Non-FXR Mediated Benefits of Bile Acids on NAFLD

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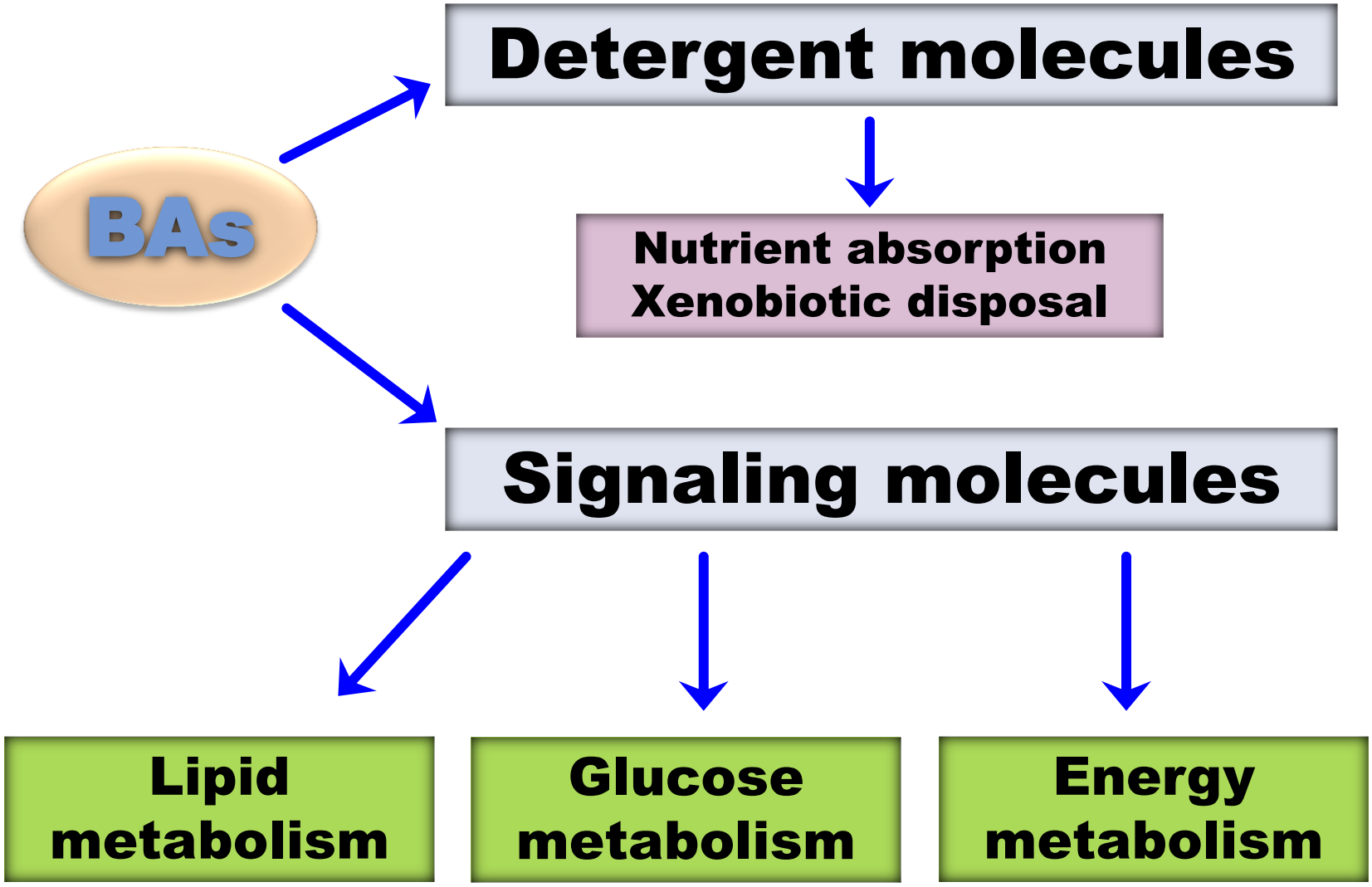
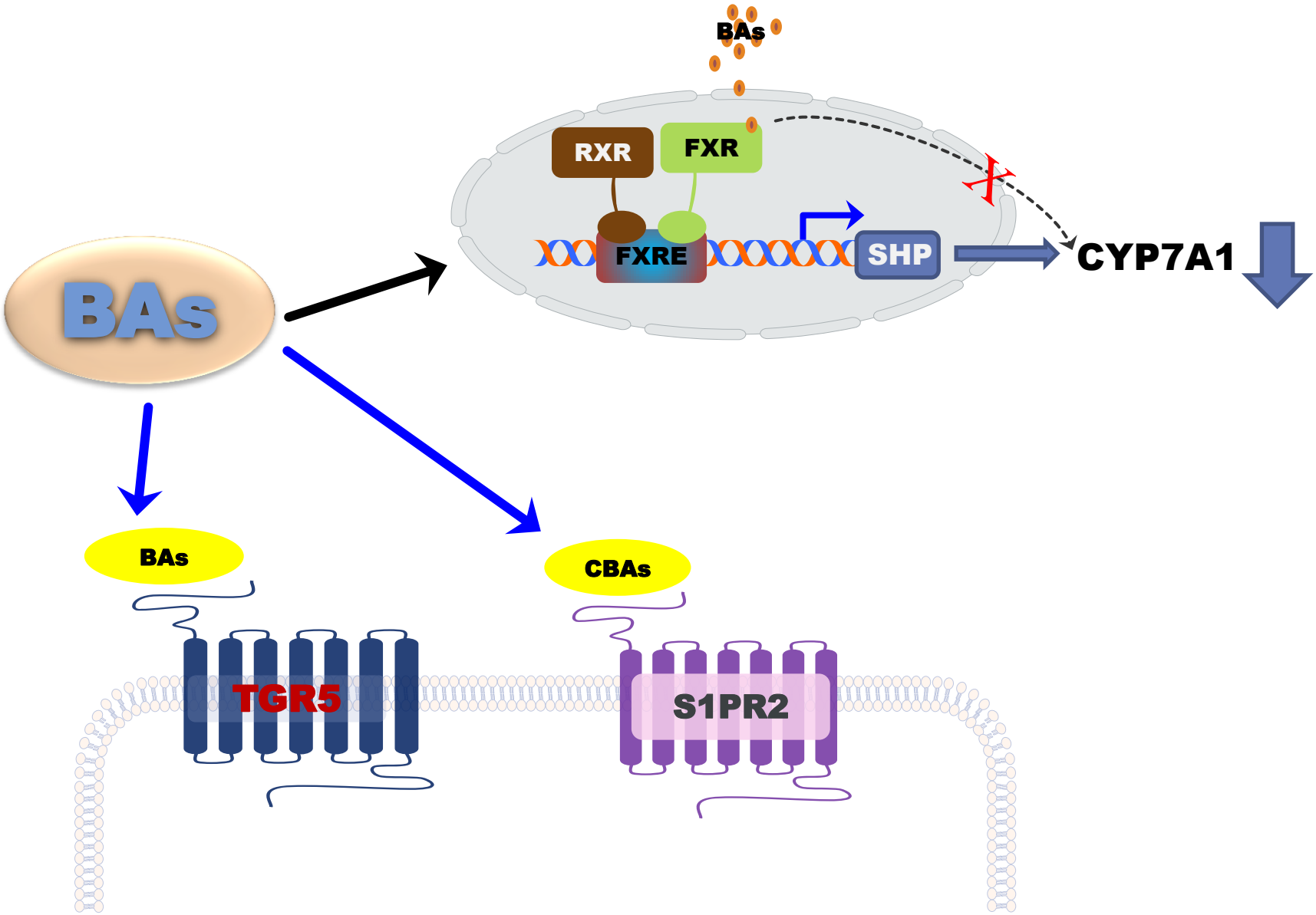
July 1, 2016

