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Immunoregulatory role of miR-155 in cholestatic liver diseases: implications for primary biliary cholangitis and primary sclerosing cholangitis associated with ulcerative colitis*

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ABSTRACT

Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are chronic cholestatic liver diseases characterised by progressive bile duct injury, persistent cholestasis, fibrosis and eventual cirrhosis. Growing evidence indicates that epigenetic mechanisms, particularly microRNAs, play an important role in their pathogenesis. Among them, microRNA-155 (miR-155) has emerged as a central immunoregulatory molecule involved in both innate and adaptive immune responses. MicroRNA-155 regulates key inflammatory signalling pathways, including NF-κB and Janus kinase (JAK)/STAT, and interferes with bile acid homeostasis through suppression of the farnesoid X receptor, thereby contributing to sustained cholestasis and inflammatory injury. Increased expression of miR-155 has been observed in liver tissue, serum and peripheral blood mononuclear cells of patients with PBC and PSC, reflecting local and systemic immune activation. Importantly, miR-155 also links chronic inflammation with impairment of the mismatch repair system and microsatellite instability, promoting colorectal carcinogenesis in patients with PSC associated with ulcerative colitis. This review summarises the biogenesis, regulation and pathogenic significance of miR-155 in PBC and PSC, with particular emphasis on its role in mismatch repair dysfunction and emerging therapeutic implications.

Keywords: miR-155; cholestatic liver disease; primary sclerosing cholangitis; primary biliary cholangitis; ulcerative colitis.

INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic disease characterised by the accumulation of bile acids within the liver, which may progress to cirrhosis, end-stage liver failure, hepatocellular carcinoma (HCC) and, ultimately, death [1]. Globally, its prevalence is estimated at 14.6 cases per 100,000 individuals, with a female predominance of 9:1 and an annual incidence of 1.76 new cases per 100,000 individuals [2]. Primary biliary cholangitis is typically associated with the presence of anti-mitochondrial antibodies targeting pyruvate dehydrogenase complex subunit E2 [3]. Laboratory findings typically include elevated alkaline phosphatase and gamma-glutamyl transferase [4], along with increased serum immunoglobulin M (IgM) levels [5, 6, 7]. First-line therapy is ursodeoxycholic acid (UDCA) [4, 8]. However, patients with an inadequate biochemical response may be treated with obeticholic acid (OCA) [9], an agonist of the nuclear farnesoid X receptor (FXR) or with emerging nuclear receptor agonists such as peroxisome proliferator-activated receptor (PPAR) ligands (e.g., elafibranor and seladelpar) [10, 11, 12].

Primary sclerosing cholangitis (PSC) is a chronic, progressive, fibro-inflammatory disorder that affects both intra- and extra-hepatic bile ducts, resulting in alternating segments of stricturing and dilation [13]. Its prevalence varies widely across regions, ranging 0–31.7 cases per 100,000 individuals [14]. Primary sclerosing cholangitis occurs more commonly in males (65–70%) and carries an approx. 20% lifetime risk of developing cholangiocarcinoma (CCA), representing a 600-fold increase compared with the general population [15, 16]. Immunological mechanisms are implicated in the pathogenesis of both PSC and CCA, as reflected by the presence of multiple auto-antibodies in patient sera and the partial efficacy of select immunotherapeutic strategies for CCA. Anti-gliadin and anti-F-actin IgA antibodies have been identified as independent predictors of mortality and CCA development [17]. Primary sclerosing cholangitis is strongly associated with inflammatory bowel disease (IBD), particularly ulcerative colitis (UC), which coexists in 70–80% of patients (the PSC-UC phenotype) [18]. This phenotype confers a 4- to 10-fold increased risk of colorectal cancer, which typically exhibits right-sided predominance and tends to develop at a younger age [19, 20].

Accumulating evidence suggests that epigenetic mechanisms, including DNA methylation mediated by DNA (cytosine-5)-methyltransferases (DNMTs) and microRNA (miRNA)-driven, post-transcriptional gene regulation, play important roles in the development of numerous diseases. MicroRNAs are short (20–24 nt), non-coding RNAs that regulate gene expression post-transcriptionally by binding to the 3′ untranslated regions (3′-UTRs) of target mRNAs, suppressing translation or inducing transcript degradation [21]. MicroRNA-155 can amplify

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inflammatory responses, and its expression is upregulated following lymphocyte activation to regulate cellular proliferation and differentiation [22]. It plays a central role in promoting autoimmune inflammation by enhancing the development of effector T lymphocytes – particularly T helper (Th)17 and Th1 subsets and by influencing the transcriptional landscape of inflammatory pathways. Conversely, reduced miR-155 expression diminishes the production of pro-inflammatory cytokines and weakens the ability of T lymphocytes to induce inflammation, underscoring its position as a critical regulatory hub in adaptive immunity.

This review aims to provide a comprehensive overview of the biogenesis, regulation and functional significance of miR-155 in the pathogenesis of PBC and PSC, with a particular focus on its effect on the mismatch repair (MMR) system and microsatellite instability (MSI) in the colon of patients with PSC-UC, as well as to discuss the potential therapeutic implications emerging from these mechanisms.

