Role of Nuclear Factors In Pathogenesis of Liver Diseases

Essay
Submitted for Partial Fulfillment of Master Degree in
Internal Medicine

Presented by
Mohammad Hassani Hosni
(M. B, B. Ch)

Supervised by

Prof. Dr. Osama Abo El Fotouh El Sayed

Professor of Internal Medicine
Faculty of Medicine - Ain Shams University

Dr. Noha Abd El Razek El Nakeeb

Assistant Professor of Internal Medicine
Faculty of Medicine – Ain Shams University

Dr. Amir Helmy Samy

Assistant Professor of Internal medicine
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain-Shams University
2013

بسم الله الرحمن الرحيم

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ وَرَسُولُهُ والْمُؤْمِنُونَ

صدق الله العظيم

سورة التوبة آية (١٠٥)

First, thanks are all due to ***Allah*** *for Blessing this work until it has reached its end, as a part of his generous help throughout our life.*

I would like to express my deep gratitude and appreciation to ***Prof. Dr. Osama Abo Elfotoh Elsayed,*** *Professors of Internal Medicine, Faculty of Medicine, Ain Shams University, for his great supervision, great help, available advises, continuous encouragement and without his support it was impossible for this study to be achieved in this form. I had the privilege to benefit from his great knowledge, and it is an honor to work under his guidance and supervision.*

I am sincerely express my great appreciation to ***Dr. Noha Abdel Razek ElNakeeb****, Assistant Professors of Internal Medicine, Faculty of Medicine, Ain Shams University, for his efforts and all advices he offered to make this work possible.*

I am deeply thankful to ***Dr. Amir Helmy Samy,*** *Assistant prof of Internal Medicine, Faculty of Medicine, Ain Shams University, for his meticulous revision, constant support and valuable advice.*

Last but not least, I dedicate this work to my family mother, sisters, my wife, my daughter and my colleagues.Whom without their sincere emotional support, this work could not have been completed.

Mohammad Hassani Hosni

Table of contents

List of Abbreviations

Abbreviations	Interpretation
ALD	Alcoholic liver disease
ALT	Alanine aminotransferase
ASBT	Apical sodium-dependent bile acid transporter
BA	Bile acid
BSEP	Bile salt export pump
CA	Cholic acid
CAR.	Constitutive androstane receptor
CDCA	Chenodeoxycholic acid
CYP27A1/Cyp27a1	Sterol 27-hydroxylase
CYP7A1/Cyp7a1	Cholesterol 7alpha-hydroxylase
CYP8B1/Cyp8b1	Sterol 12alpha hydroxylase
CYP	Cytochrome P450 enzyme
DBD	DNA-binding domain
DCA	Deoxycholic acid
EMT	Epithelial mesenchymal transition
FDA	Food and Drug Administration
FGFs.	Fibroblast growth factors
FTF	Fetoprotein transcription factor
FXR.	Farnesoid X receptors
GR	Glucocorticoid Receptor
HAT	Histone Acetyltransferase
HCC	Hepatocellular carcinoma
HNFs	Hepatocyte nuclear factors
HRE	Hormone Response Elements
HSCs	Hepatic stellate cells
HSP	Heat shock proteins
IGF	Insulin-like growth factors
iNOS	Inducible nitric oxide synthase
KGF	Keratinocyte growth factor
LBD	Ligand binding domain
LCA	Lithocholic acid
Lcat	Cholesterol acyl transferase

List of Abbreviations (Cont.)

