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Nuclear receptors: pathophysiological mechanisms and drug targets in liver disease

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Abbreviations

ALD: alcohol-related liver diseases

AR: androgen receptor

BEC: biliary epithelial cell

DBD: DNA binding domain

ER: estrogen receptor

FDA: Food and Drug Administration FXR: farnesoid X receptor

HNF4A: hepatocyte nuclear factor 4 alpha

HSC: hepatic stellate cell

KC: Kupffer cell

LBD: ligand binding domain

LSEC: liver sinusoidal endothelial cell

LXR: liver X receptor

MASLD: metabolic dysfunction-associated liver disease

MASH: metabolic dysfunction-associated steatohepatitis

NR: nuclear receptor

PBC: primary biliary cholangitis

PPAR: peroxisome proliferator-activated receptor

PXR: pregnane X receptor

RAR: retinoic acid receptor

RXR: retinoid X receptor

TF: transcription factor

ABSTRACT

Nuclear receptors (NRs) are ligand-dependent transcription factors required for liver development and function. As a consequence, NRs have emerged as attractive drug targets in a wide range of liver diseases. However, liver dysfunction and failure is linked to loss of hepatocyte identity characterized by deficient NR expression and activities. This might at least partly explain why several pharmacological NR modulators have proven insufficiently efficient to improve liver functionality in advanced stages of diseases such as Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD). In this perspective, we review the most recent advances in the hepatic NR field and discuss the contribution of multi-omic approaches to our understanding of their role in the molecular organization of an intricate transcriptional regulatory network, as well as in liver inter-cellular dialogues and inter-organ cross-talks. We discuss the potential benefit of novel therapeutic approaches simultaneously targeting multiple NRs, which would not only reactivate the hepatic NR network and restore hepatocyte identity, but also impact inter-cellular and inter-organ interplays whose importance to control liver functions is being further defined. Finally, we highlight the need of considering individual parameters such as sex and disease stage in the development of NR-based clinical strategies.

What is a nuclear receptor?

Liver functions rely on hepatocytes, which sense incoming signals and adapt their activities to maintain energy and iron homeostasis, promote detoxification, coagulation or acute phase responses. Even though these processes are controlled at multiple levels, modulation of hepatocyte gene expression is a well-defined primary regulatory layer underlying the ability of this organ to execute its functions ¹. ². In this context, the importance of nuclear receptors (NRs) has been firmly established. The NR superfamily is one of the largest families of transcription factors (TFs) comprising 48 members in humans ³. NRs are modular proteins molecularly characterized by two well-conserved domains across members. First, NRs have a highly conserved DNA binding domain (DBD) allowing for recognition of highly similar DNA recognition motifs. Since most NRs operate as dimers, their actual DNA binding sites are composed of two copies of this motif, which can be differently organized in terms of orientation (direct or inverted repeats) and/or spacing ⁴. NR DNA binding occurs after heterodimerization with the obligatory retinoid X receptor (RXR; NR2B) partner, homodimerization or the still poorly characterized formation of higher order oligomers ⁵. While this allows to introduce some specificity, NR recruitment to common DNA sequences within gene expression regulatory regions is widespread ⁴. Second, and of utmost importance since this discriminates NRs from other TF families, NRs possess a ligand binding domain (LBD) granting them the ability to directly sense the presence of small molecules including not only natural ligands, but also xenobiotics ⁶. Among natural NR ligands are lipophilic molecules including steroid hormones, thyroid hormones, retinoids and (dietary) lipids. While the three-dimensional organization of the LBD is globally conserved across NRs, slight variations in its structure create NR-specific ligand binding pockets and therefore underlie NR ligand specificity. Reciprocally, ligands induce structural re-arrangements of the LBD structure, which influence protein-protein interactions and the transcriptional regulatory signals conveyed by NRs ³ (Fig.1). Indeed, NRs control gene expression through interaction with other transcriptional regulators. In particular, NRs serve as protein-protein interaction platforms for the recruitment of coregulators. These coregulators comprise enzymes which modulate the chromatin structure and recruitment of RNA polymerase to control gene expression. Leveraging on the ability of NRs to avidly bind small molecules, drugs have been designed to bind to the LBD pocket of NRs to mimic or block (part of) endogenous ligand responses. As an

example, a recently developed class of NR targeting drugs is based on PROteolysis Targeting Chimera (PROTAC)-mediated degradation, which might prove of primary interest to suppress pro-oncogenic NR activities ⁷. Emergence of advanced structural biology techniques, such as nuclear magnetic resonance crystallography and cryo-electron microscopy, has allowed for a refinement of our understanding of NR structure-function relationships, including quaternary structure and interdomain communication ^{8, 9}, hence improving the search for novel ligands/drugs targeting these NRs (e.g. ¹⁰). However, no ligands have so far been identified for some NRs, which therefore remain labelled as “orphan” NRs. Among those, a subset lacks a proper LBD binding pocket ³.