BIOGENESIS AND REGULATION OF microRNA-155

MicroRNA-155 is a short, non-coding RNA encoded by the microRNA 155 host gene (MIR155HG), originally identified as the B cell integration cluster (BIC) on chromosome 21 [23, 24]. The MIR155HG/BIC gene consists of 3 exons spanning approx. 13 kb within the 21q21 chromosomal region [23]

Following transcription of the MIR155HG/BIC locus by RNA polymerase II, a primary microRNA transcript (pri-miR-155) is generated. This transcript is recognised in the nucleus by the Drosha-DiGeorge syndrome critical region 8 microprocessor complex and cleaved into a shorter precursor form, pre-miR-155 (~65 nt). Pre-miR-155 is then exported to the cytoplasm by the exportin-5/Ran-GTP transport system, where it undergoes further processing by the Dicer/TAR RNA-binding protein complex into a ~22-nt miRNA duplex. One strand, miR-155-5p, is subsequently incorporated into the RNA-induced silencing complex (guided by the Argonaute 2 protein), enabling regulation of target gene expression by mRNA degradation or translational repression [24, 25, 26].

Multiple transcription factor binding sites have been mapped within the BIC gene, including binding motifs for nuclear factor kappa B (NF-κB) at –1697 bp and –1150 bp, SMAD4 at –600 bp, an interferon-sensitive response element at –311 bp, interferon regulatory factors (IRFs) at –200 bp and AP-1 at –40 bp. Additionally, 2 E26 transformation-specific transcription factors (Ets)-binding sites are located at the transcription start site, two Foxp3-binding sites lie within intron 2, and 3 hypoxia-inducible factor 1 alpha (HIF-1α) binding sites are present in the promoter region [24]. Transcriptional regulation of miR-155 by NF-κB, AP-1, signal transducer and activator of transcription (STAT) proteins and IRFs follow a shared mechanism: the activation of these factors through toll-like receptors (TLRs) or cytokine signalling, which constitutes a major pathway driving MIR155HG induction in immune cells [27].

The expression of miR-155 varies across cell types and tissue microenvironments and is orchestrated by multiple pathways responding to diverse cellular signals. MicroRNA-155 has been shown to directly target the transcription factor Ets1, thereby modulating the expression of a subset of Th17 effector genes, including IL-23 receptor (*IL-23R*) [28]. One transcription factor known to induce miR-155 in lipopolysaccharide (LPS)-stimulated cells is Ets2, which binds to the miR-155 promoter [29]. Ets2 is robustly induced in response to LPS at the protein level, while its close homolog, Ets1, does not exhibit the same responsiveness. Further studies have demonstrated that Ets2 induction by LPS requires the adaptor proteins myeloid differentiation primary response 88 (MyD88) and TIR-domain-containing adaptor-inducing interferon-β (TRIF), confirming its role as a key mediator of downstream TLR4 signalling [29].

Interleukin 10 (IL-10) can suppress the expression of *Ets2* mRNA and its protein through a STAT3-dependent pathway. In cells treated with small interfering RNA targeting STAT3, IL-10 fails to inhibit luciferase promoter activity, demonstrating that IL-10-mediated repression of miR-155 transcription is contingent upon STAT3 activation [29, 30].

MicroRNA-155 expression can also be induced under hypoxic conditions. Mouse tissues exposed to hypoxia show increased miR-155 expression in the colon and liver. In Caco-2 and HeLa cell lines, hypoxia triggers an elevation in the primary pri-miR-155 transcript. These findings indicate that miR-155 is a hypoxia--responsive miRNA, with its induction occurring in a tissue- and cell-type-specific manner, at least partly through enhanced transcriptional activation of the *MIR155HG* gene [31] – Table 1.

TABLE 1. Selected stimuli and the regulation of microRNA-155 expression

Stimulus/Factor	Target point/Mechanism	Effect on miR-155	Key pathways/mediators	Model/Tissue	References
LPS (TLR4)	activation of the transcription factor Ets2 dependent on adaptor proteins MyD88 and TRIF, leading to induction of MIR155HG transcription	↑ expression of MIR155HG/ miR-155	TLR4 → MyD88/TRIF → NF-κB/Ets2 → MIR155HG (miR-155)	cells of the innate immune system (macrophages, monocytes)	[29]
IL-10	activation of transcription factor STAT3, which then inhibits Ets2 activity and MIR155HG transcription, limiting miR-155 induction after stimulation	↓ expression of miR-155	IL-10 → JAK/STAT3 → ↓ Ets2 → ↓ MIR155HG (miR-155)	innate immune system cells (macrophages, monocytes, PBMCs)	[30]
HIF-1α (hypoxia)	hypoxia-induced activation of HIF-1α, which binds HRE in MIR155HG/ BIC promoter region and enhances transcription	↑ induction of miR-155 under hypoxia	HIF-1α pathway	Caco-2, HeLa cell lines; mouse colon and liver under hypoxia	[31, 32]

Stimulus/Factor	Target point/Mechanism	Effect on miR-155	Key pathways/mediators	Model/Tissue	References
Interleukin 23 (Th17)	miR-155 inhibits Ets1, which normally suppresses Th17 differentiation, thereby enhancing Th17 cell function	↑ enhancement of Th17-mediated inflammatory response	miR-155 → ↓ Ets1 → IL-23R/Th17 axis; NF-κB/ JAK-STAT involvement	Th17 lymphocytes/ intestinal mucosa	[28, 33, 34]

Ets1/Ets2 – E26 transformation-specific transcription factors; HIF-1α – hypoxia-inducible factor 1 alpha; HRE – hypoxia-responsive elements; IL-10 – interleukin 10; IL-23R – interleukin 23 receptor; JAK – Janus kinase; LPS – lipopolysaccharide; miR-155 – microRNA-155; MIR155HG/BIC – microRNA 155 host gene/B cell integration cluster; MyD88/TRIF – myeloid differentiation primary response 88 / TIR-domain-containing adaptor-inducing interferon-β; NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells; PBMC – peripheral blood mononuclear cells; STAT – signal transducer and activator of transcription; TLR4 – toll-like receptor 4; ↑/↓ – increase/decrease of expression or pathway activity

