The Transcription Factor ATF4 in the Kidney & ccRCC (Clear Cell Renal Cell Carcinoma)

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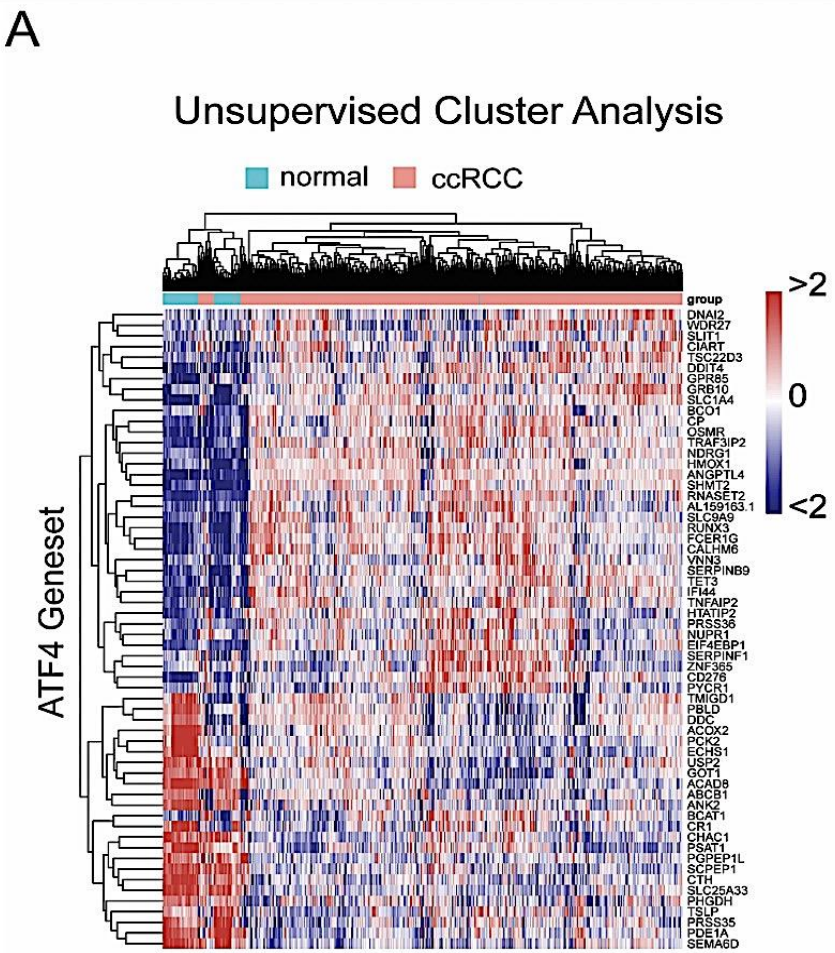
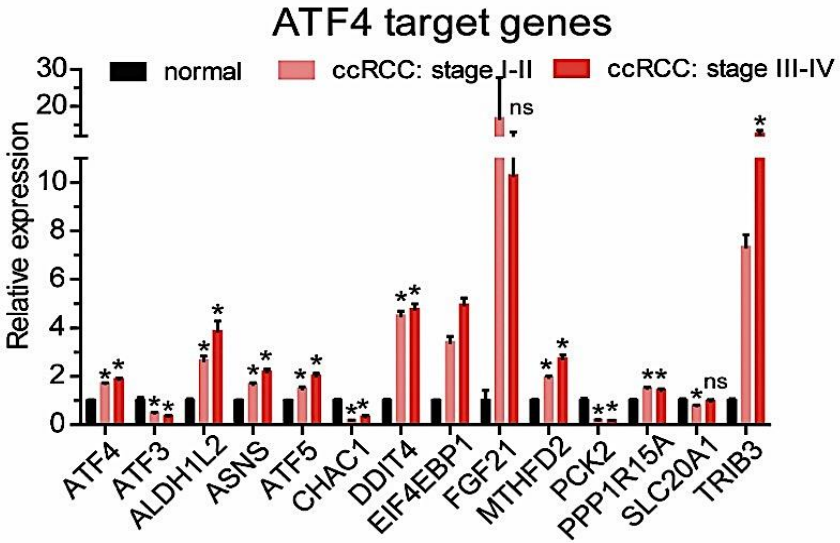
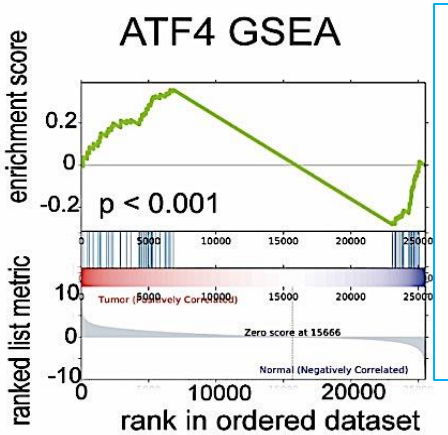
September 12, 2025

A Strong ATF4/Integrated Stress Response Signal in Human Clear Cell Renal Cell Carcinoma vs. Normal Kidney







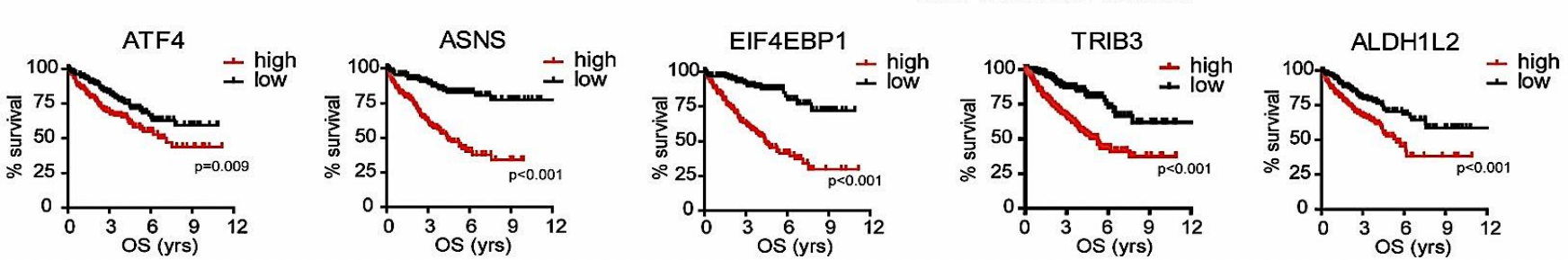
> Mol Carcinog. 2022 Sep;61(9):851-864. doi: 10.1002/mc.23437. Epub 2022 Jun 21.

Transcriptional and metabolic remodeling in clear cell renal cell carcinoma caused by ATF4 activation and the integrated stress response (ISR)

Johannes C van der Mijn [1], Qiuying Chen [1], Kristian B Laursen [1], Francesca Khani [2 3], Xiaofei Wang [4 5], Princesca Dorsaint [4 5], Andrea Sboner [2 5 6 7], Steven S Gross [1], David M Nanus [8 3], Lorraine J Gudas [1 3]