For classical ligand-dependent NRs, structurally distinct ligands can induce different conformational changes upon LBD binding. As a consequence, distinct ligands differentially affect NR interaction with transcriptional coregulators (coactivators or corepressors) to activate or repress NR target gene expression. Some ligands display gene and/or cell-type specific activities owing to their effects on the LBD structure, triggering different functional outputs according to, for example, the relative concentration of different coregulatory complexes ^{11, 12}. Indeed, continued advances in proteomic analyses of transcriptional regulatory complexes involving NRs have further revealed the breadth and complexity of interactions at play within protein mega-complexes ^{13, 14}. These multiple interactions occur in a highly dynamic process intimately coupled with nuclear architecture and gene expression ¹⁵. Another key related concept, which is still under functional investigation, is that a substantial number of NR-recruiting DNA regulatory regions are distal enhancers and that the three-dimensional chromatin folding is crucial to connect promoters and enhancers. Functionally, this would relate to NRs operating in sub-nuclear spaces where transcriptional regulators and their targeted genes are highly concentrated ^{16, 17}. Finally, other recent advances in our understanding of NR activities have expanded the wealth of activities of these proteins beyond their role as TFs. For instance, so called non-genomic activities have been reported where NRs, often through non-nuclear localization, modulate signaling pathways such as phosphorylation cascades (Box1). While the pathophysiological role of NR non-genomic activities has been established for example in endothelial healing ¹⁸, their relevance with regards to the control of liver functions remains to be defined ¹⁸. Also, a subset of NRs has been ascribed with RNA binding activities empowering these factors with regulation of mRNA stability and translation

¹⁹. These findings raise novel questions such as how natural and pharmacological ligands modulate these non-TF functions and how those additional activities of NRs relate to their gene expression modulatory functions to impact liver pathophysiology (Fig.1).

NRs control liver development and function

Historically, liver gene expression has been studied using the whole organ. Considering that hepatocytes constitute by far the most substantial fraction of liver cells, the scientific community has primarily gained knowledge on hepatocyte gene expression. In this context, interest in NRs stems from the observation that many of them display high hepatic expression levels and were subsequently shown to regulate liver functions. For instance, hepatocyte nuclear factor 4 alpha (HNF4A; NR2A1) is a master regulator of hepatocyte differentiation and required to maintain functional adult hepatocytes [^{20, 21}; reviewed in ²²]. Many additional NRs exert key functions in adaptative liver gene regulation, especially with regards to energy homeostasis. For instance, NRs whose ligands are molecules derived from intracellular cholesterol or lipid metabolism, such as peroxisome proliferator-activated receptor alpha (PPARA) and farnesoid X receptor (FXR; NR1H4), or sensors of circulating steroid hormones, such as the glucocorticoid receptor (GR; NR3C1), the androgen receptor (AR; NR3C4) and the estrogen receptor alpha (ESR1 also known as ERα; NR3A1) as well as the heme-regulated REVERB alpha (REVERBA; NR1D1) and REVERB beta (REVERBB; NR1D2), which are at the cross-road between nutritional sensing and the core circadian machinery, are instrumental regulators of liver functions ²³. Importantly, many of these NRs cooperate to finely tune the hepatic metabolic response to e.g. fluctuating nutritional availability ²⁴. This is exemplified by PPARA cooperating with GR to orchestrate the liver's adaptation to prolonged fasting ²⁵. In addition, several of these NRs exist in multiple isoforms that exert distinct, but complementary actions in the regulation of liver function. For instance, *HNF4A* isoforms issued from its alternative promoters P1 and P2, which give rise to proteins harboring or lacking an N-terminal transactivation domain characterized by different abilities to interact with DNA and transcriptional cofactors [²⁶⁻²⁹; reviewed in ²²], have different roles in the maintenance of energy homeostasis. Indeed, P1-HNF4A drives gluconeogenesis, whereas P2-HNF4A is required for hepatic fat storage as well as ketogenesis ³⁰. FXR is another example of how different NR isoforms coordinate liver

functions, with bile acid homeostasis being modulated by the isoforms FXR α 1-4, but carbohydrate and lipid metabolism being controlled by FXR α 2/4³¹. Of note, while many of the above-mentioned NRs are expressed in a wide variety of tissues and regulate physiological processes that extend far beyond hepatic metabolism, some NRs such as HNF4A, the liver X receptor alpha (LXRA; NR1H3) or the constitutive androstane receptor (CAR; NR1I3) are predominantly expressed in hepatocytes and contribute to the orchestration of their function. As an example, CAR serves as a xenobiotic receptor and its function has later been extended to the regulation of gluco-lipid metabolism²³.