Expression of the *MIR155HG/BIC* gene is also subject to epigenetic modulation. Hypermethylation of promoter regions within the *BIC* gene has been shown to silence its transcription, whereas promoter demethylation and histone acetylation – particularly histone H3 lysine 9 acetylation and histone H3 lysine 27 acetylation – enhance its expression. Enzymes such as DNMT1, histone deacetylases 1 and 2, and ten-eleven translocation 2 represent key regulators of this epigenetic axis [35, 36]. In liver diseases, including PBC and PSC, decreased DNMT1 activity accompanied by increased miR-155 expression has been observed, suggesting that epigenetic dysregulation of *MIR155HG* may amplify inflammation and fibrosis [37].

The complex network of transcription factors (NF-κB Ets1/2, STAT3 and HIF-1α) and epigenetic regulators provide a finely tuned control system for miR-155 expression in response to inflammatory stimuli, hypoxia and cytokines (Tab. 1). Such dynamic regulation enables miR-155 to react rapidly to fluctuations within the immune microenvironment, making it a critical mediator that coordinates innate and adaptive immunity. These characteristics position miR-155 as a central immunoregulatory hub in the pathogenesis of PBC and PSC.

IMMUNOREGULATORY ROLE OF microRNA-155 IN INNATE AND ADAPTIVE IMMUNE RESPONSES

MicroRNA-155 is an integral component of the early macrophage response to diverse inflammatory mediators. It is induced by polyinosinic:polycytidylic acid (poly(I:C)), a potent TLR3 agonist, as well as by interferon beta (IFN-β). Beyond poly(I:C), miR-155 expression is triggered by multiple TLR ligands (through MyD88- or TRIF-dependent pathways) and by cytokines such as IFN-β and interferon gamma (IFN-γ) acting via autocrine and paracrine tumour necrosis factor alpha (TNF-α) signalling [38]. MicroRNA-155 levels also rise in macrophages during infection with *Pseudomonas aeruginosa*, both in human monocyte-derived macrophages and murine peritoneal macrophages. Moreover, activation of protein kinase B (Akt) via phosphatidylinositol (3,4,5)-trisphosphate (a pathway involved in miR-155 regulation) enhances macrophage apoptosis during *P. aeruginosa* infection [39]. Another crucial aspect of miR-155 activity is its role in promoting T cell-driven tissue inflammation. MicroRNA-155 supports Th17 cell development during the inflammatory process and augments the production of cytokines that direct activated T cells toward pro-inflammatory phenotypes. It also facilitates the differentiation of cluster of differentiation 4 positive T lymphocytes ($CD4^+$ T cells) into pro-inflammatory Th1 and Th17 subsets, which produce IFN-γ and IL-17, respectively – both essential mediators of inflammation and autoimmunity [22]. However, miR-155's function is not restricted to T cell-dependent responses; it also plays key roles in B cell-intrinsic mechanisms. In miR-155-deficient mice, decreased levels of IL-2, IFN-γ and IL-4 compromise T cell help for B cells, resulting in smaller germinal centres, reduced B cell proliferation, diminished plasma cell formation and lower immunoglobulin G (IgG) antibody titres following immunisation [40]. Moreover, miR-155 facilitates class-switch recombination and the generation of effector plasma cells, underscoring its intrinsic role within B lymphocytes as a regulator of humoral immunity [41, 42]. Its deficiency leads to reduced secretion of IgG1, IgG2b and IgG3, as well as impaired affinity maturation – effects attributable to cell-autonomous dysfunction within B cells [42]. MicroRNA-155 also acts as an oncogenic microRNA (onco-miR) in B lymphocytes, in part by inhibiting the tumour-suppressive transforming growth factor beta/bone morphogenetic protein (TGF-β/BMP) pathway. This mechanism involves the downregulation of SMAD5, a direct miR-155 target. Through these effects, miR-155 enables malignant B cells to evade TGF-β/BMP-dependent anti-proliferative mechanisms, thereby facilitating the development and progression of lymphoma [43].

MicroRNA-155 represents a key regulator of both innate and adaptive immune mechanisms, modulating the responses of macrophages, T cells and B cells in ways that sustain inflammatory activity and shape the host immune profile. Its ability to enhance TLR-dependent signalling, promote Th1 and Th17 differentiation and regulate immunoglobulin class switching underscores its broad influence on immune homeostasis. In the context of cholestatic liver diseases, excessive miR-155 activity may contribute to chronic effector cell activation, maintenance of a pro-inflammatory milieu and disruption of the balance between immune response and tissue tolerance. Thus, understanding the complex interactions between miR-155 and immune cells is crucial for identifying novel therapeutic targets and may form the basis for future strategies aimed at modulating inflammatory responses in PBC and PSC.

MECHANISMS OF ACTION AND THE BIOLOGICAL FUNCTIONS OF microRNA-155

MicroRNA-155 influences not only the course of the immune response but also directly modulates molecular pathways that

regulate proliferation, survival, differentiation and the fibrogenesis of hepatic cells. As an onco-miR, it targets multiple tumour suppressor genes, kinases and signalling proteins, thereby affecting the balance between tissue regeneration and injury. In cholestatic liver diseases such as PBC and PSC, its overexpression results in sustained activation of phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), JAK/STAT and TGF-β/SMAD family protein signalling pathways, which collectively drive inflammation, fibrosis and malignant transformation (Tab. 2).