FUNCTIONS OF BILE ACIDS



Bile acids are signaling molecules

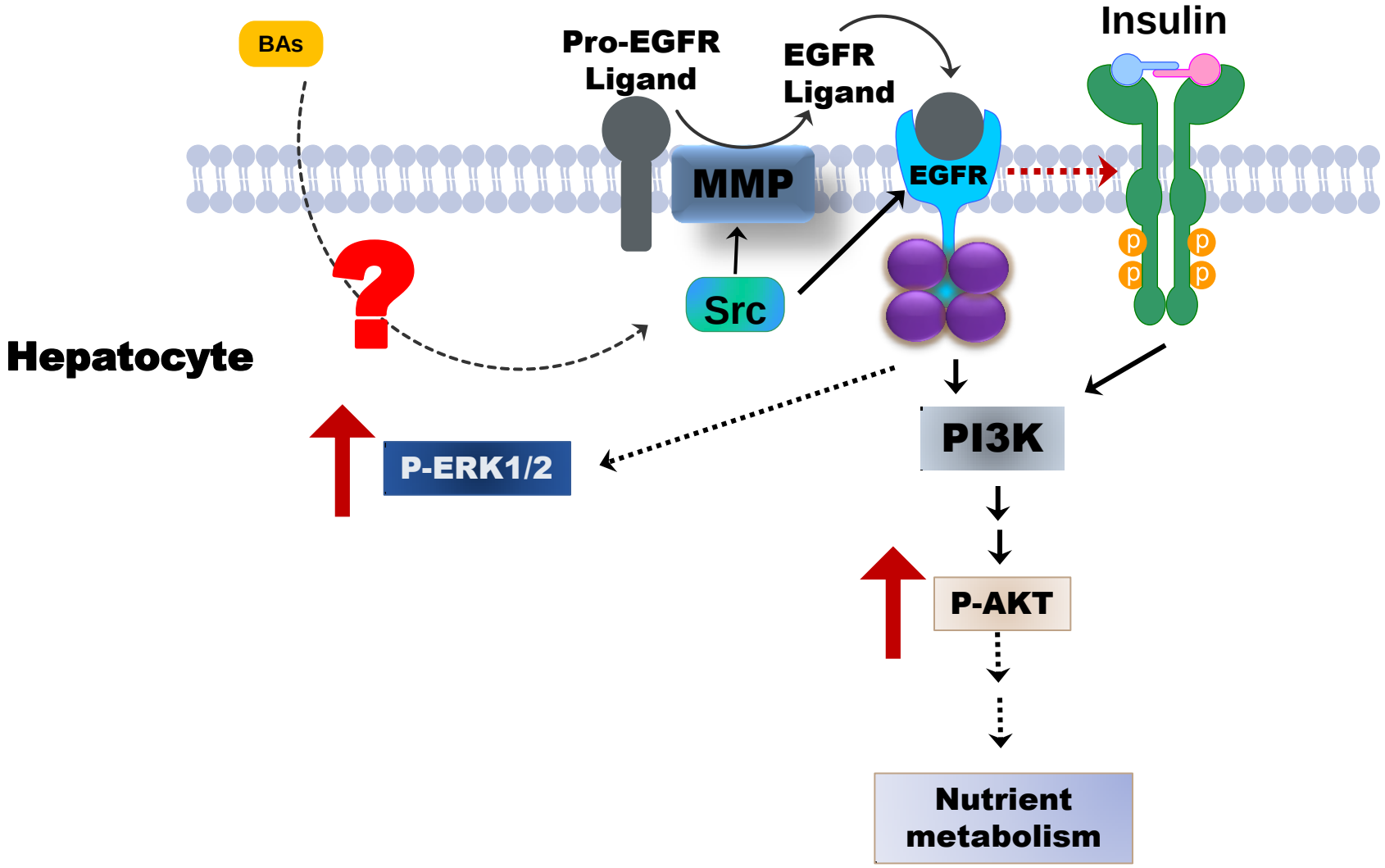


Outline

I. Bile acids and S1PR2 in hepatic lipid metabolism

II. Bile acids and TGR5 in glucose metabolism

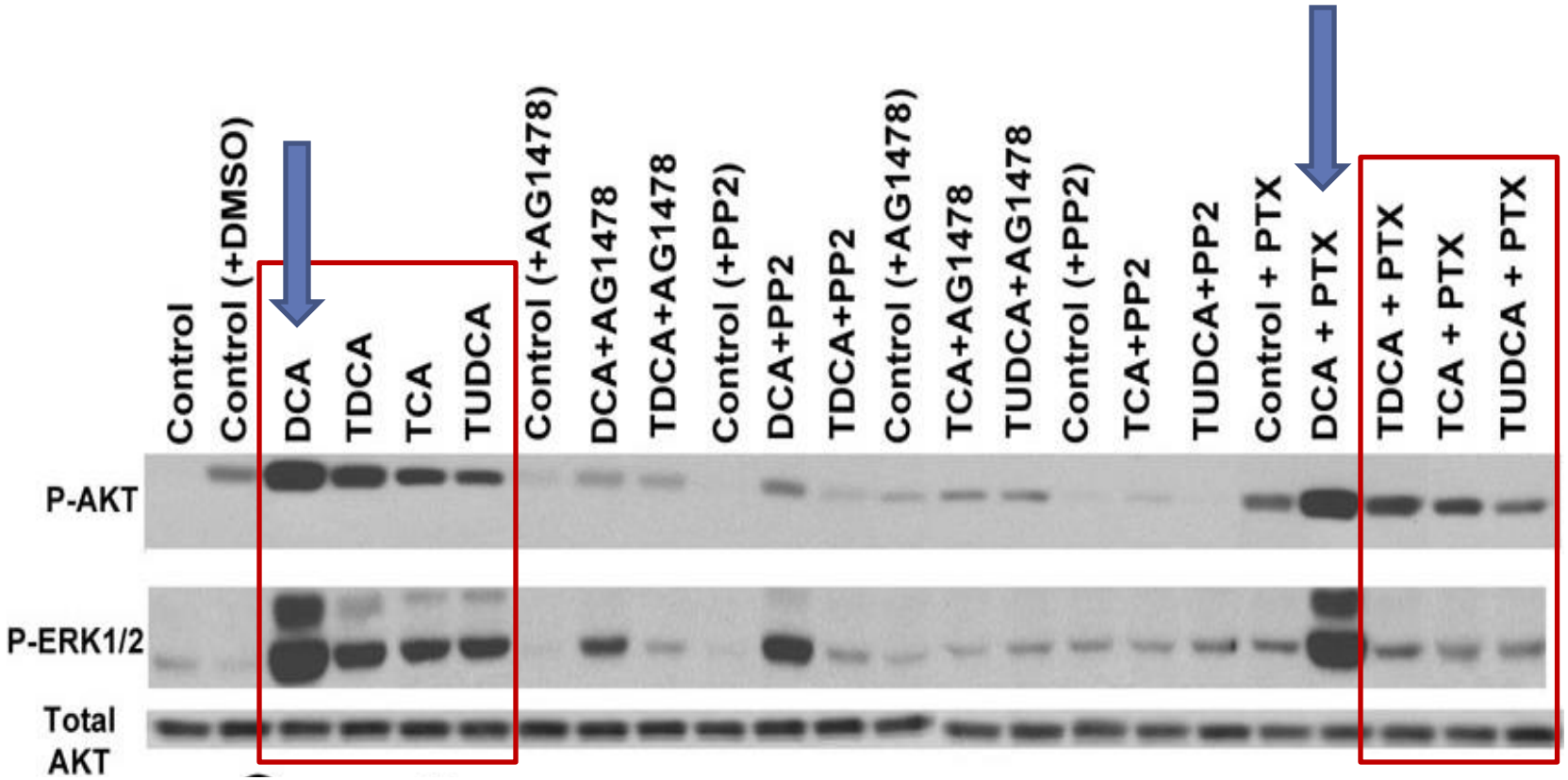
BILE ACID-MEDIATED SIGNLING PATHWAYS



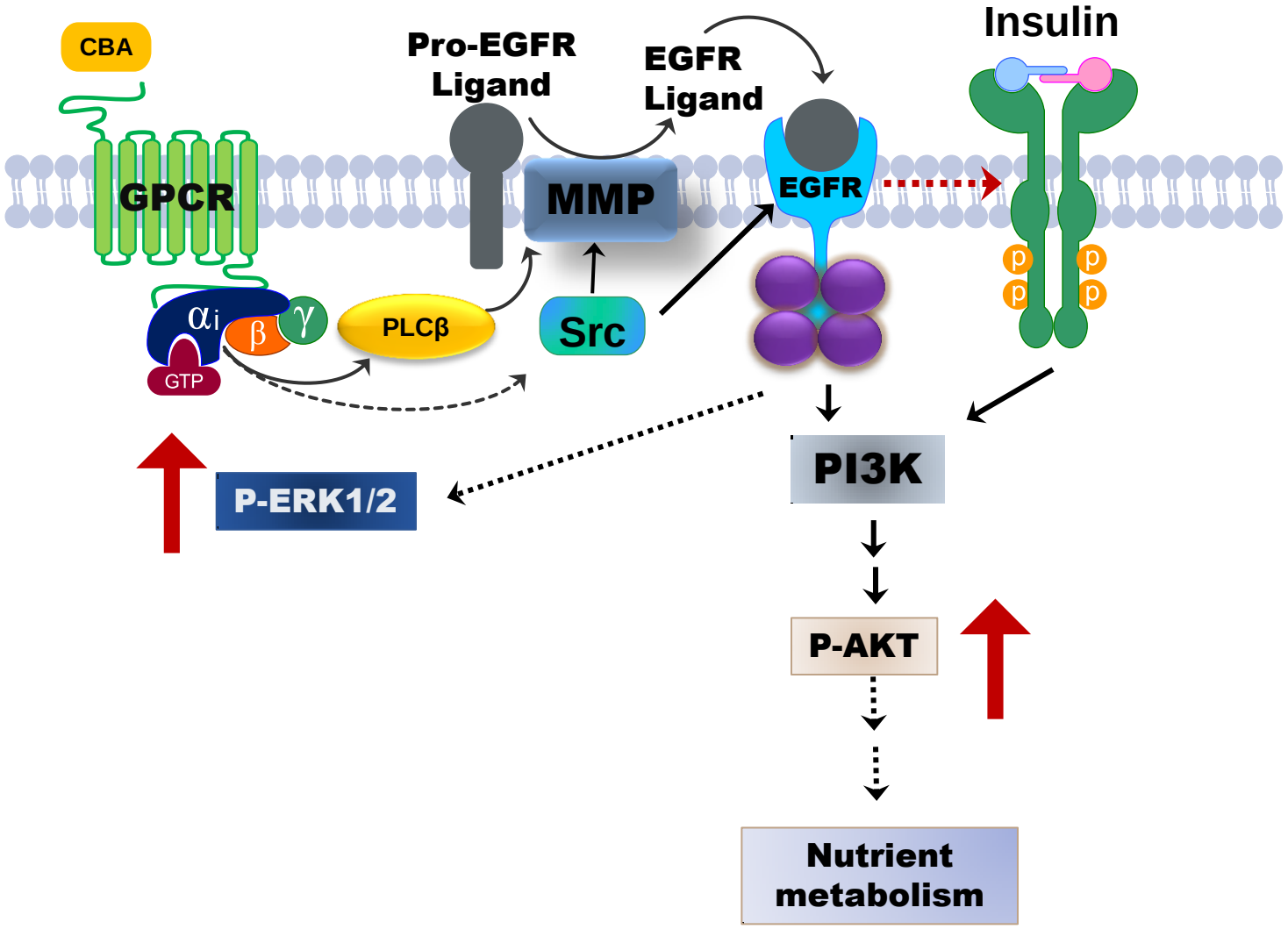
Hepatology. 2005 Dec;42(6):1291-9.

Conjugated Bile Acids Promote ERK1/2 and AKT Activation Via a Pertussis Toxin–Sensitive Mechanism in Murine and Human Hepatocytes

Paul Dent,[1] Youwen Fang,[1,2] Seema Gupta,[3] Elaine Studer,[2] Clint Mitchell,[1] Sarah Spiegel,[1] and Philip B. Hylemon[2]



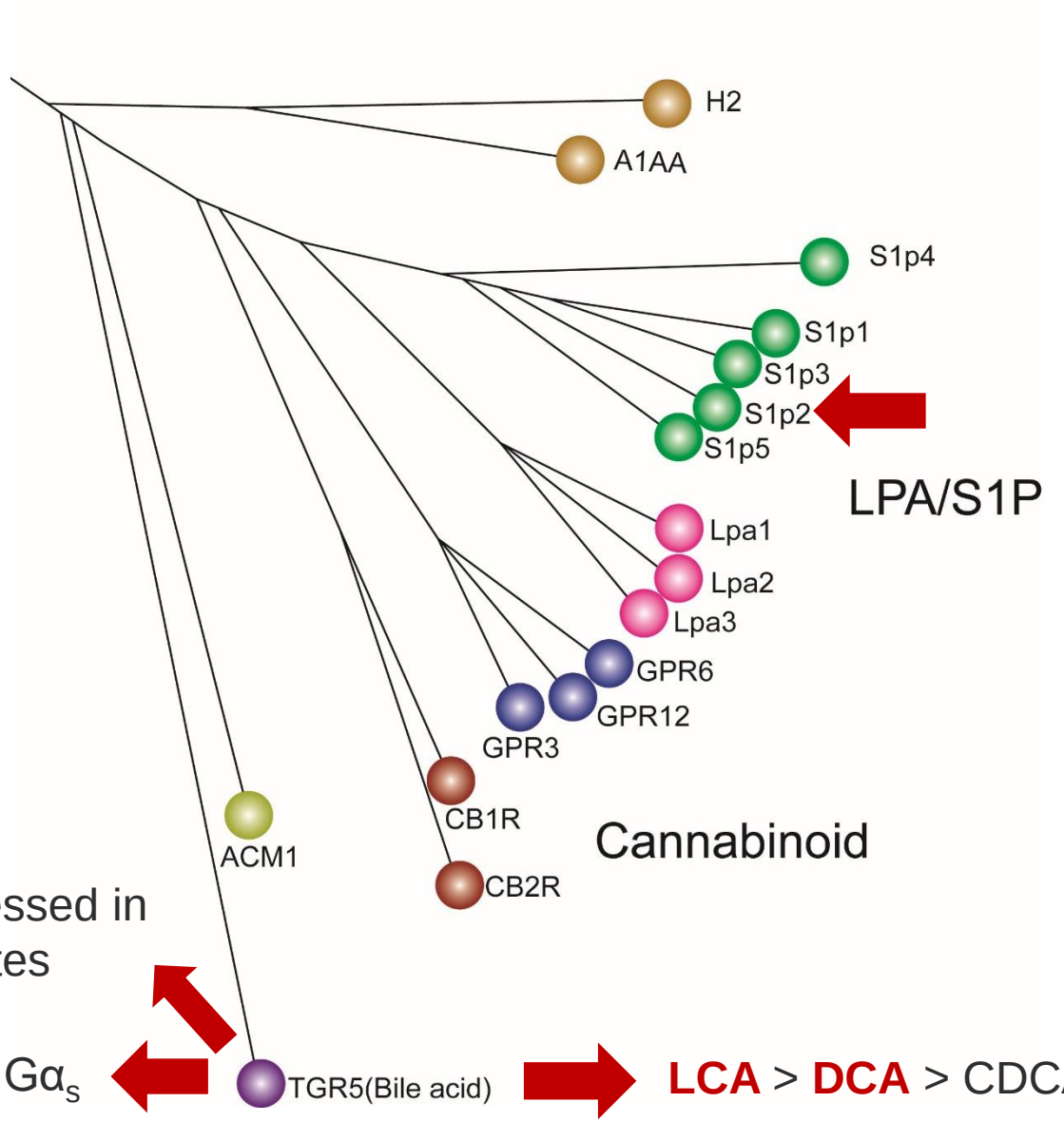
BILE ACID-MEDIATED SINGALING PATHWAYS



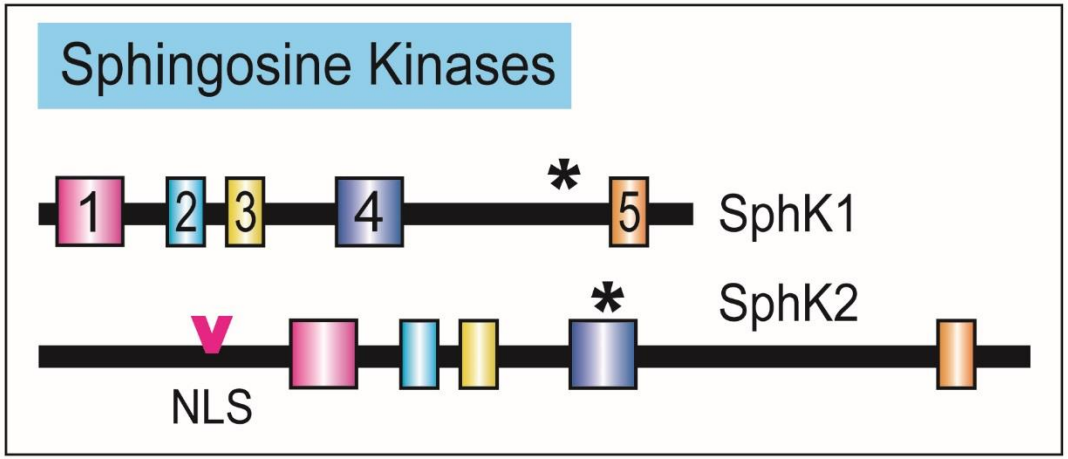
QUESTION #1

Which Gαi-coupled GPCR is responsible for conjugated bile acid-induced ERK1/2 activation in hepatocytes?

