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Nuclear Receptor-Mediated Hepatomegaly and Liver Regeneration: An Update[S]

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ABSTRACT

Nuclear receptors (NRs), a superfamily of ligand-activated transcription factors, are critical in cell growth, proliferation, differentiation, metabolism, and numerous biologic events. NRs have been reported to play important roles in hepatomegaly (liver enlargement) and liver regeneration by regulating target genes or interacting with other signals. In this review, the roles and involved molecular mechanisms of NRs in hepatomegaly and liver regeneration are summarized and the future perspectives of NRs in the treatment of liver diseases are discussed.

SIGNIFICANCE STATEMENT

NRs play critical roles in hepatomegaly and liver regeneration, indicating the potential of NRs as targets to promote liver repair after liver injury. This paper reviews the characteristics and molecular mechanisms of NRs in regulating hepatomegaly and liver regeneration, providing more evidence for NRs in the treatment of related liver diseases.

Introduction

Liver possesses many physiologic functions in mammals, such as metabolism and detoxification. A constant size and mass is critical for a liver to exert its functions (Michalopoulos, 2017). Under normal conditions, a liver maintains the relative liver weight and hepatocyte numbers by preprogrammed processes. Hepatomegaly (liver enlargement) refers to increased liver mass, enlarged hepatocyte size, hyperproliferation, and increased activity of metabolizing enzymes that modulate the metabolism of endobiotics and xenobiotics, such as the kinds of drugs (Zhao et al., 2021), that can be characterized by hepatocyte hypertrophy and hyperplasia. Hypertrophic process refers to the increase in the volume of hepatocyte, and hyperplasia process refers to the hepatocellular proliferation (Ross et al., 2010). Hepatomegaly can be induced by numerous factors such as alcohol, drug, viral hepatitis, tumor, hormone, inflammation, excessive nutrition, fatty liver disease, etc. (Wolf and Lavine, 2000). In addition, hepatomegaly may be induced by primary liver diseases or might be involved secondly in diseases elsewhere in the body (Kaude and Deland, 1975). It can be divided into two types: adverse hepatomegaly and nonadverse hepatomegaly (benign hepatomegaly). Nonadverse hepatomegaly is always induced by drugs or chemicals and would recover after withdrawal (Hall et al., 2012). The way to distinguish these two types of hepatomegaly is to evaluate the clinic pathologic evidence of some biochemical indicators related to liver injury (Hall et al., 2012).

Liver regeneration is an adaptive response induced by specific stimuli, including continuous changes in morphologic reconstruction and gene expression. Various extrinsic and intrinsic factors are involved in liver regeneration (Forbes and Newsome, 2016). The introduction of the partial hepatectomy (PHx) model in 1931 greatly promoted studies on

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ABBREVIATIONS: AKT, protein kinase B; BEC, biliary epithelial cells; CAR, constitutive androstane receptor; CITCO, (6-(4-chlorophenyl) imidazo[2,1-b][1,3]thiazole-5-carbaldehydeO-(3,4-dichlorobenzyl)oxime); c-Myc, MYC proto-oncognene; CTNNB1, β-Catenin; CV, central vein; FoxM1, forkhead box M1; FXR, farnesoid X receptor; GADD45β, DNA damage-inducible 45β; IL-6, interleukin-6; LBD, ligand binding domain; LPCs, liver progenitor cells; LXR, liver X receptor; *Mdm2*, Mdm2 proto-oncogene; NRs, nuclear receptors; OCA, obeticholic acid; PCN, pregnenolone-16α-carbonitrile; PHx, partial hepatectomy; PPAR, peroxisome proliferators-activated receptor; PV, portal vein; PXR, pregnane X receptor; SFSS, small-for-size-syndrome; TCPOBOP, 1,4-bis [2(3,5-dichloropyridyloxy)] benzene; TEAD, TEA domain family member; TNF, tumor necrosis factor; YAP, yes-associated protein.

liver regeneration (Higgins and Anderson, 1931). Liver regeneration consists of a variety of stages, however, mainly including the following three: hepatocytes transition into the G1 phase once PHx happens, followed by the S phase in 12–15 hours, and then hepatocytes enter the G2 phase after about 6–8 hours (Court et al., 2002). Liver regeneration consists of quick induction of proliferation factors to activate quiescent hepatocytes and start the subsequent process in the cell cycle: acceleration of the recovery of normal liver size and reconstruction of hepatocyte quiescence (Fausto, 2000). Hepatocyte hypertrophy is the first stage of liver regeneration after 70% PHx; in fact, it is sufficient for hepatocyte hypertrophy to promote the recovery of liver mass after 30% PHx (Miyaoka et al., 2012). After that, hepatocytes proliferation begins, which is stimulated by hepatocytes and bile duct epithelial cells to deal with functional defects (Malato et al., 2011). Previous studies demonstrated that various signaling pathways participated in liver regeneration. At the very beginning of liver regeneration, cytokines including interleukin-6 (IL-6) and tumor necrosis factor (TNF) can activate nuclear factor kappa-B and signal transducer and activator of transcription 3, then the hepatocyte proliferation process is induced (Taub, 2004). In addition, some growth factors also take part in liver regeneration. Hepatocyte growth factor can activate phosphatidylinositol 3-kinase/protein kinase B (AKT) as well as extracellular-regulated kinase pathway to promote DNA replication and hepatocyte proliferation (Taub, 2004). MicroRNAs such as miRNA-21 participate in the regulation of the liver regeneration process (Chen et al., 2016). Liver progenitor cells (LPCs) also take part in liver regeneration by acting as the origin of new hepatocytes when normal hepatocyte proliferation is severely impaired (Jiang et al., 2019). Other signaling pathways such as nuclear receptors also play very important roles in liver enlargement and regeneration.

