Vitamin A and Liver Health

Yu-Jui Yvonne Wan, PhD

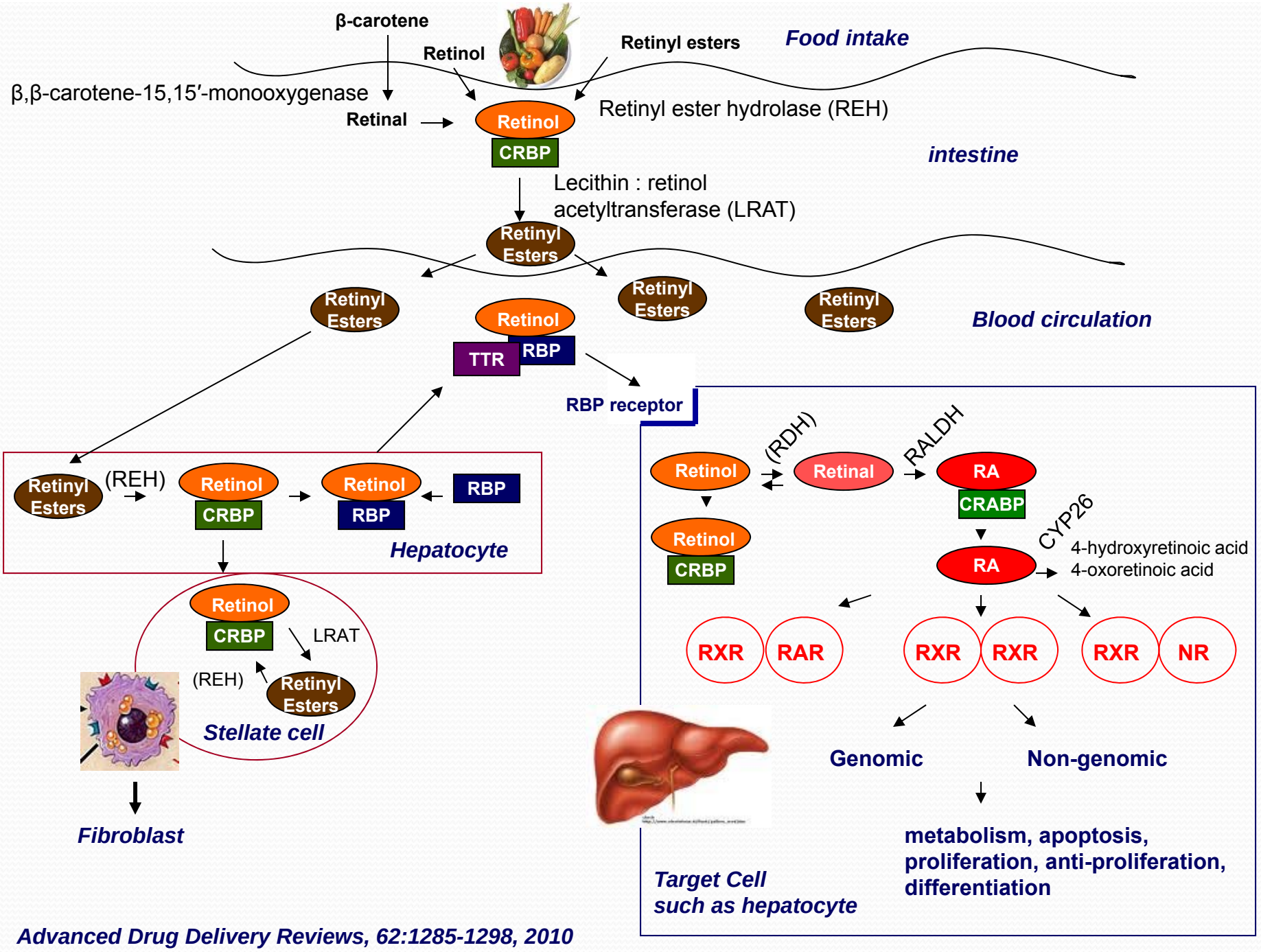
Professor and Vice Chair for Research

Department of Pathology

University of California, Davis

Retinoic acid

- Vitamin A is important for development, growth, and differentiation
- Essential for vision
- Maintain normal skin health



Advanced Drug Delivery Reviews, 62:1285-1298, 2010

Nuclear receptor subfamily (based on ligands)

Endocrine receptors

AR Androgen

ER Estrogen

GR Glucocorticoid

MR Mineralcorticoid

PR Progesterone

Adopted orphan receptors

RARs all trans-RA

RXRs 9 cis-RA

VDR Vitamin D3

TR Thyroxine T4

CAR Androstane

Rodent PXR PCN

Human PXR Rifampicin

ERR Diethylstilbestrol

FXR Bile acids

HNF4 Fatty acids

LXRs Oxysterol

PPARα Fatty acids

PPARγ 15d-PGJ2

PPARδ cPG1

RORs Cholesterol/melatonin

SF-1 Phospholipids

Orphan receptors

COUP-TFs

GCNF (germ cell nuclear factor)

NOR1 (RA receptor-related protein)

NURR1 (*Nur*-related protein)

NUR77 (TR3, NGF1-B)

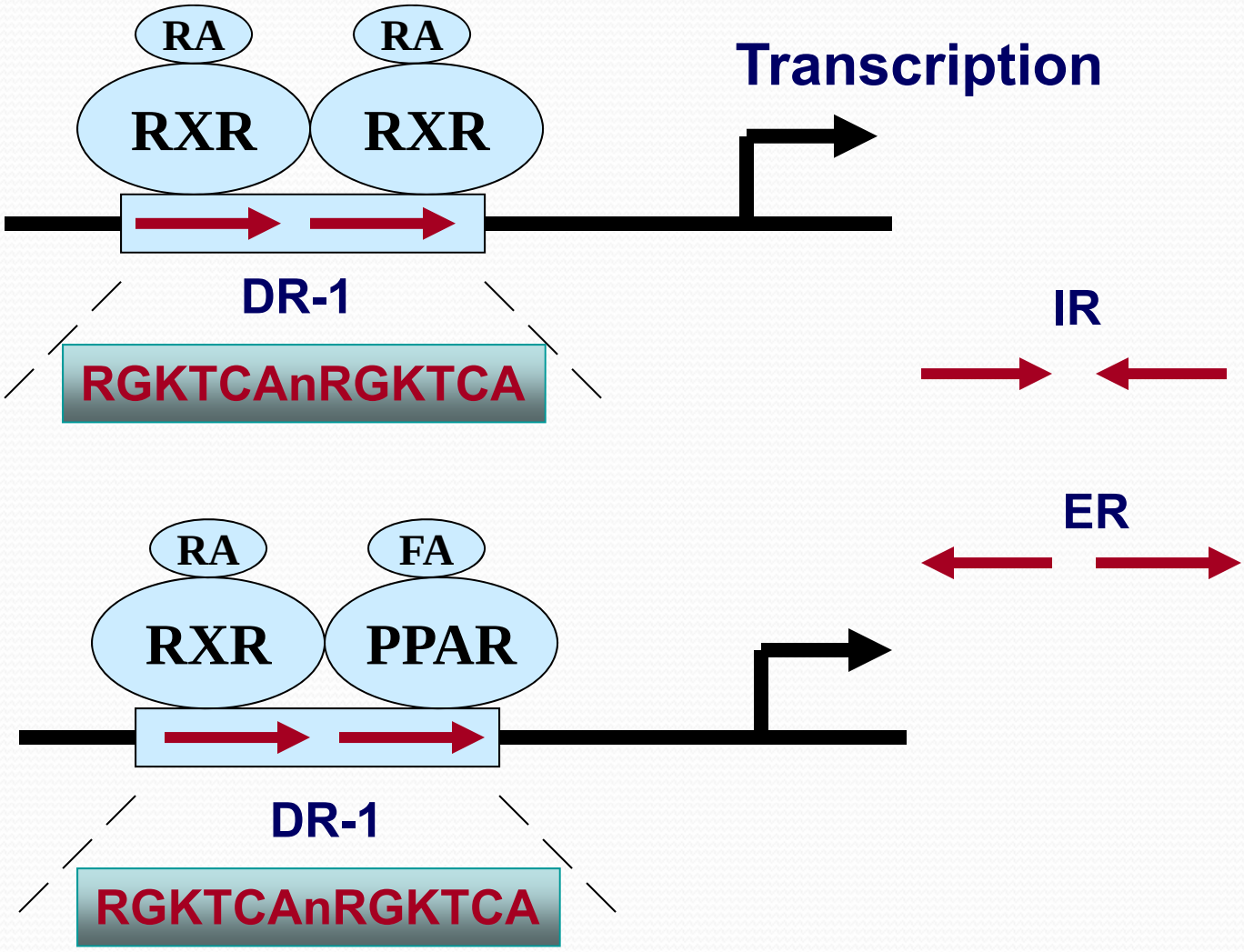
PNR (photoreceptor cell-specific nuclear receptor)