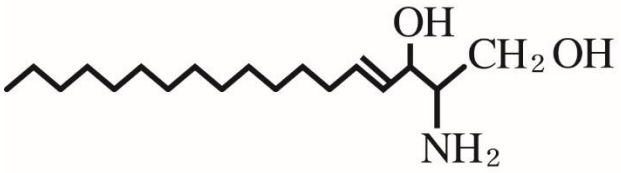
Phylogenetic Tree of the Lipid-Activated G Protein Coupled Receptors



Sphingosine Kinases



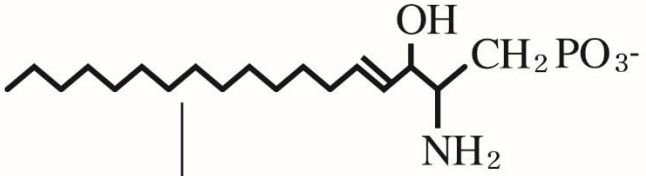
Sphingosine Kinases



Backbone of sphingolipids

Sphingosine **S1P**

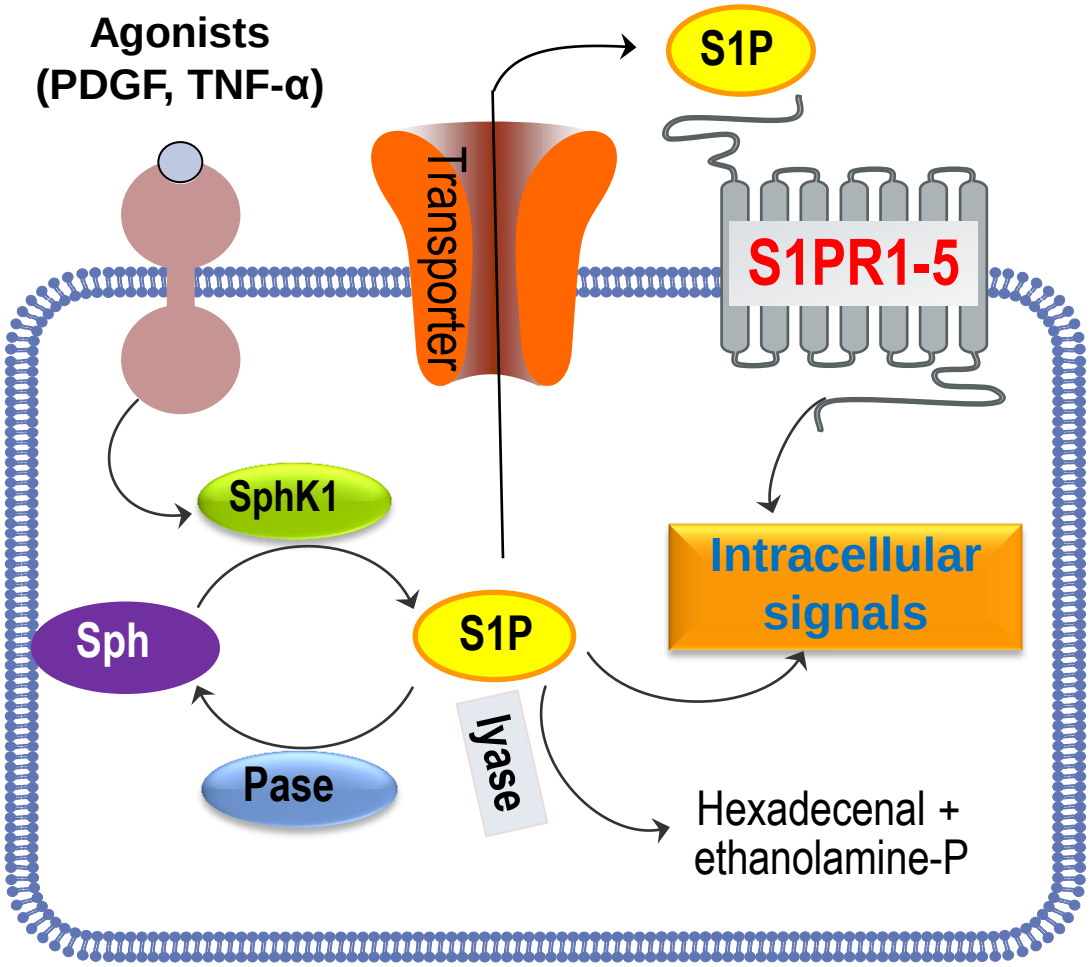
S1P Phosphatase



S1P Lyase

Phosphoethanolamine + Hexadecenal

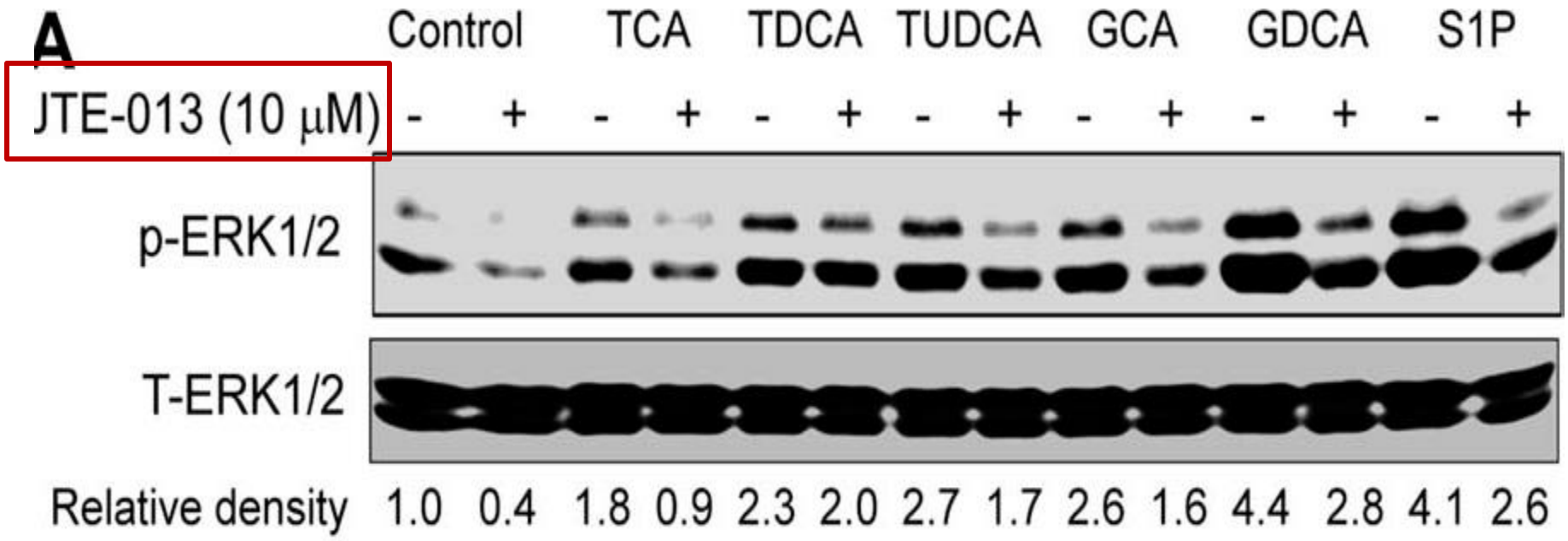
"Inside Out" Signaling by S1P



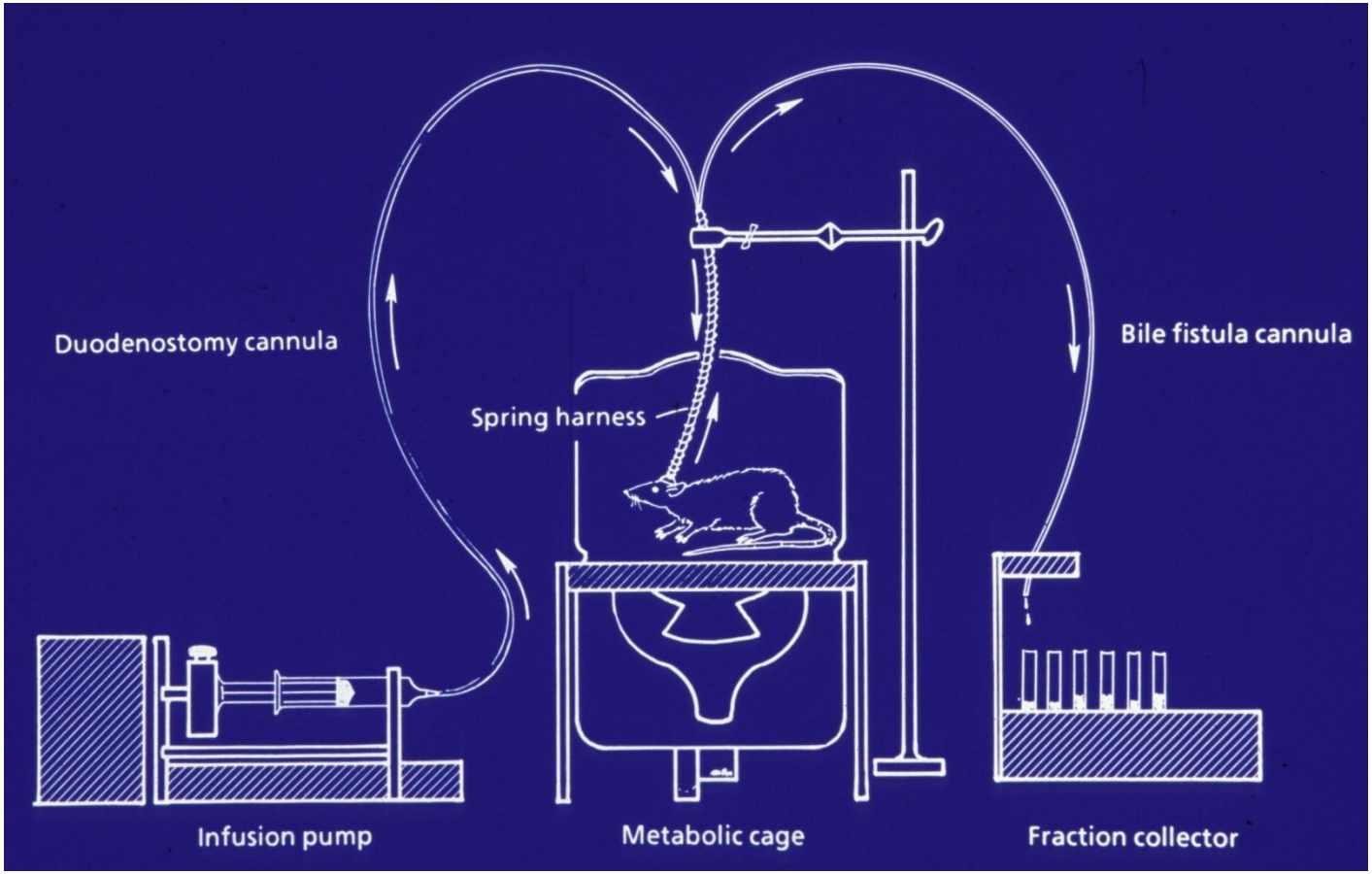
Hepatology. 2012; 55(1):267-76.

Conjugated Bile Acids Activate the Sphingosine-1-Phosphate Receptor 2 in Primary Rodent Hepatocytes

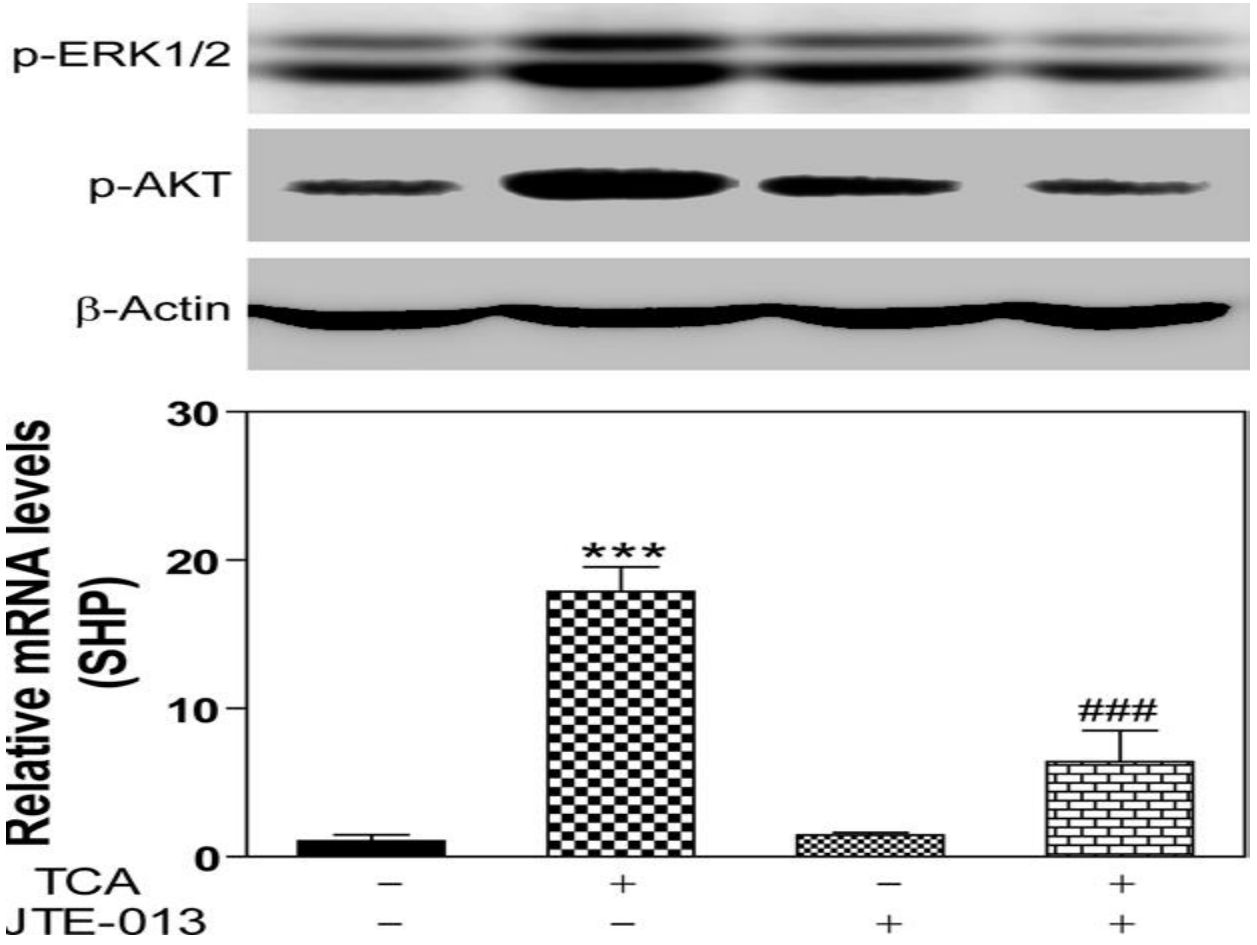
Elaine Studer,[1]* Xiqiao Zhou,[1,6]* Renping Zhao,[1,8]* Yun Wang,[1,8] Kazuaki Takabe,[3] Masayuki Nagahashi,[3] William M. Pandak,[2] Paul Dent,[4] Sarah Spiegel,[5] Ruihua Shi,[6] Weiren Xu,[7] Xuyuan Liu,[7] Pat Bohdan,[1] Luyong Zhang,[8] Huiping Zhou,[1,2] and Phillip B. Hylemon[1,2]