Nuclear receptors (NRs) are a superfamily of ligand-activated transcription factors that convert different signals into the gene regulation (Mangelsdorf et al., 1995). Forty-eight types of NRs are now known in the human body and forty-nine types of NRs are found in mice (Zhang et al., 2004; Helsen and Claessens, 2014). NRs consist of seven subfamilies (NR0-NR6) (Yang et al., 2020); the first six subfamilies were classified according to sequence homology in 1999 by the Nuclear Nomenclature Committee, and the newly found NR subfamily with the one-conserved domain is categorized into subfamily 0 (Liu et al., 2017). There are typically five domains, which are named as A/B, C, D, E, and F domain. The A/B domain contains an amino-terminal ligand-dependent activation function domain. The C domain is a DNA-binding domain containing two zinc fingers. The D domain contains the nucleus localization sequence, which connects to the DNA-binding domain with the E domain, which is also known as the ligand binding domain (LBD). The function of the F domain is still unclear (Vacca et al., 2013; Liu et al., 2017). The main function of NRs is xenobiotic sensing and detoxification (Yen, 2015), although they are also significant for cell growth, proliferation, differentiation, and metabolism and are associated with numerous liver diseases including nonalcoholic fatty liver disease, cholestatic liver disease, and drug-induced liver disease (Rudraiah et al., 2016). Based on these findings, the structure and function of NRs and related liver diseases are summarized in Fig. 1. Studies on NRs have provided better understanding of liver pathology and physiology and some new strategies to treat liver diseases.

Mounting evidence shows that some NRs are important regulators of hepatomegaly and liver regeneration. For example, pregnane X receptor (PXR), constitutive androstane receptor (CAR), peroxisome proliferators-activated receptors (PPARs), farnesoid X receptor (FXR), and liver X receptor (LXR) have been reported to be closely related to hepatomegaly and liver regeneration (Rudraiah et al., 2016; Hall et al., 2012). Thus, this review aims to summarize the role of NRs in hepatomegaly, liver regeneration, and the involved molecular mechanisms and discuss future perspectives of NRs in the treatment of liver diseases.

NRs in Hepatomegaly and Liver Regeneration. In this section, we will review the roles of NRs such as PPARs, PXR, CAR, LXR, and FXR in hepatomegaly and liver regeneration and the molecular mechanisms involved. The major agonists and antagonists of these NRs are summarized in Table 1.

PPARs. PPARs are transcription receptors that exert critical functions in regulating energy homeostasis and cell differentiation (Tontonoz and Spiegelman, 2008). PPARs consist of PPARα, PPARβ/δ, and PPARγ (Vacca et al., 2013). Each of these isotypes shows unique physiologic distribution and function in the tissues (Wang, 2010). PPARα is mainly expressed in the liver, heart, kidney, and intestine, which exerts critical functions in fatty acid uptake, β-oxidation, and lipid catabolism (Kersten and Stienstra, 2017). PPARγ is mainly expressed in adipose tissue and is involved in the regulation of adipogenesis, lipid storage, and glucose homeostasis. PPARβ/δ is widely expressed in the liver, brain, kidney, heart, and adipose tissue, which is associated with lipid catabolism, adipogenesis, wound cure, and keratinocyte differentiation (Huang et al., 2009; Derosa et al., 2018; Mirza et al., 2019).

It has been reported that PPARα activation by its agonists clofibrate and gemfibrozil can induce liver enlargement (Lenhard et al., 1999). Moreover, PPARα is related to direct and compensatory hyperplasia by inducing the expressions of cell cycle-related genes (Morimura et al.,

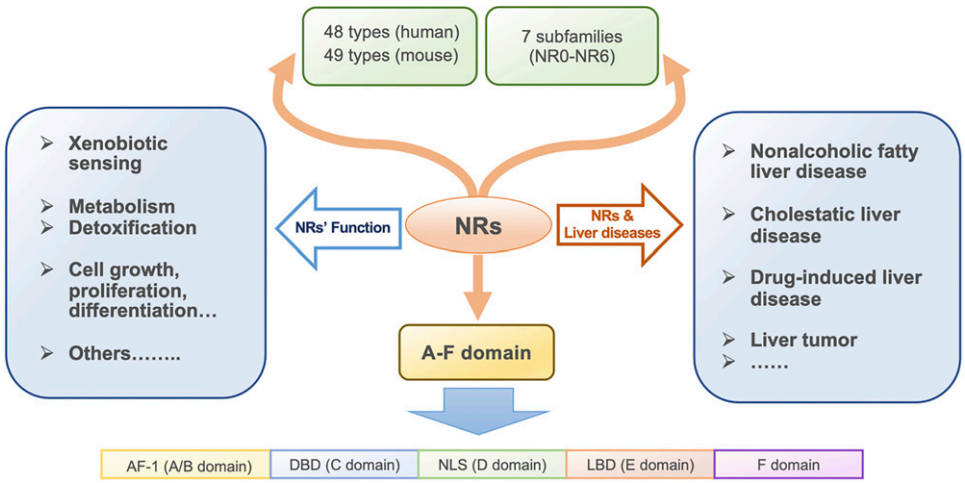

Fig. 1. The structure, function of NRs, and related liver diseases.

