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The Pathological Mechanisms of Estrogen-Induced Cholestasis: Current Perspectives

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Estrogens are steroid hormones with a wide range of biological activities. The excess of estrogens can lead to decreased bile flow, toxic bile acid (BA) accumulation, subsequently causing intrahepatic cholestasis. Estrogen-induced cholestasis (EIC) may have increased incidence during pregnancy, and within women taking oral contraception and postmenopausal hormone replacement therapy, and result in liver injury, preterm birth, meconium-stained amniotic fluid, and intrauterine fetal death in pregnant women. The main pathogenic mechanisms of EIC may include deregulation of BA synthetic or metabolic enzymes, and BA transporters. In addition, impaired cell membrane fluidity, inflammatory responses and change of hepatocyte tight junctions are also involved in the pathogenesis of EIC. In this article, we review the role of estrogens in intrahepatic cholestasis, and outlined the mechanisms of EIC, providing a greater understanding of this disease.
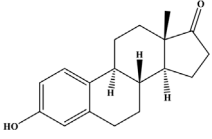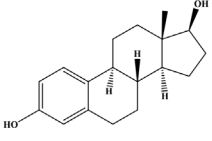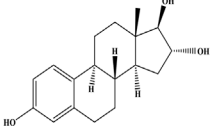
Keywords: estrogens, bile acid homeostasis, transporter, membrane fluidity, inflammation, intrahepatic cholestasis

INTRODUCTION

Estrogens are steroid hormones, including several entities, mainly estrone, estriol, 17α-ethinyl estradiol (EE) and the biologically active metabolite 17β-estradiol (E2) (Chen et al., 2019). Estrogens play important roles in cardiovascular system, central nervous system and reproductive system, and participate in the regulation of cholesterol mobilization, electrolyte balance, brain function (Chen et al., 2019). Importantly, estrogens and their metabolites can cause cholestasis in pregnant women and premenopausal women who receive oral contraceptive or use hormone replacement therapy, especially in susceptible people (Schreiber and Simon, 1983; Meier et al., 2008; Pan and Jeong, 2015). In the second or third trimester of sensitive pregnant women, estrogen-induced cholestasis (EIC) is a pregnancy-specific disease with incidence varying between 0.2 and 5.6% and is closely related to the ethnicity and geographic location (Liu and He, 2011; Williamson and Geenes, 2014; Smith and Rood, 2020). In pregnant women, the disease can increase the risk of adverse perinatal outcomes such as preterm birth, meconium-stained amniotic fluid and intrauterine fetal death (Bicocca et al., 2018; Mor et al., 2020). However, there is no specific medicine for clinical treatment of EIC, and the main focus is to protect the liver and reduce cholic acid, so as to improve the clinical pregnancy outcome.

The pathogenesis of EIC is not fully understood. Up to now, bile acid (BA) homeostasis disorder, inflammatory responses, impaired cell membrane fluidity and change of hepatocyte tight junctions are supposed to take part in the development of EIC (Carreras et al., 2007; Mottino et al., 2007; Pan and Jeong, 2015; Xu et al., 2017; El-Hawary et al., 2019; Xiang et al., 2019). Estrogens can induce acute cholestasis by impairing the synthesis, metabolism and transport of bile acids, causing downstream dysfunction of BA homeostasis and a decrease in bile flow (Brouwers et al., 2015; Rezai et al., 2015;

TABLE 1 | Structures and properties of the estrogens.

Chemical	Structure	Molecular weight	Relative estrogenic activity (yes bioassay)
Estrone (E1)		272.39	0.20
Estradiol (E2)		270.37	1.00
Estriol (E3)		288.39	0.01

Yang et al., 2020). Accordingly, in EIC, accumulated bile acids in the liver can induce oxidative stress and inflammatory reactions, further causing liver injury (Petr et al., 2014). In addition, serum total BAs, total bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP) and aspartate aminotransferase (AST) levels increase in patients with EIC, while total cholesterol levels decrease (Chen et al., 2013; Zhou et al., 2016; Li et al., 2017). In this review, we summarized the main pathological mechanisms of EIC, aiming to provide an important theoretical basis for clinical management of EIC.

