Regulatory long non-coding RNAs of hepatic stellate cells in liver fibrosis (Review)

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Abbreviations: AHF, alcoholic hepatic fibrosis; BDL, bile duct ligation; CCl4, carbon tetrachloride; ceRNA, competing endogenous RNA; DVL2, disheveled segment polarity protein 2; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; Fz, frizzled; HCC, hepatocellular carcinoma; HCs, hepatocytes; HCV, hepatitis C virus; Hey, Hes-related with YRPW motif; Hes, hairy-enhancer of split; Hh, Hedgehog; HOTAIR, homeobox transcript antisense RNA; HOTTIP, HOXA distal transcript antisense RNA; HpSCs, hepatic stem/progenitor cells; HSCs, hepatic stellate cells; LF, liver fibrosis; IncRNA, long non-coding RNA; IncRNA-ATB, IncRNA-activated by TGF-β; Inc-LFAR1, liver fibrosis-associated IncRNA1; lincRNA-p21, long intergenic non-coding RNA-p21; LPS, lipopolysaccharide; LRP, low-density lipoprotein receptor-related protein; MEG3, IncRNA-maternally expressed gene 3; MFs, myofibroblasts; miRNA, microRNA; MMP, matrix metalloproteinase; MRE, miRNA responsive element; NEAT1, encoding nuclear paraspeckle assembly transcript 1; PTCH, Patched; PVT1, plasmacytoma variant translocation 1; Sal B, salvianolic acid B; SMO, Smoothened; SNHG7, small nuclear RNA host gene 7; TIMP, tissue inhibitors of metalloproteinase; TGFβR, transforming growth factor-β receptor; TUG1, IncRNA taurine upregulated gene 1; USP4, ubiquitin-specific protease 4.

Key words: long non-coding RNAs, liver fibrosis, hepatic stellate cells involved in HSC activation, participate in the development of LF and are likely to be therapeutic targets for LF. In the present review, the cellular signaling pathways of LF with respect to HSCs were discussed. In particular, this present review highlighted the current knowledge on the role of lncRNAs in activating or inhibiting LF, revealing lncRNAs that are likely to be biomarkers or therapeutic targets for LF. Additional studies should be performed to elucidate the potential of lncRNAs in the diagnosis and prognosis of LF and to provide novel therapeutic approaches for the reversal of LF.

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1. Introduction

Liver fibrosis (LF) results from impaired wound healing caused by acute or chronic exposure to detrimental factors, including alcohol, viral diseases, drugs, cholestasis, toxins and metabolic disorders (1,2). Slight or transient fibrosis is necessary for wound healing and maintenance of tissue architecture integrity (3). Fibrosis is a reversible process that may be halted by removing the harmful stimulus (4,5). However, severe or advanced fibrosis is characterized by abnormal connective tissue hyperplasia and extracellular matrix (ECM) protein deposition (6), leading to liver structural destruction and even organ failure (7). The accumulation of ECM proteins results in the distortion of hepatic architecture due to scar formation, along with the appearance of regenerating hepatocyte nodules,
which define cirrhosis (8). Cirrhosis is characterized by hepatocellular dysfunction, portal hypertension, hepatocellular carcinoma (HCC) and eventual liver failure (9,10).

Liver fibrogenesis is initiated by hepatic stellate cells (HSCs). Under specific conditions, quiescent HSCs are transformed into myofibroblasts (MFs) to generate ECM proteins, tissue inhibitors of metalloproteinases (TIMPs) and matrix metalloproteinases (MMPs) (11-14). HSC activation involves a systemic and complex pathological process involving multiple cytokines and multiple cellular signaling pathways (15).

The healthy liver has a strong regenerative potential due to the unlimited proliferative potential of cholangiocytes and hepatocytes (HCs). Hepatic stem/progenitor cells (HpSCs) are positioned within the canals of Hering (16). These cells are quiescent in the healthy liver but may be activated in response to liver injury by proliferating and differentiating towards cholangiocytes and HCs (17). In injured tissue, activated HSCs, macrophages and MFs produce a variety of signals through signaling pathways including the Wnt and Notch pathways to drive HSC proliferation and differentiation (18). HpSCs are also able to activate stellate cells through signaling pathways, including the Hedgehog (Hh) pathway, resulting in the release of various types of matrix components during liver regeneration (19).

