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editorial

Liver-Enriched Nuclear Receptors: Therapeutic Opportunities

Liver-enriched nuclear receptors (NRs) affect gene activation and coordinately modulate the homeostasis of drugs, lipids, bile acids, and glucose in mammals. These ligand-activated transcription factors are also responsive to certain cell signaling pathways that are altered during pathological conditions including inflammation, diabetes, and obesity (Figure 1). The role of liver-enriched NRs in coordinately modulating the expression and activity of key enzymes and transporter proteins in liver has large implications for the development and progression of these pathological conditions. Liver-enriched NR-activation also plays a pivotal role in mediating drug–drug and disease–drug interactions. Recent research efforts are unveiling numerous potential therapeutic opportunities presented by these ligand-activated transcription factors.

This special issue, "Liver-Enriched Nuclear Receptors: Therapeutic Opportunities", focuses on the latest developments in the field through several reviews and articles. The reviews "Nonalcoholic Fatty Liver Disease: Pathogenesis and Potential for Nuclear Receptors as Therapeutic Targets" (George and Liddle), "Xenoreceptors CAR and PXR Activation and Consequences on Lipid Metabolism, Glucose Homeostasis, and Inflammatory Response" (Moreau et al.), and "PXR and LXR in Hepatic Steatosis: A New Dog and an Old Dog with New Tricks" (Lee et al.) summarize newly discovered aspects of NR involvement in the genesis of fatty liver disease, inflammation, lipid metabolism, and glucose homeostasis. Each of these reviews outlines the exciting potential for NRs as drug targets in the context of diabetes and hyperlipidemia. In "Regulation of Transporters by Nuclear Hormone Receptors: Implications during Inflammation", Teng and Piquette-Miller discuss recent advances in knowledge regarding the impact this pathological condition has upon the expression and activity of several drug transporter proteins and also includes a discussion of the potential role of NRs in mediating such a response. The review "Endocrine Actions of Fibroblast Growth Factor 19" (Stacey Jones) summarizes recent advances in the biology of the atypical FGF19 including its role in entero-hepatic signaling, regulation of bile acid biosynthesis, and gall bladder filling. This review also discusses recent advances in understanding the role of the β-Klotho protein in regulating FGF19 signaling as well as the metabolic and hepato-cellular aspects of FGF19 biology. The review "Cell Signaling and Nuclear Receptors: New Opportunities for Molecular Pharmaceuticals in Liver Disease" (Staudinger and Lichti) focuses on recent advances in the understanding of how specific signal transduction pathways interface with liver-enriched NRs multiprotein transcriptional complexes. This review article is a comprehensive overview that emphasizes the extent to which the regulation of NR-target gene activation

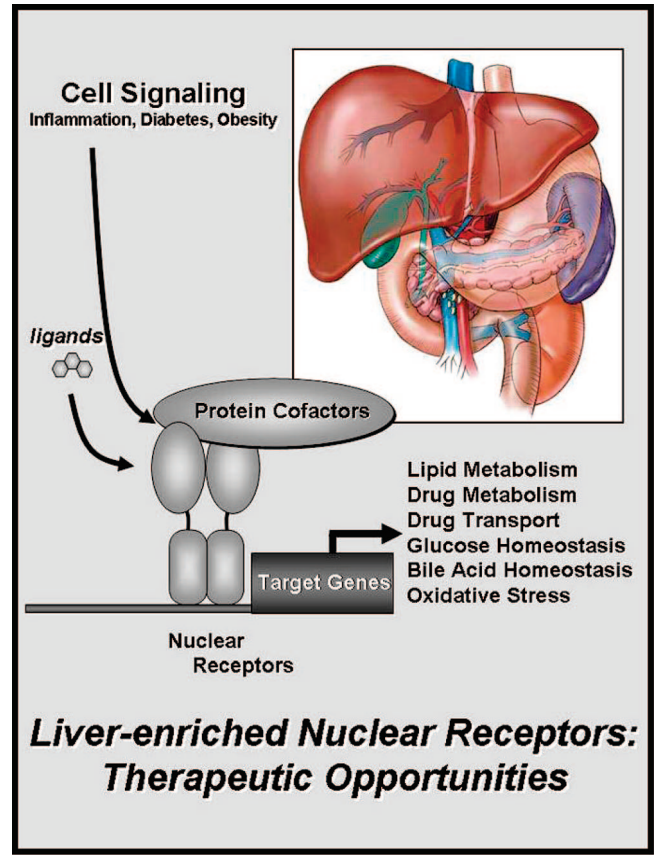

Figure 1. This issue of *Molecular Pharmaceutics* highlights recent research developments in the field of nuclear receptor signaling that have major implications for the development of novel pharmaceutical agents for treatment of clinically significant diseases. Specifically, new knowledge regarding how inflammation, diabetes, and obesity impact liver-enriched nuclear receptor function is featured. Additionally, how these disease states impact important physiological parameters including lipid metabolism, drug metabolism, drug transport, glucose homeostasis, bile acid homeostasis, and oxidative stress through alterations in cell signaling pathways and post-translational modification of nuclear receptor and protein cofactor function is discussed.

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is altered during specific pathological conditions including diabetes, obesity, and inflammation.

Contributed articles include an article that investigates the interaction of a mouse model of diabetes and obesity (*Ob/Ob*) with a range of drug-metabolizing enzymes and drug transporter proteins (Cheng et al.). This recent thrust of research describes the impact of such pathologies on the potential for adverse drug reactions and targeted drug delivery. Finally, Bi et al. establish novel methodologies to identify additional NR-target genes "*in silico*" and discuss computational issues and algorithms for the two-block motif discovery problem.

Liver-enriched NRs comprise a complex and intertwined biological system that requires a full complement of laboratory tools and study designs to push the area forward. This special issue of *Molecular Pharmaceutics* provides contemporary insights and describes recent advances in our understanding of this new thrust of research. While much is known about the identity of prototypical NR-activating ligands and target genes, further progress is needed to better understand molecular mechanisms that control drug, lipid, bile acid, and glucose homeostasis in the context of pathological conditions such as inflammation, diabetes, and obesity. These recent advances are extremely likely to reveal novel therapeutic targets and allow for the anticipation and avoidance of drug−drug and disease−drug interactions.

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