Overexpressed in Adenocarcinomas Relative to Normal Controls

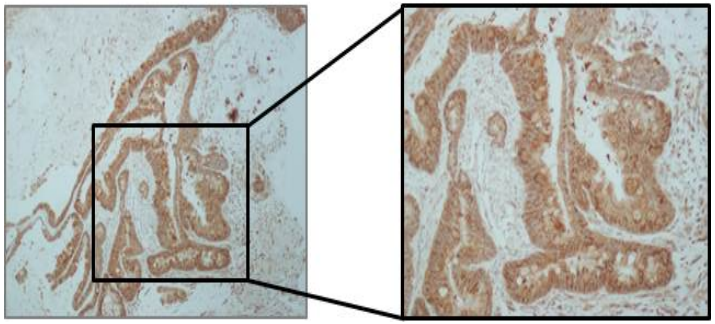
Normal



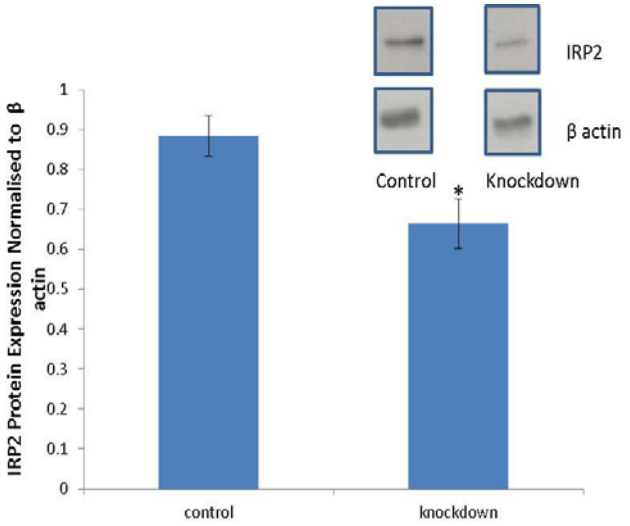
Tumour

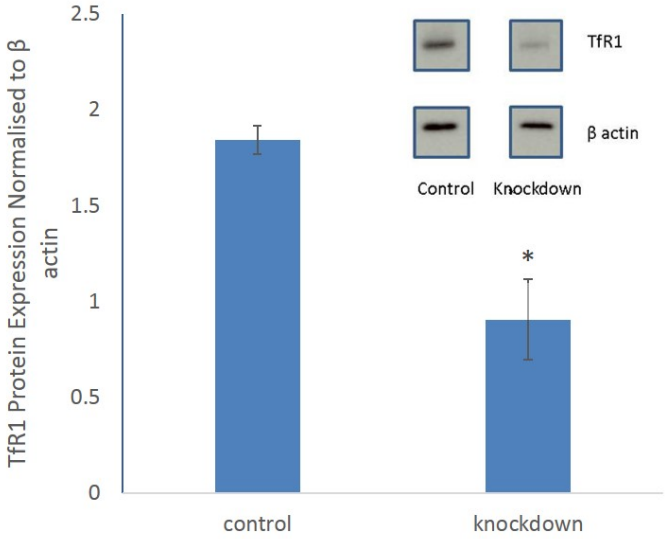


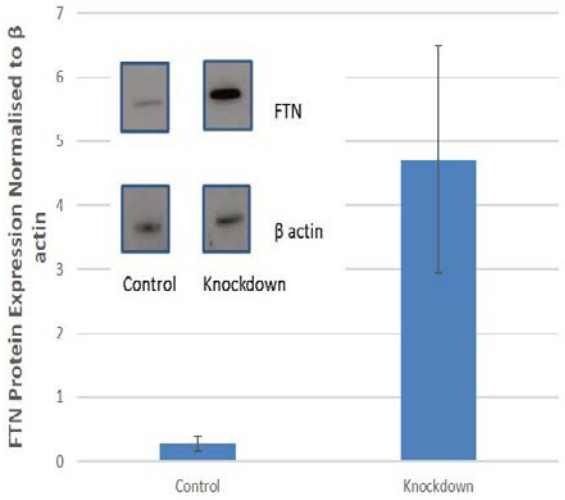
Mucinous Subtype



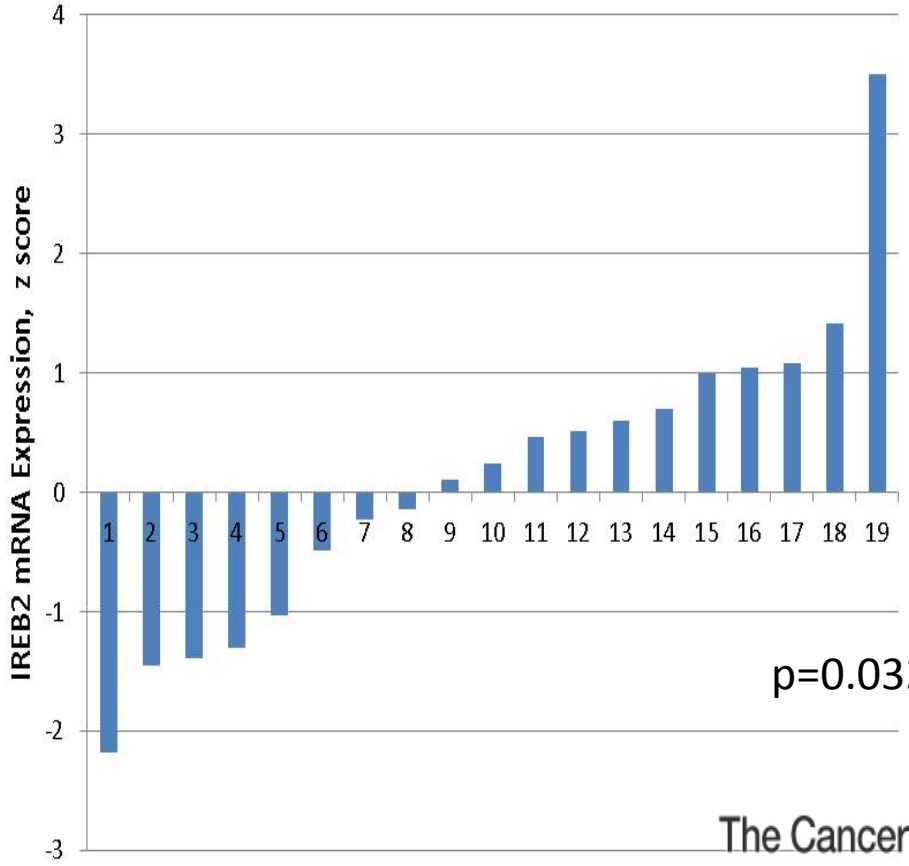
IRP2 Knockdown is Associated with Decreased TfR1 and Increased FTN Protein Expression







