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Review Article

Emerging role of the orphan nuclear receptor estrogen-related receptor gamma in liver metabolic diseases☆

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ABSTRACT

Estrogen-related receptor gamma (ERRγ) is one of three members of the ERR family and remains an orphan, as there are no known natural ligands. ERRγ is an inducible transcription factor, and its ligand-independent transcriptional activity is regulated by co-regulator interactions and post-transcriptional modifications. Recent findings from animal models show that ERRγ, as a downstream mediator of multiple extracellular signals, plays a key role in coordinating endocrine and metabolic signals, resulting in changes in glucose, alcohol, lipid, and iron metabolism in the liver. Therefore, dysregulation of this receptor contributes to the pathogenesis of metabolic diseases such as hyperglycemia, insulin resistance, and alcoholic liver injury. Interestingly, ERRγ is also involved in responses to bacterial infection. These findings establish the importance of ERRγ in the endocrine and metabolic control of liver metabolism, and suggest that ERRγ may be a promising therapeutic target for metabolic diseases of the liver.

1. Introduction

The nuclear receptor (NR) superfamily is a large group of ligand-dependent transcription factors that regulate the expression of genes involved in development, homeostasis, and metabolism.[1] However, there are a few orphan NRs, for which endogenous ligands have not yet been identified. The estrogen-related receptor (ERR) subfamily consists of three members, ERRα (NR3B1), ERRβ (NR3B2), and ERRγ (NR3B3), all of which are orphans.[2] ERRα and ERRβ, which were identified before ERRγ, have been extensively studied.[2–4] However, the role of ERRγ is not well understood, because *ERR*γ-null mice are not viable after birth.[5] Recently, the generation of tissue-specific *ERR*γ knockout mice, gain- and loss-of-function studies, and the use of small synthetic ligands to modulate the transcriptional activity of ERRγ have allowed for rapid advances in our understanding of the metabolic functions of ERRγ in various tissues, such as the heart, muscle, pancreas, and liver. Indeed, it has been shown that ERRγ plays critical roles in multiple metabolic processes in the liver, including the regulation of glucose, lipid, alcohol, and iron metabolism, by modulating the expression of specific genes involved in endocrine and metabolic processes.[6] Furthermore, abnormal regulation of ERRγ is associated with the pathogenesis of metabolic diseases. Interestingly, ERRγ has also been implicated in hepatocellular carcinoma, because it regulates the expression of microRNAs or deoxyribonucleic acid (DNA) methyltransferase.[7,8]

In this review, we focus on the major findings and recent advances regarding the emerging role of ERRγ in the control of liver metabolism, and discuss the role of ERRγ in the pathogenesis of liver diseases.

2. ERRγ: Background

ERRγ was first identified through its linkage with a critical region of Usher syndrome type IIa, and then as a protein that functionally interacts with the NR coactivator glucocorticoid receptor-interacting protein (GRIP)-1.[9,10] It is primarily expressed in key metabolic tissues, such as the muscle, heart, brain, liver, and adipose tissue.[2] ERRγ contains the typical structural features of the NRs (Fig. 1A), including a poorly conserved N-terminal domain