Studies have confirmed that fibrosis is regulated through the expression of various genes (20). As key regulators of multiple biological processes, long non-coding RNAs (lncRNAs), commonly defined as RNAs longer than 200 nucleotides without any protein-coding capacity, have attracted much research interest (21). Although the classification system of lncRNAs is currently incomplete, they are generally divided into two broad types according to their position relative to protein-coding genes: i) Intergenic lncRNAs and ii) coding gene-overlapping lncRNAs (22). lncRNAs regulate gene expression and protein synthesis through multiple mechanisms (23) and are considered to include ~30,000 different mRNAs (33,34). TGF-β1 promotes matrix formation through Smad3-dependent as well as Smad3-independent mechanisms (35).

lncRNA-activated by TGF-β (lncRNA-ATB) is an important regulator of the TGF-β/Smad signaling pathway. Studies have reported that lncRNA-ATB, Smad2 and TGF-βRII share a common microRNA (miRNA) response element (MRE) for miRNA (miR)-425-5p. lncRNA-ATB was indicated to induce the expression of Smad2 and TGF-βRII by inhibiting the expression of endogenous miR-425-5p in hepatitis C virus (HCV)-induced hepatic fibrosis in a study on hepatic stellate LX-2 cells treated with hepatoblastoma HepG2 cells carrying the HCV core protein. Consequently, lncRNA-ATB caused hepatic fibrosis by enhancing collagen I synthesis and stimulating HSCs through competitive binding to miR-425-5p (36).

LF-associated lncRNA1 (Inc-LFAR1) was indicated to facilitate the interaction between Smad2/3 and TGF-βRII and promote Smad2/3 phosphorylation in carbon tetrachloride (CCL4)/bile duct ligation (BDL)-induced LF. In addition, Inc-LFAR1 is able to directly bind to Smad2/3. On this basis, the TGF-β1/Smad2/3/Inc-LFAR1 signaling pathway creates an active feedback loop that enhances Smad2/3 functions in hepatic fibrosis (37).

HOXA distal transcript antisense RNA (HOTTIP) has been implicated in liver fibrogenesis (38). Li et al (39) determined that HOTTIP was upregulated in mice with hepatic fibrosis and that inhibition of HOTTIP by adenosvir delivery of short hairpin RNA-HOTTIP markedly reduced LF (39). miR-148a participates in the initiation and progression of HCC in the presence of LF and HOTTIP inhibits miR-148a expression (40). miR-148a may regulate TGFβRI/TGFβRII, subsequently decreasing their expression levels, in human and mouse HSCs. Collectively, these results suggest that HOTTIP may promote LF by downregulating miR-148a and upregulating TGFβRI and TGFβRII.

H19 is a maternally inherited gene (41) and is overexpressed in human hepatic fibrosis specimens, as well as in the livers of mice with CCl4/BDL-induced fibrosis (42). H19 functions as a competing endogenous RNA (ceRNA) by sponging miR-148a and maintaining the expression levels of ubiquitin-specific protease 4 (USP4), a key miR-148a target that stabilizes TGFβRI and promotes TGF-β signalling (43). The H19/miR-148a/USP4 axis activates hepatic fibrosis through the TGF-β pathway, indicating that H19 may be a therapeutic target for fibrosis (44).

The lncRNA Gm5091 significantly negatively regulates HSCs in mice with alcoholic hepatitis fibrosis (AHF) (45). Zhou et al (45) reported that Gm5091 downregulates cell migration, collagen I expression and HSC activation marker expression, including Desmin and α-smooth muscle actin. In addition, data based on a bioinformatic analysis revealed that the Gm5091 sequence contains binding sites for miR-24, TGF-β1 acts as an important regulator of fibrogenesis, notably in inflammation-induced LF (32). TGF-β1 binding to TGF-β receptor (TGFβRI) and TGFβRII triggers the phosphorylation of downstream Smad proteins (particularly Smad3) and contributes to the transcription of type I and type III collagen mRNAs (33,34). TGF-β1 increases TIMP expression and decreases MMP levels, thereby inhibiting ECM degradation. In addition, TGF-β1 induces MF production by promoting epithelial-mesenchymal transition (EMT). TGF-β1 promotes matrix formation through Smad3-dependent as well as Smad3-independent mechanisms (35).
miR-23b and miR-27b. Full-length Gm5091 decreases the expression levels of miR-27b/23b/24 (45). In addition, miR-27, miR-24 and miR-23 are positive regulators of HSC proliferation and differentiation, as they activate TGF-β and Smad4 in mice with LF (46,47). As a ceRNA, Gm5091 sponges miR-27b/23b/24, which alleviates liver injury and the progression of AHF in mice by inhibiting HSC activation.