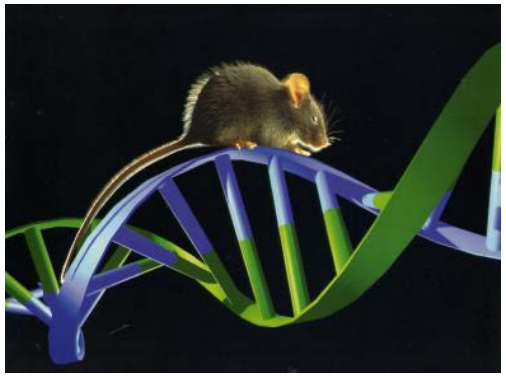
IRP2 is Overexpressed in BRAF Mutant Tumours

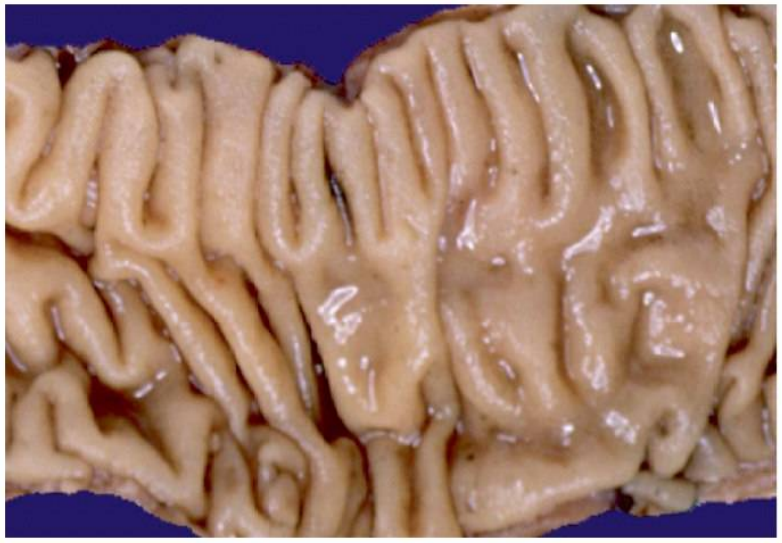


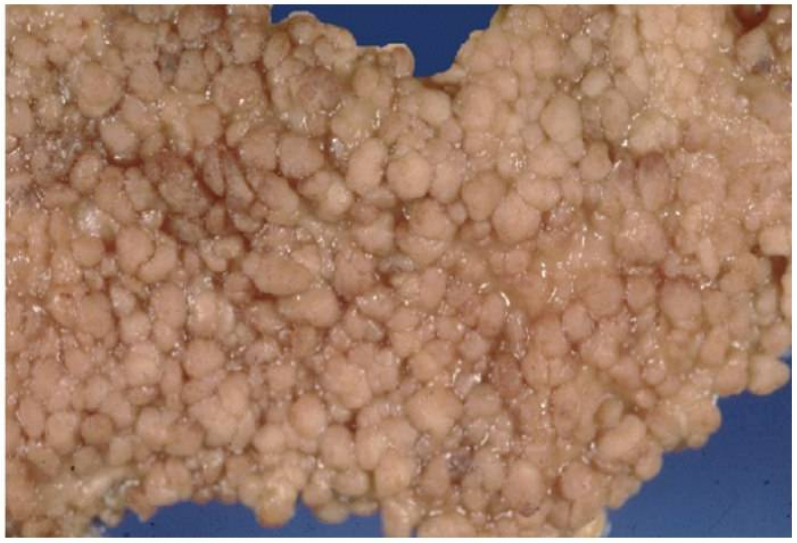
The Cancer Genome Atlas

Understanding genom
to improve cancer ca

Determination of source of iron