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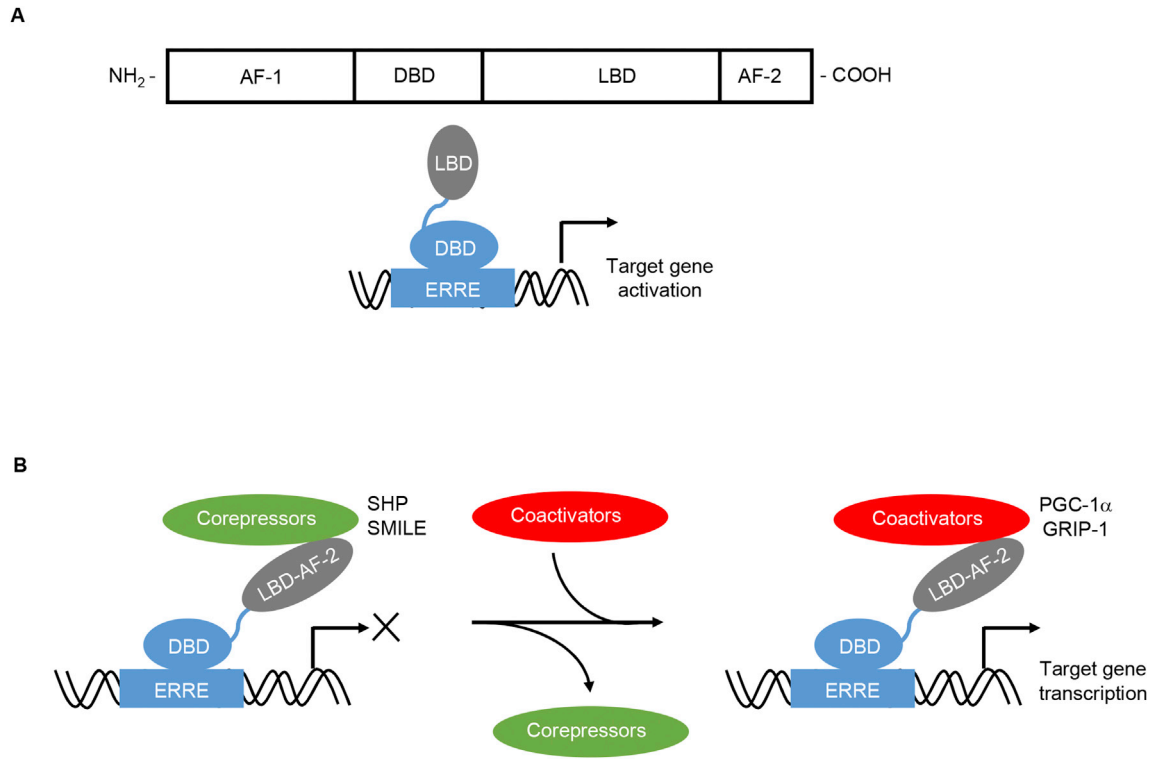

Fig. 1. Structural features and activation of ERRγ. (A) ERRγ possesses a poorly conserved N-terminal domain containing an AF-1 domain, a central zinc finger DBD that binds to an extended half-site core sequence, and a C-terminal LBD containing an AF-2 domain that interacts with co-regulators. ERRγ directly binds to the ERRE on target gene promoters. **(B)** ERRγ interacts with corepressors, such as SHP and SMILE, leading to inactivation of target gene transcription. In response to endocrine or metabolic signals, ERRγ dissociates from the corepressor and recruits coactivators, such as GRIP-1 and PGC-1α, to activate target gene expression. Abbreviations: AF, activation function; DBD, DNA-binding domain; LBD, ligand-binding domain; ERRE, ERR response element; GRIP-1, glucocorticoid receptor-interacting protein-1; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-α; SHP, small heterodimer partner; SMILE, small heterodimer partner-interacting leucine zipper protein.

containing an activation function (AF)-1 domain, a central zinc finger DNA-binding domain (DBD) that binds to the ERR response element (ERRE; TCAAGGTCA), and a C-terminal ligand-binding domain (LBD) that contains an AF-2 domain, which interacts with coactivators such as GRIP-1 and peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α) and corepressors such as small heterodimer partner (SHP) and small heterodimer partner-interacting leucine zipper protein (SMILE) (Fig. 1B).[10–13]

As ERR isoforms have a highly conserved DBD, and their transcriptional activities rely on cooperation with similar coactivator and corepressor proteins, the transcriptional and physiological outcomes of ERRγ signaling are similar to the outcomes of ERRα and ERRβ signaling in several tissues where they are co-expressed, including the heart, kidney, stomach, and skeletal muscle.[5,14–18] However, ERRγ can also regulate genes that are important in various metabolic processes in the liver, independently of the other two isoforms.[19–22] Interestingly, the transcriptional activity of the ERRs depends on their ability to bind to the ERRE as monomers, as homodimers, or as heterodimers comprised of two distinct ERR isoforms, suggesting that the mode of ERRγ binding to its target gene promoters may affect the transcriptional and physiological outcomes in a cell- or tissue-specific manner.[18,23–26]

ERRγ is constitutively active in the absence of endogenous ligand.[27] However, several synthetic ligands that can repress or induce ERRγ function by disrupting ERRγ-coactivator interactions have been reported to date. The estrogen receptor modulators diethylstilbestrol (DES) and 4-hydroxytamoxifen (4-OHT) act as inverse agonists to suppress the intrinsic transcriptional activity of ERRγ.[28] GSK5182, a 4-OHT analog, is thought to show higher inverse agonist specificity for ERRγ than 4-OHT, because it contributes to non-covalent interactions with Y326 and N346 at the active site of the ERRγ LBD.[29] In addition, GSK4716 and DY131, phenolic acyl hydrazines, increase the basal activity of ERRβ and ERRγ.[30,31] Bisphenol A, an endocrine disruptor, binds to human ERRγ with high affinity and acts as an antagonist of the inverse agonist activity of 4-OHT on ERRγ.[32] As these synthetic ligands affect various metabolic functions of ERRγ *in vitro* and *in vivo*, they are useful tools for studying the metabolic functions of ERRγ and may also have therapeutic potential in metabolic diseases caused by ERRγ dysregulation.