Rev-erb alpha and beta

TLX (tailless homolog)

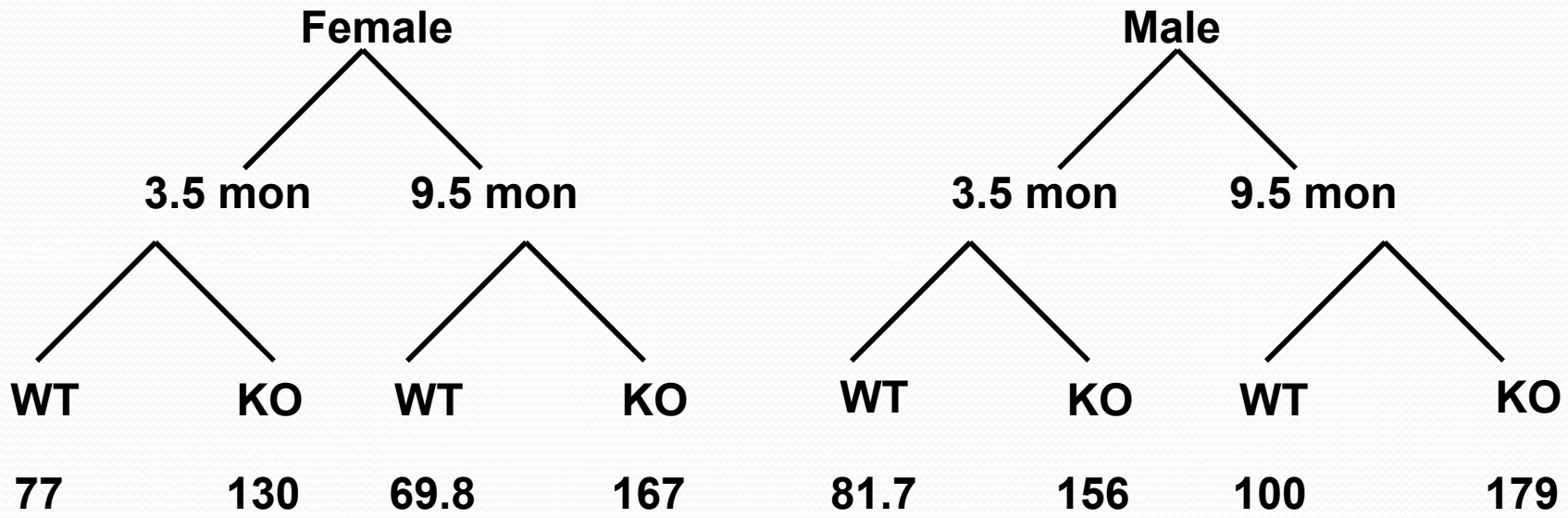
TR2, 4 (testicular receptor)

