Pomeranian J Life Sci 2025;71(4):49-59 doi: 10.21164/pomjlifesci.1167

miR-125a/b as key regulators of the pathogenesis of cholestatic liver diseases: a review of molecular mechanisms*

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ABSTRACT

MicroRNAs are small, non-coding RNA molecules that play a crucial role in the regulation of gene expression at the post-transcriptional level, influencing various physiological and pathological processes. The microRNAs miR-125a and miR-125b have divergent roles in the pathogenesis of chronic cholestatic liver diseases such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). miR-125a exerts protective effects by inhibiting the expression of pro-inflammatory cytokines (tumour necrosis factor-α, interleukin-1β), limiting transforming growth factor (TGF)-β-dependent activation of hepatic stellate cells, and reducing oxidative stress. Additionally, microR-125a supports hepatocyte regeneration, promotes the M2 macrophage phenotype, and maintains immune homeostasis. Consequently, its expression is associated with protective effects, significant therapeutic potential, and may have possible utility as a protective and prognostic biomarker. In contrast, miR-125b primarily fulfils pathological functions. Its overexpression enhances the production of pro-inflammatory cytokines, activates T lymphocytes, and potentiates TGF-β signalling – promoting fibrogenesis. It also increases hepatocyte apoptosis and oxidative stress, contributing to disease progression and the development of hepatocellular carcinoma and cholangiocarcinoma. The expression of both microRNAs is modulated by epigenetic factors and is dependent on age and sex, underscoring their significance in the personalisation of therapy for PBC and PSC. Understanding the distinct mechanisms of action of miR-125a and miR-125b can open new avenues for developing targeted therapeutic strategies that could improve prognosis and quality of life in patients with cholestatic liver diseases.

Keywords: microRNA; primary biliary cholangitis; primary sclerosing cholangitis; liver fibrosis; immune response; biomarkers.

INTRODUCTION

Cholestatic liver diseases result from abnormal bile production or impaired bile flow. Damage to the bile ducts or hepatocytes can lead to a spectrum of clinical manifestations, ranging from abnormalities in liver biochemistry to liver failure, and ultimately to the development of liver and bile duct cancers. In response to this damage, cholangiocyte and hepatocyte proliferation occurs, which may promote the development of periductal and bile duct fibrosis, ultimately progressing to liver cirrhosis. Among the rare cholestatic liver diseases are primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) [1].

There is evidence that epigenetic modifications, including gene expression regulated by microRNAs, influence the development of cholestatic diseases. MicroRNAs are short (~20 nucleotides), non-coding RNA molecules that constitute a crucial class of endogenous gene expression regulators acting through translational inhibition and mRNA destabilisation [2, 3]. Depending on their target genes, microRNAs may act as tumour suppressors or oncogenes and have been recognized as key initiators and/or drivers in certain cholangiopathies [4, 5]. Transcriptomic studies have highlighted the significant role of miR-125 in the pathogenesis of cholestatic liver diseases [6, 7, 8, 9]. The miR-125 family is involved in regulating inflammatory pathways, apoptosis, and cellular differentiation, and its importance has been documented in numerous liver diseases, including cancers and chronic inflammatory states [10, 11]. Mounting data have indicated that members of this family may also play a critical role in the pathogenesis of cholestatic liver diseases such as PSC and PBC [6, 9, 11].

This review aims to present the current state of knowledge regarding the role of miR-125a and miR-125b in regulating inflammatory processes, fibrosis, and tumorigenesis in the course of PBC and PSC. This article seeks to analyse available experimental and clinical data on the molecular mechanisms through which miR-125a/b influences inflammatory cell activation, hepatic stellate cell (HSC) trans-differentiation, and the development of neoplastic changes. The review also aims to identify the potential diagnostic and therapeutic significance of these microRNAs as biomarkers or molecular targets in the treatment of cholestatic liver diseases.

PRIMARY BILIARY CHOLANGITIS AND PRIMARY SCLEROSING CHOLANGITIS

Primary biliary cholangitis is a chronic, slowly progressive disease characterised by the gradual destruction of liver structures [12]. The aetiology and pathogenesis of the disease, as well

* This research was funded by the National Science Centre in Poland, grant No. 2020/39/O/NZ4/01732.

as the mechanisms underlying therapeutic responses, have not been fully elucidated; however, the involvement of an autoimmune response is undeniable. One characteristic marker of PBC is the presence of anti-mitochondrial antibodies of the AMA M2 type in sera, detectable in up to 95% of patients [13]. The disease affects females in 80–90% of cases [14] and is characterised by persistent pruritus and chronic fatigue, although it may be asymptomatic in a significant proportion of patients [15]. Individuals with PBC frequently have concomitant autoimmune diseases, including Sjögren's syndrome [16], thyroid disorders [17], limited systemic sclerosis [18], and rheumatoid arthritis [19]. Patients are at risk of developing hepatocellular carcinoma (HCC) within 5–10 years, with the highest risk observed in males, individuals with advanced disease, and those who are unresponsive to ursodeoxycholic acid (UDCA) therapy [20].