In a rat model of HCC, miR-155-5p levels were markedly elevated in tumour tissues and accompanied by a significant reduction in phosphatase and tensin homolog (PTEN) mRNA. Similar patterns have been observed in human HCC samples, where miR-155-5p expression is approx. 6-fold higher in tumour tissue compared with adjacent non-tumour tissue, while PTEN mRNA levels are substantially reduced. Moreover, high miR-155-5p expression and low PTEN levels correlate with more advanced tumour-node-metastasis (TNM) III/IV stages compared with stages I/II. Inhibition of miR-155-5p reduces phosphorylated Akt (p-Akt), whereas miR-155-5p overexpression increases p-Akt levels. Thus, miR-155-5p functions as an onco-miR in HCC by directly targeting PTEN and dysregulating PI3K/Akt signalling [44], promoting increased cancer cell proliferation, migration, invasion and reduced apoptosis.

Src homology 2-containing inositol 5′-phosphatase 1 (SHIP1), a well-established negative regulator of Akt, is also a direct target of miR-155. In mouse macrophages stimulated with LPS, miR-155 suppresses SHIP1 expression following their co-induction by LPS [45]. In murine models of liver fibrosis and cirrhosis, as well as in human clinical samples, increased hepatic and circulating miR-155-5p levels correlate with fibrosis severity. M1 macrophages (classically activated) display higher miR-155-5p expression compared with alternatively activated M2 macrophages or unpolarized M0 macrophages. MicroRNA-155-5p acts as a negative regulator of suppressor of cytokine signalling 1 (SOCS1), decreasing its expression. Moreover, because SOCS1 inhibits the JAK/STAT pathway, its downregulation leads to the activation of JAK1/STAT1 signalling. Activation of this pathway supports M1 macrophage polarisation and enhances hepatic lymphangiogenesis (evidenced by increased lymphatic marker expression and higher lymphatic vessel density in fibrotic tissues). MicroRNA-155-5p inhibition (or SOCS1 restoration attenuated JAK1/STAT1 activity) has reduced M1 macrophage numbers and suppressed lymphangiogenesis in experimental models [46].

Patients with liver cirrhosis demonstrate strong miR-155 overexpression – approx. a 7-fold increase relative to controls. Elevated miR-155 correlates with increased p-STAT3 levels in hepatocytes and hepatic stellate cells (HSCs), leading to activation of STAT3 signalling. Furthermore, miR-155 expression positively correlates with alpha-smooth muscle actin and the collagen type I alpha 1 chain, both key markers of HSC activation and fibrosis. In mouse models (wild-type and miR-155 knockouts), miR-155 expression consistently rises during liver fibrosis. Genetic deletion or pharmacologic inhibition of miR-155 reduces fibrosis by approx. 50%, suppresses TGF-β/SMAD and STAT3 pathway activation and diminishes HSC activation [47].

MicroRNA-155 also regulates monocyte-macrophage responses to TGF-β by suppressing SMAD2 expression. Luciferase reporter assays have confirmed miR-155 binding to a predicted site in the 3′-UTR of *SMAD2* mRNA, reducing reporter activity. In THP-1 monocytes engineered to overexpress miR-155, doxycycline-induced miR-155 upregulation decreased SMAD2 protein levels without proportionally reducing *SMAD2* mRNA, indicating post-transcriptional regulation. MicroRNA-155 overexpression also impairs TGF-β1-induced expression of matrix metallopeptidase 9, intercellular adhesion molecule 1, IL-4 receptors, and dendritic cell-specific intercellular adhesion molecule-3 grabbing non-integrins, demonstrating that miR-155 inhibits TGF-β signalling primarily through SMAD2 suppression, leading to reduced gene expression related to adhesion, angiogenesis, matrix remodelling and fibrosis [48].

Additional mechanisms of miR-155 action include the modulation of lipid metabolism (via PPARα/γ), macrophage polarisation (through CCAAT/enhancer-binding protein beta – C/EBPβ), activation of TGF-β/epithelial-to-mesenchymal transition/fibrotic gene programmes and the regulation of TLR4 signalling. In miR-155 knockout mice, hepatic PPARα activity is increased, and PPARγ expression is higher in macrophages after miR-155 inhibition *in vitro*. In wild-type mice, alcohol feeding has induced macrophage and neutrophil infiltration and elevated monocyte chemoattractant protein 1, TNF-α and IL-1β levels, whereas these responses are markedly reduced in miR-155 knockout mice. Kupffer cells isolated from miR-155 knockout mice display a shift toward an M2 phenotype upon LPS/IL-4/IFN-γ stimulation, which is associated with increased C/EBPβ expression, supporting the role of miR-155 in promoting pro-inflammatory M1 polarisation [49].

MicroRNA-155 also regulates lipid accumulation in HepG2 hepatocytes. Under exposure to free fatty acids (FFA; oleate : palmitate 2:1), miR-155 overexpression is protective (limiting lipid deposition), while miR-155 inhibition in basal (non-FFA) conditions enhances lipid accumulation. This effect is associated with suppression of C/EBPβ, a key transcription factor controlling lipogenesis and lipid metabolism genes [50].

Chronic alcohol exposure in hepatic macrophages induces miR-155 upregulation, enhancing TNF-α production by increasing TNF-α mRNA stability. Nuclear factor kappa B activation is a major driver of miR-155 induction in this setting. The inhibition of NF-κB markedly reduces miR-155 induction by ethanol/LPS in Kupffer cells of alcohol-fed mice, which is consistent with findings in macrophages [51]. Similar results have been observed in a rat model of metabolic dysfunction-associated fatty liver disease, where NF-κB overexpression elevated both NF-κB and miR-155-5p levels, while NF-κB silencing reduced expression of both factors [52].