Interaction between nuclear receptor and DNA



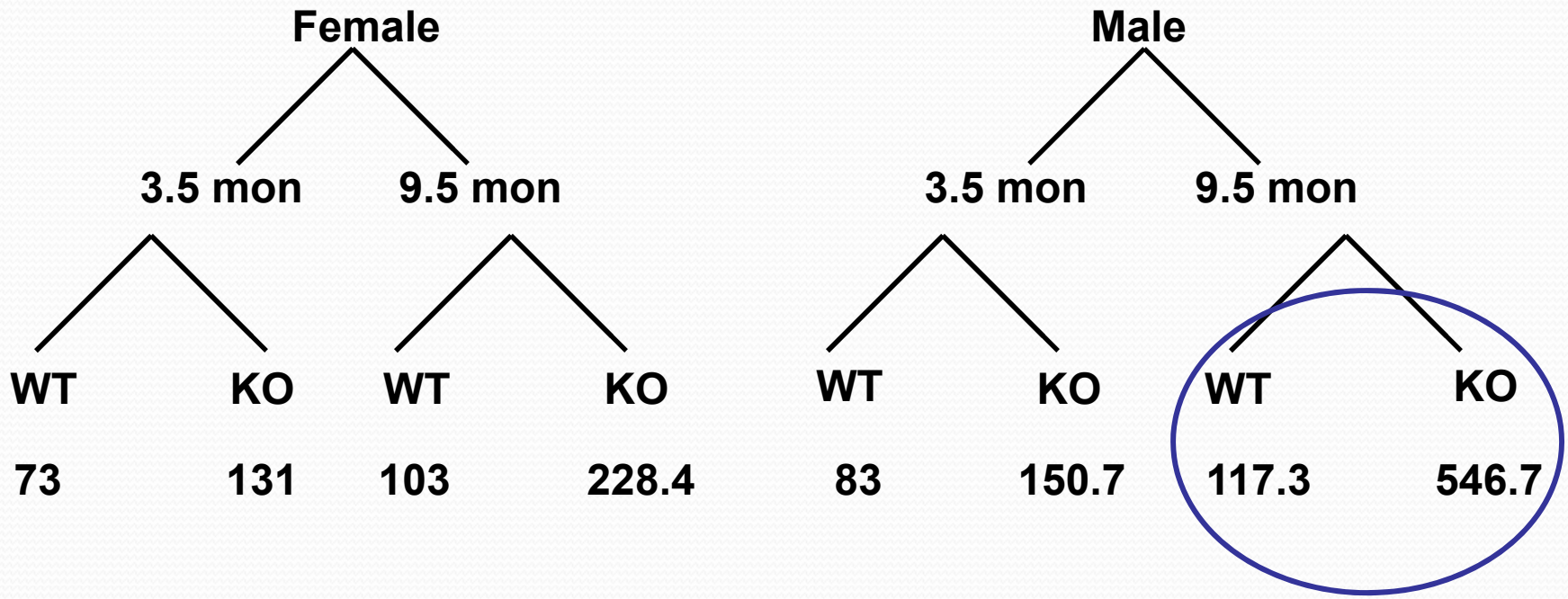
Core: RGKTCA = (A/G)G(T/G)TCA

Serum cholesterol level is elevated due to hepatocyte RXRα deficiency

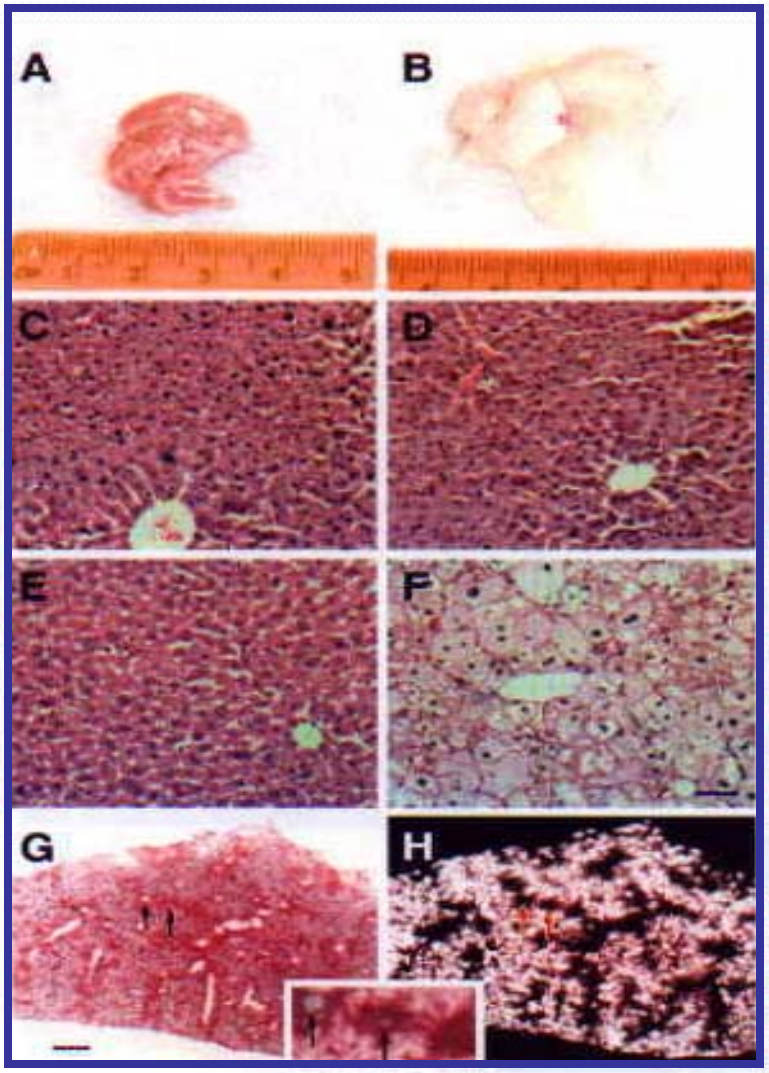


Molecular and Cellular Biology 20: 4436-4444, 2000
Journal Biological Chemistry 275: 28285-28290, 2000

Serum triglyceride level is elevated due to hepatocyte RXRα deficiency



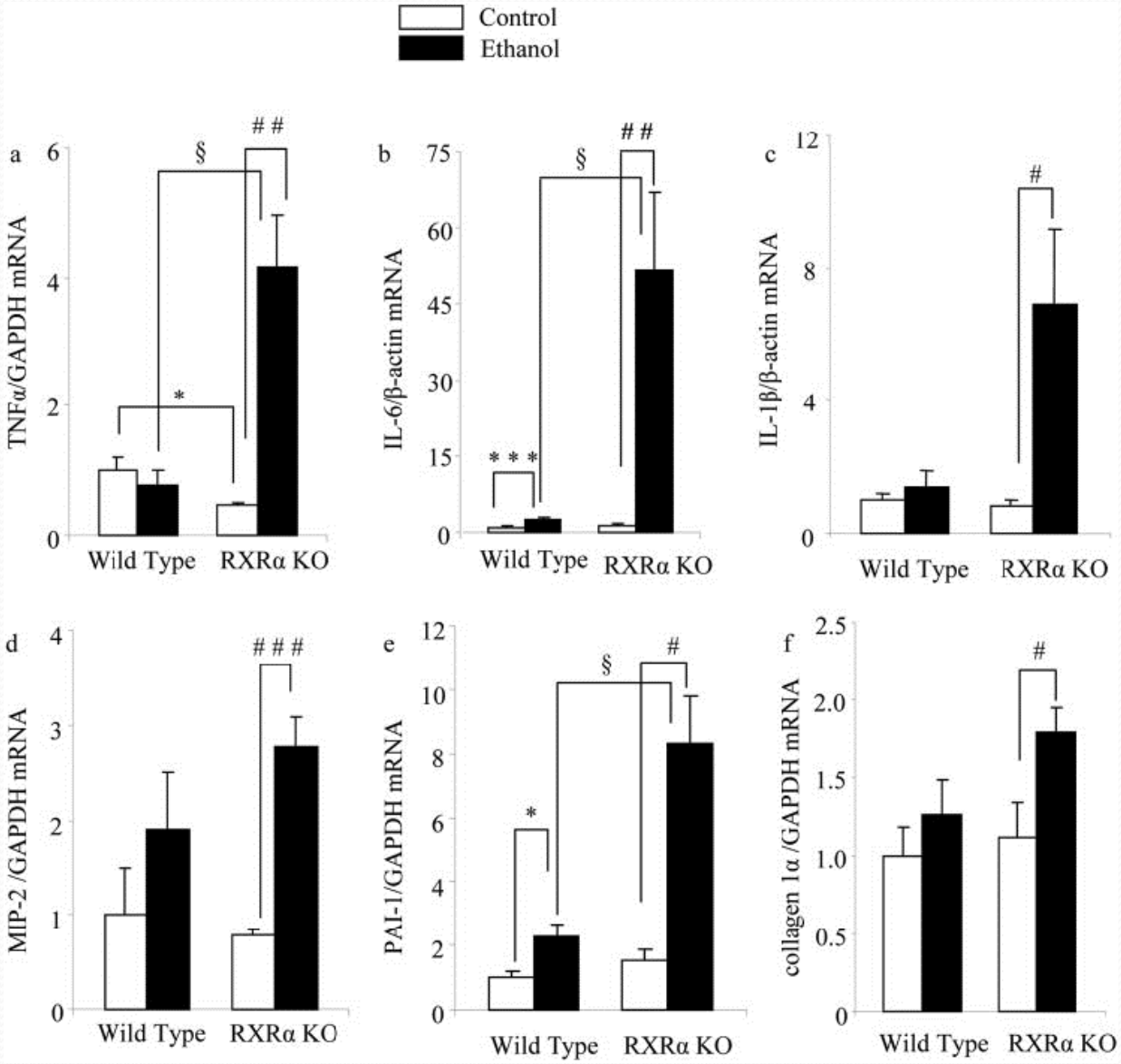
Molecular and Cellular Biology 20: 4436-4444, 2000
Journal Biological Chemistry 275: 28285-28290, 2000



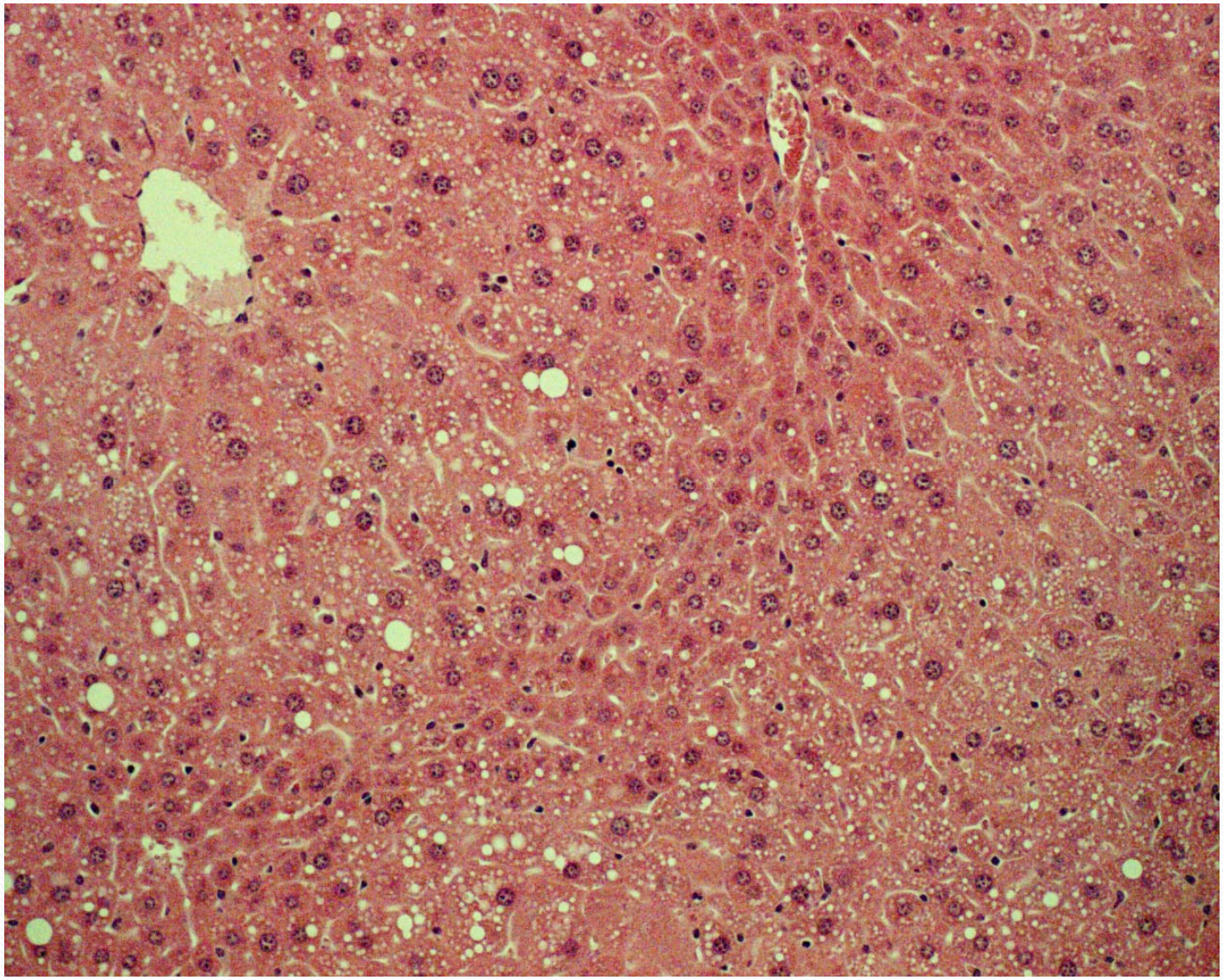
Hepatic cholesterol metabolism is compromised due to hepatocyte RXRα deficiency