TABLE 1

Major agonists and antagonists of NRs

Target	Agonist/Antagonist	Drug/Compound	Reference(s)
PXR	Agonist	PCN	Jiang et al., 2019
		Rifampicin	Jiang et al., 2019
		Imazalil	Shizu et al., 2018
		Dexamethasone	Jiao et al., 2020
		Schisandrol B	Zhao et al., 2021
		Mifepristone	Yao et al., 2021
	Antagonist	ET-743	Chai et al., 2020
		Polychlorinated Biphenyls	Mani et al., 2013
		Biphenyls	Mani et al., 2013
		Fluconazole	Mani et al., 2013
		Enilconazole	Mani et al., 2013
		Sesamin	Mani et al., 2013
		Metformin	Mani et al., 2013
PPARα	Agonist	Clofibrate	Lenhard et al., 1999
		WY-14643	Fan et al., 2022
		Gemfibrozil	Lenhard et al., 1999
		Fenofibrate	Willson et al., 2000
	Antagonist	GW6471	Stebbins et al., 2017
		MK886	Stebbins et al., 2017
		NXT629	Stebbins et al., 2017
PPARγ	Agonist	Rosiglitazone	Turmelle et al., 2006
		Pioglitazone	Collino et al., 2010
	Antagonist	GW9662	Almahmoud et al., 2021
		T0070907	Almahmoud et al., 2021
CAR	Agonist	CITCO	Tschuor et al., 2016
		Phenobarbital	Huang et al., 2005
		TCPOBOP	Gao et al., 2021
	Antagonist	PK11195	Mackowiak et al., 2019
		CINPA1	Mackowiak et al., 2019
LXR	Agonist	T0901317	Jung et al., 2011
		GW3965	Minniti et al., 2020
	Antagonist	GSK2033	Helder et al., 2020
FXR	Agonist	WAY-362450	Wu et al., 2019
		OCA	de Haan et al., 2021
	Antagonist	DY268	Jiang et al., 2021
		FLG249	Jiang et al., 2021

2006). In addition, activation of PPARα by its agonist WY-14643 can induce the expression of MYC proto-oncogene (c-Myc) and miR-17-92 by inhibiting let-7c, which further promotes hepatocytes proliferation (Shah et al., 2007). Most recently, it's found that the activation of PPARα by WY-14643 can induce hepatomegaly via the yes-associated protein (YAP)-TEA domain family member (TEAD) signaling pathway by inducing hepatocytes hypertrophy around the central vein (CV) area and promoting hepatocytes proliferation around the portal vein (PV) area in mice liver (Fan et al., 2022). Therefore, PPARα is a potential modulator for hepatomegaly.

PPARs are also involved in liver regeneration. PPARα deficiency impairs liver regeneration via altering the expression of the proliferation-related genes in mice (Anderson et al., 2002). Aldose reductase can accelerate the liver regeneration process by increasing the PPARα and PPARγ expression in aldose reductase-deficient mice liver (Li et al., 2020). Recent studies showed that hepatocyte PPARα activation accelerates the liver regeneration process after PHx, which is associated with the regulation of cell cycle and lipid metabolism (Xie et al., 2019). PPARα agonist WY-14643 was found to accelerate liver regeneration after PHx by interacting and activating the YAP-TEAD signaling pathway (Fan et al., 2022).

The activation of PPARγ was reported to restrain liver regeneration in rats. One of the mechanisms is that the activation of PPARγ can inhibit TNF and IL-6, which are important in the early stage of liver regeneration (Collino et al., 2010). The PPARγ agonist thiazolidinedione, rosiglitazone can impair liver regeneration by inhibiting the expression of cyclins in mice (Turmelle et al., 2006). Yu et al. (2003) reported that PPARγ transgenic mice showed hepatic steatosis and impaired liver regeneration post PHx. Furthermore, PPARγ can downregulate cyclin D1, cyclin B1m, and p27 and upregulate p38 mitogen activated protein kinase, which suppresses the cell cycle in mice (Turmelle et al., 2006; Yamamoto et al., 2008). PPARγ activation exerts anti-inflammatory effects by inhibiting nuclear factor kappa-B and activator protein-1 transcription factors in hepatocytes and macrophages (Ogawa et al., 2005). As a result, PPARγ is an important regulator in inflammation-induced liver regeneration and hepatomegaly. PPARβ can modulate the phosphoinositide-dependent kinase 1/AKT and E2f transcription factor signaling pathway, which is closely related to hepatocyte proliferation and liver regeneration in mice (Liu et al., 2013). Bezafibrate, a pan-agonist for all PPAR isotypes, suppresses the liver regeneration process after PHx in rats by inhibiting serine palmitoyltransferase, suggesting a negative effect of activation of PPARs on liver regeneration (Zabielski et al., 2010).

PXR. PXR, a ligand-activated transcription factor, is highly expressed in liver and gut (Kliewer et al., 1998). It usually interacts with retinoid X receptor α and exerts important functions in regulating the expression of drug-metabolizing enzymes and transporters that can affect drug disposition and drug-induced liver injury (Shehu AI, 2018). PXR is also involved in the progression of various liver diseases such as liver fibrosis and cholestatic liver disease (Cave et al., 2007; Wallace et al., 2010).