ESTROGENS

Estrogens are steroid hormones. Three main forms of physiological estrogens, estrone (E1), estradiol (E2, or 17β-estradiol), and estriol (E3) are derived from cholesterol (Conroy et al., 2007; Cui et al., 2013). E2 is the primary reproductive hormone synthesized in the ovary under the stimulation of the follicular stimulating hormone and the luteinizing hormone. E1 and E3 are mostly synthesized in the liver from E2 (Hsu et al., 2017). In terms of estrogenic effect, the most potent and dominant estrogen in humans is E2, with 10-fold more potent than E1 and about 80-fold more potent than E3 (Chung et al., 2010; Gambino et al., 2012; Liu et al., 2018). The structures and properties of these three estrogens are shown in **Table 1**.

Estrogens mediate physiological effects by binding to specific estrogen receptors (ER): estrogen receptor α (ERα), estrogen receptor β (ERβ) and G protein-coupled estrogen receptor 1 (GPER1, also known as GPR30), which are encoded by different genes (Gustafsson, 2003; Nair and Sachdeva, 2018). ERα is predominant receptor. ERβ and GPR30 have also been reported, but there are few studies of them and need to be further explored.

Estrogens can interact with intracellular estrogen receptors to exert direct effects by binding to target genes (Freedman and Luisi, 1993). Alternatively, estrogens can activate intracellular signaling cascades via interaction with estrogen receptors (Yasar et al., 2017). Through the above-mentioned ways, estrogens exert a vast range of biological effects in the cardiovascular, musculoskeletal, metabolism, immune, central nervous and reproductive systems (Heldring et al., 2007).

The Susceptibility of EIC

Our current understanding of EIC during pregnancy is that the elevated levels of estrogens unmask genetic susceptibility in some women, resulting in cholestasis and elevated serum bile acids (Dixon and Williamson, 2016). Clinical studies have found that the susceptibility to cholestasis during pregnancy is associated with heritage, environment and diet (Meier et al., 2008; Pauli-Magnus et al., 2010). The mutations of the hepatobiliary transporter genes, especially bile salt export pump (BSEP), multidrug resistance protein 3 (MDR3) and multidrug-resistance-associated protein 2 (MRP2), can increase the susceptibility to EIC (Sookoian et al., 2008; Anzivino et al., 2013). In addition, the lack of selenium (Se) in the diet may affect the susceptibility to EIC (Kauppila et al., 1987; Reyes et al., 2000). However, the lack of correlation between Se plasma levels and the clinical and biochemical feature of the disease suggests that the role of selenium in the pathogenesis of EIC may be indirect. It is likely that this susceptibility of EIC increases further following the onset of cholestasis.

PATHOPHYSIOLOGICAL MECHANISMS OF EIC

Disturbance of BA Homeostasis

The concentration of BAs in cells and tissues is kept within a certain range under the fine regulation of the normal body functions. This plays an important role in maintaining of the physiological functions of the liver and intestine (Yang et al., 2017; Yang et al., 2019). Bile acids are mainly composed of free and conjugated bile acids (**Figure 1**), free bile acids: cholic acid (CA), deoxycholic acid (DCA), chenodeoxycholic acid (CDCA) and lithocholic acid (LCA); conjugated bile acids: glycocholic acid (GCA), glycine chenodeoxycholic acid (GCDCA), taurocholic acid (TCA), taurohyodeoxycholic acid (THDCA), and glyuroursodeoxycholic acid (GUDCA), etc.(Carulli et al., 1990). Among them, CA, DCA, CDCA, GCDCA and LCA are hydrophobic bile acids, which can damage hepatocytes. BA homeostasis is tightly related to the process of BA synthesis, metabolism, and transport (Trauner et al., 2017).