Molecular and Cellular Biology 20: 4436-4444, 2000

Alcohol-feed RXRα-null mouse livers have increased expression of pro-inflammatory cytokines

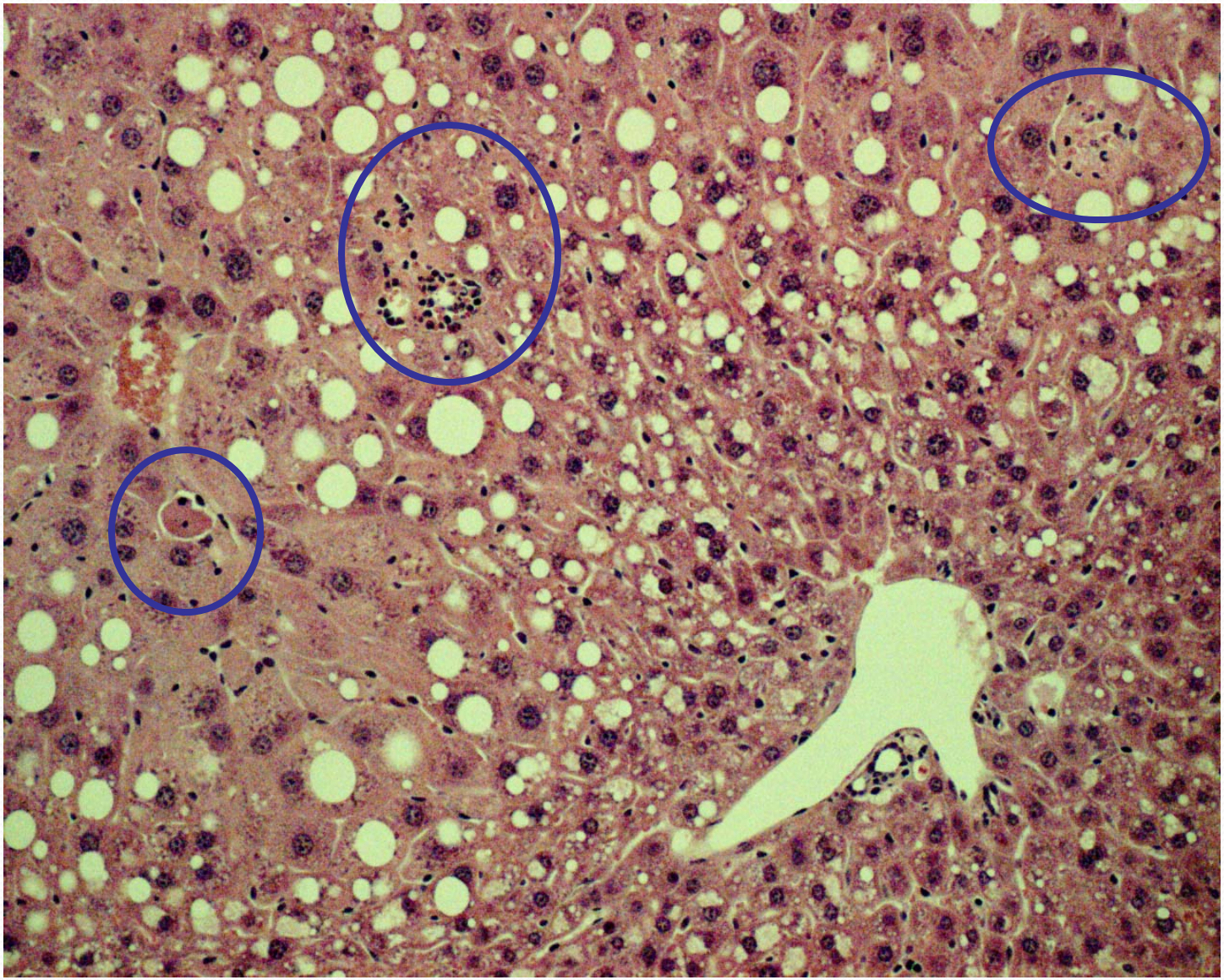


Wild Type Mice / Alcohol



Experimental and Molecular Pathology 75: 194-200, 2003
Journal of Pharmacology and Experimental Therapeutics, 319: 360-368, 2006

Hepatocyte RXRα-deficient Mice / Alcohol



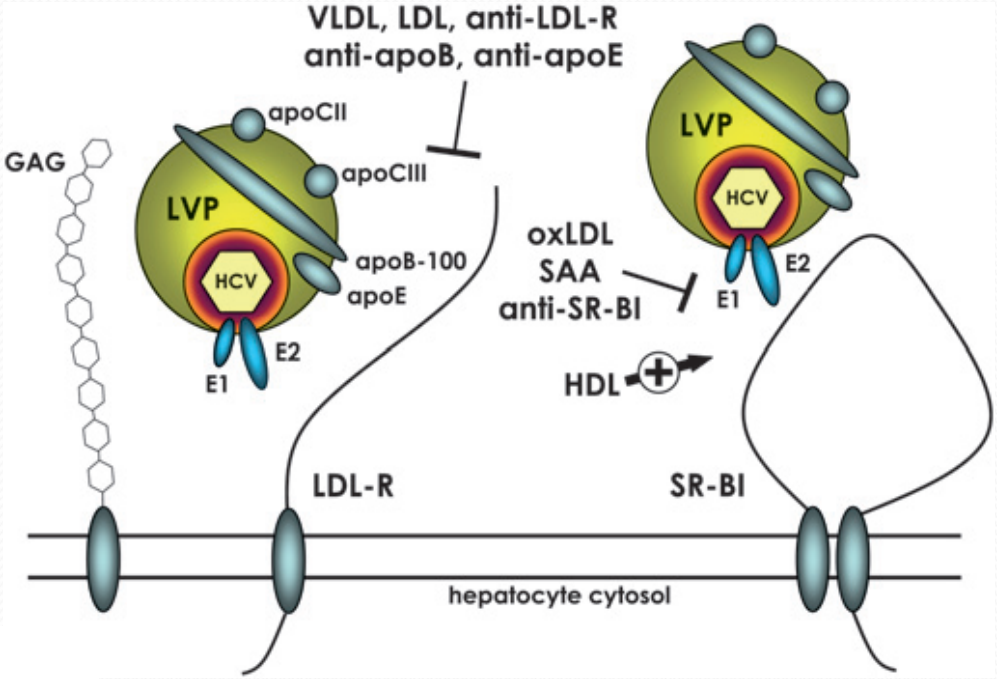
Experimental and Molecular Pathology 75: 194-200, 2003
Journal of Pharmacology and Experimental Therapeutics, 319: 360-368, 2006