PXR plays a critical role in hepatocyte proliferation and liver size control. The murine PXR agonist, pregnenolone-16α-carbonitrile (PCN), can induce liver enlargement, which is abolished in *Pxr*-deficient mice (Garg et al., 1975; Staudinger et al., 2001). Zhou et al. (2006) found that the activation of PXR can induce hepatomegaly with lipid accumulation

in PXR-humanized mice by treating with rifampicin, which is a typical agonist of human PXR. YAP is an important transcriptional coactivator in Hippo pathway and crucial in the control of organ size (Kowalik et al., 2011). It works as a transcriptional cofactor to participate in organ size control by binding with TEAD or interaction with other transcription factors. It can also regulate liver size and liver regeneration by modulating hepatocyte proliferation and apoptosis (Patel et al., 2017). *Pxr* knockout mice undergoing PHx showed delayed liver regeneration, and signal transducer and activator of transcription 3 inactivation was involved in the delayed regeneration process (Dai et al., 2008). Absence of PXR reduced hepatic fat accumulation accompanied by suppressed hepatocyte proliferation after PHx, suggesting that PXR-induced lipid accumulation is required for the hepatic regenerative response after PHx (Dai et al., 2008). Recent studies showed that PXR-induced hepatomegaly by PCN is YAP-dependent in mice and PXR interacts with YAP to promote nuclear YAP accumulation and then upregulation of YAP target genes (Jiang et al., 2019). Schisandrol B, a PXR agonist, can induce hepatomegaly and promote liver regeneration in mice via activation of PXR and YAP (Zhao et al., 2021). Besides, schisandrol B can also promote liver regeneration after cholestatic liver injury in mice via increasing cyclin D1 and proliferating cell nuclear antigen expression while reducing p53 and p21 expression (Zeng et al., 2017). High dose dexamethasone treatment can induce hepatomegaly and hepatocyte enlargement in mice by the activation of PXR and YAP signaling pathway and lipid accumulation (Jiao et al., 2020). Furthermore, a high dose of mifepristone, which is a synthetic antiprogesterone drug, can induce hepatomegaly in mice by activation of PXR, promoting PXR and YAP nuclear translocation, and then upregulating their downstream targets such as CYP3A11, CYP2B10, UGT1A1, ANKRD1, and CTGF (Yao et al., 2021). Additionally, PXR can elevate CAR- and PPARα-mediated, xenobiotic-induced hepatic proliferative response in mice (Shizu et al., 2013). Yoshinari (2019) found that Imazalil can activate PXR to promote hepatocyte proliferation induced by CAR agonist 1,4-bis [2-(3,5-dichloropyridyloxy)] benzene (TCPOBOP) in mice liver (Yoshinari, 2019). PXR-promoted liver regeneration can be inhibited by forkhead box O3 (Shizu et al., 2016). DNA damage-inducible 45β (GADD45β) is a direct target of PXR (Kodama and Negishi, 2011), which facilitates hepatocyte survival by regulating c-Jun N-terminal kinase pathway in the liver regeneration in mice (Papa et al., 2008).

CAR. CAR is an important intracellular xenobiotic sensor, which is mainly expressed in the small intestine and liver (Xu et al., 2016). Like PXR, CAR regulates various genes encoding drug metabolizing enzymes such as CYP3A3 and CYP2B subfamily members, uridine 5′-diphosphate-glucuronosyltransferases, sulfotransferases, and glutathione S-transferases (Gotoh et al., 2015). CAR is located in the cytoplasm by forming a complex with the cytoplasmic CAR retention protein and heat shock protein 90. Once activated, the complex is dissociated and CAR is translocated into the nucleus, where it can bind with retinoid X receptor α, then the downstream target genes are activated (Kodama and Negishi, 2006). CAR plays a critical role in gluconeogenesis, lipid metabolism, hormone regulation, and hepatocyte proliferation. It is expressed at a higher level in the developing liver compared with the adult liver (Pascussi et al., 2007).

CAR also plays a vital role in hepatomegaly and liver regeneration. CAR activators, including phenobarbital and "barbital-like" compound TCPOBOP, can directly induce hepatomegaly (Costa et al., 2005), which is the consequence of hyperplasia and hypertrophy. Hepatocytes enlargement around the CV area and hepatocytes proliferation around the PV area were observed in TCPOBOP-treated mice (Gao et al., 2021). It has been reported that CAR activation can promote the Mdm2 proto-oncogene (*Mdm2)* gene expression to start the cell cycle and restrain apoptosis (Huang et al., 2005; Gao et al., 2021). The YAP-TEAD signaling pathway is also involved in CAR-mediated hepatomegaly. TCPOBOP-induced CAR activation promotes the translocation of YAP and elevates the expression of YAP-TEAD downstream targets, whereas CAR-dependent hepatocyte proliferation was milder in *Yap* knockout mice, suggesting that YAP is critical in CAR-promoted hepatomegaly (Abe et al., 2018; Gao et al., 2021). Verteporfin, a compound which can inhibit the interaction of YAP/TEAD, can relieve TCPOBOP-induced hepatomegaly in mice (Abe et al., 2018). Besides, c-Myc and forkhead box M1 gene are the key mediators of TCPOBOP-induced hepatomegaly (Blanco-Bose et al., 2008). Forkhead box M1 (FoxM1) represses phosphatase and tensin homolog and activates the AKT signal pathway to promote liver growth (Yarushkin et al., 2019). Additionally, GADD45β has been reported to be related to the CAR-associated liver hypertrophy (Columbano et al., 2005). CAR can interact with GADD45β to suppress p38 mitogen activated protein kinase signaling and promote hepatocyte proliferation in mice (Hori et al., 2018). A previous study showed that the lack of β-Catenin (CTNNB1) can suppress CAR activation-induced hepatocyte proliferation (Kodama and Negishi, 2006). Besides, TCPOBOP-induced proliferation is impeded by co-interruption of the mesenchymal epithelial transition factor receptor and epidermal growth factor receptor signaling, even if CAR is activated (Bhushan et al., 2019).