Primary sclerosing cholangitis is a chronic disease of complex aetiology, characterised by progressive destruction of the bile ducts and, consequently, the liver, through mechanisms of autoimmunity and cholestasis [1]. Early symptoms may include pruritus, fatigue, and jaundice. One of the most serious complications is cholangiocarcinoma (CCA), with a lifetime risk of approx. 20%, which is 600 times higher than in the healthy population. In its early stages, the tumour is asymptomatic and difficult to detect, thus diagnosis often occurs at an inoperable stage. Systemic treatment is largely ineffective, resulting in a poor prognosis, with a median survival time of less than 12 months [21, 22, 23, 24, 25, 26, 27]. Patients may also have an elevated risk of gallbladder cancer (GBC), especially in the presence of inflammatory changes or polyps, with a lifetime risk estimated at approx. 3–6% [28]. The risk of HCC in PSC patients is significantly lower but may increase in the presence of co-existing liver cirrhosis [29]. Approximately 70–80% of PSC patients are diagnosed with ulcerative colitis (UC) [30, 31]. Primary sclerosing cholangitis associated with UC represents a distinct phenotype of PSC that increases the risk of colorectal cancer (CRC) by 4–10 times, occurring at a significantly younger age compared to patients with UC alone. The factors linking PSC and UC are being actively studied; however, the reasons for the increased CRC risk remain unknown [32].

THE miR-125 FAMILY

The miR-125 microRNA family is among the oldest and most evolutionarily conserved group of small RNA regulators. Its history traces back to the early 1990s, when a small RNA molecule, lin-4, was first discovered in the nematode *Caenorhabditis elegans*. Initially, no one suspected that such a short segment of non-coding RNA could perform significant biological functions; however, lin-4 turned out to be crucial in regulating organismal development, as it blocked the translation of one of the regulatory genes, *lin-14* [33]. A few years later, another microRNA, let-7, was discovered, and, to scientists' surprise, was found not only in nematodes but also in humans and other mammals [34]. This marked a breakthrough, revealing that microRNAs are a universal and deeply embedded regulatory mechanism in animal biology. The direct mammalian homolog of lin-4 is miR-125, which exhibits an almost unchanged sequence and a similar regulatory function in neuronal development and heterochronic gene expression, as confirmed in mammals [35]. In the following years, it was established that, in humans, miR-125 is encoded at 3 genomic loci: *MIR125A* (19q13.41), *MIR125B1* (11q24.1), and *MIR125B2* (21q21.1), with each transcribing precursors processed into nearly identical, mature microRNA forms [36]. These homologs share an identical short nucleotide fragment responsible for recognising and binding to target mRNAs (the 'seed sequence'), although they reside in different chromosomal clusters. miR-125a is located on chromosome 19q13.41 [36], while miR-125b is transcribed from 2 loci on chromosomes 11q24.1 (hsa-miR-125b-1) and 21q21.1 (hsa-miR-125b-2) [37]. Each member of the miR-125 family produces 2 distinct mature microRNAs, known as 5p and 3p, derived respectively from the 5′ and 3′ arms of the pre-microRNA hairpin structure. Among these variants, miR-125-5p is generally expressed at higher levels than miR-125-3p [36]. The miR-125 family influences the immune response by regulating T cell differentiation and activation [38], as well as macrophage polarisation [39]. Moreover, by modulating signalling pathways such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [40], signal transducer and activator of transcription 3 (STAT3) [41], phosphoinositide 3-kinase (PI3K)/serine/threonine kinase (Akt) [42], and tumour protein p53 (p53) [43]. These microRNAs play key roles in controlling inflammatory processes and tumorigenesis.

LIVER FIBROSIS: THE ROLE OF miR-125a/b IN MODULATING TRANSFORMING GROWTH FACTOR-β, PROFIBROGENIC PATHWAYS, AND HEPATIC STELLATE CELL ACTIVATION

Both miR-125a and miR-125b play important roles in the pathogenesis of liver fibrosis, a pivotal stage in the progression of cholestatic liver diseases. Both microRNAs regulate the activation of HSCs, the principal mediators of fibrosis, and influence molecular pathways responsible for collagen synthesis and inflammatory responses (Tab. 1). miR-125a participates in HSC activation via the factor inhibiting hypoxia-inducible factor 1–hypoxia-inducible factor 1-alpha (FIH1-HIF-1α) pathway [44] and disrupts hepatocyte autophagy via modulation of the vitamin D receptor (VDR) [45]. Its level correlates with the stage of fibrosis, making it a promising biological marker and potential therapeutic target. miR-125b also exerts dual effects – it promotes fibrosis through the Ras homolog family member A/StAR-related lipid transfer domain containing 13 (RhoA/Stard13) axis [10], but also inhibits fibrogenesis via regulation of GLI family zinc finger 3 (Gli3) [46]. In the context of acute liver failure, miR-125b provides protection via the Kelch-like ECH-associated protein 1/nuclear factor, erythroid 2-like 2 (KEAP1/NRF2) pathway [10]. In cholestatic diseases, its deficiency in cholangiocytes may accelerate bile duct fibrosis through transforming growth factor beta 1/vascular

endothelial growth factor (TGF-β1/VEGF) signalling [9]. It may also regulate inflammatory and immune processes (Tab. 1). In PBC and PSC, where chronic inflammation of the bile ducts progressively triggers HSC activation and fibrosis development, dysregulation of miR-125a and miR-125b expression correlates with the severity of fibrotic changes and liver function. Increased expression of miR-125a is associated with a poor prognosis, whereas variable expression of miR-125b is linked to different stages of the disease and therapeutic response. Our studies indicate that elevated miR-125b expression correlates with higher degrees of liver fibrosis and reduced levels of apelin and androgen receptor, particularly in men with PSC [47, 48, 49, 50, 51]. Thus, assessing miR-125a and miR-125b levels may serve as a potential biomarker for fibrosis progression and therapeutic response in patients with PBC and PSC and may represent a target for new treatment strategies for these chronic liver diseases.