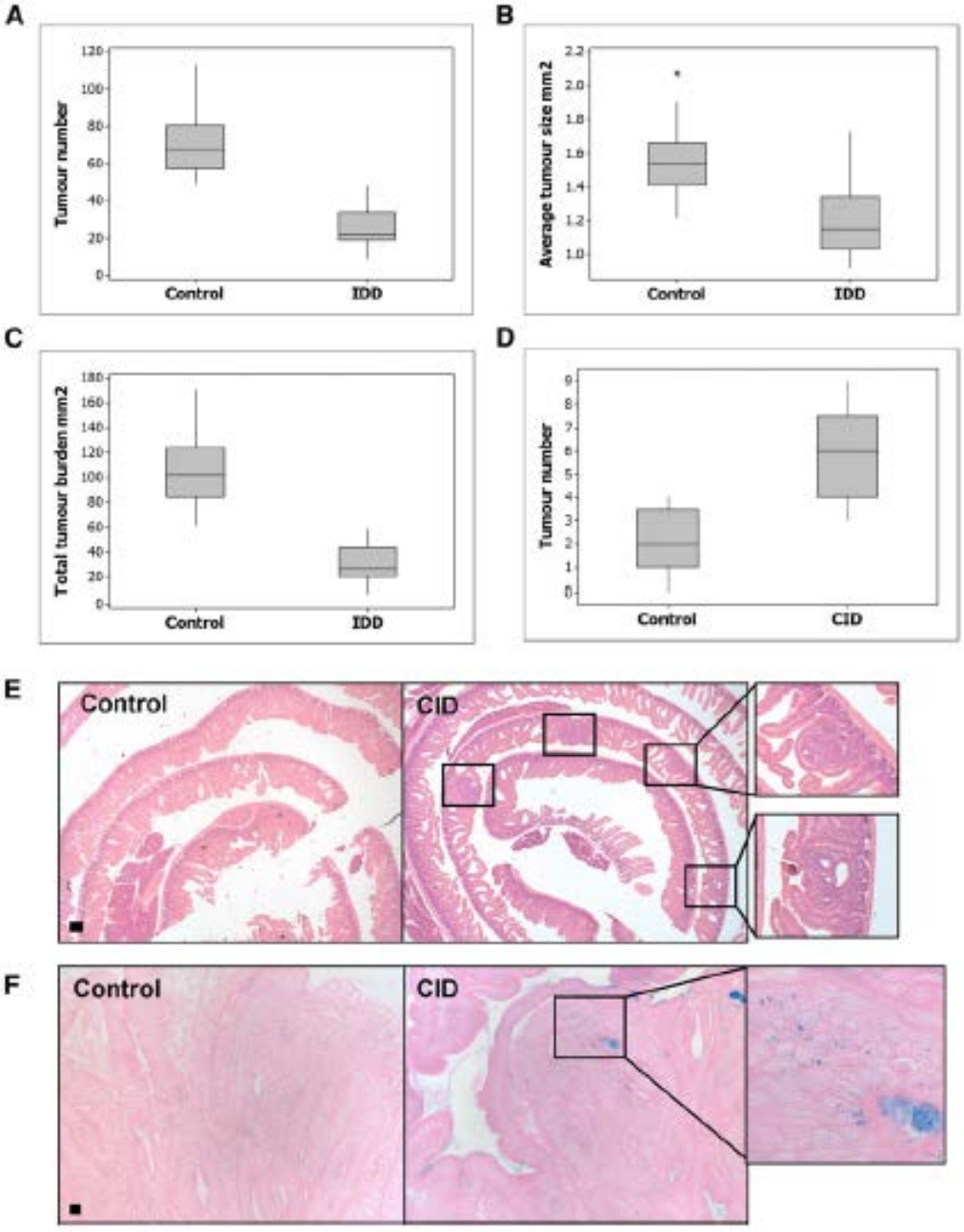
Regimes

- High Iron Diets
- Iron free Diets
- Manipulation of systemic iron levels

Cell Reports
Article

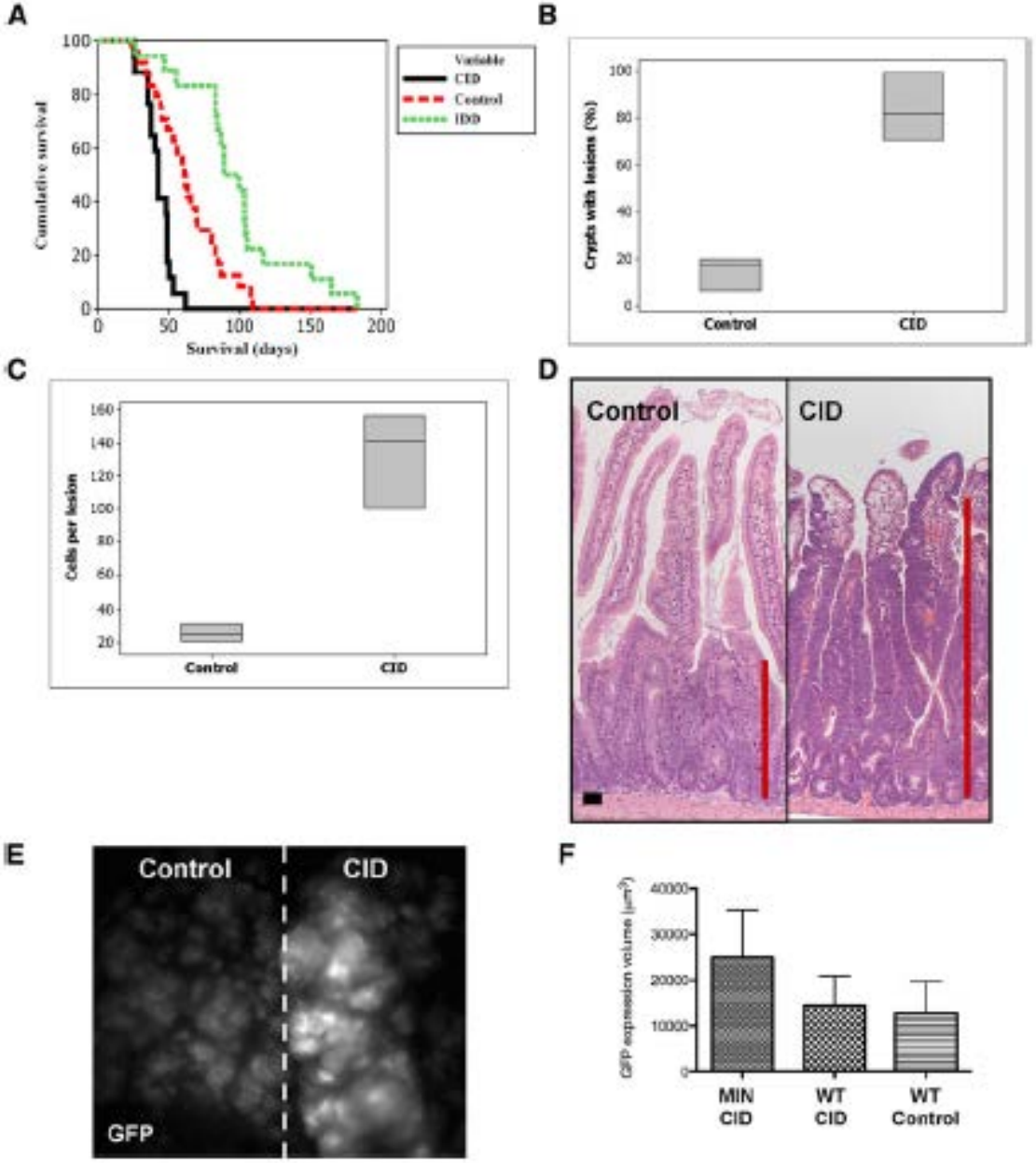
Luminal Iron Levels Govern Intestinal Tumorigenesis after *Apc* Loss In Vivo