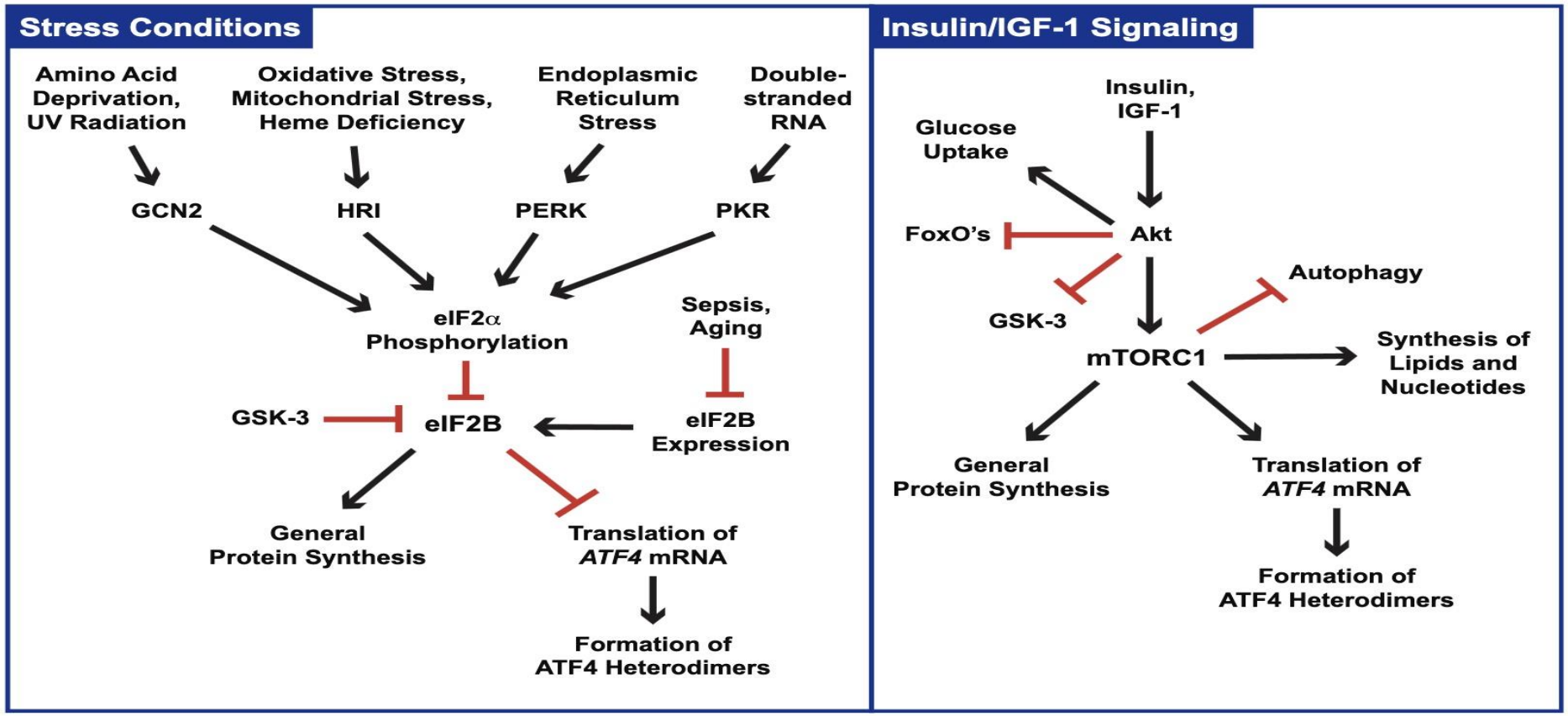
Affiliations + expand

PMID: 35726553 PMCID: PMC9378514 DOI: 10.1002/mc.23437



What is ATF4? A transcription factor that is involved in the Integrated Stress Response (ISR).

The integrated stress response (ISR) is an elaborate signaling pathway present in eukaryotic cells which is activated in response to a range of physiological changes and different pathological conditions.
Such stresses commonly include cell extrinsic factors such as hypoxia, amino acid deprivation, glucose deprivation, and viral infection. The ISR can also be activated by oncogene activation...



from J. Nutrition 2022 152:926 *Ebert et al.*

ATF4 has multiple roles in cognition, aging, & mitochondria

> Front Cell Neurosci. 2022 Sep 21:16:992869. doi: 10.3389/fncel.2022.992869. eCollection 2022.

Inhibition of the integrated stress response reverses oxidative stress damage-induced postoperative cognitive dysfunction

Linhao Jiang [1 2 3 4], Rui Dong [1 2 3 4], Minh
Zhengliang Ma [1], Tianjiao Xia [2 3 4], Xiaoping

Affiliations + expand

PMID: 36212697 PMCID: PMC9534309 DO

> Science. 2021 Sep 3;373(6559):1156-1161. doi: 10.1126/science.abb3414. Epub 2021 Sep 1.

The integrated stress response contributes to tRNA synthetase-associated peripheral neuropathy

E L Spaulding [1 2], T J Hines [1], P Bais [1], A L D Tadenev [1], R Schneider [1], D Jewett [1], B Pattavina [1], S L Pratt [1 3], K H Morelli [1 2], M G Stum [1], D P Hill [1], C Gobet [4], M Pipis [5], M M Reilly [5], M J Jennings [6], R Horvath [6], Y Bai [7], M E Shy [7], B Alvarez-Castelao [8], E M Schuman [8], L P Bogdanik [1], E Storkebaum [9], R W Burgess [1 2 3]

Affiliations + expand

> J Cell Biol. 2017 Jul 3;216(7):2027-2045. doi: 10.1083/jcb.201702058. Epub 2017 May 31.

Multi-omics analysis identifies ATF4 as a key regulator of the mitochondrial stress response in mammals

Pedro M Quirós [1], Miguel A Prado [2], Nicola Zamboni [3], Davide D'Amico [1], Robert W Williams [4], Daniel Finley [2], Steven P Gygi [2], Johan Auwerx [5]

Affiliations + expand

PMID: 28566324 PMCID: PMC5496626 DOI: 10.1083/jcb.201702058

> Geroscience. 2023 Aug;45(4):2525-2543. doi: 10.1007/s11357-023-00772-y. Epub 2023 Apr 4.

The transcription regulator ATF4 is a mediator of skeletal muscle aging

Matthew J Miller [1 2], George R Marcotte [1 2], Nathan Basisty [3 4], Cameron Wehrfritz [3], Zachary C Ryan [1], Matthew D Strub [1], Andrew T McKeen [2], Jennifer I Stern [1], Karl A Nath [1], Blake B Rasmussen [5 6], Andrew R Judge [7 6], Birgit Schilling [3], Scott M Ebert [8 9], Christopher M Adams [10 11 12]

Affiliations + expand

nature communications

Article

https://doi.org/10.1038/s41467-024-46696-9

A fast-acting lipid checkpoint in G1 prevents mitotic defects

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Check for updates

Marielle S. Köberlin [1,2], Yilin Fan[1,6], Chad Liu [1,7], Mingyu Chung[1,8], Antonio F. M. Pinto[3], Peter K. Jackson[2,4], Alan Saghatelian[3] & Tobias Meyer [1,5]

Lipid synthesis increases during the cell cycle to ensure sufficient membrane mass, but how insufficient synthesis restricts cell-cycle entry is not understood. Here, we identify a lipid checkpoint in G1 phase of the mammalian cell cycle by using live single-cell imaging, lipidome, and transcriptome analysis of a non-transformed cell. We show that synthesis of fatty acids in G1 not only increases lipid mass but extensively shifts the lipid composition to unsaturated phospholipids and neutral lipids. Strikingly, acute lowering of lipid synthesis rapidly activates the PERK/ATF4 endoplasmic reticulum (ER) stress pathway that blocks cell-cycle entry by increasing p21 levels, decreasing Cyclin D levels, and suppressing Retinoblastoma protein phosphorylation. Together, our study identifies a rapid anticipatory ER lipid checkpoint in G1 that prevents cells from starting the cell cycle as long as lipid synthesis is low, thereby preventing mitotic defects, which are triggered by low lipid synthesis much later in mitosis.

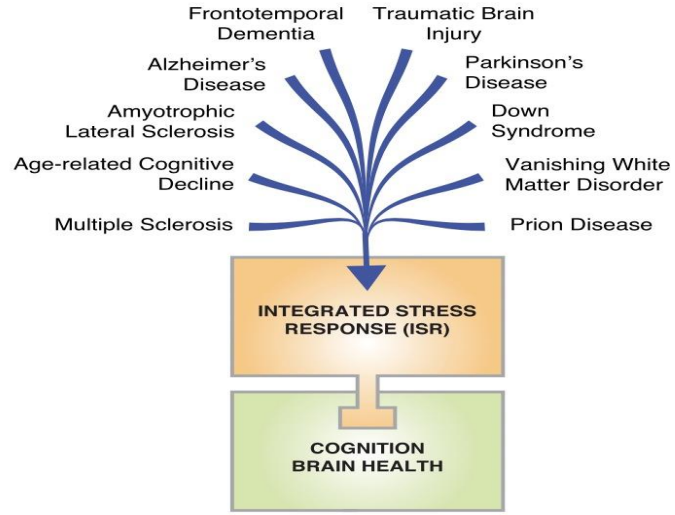


Fig. 3. The ISR in brain disorders. The ISR is a causative mechanism underlying the cognitive deficits and neurodegeneration in a wide broad range of brain disorders.

> Cancer Res. 2021 Aug 1;81(15):4066-4078. doi: 10.1158/0008-5472.CAN-20-3956. Epub 2021 Jun 28.

Stress-Mediated Reprogramming of Prostate Cancer One-Carbon Cycle Drives Disease Progression

Nora Pällmann [# 1], Ke Deng [# 2], Marte Livgård [1 2], Martina Tesikova [3], Yixin Jin [1], Nicolai Sebastian Frengen [1], Nermin Kahraman [4], Hamada M Mokhlis [4 5], Bulent Ozpolat [4], Wanja Kildal [2], Havard Emil Danielsen [2 6 7 8], Ladan Fazli [9], Paul S Rennie [9], Partha P Banerjee [10], Aykut Üren [11], Yang Jin [1], Omer F Kuzu [12], Fahri Saatcioglu [12 2]

Affiliations + expand

PMID: 34183356 DOI: 10.1158/0008-5472.CAN-20-3956

Abstract

One-carbon (1C) metabolism has a key role in metabolic programming with both mitochondrial (m1C) and cytoplasmic (c1C) components. Here we show that activating transcription factor 4 (ATF4) exclusively activates gene expression involved in m1C, but not the c1C cycle in prostate cancer cells. This includes activation of methylenetetrahydrofolate dehydrogenase 2 (MTHFD2) expression, the central player in the m1C cycle. Consistent with the key role of m1C cycle in prostate cancer, MTHFD2 knockdown inhibited prostate cancer cell growth, prostatosphere formation, and growth of patient-derived xenograft organoids. In addition, therapeutic silencing of MTHFD2 by systemically administered nanoliposomal siRNA profoundly inhibited tumor growth in preclinical prostate cancer mouse models. Consistently, MTHFD2 expression is significantly increased in human prostate cancer, and a gene expression signature based on the m1C cycle has significant prognostic value. Furthermore, MTHFD2 expression is coordinately regulated by ATF4

> J Clin Invest. 2012 Dec;122(12):4621-34. doi: 10.1172/JCI62973. Epub 2012 Nov 12.