Abbreviations	Interpretation
LPS	Lipopolysaccharide
LRH1	Liver receptor homologue
LXR.	Liver X receptor
MCD	Methionine and choline deficient
Mdr2	Multidrug resistance gene 2
MDR3	Human homologue to rodent Mdr2
MODY	Maturity-Onset of Diabetes of the youngs
MRP/Mrp	Multidrug resistance-associated protein
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NCoR	Nuclear receptor corepressor
NFκB	Nuclear factor kappa B
NR2A1	Hepatocyte nuclear factor 4 alpha
NRs	Nuclear receptors
NTCP	Na^+/taurocholate cotransporter
OATP	Organic anion transporting peptide
OSTα/β	Organic solute transporter alpha/beta
PBC	Primary biliary cirrhosis
PFIC	Progressive familial intrahepatic cholestasis
PGC1	Proliferator-activated receptor-gammacoactivator-1
PPARs	Peroxisome proliferator – activated receptors
PXR	Pregnane X receptor
RXR.	Retinoid X receptor
SARMs	Selective Androgen Receptor Modulators
SHP	Short heterodimeric partner
SMRT	Silent mediator of retinoic acid receptor and thyroid receptor
SPRMs	Selective Progesterone Receptor Modulators
SRMs.	Selective receptor modulators
SULT2A1	Dehydroepiandrosterone sulfotransferase

List of Abbreviations (Cont.)

Abbreviations	Interpretation
SVCTs	Sodium-dependent vitamin C transporters
TCF	Transcription factor
TCPOBOP	1, 4 bis[2-3, 5-dichloropyridyloxy]benzene
TGs	Triglycerides
TNF	Tumor necrosis factor
TZDS	Thiazolidinediones
UGT	UDP-glucuronosyl transferase
VDR	Vitamin D receptor
αSMA	α smooth muscle actin

List of Figures

List of tables

Introduction and Aim of The Work

Introduction

Nuclear receptors (NRs) in the gut and liver is expanding rapidly, Eight NRs are effectively limited in expression to the liver and gut, including the farnesoid X receptor (FXR), pregnane X receptor (PXR), constitutive androstane receptor (CAR), and hepatocyte nuclear factor 4a (HNF4a). Extensions of the NR expression profiling studies are now underway to explore subpatterns of NR expression within minority cell populations of larger tissues (**Bookout et al., 2006).**

Nuclear Receptors (NRs) are transcription factors that regulate diverse processes, including reproduction, embryonic development, cell differentiation and cellular homeostasis., NRs are expressed differentially among tissues, and are comprised of at least 49 members, some of which in a circadian manner. Most NRs are composed of four independent but interacting functional modules. A number of NRs are important in the pathogenesis of Alcoholic Liver Disease (ALD) because they act as intracellular sensors of free fatty acids and cholesterol metabolites as well as being involved in inflammatory and xenobiotic signaling (**Gyamfi et al., 2010).**

Preliminary results have revealed discrete expression patterns in specific cell types. For example, the hepatic stellate cell (HSC), which represents only a small percentage of the liver mass plays a pivotal role in hepatic fibrogenesis and vitamin A storage. Profiling of HSCs reveals a very different NR complement as compared to hepatocytes, the dominant hepatic cell type. These types of observations are important not only for the purposes of understanding these cells' molecular and cellular contributions to normal and disease states but also in identifying differential targets for pharmacological manipulation. While related oxidized cholesterol metabolites (oxysterols) are ligands for the liver X

receptors (LXRs). In addition, it is now apparent that NR regulation of fibroblast growth factors (FGFs) is important for their ability to maintain metabolic homoeostasis of the body (**Margolis et al., 2005).**

These studies showed that in the fasted and fed states, peroxisome proliferator-activated receptor a (PPARα) and FXR respectively induce the expression of a specific class of autocrine-functioning FGFs, thereby identifying new potential therapeutic targets. In the early fed state, oxysterols in the liver, rapidly formed by as yet unknown mechanisms coupled to dietary cholesterol load, activate LXR to engage gene programs that promote the conversions of dietary fats and carbohydrates to triglycerides as well as promoting the elimination of excess cholesterol through metabolism to bile acids **(Kalaany and Mangelsdorf, 2006).**

Hepatocyte nuclear factor 4α (HNF4α), an important transcriptional factor of the nuclear hormone receptor family, is essential for normal liver architecture, morphological and functional differentiation of hepatocytes, and generation of a hepatic epithelium. Over-production of HNF4α in cultured rat hepatocytes could result in the maintenance of the cell viability. Recent studiez demonstrate that upregulation of HNF4α expression could induce the differentiation of hepatoma cells into hepatocytes with re-expression of characteristic hepatocyte markers. 19 Additionally, it has been proven that epithelial mesenchymal transition (EMT) in hepatocytes induced by transforming growth factor (TGF)β correlates with the downregulation of HNFs, in particular of HNF4α. Most interestingly, ectopic HNF4α expression in fibroblasts is sufficient to induce a mesenchymal-to-epithelial transition (MET). Based on these findings, over-expression of HNF4α might ameliorate function in fibrotic liver and attenuate hepatic fibrogenesis with the inhibition of EMT **(Yin et al., 2010).**