The development of functional genomics, which occurred within the last two decades, allowed to study genome-wide NR activities and prompted the scientific community to revisit NR modes of action. Indeed, recent developments of multi-omics approaches empowered our understanding of NR activities by combining transcriptomic, epigenomic and interactomic data revealing that NRs are functionally interconnected at least at two main levels (Fig.2). First, NRs are involved in an intricate cross-regulatory network of mutual regulation, defined as the hepatic core transcriptional regulatory circuitry (CoRC)³². The hepatic CoRC is built-up during the course of liver development and hepatocyte differentiation, but is also essential in adulthood to maintain hepatocyte identity. Indeed, CoRC TFs ensure self-sustained high expression of its members through extensive auto- and cross-regulatory loops³³. While the concept of CoRC by definition implied that hepatocyte identity is controlled by a limited set of NRs, including the most hepatocyte-specific ones, recent re-assessment revealed that this CoRC is actually embedded into an extended network involving additional NRs with more intermediate cell/tissue expression specificity including the thyroid hormone receptor beta (THR β ; NR1A2)³⁴. The second layer of NR functional interconnections relates to NRs sharing many effector target genes (defined as genes carrying out hepatocyte-specific activities)³⁵, largely explained by the previously described binding to shared DNA binding motifs⁴. In addition, NR co-recruitment through atypical heterodimers or through tethering (where only one of two interacting NRs directly binds to the DNA) might also be involved⁴. A few specific pairs of hepatic co-recruited NRs have been functionally assessed such as GR and PPARA²⁵, but overall, how multiple NR co-recruitment results in context-specific effects on gene transcription modulation remains poorly understood. For instance, redundancy versus specificity as well as cooperative regulations by different NRs are still ill-defined. In this context,

a more refined understanding might in the future come from computational modeling, which has recently gained significant attention in the liver field ^{36,37}, including in NR-related studies ³⁸.

Recent considerations of the role of the other liver cell-types beyond hepatocytes resulted in a refined and more complex picture of the role exerted by NRs in this organ (Fig.2), as exemplified by the effects of FXR and PPARA activation on hepatic stellate cell (HSC) and Kupffer cell activities, although it is still unclear whether their anti-fibrotic and anti-inflammatory activities result from direct actions on those cells or are indirectly mediated via hepatocyte-specific effects [^{39, 40}; reviewed in ⁴¹]. Of note, expanding our understanding of NR functions in the liver beyond hepatocytes has notably been enabled by technological breakthroughs, especially those related to purification of individual liver cell-types and/or single-cell/nuclei resolution analyses of gene expression, which allowed researchers to better appreciate cellular heterogeneity and inter-cellular dialogues. This will be further enhanced by the rapid development of spatial transcriptomics allowing to monitor the transcriptome of cells *in situ* ^{42, 43}

NR activities are disrupted in liver diseases

Owing to the aforementioned instrumental role exerted by NRs in the liver, disruption of their activities defines a key event underlying liver dysfunction [e.g. ⁴⁴⁻⁴⁶; reviewed in ^{22, 47}]. While inherited mutations in NRs, such as HNF4A, FXR or the pregnane X receptor (PXR; NR112), are linked to liver disease predisposition and progression ^{22,48}, perturbed NR activity is mostly due to environmental factors involved in the development of acute or chronic liver diseases. Indeed, associated with perturbed blood flow and (para)sympathetic innervation, alterations in the hepatocyte micro-environment characterizes liver diseases ^{49, 50}. These alterations include heightened inflammatory cytokine levels and extracellular matrix remodeling associated with excessive and/or unresolved cellular stress which trigger impaired hepatic NR activities. Interleukin 1, tumor necrosis factor alpha and the pro-fibrotic transforming growth factor beta as well as endoplasmic reticulum stress trigger a yet to be fully understood intricated cellular response which compromises maintenance of fully functional hepatocytes by NRs ⁴⁴⁻⁴⁶ (Fig.3). Indeed, recent system-wide assessment of rodent liver injury models and of human hepatic biopsies has revealed that the hepatic NR network is disrupted as a whole in severely injured livers, i.e. the expression of interconnected NRs is dampened ^{33, 34, 44} (Box 1). This occurs in acute liver injury, such as sepsis-related