ER stress-mediated autophagy promotes Myc-dependent transformation and tumor growth

Lori S Hart [1], John T Cunningham, Tatini Datta, Souvik Dey, Feven Tameire, Stacey L Lehman, Bo Qiu, Haiyan Zhang, George Cerniglia, Meixia Bi, Yan Li, Yan Gao, Huayi Liu, Changhong Li, Amit Maity, Andrei Thomas-Tikhonenko, Alexander E Perl, Albert Koong, Serge Y Fuchs, J Alan Diehl, Ian G Mills, Davide Ruggero, Constantinos Koumenis

Affiliations + expand

PMID: 23143306 PMCID: PMC3533536 DOI: 10.1172/JCI62973

Abstract

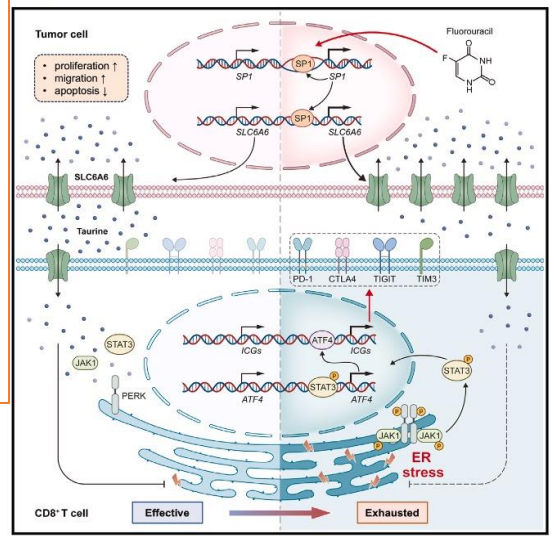
The proto-oncogene c-Myc paradoxically activates both proliferation and apoptosis. In the pathogenic state, c-Myc-induced apoptosis is bypassed via a critical, yet poorly understood escape mechanism that promotes cellular transformation and tumorigenesis. The accumulation of unfolded proteins in the ER initiates a cellular stress program termed the unfolded protein response (UPR) to support cell survival. Analysis of spontaneous mouse and human lymphomas demonstrated significantly higher levels of UPR activation compared with normal tissues. Using multiple genetic models, we demonstrated that c-Myc and N-Myc activated the PERK/eIF2α/ATF4 arm of the UPR, leading to increased cell survival via the induction of cytoprotective autophagy. Inhibition of PERK significantly reduced Myc-induced autophagy, colony formation, and tumor formation. Moreover, pharmacologic or genetic inhibition of autophagy resulted in increased Myc-dependent apoptosis. Mechanistically, we demonstrated an important link between Myc-dependent increases in protein synthesis and UPR activation. Specifically, by employing a mouse minute (L24+/-) mutant, which resulted in wild-type levels of protein synthesis and attenuation of Myc-induced lymphomagenesis, we showed that Myc-induced UPR activation was reversed. Our findings establish a role for UPR as an enhancer of c-Myc-induced transformation and suggest that UPR inhibition may be particularly effective against malignancies characterized by c-Myc overexpression.

Cell

Article

Cancer SLC6A6-mediated taurine uptake transactivates immune checkpoint genes and induces exhaustion in CD8$^+$ T cells

Graphical abstract



Authors

Tianyu Cao, Wenyao Zhang, Qi Wang, ..., Yongzhan Nie, Yuanyuan Lu, Xiaodi Zhao

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In brief

Through SLC6A6-mediated taurine uptake, cancer cells become more aggressive and induce CD8$^+$ T cell exhaustion by increasing ER stress and ATF4 transcription, resulting in immune evasion and tumor progression.

Highlights

- Tumoral SLC6A6 is associated with unfavorable clinical outcomes in multiple cancers
- Tumor cells that overexpress SLC6A6 outcompete CD8$^+$ T cells for taurine
- Taurine deficiency in CD8$^+$ T cells increases ER stress and ATF4 transcription
- ATF4 transactivates immune checkpoint genes and induces CD8$^+$ T cell exhaustion

Cao et al., 2024, Cell *187*, 1–17
April 25, 2024 © 2024 Elsevier Inc.
https://doi.org/10.1016/j.cell.2024.03.011

CellPress

> Nat Cell Biol. 2019 Jul;21(7):889-899. doi: 10.1038/s41556-019-0347-9. Epub 2019 Jul 1.

ATF4 couples MYC-dependent translational activity to bioenergetic demands during tumour progression

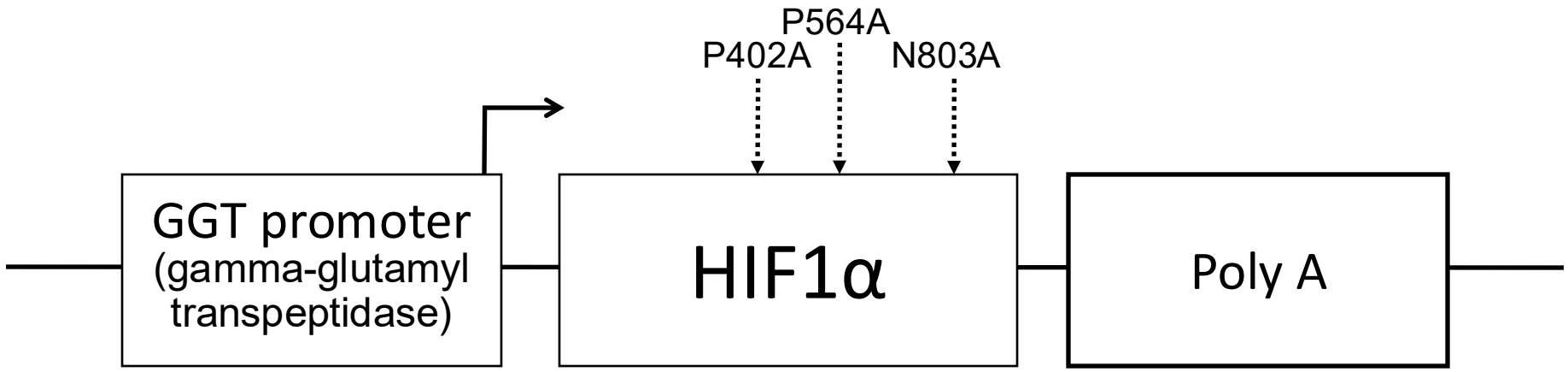
Feven Tameire [1], Ioannis I Verginadis [1], Nektaria Maria Leli [1], Christine Polte [2], Crystal S Conn [3], Rani Ojha [4], Carlo Salas Salinas [1], Frank Chinga [1], Alexandra M Monroy [1], Weixuan Fu [5], Paul Wang [5], Andrew Kossenkov [6], Jiangbin Ye [7], Ravi K Amaravadi [4], Zoya Ignatova [2], Serge Y Fuchs [8], J Alan Diehl [9], Davide Ruggero [3], Constantinos Koumenis [10]

Affiliations + expand

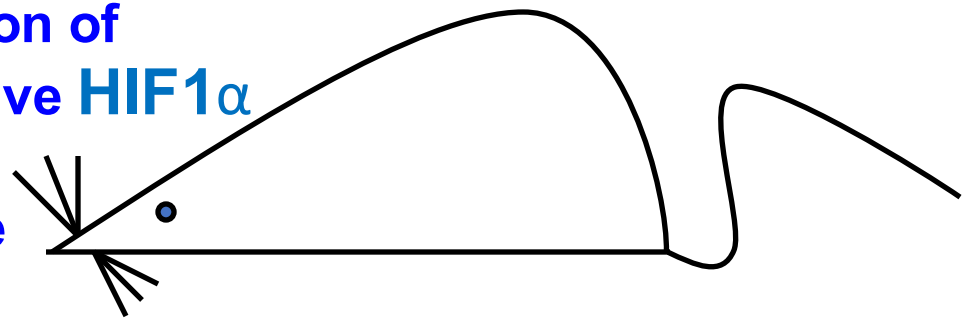
PMID: 31263264 PMCID: PMC6608727 DOI: 10.1038/s41556-019-0347-9

ATF4 is involved in Tumor Progression

Transgenic Mouse Construction: γ-HIF1α-M3 (TRACK; Transgenic Cancer of the Kidney) Mice



Specific expression of constitutively active HIF1α in proximal tubule cells of the kidney