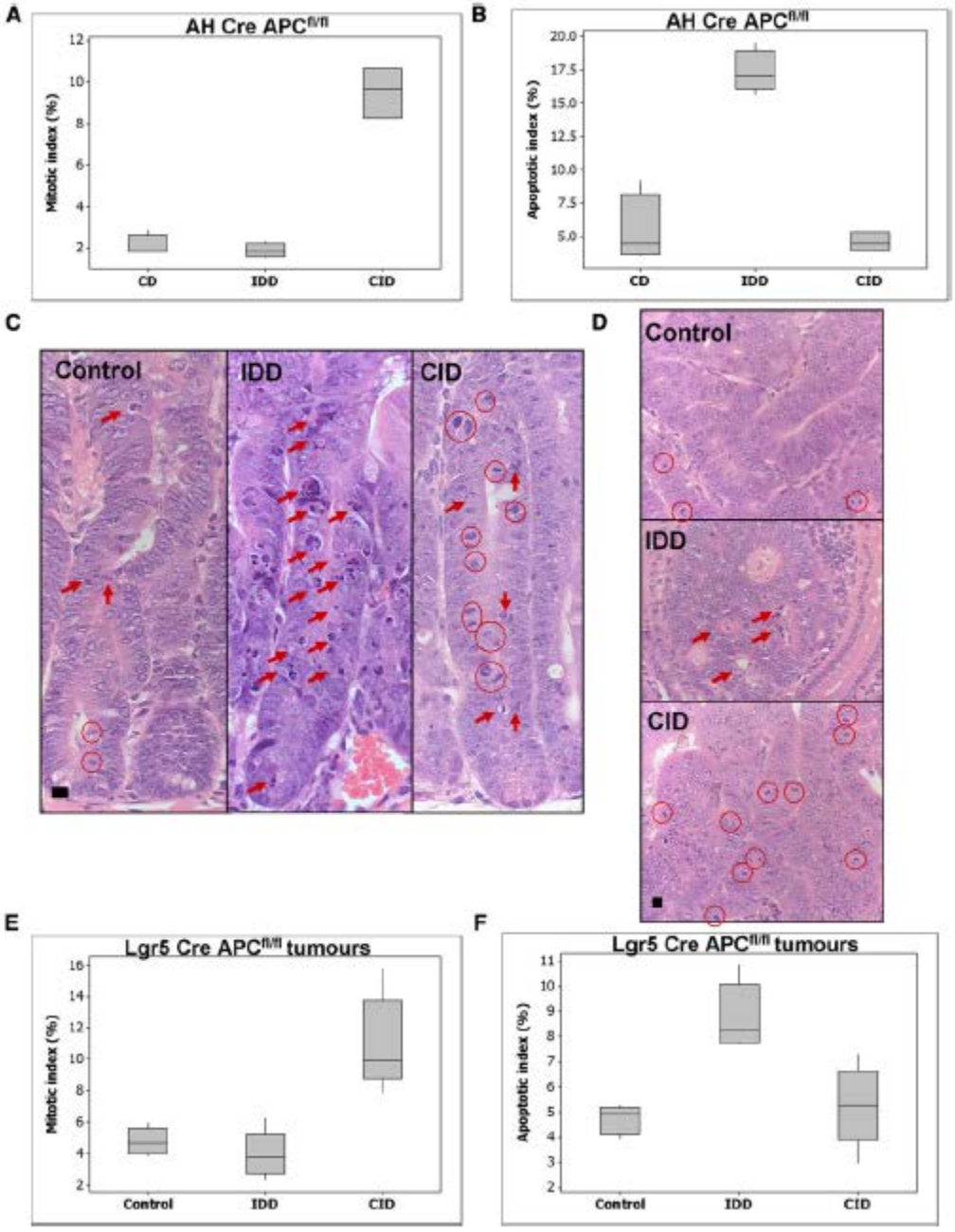
Sorina Radulescu,[1] Matthew J. Brookes,[2] Pedro Salgueiro,[1] Rachel A. Ridgway,[1] Ewan McGhee,[1] Kurt Anderson,[1] Samuel J. Ford,[2] Daniel H. Stones,[2] Tariq H. Iqbal,[2] Chris Tselepis,[2,*] and Owen J. Sansom[1,*]
[1]Beatson Institute of Cancer Research, Glasgow, G61 1BD, UK
[2]Birmingham Cancer Research UK Centre, School of Cancer Sciences, University of Birmingham B15 2TH, UK
*Correspondence: c.tselepis@bham.ac.uk (C.T.), o.sansom@beatson.gla.ac.uk (O.J.S.)
http://dx.doi.org/10.1016/j.celrep.2012.07.003