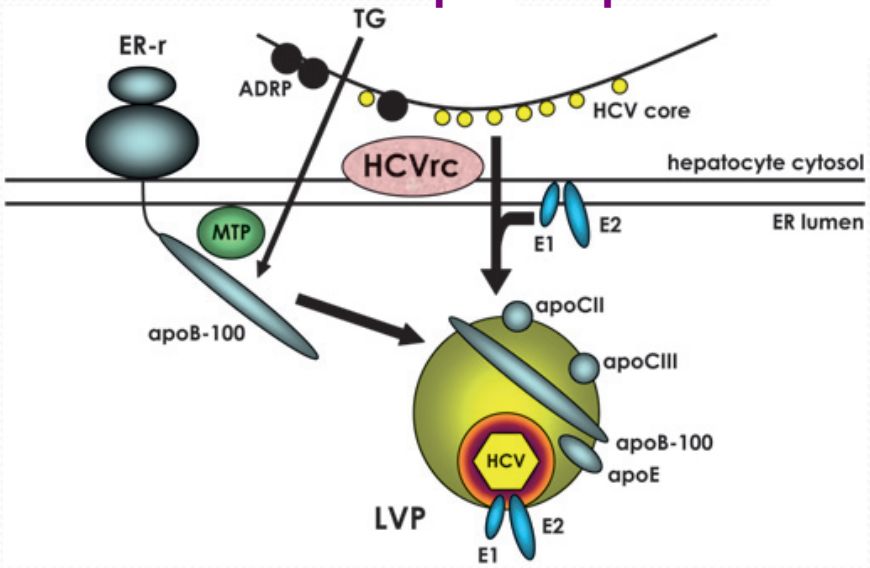
Using chronic hepatitis C as a model to study the role of hepatic nuclear receptors in metabolism and inflammation in human livers

Dr. Chuanghong Wu
Director, Department of Infectious Disease,
the People's Hospital of Shekou, Shenzhen
China

Hepatology
November 2011 issue
Cover story

Lipid and HCV life cycle





Negro F. Gut, 2010; 59: 1279-1287

Hypotheses

HCV infection is associated with dysregulation of hepatic nuclear receptor-mediated pathways, which in turn contribute to viral replication and pathological process.

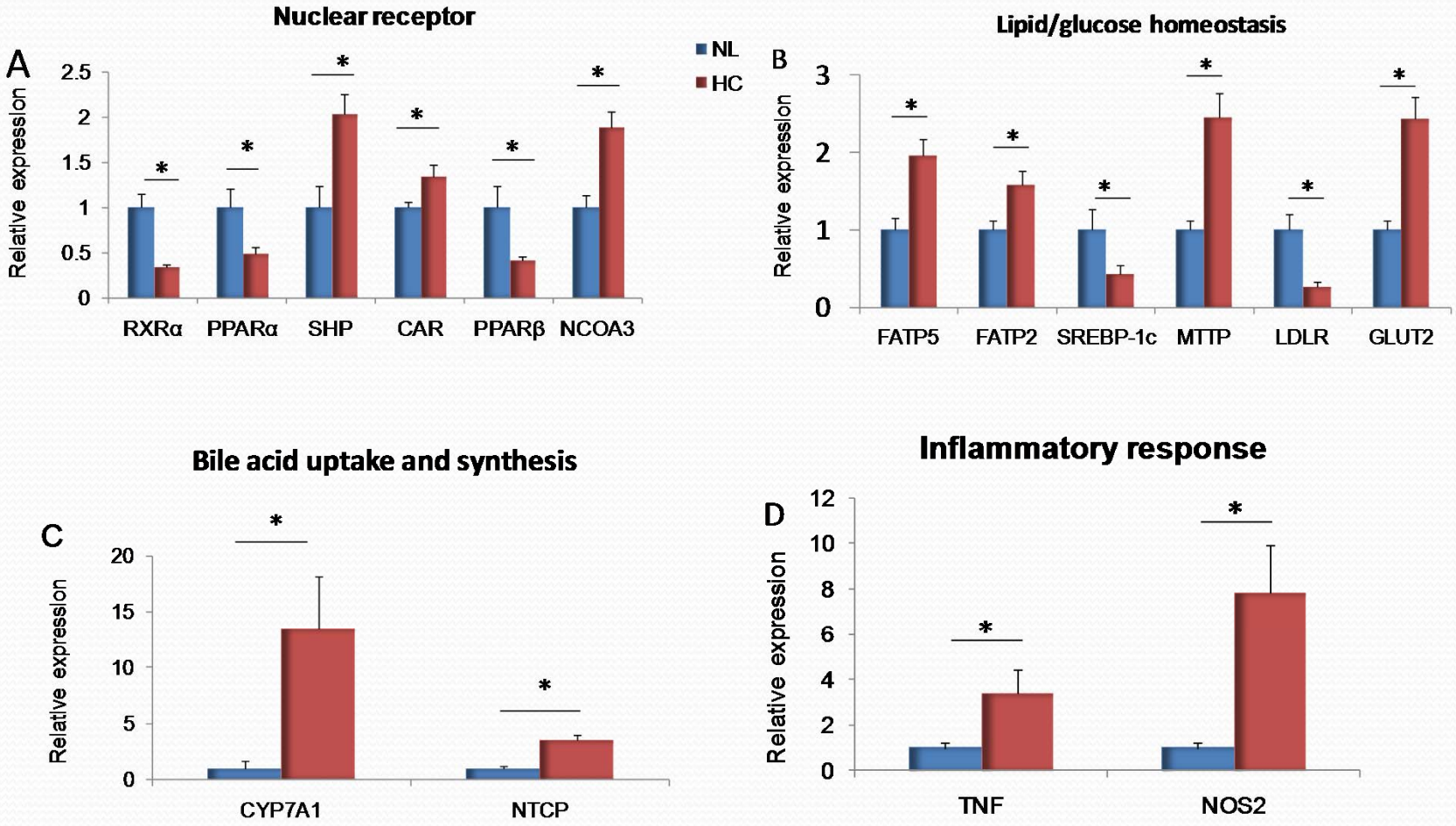
Test the impact of HCV infection on nuclear receptor-mediated pathway

Inclusive criteria:
Controls: 15 normal liver specimens from donors
Experiment group: 23 liver specimens from chronic hepatitis C patients
Anti-HCV and HCV RNA positive patients
Age, gender, BMI-matched

Exclusive criteria: positive for hepatitis B virus surface antigen; primary biliary cirrhosis, autoimmune hepatitis, Wilson's disease, hemochromatosis, co-infection with human immunodeficiency virus; treatment with antiviral or immunosuppressive agents within 6 months; post-transplant patients

Gene Selection: >120 genes that include nuclear receptors, co-regulators, and their downstream targets