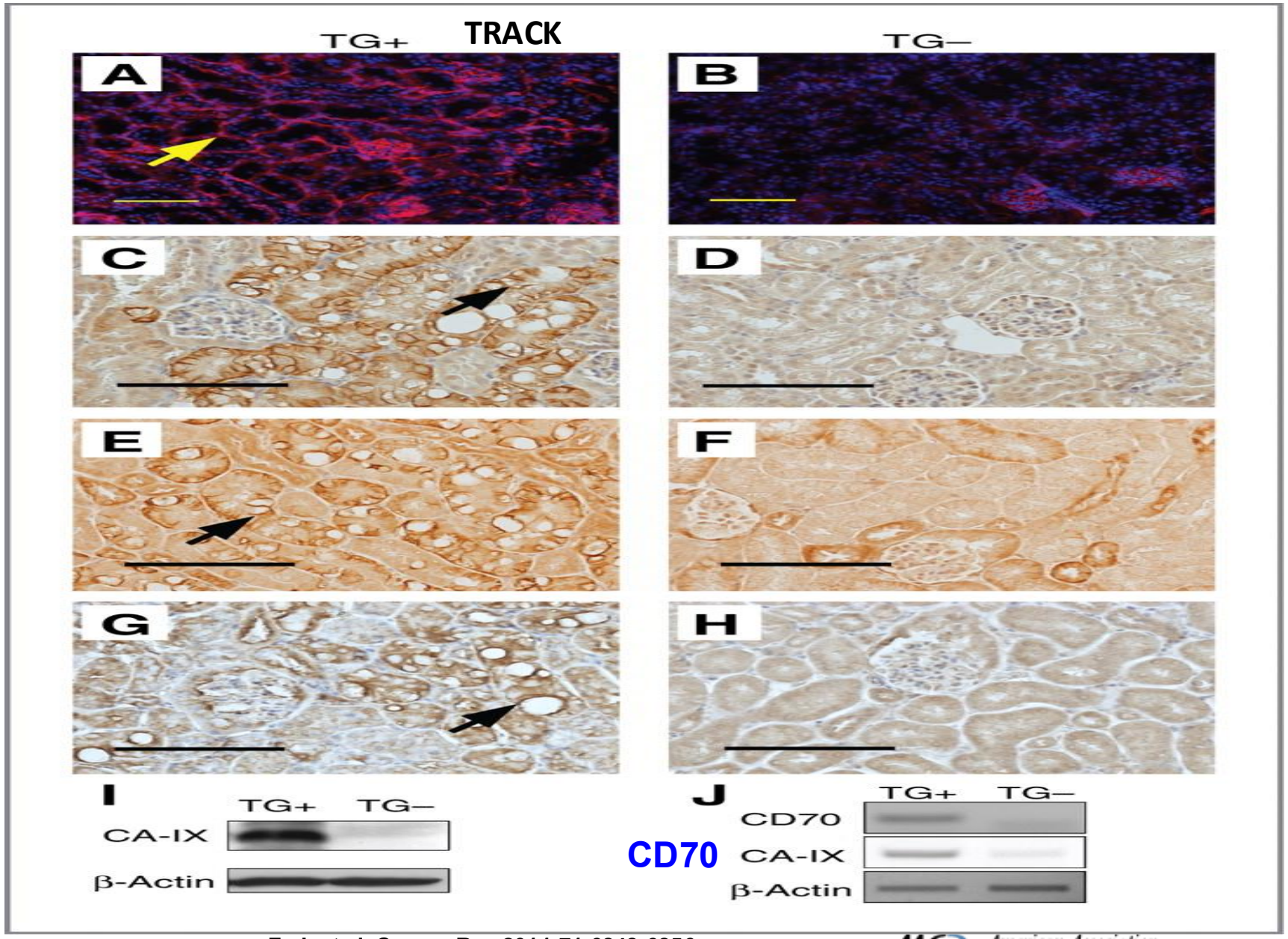
Expression of Early ccRCC markers in γ-HIF1α-M3-43 TRACK kidneys

CD31

CA9 (Carbonic Anhydrase 9)

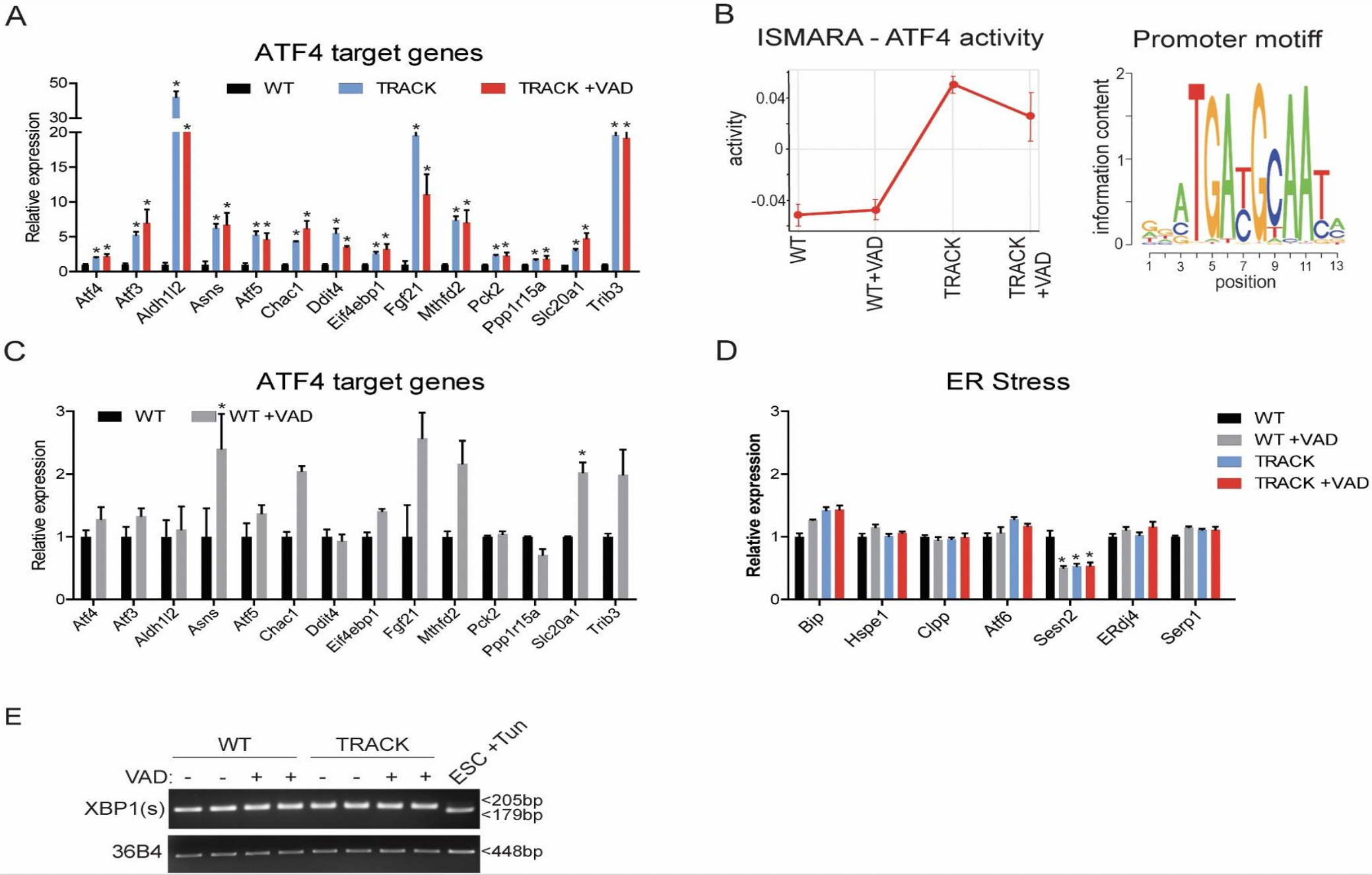
Glut1 (Slc2a1)