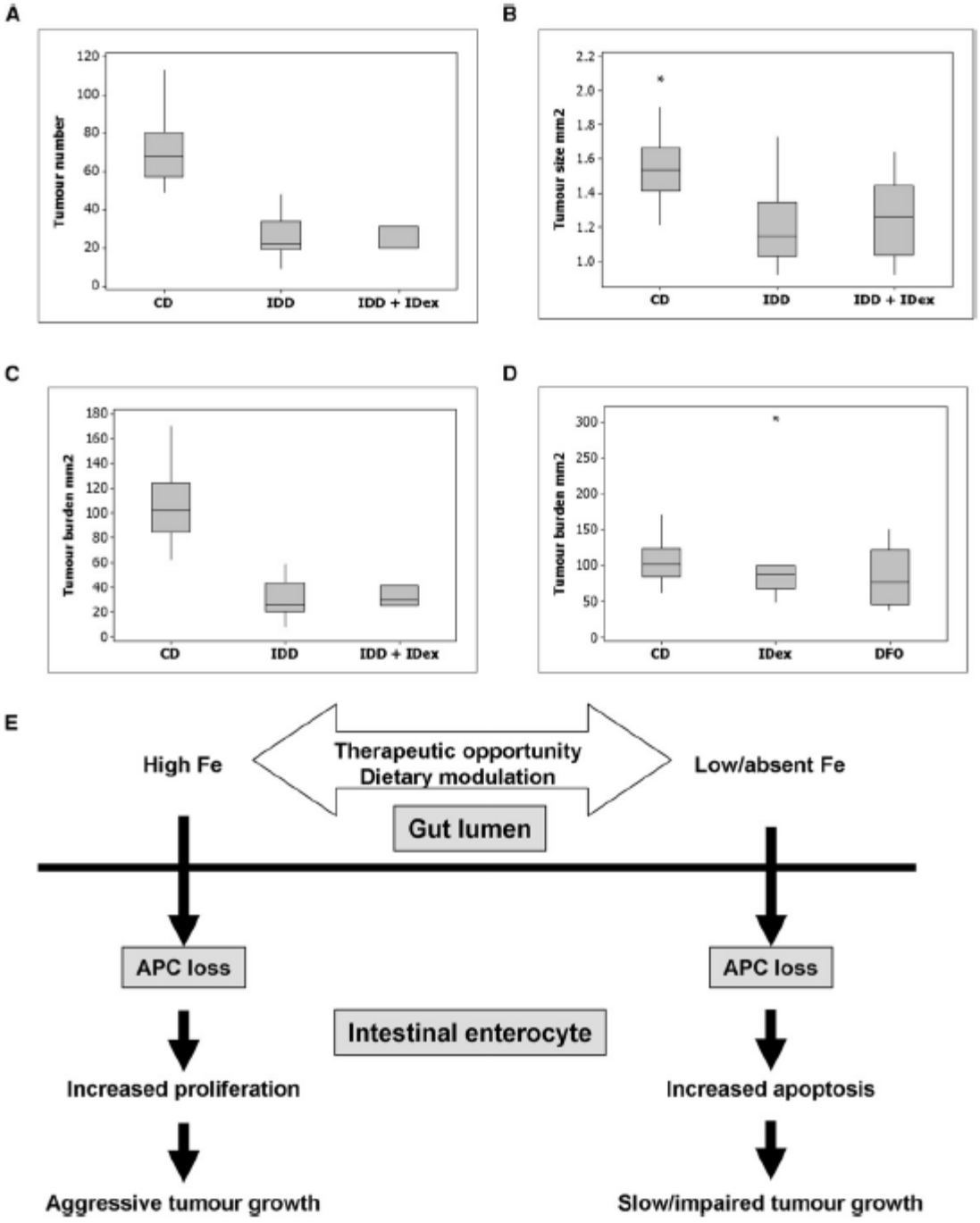

A
Tumour number
120
100
80
60
40
20
0
Control
IDD
B
Average tumour size mm2
2.2
2.0
1.8
1.6
1.4
1.2
1.0
*
Control
IDD
C
Total tumour burden mm2
180
160
140
120
100
80
60
40
20
0
Control
IDD
D
Tumour number
9
8
7
6
5
4
3
2
1
0
Control
CID
E
Control
CID
F
Control
CID