liver failure, as well as in the most advanced stages of chronic liver diseases, including MASLD and alcohol-related liver diseases (ALD). This phenomenon led to the identification of loss of hepatocyte identity as one of the molecular mechanisms underlying impaired liver functions [44, 45, 51-55; reviewed in 44, 47]. Disrupted NR activities in loss of hepatocyte identity does not only stem from impaired expression of their encoding genes, but also involves changes in isoforms, subcellular localization and interacting partners through alterations in RNA splicing and protein post-translational modifications (Fig.3). An emerging concept suggests that functional compensation can occur, at least transiently, in injured livers through induction of alternative transcriptional regulators in hepatocytes^{56,57}. An additional mechanism of primary importance might be the modulation of endogenous NR ligand availability. Indeed, changes in lipid, thyroid hormone or retinoid metabolism occur in liver diseases^{58,59}. Of interest, a transient rise in retinoic acid may promote activation of the retinoic acid receptor (RAR; NR1B) to maintain hepatocyte gene expression^{59, 60}. Since liver injuries are controlled through intense inter-cellular communications, retinoic acid release by activated HSCs might orchestrate the liver response to injury by triggering transcriptional effects in multiple additional surrounding liver cell populations including biliary epithelial cell (BECs), liver sinusoidal endothelial cells (LSECs) and Kupffer cells (KCs)⁶¹. Indeed, many NRs are expressed in liver cells besides hepatocytes⁶², where alterations in their activities may also modulate liver diseases. This includes a role for NRs in HSCs, as exemplified by FXR and thyroid hormone receptor alpha (THRA; NR1A1) signaling to repress their fibrogenic activity^{40, 63-65}. Extending on this notion, the recent literature indicates the need to take into account the role of inter-organ cross-talks in controlling NRs activities in the liver. For instance, signaling molecules or metabolites issued from the gut or adipose tissues have the ability to modulate the activities of hepatic FXR or PPARs [e.g. ^{66,67}; reviewed in ^{68,69}] and could contribute to their dysfunction in liver diseases.

Targeting NRs to treat liver diseases today and tomorrow

With the pandemic rise in obesity and type 2 diabetes, MASLD has become a major health burden affecting approximately one-quarter of the global adult population and a leading cause of liver failure and cancer worldwide^{70, 71}. In this context, identifying therapeutic treatments for MASLD remains a major challenge^{70, 72, 73}. The initial interest in targeting NRs in MASLD and its more advanced

form metabolic dysfunction-associated steatohepatitis (MASH) stems from their central role in the control of energy homeostasis including glucose and lipid metabolism. In this context, pharmacological ligands for the NRs FXR and THRβ have been developed. In a phase 3 clinical trial, the FXR agonist obeticholic acid improved fibrosis, but failed to improve MASH and was furthermore associated with safety concerns ⁷⁴, prompting the U.S. Food and Drug Administration (FDA) to recommend against approval. On the other hand, the THRβ agonist resmetirom showed a significant benefit on both key endpoints in a phase 3 trial – improvement in fibrosis without worsening of MASH in 26% of patients receiving the highest of two doses of resmetirom compared with 14% on placebo, and resolution of MASH without worsening fibrosis in 30% of patients treated with the highest dose of resmetirom compared with 10% of patients on placebo ⁷⁵. Thus, resmetirom became very recently the first FDA-approved treatment for MASH. Although these results are encouraging, it should be noted that the improvement in both primary endpoints occurred in less than 50% of patients. Moreover, since THRA but not THRβ defines the main active thyroid hormone receptor in HSCs ⁶⁴, resmetirom may only indirectly and sub-optimally target HSC activities. Therefore, new strategies may become necessary to increase the percentage of responders as well as to augment the magnitude of response to THRβ agonists ⁷⁶. In light of the disruption of the NR network observed in injured liver discussed above, it might be hypothesized that decreased NR expression/activity in liver disease may contribute to an inefficient response to NR agonists, especially in the most advanced stages of MASLD. In this scenario, loss of hepatocyte identity would desensitize hepatocytes to the beneficial pharmacological effects of NR ligands. In this context, considerations may be given to strategies aiming at correcting deficient NR expression/activity, which would therefore go along improving or restoring NR ligand sensitivity. Here, the potential for combined modulation of several NRs is to be mentioned. Indeed, since hepatic NRs are organized into a cross-regulatory network, targeting several NRs simultaneously may help facilitate the reactivation of this network, hence restoring NR expression and activity. Additionally, simultaneous pharmacological targeting of independent NRs may allow to trigger beneficial effects by targeting different liver cell-types and/or different organs. This is exemplified by the increased performance of pan-PPAR agonists over agonists targeting only one member of the PPAR family in tackling the various histological characteristics of MASLD including steatosis, inflammation and fibrosis ^{77,78}. Lanifibranor,

an agonist of the three PPAR isotypes, i.e. PPARA, PPARG and PPARD, is currently in a phase 3 clinical trial in adults with MASH and liver fibrosis. The benefits of lanifibranor might be explained by the PPAR isotypes' expression territories allowing to target simultaneously different liver cell-types and organs such as the adipose tissue [79-84; reviewed in 85]. Following up on the notion of different organs being intrinsically linked in MASLD, this disease is clinically associated with a high risk of adverse cardiovascular events (atherosclerosis, heart failure). Indeed, the risk for major adverse cardiovascular events increases with worsening disease severity across all stages of MASLD 86. In our opinion, this observation needs to be better apprehended when considering future drug development. More specifically, besides monitoring cardiovascular risk factors and adverse events, potential beneficial effects of NR ligands on the cardiovascular system should also be taken into account in the decision-making process. Favorable effects might arise from direct NR actions on heart and vessels [87-89; reviewed in 90] and/or occur secondary to systemic changes in gluco-lipid homeostasis via modulation of NR activities in metabolic tissues such as the adipose tissue and skeletal muscle. Altogether, in light of our growing understanding of the role exerted by the dialogue between liver cell-types and multiple organs in liver diseases, the contemporary vision of pharmacological intervention for treating MASLD now needs to embrace its intrinsic multi-cellular and multi-organ nature (Fig.4)(Box 1).

