Meeting Report

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The new therapeutic frontier – Nuclear receptors and the liver

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A joint EASL/AASLD Monothematic Conference on 'Nuclear Receptors and Liver Disease' was held from February 27th to March 1st, 2009, in Vienna, Austria, to discuss the latest advances at the forefront of basic and clinical nuclear receptor research and its potential implications for liver diseases. This article reports the highlights of the conference and summarizes the main conclusions emphasizing the relevance for clinical and experimental hepatology. The confluence of nuclear receptors as central transcriptional regulators, acting as sensors and adaptors to many of the small molecules present in the intracellular milieu of all the cells of the liver, provides a current framework to address a broader physiological understanding of the liver. The next stage will be the design and testing of safe and effective therapeutics.

Introduction

The discovery that the largest group of transcriptional regulators in humans – members of the nuclear receptor (NR) superfamily – play strong and pervasive roles in liver cells represents one of the more recent findings in biology that has had a major impact upon our understanding of liver function [1–4]. This family consists of 48 members in humans, 49 in mice, and >200 in the nematode *Caenorhabditis. elegans*. NRs are not present in plants or yeast, but are essential components of the functioning of animal cells. These transcriptional regulators are perfectly poised to elaborate responses to their environment and fine-tune the response through various multifunctional regions – N terminal AF1, a DNA-binding Domain (DBD), a Ligand Binding Domain (LBD), and a C Terminal AF2 [5]. Moreover, NRs are targets for post-translational modifications (see below). Such covalent additions to subsets of expressed NR proteins broaden their functionality, both for DNA-binding elements and for interactions with other regulatory proteins. The LBD includes the site for ligand binding and thus is the seat of agonist or antagonist action, the focus of therapeutic targeting. What has recently been determined is that a large number of biologically relevant small molecules that are handled or pass through the liver are actually minute-to-minute regulators of liver function interacting with NRs. With these newly-discovered essential roles for NRs in liver biology and pathobiology in mind, along with the therapeutic consideration for diseases which currently have no effective treatments, the Joint EASL-AASLD Monothematic Conference on Nuclear Receptors and Liver Disease was created. The conference was organized by Michael Trauner (on behalf of EASL) and Saul Karpen (on behalf of AASLD).

From February 27th to March 1st, 2009, 188 participants from 31 countries came to hear 23 speakers and review 72 poster presentations at the Hilton Vienna Conference Center. The purpose and design of this Conference was to identify and convey the newly relevant basic biology of NRs to clinicians and have clinicians reveal opportunities and therapeutic results for NR modulation to basic scientists. This Meeting Report is thus intended to reflect this translational spirit, highlighting themes, unknowns, and opportunities – rather than a strict transcription of the Meeting from start to finish. There were many thoughtful and engrossing personal interactions, new unpublished information, as well as a spirited public give-and-take at the microphones. With this translational future focus in mind, this report will highlight the themes of the Meeting, which was possible only due to the enthusiastic participation of speakers and attendees. We are indebted to all. For those interested in the full list of invited speakers and talk titles, please visit the online site http://www.easl.eu/_events/easl-monothematic-conference/nuclear-receptors-and-liver-disease (also see Supplementary Table 1).

The first NR identified was the estrogen receptor (ER), by Elwood Jensen in 1958, while the Evans' group cloned the first NR (the glucocorticoid receptor) in 1985 [1–6]. At first, NR family members were considered part of the endocrine family (estrogen,

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Abbreviations: AR (NR3C4), androgen receptor; BA, bile acid; CAR (NR1I3), constitutive androstane receptor; DKO, double knockout; ER (NR3A1), estrogen receptor; FA, fatty acid; FGF, fibroblast growth factor; FXR (NR1H4), farnesoid X receptor/bile acid receptor; GWAS, genome wide association study; GR (NR3C1), glucocorticoid receptor; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HNF, hepatocyte nuclear factor; HSC, hepatic stellate cells; ICP, intrahepatic cholestasis of pregnancy; LRH-1 (NR5A2), liver receptor homolog-1; MTP, microsomal transfer protein; NAFLD, non alcoholic fatty liver disease; NR, nuclear (hormone) receptor; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; PPARα (NR1C1), peroxisomal proliferator-activated receptor alpha; PPARγ (NR1C3), peroxisomal proliferator-activated receptor gamma; PXR (NR1I2), pregnane X receptor; RARα (NR1B1), retinoic acid receptor; RXRα (NR2B1), retinoid X receptor; SHP (NR0B2), short heterodimer partner; VDR (NR1I2), vitamin D receptor; WAT, white adipose tissue.

