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# PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 87029

**Title:** New in the pathogenesis of the primary biliary cholangitis asymptomatic stage

**Provenance and peer review**: Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 01221925
**Position:** Editorial Board
**Academic degree:** AGAF, FACS, FICS, MD, PhD

**Professional title:** Professor

**Reviewer's Country/Territory:** Greece

**Author's Country/Territory:** Russia

**Manuscript submission date:** 2023-07-19

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2023-07-19 20:42

**Reviewer performed review:** 2023-07-21 20:32

**Review time:** 1 Day and 23 Hours

| | |
|---|---|
| **Scientific quality** | [ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
| **Novelty of this manuscript** | [ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair<br>[ ] Grade D: No novelty |
| **Creativity or innovation of this manuscript** | [ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair<br>[ ] Grade D: No creativity or innovation |

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| | |
|---|---|
| **Scientific significance of the conclusion in this manuscript** | [ ] Grade A: Excellent [ Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance |
| **Language quality** | [ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection |
| **Conclusion** | [ ] Accept (High priority) [ ] Accept (General priority) [ Y] Minor revision [ ] Major revision [ ] Rejection |
| **Re-review** | [ ] Yes [ Y] No |
| **Peer-reviewer statements** | Peer-Review: [ Y] Anonymous [ ] Onymous |
| | Conflicts-of-Interest: [ ] Yes [ Y] No |

## SPECIFIC COMMENTS TO AUTHORS

This is an interesting paper presenting a hypothesis regarding the pathogenesis of the first signs of PBC in the asymptomatic stage. The authors present us with a very thorough overview of the various mechanisms involved in the pathogenesis of PBC at various levels. This is essentially a detailed review paper, and not necessarily a novel hypothesis, it is more a synthesis of existing data. Additionally, to suggest a hypothesis, it is necessary to provide experimental proof. This is not to diminish the value of this paper, but it should be formulated, including a possible change in the title, so as to show that it is a review on the topic

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**Peer-review model:** Single blind

**Reviewer's code:** 02936529
**Position:** Editorial Board
**Academic degree:** FRCS (Hon), MD, PhD

**Professional title:** Professor, Surgical Oncologist

**Reviewer's Country/Territory:** Brazil

**Author's Country/Territory:** Russia

**Manuscript submission date:** 2023-07-19

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2023-07-23 11:32

**Reviewer performed review:** 2023-07-27 20:41

**Review time:** 4 Days and 9 Hours

| | |
|---|---|
| **Scientific quality** | [ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
| **Novelty of this manuscript** | [ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair<br>[ ] Grade D: No novelty |
| **Creativity or innovation of this manuscript** | [ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair<br>[ ] Grade D: No creativity or innovation |

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| **Conclusion** | [ ] Accept (High priority) [ Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection |
| **Re-review** | [ ] Yes [ Y] No |
| **Peer-reviewer statements** | Peer-Review: [ Y] Anonymous [ ] Onymous |
| | Conflicts-of-Interest: [ ] Yes [ Y] No |

## SPECIFIC COMMENTS TO AUTHORS

This manuscript reviews the mechanisms contributing to the cellular damage, AMA formation and development of ductulopenia in PBC in the asymptomatic stage of the disease. The authors propose a hypothesis explaining the pathogenesis of the first morphological, immunologic and clinical signs of the disease in the asymptomatic stage, suggesting that in susceptible individuals, an initial trigger causes an X-linked epigenetic change that leads to gene reactivation and increased expression of miR-506 . Triggering increased synthesis and activation of miR-506 leads to inhibition of InsP3R3 and AE2 translation. As a result, bicarbonate entry into the bile duct lumen is reduced and HCO3- accumulation in the cytosol of cholangiocytes occurs. Changes in extra- and intracellular pH alter the protonation and deprotonation of bile acids. uncontrolled entry and accumulation of unconjugated and glycine-conjugated bile acids into the BECs is increased. The detergent properties of bile acids trigger cell membrane disruption, senescence and apoptosis of cholangiocytes, mitochondrial permeabilization, destruction and immunomodification of E2 PDG followed by AMA formation. Senescence, apoptosis and proliferation of cholangiocytes leads to the gradual development of

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ductulopenia. Involvement of PDG in the pathological process contributes to insufficient ATP synthesis, development of energy deficiency, and appearance of a nonspecific clinical sign. This review is of high scientific quality, the text is concise with a logical sequence of ideas for the reader. The figures are illustrative and well displayed. Minor english polisshing is needed. Congratulations for the authors.