REGULATION OF IMMUNE RESPONSE AND INFLAMMATION: THE EFFECT OF miR-125a/b CYTOKINES, LYMPHOCYTES, AND TRANSCRIPTION FACTORS (NF-Kβ, STAT3, ACTIVATOR PROTEIN-1)

Inflammation and the immune response are critical in the pathogenesis of cholestatic liver diseases, and they follow fibrosis as key pathogenic steps. In PSC and PBC, chronic inflammation in the bile ducts is a central pathogenic factor. miR-125a may alleviate chronic inflammation by shifting macrophage polarisation from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 [52, 53, 54] phenotype, reducing tumour necrosis factor alpha (TNF-α) expression [55, 56] and modulating toll-like receptor 2/4 expression [52, 57, 58] – Table 2. Conversely, miR-125b enhances the inflammatory response, which, in the context of autoimmunity, may exacerbate bile duct injury. Thus, its modulation could be a therapeutic target, e.g. through inhibition of excessive M1 activation or regulation of T helper 17 cells and regulatory T cell interactions [39, 59, 60, 61] – Table 2. Direct data from PSC/PBC models are limited; however, the mechanisms described above are highly relevant and provide a robust foundation for further research.

CELLULAR MICROENVIRONMENTS AND INTERCELLULAR INTERACTIONS – INCLUDING miR-125a/b INTERACTIONS WITH IMMUNE CELLS

miR-125a and b play an important role in modulating the hepatic cellular microenvironment, which is crucial for the development and progression of cholestatic liver diseases. Both microRNAs affect the function of various immune cells, including macrophages and T lymphocytes, which play a central role

TABLE 1. The role of miR-125a/b in liver fibrosis in the context of primary biliary cholangitis and primary sclerosing cholangitis

Aspect/Function	miR-125a	miR-125b	Context of PBC and PSC
Role in liver fibrosis	Increased expression observed in fibrosis models and in patients with chronic HBV infection and cirrhosis [48]. Inhibition of miR-125a-5p alleviates fibrosis by affecting the FIH1/HIF-1α and autophagy in HSCs [44].	Modulates HSC activity by regulating TGF-β signalling, influencing collagen production and pro-inflammatory cytokines [10]. Inhibits RhoA protein activity; its downregulation promotes fibrosis [10]. May exert protective effects by regulating GLI family zinc finger 3 (Gli3), reducing HSC activation and α-SMA levels [46].	In PBC and PSC, chronic inflammation of the bile ducts leads to activation of HSCs and fibrosis. miR-125a and miR-125b may regulate these processes, influencing fibrosis progression and liver function.
Molecular mechanisms	Through modulation of FIH1, it stabilizes HIF-1α, which activates HSCs and stimulates expression of fibrosis-related genes. Inhibits VDR, disrupting hepatocyte autophagy, leading to cell damage and promoting fibrosis [45]. Induced by TGF-β in hepatocytes and HSCs [49].	Regulates TGF-β1/VEGF-A pathway in cholangiocytes; decreased miR-125b → increased TGF-β1 → HSC activation → fibrosis [9].	Dysregulation of these pathways is characteristic of PBC and PSC progression, where miR-125a and miR-125b may modulate both fibrosis and inflammation.
Clinical significance	Increased expression of miR-125a correlates with the severity of fibrosis [45, 50]; potential therapeutic target.	miR-125b serves as a biomarker of fibrosis and a protective marker in acute liver failure [51]; therapeutic target in liver fibrosis.	miR-125a and miR-125b may serve as biomarkers of fibrosis progression and therapeutic response in patients with PBC and PSC.

HSC – hepatic stellate cell; PBC – primary biliary cholangitis; PSC – primary sclerosing cholangitis; TGF – transforming growth factor; VDR – vitamin D receptor; VEGFA-A – vascular endothelial growth factor; HBV – hepatitis B virus; FIH1 – factor inhibiting hypoxia-inducible factor 1; HIF-1α – hypoxia-inducible factor 1-alpha; RhoA – Ras homolog family member A

TABLE 2. Role of miR-125a/b in the regulation of immune response and inflammation in the context of primary biliary cholangitis and primary sclerosing cholangitis