In line with the general concept of personalized-medicine, better stratifying MASLD patients is also required to improve the efficacy of carefully selected drugs. In this context, computational modeling and artificial intelligence are beginning to be leveraged to define how patients could be better stratified to inform the decision-making process for the best treatment option(s) 91. Artificial intelligence might additionally be used to assist pathologists with histological analyses in order to reduce the impact of scoring variability in the diagnosis and follow-up of MASLD patients in clinical trials 92. Another key consideration will be to translate to the clinic our growing understanding of MASLD being a sexually dimorphic condition exhibiting sex-specific liver gene dysregulation 93. Indeed, sex hormone signaling through their cognate NRs, i.e. AR and ERa, has emerged as a key factor in the sex differences in MASLD prevalence and progression [94-98; reviewed in 99, 100]. Taking advantage of the well-established anti-steatotic and anti-fibrotic effects of estrogens, the ER ligand 17 β -estradiol is currently being investigated as a therapeutic option for post-menopausal women with MASH 101.

Finally, targeting REVERBA and REVERBB as well as the RORA nuclear receptors may appear as an alternative or complementary therapeutic strategy. These NRs are components of the molecular clock and REVERBA agonists display anti-fibrotic activities in various settings [¹⁰²⁻¹⁰⁴; reviewed in ¹⁰⁵]. The molecular clock is a transcriptional network ensuring the rhythmic accumulation of gene transcripts and effector proteins with a period of about 24 hours, and is required for the liver (and other organs) to anticipate daily fluctuations in activity and to maintain whole-body homeostasis [¹⁰⁶⁻¹⁰⁸; reviewed in ¹⁰⁹]. MASH patients display perturbed time-of-day-dependent accumulation of gene transcripts and metabolites ¹¹⁰. Dyssynchrony of the molecular clock triggered by, for example, the disruption of the sleep-wake schedule is associated with metabolic abnormalities including liver steatosis and MASH. Therefore, chrono pharmacology might increase the therapeutic success rate in liver diseases ¹¹¹.

Importantly, synthetic NR ligands originally developed as drugs targeting MASH may, in some instances, benefit in the treatment of rare liver diseases. Indeed, owing to their key regulatory roles in hepatocytes and other liver cell-types, drug-repurposing strategies have been implemented for the treatment of rare liver diseases in need of novel therapeutic approaches such as Primary Biliary Cholangitis (PBC). In this context, the dual PPARA/PPARD agonist elafibranor, which was initially developed and assessed for the treatment of MASH ¹¹², was recently shown to improve disease indicators in patients with PBC not sufficiently responding upon treatment with ursodeoxycholic acid, the universal first-line standard of treatment ¹¹³. In this context, obeticholic acid and novel FXR agonists may also prove useful to extend therapeutic opportunities for PBC, although increase in pruritus and LDL cholesterol are also observed.

Final discussion

NRs are undoubtedly central players in the physiological regulation of liver gene expression and the modulation of pathological responses. Many unknowns related to our understanding of their precise mechanisms of action preclude us from refining strategies to better pharmacologically modulate their activities to treat liver diseases. In particular, understanding NR activities at the transcriptomic, epigenomic and interactomic levels needs to be improved, including how different NRs combine functions in a given cell and how NRs' activities are integrated in a context of liver inter-cellular

dialogues and inter-organ cross-talks. Efforts such as the Virtual Liver Network ^{37, 114} may help pave the way towards this goal. This might further accelerate successful drug repurposing for the treatment of rare liver diseases as exemplified by elafibranor for PBC ¹¹³. Moreover, in the perspective of the precision-medicine era, predictive factors for drug efficiency including the influence of genetics, sex, disease etiology and stage will need to be refined.

While in general NRs constitute a unique TF family amenable to pharmacological modulation, some NRs such as the master hepatocyte regulator HNF4A remain vexingly untargetable. In this context, alternative non-pharmacological strategies based on other properties of NRs, including molecules interfering with NR dimerization or interaction with coregulators, may be developed ^{115, 116}.

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Competing interest statement

The authors declare no competing interests.

