Advanced Pharmaceutical Bulletin

Accepted Manuscript (unedited)

The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form.

Letter to Editor

How to cite this article:
Ahmed El-Arabey A, Upadhyay KK. miR-34a in PFIC: Hypothesized Links to Dyslipidemia and Liver Regeneration. Advanced Pharmaceutical Bulletin, doi: 10.34172/apb.46776

miR-34a in PFIC: Hypothesized Links to Dyslipidemia and Liver Regeneration

Amr Ahmed El-Arabey[1,2,3*] and Kapil K. Upadhyay[4]

[1] Health and Medical Research Center, King Khalid University, P.O. Box 9004, Abha 61413, Saudi Arabia.
[2] Center of Bee Research and its Products, King Khalid University, P.O. Box 9004, Abha 61413, Saudi Arabia.
[3] Applied College, King Khalid University, P.O. Box 9004, Abha 61413, Saudi Arabia.
[4] Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA.

***Corresponding Author**
Amr Ahmed El-Arabey, E-mail: ph.amrcapa@gmail.com, ORCID: 0000-0003-0420-7191

Received: November 15, 2025, **Revised**: March 26, 2026, **Accepted**: May 07, 2026, **epublished**: May 19, 2026

To Editor,

To the Editor:

Progressive Familial Intrahepatic Cholestasis (PFIC), also known as Byler syndrome, is a rare group of autosomal recessive liver disorders characterized by early-onset, severe, and progressive cholestasis. This disease disrupts bile secretion from hepatocytes, resulting in intrahepatic accumulation of toxic bile acids, driving progressive liver injury that culminates in fibrosis, cirrhosis, and liver failure. PFIC is estimated to affect approximately 1 in 50,000 to 100,000 individuals worldwide. The molecular basis of PFIC typically involves mutations in genes encoding key bile transporters like ATP8B1, ABCB11, and ABCB4, essential for normal bile formation and export. Although defects in these genes leads to overlapping clinical and biochemical features, they also form the basis for the classification of inherited cholestatic liver diseases. [1] Diagnosis of PFIC relies on comprehensive clinical evaluation, laboratory and genetic testing, and, increasingly, the application of non-invasive biomarkers. In recent years, microRNAs, particularly miR-34a, have emerged as key mediators of hepatic inflammation and dysfunction, extending their relevance beyond adult cirrhosis and metabolic dysfunction associated steatotic liver disease (MASLD) to pediatric and genetic cholestatic disorders.[2] Growing evidence from MASLD demonstrates consistently elevated hepatic and circulating miR-34a correlating with disease severity, suggesting its dual role as a pathobiology mediator and diagnostic marker.[2] This context heightens the significance of reports describing substantially increased serum miR-34a in PFIC patients relative to healthy controls (mean fold change around 3.39 in PFIC versus 0.6 in controls; *p value* = 0.0327).[3] While these data collectively underscore an important association, there remains a pressing need for rigorous investigation to establish causality, clarify mechanistic pathways, and validate the practical utility of miR-34a measurement for disease monitoring and longitudinal risk stratification.[3] Beyond its hepatic implications, PFIC possess several challenges for cardiometabolic health. Patients with PFIC experience atypical dyslipidemia, not as overt hypercholesterolemia, but rather as the paradoxical buildup of triglyceride-rich low-density lipoproteins