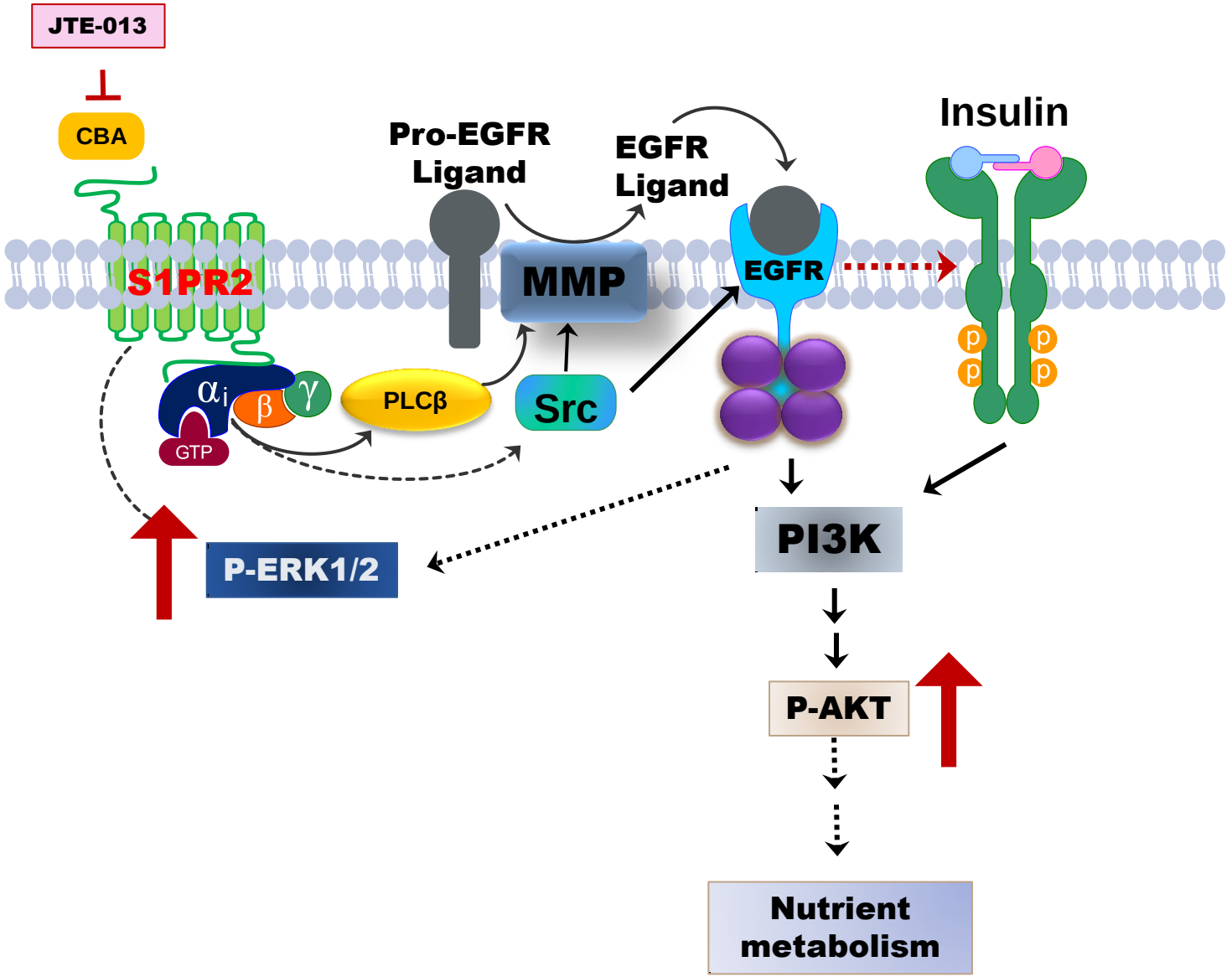
Chronic Bile Fistula Rat Model



Effect of JTE-013 on TCA-induced Activation of ERK1/2 and AKT as well as SHP Expression in Bile Fistula Rats



Summary #1


JTE-013
CBA
S1PR2
Pro-EGFR Ligand
MMP
EGFR Ligand
EGFR
Insulin
α_i
β
γ
GTP
PLCβ
Src
P-ERK1/2
PI3K
P-AKT
Nutrient metabolism

Hait NC, et al. J Biol Chem. 2007 Apr 20;282(16):12058-65

Sphingosine Kinase Type 2 Activation by ERK-mediated Phosphorylation*

Received for publication, October 10, 2006, and in revised form, January 29, 2007 Published, JBC Papers in Press, February 20, 2007, DOI 10.1074/jbc.M609559200

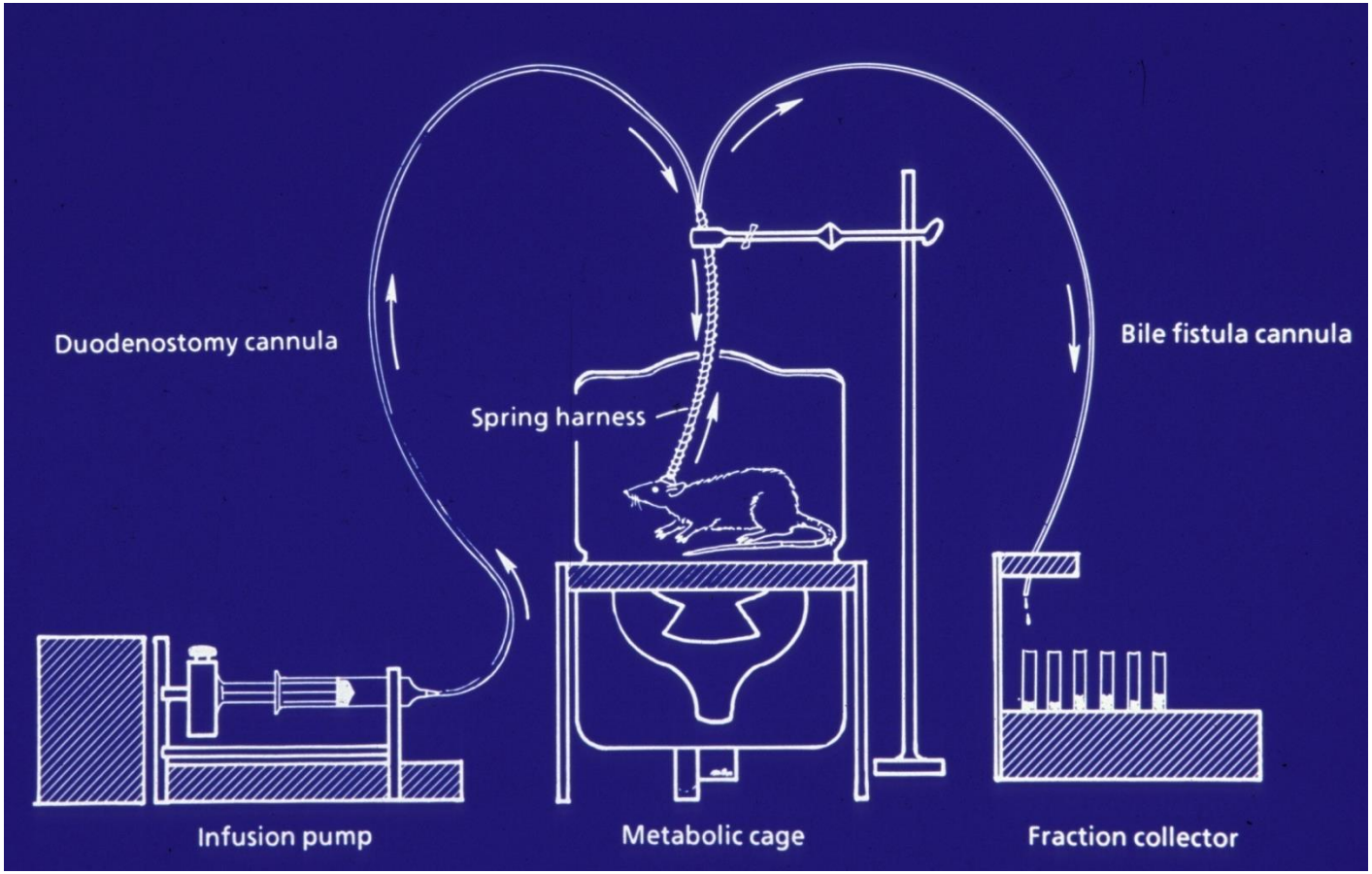
Nitai C. Hait[‡], Andrea Bellamy[‡], Sheldon Milstien[§], Tomasz Kordula[‡1], and Sarah Spiegel[‡1,2]

From the [‡]Department of Biochemistry and the Massey Cancer Center, Virginia Commonwealth University School of Medicine, Richmond, Virginia 23298 and the [§]Laboratory of Cellular and Molecular Regulation, National Institute of Mental Health, Bethesda, Maryland 20892

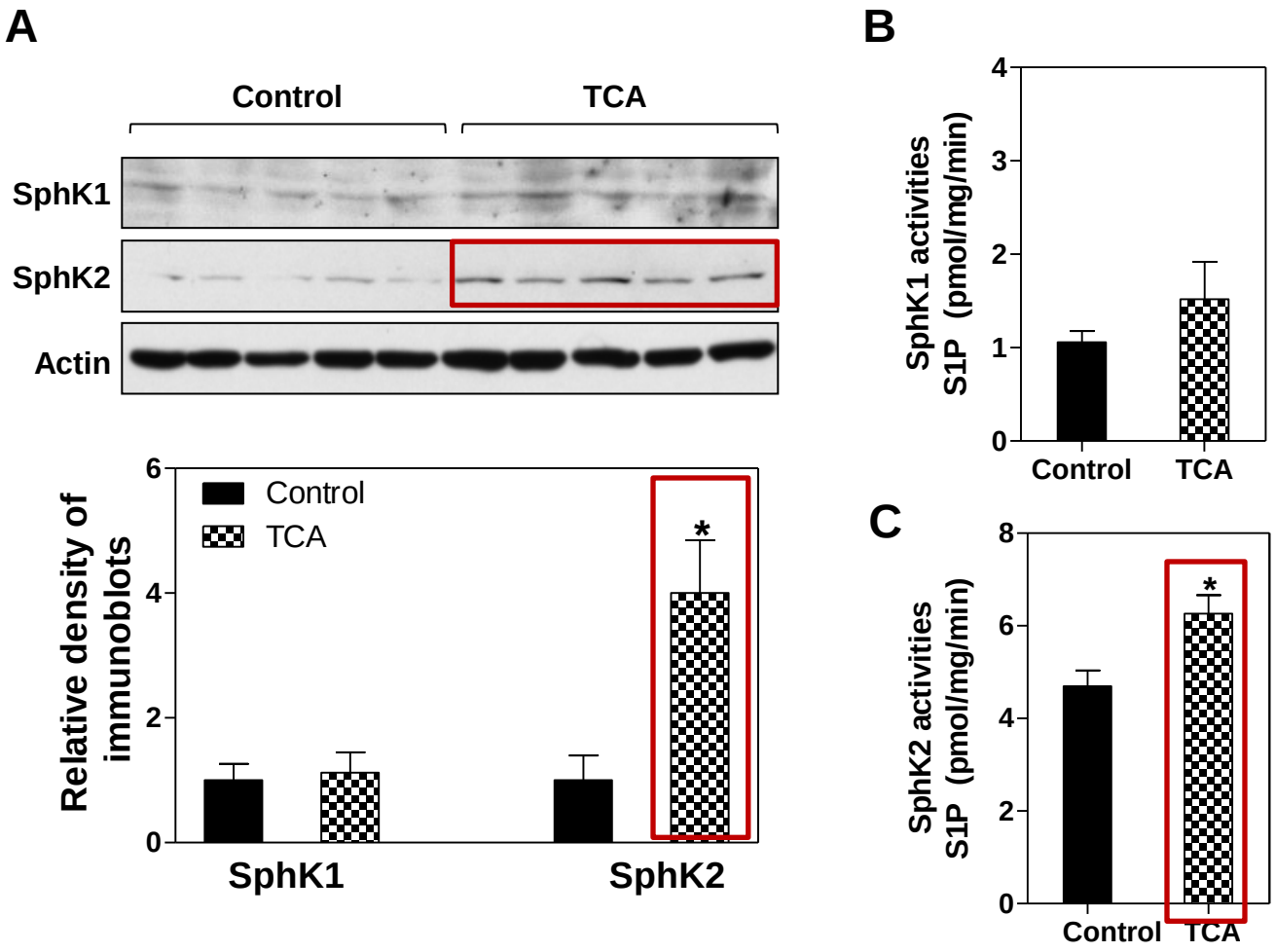
QUESTION #2

Does TCA-mediated activation of ERK have any effect on hepatic SphK2 Activation?