Collectively, miR-155 regulates a network of interconnected signalling pathways that integrate inflammation, fibrogenesis and carcinogenesis in the liver. Through its coordinated effects on PTEN, SHIP1, SOCS1 and SMAD2 (Tab. 2), miR-155 functions as a master regulator of degenerative and proliferative processes in hepatocytes and cholangiocytes. In PBC and PSC, dysregulation of these pathways drives a self-sustaining cycle of inflammation, fibrosis and malignant transformation. Understanding these mechanisms provides a foundation for the development of next-generation miR-155-targeted therapeutic strategies and biomarker-based diagnostics.

TABLE 2. Key molecular targets of microRNA-155 and their clinical significance in PBC and PSC/PSC-UC

Target/Pathway	Tissue/Target cell	Functional effect of miR-155	Clinical implications in PBC	Clinical implications in PSC/PSC-UC	References
SOCS1 (SOCS1, JAK/STAT pathway)	macrophages, cholangiocytes	miR-155 ↓ SOCS1 → ↑ STAT1/ STAT3 (excessive cytokine signal transduction)	enhancement of Th1/ Th17 responses, progression of bile duct fibrosis; in PBC, increased miR-155 expression with inverse correlation to SOCS1; reports of correlations between miR-155 and ALP, GGT, bilirubin and IgM	persistent STAT3 activation; involvement of IL-6 → STAT3 axis in PSC; in PSC-UC, the S1PR1-STAT3 loop contributes to sustained inflammation and mucosal angiogenesis	[22, 46, 53, 54, 55, 56]
SHIP1 (SHIP1/ INPP5D; PI3K/Akt pathway)	KCs	miR-155 ↓ SHIP1 → ↑ PI3K/Akt → M1 polarization → ↑ TNF-α, IL-6, IL-1β	maintenance of M1 macrophage activation and increased secretion of pro-inflammatory cytokines; indirectly promotes epithelial injury and activation of HSCs, contributing to progression of biliary fibrosis	long-term activation of the PI3K/Akt/NF-κB axis in KCs → chronic inflammation, increased TNF-α, IL-6, IL-1β, promotion of fibrogenesis and a pro-tumorigenic microenvironment (HCC, epithelial dysplasia in PSC-UC)	[45, 49, 57, 58, 59, 60, 61]
PTEN (PI3K/Akt pathway)	hepatocytes, HCC cells	miR-155 ↓ PTEN → ↑ PI3K/Akt → ↑ proliferation and survival; ↓ apoptosis	enhancement of proliferative and anti-apoptotic signalling in hepatocytes during advanced PBC	loss of PTEN activates PI3K/Akt, promotes HCC progression, and increases risk of CCA development in PSC	[44, 54, 62]
SMAD2 (SMAD family member 2, TGF-β/SMAD pathway)	monocytes, macrophages, HSCs	miR-155 ↓ SMAD2 → reduced TGF-β--dependent gene transcription → decreased collagen deposition and modulation of fibrogenesis	reduced TGF-β/SMAD activity limits periportal fibrosis and modifies ECM composition	dysregulation of ECM remodelling during chronic colonic inflammation (PSC-UC) may contribute to epithelial dysplastic changes	[47, 48, 63]

Akt – protein kinase B; ALP – alkaline phosphatase; CCA – cholangiocarcinoma; ECM – extracellular matrix; GGT – gamma-glutamyl transferase; HCC – hepatocellular carcinoma; HSC – hepatic stellate cell; IgM – immunoglobin M; IL – interleukin; INPP5D – inositol polyphosphate-5-phosphatase D; JAK – Janus kinase; KC – Kupffer cell; miR-155 – micoRNA-255; NF-κB – nuclear factor kappa B; PBC – primary biliary cholangitis; ; PI3K – phosphoinositide-3-kinase; PSC – primary sclerosing cholangitis; PTEN – phosphatase and tensin homolog; S1PR1 – sphingosine-1-phosphate receptor 1; SHIP1 – Src homology 2-containing inositol 5′-phosphatase 1; SOCS1 – suppressor of cytokine signalling 1; STAT – signal transducer and activator of transcription; TGF-β – transforming growth factor β; TNF-α – tumour necrosis factor alpha; UC – ulcerative colitis; ↑/↓ – increase/decrease of expression or pathway activity

microRNA-155 IN PRIMARY BILIARY CHOLANGITIS

In PBC, a significant upregulation of miR-155 has been demonstrated in peripheral blood mononuclear cells (PBMCs) and liver tissue [54, 64]. At the molecular level, miR-155 acts as a pro-inflammatory regulator of the immune response. By suppressing the expression of SOCS1 and SHIP1, it removes their inhibitory influence on the JAK/STAT and NF-κB pathways. The resulting excessive activation of cytokine signalling leads to increased production of IL-6, IL-17 and IFN-γ and strengthens Th1/Th17-driven immunity [49]. In PBC, decreased expression of the vitamin D receptor (VDR) further amplifies the miR-155/SOCS1 signalling axis [64]. Vitamin D receptor, a ligand-activated transcription factor with immunomodulatory properties, represses MIR155HG transcription by binding to its promoter. Reduced VDR levels, therefore, lead to derepression of miR-155, enhanced production of pro-inflammatory cytokines and dysregulation of Th1 and Th17 cell activity. In cellular models, restoration of VDR expression reduces miR-155 levels and increases SOCS1 expression, confirming the existence of a functional VDR/miR-155/SOCS1 axis that plays an important role in PBC pathogenesis [64].