Aspect/Function	miR-125a	miR-125b	Context of PBC and PSC
Modulation of immune response	Inhibits polarisation of macrophages from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype M2 [52, 53, 54].	Enhances macrophage activation, increasing MHC II and CD40/CD86 expression, leading to stronger antigen presentation and T-cell activation [39].	In PBC and PSC, hyperactivity of the immune system plays a key role; modulation of miR-125 may help mitigate this response.
Effect on inflammatory cytokines	Suppresses production of IFN-γ, TNF-α, and IL-17A [55, 56]. Reduces TNF-α, IL-12, and iNOS expression in macrophages [52].	Decreases nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα) phosphorylation, reducing transcription factor p65/ nuclear factor NF-kappa-B p105 subunit (p65/ p50) activation and transcription of pro-inflammatory genes [62]. Lowers STAT3 protein expression, limiting synthesis of STAT3-dependent cytokines [60].	Inflammatory cytokines are major mediators of tissue damage in PBC and PSC; controlling their expression is crucial for therapy.
Interaction with TLR	Activated by TLR2/4 via the myeloid differentiation primary response gene 88 (MyD88) pathway (rapid inflammatory response), not via TIR domain-containing adaptor molecule 1 (TRIF) [52, 57]. Suppresses inflammatory differentiation, including TLR4 and IRAK1 expression [58].	Suppresses TNFSF4 expression, weakening the TLR4/NF-κB signalling pathway [61].	Excessive TLR activation contributes to chronic inflammation in PBC and PSC; miR-125 may help suppress this process.
Regulation of inflammatory cells	Reduces MHC II expression and regulates phagocytosis [63]. Inhibits monocyte adhesion and migration by suppressing JAM-A, JAM-L, and CCR2 genes [64]; acts as an NF-κB pathway activator via negative regulation of TNFAIP3 [59].	Acts bidirectionally: negatively regulates TNF-α & iNOS through TRAF6 and IRF4 [65, 66]; influences macrophage activation, including expression of co-stimulatory molecules such as MHC II, CD40, CD80, and CD86 [39]; acts as an NF-κB activator via TNFAIP3 regulation [59].	The balance between pro- and anti-inflammatory macrophages is crucial for PBC and PSC progression.
Therapeutic potential	Potential target for anti-inflammatory and immunomodulatory therapy in PBC and PSC.	Promising candidate biomarker and therapeutic target for controlling inflammation.	Modulating miR-125 could improve treatment outcomes and slow disease progression.

IL – interleukin; JAM – junctional adhesion molecule; MHC – major histocompatibility complex; NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells; STAT3 – signal transducer and activator of transcription 3; TLR – toll-like receptors; TNF –tumour necrosis factor alpha; PBC – primary biliary cholangitis; PSC – primary sclerosing cholangitis; IFN-γ – interferon gamma; iNOS – nitric oxide synthase 2; IRAK1 – interleukin 1 receptor associated kinase 1; CCR2 – C-C motif chemokine receptor 2; TNFAIP3 – tumor necrosis factor alpha-induced protein 3; TNFSF4 – tumor necrosis factor (ligand) superfamily, member 4; TRAF6 – tumor necrosis factor receptor-associated factor 6; IRF4 – interferon regulatory factor 4

in chronic bile duct inflammation (Tab. 3). Additionally, miR-125a regulates intercellular communication by suppressing excessive activation of HSCs and influencing TGF-β signalling, supporting immune homeostasis and regenerative processes [50, 52, 67, 68] – Table 3. Conversely, miR-125b exhibits more complex effects, modulating T cell and macrophage activation such that it that may enhance inflammation and promote pro-inflammatory cytokine production [39, 69, 70]. It also interacts with endothelial and stellate cells, intensifying inflammatory processes and fibrogenesis [71, 72, 73]. As a result, miR-125b may contribute to maintaining chronic inflammation and fibrosis progression. Therefore, the balance of miR-125a and miR-125b expression and function is crucial for regulating the hepatic microenvironment and the course of cholestatic diseases. Understanding these mechanisms may lead to the development of new therapeutic strategies targeting these microRNAs to alleviate chronic inflammation and slow PBC and PSC progression.

THE ROLES OF miR-125a/b IN CHOLANGIOCARCINOMA HEPATOCELLULAR CARCINOMA GALLBLADDER CANCER, AND COLORECTAL CANCER

Both miR-125a and miR-125b play distinct roles in carcinogenesis within cholestatic liver diseases, particularly in CCA, HCC, and GBC (Tab. 4). In CCA, miR-125a functions as a tumour suppressor. miR-125a is epigenetically silenced in CCA cells, and its restoration inhibits cell proliferation and invasion, partly by targeting the oncogene *CAC1* (*CACUL1*, CDK2-Associated Cullin Domain 1) [74, 75, 76]. In HCC, miR-125a inhibits cancer

TABLE 3. Role of miR-125a/b in the cellular microenvironment and intercellular interactions in primary biliary cholangitis and primary sclerosing cholangitis

Aspect/Function	miR-125a	miR-125b	Context of PBC and PSC
Effect on immune cells	Modulates macrophage activity, suppressing the production of pro-inflammatory cytokines (TNF-α, IL-1β), promoting polarisation from the M1 toward the M2 phenotype [52, 68, 73].	Regulates T cell and macrophage activation, promoting pro-inflammatory cytokine expression and immune response [39, 69, 70].	In PSC and PBC, chronic bile duct inflammation is associated with increased numbers of macrophages and lymphocytes; miR-125a and miR-125b may modulate their functions, affecting inflammation and fibrosis progression.
Intercellular interactions	Involved in regulating endothelial permeability and monocyte migration during acute inflammation [67].	Regulates macrophages and their inflammatory response [69]; influences hematopoietic stem cell expansion and preferential differentiation toward lymphoid lineages, important for immune balance and regenerative capacity [72]; miR-125b in MSC-derived exosomes has protective, anti-inflammatory effects, limiting adverse vascular changes [74].	In PSC and PBC, these interactions are crucial for maintaining chronic inflammation and fibrosis progression; miR-125a/b may modulate these signals and affect disease dynamics.
Regulation of the liver microenvironment	Indicates a positive effect of miR-125a-3p on regenerative processes, suggesting modulation of inflammatory responses [74, 75].	May support chronic activation of inflammatory cells and promote fibrogenesis through increased expression of pro-inflammatory factors [71, 72].	In PSC and PBC, the cellular microenvironment is disrupted by chronic inflammation; modulation of miR-125a/b may influence the balance between regenerative and pathological processes.