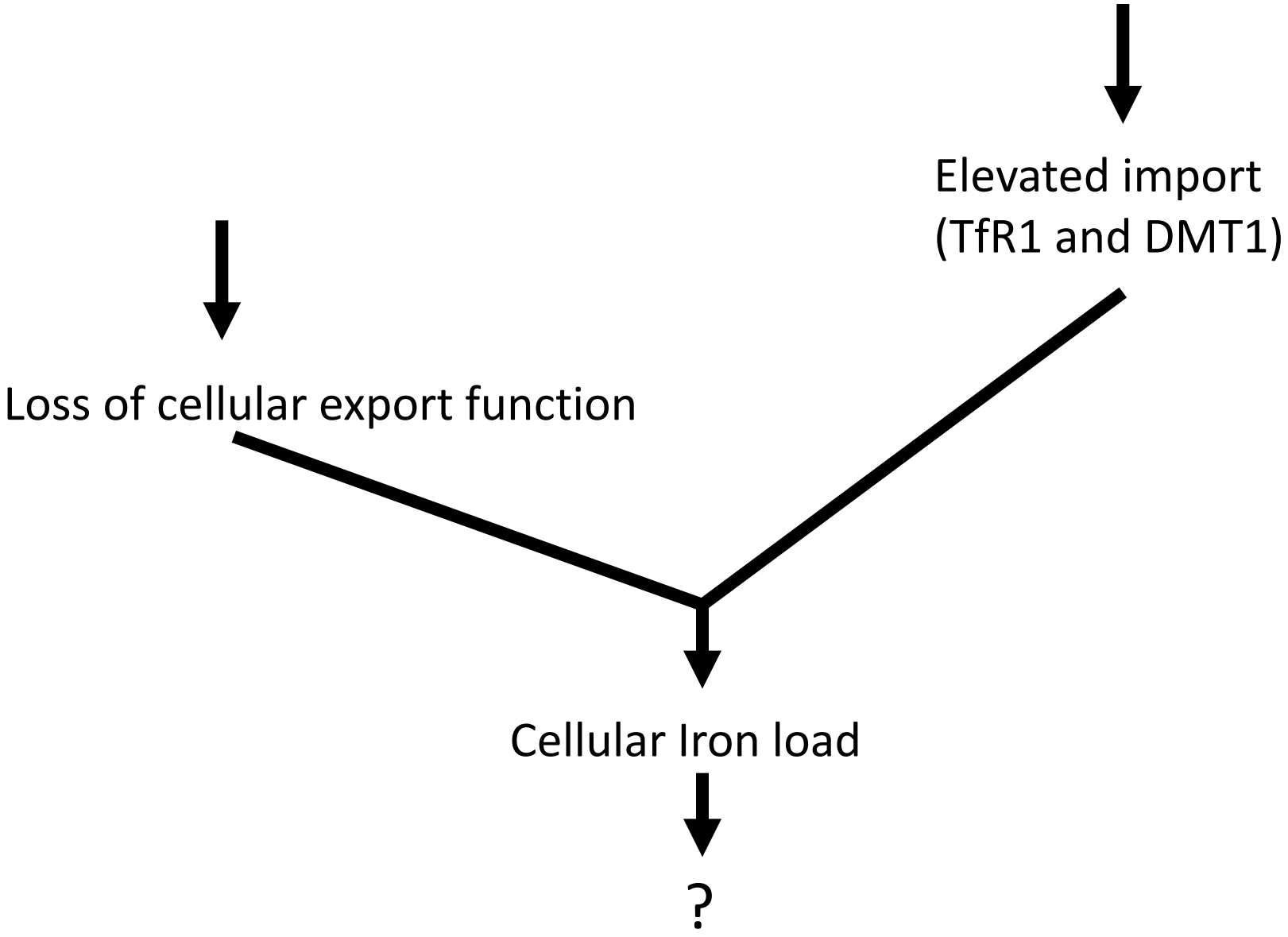
Summary

- Colon tissue expresses the machinery to metabolise luminal iron
- Iron transport machinery likely to be regulated by iron mediated wnt induction (cmyc)and IRP2.
- Importance of APC and BRAF
- Luminal iron exacerbates the cancer phenotype in APC mutant min mice

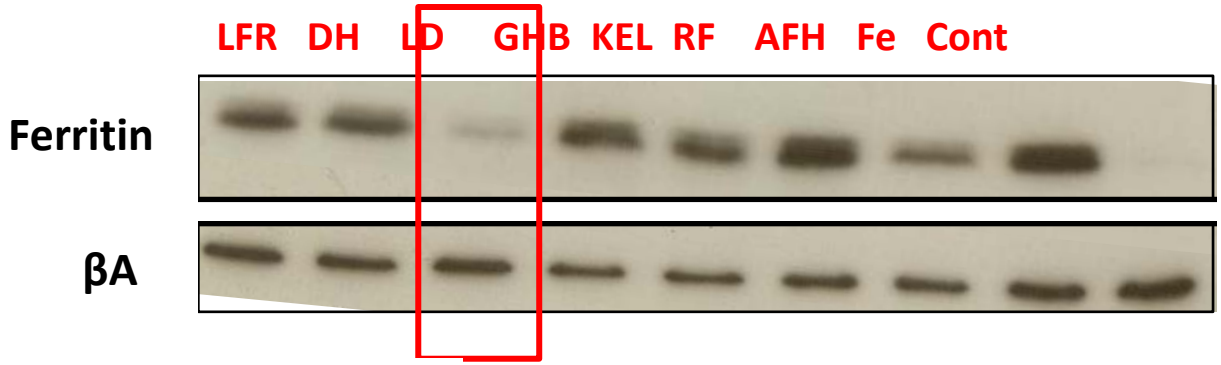

A
Cumulative survival
Survival (days)
Variable
CID
Control
IDD
B
Crypts with lesions (%)
Control
CID
C
Cells per lesion
Control
CID
D
Control
CID
E
Control
CID
GFP
F
GFP expression volume (μm³)
MIN CID
WT CID
WT Control