(LDL) and suppressed high-density lipoproteins (HDL), a phenotype distinct from adult cholestatic liver disease but nonetheless capable of driving atherogenesis.[4] Prior studies in congenital cholestasis utilized surrogate subclinical indicators, yet robust registry data and prospective trials remain limited concerning cardiovascular events and outcomes in PFIC.[5] Critically, the molecular connection between hepatic and vascular injury may be solidified by miR-34a. Research demonstrate that miR-34a modulates macrophage cholesterol metabolism and inflammatory polarization, specifically enhancing M1 (pro-inflammatory) and restraining M2 (anti-inflammatory) macrophage phenotypes by influencing liver X receptor α (LXRα), a key regulator of cholesterol homeostasis.[6] This pivotal role positions miR-34a not only as a modulator of hepatic inflammation but also as a key connecting link between dysregulated lipid metabolism and vascular injury.[4] Despite these mechanistic insights, there is currently no direct clinical evidence linking circulating miR-34a levels to atherosclerotic or subclinical cardiovascular outcomes in PFIC, so its proposed cardiometabolic role should be considered a hypothesis that requires validation in well-designed prospective studies. Furthermore, the dyslipidemic profile seen in PFIC must be approached with caution, since it may differ among subtypes (ATP8B1, ABCB11, and ABCB4), and comprehensive quantitative data delineating these variations are currently limited. miR-34a plays a complex role in PFIC by affecting both liver regeneration and bile acid production. During liver regrowth after significant loss (e.g., partial hepatectomy), miR-34a expression surges, inhibiting the activin member INHBB and hepatocyte growth factor receptor MET, thereby impairing proliferation at critical junctures.[7] Simultaneously, miR-34a has been reported to upregulate hepatic cholesterol 7α-hydroxylase (CYP7A1) and sterol 12α-hydroxylase (CYP8B1), key enzymes in classical bile acid synthesis, potentially contributing to bile acid accumulation in hepatocytes.[8,9] Notably, temporary inhibition of CYP7A1 is physiologically required for hepatoprotection.[10] We suggest that the sustained upregulation of miR-34a in PFIC could disrupt the physiological downregulation of CYP7A1 necessary for efficient liver regeneration; however, this association has yet to be directly confirmed in PFIC-specific models. If elevated circulating miR-34a is indeed a signature of greater disease activity in PFIC, it may serve not only as a biomarker of hepatic injury but also as a harbinger of increased cardiovascular ring to its regulatory effects on lipid metabolism and macrophage polarization (Figure 1). Future research priorities include validating miR-34a as a predictive marker in larger, genotype-characterized PFIC cohorts, defining its disease specificity relative to other cholestatic and metabolic liver disorders, and exploring targeted therapies that modulate miR-34a signalling. Looking forward, the dual roles of miR-34a in mediating both liver and vascular disease progression, through bile acid–induced toxicity, inflammation, dyslipidemia, and effects on regenerative capacity, position it as a uniquely promising candidate for multidisciplinary research at the interface of hepatology and cardiology.

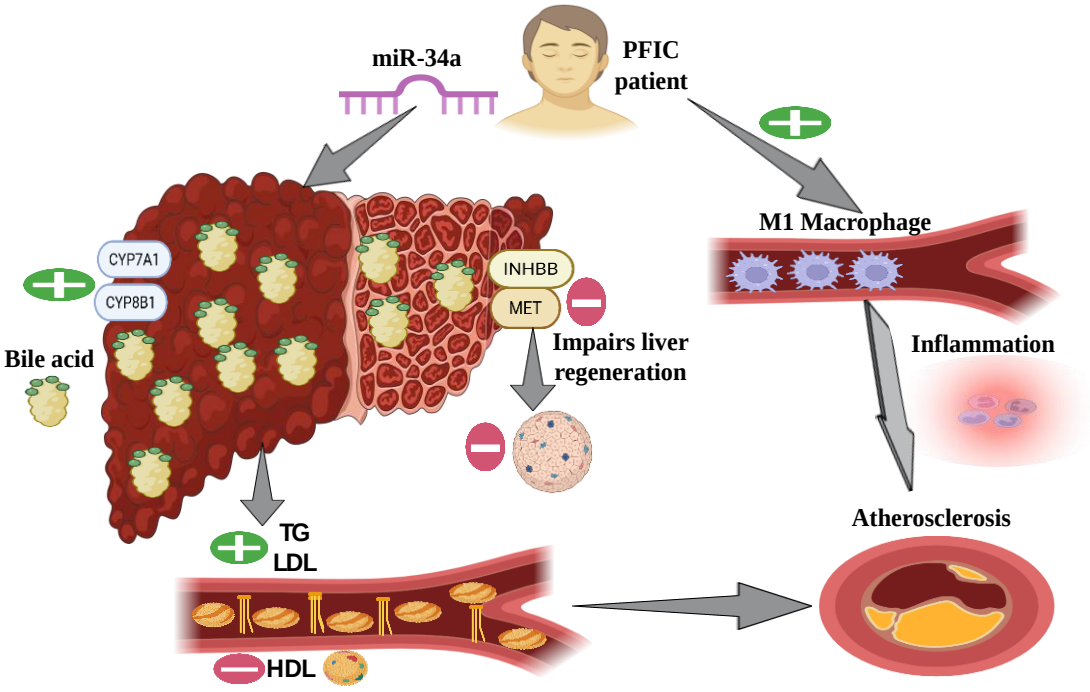

Figure 1: Proposed functions of miR-34a in liver and cardiovascular complications of Progressive Familial Intrahepatic Cholestasis (PFIC). Cohort studies reveal elevated serum miR-34a levels in PFIC patients. Experimental models suggest that miR-34a regulates macrophage activity and lipid metabolism, contributing to dyslipidemia and increased cardiovascular risk. miR-34a is shown to directly promote bile acid synthesis via upregulation of cholesterol 7α-hydroxylase (CYP7A1) and sterol 12α-hydroxylase (CYP8B1), while also impairing liver regenerative signaling by inhibiting hepatocyte growth factor receptor (MET) and INHBB. These pathways may underlie compromised liver adaptation and heightened cardiometabolic risk in PFIC, though direct evidence in PFIC patients remains to be established.