VEGF

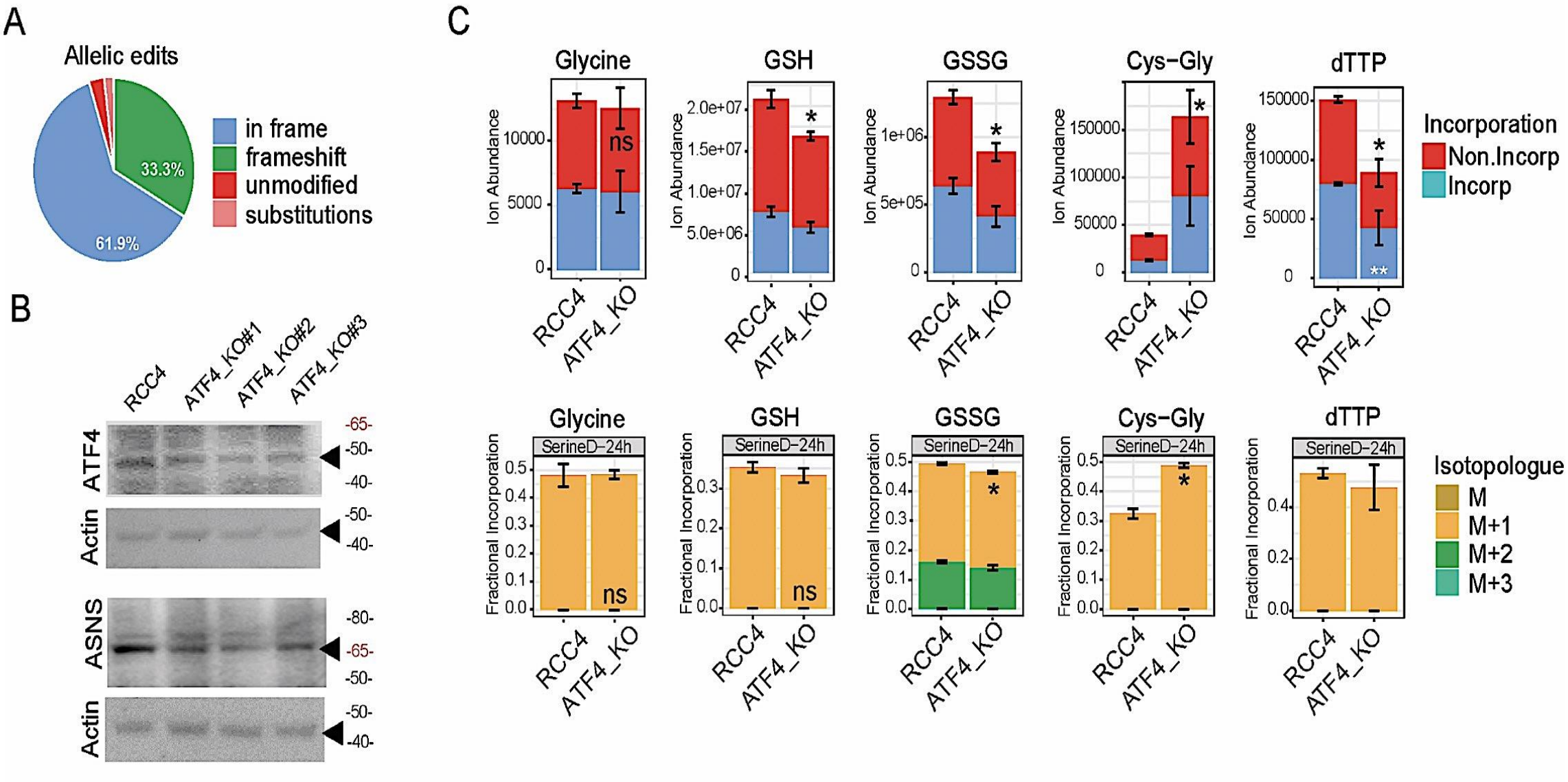


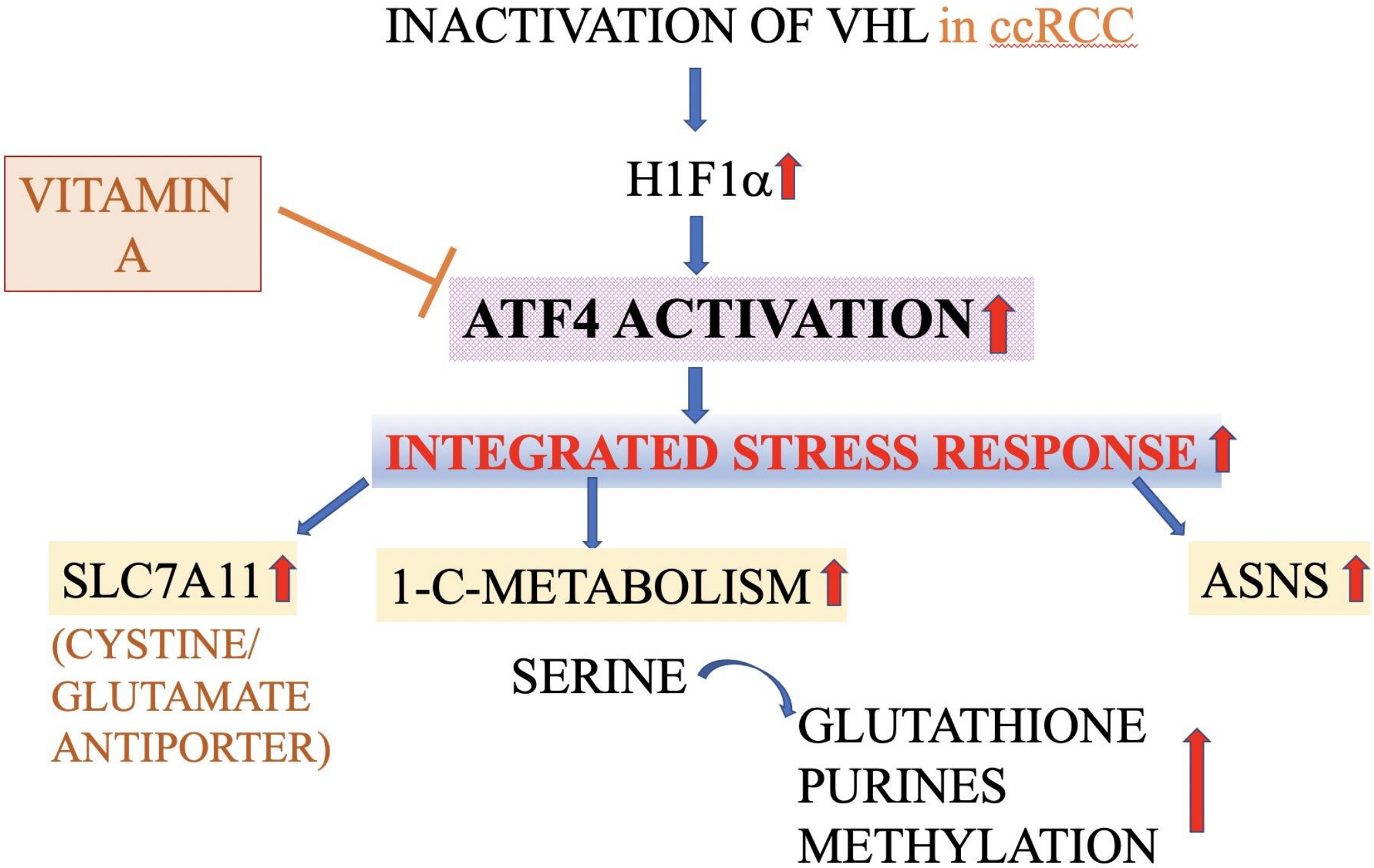
Fu L et al. Cancer Res 2011;71:6848-6856

ATF4 Target Genes are Also Highly Expressed in TRACK Mouse Kidneys vs. Wt Kidneys

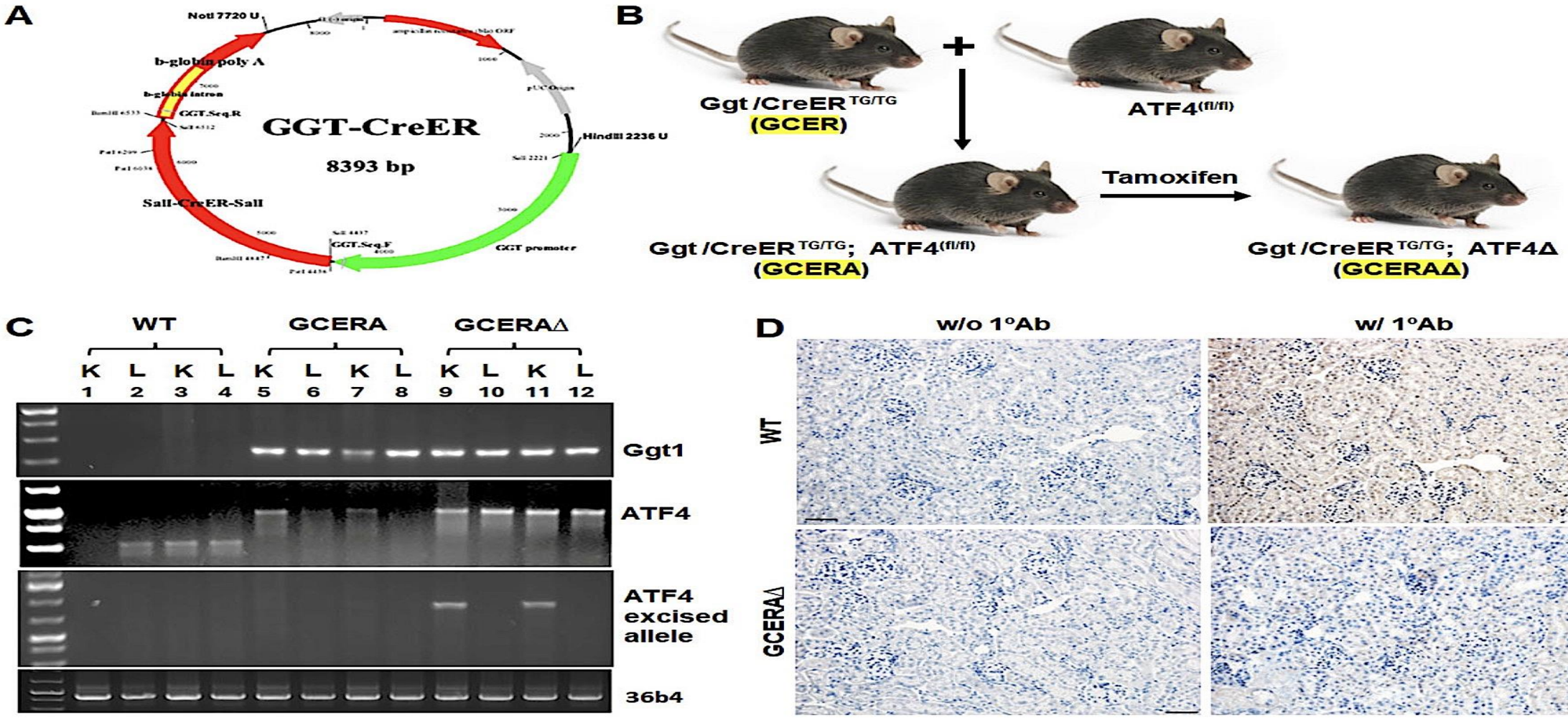


Metabolic isotope tracing demonstrates that ATF4 controls GSH (glutathione) biosynthesis through the mitochondrial one-carbon metabolism pathway.