3. Roles of ERRγ in liver metabolism and disease

3.1. Hepatic gluconeogenesis and insulin resistance

Glucose homeostasis is tightly controlled by the pancreatic endocrine hormones glucagon and insulin during fasting and feeding. Dysregulation of this system is associated with the pathogenesis of type 2 diabetes mellitus (T2DM), which is characterized by systemic hyperglycemia and insulin resistance.[33] Under low glucose conditions, such as during prolonged fasting, glucagon promotes *de novo* synthesis of glucose (gluconeogenesis) in the liver by activating 3′, 5′-cyclic adenosine monophosphate (cAMP) signaling, whereas in the fed state, insulin suppresses hepatic gluconeogenesis by activating hepatic protein kinase B (PKB/AKT) signaling.

ERRγ is reported to play an important role in the regulation of hepatic gluconeogenesis by glucagon and insulin. Hepatic *ERRγ* gene transcription is upregulated as a result of fasting-induced activation of the cAMP response element (CRE)-binding protein (CREB)- regulated transcription coactivator 2 complex (CRTC2), which binds to a CRE site in its promoter.[20] PGC-1α expression is

also induced by the same pathway during fasting. As a result, PGC-1α enhances the ability of ERRγ to upregulate gluconeogenic gene expression. PGC-1α also contributes to hepatic gluconeogenesis via other transcriptional partners, including forkhead box protein O1 (FOXO1) and hepatocyte nuclear factor 4α (HNF4α).[34–36] Interestingly, ERRγ can also increase PGC-1α expression, indicating that ERRγ can act as a positive feedback-based gluconeogenic gene amplifier, in which PGC-1α induced by ERRγ enhances the gluconeogenic activity of ERRγ, as well as of FOXO1 and HNF4α.[37]

The gluconeogenic activity of ERRγ is also regulated by post-translational regulation during fasting and re-feeding cycles. In the fasting state, glucagon promotes O-GlcNAcylation of ERRγ, which is required for the induction of hepatic gluconeogenesis in mice (Fig. 2).[38] By contrast, in the fed state, insulin inhibits the ability of ERRγ to upregulate hepatic gluconeogenesis by promoting PKB-mediated phosphorylation of ERRγ and by inducing the cytoplasmic translocation of nuclear ERRγ.[39] Moreover, a phosphorylation-deficient mutant ERRγ is resistant to insulin-induced repression of hepatic glucose production in normal mice. Consistent with these observations, the ability of insulin to inhibit the gluconeogenic activity of ERRγ in re-fed normal mice is abolished in animal models of insulin resistance, such as the *liver-specific insulin receptor* knockout mice and *PKBβ*-deficient mice.[38,39] These findings indicate that both transcriptional and post-translational regulation of ERRγ are important for its gluconeogenic activity.

The regulation of ERRγ expression and function by nutrient signals is linked to hepatic glucose metabolism. Initial studies on the function of hepatic ERRγ showed that ERRγ expression is significantly higher in the liver in animal models of diabetes, such as *leptin*-deficient (*ob/ob*) mice, *leptin receptor*-deficient (*db/db*) mice, and diet-induced obesity (DIO) mice.[40] Consistently, it has been reported that ERRγ is directly associated with the regulation of hepatic gluconeogenesis through the induction of key gluconeogenic genes, including phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase).[20,38–40] Overexpression of ERRγ in the liver induced gluconeogenic gene expression and increased fasting blood glucose levels, resulting in delayed glucose clearance during glucose tolerance tests without significant changes in plasma levels of insulin, triglycerides (TGs),