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Box 1 Current considerations regarding liver NR activities and pharmacological modulation

Recent updates to our understanding of NRs' activities in liver pathophysiology

- Control of gene expression by NRs can involve regulatory activities beyond their archetypal role as TFs due to their RNA binding potential or non-nuclear localizations
- NRs form an intricately regulated network in hepatocytes, whose disruption triggers loss of hepatocyte identity and liver dysfunction
- NRs are expressed and active in multiple liver cell-types and organs, thereby orchestrating integrated responses through inter-cellular and/or inter-organ dialogues

Steps towards improving NR pharmacological targeting for treatment of liver diseases

- Besides normalization of metabolic parameters and/or inflammation, NR pharmacological activation in liver failure may serve to restore the hepatic network expression/activity and hepatocyte identity and function
- Strategies to simultaneously modulate different NRs expressed in distinct liver cell-types and/or organs might prove beneficial considering the importance of inter-cellular and inter-organ cross-talks in development and progression of liver diseases

Legends to Figures

Fig.1 Control of gene expression by NRs

The archetypal function of NRs is to serve as ligand-controlled transcription factors through recruitment to the chromatin. Recent findings indicate that at least a subset of NRs also control gene expression through additional means involving modulation of intracellular signaling (e.g. kinase cascades) or through RNA binding-mediated control of mRNA stability and/or translation.

Fig.2 Control of liver gene expression and functions by NRs

The core NR network, i.e. the most hepatocyte-specific NRs, connect to additional NRs such as THRβ or the sex steroid receptors ERα and AR to conjointly drive expression of effector genes, which encode for proteins involved in hepatocyte homeostatic functions. Arrows are illustrative and not meant to extensively define functional connections between individual NRs. Functions of NRs in additional liver cell-types is being given greater attention towards understanding how a multi-cellular response to NR ligands promoted adaptive gene regulation and liver activities.

Fig.3 Impaired hepatic NR network expression/activity in liver dysfunction and failure

In diseased liver, alterations to the hepatocyte micro-environment such as inflammation as well as hepatocellular stress lead to modulation of NR activities including a failure to maintain their expression, ultimately disrupting the hepatic NR network resulting in a loss of hepatocyte identity and further compromising liver function.

Fig.4 Targeting multiple NRs as a novel therapeutic approach for MASLD

(A) Existing strategies targeting individual NRs have shown promising anti-steatotic and anti-inflammatory effects but failed to efficiently tackle the fibrotic process. This might relate to decreased NR expression and activity in diseased liver, resulting in identity loss and desensitization to the beneficial effects of NR pharmacological ligands. **(B)** Novel therapeutic approaches might include the simultaneous targeting of multiple NRs, as this will reactivate the hepatic NR network thereby increasing their expression/activity and improving ligand sensitivity. In addition, multiple NR targeting might prove beneficial as this strategy takes into account inter-cellular dialogues and inter-organ cross-talks.