Gene signatures for HCV infection in human livers

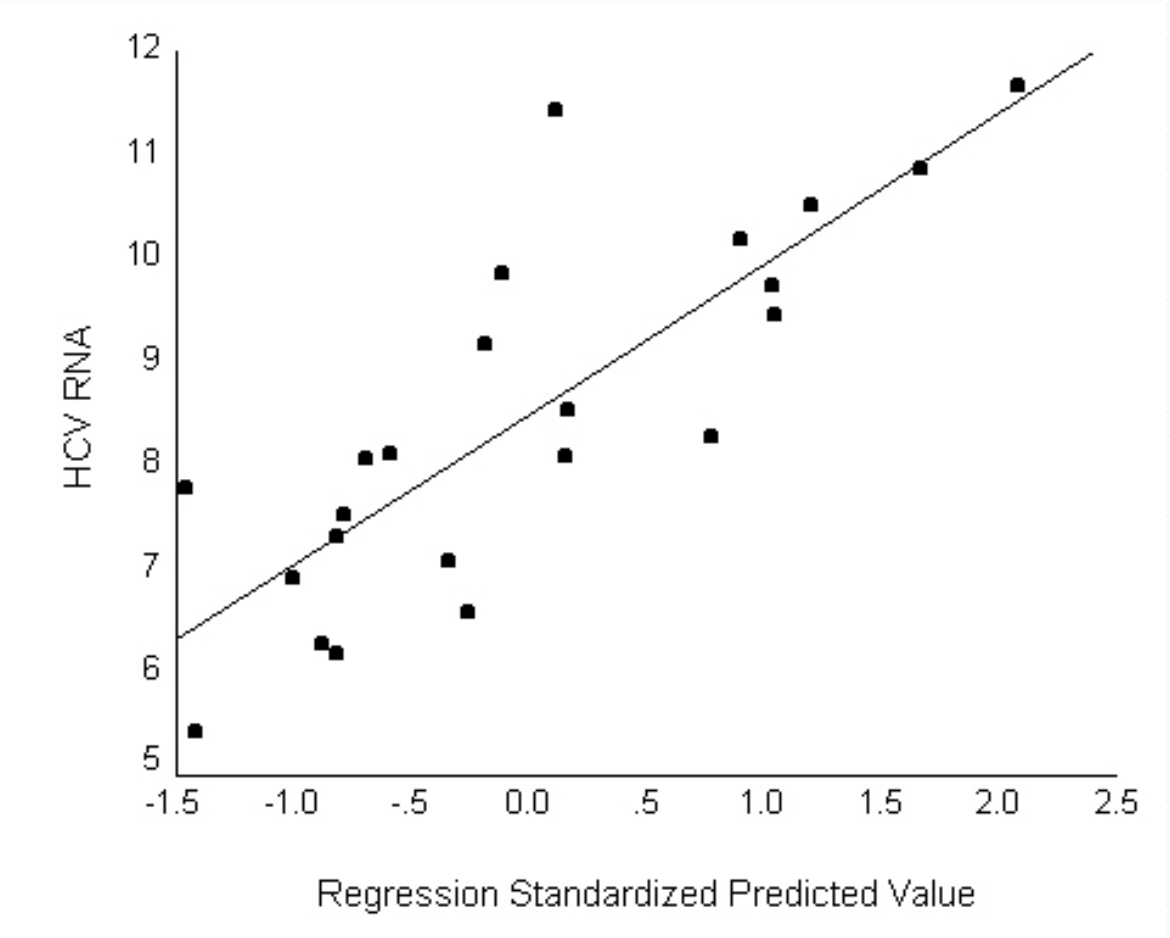


NL: normal liver
HC: HCV positive patients. *: $p<0.05$

Bivariate correlations analysis between Hepatic HCV RNA level and the expression of the hepatic genes

Genes functions	Genes	Correlation coefficients	*P* value (2 tails)
Nuclear Receptor	PPARγ	0.42	0.045
	RARβ	0.48	0.021
	RARγ	0.57	0.004
	LRH-1	0.45	0.031
	FXR	0.46	0.028
Lipid and glucose metabolism pathway	SCD	0.47	0.020
	FASN	0.46	0.027
	FGF21	-0.48	0.019
	G6P	0.43	0.039
Immune response and inflammatory pathway	IL10	0.48	0.021
	RIG1	0.42	0.048

Hepatic FGF21, IL-10, and FAS mRNA levels are independently correlated with hepatic HCV RNA levels in multivariate analysis

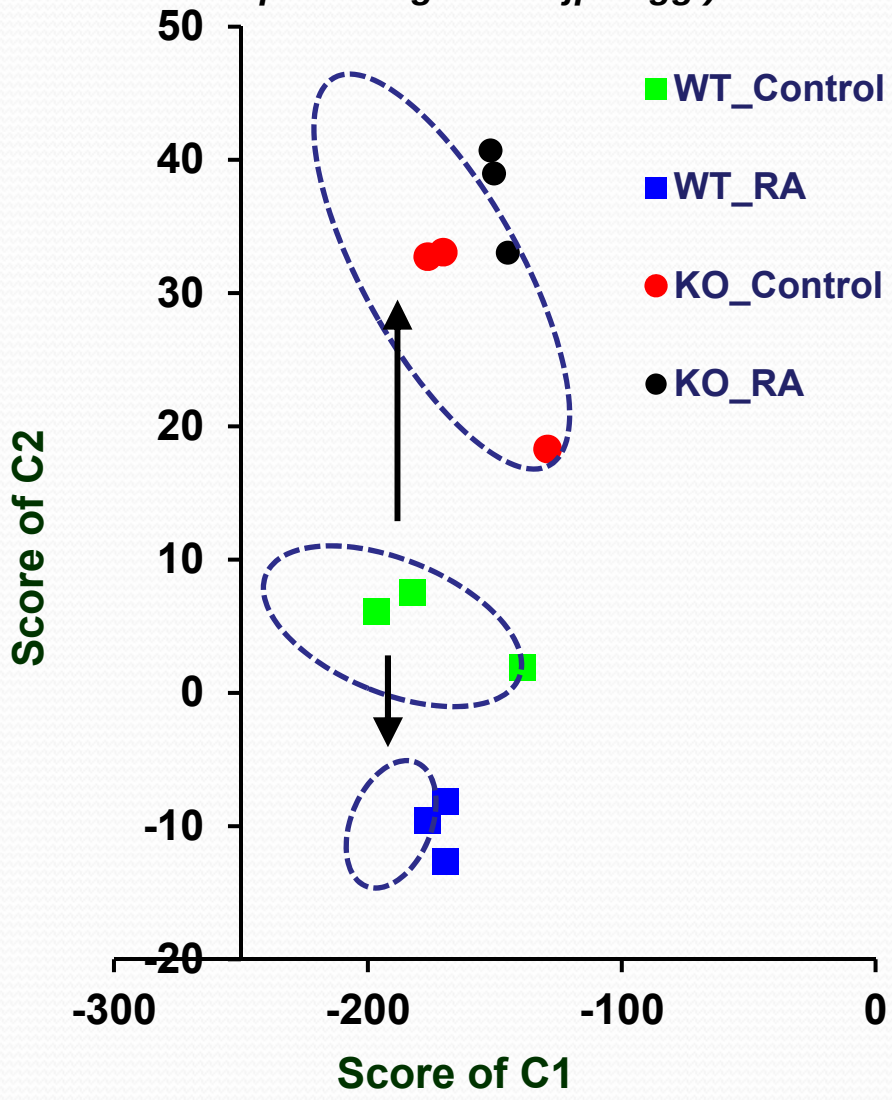


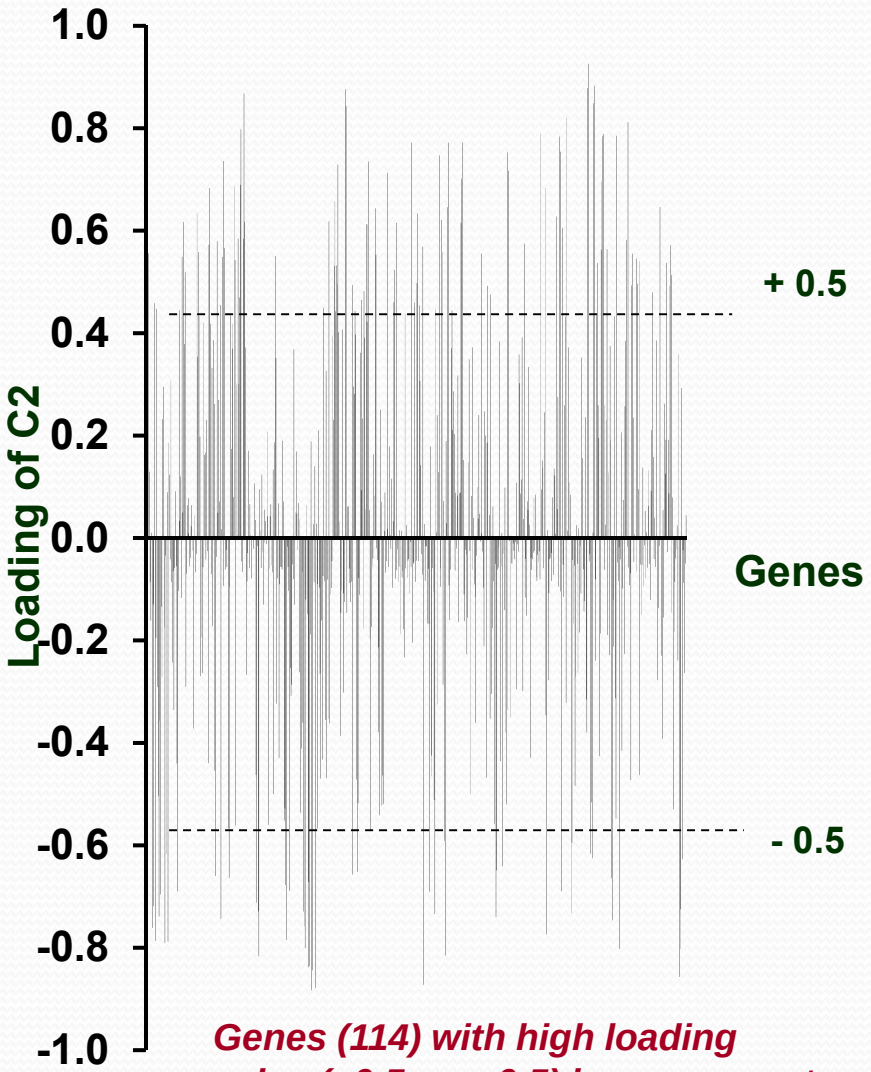
Conclusions

- Hepatic RXRα regulates basal serum lipid levels
- Liver RXRα knockout mice are susceptible to develop NASH and ASH.
- Nuclear receptor-mediated pathways that dictate lipid and glucose homeostasis as well as inflammatory response are dysregulated due to HCV infection.
- The dysregulation of nuclear receptor-mediated pathways is associated with viral replication.
- Nuclear receptors can be potential drug targets.