As for liver regeneration, *Car* knockout mice displayed impaired capability of liver regeneration (Tschuor et al., 2016), whereas TCPOBOP can accelerate liver regeneration post PHx by promoting hepatocyte hypertrophy around the CV area and hepatocytes proliferation around the PV area in mice (Gao et al., 2021). The induction of CAR might be a possible therapeutic way to prevent small-for-size-syndrome (SFSS). It has been demonstrated that insufficient CAR induction can lead to liver failure after excessive tissue loss. Reactivation of CAR by its agonist (6-(4-chlorophenyl) imidazo[2,1-b][1,3]thiazole-5-carbaldehydeO-(3,4-dichlorobenzyl)oxime) (CITCO) can promote the restoration of biochemical indicators related to liver injury after SFSS (Tschuor et al., 2016). As a result, CAR is considered to be a primary mitogen to induce hepatocyte proliferation after PHx (Costa et al., 2005).

LXR. Up to now, there are two family members of LXR: LXRα and LXRβ (Peet et al., 1998). LXRα is mainly expressed in the liver, but LXRβ is relatively low in liver. LXR participates in modulating the expression of the genes which are involved in lipid and cholesterol homeostasis and plays critical roles in membrane synthesis, cellular differentiation, and proliferation (Lo Sasso et al., 2010).

It has been reported that LXR is associated with hepatomegaly, but the mechanism involved remains unclear. Mice treated with LXR agonist T0901317 showed hepatomegaly, with a triglyceride accumulation (Jung et al., 2011). However, the LXR agonist T0901317 is also an agonist of PXR in vivo and in vitro, so the effect could have been mediated by PXR activation. The modulation of hepatomegaly and hepatocyte proliferation by T0901317 should be further studied to find out whether this effect is mediated by PXR activation or LXRα inhibition (Mitro et al., 2007; Zhang et al., 2020). Besides, LXR is inhibited in the liver regeneration process. After PHx, hepatocyte proliferation is induced accompanied by suppression of LXR in mice liver (Lo Sasso et al., 2010). Inhibition of LXR-transcriptional pathways is crucial to ensure cholesterol levels of regenerating hepatocytes, and the activation of LXR by its agonist GW3965 can significantly reduce liver regeneration capacity during PHx (Lo Sasso et al., 2010). Previous studies showed that hydroxysteroid sulfotransferase 2B1b can promote liver regeneration by inhibiting LXRα activation in fatty liver and T0901317 treatment can attenuate the effect (Zhang et al., 2020). However, whether the inhibition of LXR causes liver regeneration is still questionable.

FXR. There are two FXR family members: FXRα and FXRβ. However, FXRβ is considered as a pseudogene in humans (Otte et al., 2003). FXR is mainly expressed in the liver, kidney, intestine, and adrenal cortex (Parks et al., 1999). FXR is one of the main transcriptional regulators of bile acid homeostasis. It can interact with RXR to activate or inhibit FXR response element target genes by working with diverse coactivators that participate in the modulation of cell cycle, apoptosis, and lipid metabolism (Modica et al., 2010).

Hepatomegaly is induced and alanine aminotransferase and alkaline phosphatase are increased in *Fxr*-null mice, which is related to elevated bile acid levels (Sinal et al., 2000; Kitada et al., 2003; Yang et al., 2007). However, long-term treatment of FXR agonist WAY-362450 can induce hepatomegaly in mice liver by activating cyclin D1 (Wu et al., 2019), and the mechanism of inducing hepatomegaly is different from *Fxr*-null mice. Although FXR is not necessary for liver growth induced by pregnancy, lack of FXR affects its normal mechanisms. In *Fxr*-deficient mice, hepatomegaly induced by pregnancy is carried out by the adaptive hepatocyte hyperplasia rather than hypertrophy (Milona et al., 2010).

FXR is also necessary in modulating liver regeneration. FXR plays a critical role in restoring the CCl_4-injured liver by disrupting hepatocyte death and inducing liver regeneration (Meng et al., 2010). *Fxr* knockout mice undergoing PHx showed elevated bile acid level, higher mortality, and delayed liver regeneration (Huang et al., 2006). Bile acid overloading can induce DNA oxidative damage, inflammation, and cell overproliferation in *Fxr*-deficient mice (Vacca et al., 2013). The activation of FXR mediated by liver injury or bile acid signaling after hepatectomy can induce liver regeneration via different mechanisms (Modica et al., 2010). The hepatic bile acid level tends to elevate after PHx under normal conditions. Increased bile acid can activate FXR to induce FoxM1b and c-Myc expression to protect hepatocytes from bile acid toxicity damage. Besides, it is also found that FXR alleviates the defects of age-related liver regeneration by inducing the expression of Foxm1b with elevated DNA-duplication of hepatocytes (Chen et al., 2010).

It was confirmed that FXR activation can improve the liver metabolic ability, promote liver regeneration, and inhibit cell death, which shows the therapeutic potential for the FXR agonist for the prevention of liver failure during liver transplantation and resection (Vacca et al., 2013). It has been reported that the FXR agonist, obeticholic acid (OCA), can promote liver growth and liver regeneration during obstructive cholestasis. However, another study challenges the finding mentioned above because OCA treatment of rats cannot promote liver regeneration after cholestasis (de Haan et al., 2021). Some studies show that biliary epithelial cells (BEC) of zebrafish can transform into new hepatocytes by dedifferentiation into LPCs and then LPCs differentiated into hepatocytes, and BEC-derived cells proliferation also makes contributions to new hepatocytes formation (Choi et al., 2014). It has been reported that FXR activation in zebrafish can increase phosphatase and tensin homolog activity and inhibit phosphatidylinositol 3-kinase-mammalian target of the rapamycin pathway, which impedes BEC-driven liver regeneration, suggesting that targeting FXR for liver regeneration in clinical trials should be more personalized (Jung et al., 2020). Taken together, FXR is necessary in the modulation of liver repair and regeneration.