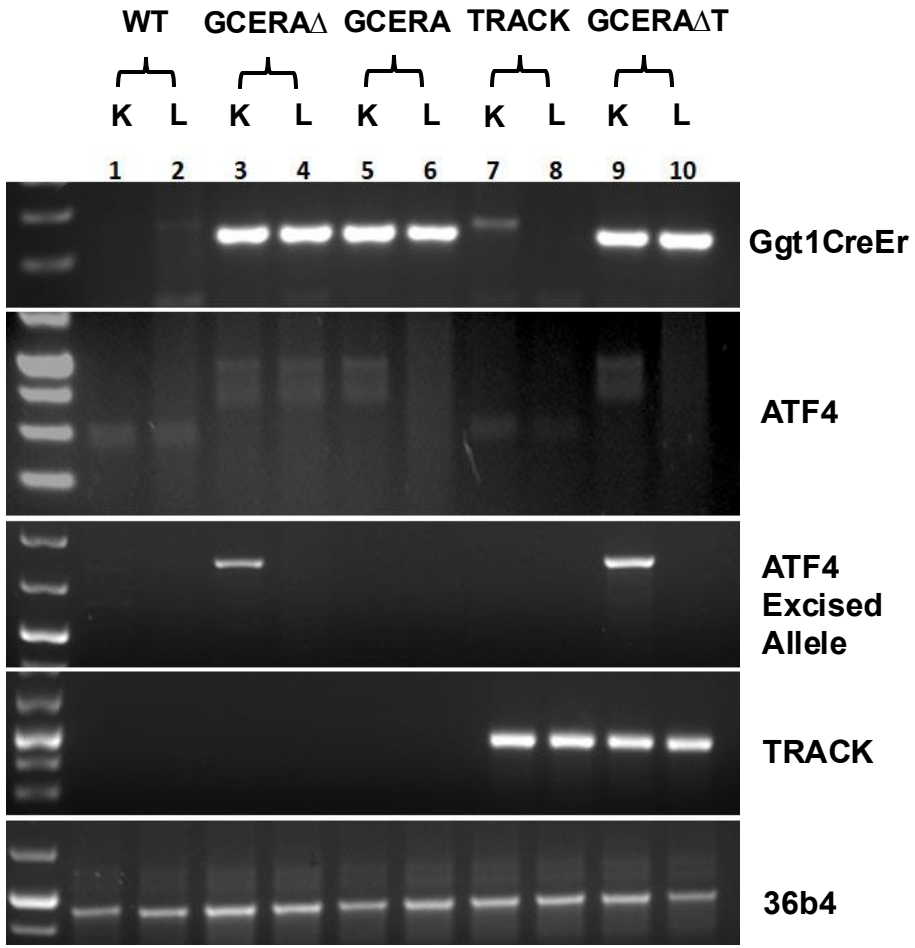



INACTIVATION OF VHL in ccRCC
H1F1α
VITAMIN A
ATF4 ACTIVATION
INTEGRATED STRESS RESPONSE
SLC7A11
(CYSTINE/ GLUTAMATE ANTIPORTER)
1-C-METABOLISM
SERINE
GLUTATHIONE
PURINES
METHYLATION
ASNS

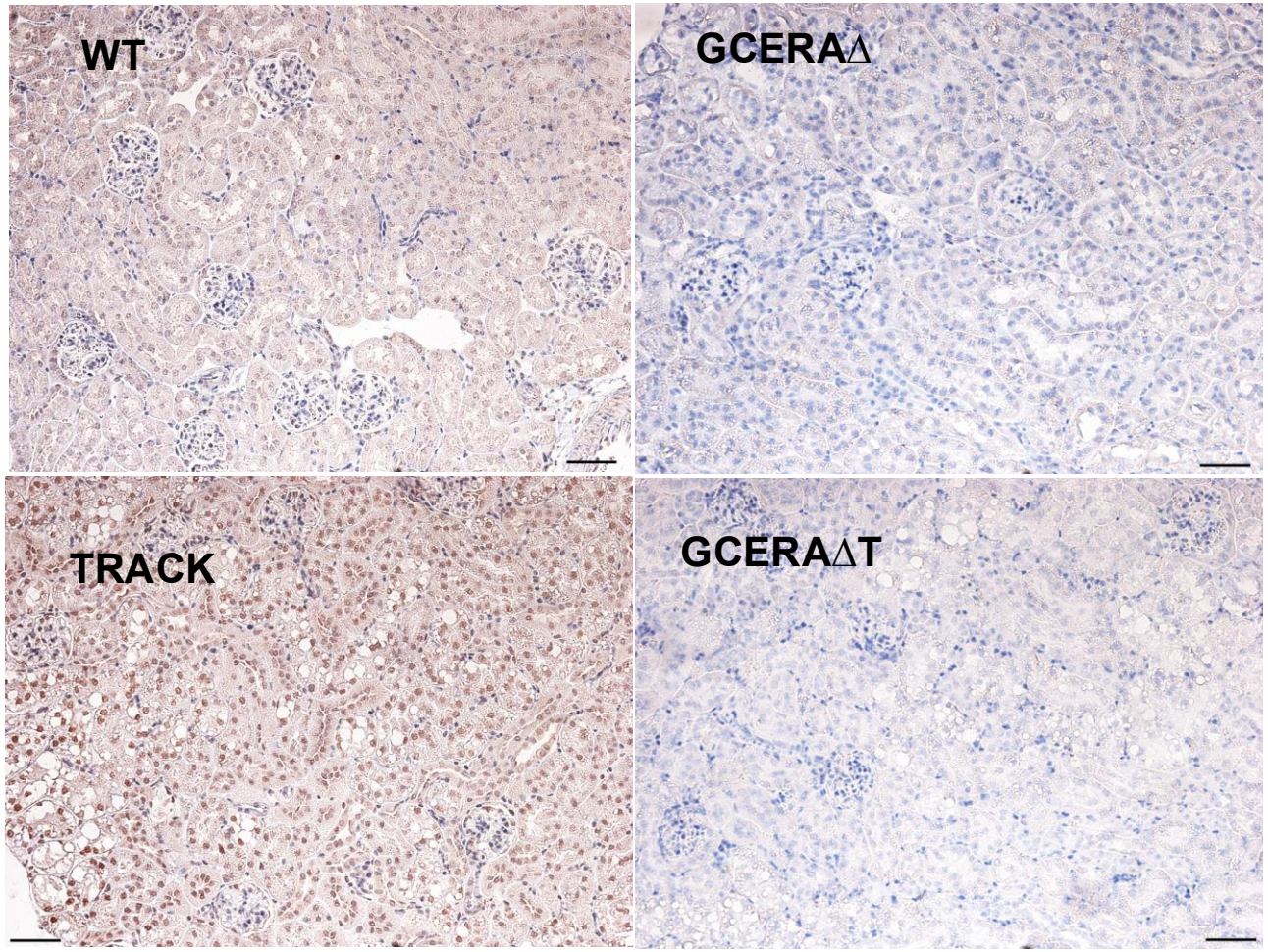
We next explored the effects of ATF4 in the normal kidney and in our murine model of ccRCC by knocking out ATF4 specifically in proximal tubule cells



We then crossed ggt/CreER;ATF4$^{fl/fl}$ mice with TRACK mice to assess how loss of ATF4 in kidney proximal tubule cells influenced the TRACK Tumorigenic Phenotype