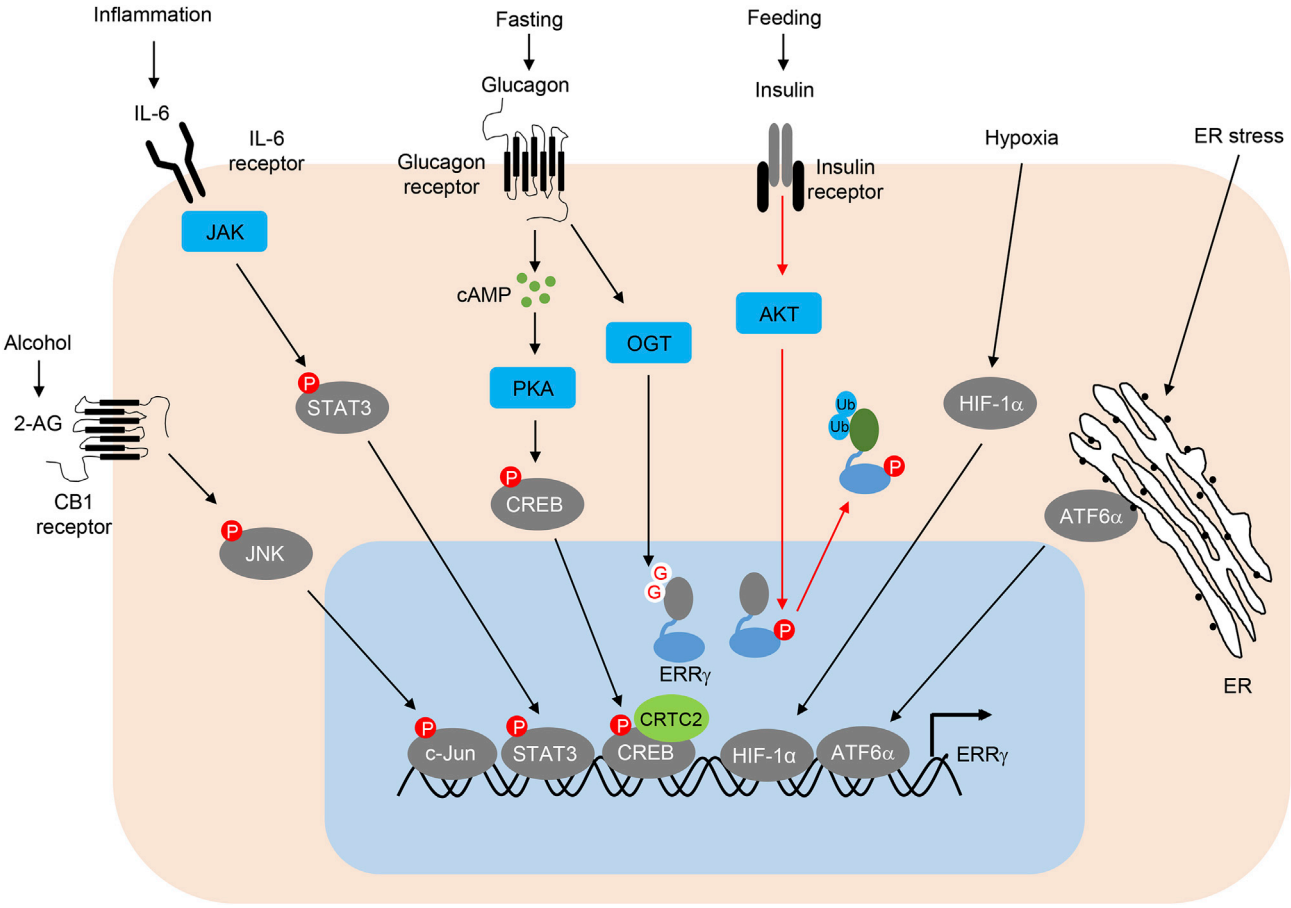

Fig. 2. Transcriptional regulation and post-translational modification of ERRγ by multiple endocrine and metabolic signals. In the fasting state, glucagon increases *ERRγ* gene expression through the activation of the CREB-CRTC2 pathway. Concomitantly, glucagon promotes the O-GlcNAcylation and stabilization of ERRγ through induction of O-GlcNAc transferase (OGT). In the fed state, however, insulin suppresses the transcriptional activity of ERRγ by promoting AKT-mediated phosphorylation of ERRγ at S179 and inducing the cytoplasmic translocation of nuclear ERRγ. Insulin also inhibits glucagon-induced O-GlcNAcylation of ERRγ, which results in ubiquitin-mediated protein degradation. Chronic alcohol consumption induces 2-AG, which binds to the CB1 receptor and promotes JNK activity, which in turn increases c-Jun occupancy at the AP-1 site on the ERRγ promoter and induces its expression. The pro-inflammatory cytokine IL-6 binds to its receptor and activates the JAK2-STAT3 pathway upon bacterial infection. Subsequently, activated STAT3 induces *ERRγ* gene expression by directly binding to the ERRγ promoter. In response to hypoxia, HIF-1α directly upregulates ERRγ transcription. ER stress is also a major transcriptional regulator of ERRγ. ER stress-mediated activation of ATF6α positively regulates *ERRγ* gene expression. Abbreviations: 2-AG, 2-arachidonyl glycerol; CB1, cannabinoid type 1; JNK, c-Jun N-terminal kinase; AP-1, activator protein 1; IL-6, interleukin-6; JAK, janus kinase; STAT3, signal transducer and activator of transcription 3; cAMP, 3′, 5′-cyclic adenosine monophosphate; PKA, protein kinase A; AKT, protein kinase B; CREB, cAMP response element-binding protein; CRTC2, CREB regulated transcription coactivator 2; HIF-1α, hypoxia-inducible factor-1α; ER, endoplasmic reticulum; ATF6α, activating transcription factor 6α; ERRγ, estrogen-related receptor γ; P, phosphate; G, glycosylation; Ub, ubiquitin. Black arrows indicate activating pathways. Red arrows indicate inhibitory pathways.