TABLE 2

Effects of NRs and their agonists on liver size and liver regeneration

NRs	Activators or Agonists	Effects on liver size and Regeneration	Reference(s)
PXR	PCN	Induces liver enlargement and liver regeneration via activation of YAP signaling pathway	Jiang et al., 2019
PXR	Rifampicin	Induces liver enlargement and liver regeneration via activation of YAP signaling pathway	Jiang et al., 2019
PXR	Imazalil	Activates PXR to elevate hepatocyte proliferation induced by CAR	Shizu et al., 2018
PXR	Dexamethasone	Induces hepatomegaly by the activation of YAP signaling pathway and lipid accumulation	Jiao et al., 2020
PXR	Schisandrol B	Induces hepatomegaly and hepatocyte proliferation by activation of YAP signaling pathway	Zhao et al., 2021
PXR	Mifepristone	Induces hepatomegaly by promoting PXR and YAP nuclear translocation	Yao et al., 2021
PPARα	Clofibrate	Induces liver enlargement	Lenhard et al., 1999
PPARα	WY-14643	Promotes liver enlargement and liver regeneration via activation of YAP-TEAD signaling pathway	Fan et al., 2022
PPARα	Gemfibrozil	Induces liver enlargement	Lenhard et al., 1999
PPARγ	Rosiglitazone	Impairs liver regeneration process by down-regulation of cyclin expression	Turmelle et al., 2006
CAR	CITCO	Promotes hepatomegaly and liver regeneration in SFSS model	Tschuor et al., 2016
CAR	Phenobarbital	Induces hepatomegaly by activating *Mdm2* gene expression	Huang et al., 2005
CAR	TCPOBOP	Promotes hepatomegaly by activating YAP signaling pathway	Abe et al., 2018; Gao et al., 2021
LXR	T0901317 (LXRT)	Induces hepatomegaly with an increased level of triglyceride	Jung et al., 2011
FXR	WAY-362450	Induces hepatomegaly by activating cyclin D1	Wu et al., 2019

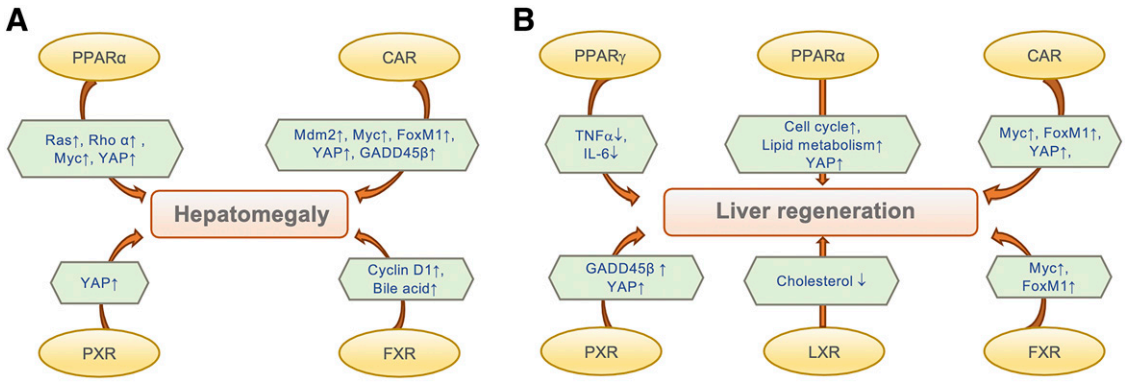

Fig. 2. Mechanisms involved in NR-mediated hepatomegaly (A) and liver regeneration (B).

Discussion and Perspectives

Hepatomegaly can be induced by numerous factors and divided into nonadverse hepatomegaly and adverse hepatomegaly (Wolf and Lavine, 2000). Liver regeneration is a critical process in liver repair post injuries, and it can be affected by many intrinsic and extrinsic factors (Forbes and Newsome, 2016). Liver regeneration after PHx is a process in which the residual liver tissue expands to function normally, and it is also known as compensatory hepatomegaly (Fausto et al., 2006). NRs take part in the

TABLE 3

Mechanisms involved in NR-promoted hepatomegaly and liver regeneration

NRs	Effects	Mechanisms	Reference(s)
PXR	Hepatomegaly↑	Induces hyperplasia and hypertrophy by YAP signaling pathway	Jiang et al., 2019
PXR	Liver regeneration↑	Accelerates liver regeneration by YAP signaling pathway	Yoshinari, 2019; Jiang et al., 2019
PPARα	Hepatomegaly↑	1. Induces gene expression of *Ras*, *Rho* α, and *c-Myc* oncogene expression, which are important for hepatocyte proliferation and hepatic hyperplasia; 2. Interacts with YAP-TEAD signaling pathway	Morimura et al., 2006, Shah et al., 2007; Fan et al., 2022
PPARα	Liver regeneration↑	1. Interacts with YAP-TEAD signaling pathway and induces liver regeneration 2. Regulates cell cycle and lipid homeostasis	Fan et al., 2022; Xie et al., 2019
PPARγ	Liver regeneration↓	Reduces TNF and IL-6 in the liver, which are important in the early phase of liver regeneration	Collino et al., 2010
CAR	Hepatomegaly↑	1. Activates the expression of the *Mdm2* gene to start the cell cycle and restrain apoptosis; 2. YAP can regulate the expression of proliferation genes such as *c-Myc* and *FoxM1* 3. GADD45*β* has been reported to be related to the CAR-associated liver hypertrophy 4. Interacts with YAP-TEAD signaling pathway	Huang et al., 2005, Costa et al., 2005, Hori et al., 2018; Gao et al., 2021
CAR	Liver regeneration↑	YAP activation induced by CAR can regulate the expression of proliferation-related genes such as c-Myc and FoxM1	Costa et al., 2005; Gao et al., 2021
LXR	Hepatomegaly	Not clear	—
LXR	Liver regeneration↓	LXR activation can reduce liver regeneration capacity during PHx	Lo Sasso et al., 2010
FXR	Hepatomegaly	1. *Fxr*-null mice showed increased bile acid level and hepatomegaly 2. Chronic activation by WAY-362450 induces hepatomegaly by activating cyclin D1	Wu et al., 2019; Yang et al., 2007
FXR	Liver regeneration↑	Induces the expression of *Foxm1b* and *c-Myc*	de Haan et al., 2021