PBC – primary biliary cholangitis; PSC – primary sclerosing cholangitis; TNF-α – tumour necrosis factor alpha, IL – interleukin; MSC – mesenchymal stem cells

cell proliferation and migration through the modulation of the PI3K/AKT/mTOR pathway [42], highlighting its significant role as a negative regulator of HCC progression. In HCC, miR-125b suppresses cancer cell proliferation and migration by directly targeting molecules such as sirtuin 7 [77] and thioredoxin reductase 1 [78], and regulates apoptosis via the modulation of myeloid cell leukaemia sequence 1, and the interleukin (IL)-6 receptor [79]. In GBC, miR-125b functions as a suppressor, inhibiting proliferation through the regulation of the anti-apoptotic protein c-FLIP (CASP8 and FADD-like apoptosis regulator) [80]. Additionally, miR-125b reduces angiogenesis in cholestatic models by inhibiting VEGF A and histidine decarboxylase expression in cholangiocytes – Table 4 [6]. Although direct oncologic data in CCA remain limited, these mechanisms suggest miR-125b may indirectly inhibit tumour progression via modulation of the tumour microenvironment and angiogenesis. Both miR-125a and miR-125b act as tumour suppressors in cholestatic liver cancers, although their scope of action varies by cancer type and molecular mechanism. miR-125a primarily exerts an inhibitory effect in CCA and HCC by directly suppressing cell proliferation and invasion. In contrast, miR-125b demonstrates a broader tumour-suppressive activity in HCC and GBC and the ability to limit angiogenesis under cholestatic conditions – an effect that may be critical in controlling tumour progression.

In PSC, a condition associated with a high risk of developing CRC, miR-125a and miR-125b play significant, though partially distinct, roles in regulating oncogenic and inflammatory processes. Both miR-125a and miR-125b can function as tumour suppressors. miR-125a inhibits CRC development and metastasis [81] – Table 5, whereas miR-125b exhibits a more complex role – it may suppress proliferation, or, depending on the context, promote an aggressive tumour phenotype (Tab. 5). miR-125a modulates tumour cell

TABLE 4. Comparison of the role of miR-125a and miR-125b in cholangiocarcinoma, hepatocellular carcinoma and gallbladder cancer

Feature	miR-125a	miR-125b
Role in CCA	Tumour suppressor; inhibits proliferation and invasion by targeting CDK2-Associated Cullin Domain (CAC1) [76].	No direct oncologic data in CCA; anti-angiogenic mechanisms (inhibition of VEGF-A, HDC) suggest potential anti-tumour activity [6].
Role in HCC	Tumour suppressor; inhibits proliferation and migration via the phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin (PI3K/AKT/mTOR) pathway [42].	Tumour suppressor; inhibits proliferation SIRT7 [77], migration TXNRD1 [78]; regulates apoptosis via Mcl-1 and IL6R [79].
Role in GBC	No data available.	Tumour suppressor; inhibits proliferation by regulating c-FLIP [80].
Molecular mechanisms of anti-angiogenesis	No data available.	Inhibits VEGF-A and HDC expression in cholangiocytes, reducing cholestatic angiogenesis [6].

CCA – complications is cholangiocarcinoma; GBC – gallbladder cancer; HCC – hepatocellular carcinoma; IL – interleukin; HDC – histidine decarboxylase; VEGF – vascular endothelial growth factor; SIRT7 – sirtuin 7; TXNRD1 – thioredoxin reductase 1; Mcl-1 – myeloid cell leukaemia sequence 1

proliferation and migration primarily through the regulation of the Wnt/β-catenin signalling pathway (wingless-type MMTV integration site family, member 1/Catenin beta 1) [82] as well as the TGF-β pathway [83] – Table 5. In contrast, miR-125b influences the NF-κB and IL-6/STAT3 pathways [59, 84], which determine its role in apoptosis regulation and the epithelial-mesenchymal transition – both critical processes in tumour progression. Our studies have shown that miR-125b overexpression in the ascending colon of PSC patients disrupts the sphingosine-1-phosphate/ceramide axis [11]. These alterations may contribute to the development of microsatellite instability-high CRC in PSC patients. As miR-125a acts as a negative regulator of pro-inflammatory cytokines, it suppresses intestinal inflammation (Tab. 5) [52, 64, 85]. In contrast, miR-125b actively modulates inflammatory responses and mucosal regeneration, shaping a microenvironment conducive to tumorigenesis [86]. Both microRNAs serve as key regulators of tumorigenic and inflammatory processes in the colon of patients with PSC. Thus, their modulation represents a promising avenue for future research aimed at developing novel diagnostic and therapeutic strategies for this patient population [87, 88, 89, 90, 91, 92].

EFFECT OF URSODEOXYCHOLIC ACID AND 5-AMINOSALICYLIC ACID THERAPY ON miR-125a/b LEVELS

The standard treatment for PBC is UDCA therapy, which is also used in PSC. The American Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommend UDCA as the first-line therapy for PBC. Its clinical efficacy has also been confirmed in PSC patients [43, 93, 94, 95, 96, 97]. A key role of this hydrophilic bile acid is protecting hepatocytes from bile acid-induced apoptosis [98]. Ursodeoxycholic acid demonstrates the ability to modulate microRNA expression, including miR-125a and miR-125b, which play crucial roles in regulating inflammatory processes, fibrogenesis, and immune responses in the liver. Studies have indicated that UDCA may increase miR-125a expression levels, contributing to the suppression of inflammation and fibrogenesis (Tab. 6). In the case of miR-125b, our research has shown that UDCA lowers its level, suggesting it may be a promising therapeutic strategy for liver fibrosis in PSC [47]. Ursodeoxycholic acid also decreases NF-κB and STAT3 pathway activity, which helps reduce chronic inflammation and protect hepatocytes (Tab. 6).