or fatty acids.[40] Therefore, an upregulation of hepatic ERRγ activity could contribute to the systemic hyperglycemia and insulin resistance in diabetes. Consistent with these findings, ablation of hepatic ERRγ mRNA reduced *PEPCK* and *G6Pase* gene expression and ameliorated fasting hyperglycemia and glucose intolerance in *db/db* and DIO mice.[40] Importantly, *db/db* and DIO mice administered GSK5182, an ERRγ-selective inverse agonist, displayed lower gluconeogenic gene expression, hyperglycemia, food intake, body weight, and hepatic fat accumulation. Therefore, the selective control of ERRγ-dependent gluconeogenesis in the liver could be considered as a novel therapeutic approach to ameliorate hyperglycemia and insulin resistance in T2DM.

3.2. Alcohol metabolism and liver injury

The role of ERRγ in the liver is not confined to the regulation of glucose metabolism; it is also involved in alcohol metabolism. Alcohol is metabolized into acetaldehyde in the liver through two major enzymes, alcohol dehydrogenase and the microsomal enzyme cytochrome P450 2E1 (CYP2E1).[41–43] Although CYP2E1 increases the capacity of the liver to oxidize alcohol after chronic alcohol consumption, it also results in the generation of reactive oxygen species (ROS), causing liver damage that can ultimately result in alcoholic liver disease. Indeed, a number of studies have shown that CYP2E1 is a major contributor to the pathogenesis of liver disease caused by alcohol abuse.[42,44,45] ERRγ has been reported to be involved in alcohol metabolism through the transcriptional regulation of CYP2E1 expression. Hepatic *ERRγ* gene expression is induced by 2-arachidonyl glycerol (2-AG), an endocannabinoid that is produced in hepatic stellate cells in response to chronic alcohol exposure.[46,47] Binding of 2-AG to the G-protein-coupled receptor cannabinoid type 1 (CB1) receptor activates c-Jun N-terminal kinase (JNK), resulting in the activation of c-Jun, which in turn induces ERRγ expression via the activator protein (AP)-1 site on the ERRγ promoter.[46] Moreover, alcohol-induced ERRγ expression is nearly abolished in *CB1* knockout mice, suggesting that ERRγ is a key downstream effector of the CB1 receptor.

The induction of ERRγ expression by alcohol is linked to enhanced oxidative stress and liver damage. Hepatic overexpression of ERRγ significantly induces CYP2E1 expression through its binding to an ERRE in the CYP2E1 promoter.[46] Interestingly, the regulation of hepatic CYP2E1 by ERRγ is ERRγ-specific. As a result, CYP2E1-mediated generation of ROS, such as hydrogen peroxide and 4-hydroxynonenal, is elevated in the liver, leading to mitochondrial damage and apoptotic cell death. Importantly, systemic treatment with GSK5182 normalizes alcohol-induced CYP2E1 expression, ROS generation, and apoptotic cell death in the livers of mice chronically exposed to alcohol, as effectively as the CYP2E1 inhibitor chlormethiazole.[46,48,49] These observations suggest that an ERRγ inverse agonist could ameliorate oxidative liver injury due to chronic alcohol exposure. Furthermore, recent findings showed that the CB1 receptor contributes to the pathogenesis of a variety of metabolic diseases, such as diabetes and diabetic microvascular and cardiovascular complications.[50] This emerging evidence implies that ERRγ could have the ability to regulate other CB1-mediated metabolic diseases, further raising hopes for the therapeutic potential of ERRγ inverse agonists. Therefore, it is clearly essential to understand the specific contributions of ERRγ to liver metabolic functions in a variety of physiological states.