Chronic Bile Fistula Rat Model

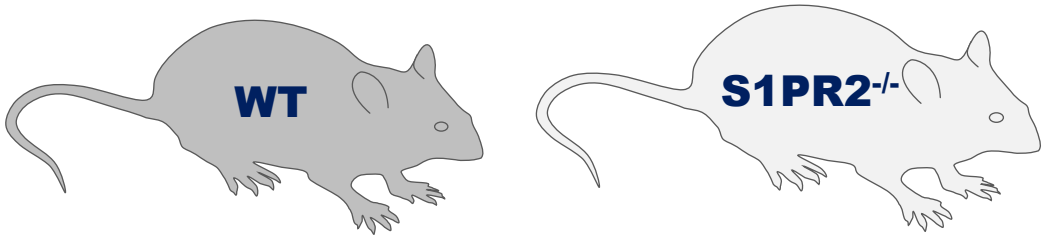


TCA Increased SphK2 Protein Levels and Enzyme Activities in the Livers of Bile Fistula Rat Models

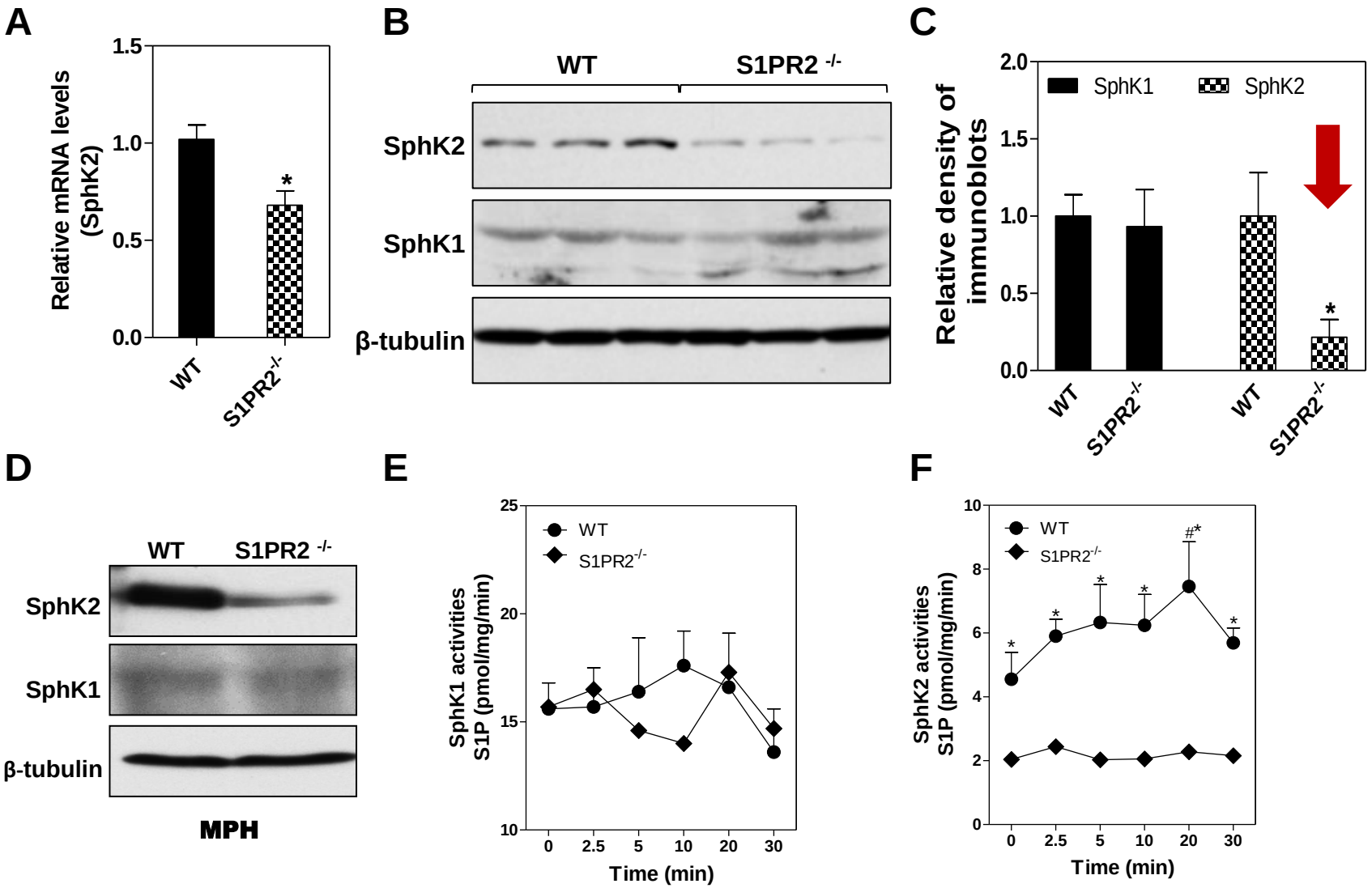


QUESTION #3

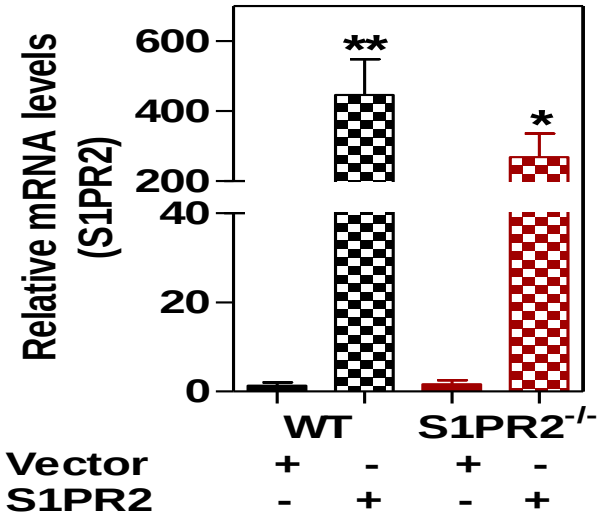
Is TCA-induced SphK2 activation mediated by S1PR2?