Estrogens can reduce the influx and efflux of BA in hepatocytes, resulting in a decrease in bile flow (Yamamoto et al., 2006). Estrogens can also cause abnormal BA compositions, bile obstruction and accumulation of BA, leading to liver toxicity (Yamamoto et al., 2006; Pan and Jeong, 2015; El-Hawary et al., 2019; Dixon and Williamson, 2016). Patients with EIC were associated with a rise in conjugated primary bile acids, particularly the tauroconjugates of CA and CDCA (**Table 2**) (Tribe et al., 2010). In EIC rats, the
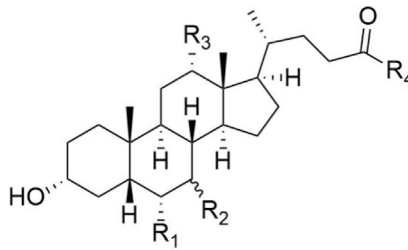
Bile acids	Name	R1	R2	R3	R4
Free bile acids	CA	H	α-OH	OH	OH
	DCA	H	H	OH	OH
	CDCA	H	α-OH	H	OH
	LCA	H	H	H	OH
Conjugated bile acids	GCA	H	α-OH	OH	$NHCH_2COOH$
	GCDCA	H	OH	H	$NHCH_2COOH$
	TCA	H	α-OH	OH	$NHCH_2CH_2SO_3H$
	THDCA	OH	H	H	$NHCH_2CH_2SO_3H$
	GUDCA	H	OH	H	$NHCH_2COOH$

FIGURE 1 | The chemical structure and compositions of BA.

TABLE 2 | The change of BA compositions in patients and rats with EIC.

Species	BA compositions	References
Human	CA ↑, CDCA ↑	Tribe et al. (2010)
Rat	TCA ↑, DCA ↑, TUDCA ↑	Dong et al. (2019)
Rat	TCA ↑, GCA ↓, CA ↑, GUDCA ↓, DCA ↑, GDCA ↓, THDCA ↑	Yang et al. (2020)