3.3. Bile acid metabolism and cell signaling

In addition to the role of ERRγ in regulating glucose and alcohol metabolism, it also regulates hepatic cholesterol metabolism through the induction of cholesterol 7-hydroxylase (CYP7A1), a rate-limiting enzyme in bile acid biosynthesis.[21] CYP7A1 expression is tightly regulated by several NRs, including liver-related homolog-1 (LRH-1), HNF4α, and chicken ovalbumin upstream promoter transcription factor 2 (COUP-TFII), as well as by the NR coactivator PGC-1α.[51] Farnesoid X receptor (FXR), LRH-1, and SHP participate in a negative feedback loop to repress CYP7A1 activity.[52] In response to bile acids, FXR promotes SHP expression, and SHP in turn negatively interacts with LRH-1 and HNF4α to inhibit *CYP7A1* gene transcription. CYP7A1-mediated bile acid synthesis displays a circadian rhythm, which is regulated by fasting and re-feeding, as well as nutrient status, and plays a key role in maintaining cholesterol homeostasis.[53,54] Interestingly, recent studies showed that the activation of CB1 receptor signaling by alcohol involves CYP7A1-induced bile acid synthesis.[21,55] ERRγ induced by 2-AG directly binds to ERREs on the CYP7A1 promoter, which results in the induction of bile acid synthesis both *in vitro* and *in vivo*. The NR corepressor SHP also inhibits the transcriptional activity of ERRγ on the CYP7A1 promoter. Given the ability of ERRγ to induce SHP expression, ERRγ could also be involved in the feedback repression of bile acid homeostasis.[12] Importantly, GSK5182 significantly reduces CB1 receptor-induced CYP7A1 expression and bile acid synthesis *in vivo* through the inhibition of ERRγ activity, suggesting that an ERRγ-selective inverse agonist would dramatically normalize alcohol-mediated perturbation of bile acid homeostasis.

3.4. Lipid metabolism and insulin signaling

ERRγ is also involved in hepatic lipid metabolism through the induction of lipin-1, a mammalian Mg^{2+}-dependent phosphatidic acid phosphatase (PAP) type 1. Lipin-1 plays a key role in catalyzing the conversion of phosphatidate to diacylglycerol (DAG), a direct precursor of TGs and phospholipids.[56,57] Interestingly, DAG, a second messenger in signaling cascades, activates protein kinase C (PKC) ε, indicating a link between lipid accumulation and insulin signaling in the liver.[58] In addition, the PAP activity of lipin-1 results in impaired insulin receptor signaling in the liver through DAG-induced PKCε activity in mice.[59,60] ERRγ upregulates hepatic lipin-1 expression through direct binding to an ERRE in its promoter. PGC-1α potentiates the transcriptional activity of ERRγ, while SHP counteracts the stimulatory effect of PGC-1α.[19] Systemic overexpression of ERRγ increased lipin-1 expression and DAG levels in the livers of mice, resulting in PKCε activation and therefore impaired insulin receptor signaling. Consistent with these observations, GSK5182 reduced lipin-1-mediated DAG synthesis and normalized the PKCε-mediated impairment in hepatic insulin signaling.[19] Therefore, GSK5182 may contribute to the normalization of glucose status, not only by improving hepatic insulin signaling, but also by improving hyperglycemia in diabetic mice.

3.5. Iron metabolism and bacterial infection

The hepatic peptide hormone hepcidin plays a critical role in systemic iron homeostasis by binding to and degrading ferroportin, an iron exporter expressed on the surface of macrophages, resulting in less iron export from these cells.[61,62] Hepcidin is expressed in hepatocytes in response to pro-inflammatory stimuli that are upregulated during bacterial infection, such as interleukin-6 (IL-6), leading to a reduction in serum iron levels. Importantly, the resultant hypoferremia and elevation in intramacrophage iron content promote the intracellular growth of bacteria such as *Salmonella enterica var. Typhimurium* (*S. typhimurium*), suggesting that this response, which is part of the innate immune response to protect the host from bacterial infection, is instead beneficial to the bacteria.[63–65] In the liver, ERRγ controls proliferation of intramacrophage bacteria through hepcidin-mediated regulation of host

iron metabolism, and its inverse agonist GSK5182 has an antimicrobial effect on intracellular bacteria, resulting in improved host survival.[66] In response to *S. typhimurium* infection, IL-6 activates janus kinase (JAK) 2-signal transducer and activator of transcription 3 (STAT3) signaling in hepatocytes, which in turn induces ERRγ expression through a conserved STAT3-binding site on the *ERRγ* gene promoter.[66] The *hepcidin* gene promoter possesses a conserved ERRE, which is crucial for responding to *S. typhimurium* infection. Of note, GSK5182 could control the intracellular growth of multidrug-resistant bacteria by altering host iron metabolism, although additional studies are needed to ascertain its clinical potential as an antimicrobial agent.[66] Interestingly, hepcidin expression is regulated by glucagon, a gluconeogenic signal, during prolonged starvation.[67] Given the role of ERRγ in hepatic gluconeogenesis, as described in Section 3.1, these observations suggest that ERRγ may mediate a link between glucose metabolism and iron metabolism through the regulation of hepcidin expression.