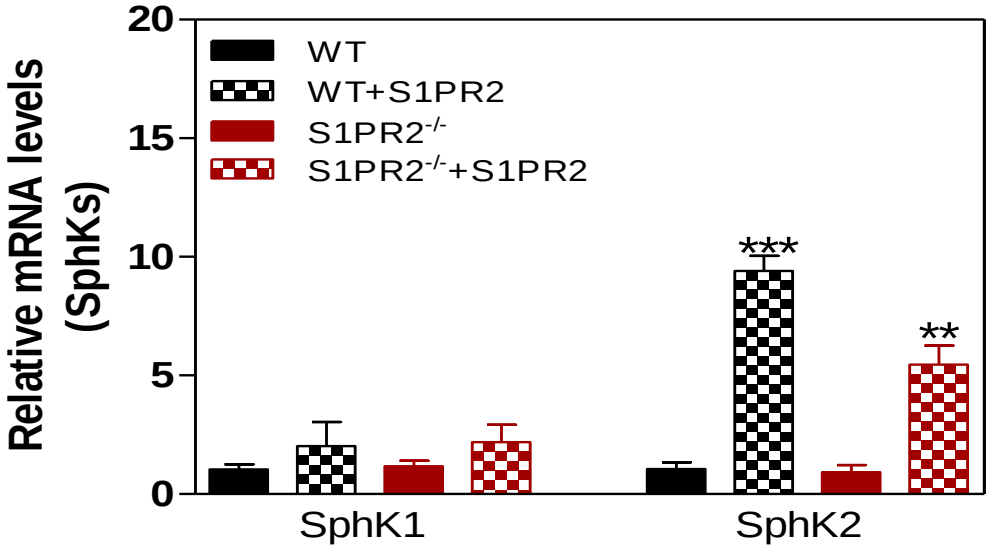


Role of S1PR2 in TCA-induced Activation of Hepatic SphK2

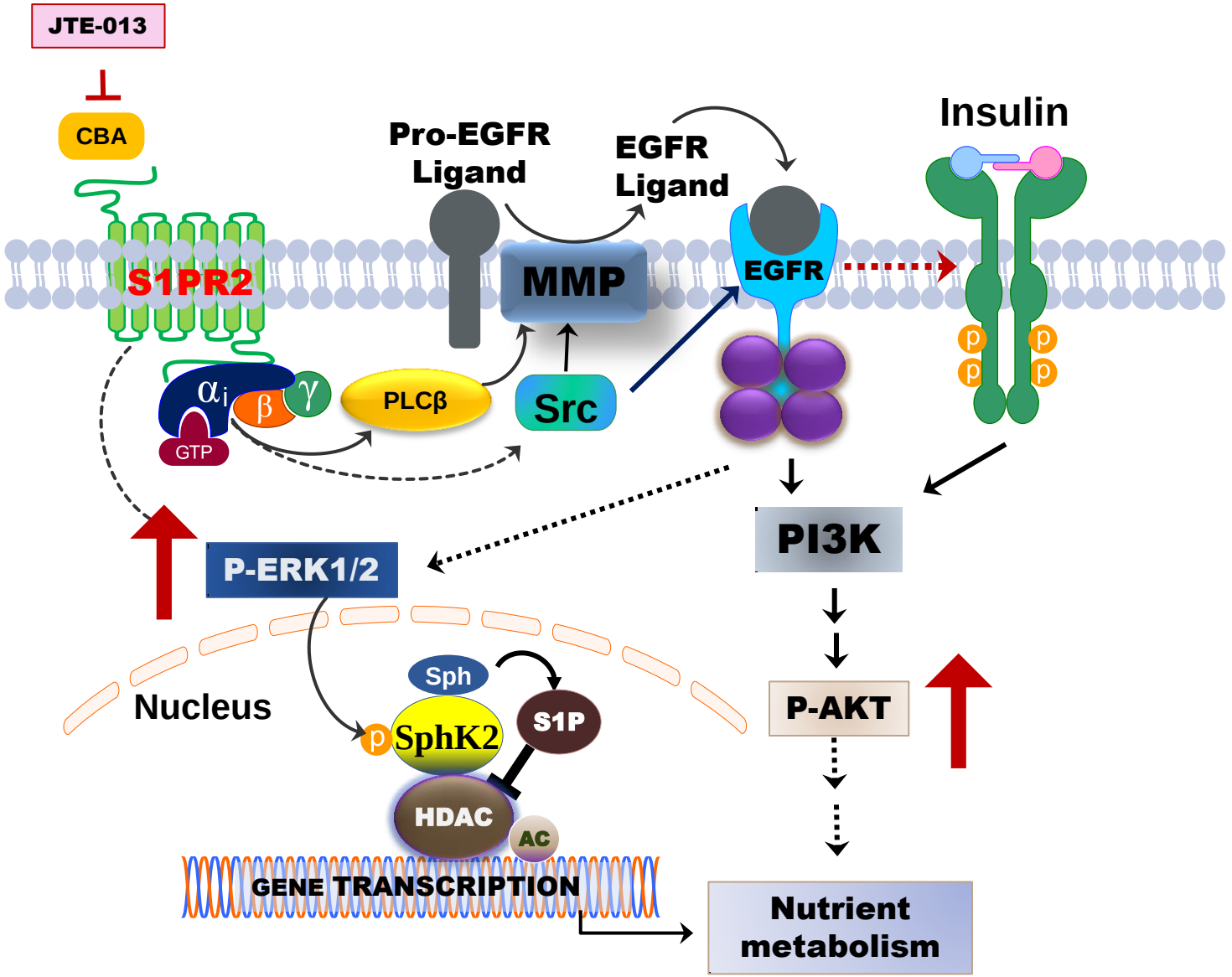


Overexpression of S1PR2 Up-regulates SphK2 in Hepatocytes





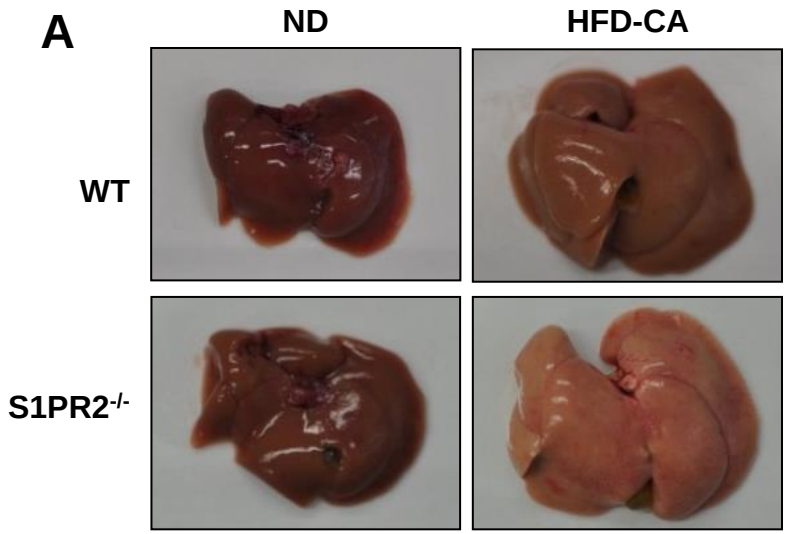
Summary #2

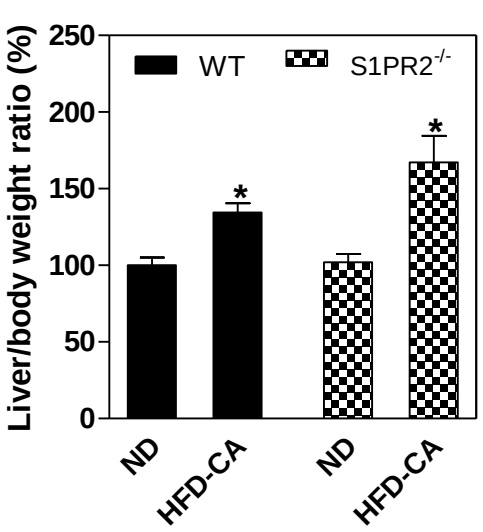

JTE-013
CBA
S1PR2
Pro-EGFR Ligand
MMP
EGFR Ligand
EGFR
Insulin
α_i
β
γ
GTP
PLCβ
Src
p
p
p
p
PI3K
P-ERK1/2
Nucleus
Sph
S1P
pSphK2
HDAC
AC
P-AKT
GENE TRANSCRIPTION
Nutrient metabolism

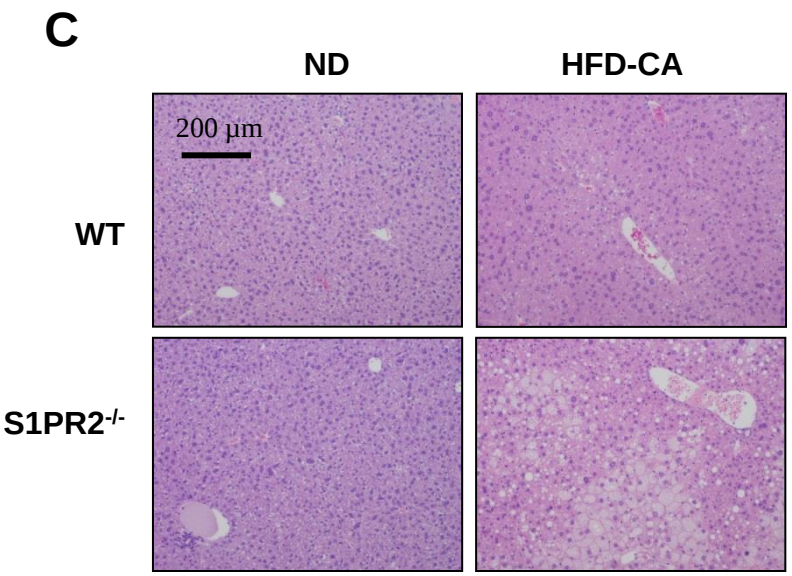
QUESTION #4

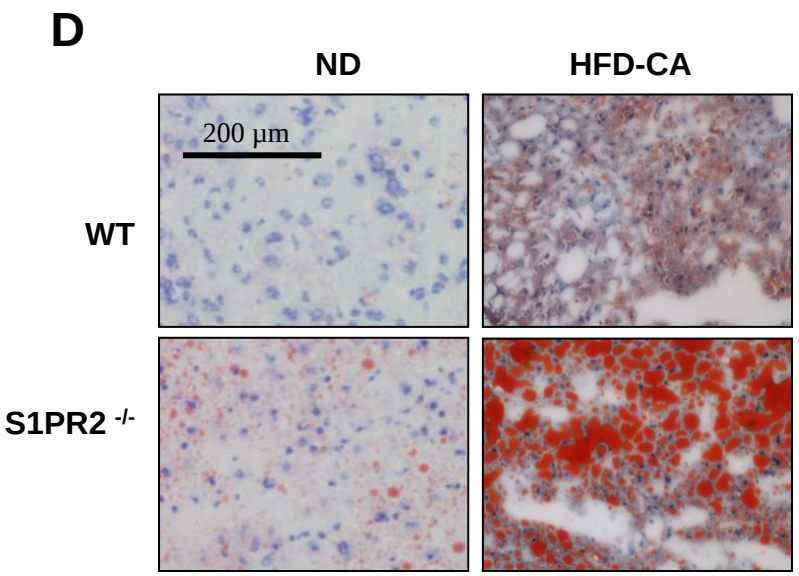
What is the physiological function of bile acid-induced activation of S1PR2 and SphK2 *in vivo*?

Phenotype of S1PR2$^{-/-}$ Mice

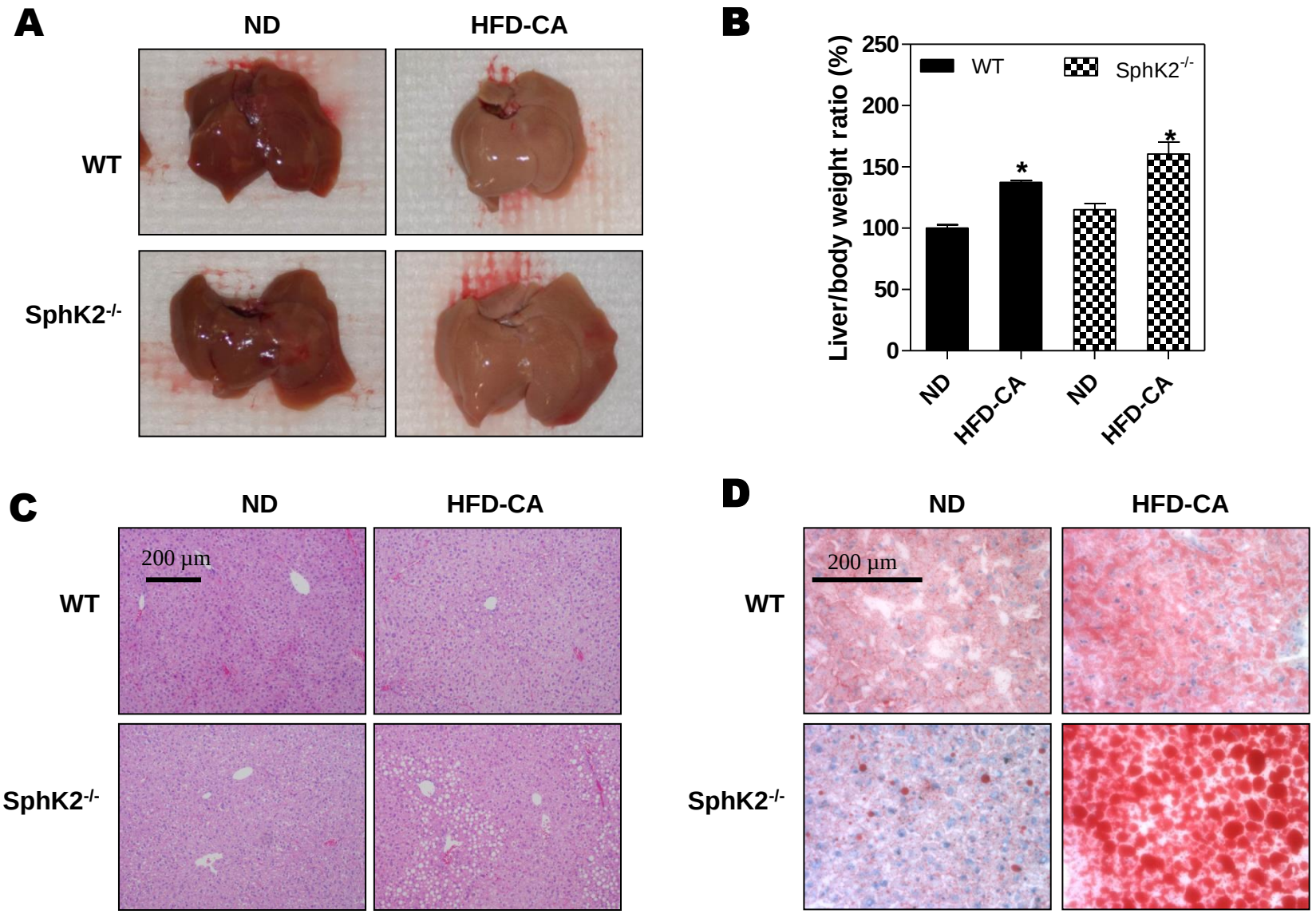








Phenotype of SphK2$^{-/-}$ Mice



HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
2015; 61(4):1216-26.

Conjugated Bile Acid–Activated S1P Receptor 2 Is a Key Regulator of Sphingosine Kinase 2 and Hepatic Gene Expression

Masayuki Nagahashi,[1,2,3] Kazuaki Takabe,[1,2] Runping Liu,[4,5] Kesong Peng,[4] Xiang Wang,[4] Yun Wang,[4,5] Nitai C. Hait,[2] Xuan Wang,[4,5] Jeremy C. Allegood,[2] Akimitsu Yamada,[1,2] Tomoyoshi Aoyagi,[1,2] Jie Liang,[2] William M. Pandak,[5] Sarah Spiegel,[2] Phillip B. Hylemon,[4,5] and Huiping Zhou[4,5]

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Sphingosine-1-Phosphate Receptor 2: A Novel Bile Acid Receptor and Regulator of Hepatic Lipid Metabolism?

See Article on Page 1216

secreted into the blood circulation to hepatocytes to activate FGF receptor 4 (FGFR4) that activates the mitogen

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
2015; 62(1):135-46
AASLD

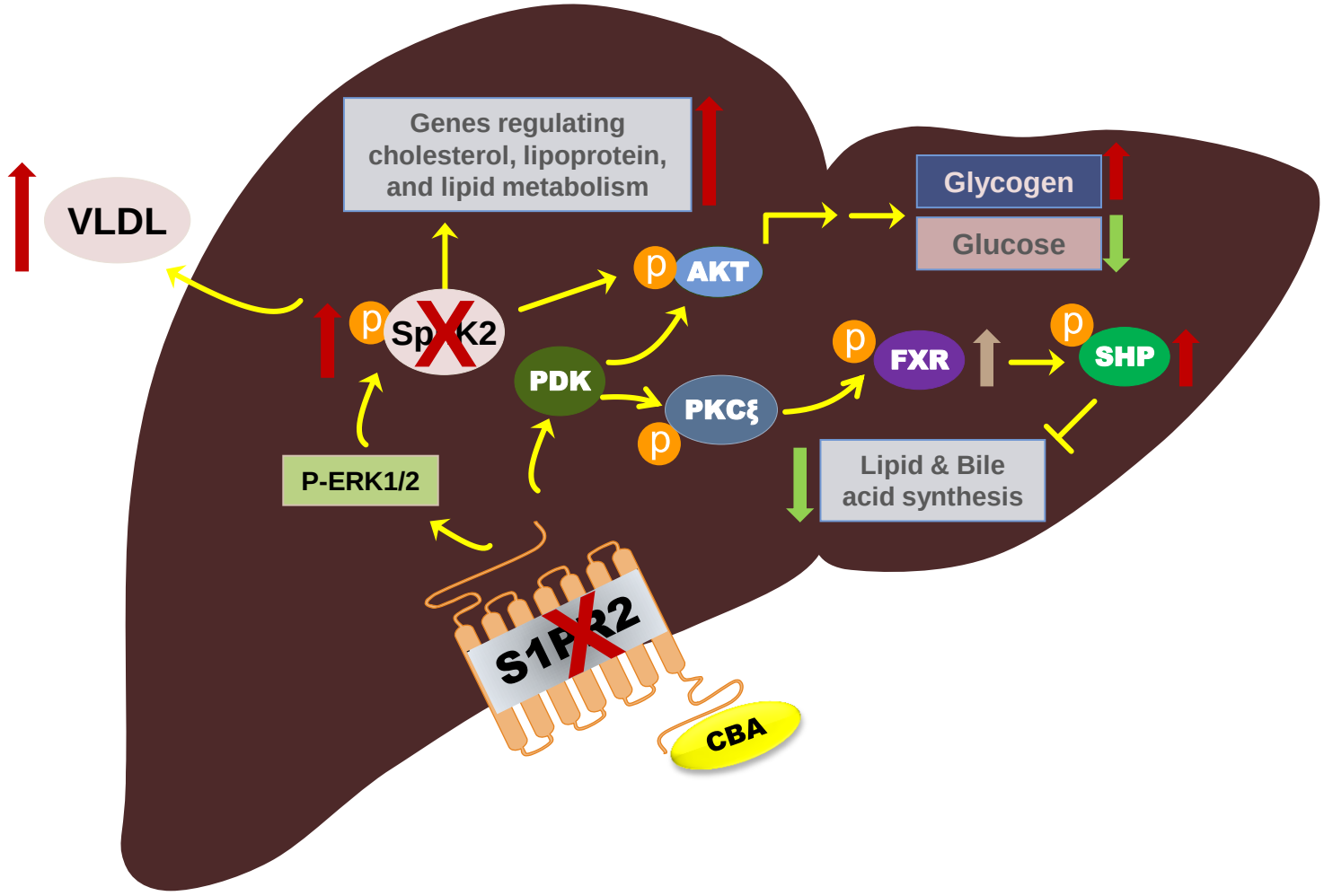
STEATOHEPATITIS/METABOLIC LIVER DISEASE

Activation of Sphingosine Kinase 2 by Endoplasmic Reticulum Stress Ameliorates Hepatic Steatosis and Insulin Resistance in Mice

Su-Yeon Lee,[1]* In-Kyung Hong,[1]* Bo-Rahm Kim,[1] Soon-Mi Shim,[2] Jae Sung Lee,[3] Hui-Young Lee,[3] Cheol Soo Choi,[3] Bo-Kyung Kim,[4] and Tae-Sik Park[1]

Hepatic overexpression of SphK2 activates fatty acid oxidation, decreases hepatic lipid accumulation *via* activation of AKT.