Nuclear paraspeckle assembly transcript 1 (NEAT1) is critical for the formation of paraspeckles (48) and hence to the initiation of tumors. It is highly expressed in activated HSCs and liver tissue of mice with CCl4-induced LF. In human fibrotic liver samples, upregulated expression levels of NEAT1 are positively correlated with fibrosis markers (49). In a mouse model of CCl4-induced fibrosis, NEAT1 overexpression promoted HSC activation in vivo, and similar results were obtained in vitro (50). A previous study suggested that miR-122 inhibits HSC activation and the expression of fibrosis-associated genes induced by TGF-β (51). Stimulated expression of Kruppel-like factor 6 (KLF6), an immediate-early gene in LF, induces the expression of TGFβRI and TGFβRII in activated HSCs (52). Furthermore, miR-122 targets NEAT1 as well as KLF6 (53). Collectively, these results suggest that NEAT1 competitively binds to miR-122 and regulates KLF6 expression in hepatic fibrosis, indicating that the NEAT1/miR-122/KLF6 axis promotes HSC activation.

The IncRNA ENSMUST00000158992 (SCARNA10) is upregulated in liver tissues of fibrotic mice as well as in the serum and liver tissue of humans with advanced LF (54). Several studies have indicated that SCARNA10 is a positive regulator of LF, as it induces HC apoptosis and HSC activation (55,56). Mechanistically, SCARNA10 functions as a mediator of LF by inhibiting the binding of polycomb repressive complex 2 to the promoters of genes involved in the TGF-β pathway, thereby promoting the transcription of these genes.

3. Hh signaling and lncRNAs

The Hh signaling pathway is a morphogenetic pathway that has multiple roles in cell proliferation, apoptosis, migration and differentiation. It was first reported in Drosophila by Nüsslein-Volhard and Wieschaus (57) in 1980. The Hh pathway comprises Glioblastoma (GLI) family transcription factors (GLI1, GLI2, GLI3), Smoothened (SMO), sonic Hh and Patched 1 (PTCH1) (58) and is driven by PTCH receptors that are activated by Hh ligands, which abolish the inhibitory effect of PTCH1 on SMO. In turn, SMO transduces Hh signals to regulate gene expression via GLI transcription factors (59,60). Normal adult HCs generally do not produce Hh ligands but hepatic synthesis of Hh ligands is increased in mice treated with CCl4 (76). miR-212 is significantly downregulated in MEG3-overexpressing cells and is able to target PTCH1. Furthermore, MEG3 induces Hh pathway activation by sponging miR-212, promoting PTCH1 expression and decreasing SMO expression.

4. Wnt/β-catenin signaling and lncRNAs

Wnt signaling modulates cellular apoptosis, proliferation and differentiation. Wnt proteins are 350-400 amino acids long with a conserved cysteine-rich binding domain containing 23-24 cysteine residues (80). Of note, two cell surface receptor families participate in the reception and transduction of Wnt signals: The low-density lipoprotein receptor-related protein (LRP) family and members of the Frizzled (Fz) gene family (81). When Wnt binds to its receptor, either Fz or a complex formed by Fz and LRP5/6, a signal is transduced to the cytoplasmic phosphoprotein disheveled (82). Mammals have three types of Dsh proteins (Dsh-3, Dsh-2 and Dsh-1) (83). Wnt signaling is divided into three independent pathways according to the affected Dsh protein: The canonical ‘Wnt/β-catenin’ pathway, the ‘Wnt/polarity’ pathway (also called the ‘planar cell polarity’ pathway) and the ‘Wnt/Ca2+’ pathway (84-86). In these three pathways, Dsh is a key transducer of the Wnt signal.