3.6. Hypoxia, endoplasmic reticulum (ER) stress, and hyperglycemia

ERRγ may contribute to glucose metabolism through transcriptional regulation of genes in response to different metabolic signals. For example, in hepatocytes, hypoxia increases ERRγ expression through the activation of hypoxia-inducible factor-1 (HIF-1) α, and thereby promotes pyruvate dehydrogenase kinase isozyme 4 (PDK4) expression.[68] PDK4 is reported to contribute to the maintenance of normal blood glucose during starvation by inhibiting the activity of pyruvate dehydrogenase complex (PDC), which converts pyruvate into acetyl-CoA.[68–70] Furthermore, PDK4 expression induced in T2DM promotes hepatic gluconeogenesis through inactivation of PDC, and consequently contributes to hyperglycemia and insulin resistance.[71,72] Interestingly, hypoxia also induces PEPCK expression by activating HIF-1α signaling, leading to hepatic glucose production.[73] These findings imply that ERRγ plays a major role in hypoxia-mediated regulation of hepatic glucose metabolism. In addition, considering the ability of GSK5182 to restrict hypoxia-induced PDK4 expression, an ERRγ inverse agonist may prove useful in the amelioration of hypoxia-induced hyperglycemia and insulin resistance.[68]

In addition to the role of ERRγ in hypoxia, it has also been linked to ER stress signals that regulate metabolism in response to cellular stress. ERRγ upregulates the expression of ER-bound transcription factors, such as activating transcription factor 6α (ATF6α) and cAMP-responsive element-binding protein 3-like protein 3 (CREBH), and this activity is inhibited by GSK5182.[74,75] It is reported that CREBH expression is significantly induced during fasting in mice in a glucocorticoid- and PGC-1α-dependent manner.[76] In addition, CB1 receptor signaling is also involved in CREBH-dependent induction of hepatic gluconeogenesis in primary rat and human hepatocytes.[77] Hepatic CREBH expression increased hepatic glucose production and fasting hyperglycemia by inducing gluconeogenesis.[76] Interestingly, ER stress induces ERRγ expression in hepatocytes by activating ATF6α, suggesting the existence of a positive feedback loop between ER stress signals and ERRγ that contributes to ERRγ-mediated hyperglycemia.

3.7. Secreted proteins and liver metabolism

The finding that ERRγ is induced by 2-AG, as described in Section 3.2, has revealed insights into the cellular context of ERRγ function and suggested a role for ERRγ in CB1 receptor signaling. Indeed, the activation of CB1 receptor by arachidonyl-2′-choroethylamide (ACEA), a CB1 receptor-specific agonist, induces fibroblast growth factor (FGF) 21, an inducible hepatokine, through the induction of ERRγ expression.[22] FGF21 is reported to act as an endocrine factor because it lacks heparin-binding domains.[78] FGF21 released into the circulation acts as a potential metabolic regulator of glucose and lipid metabolism through cell surface FGF receptors complexed with β-Klotho, which is abundantly expressed in metabolic tissues. In the liver, FGF21 expression induced by prolonged starvation promotes PGC-1α expression and stimulates hepatic gluconeogenesis, fatty acid oxidation, and ketogenesis,[79] suggesting that the metabolic functions of FGF21 in the liver are mediated in part through PGC-1α, an ERRγ coactivator. ERRγ increases *FGF21* gene expression by binding to a putative ERRγ-binding motif in the *FGF21* gene promoter.[22] By contrast, ectopic knockdown of hepatic ERRγ attenuates the induction of FGF21 expression by ACEA. Similarly, GSK5182 strongly suppresses ACEA- and alcohol-mediated FGF21 secretion in mice.[22] These findings suggest that ERRγ, as a key transcriptional regulator of the CB1 receptor, plays a crucial role in linking CB1 receptor signaling to the metabolic actions of FGF21.