5-aminosalicylic acid (5-ASA) therapy in PSC patients with concomitant UC acts as an anti-inflammatory and immunomodulatory agent. Our *in vitro* functional studies have confirmed that 5-ASA at a dose of 1000 μM effectively reduces miR-125b levels [99]. Suppression of miR-125b results in de-repression of target gene expression, including VDR, suppressor of cytokine signalling 1, Forkhead box O3, and DNA (cytosine-5)-methyltransferase 1, which are involved in regulating inflammation, cell cycle control, and the inhibition of proliferation [99].

In clinical research involving PSC and PBC patients, direct data regarding the influence of UDCA and 5-ASA on miR-125a and miR-125b expression are limited. Most information derives from experimental models and *in vitro* studies. Nonetheless, correlations have been observed between UDCA therapy and changes in these microRNAs, suggesting a potential significance of these mechanisms in treatment efficacy in PBC and PSC patients (Tab. 6) [100, 101, 102, 103, 104, 105]. Further research is needed to more precisely determine the role of 5-ASA in regulating these microRNAs.

THE ROLE OF miR-125a/b IN EPIGENETIC REGULATION AND INTERACTIONS WITH OTHER MICRORNAS AND TRANSCRIPTION FACTORS IN THE CONTEXT OF PRIMARY BILIARY CHOLANGITIS AND PRIMARY SCLEROSING CHOLANGITIS

miR-125a and miR-125b are subject to complex epigenetic regulation, which determines their expression and function in the pathogenesis of cholestatic liver diseases. The expression

TABLE 5. Comparison of the role of miR-125a and miR-125b in inflammation and colorectal cancer development in primary sclerosing cholangitis patients

Feature/Function	miR-125a	miR-125b
Expression in CRC with PSC	Decreased expression in CRC, suggesting a tumour suppressor role [81].	Often reduced in CRC; involved in regulating inflammation and epithelial proliferation [87, 88, 89].
Molecular mechanisms	Inhibits migration, invasion, and EMT in CRC cells by directly suppressing TAZ expression [83]; inhibits VEGFA/VEGFR2 activation by reducing p-VEGFR2 and *p-Akt* levels [81].	Modulates the NF-κB and IL-6/STAT3 pathways [59, 84]; affects apoptosis and EMT [90, 91]; the overexpression of miR-125b is accompanied by the upregulation of S1P, ceramide synthases, ceramide kinases, and the downregulation of AT-rich interaction domain 2 in the ascending colon of PSC/UC, which contributes to the progression of high MSI-H colorectal carcinoma [11].
Role in inflammation	Negative regulator of pro-inflammatory cytokines, suppressing intestinal inflammation [52, 64, 85].	Regulates inflammation and mucosal regeneration, influencing the tumour-promoting micro-environment [86].
Effect on CRC progression	Tumour suppressor, inhibits tumour growth and metastasis [81]; suppresses tumour growth and metastasis in *in vivo* models [81].	miR-125b is elevated in metastatic CRC tumours, with expression increasing from normal tissue to primary tumours to metastases [92].

CRC – colorectal cancer; EMT – epithelial-mesenchymal transition; MSI-H – microsatellite instability; PSC – primary sclerosing cholangitis; STAT3 – signal transducer and activator of transcription 3; TAZ – transcriptional co-activator with PDZ-binding motif; S1P – sphingosine-1-phosphate; VEGF – vascular endothelial growth factor; p-Akt – phosphorylated protein kinase B (Akt); IL – interleukin

TABLE 6. Unresponsive to ursodeoxycholic acid and 5-aminosalicylic acid therapy and miR-125a/miR-125b in primary biliary cholangitis and primary sclerosing cholangitis

Aspect	UDCA	5-ASA	Studies in PBC and PSC
Effect on miR-125a	No direct studies on the effect of UDCA on miR-125a are available; however, UDCA may modulate the expression of microRNAs associated with inflammation and fibrogenesis [100, 101, 102, 103].	No direct studies on the effect of 5-ASA on miR-125a in the liver; however, 5-ASA exhibits anti-inflammatory properties and may indirectly influence miRNA regulation [99].	No direct studies on the effect of UDCA and 5-ASA on miR-125a expression.
Effect on miR-125b	UDCA may inhibit miR-125b expression [47].	5-ASA shows immunomodulatory capacity; it may inhibit miR-125b expression [99].	Direct studies on the effect of these therapies on miR-125b in PBC patients are limited, but decreased miR-125b expression has been observed after UDCA therapy in PSC patients [47].
Mechanisms of action	Protective role of UDCA in experimental colitis via modulation of intestinal barrier dysfunction and oxidative stress; [104] it reduces miR-21 levels and inhibits NF-κB activity, thereby decreasing inflammation [101]; it also affects signalling pathways involved in fibrogenesis and inflammation through modulation of TGF-β1 and SMAD family member (Smad) [103]; UDCA influences oxidative stress, apoptosis, and inflammation in the liver and other tissues [105].	5-ASA acts primarily as an anti-inflammatory immunomodulator that inhibits prostaglandin and cytokine production, and may affect microRNAs involved in inflammation [99].	