β-catenin is a major component of the canonical Wnt pathway (87-89). β-catenin forms a subunit of the cadherin protein complex (90). Previous studies have indicated that β-catenin is involved in fibrotic diseases (91,92). In the absence of Wnt, β-catenin is targeted for degradation by a
multiprotein degradation complex. Wnt signaling antagonizes the degradation complex, leading to β-catenin accumulation and target gene activation (93).

The Wnt pathway has dual modulatory effects on HSCs (94). Depending on the specific conditions, Wnt may either activate or inhibit β-catenin. Abnormal activation of Wnt/β-catenin signaling aggravates fibrogenesis. Small interfering RNA-mediated β-catenin knockdown suppresses cell proliferation and decreases the expression levels of collagen I and III, resulting in HSC apoptosis in vitro (95). PRI-724 is a selective inhibitor of the cAMP-response element-binding protein-binding protein (CBP)/β-catenin interaction, activation of HSCs by PRI-724 has been indicated to reduce hepatic fibrogenesis in mice (96). Activation of the canonical Wnt/β-catenin pathway is necessary to sustain the quiescence of HSCs in vitro (97). Roof plate-specific spondin proteins, which stimulate the Wnt pathway, have been reported to inhibit HSC activation, thereby compromising dickkopf WNT signaling pathway inhibitor 1 signaling (98). Non-canonical Wnt pathway signaling activates HSCs, as supported by the observation that overexpression of Wnt5a was activated in rat HSCs, indicating that cellular signaling involving phospho-protein dishevelled occurs (99). On the other hand, a natural Wnt5a inhibitor inhibited HSC activation by inducing the expression of secreted Fz-related protein 5 (100).

lncRNA-ATB activates EMT and promotes tumor metastasis (101), and its expression is positively correlated with liver cirrhosis in patients with HCC (102). Evidence indicates that lncRNA-ATB competitively binds to miR-200 family members (103). Furthermore, β-catenin was reported to be regulated by miR-200a (104,105). Collectively, these results suggest that lncRNA-ATB upregulates β-catenin expression by inhibiting miR-200a, resulting in collagen I synthesis and HSC activation in HCV-associated fibrosis in humans (106).

Long intergenic non-coding RNA-p21 (lincRNA-p21) inhibits Wnt/β-catenin signaling, which mediates the effects of salvianolic acid B (Sal B) on HSC activation. The inhibitory effects of Sal B on Wnt/β-catenin signaling are abolished by lincRNA-p21 suppression. lincRNA-p21 regulated by miR-17-5p is an inhibitor of miR-17-5p. Collectively, these results indicate that lincRNA-p21 inhibits HSC activation through the miR-17-5p/Wnt/β-catenin axis (107).

Small nuclear RNA host gene 7 (SNHG7) has been reported to be an oncogene in various cancer types. Yu et al (108) reported that the expression levels of SNHG7 are upregulated in the liver tissue of CCl4 mice and that silencing of SNHG7 inhibits HSCs. Furthermore, SNHG7 is able to regulate miR-378a-3p. Downregulation of miR-378a-3p reduces the effects of SNHG7 loss on HSC activation (109). SNHG7 enhances Wnt/β-catenin signaling, leading to LF, characterized by a decline in the phosphorylated β-catenin level and enhancement of T cell factor activity (110). SNHG7-mediated activation of the Wnt/β-catenin pathway is regulated by miR-378a-regulated dishevelled segment polarity protein 2 (DVL2). Therefore, miR-378a-3p is a regulator of DVL2. DVL2 inhibition abolishes SNHG7-induced HSC activation. Collectively, these results indicate that SNHG7 inhibits miR-378a-3p and moderates its effects on DVL2, leading to enhanced Wnt/β-catenin signaling and thereby promoting hepatic fibrosis.

5. NF-κB signaling and lncRNAs

The NF-κB pathway has a crucial role in innate and adaptive immunity. NF-κB is a eukaryotic transcription factor that exists in almost all cell types and is involved in various liver pathologies (111). The survival and activation of HSCs and hepatic MFs is modulated by NF-κB (112). In 1986, NF-κB was discovered to regulate immunoglobulin κ light chain expression in B cells (113). NF-κB dimers are sequestered in the cytoplasm by inhibitor of NF-κB proteins in most resting cells (114). NF-κB activation is associated with at least 2 signal transduction routes named the canonical and non-canonical pathways (115).