The expression of genes (579) involved in regulating lipid homeostasis in wild type and RXRα knockout mice treated with and without RA

(extracted from KEGG database , Kyoto Encyclopedia of Genes and Genomes, http://www.genome.jp/kegg/)





Genes (114) with high loading value (>0.5 or <-0.5) in component 2 were selected for further analysis

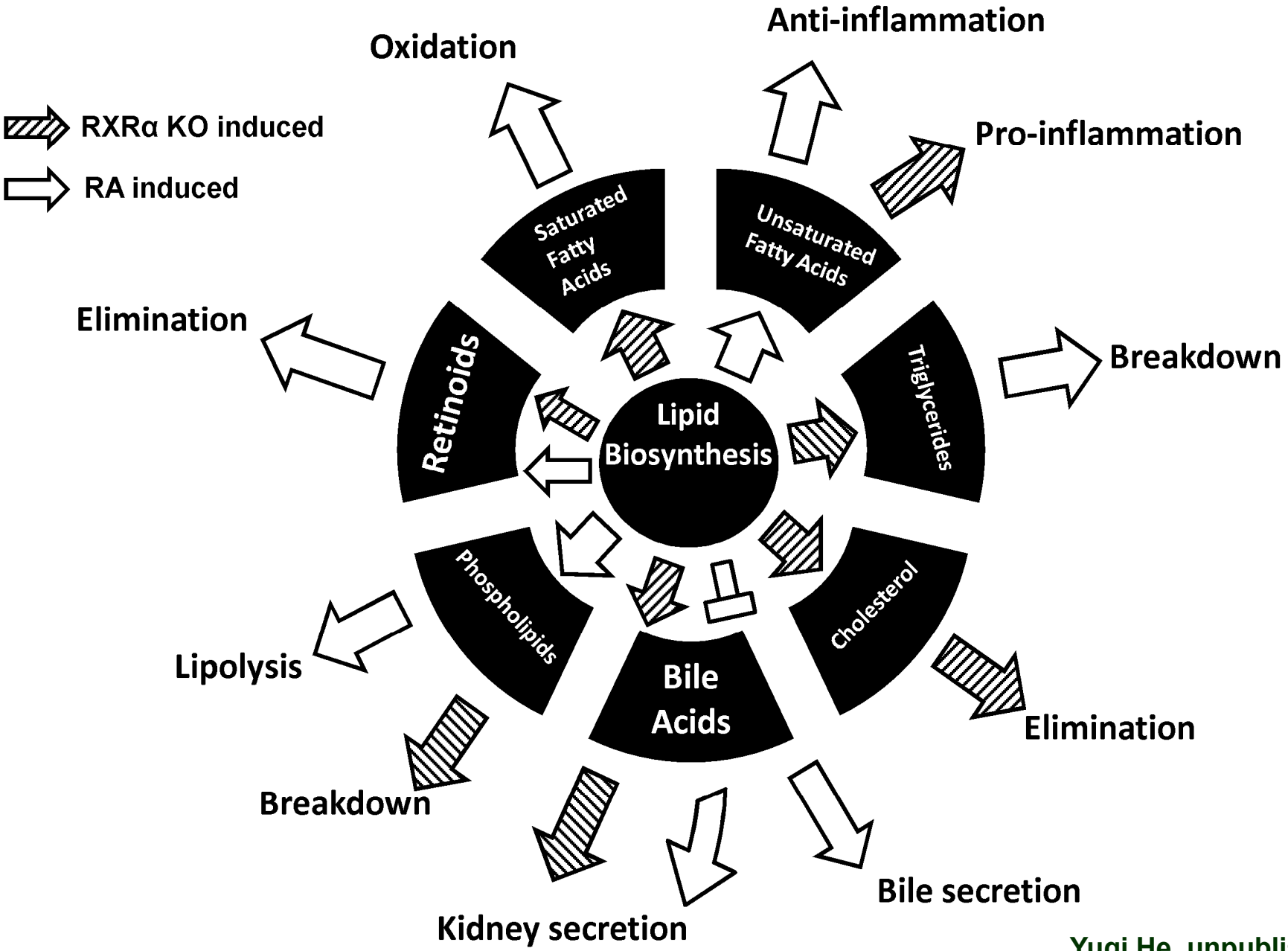
Yuqi He, unpublished

Biological function annotation of RA-regulated and RXRα-dependent genes (114)

Biological Functions	Gene Number (with RXRα bindings)	
	RA induced & RXRα KO repressed	RA repressed & RXRα KO induced
Lipid droplet growth	1 (0)	2 (2)
Transportation of bile aicds for bile excretion	1 (0)	0
Dehydrogenation of saturated fatty acids to unsaturated fatty acids	3 (2)	0
Biosynthesis of glycerol phosphalipids	4 (3)	1 (1)
Tryglyceride degration	4 (3)	0
Biosynthesis of unsaturated fatty acids responsible for aniti-inflammation	9 (7)	0
Elimination of Retinoic Acids	13 (11)	0
Biosynthesis of Bile Acids	4 (4)	4 (4)
Biosynthesis of Retinoic Acids	1 (1)	2 (2)
Biosynthesis of saturated fatty acids	5 (5)	10 (10)
Degradation of glycerol phosphalipids	1 (1)	4 (4)
Degradation of saturated fatty acids	10 (10)	5 (5)
Elimination of steroid hormones	3 (3)	5 (5)
Fat digestion and absorption	3 (3)	7 (7)
Lipid droplet breakdown (fat mobilization)	1 (1)	1 (1)
Recycle of bile acids via hepatic-intestine	1 (1)	3 (3)
S1P degradation	1 (1)	1 (1)
Transportation of bile aicds for kidney excretion	2 (2)	3 (3)
DHS1P degradation	1 (1)	0
Elimination of unsaturated fatty acids (PGE2) responsible for lipolysis inhibition	1 (1)	0
phosphatidylcholine to Phosphatidylethanolamine	1 (1)	0
Sphingolipid biosynthesis	1 (1)	0
SPH (SM) degradation	0	1 (0)
Biosynthesis of cholesterol	0	10 (10)
Biosynthesis of Steroid hormone	0	1 (1)
Biosynthesis of tryglycerides	0	1 (1)
Biosynthesis of unsaturated fatty acids responsible for pro-inflammation	0	1 (1)
Breakdown of phosphalipid to form unsaturated fatty acids	0	1 (1)
Elimination of cholesterol (from cyculation back to liver for catabolism)	0	1 (1)
Elimination of cholesterol via steoid hormone pathway	0	1 (1)
Phosphatidylethanolamine to phosphatidylcholine	0	1 (1)

Yuqi He, unpublished **55** **59**

The action of RA and hepatic RXRα in regulating lipid homeostasis



Yuqi He, unpublished

Serum cholesterol, triglyceride and bile acid level after RA treatment of wild type and liver RXRα knockout mice