5-ASA – 5-aminosalicylic acid; PBC – primary biliary cholangitis; PSC – primary sclerosing cholangitis; TGF – tumour grow factor; UDCA – ursodeoxycholic acid

TABLE 7. The role of miR-125a and miR-125b in epigenetic regulation and interaction with microRNAs and transcription factors in primary biliary cholangitis and primary sclerosing cholangitis

Aspect/Feature	miR-125a	miR-125b	PBC and PSC
Epigenetic regulation of expression	The expression of miR-125a is regulated by DNA methylation and histone modifications, which influence its suppressive role in fibrogenesis [106, 107].	miR-125b is subject to similar epigenetic mechanisms that modulate its levels in response to oxidative and inflammatory stress [108].	In PBC and PSC, epigenetic dysregulation may lead to deregulation of both microRNAs, contributing to the progression of inflammation and fibrosis.
Interactions with other microRNAs	Cooperates with miR-21, miR-29, and miR-34, forming a regulatory network controlling the expression of genes involved in fibrosis and apoptosis [109].	Interacts with other microRNAs such as miR-155 [110, 111] and miR-146a, modulating immune response and inflammatory processes [112].	Cooperation with other microRNAs may enhance or suppress pathogenic processes in cholestatic liver diseases, influencing disease dynamics.
Interaction with transcription factors	miR-125a influences the expression of factors such as NF-κB and STAT3, inhibiting pro-inflammatory signalling and fibrogenesis [50].	miR-125b modulates transcription factors such as apelin, tumor protein p53, and Smad, which may promote cell proliferation and tumour progression [47, 72, 110].	In PBC and PSC, transcription factor regulation by miR-125a/b may determine the balance between inflammation, fibrogenesis, and oncogenesis.

PBC – primary biliary cholangitis; PSC – primary sclerosing cholangitis; STAT3 – signal transducer and activator of transcription 3; NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells

of miR-125a is modulated, among other mechanisms, by DNA methylation and histone modifications, which influence its suppressive role in fibrosis – Table 7 [106, 107] . Similarly, miR-125b undergoes epigenetic regulatory mechanisms that adjust its levels in response to oxidative and inflammatory stress [108]. miR-125a and b also co-operate with other microRNAs such as miR-21, miR-29, miR-34, miR-155, and miR-146a, forming regulatory networks that control the expression of genes involved in apoptosis, fibrogenesis, and immune responses – Table 7 [109]. These interactions enable fine-tuned regulation of pathological processes and may represent targets for multi-pronged therapies.

Moreover, both microRNAs influence the activity of key transcription factors that determine disease progression. miR-125a inhibits NF-κB and STAT3 activity, thereby reducing inflammation and fibrosis – Table 7 [44, 47, 72, 110] , whereas miR-125b modulates transcription factors such as activator protein-1, p53, and SMAD family member, which are involved in cell proliferation and oncogenic risk. As a result, their epigenetic regulation and interaction with other factors make miR-125a/b crucial components in the pathophysiology of PBC and PSC and promising therapeutic targets.

CORRELATION BETWEEN miR-125a/b EXPRESSION, SEX, AND AGE IN PRIMARY BILIARY CHOLANGITIS AND PRIMARY SCLEROSING CHOLANGITIS

Primary biliary cholangitis primarily affects women aged 40–60 years. This age group is associated with hormonal changes (peri- and post-menopause) that may influence the expression profile of miR-125a and the course of the disease. Additionally, aging and chronic inflammation models show a decrease in miR-125a levels with age, a trend that can be reversed by caloric restriction – suggesting a potential involvement of metabolic and aging-related factors in its regulation – Table 8 [113]. In contrast, miR-125b, exhibits a more complex pattern depending on age and disease stage. In murine models of cholestasis (e.g. BDL, Mdr2$^{-/-}$), miR-125b expression initially decreases, then increases at later stages and in older animals, indicating a possible role in adaptive or fibrogenic processes – Table 8 [10]. The role of miR-125b is particularly noteworthy in PSC, which more frequently affects men around the age of 40, where its expression may reflect the progression of inflammation, fibrosis, and cholangiocyte response to injury – Table 8 [47, 114]. Although both microRNAs participate in the pathogenesis of cholestatic liver diseases, their expression and biological significance are strongly modulated by patient age and sex, which may have important prognostic and therapeutic implications, particularly in the context of targeted therapies and biomarker development.

FUTURE PERSPECTIVES FOR RESEARCH AND THE THERAPEUTIC POTENTIAL OF miR-125a/b IN PRIMARY BILIARY CHOLANGITIS AND PRIMARY SCLEROSING CHOLANGITIS

miR-125a and miR-125b represent a promising area of research for understanding the molecular mechanisms underlying chronic cholestatic liver diseases such as PBC and PSC. Their complex role in regulating fibrosis, inflammation, apoptosis, proliferation, and oncogenesis opens numerous potential avenues for further investigation and clinical applications. More detailed functional studies are needed to precisely determine the effects of miR-125a and miR-125b on HSC activation, inflammation, and apoptosis in both *in vitro* and *in vivo* models. Such analyses could help identify specific signalling pathways and molecular targets modulated by these microRNAs in the context of PBC and PSC. Furthermore, the expression of miR-125a and miR-125b shows potential as a diagnostic and prognostic biomarker, particularly in assessing fibrosis progression, cancer transformation risk (e.g. HCC or CCA), and treatment response monitoring. Serum measurement of these microRNAs could support therapy individualisation.