Ethics approval: Not applicable

Consent to participate: Not applicable

Consent for publication: Not applicable

Competing interests

The authors declared no conflict of interest. All the authors read and approved the final manuscript.

Acknowledgement: The authors extend their appreciation to the Deanship of Research and Graduate Studies at King Khalid University for funding this work through Small Research Project under grant number RGP1/260/46.

Compliance with Ethical Standards: Disclosure of potential conflicts of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Research involving human participants and/or animals: Not applicable

Informed consent: Not applicable

Authors Contribution:

- Conceptualization: Amr Ahmed El-Arabey (AAE)
- Methodology: Amr Ahmed El-Arabey (AAE)
- Data curation: Amr Ahmed El-Arabey (AAE)
- Formal analysis: Amr Ahmed El-Arabey (AAE)
- Visualization: Amr Ahmed El-Arabey (AAE)
- Validation: Kapil K. Upadhyay (KKU)
- Supervision: Kapil K. Upadhyay (KKU)
- Writing – original draft: Amr Ahmed El-Arabey (AAE)
- Writing – review & editing: Amr Ahmed El-Arabey (AAE); Kapil K. Upadhyay (KKU)
- Both authors have read and approved the final manuscript.

References:

1. Nayagam JS, Miquel R, Thompson RJ, Joshi D. Genetic cholestasis in children and adults. *J Hepatol* 2024;80(4):670-2. doi: 10.1016/j.jhep.2023.11.028
2. Amaral AE do, Rode MP, Cisilotto J, Silva TE da, Fischer J, Matiollo C, et al. MicroRNA profiles in serum samples from patients with stable cirrhosis and miRNA-21 as a predictor of transplant-free survival. *Pharmacol Res* 2018;134:179-92. doi: 10.1016/j.phrs.2018.06.019
3. Motazedian N, Azarpira N, Falamarzi K, Dehghani M, Ataollahi M, Esfandiari E, et al. Expression of miR-34a in Children with Progressive Familial Intrahepatic Cholestasis: A Cross-Sectional Study Based on Shiraz Pediatric Liver Cirrhosis Cohort Study. *Iran J Pediatr* 2024;34(1). doi: 10.5812/ijp-142943
4. Nagasaka H, Yorifuji T, Hirano K, Ota A, Toyama-Nakagawa Y, Takatani T, et al. Effects of bezafibrate on dyslipidemia with cholestasis in children with familial intrahepatic cholestasis-1 deficiency manifesting progressive familial intrahepatic cholestasis. *Metabolism* 2009;58(1):48-54. doi: 10.1016/j.metabol.2008.08.005
5. Nagasaka H, Yorifuji T, Egawa H, Yanai H, Fujisawa T, Kosugiyama K, et al. Evaluation of risk for atherosclerosis in Alagille syndrome and progressive familial intrahepatic cholestasis: two congenital cholestatic diseases with different lipoprotein metabolisms. *J Pediatr* 2005;146(3):329-35. doi: 10.1016/j.jpeds.2004.10.047
6. Xu Y, Xu Y, Zhu Y, Sun H, Juguilon C, Li F, et al. Macrophage miR-34a Is a Key Regulator of Cholesterol Efflux and Atherosclerosis. *Mol Ther* 2020;28(1):202-16. doi: 10.1016/j.ymthe.2019.09.008
7. Chen H, Sun Y, Dong R, Yang S, Pan C, Xiang D, et al. Mir-34a is upregulated during liver regeneration in rats and is associated with the suppression of hepatocyte proliferation. *PLoS One* 2011;6(5):e20238. doi: 10.1371/journal.pone.0020238
8. Nyholm I, Hukkinen M, Lohi J, Sjöblom N, Mutka A, Mutanen A, et al. Accumulation of altered serum bile acids predicts liver injury after portoenterostomy in biliary atresia. *J Hepatol* 2025;83(2):440-52. doi: 10.1016/j.jhep.2025.01.025
9. Xu Y, Zhu Y, Hu S, Pan X, Bawa FC, Wang HH, et al. Hepatocyte miR-34a is a key regulator in the development and progression of non-alcoholic fatty liver disease. *Mol Metab* 2021;51:101244. doi: 10.1016/j.molmet.2021.101244
10. Zhang L, Huang X, Meng Z, Dong B, Shiah S, Moore DD, et al. Significance and mechanism of CYP7a1 gene regulation during the acute phase of liver regeneration. *Mol Endocrinol* 2009;23(2):137-45. doi: 10.1210/me.2008-0198