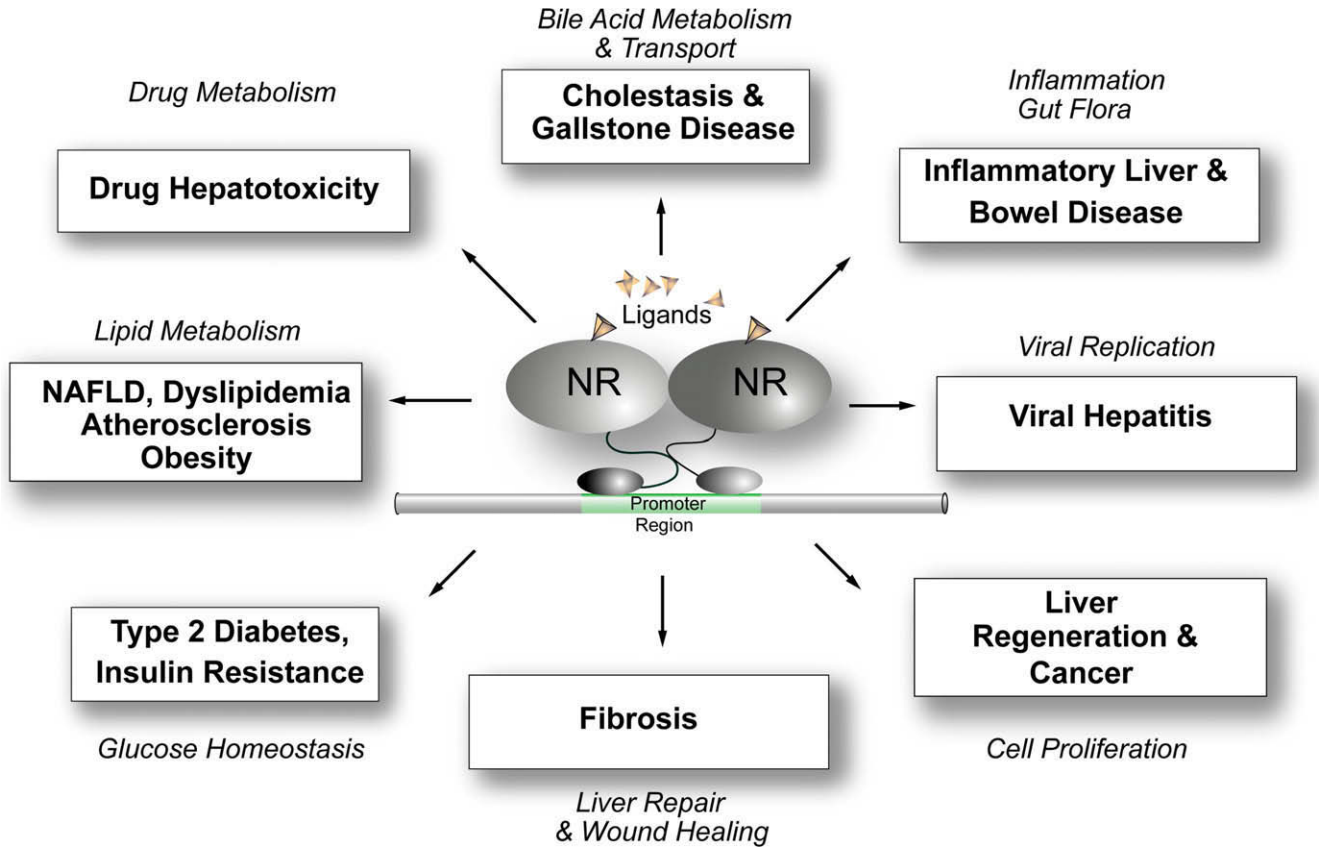

Fig. 1. Multiple roles of NRs in liver physiology and pathophysiology. NRs typically heterodimerize, have a ligand binding domain for small molecule ligands (triangles) and a DNA-binding domain for interaction with gene promoter regions. NRs are key regulators of multiple hepatic processes and related disorders (adapted from [58]).

testosterone, aldosterone), but soon it became apparent with newer cloning technologies that there were many more family members, and that for which the actual ligands were typically unidentified. Over a short period of time (some 10–15 years), prior to the Human Genome Project all 48 members of the NR superfamily were identified. What has become clear is that NRs are multifunctional, ligand-activated transcription factors at the heart of many core liver functions – intermediary metabolism, detoxification, energetics, adaptive response, and bile formation (Fig. 1) to name a few [7–9]. Several dozen NRs are expressed in liver [10,11], some of which are cell-specific (e.g., hepatocyte vs. cholangiocyte), while others are expressed by non-parenchymal cells yet crucial for inflammatory and fibrotic response (see below). All together, these multifunctional proteins, each containing a variety of domains to interact with a diverse array of intracellular protein partners and small molecule ligands, provide an understanding of how the liver is at the metabolic, adaptive, inflammatory, and nutritional crossroads of the body.

In addition to the 48 NRs, there are some 200–300 co-regulators (Fig. 2) that contribute to the 50–100 proteins that comprise the transcription complex at each gene. Many of these complex participants have a transient presence or post-translational modifying roles – thus drastically revising and increasing the complexity of the initial model of NRs as DNA-binding proteins whose sole function was to direct recruitment of RNA polymerase activity and thus RNA synthesis [12–14]. The function of each regulator protein, NR, and co-regulator are broadened by post-translational modifications (e.g., phosphorylation, ubiquitination, sumoylation, methylation, acetylation, etc.), thereby creating tissue, cell, time, and gene-specific effects for various NRs and ligands [15]. This flexibility is central to the adaptive capabilities of the liver to respond to various components of the diet, effect drug metabolism, and integrate responses to injury and regeneration.

NRs play critical roles in liver biology and pathobiology (see Figs. 1 and 2). As a group they are arguably the most important integrators of external signals to core metabolic functions in the body. Many of these NRs function as heterodimer partners with retinoid X receptor (RXR) (Fig. 2), adding another NR participant for regulatory fine-tuning [16]. For example, fats, bile acids, drugs, and food-derived toxins all present themselves to hepatocytes where they can act as ligands (agonists/antagonists) for RXR-containing NR heterodimer pairs, driving gene expression to properly respond. When overloaded (e.g., with select toxins, or excess dietary lipid), the sampling of intracellular content to the NR LBD will thus provide a means to respond. Likewise, antagonists will impair such a response. The role of NRs is not only restricted to responding to external molecules, but is also dictated by inherent circadian and feeding time rhythms that affect NR expression, leading to differential consequences of various diets and drugs, depending upon the time of administration. David Moore presented intriguing new data supporting altered responses of NRs to restricted feeding, altered feeding schedules, and endogenous circadian clocks. More is likely needed to fully flesh out these important concepts when it comes to food and drug delivery [17]. This new concept is likely to have ramifications on our patients regarding drug efficacy, metabolism and toxicity.