Bile acid-activated FXR in the liver induces expression of genes that increase gluconeogenesis and promote triglyceride clearance and fatty acid ß-oxidation concomitantly with a reduction of lipogenic gene transcription, effects largely opposed to those of LXR, PPARα also induces hepatic expression of FGF21, a ‘‘hepatokine’’ that contributes locally to ketogenesis and communicates between the liver and adipose tissue, promoting fat mobilization through lipolysis in adipocytes. FGF21 also induces an energy-conserving hibernation-like state, manifested by a decfrease in body temperature **(Inagaki et al., 2007).**

In addition, FGF15 causes relaxation of the gallbladder, allowing it to refill with bile **(Choi et al., 2006).**

Fibroblast growth factor FGF -21, a hormone produced in the liver and adipocytes, is induced in the liver by fasting and peroxisome proliferator- activated receptor α agonist. Therefore in anorexia nervosa, which is a state of chronic nutritional deprivation charecterized by growth hormone GH resistance with elevated levels of GH&IGF. A study showed that FGF-21 levels are higher in anorexia nervosa independent of the effects of percent body fat and insulin resistance and finally showed that FGF-21 may mediate a state of GH resistance in anorexia nervosa **(Pouneh et al., 2009).**

To date, human studies of NR ligands in the pharmacotherapy of NASH have concentrated on PPARγ agonists such as rosiglitazone and pioglitazone. While these agents improve insulin sensitivity and decrease hepatic steatosis, their clinical utility is limited by weight gain. Considerable effort is being directed toward identifying additional NR-targeted ligands of therapeutic value PPARδ is currently the most promising NR target for NASH and the metabolic syndrome due to its powerful regulatory actions on fat, skeletal muscle, liver, and the heart, and Its activation by fatty acids enhances fatty acid transport and oxidation,

improves glucose homeostasis via inhibition of hepatic glucose output, reduces macrophage inflammatory responses, and dramatically increases circulating high-density lipoprotein levels **(Barish et al., 2006).**

Treatment with the selective PPARδ ligand K3010 causes a reduction in visceral fat and total body fat and a reduction in both hepatic steatosis and inflammation **(Riserus et al., 2008).**

Longer-term studies of patients with insulin resistance, the broader metabolic syndrome, and NASH are eagerly anticipated. Recent studies are beginning to identify NR targets for the management of cholestasis, These studies have focused largely on FXR, which represents an interesting dichotomy, as both agonists and antagonists may have beneficial effects for cholestatic liver disease. When the biliary tract is partially blocked, activation of FXR results in enhanced bile flow through increased hepatocyte apical bile acid transporter (ABCB11) expression, augmenting excretion of bile acids into the biliary canaliculus and thereby reducing bile acid accumulation in the liver. However, in complete biliary obstruction this approach is detrimental, resulting in hydrostatic bile infarcts due to rupture of the canals of Herring. Thus, in bile duct-ligated mice, FXR knockouts fare better than wild-type, and upregulation of the basolateral bile acid export pump Mrp4 (Abcc4) facilitates export of bile acids out of the hepatocyte and into the circulation for renal excretion **(Marschall et al., 2006; Stedman et al., 2006).**

Aim of the Work

The aim of this rivew is to highlight and identify the nuclear factors as hepatocyte nuclear factors (HNFs), Peroxisome proliferator-activated receptors (PPARs), Farnesoid X receptor (FXR), Liver X receptor (LXR), pregnane X receptor (PXR), Constitutive androstane receptor (CAR), and Fibroblast growth factors (FGFs), and explain their role in the pathogenesis of liver diseases and identifying their new potential therapeutic targets.