hepatic concentration of TCA, DCA and TUDCA was increased, and the level of GCA, GDCA and GUDCA was decreased (**Table 2**) (Dong et al., 2019; Yang et al., 2020), that resulted in hepatocytes apoptosis and lead to liver damage. Decreases in bile flow and BA homeostasis disturbance by estrogens, have been demonstrated to be related to the disorder of BA enzymes and transporters systems (Henriquez-Hernandez et al., 2007; Meng et al., 2015).
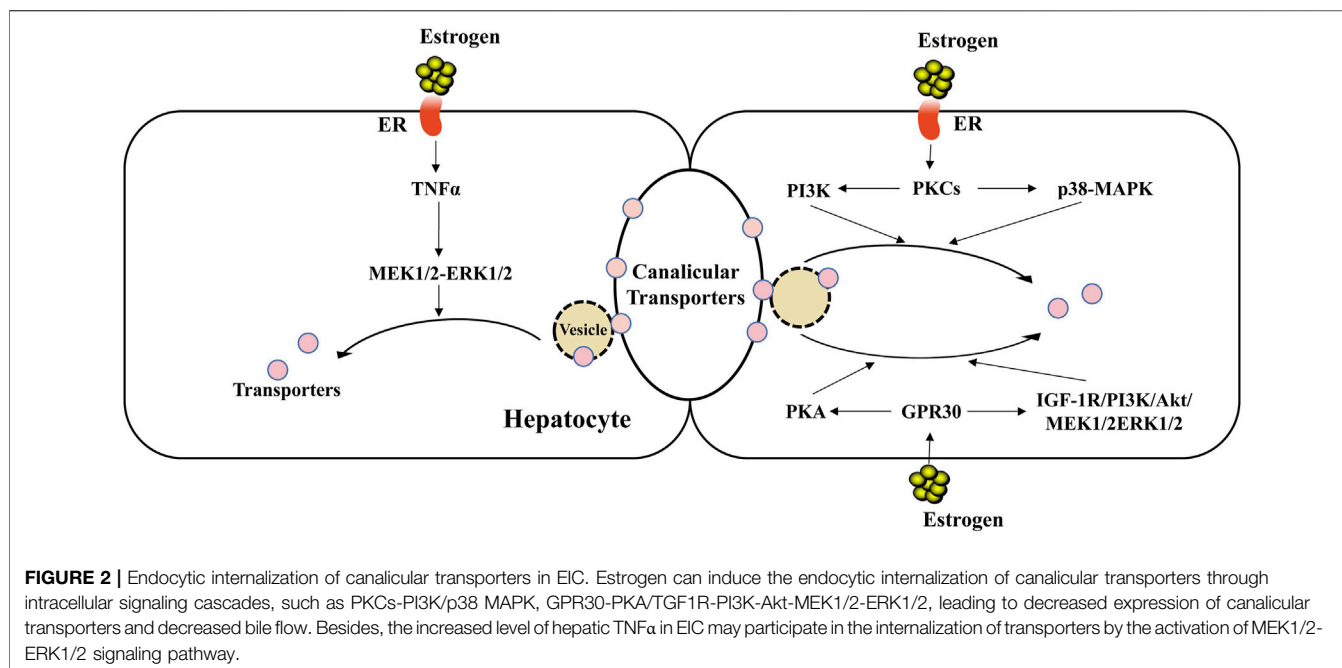
BA Synthesis and Metabolism in EIC
Estrogens emerge as important regulators of BA synthesis and metabolism through the hepatic feedback mechanisms (Phelps et al., 2019). Bile acids are synthesized from the oxidation of cholesterol in hepatocytes. Cholesterol hydroxylase enzymes play important roles in this process. Above all, three main cholesterol hydroxylase enzymes: cholesterol 7α-hydroxylase (CYP7A1), sterol 12α-hydroxylase (CYP8B1) and sterol 27-hydroxylase (CYP27A1) (Li and Dawson, 2019; Liu and Wang, 2019) are involved in BA synthesis. Studies have found that estrogens can

increase the activity CYP7A1, CYP8B1 and CYP27A1, along with small transient increases in BA production (Davis et al., 1986; Chico et al., 1996; Yang et al., 2020). In addition, estrogens can inhibit the expression of BA metabolic enzymes, especially phase II enzymes (such as hydroxysteroid sulfotransferase 2a1, Sult2a1), which in turn decreases the metabolism of bile acids, leading to an increased levels of unconjugated and hydrophobic bile acids in hepatocyte, and a decrease in bile flow (Zamek-Gliszczynski et al., 2006; Zollner and Trauner, 2006; Wang et al., 2019).

BA Transporters in EIC
High levels of circulating estrogens are associated with the inhibition of BA transporters in cholestasis (Phelps et al., 2019). The transport of BA depends on hepatic transporters, mainly including ATP-binding cassette (ABC) and solute carrier family (SLC) transporters. ABC transporters can mediate diverse ATP-driven transport processes, mainly including BSEP, MRP2, P-glycoprotein (P-gp/MDR1) ect., (Thoeni et al., 2019). SLC transporters mainly include Na^+-taurocholate co-transport polypeptide (NTCP), organic anion transporter polypeptides (OATPs) (Beaudoin et al., 2020). Among them, BSEP and MRP2 are the main two BA transporters. Estrogen diminished the transport of BA by down-regulation of these hepatic transporters. Several studies have indicated that a decreased canalicular ATP-dependent BA transport capacity is primarily responsible for the estrogen-induced impairment of BA secretion in the intact liver, resulting in decreased bile flow and increased serum BA and bilirubin (Stieger et al., 2000; Muchova et al.,

FIGURE 2 | Endocytic internalization of canalicular transporters in EIC. Estrogen can induce the endocytic internalization of canalicular transporters through intracellular signaling cascades, such as PKCs-PI3K/p38 MAPK, GPR30-PKA/TGF1R-PI3K-Akt-MEK1/2-ERK1/2, leading to decreased expression of canalicular transporters and decreased bile flow. Besides, the increased level of hepatic TNFα in EIC may participate in the internalization of transporters by the activation of MEK1/2-ERK1/2 signaling pathway.