Summary
Liver

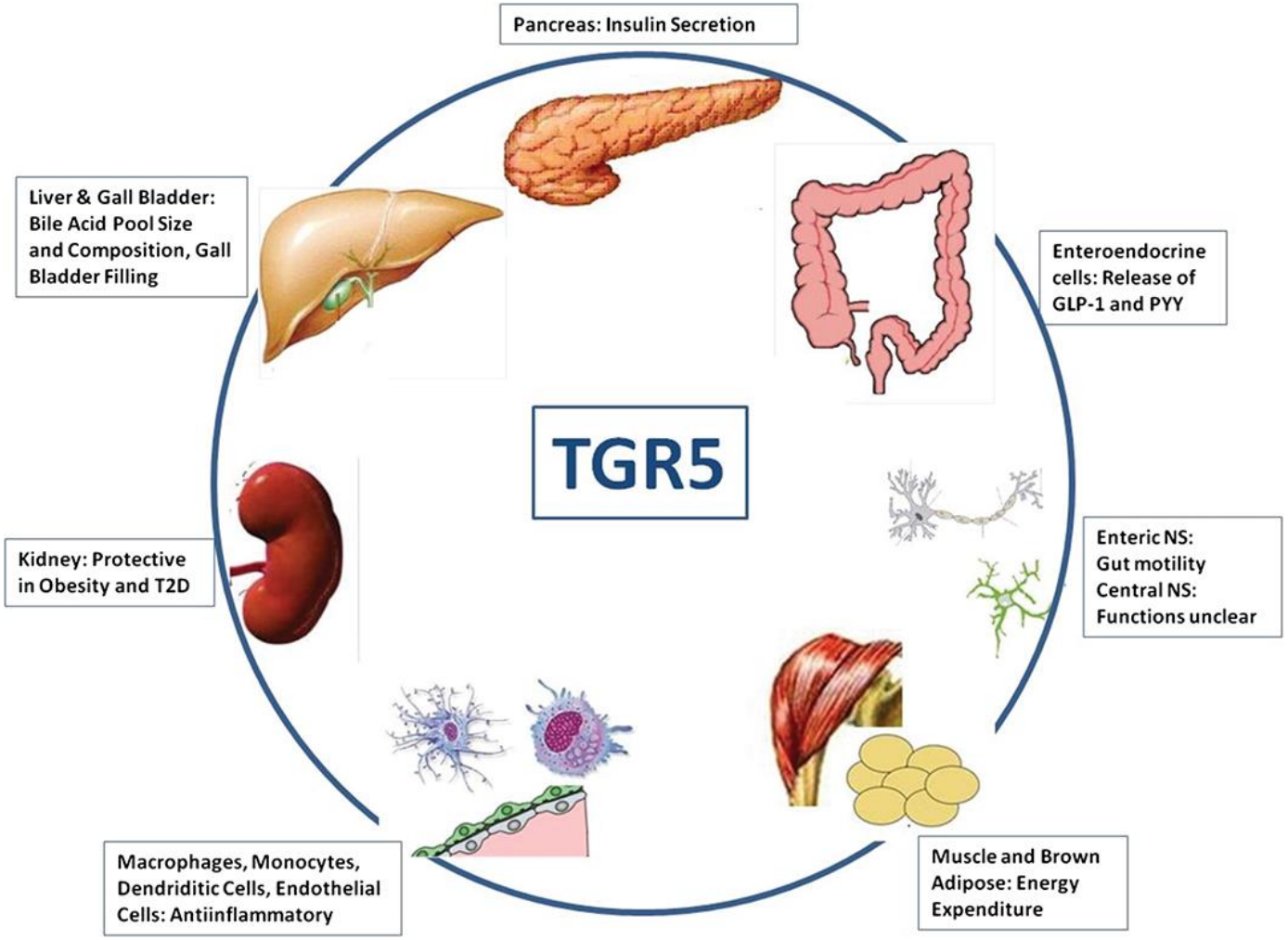


Outline

I. Bile acids and S1PR2 in hepatic lipid metabolism

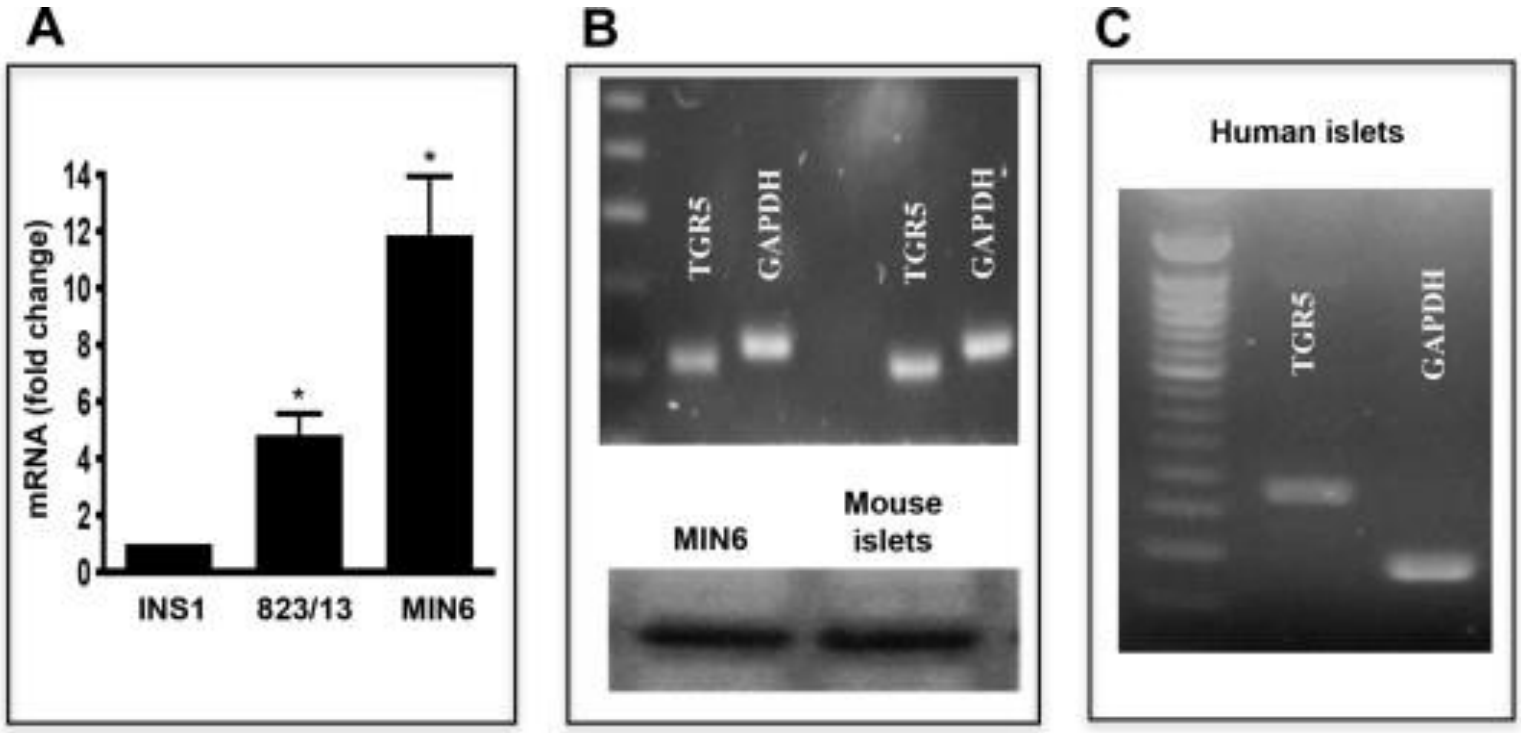
II. Bile acids and TGR5 in glucose metabolism

Therapeutic Potential of TGR5 Agonists Hope or hype?



Diabetes, Obesity and Metabolism
Volume 18, Issue 5, pages 439-443, 17 MAR 2016 DOI: 10.1111/dom.12636
http://onlinelibrary.wiley.com/doi/10.1111/dom.12636/full#dom12636-fig-0001

Expression of TGR5 in Pancreatic β Cells and Human Islets



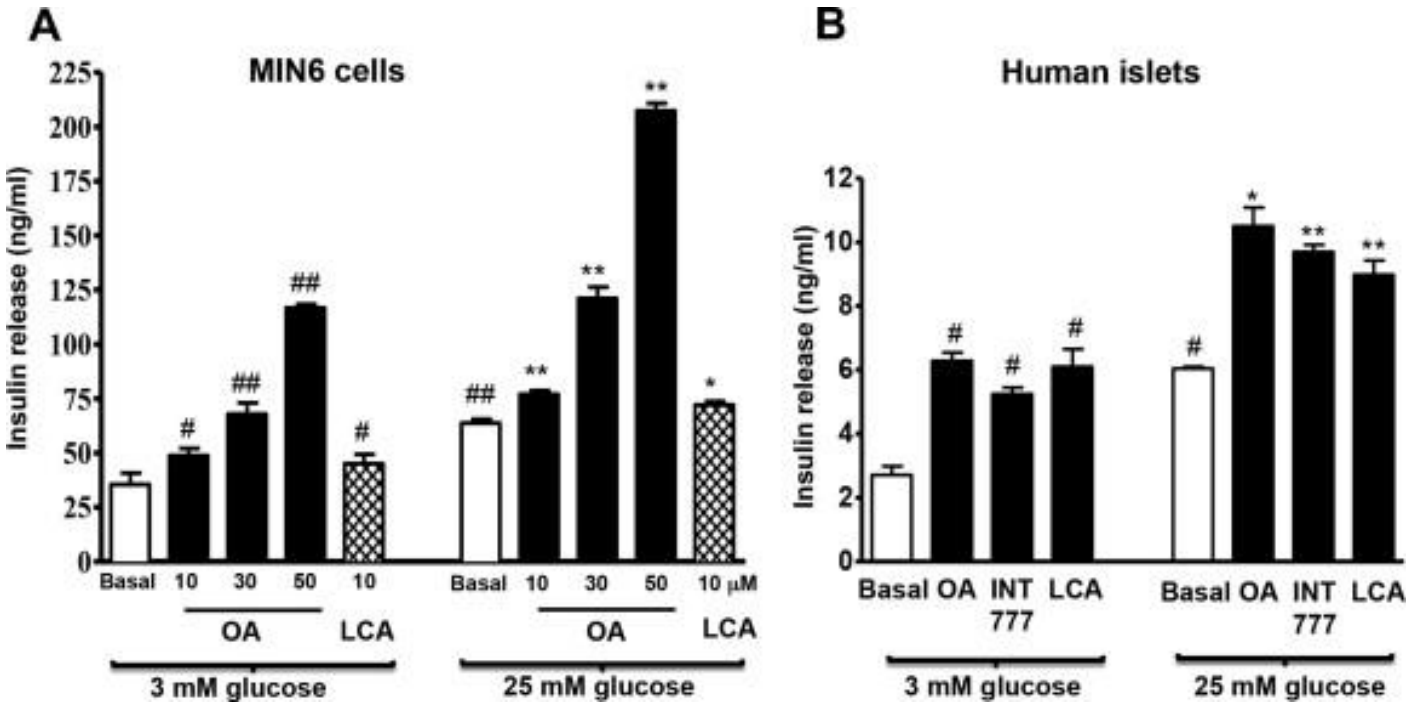
Divya P. Kumar, Senthilkumar Rajagopal, Sunila Mahavadi, Faridoddin Mirshahi, John R. Grider, Karnam S. Murthy, Arun J. Sanyal

Activation of transmembrane bile acid receptor TGR5 stimulates insulin secretion in pancreatic β cells