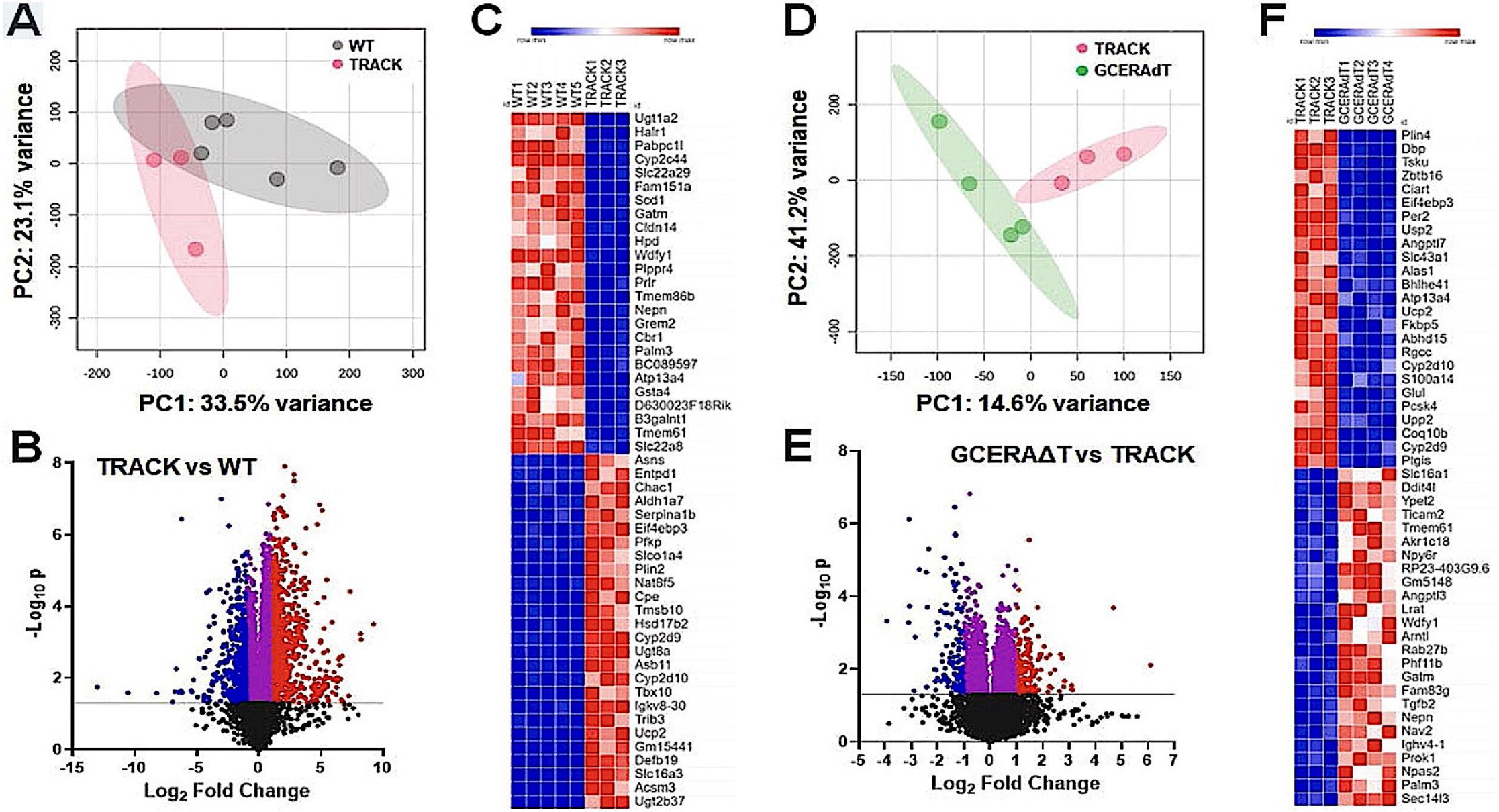


Verification of ATF4 deletion in proximal tubules and TRACK genotypes.



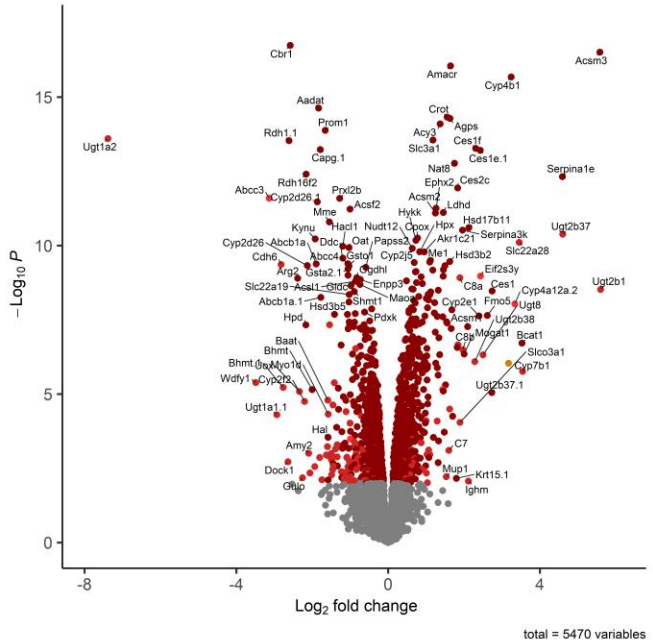
Staining for ATF4 in Proximal Tubules

Genome-wide mRNA-seq of Wt, TRACK, and Ggt/creER;ATF4ko (GCERAΔT) kidney cortices