2015). Estrogens or their metabolites, such as estradiol-17β-D-glucuronic acid ($E_2$17G), also impair the expression and function of hepatocyte efflux transporters (BSEP, MRP2, MDR) (Bossard et al., 1993; Stieger et al., 2000; Crocenzi et al., 2001; Yamamoto et al., 2006; Di Guida et al., 2018; Liu et al., 2018). Previous studies have shown that estrogens *trans*-repress BSEP through diminishing peroxisome proliferator-activated receptor-γ (PPARγ) coactivator-1 recruitment (Chen et al., 2015). Moreover, estrogens decrease the expression of multi-drug resistant 2 (MDR2), which causes bile formation disorders (Schreiber and Simon, 1983; Liu et al., 2018). However, Huang et al. found that direct inhibition of BSEP-mediated bile acids transport is not the mechanism for $E_2$17G-induced cholestasis, and the process of MRP2-mediated transport is essential for its induction of cholestasis (Huang et al., 2000). Thus, the abnormal expression and function of BA transporters play an important role in the pathogenesis of EIC. However, different estrogens and their metabolites have different effects on the functions of different transporters, and the internal mechanism still needs further study to clarify.
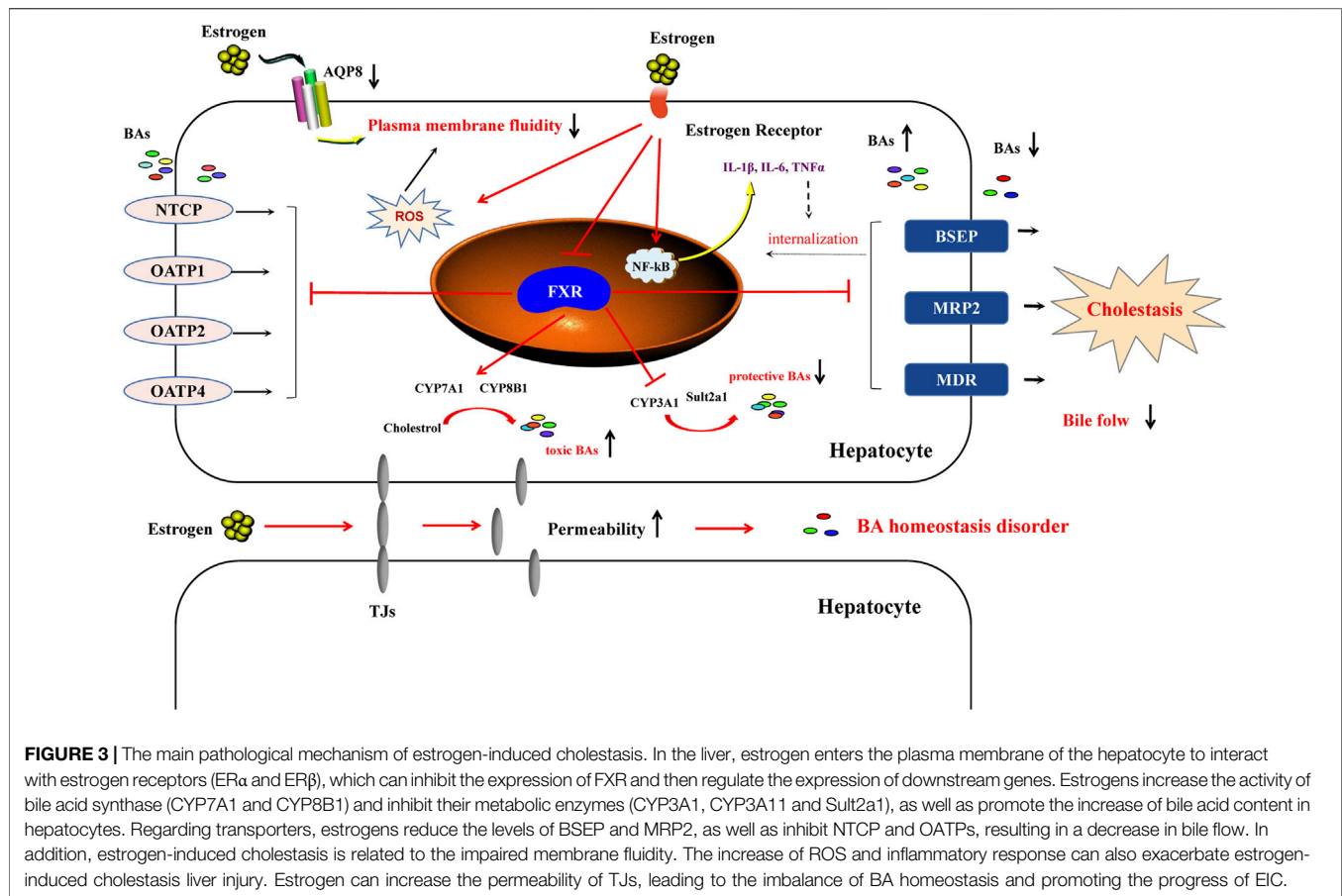
As one of the most important BA sensors in maintaining BA homeostasis, nuclear receptor, farnasol X receptor (FXR) regulates the levels of hepatic transporters to affect BA homeostasis. Estrogens and their metabolites can inhibit the expression of FXR, which decreases the expression of BA transporters in the canalicular membranes of the liver (Wang et al., 2019). This can cause retention of bile acids in hepatocytes and alters the compositions of BA, which subsequently leads to cholestatic liver injury (Lee et al., 2000; Stieger et al., 2000).