regulation of cell growth and functions and are critical regulators of hepatocyte size and proliferation, and thus hepatomegaly and liver regeneration. The effects of NRs and their agonists on liver size and liver regeneration are listed in Table 2 and the major mechanisms for NR-mediated hepatomegaly and liver regeneration are summarized in Fig. 2 and Table 3. NRs are critical in the modulation of inflammation, proliferation, lipid metabolism, and cell cycle, which plays a critical role in liver regeneration and hepatomegaly progress. Thus, the NR transcriptome can serve as a therapeutic target for liver diseases that affects the proliferation of hepatocytes (Vacca et al., 2014). Regenerative process is involved in many liver diseases including cholestasis, fatty liver diseases, hepatic fibrosis, and drug-induced liver injury, which indicates the universal potential of NRs for promoting liver repair in various hepatic diseases. In addition to the nuclear receptors mentioned above, the aryl hydrocarbon receptor is also important in hepatomegaly and liver regeneration, AhR-null mice displayed hepatomegaly after flutamide treatment (Gao et al., 2016), and the liver regeneration capability was improved in AhR-null mice after short-term CCl_4 treatment (Moreno-Marín et al., 2017). Many NRs agonists have been widely used in clinics, such as PXR agonist rifampicin, CAR agonist phenobarbital, PPARα agonist fibrates, and PPARγ agonist rosiglitazone. Future studies are required to assess their potential in promoting liver regeneration in clinics.

YAP has been reported to be the common mechanism involved in PXR, CAR, or PPARα-induced hepatomegaly and liver regeneration (Jiang et al., 2019; Gao et al., 2021; Fan et al., 2022). The mechanisms of YAP signaling pathway mediating CAR-, PXR-, and PPARα-induced hepatomegaly and liver regeneration are depicted in Fig. 3. Activation of PXR and PPARα cannot induce liver enlargement in *Yap* knockout mice, suggesting that PXR or PPARα activation-induced hepatomegaly is YAP-dependent. However, CAR activation-induced hepatomegaly is significantly suppressed but not totally abolished in *Yap* knockout mice. Other factors such as CTNNB1, c-Myc, and mesenchymal epithelial transition factor receptor signaling are also involved in the hepatomegaly induced by CAR. Further studies are required to elucidate the diverse mechanisms of YAP in NR-induced liver enlargement. After activation of PXR, CAR, or PPARα by their typical agonists, these NRs can interact with YAP and promote its nuclear translocation. E domain of PPARα was identified to be essential for the interaction with YAP. Whether the domain of PXR or CAR is necessary for their interaction with YAP remains unclear, but it has been included in our ongoing project. Further study is also required to measure the binding affinity between PXR, CAR, PPARα, and YAP and elucidate the binding sites specifically. Recent studies showed that YAP regulates gene transcription by forming liquid-liquid phase-separated bodies and engaging in superenhancers (Franklin and Guan, 2020). It is interesting to determine the function of NRs in the regulation of YAP phase separation. Moreover, YAP is reported to be modulated by post-translational modifications such as ubiquitination, phosphorylation, acetylation, methylation, sumoylation, and O-GlcNAcylation, which regulates its protein stability, transcriptional activity, and subcellular localization at different stages (Yan et al., 2020). Whether PXR, CAR, or PPARα regulates YAP activity via modulating its posttranslational modifications remains to be further studied.

YAP is required in the hepatocyte proliferation modulated by Myc, which is also one of the transcriptional targets of YAP (Choi et al., 2018; Bisso et al., 2020). The overexpression of Myc can induce hepatocellular carcinomas, and Myc plays a key role in the PPARα activation-induced liver cancer by upregulating the expression of miR-17-92 cluster and inducing the accelerated cell cycle progress and the