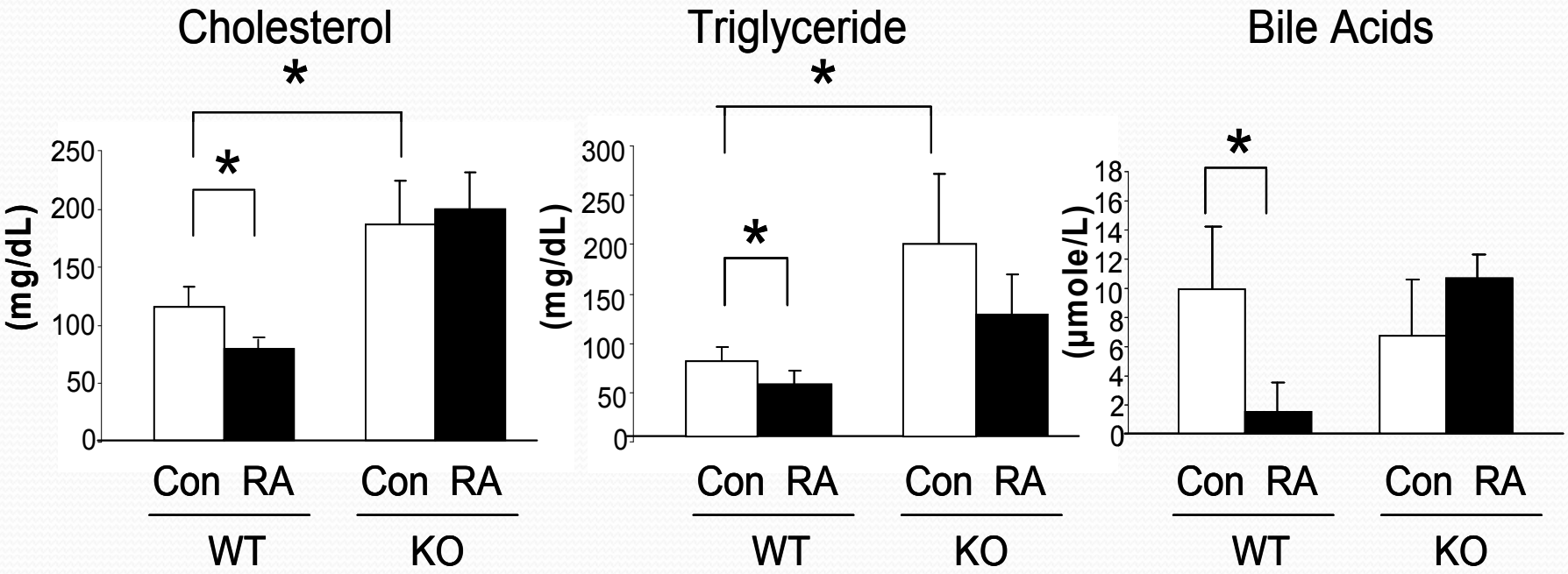
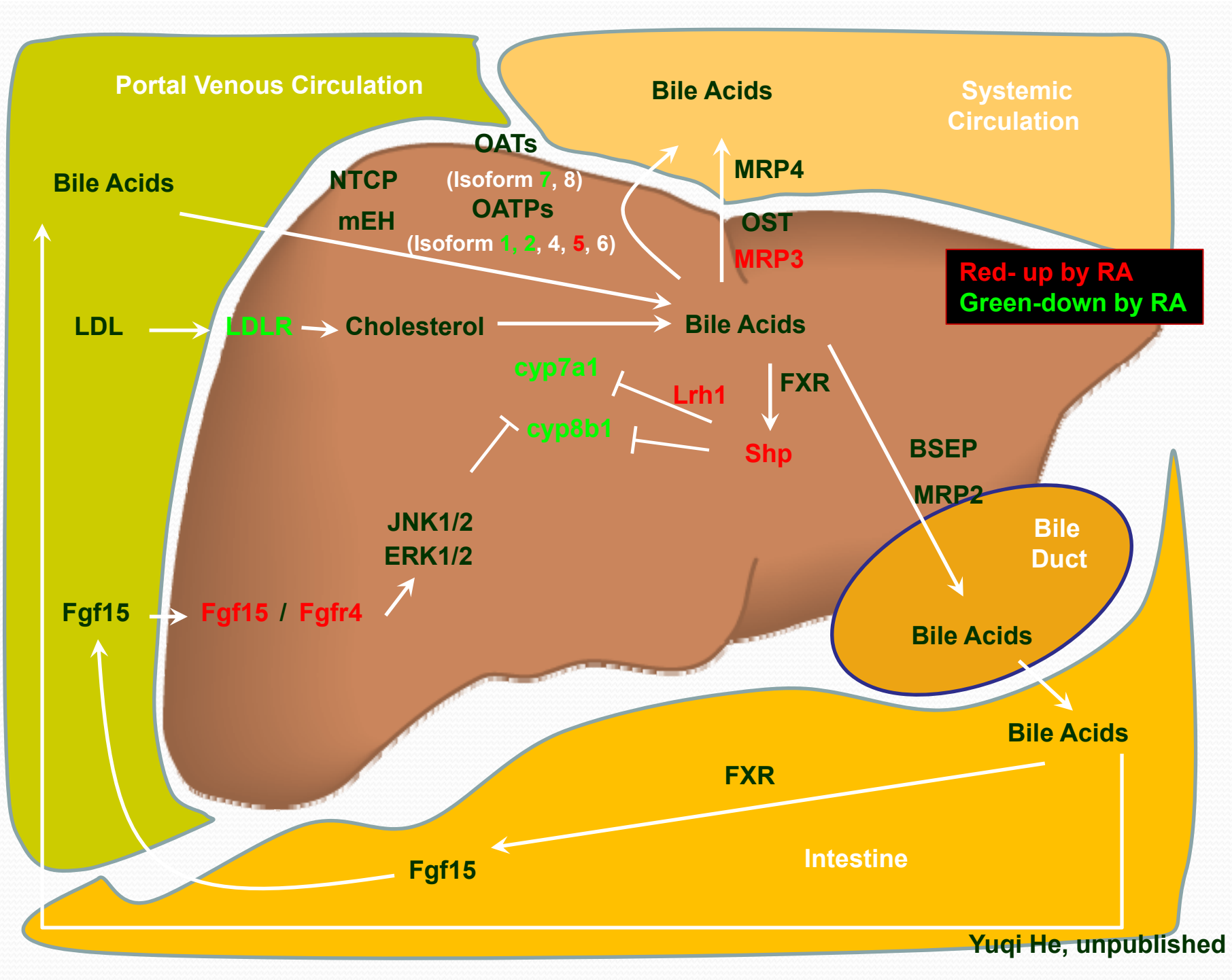


Fig. 1 Male wild type (WT) and hepatocyte RXRα (KO) were fed laboratory chow with and without all-trans RA (150 mg/kg diet) for 7 days (n = 6). Serum cholesterol, triglyceride, and bile acid levels were quantified at the end of the treatment. * $p<0.01$

unpublished

Conclusions

Retinoic acid mediated through nuclear receptors regulates lipid homeostasis


Portal Venous Circulation
Bile Acids
Systemic Circulation
Bile Acids
OATs
(Isoform 7, 8)
NTCP
mEH
OATPs
(Isoform 1, 2, 4, 5, 6)
MRP4
OST
MRP3
Red- up by RA
Green-down by RA
LDL
LDLR
Cholesterol
Bile Acids
cyp7a1
Lrh1
FXR
cyp8b1
Shp
BSEP
MRP2
JNK1/2
ERK1/2
Bile Duct
Fgf15
Fgf15 / Fgfr4
Bile Acids
Bile Acids
FXR
Intestine
Fgf15
Yuqi He, unpublished

FXR knockout mice phenotype

FXR deficiency leads to the development of cholestasis, gallstone disease, nonalcoholic steatohepatitis, as well as liver and colon tumor.

Guo and Gonzalez

Presence of HCC was observed in 100% of the FXR-KO mice at the age of 14 months- activation of Wnt/β-catenin.

Wolfe et al., JPET, 2011

Dysfunction of organic anion transporting polypeptide 1a1 alters intestinal bacteria and bile acid metabolism in mice.

Zhang et al., PLoS ONE 01/2012; 7(4):e34522.

- **Have a different BA composition in the intestinal contents.**
- **Have 10-fold more bacteria in the small intestine and 2-fold more bacteria in the large intestine, which is due to a 200% increase in Bacteroides and a 30% reduction in Firmicutes.**

Hypothesis and Future Studies

Vitamin A/nuclear receptor-- Bile acid composition --

Microbial function and composition

Vitamin A deficiency

High fat diet

Alcohol drinking

--- interrupt bile acid homeostasis

--- alter the microbiome in intestine/favor the growth of the gram negative bacteria--LPS production

--- pro-inflammatory

--- increase the risk for cancer

Primary sclerosing cholangitis