MicroRNA-155 overexpression also downregulates PPARα, a nuclear receptor that governs fatty acid metabolism, bile acid homeostasis and anti-inflammatory responses [54]. In liver samples from patients with cirrhotic-stage PBC, miR-155 levels were more than 3-fold higher than in controls, correlating with decreased PPARα transcript and protein levels [54]. *In vitro*, transfection of HepG2 hepatocytes with miR-155 mimics has resulted in reduced PPARα expression, whereas this effect has not been observed in normal human cholangiocytes, highlighting a cell-type-specific regulatory pattern. MicroRNA-155 induction has also been associated with activation of the TLR4/IL-6/STAT3 inflammatory cascade following stimulation with LPS, confirming its role as a molecular link between

inflammatory signalling and metabolic dysregulation in hepatocytes [54].

In PBC, functional crosstalk between miR-155 and FXR (NR1H4) signalling has been observed, bridging inflammatory processes with bile acid metabolism. Farnesoid X receptor acts as a nuclear receptor and bile acid sensor that suppresses bile acid synthesis (primarily by inducing fibroblast growth factor 19 – FGF19 – and secondarily repressing CYP7A1), while enhancing detoxification and transport pathways (BSEP and MDR3). Together, these effects provide strong anti-inflammatory and anti-cholestatic protection [65, 66, 67]. Pharmacological activation of FXR by OCA improves biochemical markers of cholestasis in UDCA-non-responders. In the POISE trial, ~46–47% of OCA-treated patients met the composite endpoint compared with only 10% in the placebo group (with a higher frequency of pruritus in OCA-treated patients) [68].

Conversely, miR-155, through the repression of SOCS1 and SHIP1, enhances IL-6/STAT3 and NF-κB signalling, reinforcing chronic inflammatory activation and indirectly weakening the transcriptional environment favourable for FXR activity. This represents functional antagonism, rather than a direct downregulation of NR1H4 transcription by miR-155 [54, 64]. Importantly, UDCA reduces baseline and LPS-induced miR-155 expression in hepatocyte models and restores PPARα levels, partially normalising the transcriptional control of detoxification pathways and anti-inflammatory responses. These findings support the hypothesis that combining miR-155-targeting approaches with FXR agonists may represent a future personalised therapeutic strategy for patients with sub-optimal UDCA response.

Overall, miR-155 serves as a multi-layered molecular modulator in PBC, integrating immunological, metabolic and epigenetic processes. Through repression of SOCS1, SHIP1 and PPARα, as well as through interactions with VDR and FXR signalling, miR-155 links chronic inflammation with bile acid and lipid metabolic disturbances. Dysregulation of these mechanisms contributes to persistent immune activation, cholangiocyte injury and progressive hepatic fibrosis. Recognising the role of miR-155 in these interconnected pathways opens the door to therapeutic strategies involving miR-155 inhibitors or modulators of the VDR/FXR/PPARα axes as adjunctive therapies for PBC. Moreover, circulating miR-155 shows high stability and reproducible serum/plasma levels [69], making it a promising prognostic biomarker and potential indicator of therapeutic response to UDCA or combination therapy.

microRNA-155 IN PRIMARY SCLEROSING CHOLANGITIS

The coexistence of PSC with IBD leads to the development of a distinct inflammatory phenotype known as PSC-UC. Compared to classic UC, this condition differs in terms of the distribution of inflammatory lesions, as well as immunologic, microbiologic and oncologic profiles [70]. In classic UC, inflammation is continuous and predominantly left-sided, beginning in the rectum and extending proximally. In contrast, PSC-UC lesions are often patchy and right-sided, involving the ascending and transverse colon, with relatively mild rectal involvement [71, 72]. The clinical course of PSC-UC is associated with a persistent risk of early colorectal cancer development, typically located in the right colon [71, 73].

Immunologically, PSC-UC is characterised by a predominance of Th17 lymphocytes via activation of the IL-17 axis [74], increased levels of pro-inflammatory cytokines such as IL-6 and TNF-α driven by bile acid metabolic disturbances [75, 76] and the dysregulation of the gut-liver axis, where toxic bile acids (including glycochenodeoxycholic acid – GCDCA) exacerbate the inflammatory response [76]. These same stimuli have been shown to modulate miR-155 expression, linking inflammatory responses with epigenetic processes [77].

MicroRNA-155 expression in the PBMCs of patients with PSC is higher than in PBC patients [78]. MicroRNA-155 expression in the intestinal mucosa of patients with PSC and PSC-UC is significantly higher than in patients with classic UC or in healthy controls [77]. In the ascending colon of PSC and PSC-UC patients, elevated miR-155 levels are accompanied by SOCS1 suppression and enhanced STAT3 pathway activation (including increased p-STAT3 in PBMCs). This miR-155↑/SOCS1↓/STAT3↑ axis promotes persistent IL-6/STAT3 signalling and Th17 amplification, driving chronic inflammatory activation.

Concurrently, dysfunction in the MMR system (responsible for correcting DNA replication errors and maintaining genomic stability) has been observed. Mechanistically, miR-155 binds to the 3′-UTR of MutL homolog 1 (MLH1) and MutS homolog 2 (MSH2) transcripts, inhibiting their translation and impairing DNA repair [79]. In the ascending colon of PSC and PSC-UC patients, MSH2 expression is reduced. Additionally, PSC-UC patients exhibit decreased MutS homolog 6 (MSH6), while PSC patients show reduced MLH1 expression [77]. Dysfunction of these genes leads to MSI, resulting in the accumulation of mutations in short repetitive DNA sequences. MSI-high (MSI-H) phenotypes are observed predominantly in the proximal (right) colon.