In addition to the ability of ERRγ to regulate FGF21 expression, it also positively regulates the expression of fibrinogen, a plasma glycoprotein produced in the liver. Fibrinogen consists of two sets of three different peptide chains (an Aα chain, a Bβ chain, and a γ chain (encoded by *fibrinogen Aα* (*FGA*), *fibrinogen Bβ* (*FGB*), and *fibrinogen γ* (*FGG*), respectively)) connected by disulfide bridges.[80] Fibrinogen, which is primarily regulated at the transcriptional level by IL-6 and glucocorticoids, plays a key role in many stages of wound healing, including hemostasis, inflammation, and tissue fibroblast proliferation and maturation.[80] In addition, the upregulation of fibrinogen in obesity and insulin resistance is implicated in hyperfibrinogenemia, which is implicated in cardiovascular disease (CVD), suggesting that control of fibrinogen expression could provide a therapeutic approach to the treatment of CVD.[81,82] Interestingly, our group found that gene expression of *ERRγ* and *fibrinogen*, as well as serum levels of fibrinogen, are significantly increased in the livers of patients with non-alcoholic steatohepatitis.[83] In addition, ERRγ upregulates *fibrinogen* gene transcription by binding to a conserved ERRE on the *FGG* gene promoter in both cultured mice and human hepatocytes.[83,84] The regulation of fibrinogen expression by ERRγ is fundamentally associated with CB1 receptor signaling in hepatocytes. ERRγ and fibrinogen expression in the liver was upregulated in wild-type mice, but not in *CB1* knockout mice, when they were fed a high-fat diet (HFD).[84] Surprisingly, GSK5182 attenuated hepatic expression of fibrinogen in both ACEA-treated and HFD-fed wild-type mice, indicating that the inhibition of fibrinogen expression by an inverse agonist of ERRγ contribute to the amelioration of hyperfibrinogenemia, a CVD risk factor.

4. Conclusions

Recent progress in our understanding of the ligand-independent activity of ERRγ suggests that this receptor is an inducible transcription factor that functions as a downstream mediator of endocrine and metabolic signals, such as glucagon, insulin, and endocannabinoids (Fig. 2). Moreover, the transcriptional activity of ERRγ is tightly regulated by co-regulators and post-translational modifications. As a result, ERRγ directly or indirectly regulates the expression of key metabolic enzymes and major hormones in the liver, leading to diverse metabolic outcomes. Considering the pleiotropic roles of ERRγ in different physiological and pathophysiological conditions in the liver, targeting ERRγ might provide a therapeutic approach for ERRγ-mediated metabolic diseases (Table 1). Future studies aimed at characterizing its endogenous ligand would further bolster our understanding of its function, provide us with necessary experimental tools, and facilitate the development of additional

Table 1
ERRγ target genes, their physiological effects, and their roles in metabolic diseases.

Genes	Metabolic pathways	Physiological effects	Diseases	References
FGF21	–	–	–	22
Fibrinogen (*FGA*, *FGB*, *FGG*)	–	Blood fibrinogen ↑	Hyperfibrinogenemia ↑	83,84
CYP2E1	Alcohol metabolism	ROS ↑	Liver injury ↑	46
CYP7A1	Cholesterol metabolism	Bile acid synthesis ↑	–	21
ATF6α	ER stress	–	–	74,75
CREBH (*CREB3L3*)				
G6PC, *PCK1*	Glucose metabolism	Gluconeogenesis ↑, blood glucose ↑	Hyperglycemia ↑, insulin resistance↑	20,38-40
PDK4		–	–	68,69
Hepcidin (*HAMP*)	Iron metabolism	Macrophage iron ↑	Bacterial infection ↑	66
Lipin-1 (*LPIN1*)	Lipid metabolism	DAG ↑, insulin signaling ↓	Insulin resistance ↑	19

therapeutic strategies for the treatment of metabolic disorders related to the activity of ERRγ.

Regulation of the target genes shown here was determined by quantitative polymerase chain reaction, western blot analysis, or promoter studies. ↑: upregulation, ↓: downregulation. Abbreviations: FGF21, fibroblast growth factor 21; FGA, fibrinogen Aα; FGB, fibrinogen Bβ; FGG, fibrinogen γ; CYP2E1, cytochrome P450 2E1; CYP7A1, cytochrome P450 7A1; ATF6α, activating transcription factor 6α; CREBH, 3′, 5′-cyclic adenosine monophosphate-responsive element-binding protein 3-like protein 3; G6PC, glucose-6-phosphatase; PCK1, phosphoenolpyruvate carboxykinase 1; PDK4, pyruvate dehydrogenase kinase isozyme 4; ROS, reactive oxygen species; DAG, diacylglycerol.

Authors' contributions

D.-K. Kim wrote the manuscript and designed figures and table. H.-S. Choi wrote, designed and edited the manuscript, figures and table.

Conflict of interest

The authors declare that they have no conflict of interest.

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