In addition, studies have found that cholestasis induced by $E_2$17G is related to internalization of the canalicular transporters such as BSEP and MRP2 (**Figure 2**), which is relevant to bile secretion (Crocenzi et al., 2003; Majer et al., 2007; Miszczuk et al.,

2018). Miszczuk, G. S. et al. (Miszczuk et al., 2018) have shown that in $E_2$17G-induced cholestasis, the canalicular transporters BSEP and MRP2 undergo exacerbated endocytic internalization caused by a shift of transporters from the caveolin-enriched plasma membrane microdomains (rafts) to the clathrin-enriched ones (non-rafts), resulting in a decrease in the transport activity of them and bile flow.

Estrogens can involve in the endocytosis and internalization of the hepatic transporters through intracellular signaling cascades in EIC. Previous works demonstrated that $E_2$17G reduces the expressions of transporters on the membrane through the activation of different signaling proteins to cause their insertion (Mottino et al., 2002; Mottino et al., 2005; Crocenzi et al., 2008). Up to now, there are lots of evidence demonstrated that the protein kinase C (PKC), ERα, p38-MAPK, epidermal growth factor receptor (EGFR) and Src are involved in the endocytosis and internalization of canalicular transporters in EIC (Crocenzi et al., 2008; Boaglio et al., 2012; Andermatten et al., 2019). In the other hand, $E_2$17G activates two GPR30-related signal pathway branches: adenylyl cyclase/PKA and insulin-like growth factor receptor-1 (IGF-1R)-phosphoinositide 3 kinase (PI3K)-Akt-MEK1/2-ERK1/2 signaling pathways, which can participate in endocytic internalization of transporters (Crocenzi et al., 2008; Boaglio et al., 2010; Boaglio et al., 2012; Barosso et al., 2016). However, further studies should be required to assess the specific molecular mechanisms mediated by intracellular signaling cascades to impair the localization status of canalicular transporters in EIC.