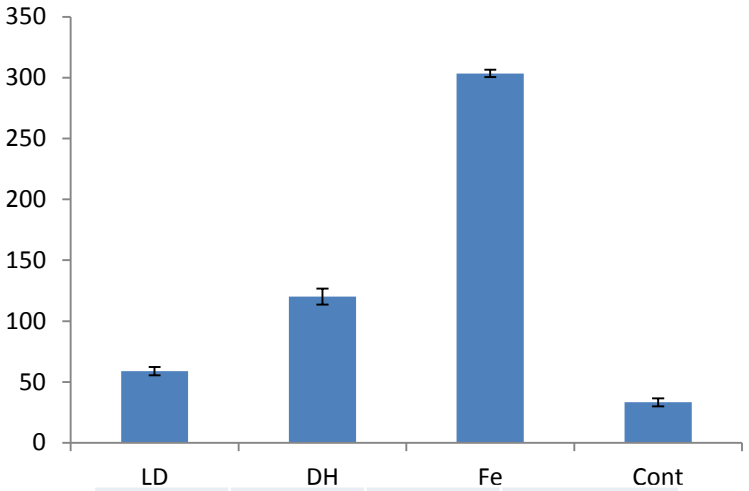

A
AH Cre APC fl/fl
Mitotic index (%)
12
10
8
6
4
2
CD
IDD
CID
B
AH Cre APC fl/fl
Apoptotic index (%)
20.0
17.5
15.0
12.5
10.0
7.5
5.0
CD
IDD
CID
C
Control
IDD
CID
D
Control
IDD
CID
E
Lgr5 Cre APC fl/fl tumours
Mitotic index (%)
16
14
12
10
8
6
4
2
Control
IDD
CID
F
Lgr5 Cre APC fl/fl tumours
Apoptotic index (%)
11
10
9
8
7
6
5
4
3
2
Control
IDD
CID


A
Tumour number
120
100
80
60
40
20
0
CD
IDD
IDD + IDex
B
Tumour size mm2
2.2
2.0
1.8
1.6
1.4
1.2
1.0
*
CD
IDD
IDD + IDex
C
Tumour burden mm2
180
160
140
120
100
80
60
40
20
0
CD
IDD
IDD + IDex
D
Tumour burden mm2
300
250
200
150
100
50
0
*
CD
IDex
DFO
E
High Fe
Therapeutic opportunity
Dietary modulation
Low/absent Fe
Gut lumen
APC loss
APC loss
Intestinal enterocyte
Increased proliferation
Increased apoptosis
Aggressive tumour growth
Slow/impaired tumour growth

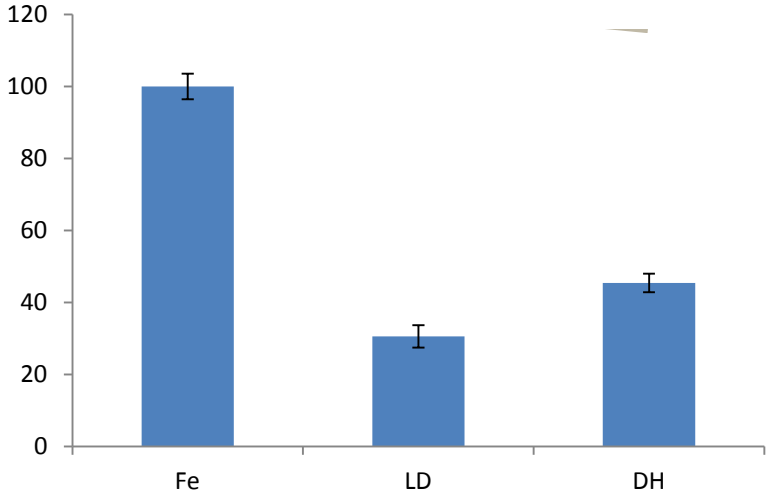

Elevated import
(TfR1 and DMT1)
Loss of cellular export function
Cellular Iron load
?

Iron chelation as a therapy?





	Mean	StD	SE	TTEST	
LD	**58.76311**	4.844179	3.425352	1.08909E-09	0.000281
DH	**120.1982**	9.298416	6.574973	3.81246E-06	
Fe	**303.4382**	4.298105	3.039219		
Cont	**33.26446**	4.567358	3.22961		



	CPM/P	StD	SE	TTEST
Fe	99.98485	8.711448	3.556434	3.74338E-07
LD	30.54795	6.913571	3.091843	4.83734E-07
DH	45.40872	6.267536	2.558711	

Ferritin expression as a biomarker to determine alginate iron chelation using ELISA

Cell Lysate (IC [Fe])