NF-κB regulates LF mainly by modulating physiological responses in HSCs (116). Activation of NF-κB in HCs confers protection by limiting apoptosis and facilitating regeneration through stimulation of HC proliferation (117). NF-κB is activated in Kupffer cells during liver injury, which further induces HSC activation and liver fibrogenesis (118,119). Further studies have indicated that NF-κB agonists, including captopril, thalidomide, silmyarin and sulfasalazine, enhance hepatic MF apoptosis and antifibrotic activities in normal liver tissue (120-122). In addition, HSCs are direct in vivo targets of regulators that activate NF-κB, including lipopolysaccharide (LPS) (123). However, prolonged accumulation of NF-κB in liver cells promotes chronic inflammation and HSC transdifferentiation into scar-forming hepatic MFs (124,125). By contrast, inhibition of NF-κB in Kupffer cells alleviates hepatic fibrosis (126).

In fibrotic livers and activated HSCs, the lncRNA taurine upregulated gene 1 (TUG1) is highly expressed, unlike in normal HCs. miR-29b has been confirmed as a TUG1-targeting miRNA (127). Previous research has demonstrated that miR-29b inhibits HSC activation and ameliorates CCl4/BDL-induced LF, as well as human advanced hepatic fibrosis (128). Treatment with a miR-29b mimic eliminates the effects of TUG1 overexpression on cellular physiological responses and inactivation of Janus kinase/STAT and NF-κB signaling in LPS-pretreated H9c2 cells (127). miR-29b downregulates fibrogenic genes associated with NF-κB and TGF-β pathways in HSCs (129,130). Murine miR-29b suppresses the expression of collagen in HSCs and is down-regulated in activated HSCs in a manner dependent on NF-κB and TGF-β signalling (131). Thus, TUG1 is a positive regulator of profibrogenic gene expression in HSCs, as it downregulates miR-29b in HSCs (132).

6. Notch signaling and lncRNAs

The Notch signaling pathway is an elementary and highly conserved pathway associated with liver development, physiology and pathophysiology (133,134). Early studies based on *C. elegans* and *Drosophila* genetic models identified a gene locus that was correlated with the phenotype of a mutant fly with a wing indentation (18,135). This locus was indicated to participate in cell fate processes during *Drosophila* embryogenesis and was later named Notch. The Notch pathway consists of receptors (Notch1-Notch4), ligands (δ-like 1, 3 and 4, as well as Jagged 1 and 2), transcriptional complex components and downstream genes, including hairy-enhancer of split (Hes)-related with YRPW motif (Hey) and Hes (136,137). Notch signaling promotes LF by regulating the inflammatory
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Xie et al. (140) reported that Notch-Hh crosstalk influences the pathogenesis of cirrhosis by regulating MFs/HSCs through EMT in vitro and in vivo. In a mouse model of liver steatosis and LF, sustained Notch activation induces hepatic fibrosis in the presence of high lipid levels and inhibition of Notch signaling or a reduction in liver fat content may ameliorate hepatic fibrosis (141, 142).

In mice models of liver fibrogenesis, the protein and mRNA levels of Notch2, Notch3, Hes1 and Hey2 are increased in lnc-LFAR1-overexpressing HSCs, while downregulation of lnc-LFAR1 reverses these effects (37). Hes is considered the prototype Notch target gene and encodes a basic helix-loop-helix inhibitory transcription factor involved in the self-renewal of target cells by inhibiting differentiation (143, 144). Furthermore, lentivirus-mediated knockdown of lnc-LFAR1 reduced the expression levels of Hey2, Notch2 and Notch3. Hes1 inhibits CCl4/BDL-induced expression of these genes; therefore, lnc-LFAR1 may activate HSCs and subsequently accelerate LF through modulation of Notch signaling.