Overexpression of miR-155 reduces MLH1/MSH2/MSH6 levels in NCM460D cells and modulates p53 expression in a cell type-dependent manner (↑ p53 in NCM460D and ↓ p53 in HT-29). Mechanistically, this links the miR-155/SOCS1/p53 axis to MMR defects, MSI and an increased risk of malignant transformation in the intestinal mucosa [77]. In the sigmoid colon of PSC-UC patients, miR-155 upregulation has not been observed; instead, IL-6/STAT3 activation predominates, accompanied by elevated sphingosine-1-phosphate receptor 1 (S1PR1) and an altered IL-17/FOXP3 ratio, which promotes chronic inflammation [77].

Activation of the IL-6/STAT3 pathway indirectly triggers the DNMT1/PTEN risk axis through DNMT1 induction and PTEN suppression [80]. *In vitro* studies complement these findings: GCDCA induces miR-155 expression in Caco-2 cells, while miR-155 inhibition increases S1PR1 expression, demonstrating a functional link between toxic bile acids, local miRNA regulation and gut-liver axis disturbances [77].

In patients with PSC and PSC-UC, elevated miR-155 levels in PBMCs are associated with decreased SOCS1 expression and

increased p-STAT3, indicating that the miR-155/SOCS1/STAT3 axis contributes to systemic inflammatory responses [77]. These molecular mechanisms have also been confirmed in experimental models. MicroRNA-155 knockout mice subjected to dextran sodium sulphate-induced colitis exhibit a milder disease course, reduced pro-inflammatory cytokine levels (IL-6, TNF-α, IFN-γ and IL-17) and limited recruitment of $CD4^+$ $CCR9^+$ lymphocytes to the mucosa [81].

In human HT-29 cells, miR-155 directly inhibits Forkhead Box O3a (FOXO3a), an anti-inflammatory transcription factor, resulting in NF-κB activation and increased IL-8 expression [82]. In colorectal cancer cells, miR-155-5p post-transcriptionally regulates the RNA-binding human antigen R protein, and its inhibition reduces migration and metastatic potential [83].

Collectively, these observations indicate that miR-155 functions as a multi-level integrator of inflammatory, epigenetic and oncogenic processes. By repressing SOCS1, MMR genes and FOXO3a, while activating IL-6/STAT3 and S1PR1/STAT3 axes, miR-155 links inflammation with genomic instability and intestinal barrier dysfunction. Excessive miR-155 expression in the PSC-UC phenotype establishes a self-amplifying, inflammatory-epigenetic loop, in which pro-inflammatory cytokines, bile acids and oxidative stress mutually enhance STAT3 and NF-κB signalling. Therefore, miR-155 may serve as both a biomarker of disease activity and colorectal cancer risk, as well as a therapeutic target for antagomirs or JAK/STAT and MMR modulators.

DIAGNOSTIC AND THERAPEUTIC SIGNIFICANCE OF microRNA-155

MicroRNA-155 is a key regulatory microRNA involved in inflammatory responses, fibrogenesis and oncogenic transformation. Depending on the biological material analysed – liver tissue, peripheral blood or intestinal biopsies – and the pathological context, miR-155 can serve as a biomarker with varying clinical relevance (Tab. 3).

TABLE 3. MicroRNA-155-based biomarkers

Example/Matrix	What we measure/Association	Potential application	References
miR-155 in liver biopsy (cholangiocytes, HSCs, macrophages)	inflammatory and fibrotic activity through regulation of SOCS1/STAT3, SHIP1/PTEN; activation of IL-6/JAK/STAT3 and PI3K/Akt pathways	risk stratification for PBC/PSC progression; qualification for targeted therapies (anti-miR-155, JAK/STAT inhibitors)	[77, 84, 85]
miR-155 in serum/plasma	correlation with ALP, IgM (PBC), PSC activity; PSC-UC vs. UC signature	non-invasive monitoring of PBC activity	[85]
miR-155 in colonic biopsy (segmental)	deregulation of MMR system (MLH1/MSH2/MSH6) and MSI-H; activation of IL-6/S1PR1/STAT3 axis; imbalance of IL-17/FOXP3	deregulation of MMR system (MLH1/MSH2/MSH6) and MSI-H; activation of IL-6/S1PR1/STAT3 axis; IL-17/FOXP3 imbalance	[77]
miR-155 in HCCs (tissue/circulation)	PTEN and SHIP1 inhibition → PI3K/Akt/NF-κB activation; increased proliferation and invasiveness	assessment of HCC aggressiveness; qualification for clinical trials of anti-miR-155/PI3K-Akt therapies	[44, 86]

ALP – *alkaline phosphatase*; HCC – *hepatocellular carcinoma*; HSC – *hepatic stellate cells*; IL – *interleukin*; IgM – *immunoglobulin M*; JAK – Janus kinase; NF-κB – nuclear factor kappa B; MLH1, MSH2, MSH6 – *MutL/MutS homologs*; MMR – *mismatch repair*; MSI – *microsatellite instability*; p-Akt – *phosphorylated Akt*; PBC – *primary biliary cholangitis*; PSC – *primary sclerosing cholangitis*; PSC-UC – *primary sclerosing cholangitis*-associated with *ulcerative colitis;* PTEN – *phosphatase and tensin homolog*; S1PR1 – *sphingosine-1-phosphate receptor 1*; SHIP1 – *Src homology 2-containing inositol-5-phosphatase 1*; SOCS1 – *suppressor of cytokine signalling 1*; STAT3 – *signal transducer and activator of transcription 3*; ↑/↓ – increase/decrease of expression or pathway activity

It reduces miR-155-5p expression and increases levels of MLH1, MSH2 and MSH6, potentially lowering the risk of developing MSI-H colorectal cancer in chronic intestinal inflammation, particularly in PSC-UC [88, 89]. ursodeoxycholic acid also suppresses miR-155 expression (both basal and LPS-induced), restoring PPARα levels and partially normalising the transcriptional regulation of detoxification and anti-inflammatory genes [54].