Biochemical and Biophysical Research Communications, Volume 427, Issue 3, 2012, 600–605

http://dx.doi.org/10.1016/j.bbrc.2012.09.104

TGR5 Regulates Insulin Secretion in Pancreatic β Cells



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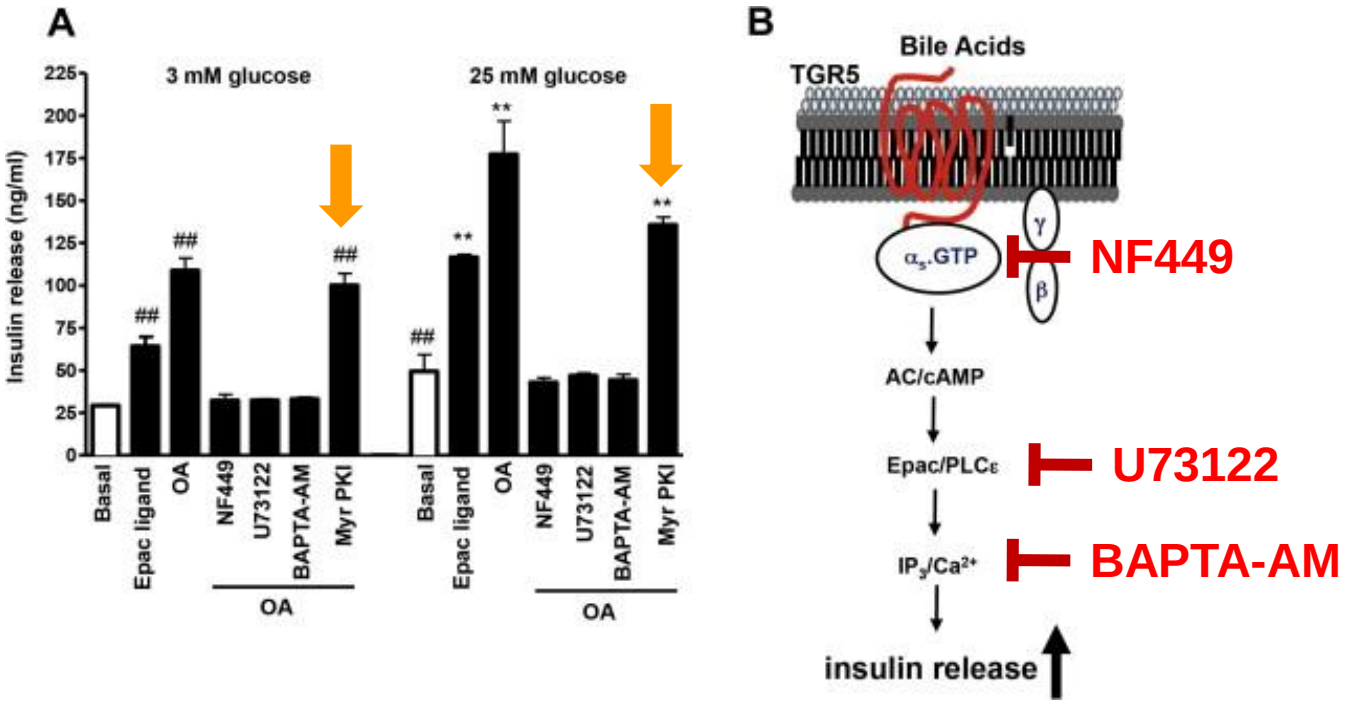
Signaling Pathways of TGR5-mediated Insulin Secretion in Pancreatic β Cells



PKA inhibitor has no effect on TGR5-induced insulin release.

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Activation of transmembrane bile acid receptor TGR5 stimulates insulin secretion in pancreatic β cells

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THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 291, NO. 13, pp. 6626–6640, March 25, 2016

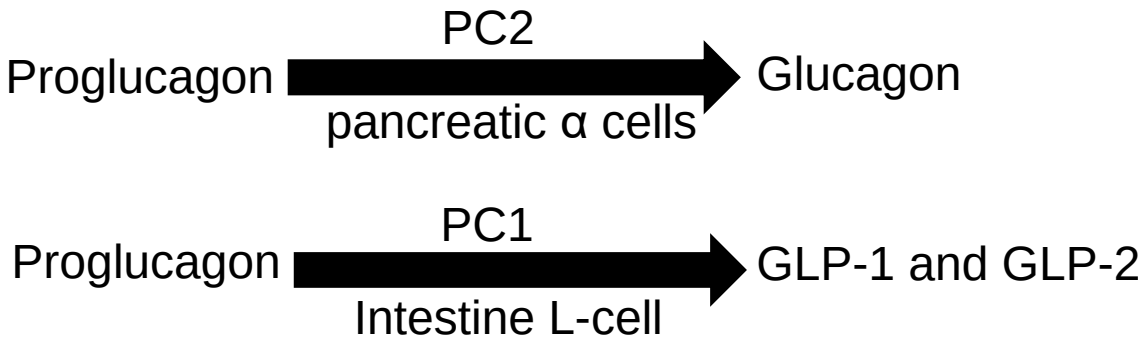
Activation of Transmembrane Bile Acid Receptor TGR5 Modulates Pancreatic Islet α Cells to Promote Glucose Homeostasis*

Received for publication, October 21, 2015, and in revised form, January 6, 2016 Published, JBC Papers in Press, January 12, 2016, DOI 10.1074/jbc.M115.699504

Divya P. Kumar[‡], Amon Asgharpour[§], Faridoddin Mirshahi[§], So Hyun Park[¶], Sichen Liu[¶], Yumi Imai[¶], Jerry L. Nadler[¶], John R. Grider[‡], Karnam S. Murthy[‡1,2], and Arun J. Sanyal[§1,3]

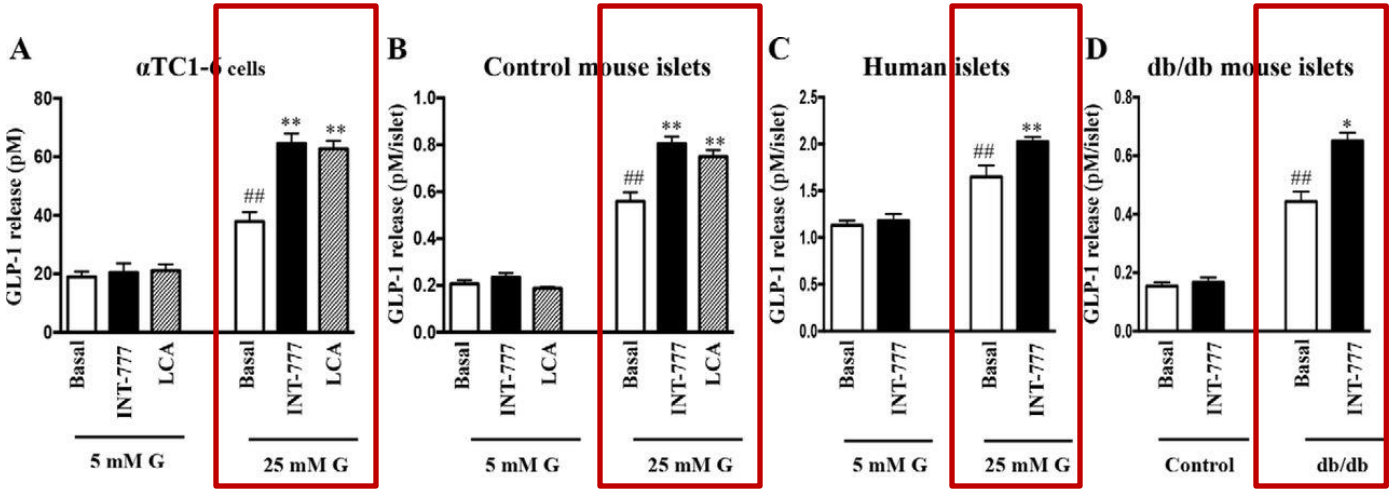
From the Departments of [§]Internal Medicine and [‡]Physiology and Biophysics, Virginia Commonwealth University School of Medicine, Richmond, Virginia 23298 and the [¶]Department of Internal Medicine, Strelitz Diabetes Center, Eastern Virginia Medical School, Norfolk, Virginia 23507

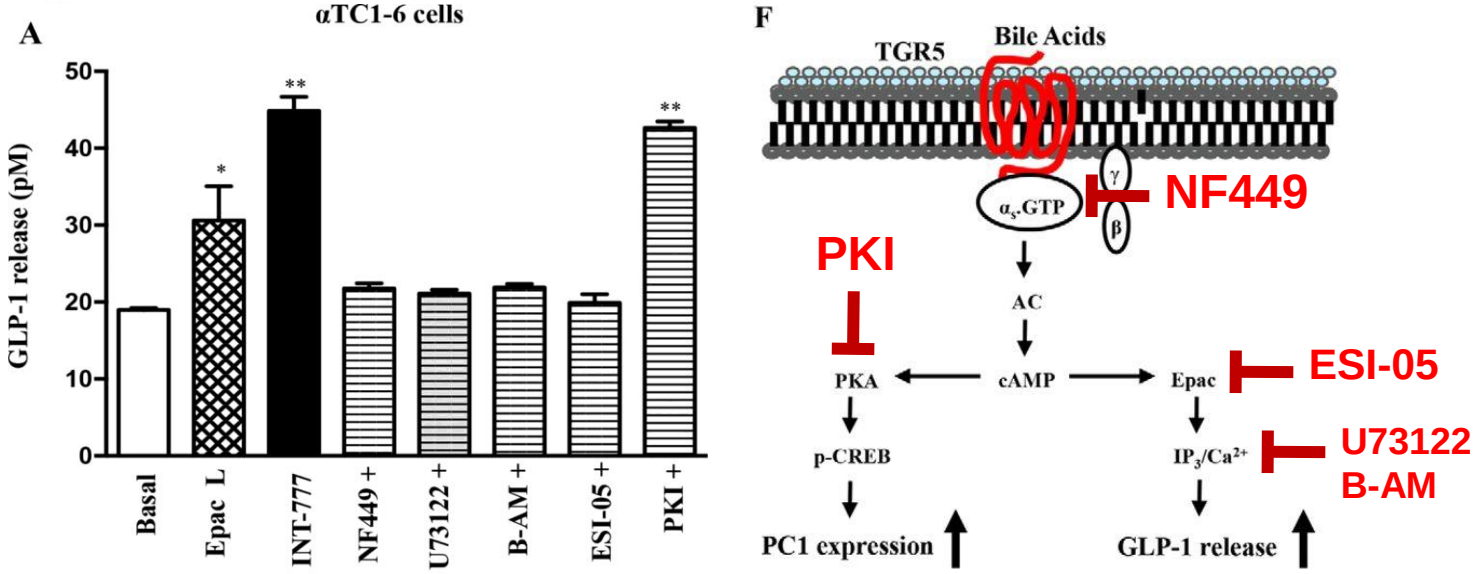
- **TGR5 activation increases hyperglycemia-induced PC1 expression in pancreatic α cells, but has no effect on PC2 expression.**



A earlier study reported that proglucagon can be processed to GLP-1 in pancreatic α cells. This process is upregulated by elevated glucose, activation of TGR5 and β-cell destruction. (Whalley NM, et al. J Endocrinol. 2011 Oct;211(1):99-106.)

INT-777 increases GLP-1 release in human and mouse islets and αTC1-6 cells under hyperglycemic conditions via Epac in a PKA-independent mechanism.





Divya P. Kumar et al. J. Biol. Chem. 2016;291:6626-6640

jbc

Summary

- **TGR5 is expressed in both pancreatic β cells and α cells.**
- **In pancreatic β cells, activation of TGR5 induced insulin release *via* activation of cAMP-Epac/PLCε/IP_3 signaling pathway.**
- **In pancreatic α cells, activation of TGR5 enhanced hyperglycemia-induced PC1 expression *via* activation of PKA.**
- **In pancreatic α cells, activation of TGR5 promoted GLP-1 release *via* activation of Epac/PLCε/IP3 signaling pathway.**
- **TGR5 activation mediates cross-talk between α and β cells by switching from glucagon to GLP-1 to restore β cell mass and function under hyperglycemic condition.**

CONCLUSIONS

- **S1PR2 and TGR5 are important players in bile acid-mediated regulation of lipid and glucose metabolism.**

- **Targeting S1PR2 and TGR5 could be leveraged as novel therapeutic strategies to treat fatty liver diseases and type 2 diabetes mellitus.**

ACKNOWLEDGEMENTS

ACKNOWLEDGEMENTS

- Dr. Renping Zhao
- Dr. Runping Liu
- Dr. Xiqiao Zhou
- Dr. Xiaoxuan Zhang
- Mrs. Xuan Wang
- Mrs. Emily C Gurley
- Mrs. Dalila Marques
- Mrs. Patricia Cooper
- Dr. Phillip B. Hylemon
- Dr. Arun Sanyal
- Dr. Kazuaki Takabe
- Dr. Masayuki Nagahashi
- Dr. Aoki Hiroaki
- Dr. Sarah Spiegel
- Dr. Nitai C. Hait
- Dr. Jeremy C. Allegood
- Dr. William M. Pandak
- Dr. Mikhail Dozmorov
- Dr. Weiren Xu

SUPPORT:

- NIH/NIDDK R01
- A.D. William Foundation
- VA Merit Award.
- China Science Foundation


Thank you for your attention!