Fig.1

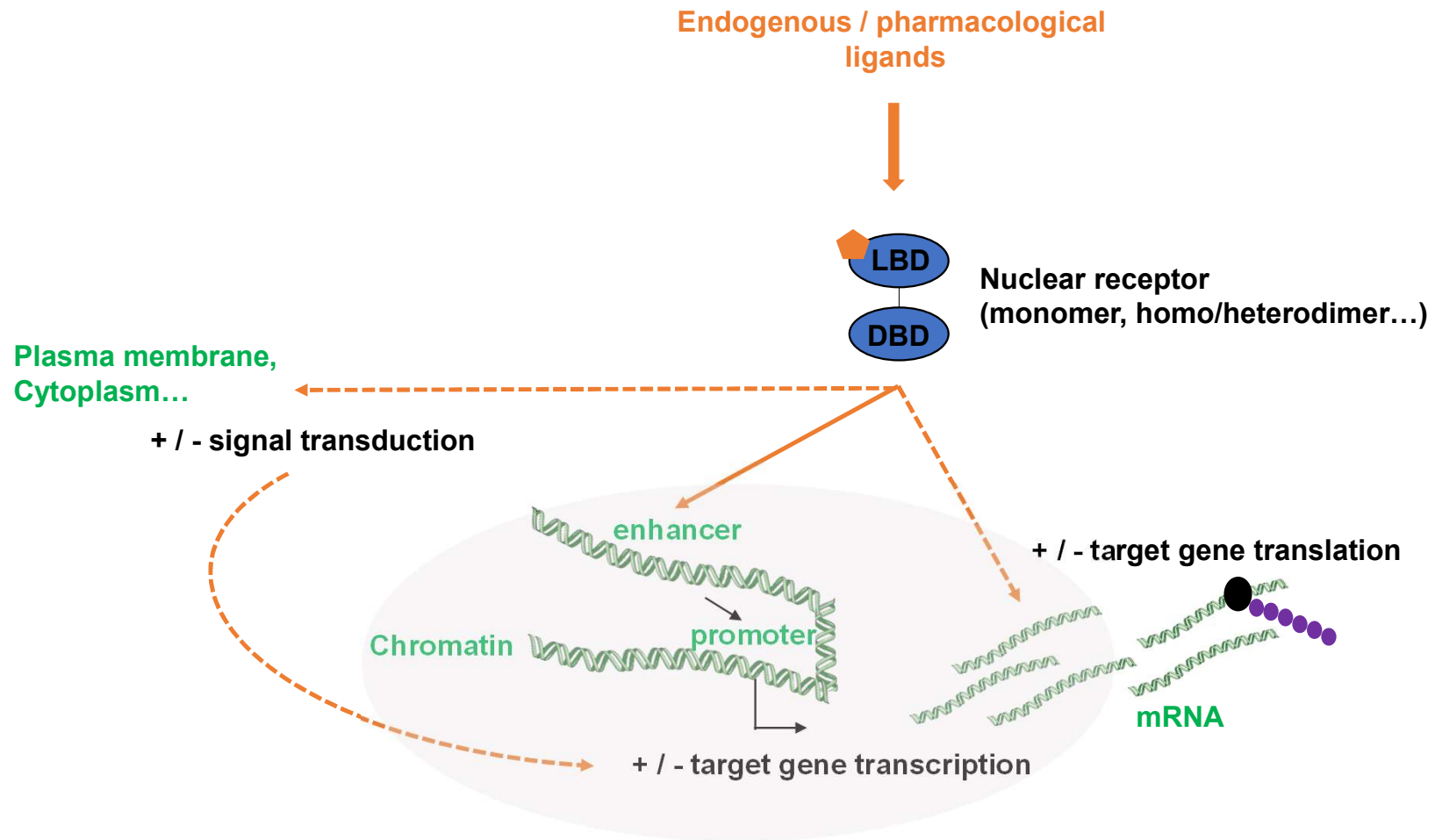


Fig.2

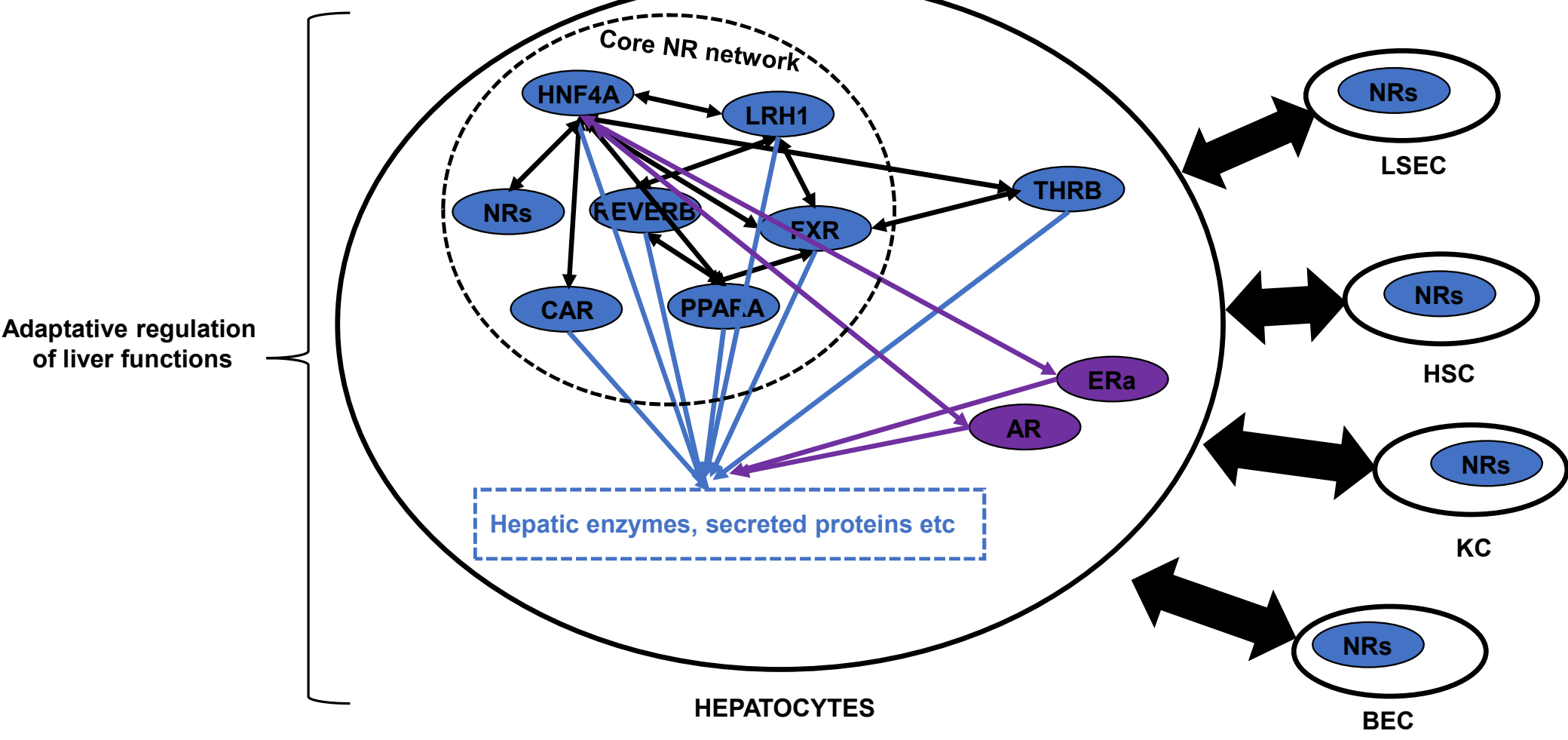