Since miR-155 regulates both immune and metabolic components, its effects extend to bile acid homeostasis and nuclear receptor activity, including PPARα [90] and FXR [65]. Overexpression of miR-155 in PBC may indirectly impair FXR signalling through increased IL-6 and STAT3 activation, perpetuating cholestatic inflammation and disrupting the feedback control of bile acid synthesis. Parallel efforts are underway to develop advanced delivery systems for miR-155 inhibitors – such as PEGylated albumin nanoparticles, lipid- and polymer-based

With a growing understanding of the pathways regulated by miR-155, therapeutic targeting of this microRNA has emerged as a potential strategy to limit chronic inflammation, fibrosis and genomic instability in PBC and PSC. AntagomiR-155 (cobomarsen, MRG-106) [87], an miR-155 inhibitor clinically evaluated in lymphoid malignancies such as cutaneous T cell lymphoma, has demonstrated biological activity and an acceptable safety profile. In cholestasis models (bile duct ligation and carbon tetrachloride – CCl_4), pharmacological inhibition of miR-155 reduces fibrosis and p-STAT3 activation while normalising markers of inflammation and oxidative stress [47].

Current evidence suggests that 5-aminosalicylic acid (5-ASA; mesalazine) is a classic anti-inflammatory agent used in IBD.

nanocarriers, microspheres and controlled-release hydrogels – which enhance both selectivity and bioavailability. Combining molecular strategies (antagomiRs, epigenetic modulation and targeted therapies) with conventional treatments (5-ASA, UDCA, OCA) could enable personalised therapeutic approaches for PBC and PSC patients in the future.

LIMITATIONS AND FUTURE DIRECTIONS

Despite extensive experimental and translational evidence, the precise role of miR-155 in the pathogenesis of cholestatic liver diseases such as PBC and PSC, and its link to IBD (PSC-UC), remains incompletely understood and requires further clinical validation. To date, most studies have relied on small, single-centre cohorts and animal models, limiting the generalisability of findings. Prospective, multi-centre analyses are lacking, and it remains unclear whether miR-155 could serve as a reliable prognostic or diagnostic biomarker for inflammation, fibrosis or colorectal cancer risk.

Additional challenges include population heterogeneity, e.g., differences in age, disease duration, co-existing IBD and therapies (UDCA, 5-ASA, immunosuppressants) and the absence of standardised analytical methods. Variations in miRNA detection platforms (quantitative PCR, next-generation sequencing, microarrays) and reference genes (e.g., U6 and miR-16) complicate cross-centre comparisons and limit meta-analyses. Developing unified pre-analytical and analytical standards, including sample type (serum, plasma, tissue), RNA stabilisation procedures and normalisation/reporting protocols is, therefore, essential.

Regarding therapy, although antagomiR-155 has demonstrated anti-inflammatory and anti-fibrotic effects in experimental models, clinical trials assessing its efficacy and safety in PBC/PSC patients are lacking. Pharmacokinetic and toxicological evaluations of advanced delivery systems such as PEGylated albumin nanoparticles, hyaluronic acid-CD44 complexes or controlled-release hydrogels are also required to ensure selective and safe delivery to liver and intestinal cells.

Future research directions should include evaluating miR-155 as part of integrated biomarker panels, exploring its role in differentiating PSC-UC and classic UC phenotypes, and integrating miRNA data with transcriptomic, proteomic and epigenomic analyses within the framework of emerging personalised medicine.

CONCLUSIONS

MicroRNA-155 represents a central regulatory node, integrating innate and adaptive immune mechanisms, fibrogenesis, and oncogenesis in cholestatic liver diseases. In PBC, the VDR--miR-155/SOCS1 axis plays a pivotal role in sustaining autoimmunity and remodelling hepatic stroma. Concomitantly, miR-155 overexpression suppresses the nuclear receptor PPARα, exacerbating oxidative stress, disrupting bile acid metabolism and activating HSCs. At the metabolic-regulatory level, miR-155 may also indirectly affect FXR (NR1H4), a key bile acid sensor with anti-inflammatory and anti-cholestatic functions.

Chronic activation of the IL-6/STAT3 and NF-κB pathways, characteristic of the miR-155↑/SOCS1↓ phenotype, limits FXR transcriptional activity and disrupts FGF19-CYP7A1 feedback, perpetuating bile acid homeostasis, dysregulation and cholestasis progression. In PSC, miR-155 links IL-6/S1PR1/STAT3 signalling with DNMT1/PTEN deregulation and MMR deficiencies, promoting high MSI and an increased risk of right-sided colorectal cancer.

Translational strategies include the development of miR-155 inhibitors and intelligent drug delivery systems that enable targeted therapy to the liver and intestine. These approaches, combined with modulation of the nuclear receptors FXR, PPARα and VDR, may form the basis for future personalised therapies and chemopreventive programmes in autoimmune cholangiopathies.

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