APC Hom Lgr5 Murine Model

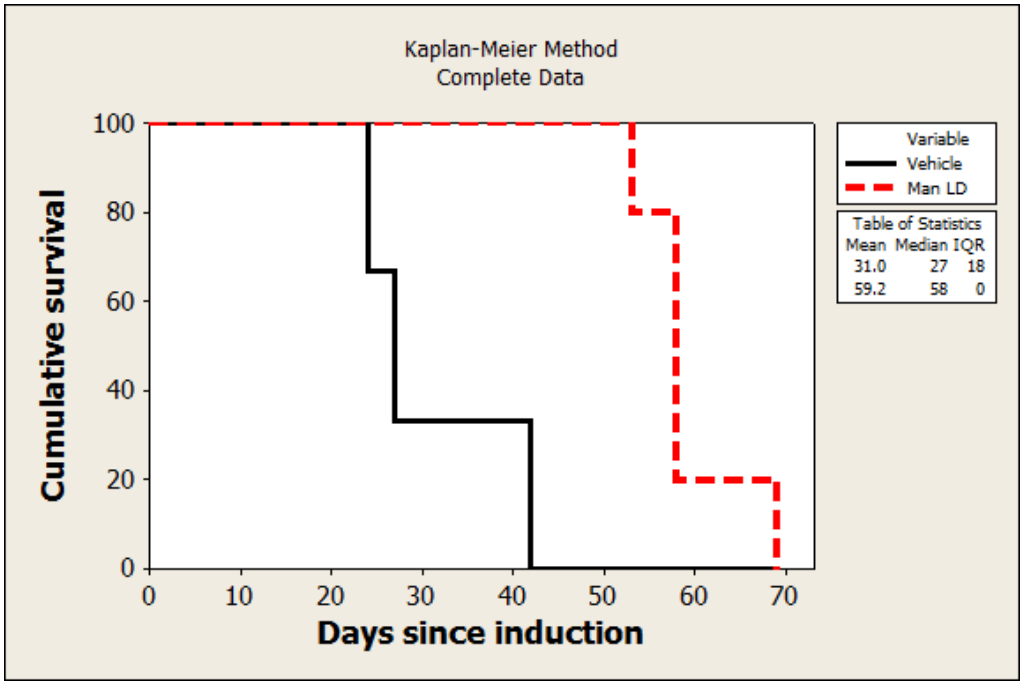
Birth

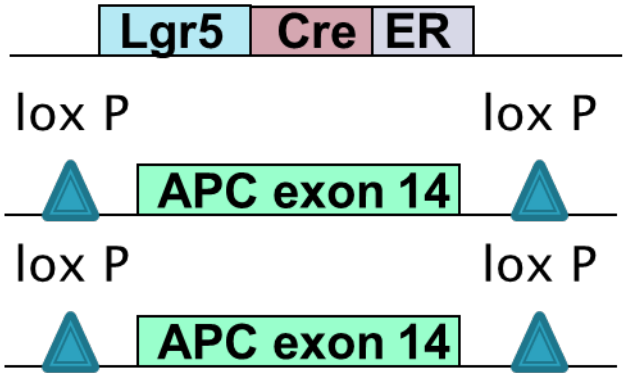
Manucol LD 8% gavage 3 times a week (Mon, Wed, Fri)

6 – 10 weeks

Tamoxifen induction 1 injection

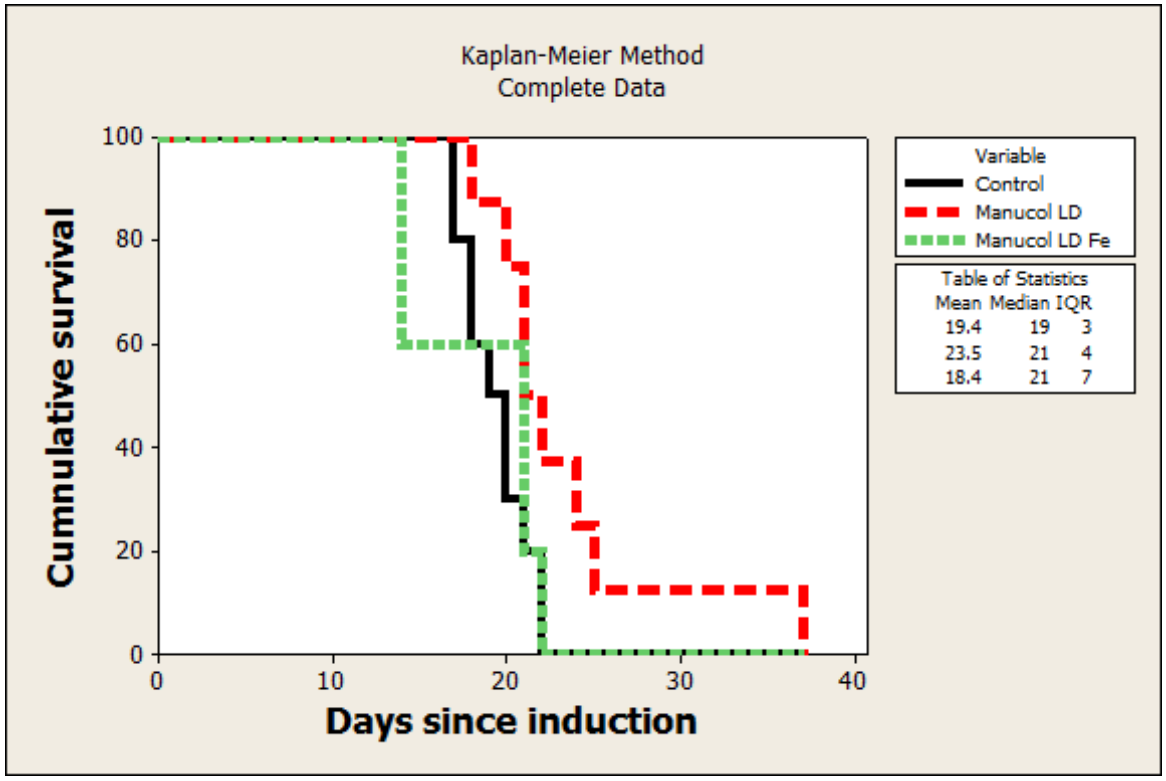
Survival





Log-Rank p = 0.004

Lgr5 tumour free survival - Manucol LD Fe loaded



APC HOM PTEN HOM Murine Model

Manucol LD 8% gavage 3 times a week (Mon, Wed, Fri)

Birth

6 – 10 weeks

Survival

Tamoxifen induction
1 injection