| IncRNA        | Experiment type | Signaling pathway                        | Function                          | (Refs.) |
|---------------|----------------|------------------------------------------|------------------------------------|---------|
| lnc-RNA-ATB   | In vitro       | TGF-β/Smad signaling                     | Promoting HSC activation           | (33)    |
| lnc-LFAR1     | In vitro and in vivo | TGF-β/Smad signaling, Notch signaling | Promoting HSC activation           | (34)    |
| HOTTIP        | In vitro and in vivo | TGF-β/Smad signaling                     | Promoting HSC activation           | (36)    |
| H19           | In vitro and in vivo | TGF-β/Smad signaling                     | Promoting HSC activation           | (39)    |
| lncRNA Gm5091 | In vitro and in vivo | TGF-β/Smad signaling                     | Inhibiting HSC activation           | (42)    |
| NEAT1         | In vitro and in vivo | TGF-β/Smad signaling                     | Promoting HSC activation           | (47)    |
| PVT1          | In vitro and in vivo | Hedgehog signaling                      | Promoting HSC activation           | (66)    |
| MEG3          | In vitro and in vivo | Hedgehog signaling                      | Inhibiting HSC activation           | (67)    |
| lncRNA-ATB    | In vitro       | Wnt/β-catenin signaling                  | Promoting HSC activation           | (94)    |
| lincRNA-p21   | In vitro       | Wnt/β-catenin signaling                  | Inhibiting HSC activation           | (95)    |
| SNHG7         | In vitro and in vivo | Wnt/β-catenin signaling                  | Promoting HSC activation           | (96)    |
| TUG1          | In vitro and in vivo | NF-κB signaling                         | Promoting HSC activation           | (110)   |

Table I. lncRNAs regulating the signaling pathways in LF.

Figure 1. Regulation of the signaling pathways in LF by IncRNAs. In response to LF, the expression of a cohort of IncRNAs is modulated. IncRNAs are implicated in the process of LF by targeting components of the signaling pathway. Normal arrows represent aggravation of LF. T-bar arrows represent alleviation of LF. LF, liver fibrosis; HOTTIP, HOXA distal transcript antisense RNA; lnc-LFAR1, LF-associated lncRNA1; lincRNA-p21, long intergenic non-coding RNA-p21; lnc/lncRNA, long non-coding RNA; lncRNA-ATB, lncRNA-activated by TGF-β; MEG3, maternally expressed gene 3; NEAT1, encoding nuclear paraspeckle assembly transcript 1; PVT1, plasmacytoma variant translocation 1; SNHG7, small nuclear RNA host gene 7; TGF-β, transforming growth factor-β; TUG1, taurine upregulated gene 1.

7. Other signaling pathways

Further signaling pathways are involved in LF. Homeobox transcript antisense RNA (HOTAIR) expression is upregulated in HSCs during LF. HOTAIR modulates PTEN levels and contributes to the activation of the ERK and AKT pathways through miR-29b (145). In addition, the IncRNA growth arrest-specific transcript 5 inhibits LF by targeting miR-23a through the PTEN/PI3K/Akt signaling pathway in a rat model of CCl4-induced hepatic fibrosis (146). Future research is expected to focus increasingly on the association of IncRNAs with LF.

8. Conclusion

Regeneration of damaged mature liver tissue is driven by multiple signaling pathways, including the TGF-β/Smad, Hh, Wnt, NF-κB and Notch pathways. A summary is provided in Table I and Fig. 1. The complex but delicate networks interconnecting these molecular signals regulate cellular response and the function of macrophages (138, 139).
proliferation, differentiation and apoptosis and thus the pathological process of fibrosis. Due to the development of high-throughput sequencing technologies, numerous lncRNAs have been identified. These lncRNAs may act on oncogenes or tumor suppressors and certain lncRNAs have been well characterized and proven to be associated with LF. In the present review, these signals and intracellular events were summarized that independently or cooperatively drive HSC activation. The roles and possible mechanisms of action of selected lncRNAs in LF were also reviewed. The potential utility of lncRNAs as therapeutic agents and biomarkers is promising, although the exact mechanisms of action behind most lncRNAs remain elusive. Given the numerous potential therapeutic anti-fibrosis strategies targeting factors that promote fibrosis, combination therapies including these lncRNAs may produce improved clinical outcomes. However, additional functions and regulatory mechanisms of action of these lncRNAs require further study prior to their use as clinically applicable biomolecules.

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Authors' contributions

ZW, SH and LT designed the article. ZW, SH, XZ and SG wrote the first draft of the manuscript. QX, YG, JZ and BF reviewed the literature. LT critically revised the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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