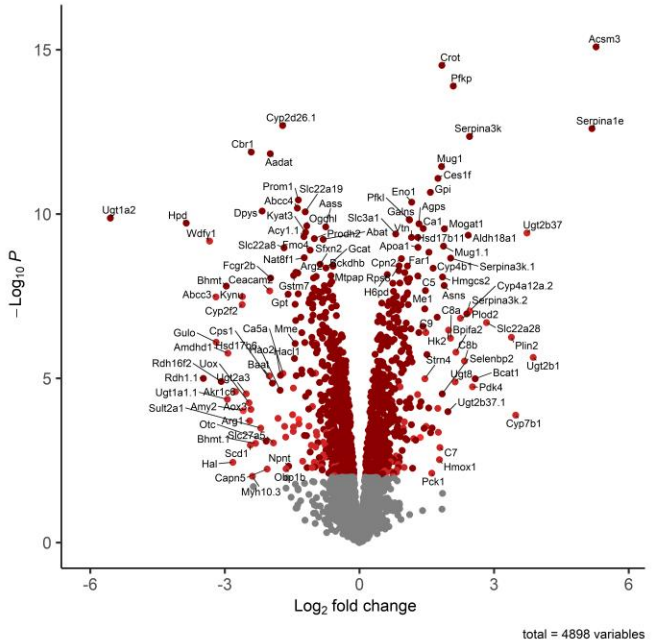


Genome-Wide Proteomics Data from Kidney Cortices of the Mice

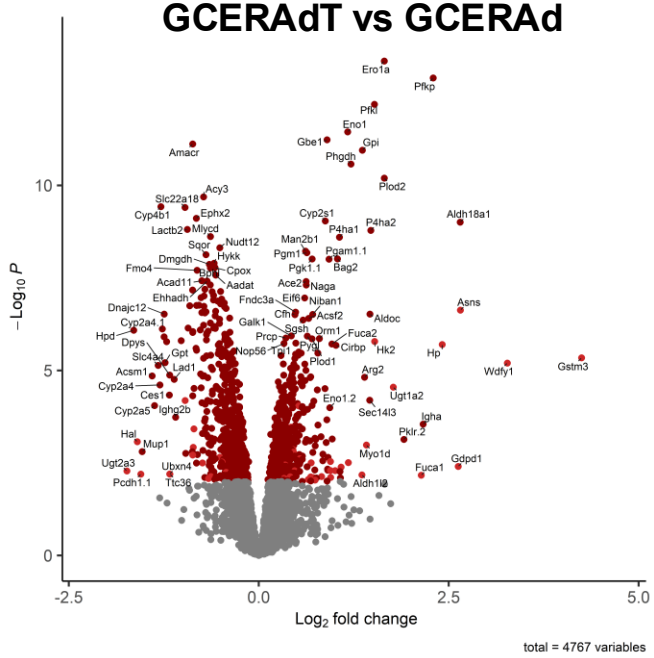
GCERAd vs WT



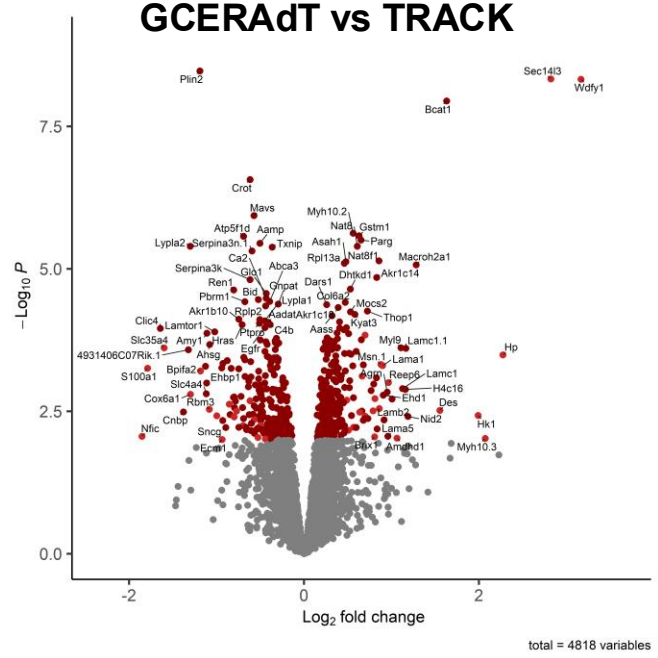
TRACK vs WT



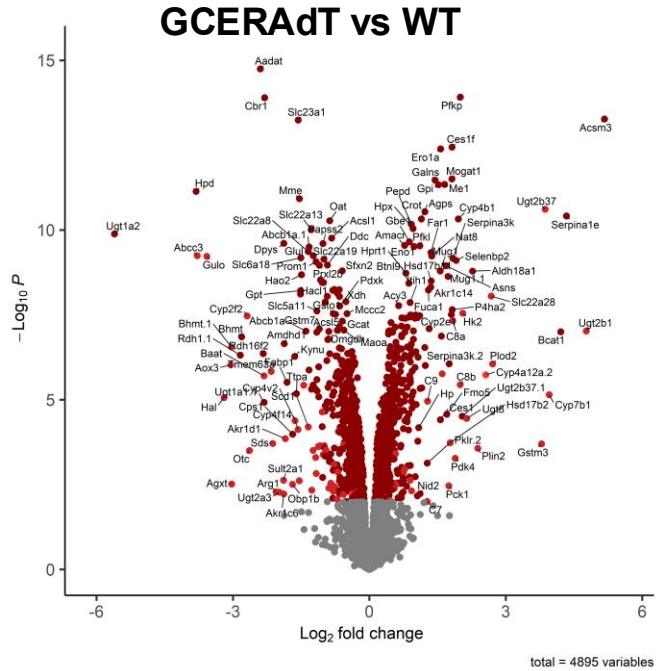
GCERAdT vs GCERAd



GCERAdT vs TRACK

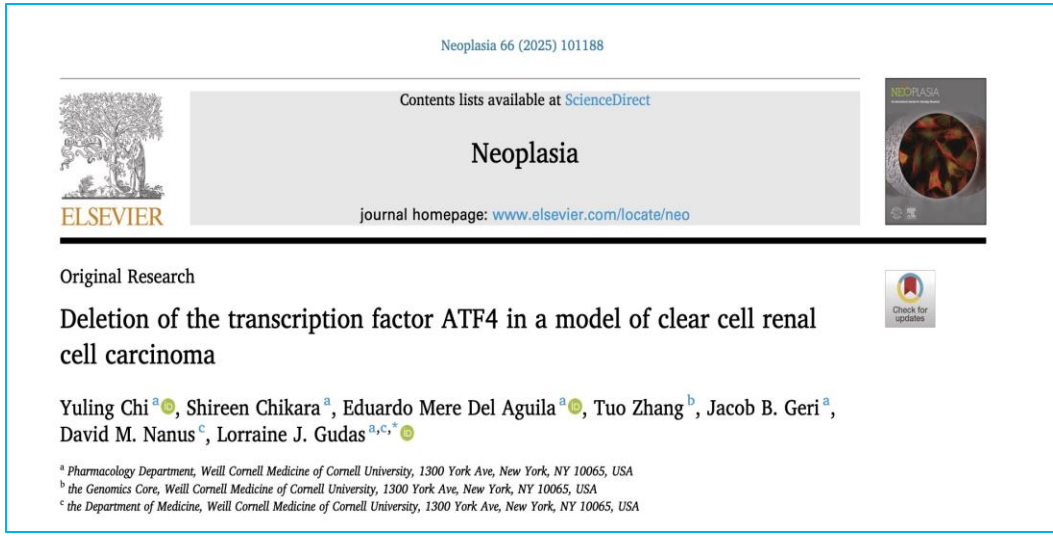


GCERAdT vs WT



Conclusions

1) More ATF4/Integrated Stress Response (ISR) Gene Expression Occurs in Human ccRCC than in Normal Kidney and in Human ccRCC High ISR Transcript Levels are Correlated with a Worse Prognosis
2) This ATF4/ISR phenotype is Recapitulated in our TRACK Murine ccRCC Model in which the Early Tumorigenic Phenotype is Generated by a Constitutively Active HIF1alpha
3) Specific Knockout of ATF4 in Proximal Tubules of Mice Results in Major Changes in Transporters of Amino Acids and other Metabolites
4) In the TRACK ccRCC Model the Lipid Phenotype is Reduced, mRNAs in Fatty Acid Metabolism, & some Transcripts associated with ccRCC are reduced when ATF4 is also Knocked out in Kidney Tubules.



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journal homepage: www.elsevier.com/locate/neo

Original Research

Deletion of the transcription factor ATF4 in a model of clear cell renal cell carcinoma

Yuling Chi [a], Shireen Chikara [a], Eduardo Mere Del Aguila [a], Tuo Zhang [b], Jacob B. Geri [a], David M. Nanus [c], Lorraine J. Gudas [a,c,*]

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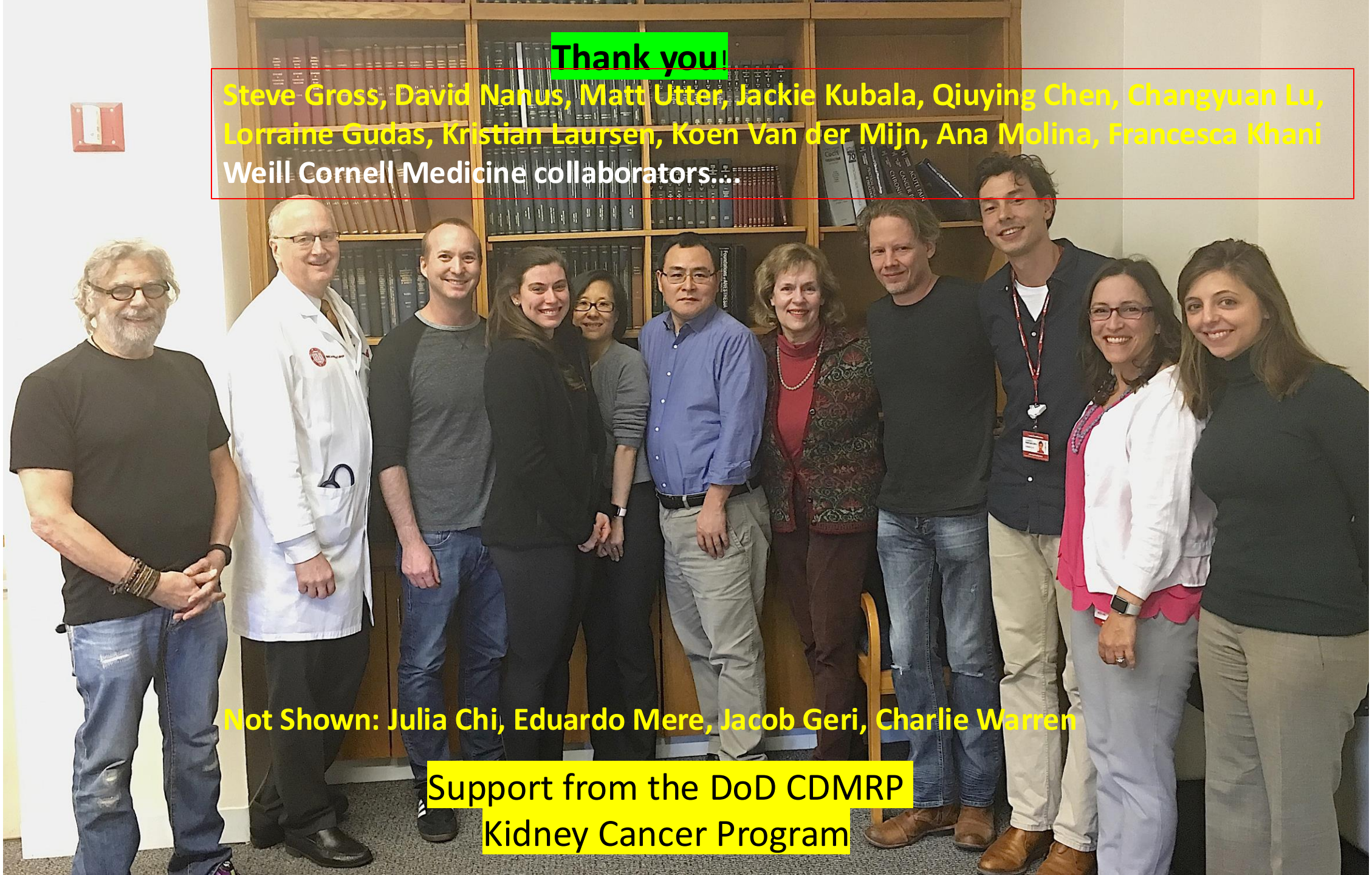
[b] the Genomics Core, Weill Cornell Medicine of Cornell University, 1300 York Ave, New York, NY 10065, USA
[c] the Department of Medicine, Weill Cornell Medicine of Cornell University, 1300 York Ave, New York, NY 10065, USA



Thank you!

Steve Gross, David Nanus, Matt Utter, Jackie Kubala, Qiuying Chen, Changyuan Lu, Lorraine Gudas, Kristian Laursen, Koen Van der Mijn, Ana Molina, Francesca Khani

Weill Cornell Medicine collaborators….

Not Shown: Julia Chi, Eduardo Mere, Jacob Geri, Charlie Warren

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