Besides canalicular transporters, estrogens and their metabolites can also inhibit transporters in the sinusoidal membrane of the liver (Simon et al., 2004; Zhang et al., 2015). Long-term use of estrogens reduced the expression of NTCP and

FIGURE 3 | The main pathological mechanism of estrogen-induced cholestasis. In the liver, estrogen enters the plasma membrane of the hepatocyte to interact with estrogen receptors (ERα and ERβ), which can inhibit the expression of FXR and then regulate the expression of downstream genes. Estrogens increase the activity of bile acid synthase (CYP7A1 and CYP8B1) and inhibit their metabolic enzymes (CYP3A1, CYP3A11 and Sult2a1), as well as promote the increase of bile acid content in hepatocytes. Regarding transporters, estrogens reduce the levels of BSEP and MRP2, as well as inhibit NTCP and OATPs, resulting in a decrease in bile flow. In addition, estrogen-induced cholestasis is related to the impaired membrane fluidity. The increase of ROS and inflammatory response can also exacerbate estrogen-induced cholestasis liver injury. Estrogen can increase the permeability of TJs, leading to the imbalance of BA homeostasis and promoting the progress of EIC.

OATPs (Kouzuki et al., 2000). In EIC rats, all basolateral OATPs (1, 2 and 4) were specifically down-regulated on the protein level by 30–40% of the controls, but less pronounced than NTCP (70–80%) (Geier et al., 2003). Therefore, hepatic transporters play an important role in the pathogenesis of EIC.

Reducing Liver Cell Membrane Fluidity in EIC

The hepatocyte surface membrane plays a pivotal role in BA secretion and excretion (Miccio et al., 1989). EIC has been correlated with structural, biochemical, and physiological abnormalities in the hepatocyte membrane (Miccio et al., 1989; Reyes and Simon, 1993). Estrogens increase the membrane sphingomyelin content and alter the fatty acid composition of the phospholipids, which may be related to the formation of cholestasis (Smith and Gordon, 1988; Malherbe et al., 2020). Studies showed that estrogens can also increase cholesterol content in the cell membrane, resulting in a decrease in membrane fluidity. Also, reduced membrane fluidity may inhibit the movement of transporters on the membrane (Kovanen et al., 1979). Simon et al. found that the decrease in membrane fluidity reduced in bile flow, Na^+-K^+-ATPase activity, and the maximum transport rate of BSEP (Simon et al., 1980). In EIC rats, S-adenosylmethionine (SAMe) can increase membrane

fluidity and Na^+-K^+-ATPase activity, and partially reverse the decrease in bile flow induced by estrogen (Boelsterli et al., 1983). In addition, a defective aquaporin-8 (AQP8) expression in plasma membrane in EIC might be associated with an impairment of the transient osmotic gradients, inducing defective canalicular functional expression of solute transporters together with a reduced canalicular water permeability, and leading to bile secretory dysfunction (Carreras et al., 2007; Lehmann et al., 2008). However, membrane fluidity and Na^+-K^+-ATPase activity may be not the only mechanism that involves in the role of hepatocyte membrane in the decreased bile flow (Boelsterli et al., 1983). Bile salts do not cross a lipid membrane. The cholestatic effect may be also produced by an alteration of transporters that are less active in a rigid milieu or there could be an allosteric interaction between cholesterol and BSEP, which should be verified. Therefore, the relationship between membrane fluidity and bile flow has yet to be fully determined.