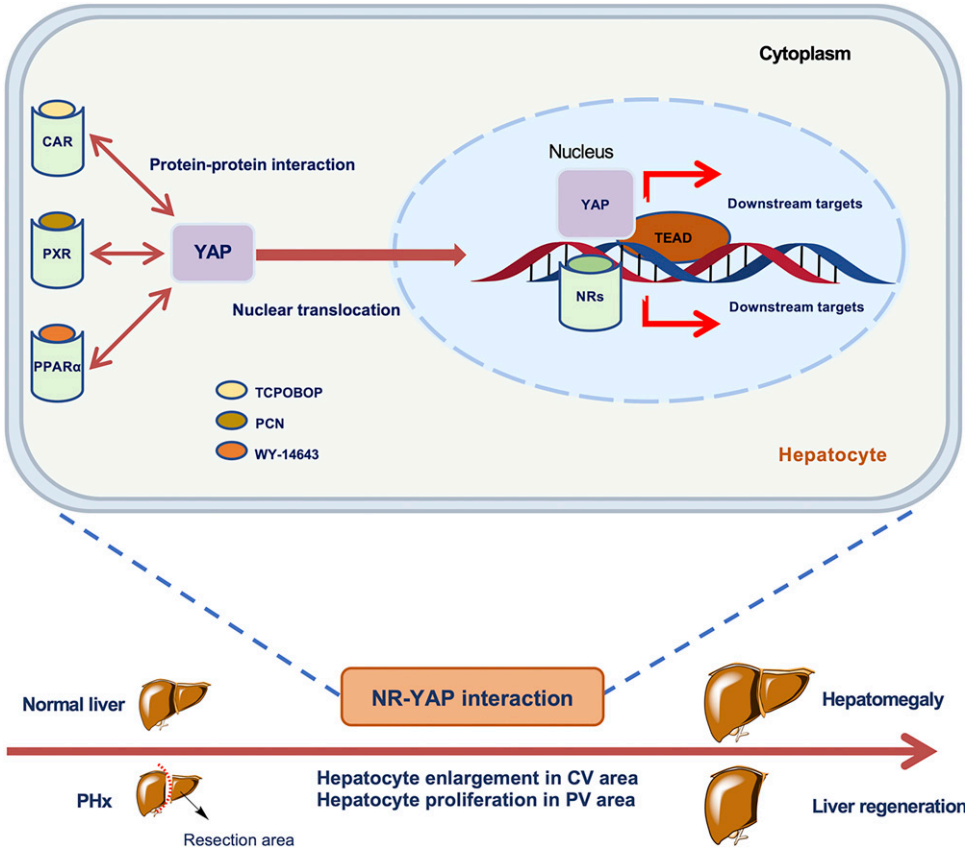

Fig. 3. YAP signaling pathway mediates CAR-, PXR-, or PPARα-induced hepatomegaly and liver regeneration.

defection of tumor cell apoptosis (Qu et al., 2014). The upregulation of the transcription of *c-Myc* mRNA might be modulated by CAR through activating CTNNB1 and YAP signaling pathway (Shizu and Yoshinari, 2020). In addition, YAP is overactivated in various types of human cancers (Zender et al., 2006; Zhao et al., 2007; Steinhardt et al., 2008), and prolonged activation of YAP promotes cancer progression in mice (Moya and Halder, 2019), suggesting the potential risk of adverse side effects such as carcinogenesis. Besides, activation of CAR and PPARα has clear mitogenic effects, which is a typical factor to cause hepatomegaly and promote tumorigenesis, at least in rodents (Locker, 2015; Yamada et al., 2021). Thus, the strategies to activate YAP by NRs agonists for regenerative therapy should be evaluated with caution.

Furthermore, crosstalk between NRs in the hepatomegaly was also reported; for example, PPARα or CAR-induced hepatomegaly can be enhanced by PXR agonists (Shizu et al., 2013). GADD45β, a transcriptional coactivator that facilitates rapid liver growth in mice, can be significantly induced by PXR or CAR activation and is associated with PXR or CAR-induced hepatic proliferative response.

The species difference between human and rodent NRs is also noted. The species difference between NRs in humans and rodents, such as PXR and CAR, might be caused by the low homology of LBD (Yoshinari, 2019). For example, rodent CAR may interact with other hepatocyte proliferation-related proteins through the protein surface of LBD, whereas human CAR may not interact with these proteins (Shizu and Yoshinari, 2020). The transcriptional interactions of PXR and YAP have no clear species difference (Abe et al., 2019). Phenobarbital treatment of human primary hepatocytes in vitro doesn't cause hepatocyte proliferation and DNA duplication, but phenobarbital treatment can induce the hepatocyte proliferation in rats (Parzefall et al., 1991; Hirose et al., 2009; Soldatow et al., 2016; Okuda et al., 2017). Furthermore, the species difference in the CAR-mediated liver tumor formation may result from the protein-protein interaction between CAR and YAP, replicative DNA synthesis, and hepatocyte proliferation (Yoshinari, 2019; Shizu and Yoshinari, 2020). The PY motif of the protein surface of mouse CAR interacts with the WW domain of YAP to activate YAP and induce hepatocyte proliferation, whereas the loss of the PY motif results in the lack of interaction in human liver (Shizu et al., 2020). It has been shown that PPARα-dependent rodent hepatocyte proliferation is absent in human liver, suggesting that PPARα-induced hepatomegaly is also species dependent (Gonzalez and Shah, 2008). PPARα agonist WY-14643 or fenofibrate-induced liver enlargement in humans and rodents is different, which might be related to distinct gene expression of PPARα and peroxisome proliferation between humans and mice (Holden and Tugwood, 1999; Ye et al., 2003). The species difference might also be associated with the PPARα target gene binding, the response to ligand activation, and the functional difference of PPARα in mouse and human liver (Foreman et al., 2009). Thus, whether and how these NRs agonists can promote liver regeneration in humans still needs further investigation.

In summary, NRs exert critical effects on hepatomegaly and liver regeneration, which provides clinical relevance for promoting liver repair after liver injuries. Especially, NRs such as PXR, CAR, or PPARα can be potential targets to rescue SFSS during liver transplantation. Many clinically used NRs agonists also possess the potential to be used for promoting liver regeneration in clinics.

Authorship Contributions

Participated in research design: Huang, Bi

Performed data analysis: Zhao, Fan, Gao.

Wrote or contributed to the writing of the manuscript: Zhao, Fan, Gao, Bi.

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