Fig.3

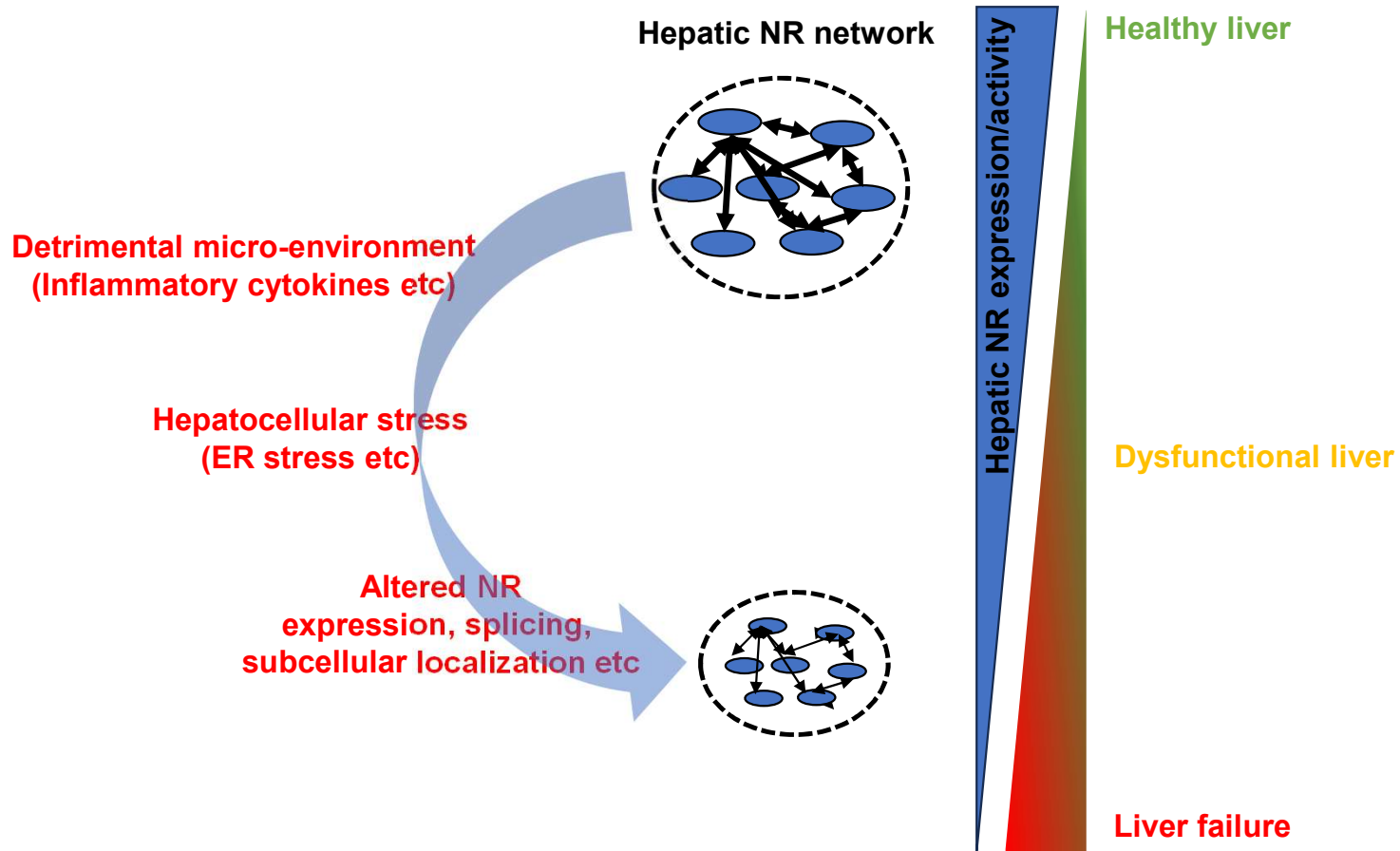


Fig.4