Oxidative Stress and Inflammatory Responses in EIC

Excess estrogens can induce oxidative stress (Diaz et al., 2019) and pro-inflammatory cytokine expression in liver (Martin-Millan and Castaneda, 2013). Study has shown that estrogens significantly decrease the content of steroid cyanide, peroxide and glutathione

(GSH) in liver cells, leading to the membrane lipid peroxidation and free radicals production, which in turn enhances the oxidative damage in EIC (Yu et al., 2016). Indeed, EIC rats show a massive oxidative stress and lipid peroxidation as evidenced by a significant drop in the hepatic GSH content and a subsequent increase in the hepatic thiobarbituric acid reactive substances (TBARS) levels (Chen et al., 2019). Besides, ROS may also cause several effects that could be implied in cholestasis, including canalicular transporter disinsertion (Ciriaci et al., 2019).

Rujuan Dai et al. (Dai et al., 2009) have revealed that *in vivo* massive estrogen exposure promotes inflammatory responses that include enhanced secretion of Th1 related cytokines (IFNγ, IL-12, IL-1β), inflammatory chemokines (MCP-1 and MCP-5), and induction of inducible nitric oxide synthase (iNOS) and cyclooxygenases-2 (Cox-2), leading to the liver damage. Estrogens lead to an obvious increase in hepatic tumor necrosis factor (TNF)-α and hepatic myeloperoxidase (MPO) levels in the liver tissues by 346 and 232%, respectively (Wadie et al., 2021). The increased level of hepatic TNFα can participate in the internalization of MRP2 by the activation of NADPH oxidase, ROS and MEK1/2-ERK1/2 signaling pathways (Ciriaci et al., 2019). Study has confirmed that the MEK-ERK signaling pathway involved in the endocytosis of MRP2 in EIC (Boaglio et al., 2012). This implies that TNFα/ROS/MEK-ERK pathway may also participate in the endocytosis of transporters in EIC (Dai et al., 2009). Besides, Bach1/Nrf2 pathway and NF-κB pathway may be also involved in liver inflammatory damage during EIC (Petrone et al., 2014; Muchova et al., 2015). Therefore, estrogens can induce oxidative stress and inflammation, promoting the progress of EIC.

Disrupted Hepatocyte Tight Junctions in EIC

Hepatocyte tight junctions (TJs) are composed of multiple proteins that are anchored directly or indirectly to the actin-based cytoskeleton (Chen et al., 2009). The integrity of TJs is of utmost importance for holding back diffusion of bile components from the canalicular to the blood. Estrogens can affect hepatocyte polarity and, in addition, disrupt TJs (Mottino et al., 2007; Chen et al., 2009). Estrogens can cause the deterioration of TJs, which

can cause disturbances in the osmotic gradient from bile to plasma and lead to the failure of the apical-basolateral diffusion barrier (Mottino et al., 2007; Zollner and Trauner, 2008).

CONCLUSION AND PERSPECTIVES

In conclusion, EIC is a complex pathological process. In-depth knowledge of the main pathological mechanisms is crucial to ensure clear understanding of EIC. Currently, the main pathological mechanisms include BA homeostasis dysfunction, poor liver cell membrane fluidity, oxidative stress, inflammatory responses, and change of hepatocyte tight junctions (**Figure 3**). These factors contribute to the accumulation of BAs in livers, which in turn results in cholestasis.

Despite the increasing attention to EIC, its pathological mechanism still need to be further explored. For instance, the influences of estrogens on the location and function of BA transporters during cholestasis have not been fully elucidated, which is critical for the development of potential therapeutic agents. Due to the complexity and change of EIC's etiology and complications, the response of existing treatment drugs (such as ursodeoxycholic acid) is not sensitive. Therefore, an in-depth understanding of the mechanisms of EIC will help to develop new drug targets.

AUTHOR CONTRIBUTIONS

DL was responsible for the integrity of the work as a whole. YZ and JY coordinated the manuscript and drafted the manuscript design. YZ participated in manuscript writing. CZ and DL contributed to reading and revision of the manuscript. All authors participated in manuscript review.

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