There is also growing interest in using miR-125a and miR-125b as therapeutic targets. Strategies based on modulating their expression (using microRNA mimics or inhibitors) may allow intervention in key pathogenic mechanisms such as inflammation, fibrosis, or excessive proliferation. This could potentially slow disease progression and reduce cancer risk. However, there is little known about the impact of currently used therapies such as UDCA or 5-ASA derivatives on miR-125a and miR-125b expression. A better understanding of these interactions could contribute to treatment optimisation or the design of combination therapies in which microRNA modulation plays a significant role.

Additionally, and in the context of the autoimmune nature of PBC and PSC, an important research direction involves elucidating the effects of miR-125a and miR-125b on inflammation and immune responses. Their role in shaping the cellular microenvironment could provide the basis for the development of novel, targeted immunomodulatory therapies. Despite limited clinical data, the biological importance and regulatory activity of miR-125a and miR-125b justify continued investigation of their use in the diagnosis, monitoring, and treatment of chronic cholestatic liver diseases.

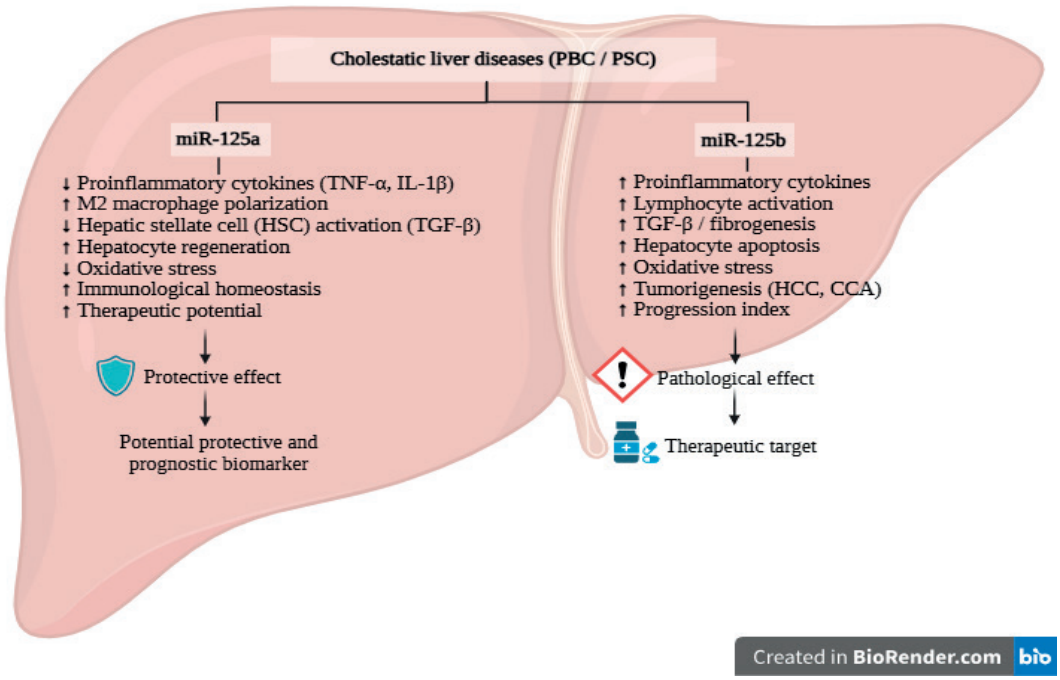
CONCLUSION

To summarise, miR-125a and miR-125b are essential components of the molecular regulatory network in PBC and PSC (Fig. 1). The identified differences in their function may have significant diagnostic, prognostic, and therapeutic implications. Further clinical and experimental research is necessary to fully elucidate their role in the pathogenesis of cholestatic liver diseases.

TABLE 8. Comparison of the roles of miR-125a and miR-125b in relation to sex and age in primary biliary cholangitis and primary sclerosing cholangitis

Factor	miR125a	miR125b	PBC	Context of primary sclerosing cholangitis
Sex	Higher expression in women; oestrogen-related effects observed in inflammatory and aging models [115].	Few data available, but a possible role of androgens and immunological sex differences has been suggested [47, 116].	PBC predominantly affects women (~9:1); oestrogen dominance may influence miR-125a expression [117, 118].	PSC occurs more often in men (~60–70%), which may determine distinct miR-125b profiles [114].
Age	In chronic inflammation and aging models, miR-125a decreases with age; however, caloric restriction reverses this trend [113].	In cholestasis models (bile duct ligation – BDL), multidrug resistance protein 2 $^{-/-}$ (Mdr2$^{-/-}$), miR-125b decreases initially but increases in older individuals or in fibrosis [10].	PBC is most often diagnosed between ages 40–60 (peri-/post-menopause), aligning with hormonal changes and possible modulation of miR-125a [118].	PSC is typically diagnosed around age 40; miR-125b expression may reflect disease stage and liver fibrosis [47, 114].

PBC – primary biliary cholangitis; PSC – primary sclerosing cholangitis



CCA – cholangiocarcinoma; HCC – hepatocellular carcinoma; HSC – hepatic stellate cell; IL – interleukin; TGF – transforming growth factor; TNF – tumour necrosis factor

FIGURE 1. A schematic drawing illustrating the opposing roles of 2 members of the miR-125 family in primary biliary cholangitis and primary sclerosing cholangitis

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