

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: *In this paper by Yan and Nan., the authors present a comprehensive review of our current understanding on HEV ORF3 protein. This is a well written review paper summarizing the most up-to-date information on this issue. I only have one minor comment; perhaps the authors could supplement their document with a figure summarizing what is known about the role of HEV ORF3 in the regulation of the host immune response. I also believe that sections 2, 3.1, 3.2 and 3.4 can be reduced significantly and moved to the introduction section. The afore mentioned sections, while interesting, are lengthy and deviate the attention from the main subject, the ORF3 protein.*

Response: We thank reviewer for these comments and suggestions. We have made a new figure (as Figure.3) in our revised manuscript to summarize the regulation of innate immune response by HEV-ORF3. Please see figure 3 in our revised manuscript. Moreover, the section 2,3.1,3.2 and 3.4 were reduced. Please see our revised manuscript.

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: *World Journal of Gastroenterology Manuscript Review-Manuscript NO: 62999: The ORF3 protein of Hepatitis E virus: Multi-function protein with endless potential This is a well written overview of the genetic structure of HEV and how the three well define ORFs effect cross species tropism and potential markers for vaccine development. My only comment is on page 3 second paragraph the author talks about the high seroprevalence of HIV in the general population that may be due to undetected HEV circulation. The author references only a Dutch paper though there are many other countries including the USA. Decline in Hepatitis E Virus Antibody Prevalence in the United States From 1988–1994 to 2009–2010 Eyasu H. Teshale, Maxine M. Denniston, Jan Drobeniuc, Saleem Kamili, Chong-Gee Teo, and Scott D. Holmberg Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia The Journal of Infectious Diseases® 2015;211:366–73 A few more epidemiological papers from other countries would be helpful to this review.*

Response: We thank reviewer for these comments and suggestions. The requested reference had been added to our manuscript. Please see line 89 to 90 in our revised manuscript.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This paper represents an excellent overview of current

knowledge about the role of different HEV proteins in transmission, pathogenesis, and immune response to infection. Review especially refers to role of HEV-ORF3 proteins. Authors indicate the directions for further research and possible role of HEV-ORF3 in vaccine development. The review represents very good quality and I have no major objections.

Response: We thank reviewer for this comment.

Reviewer #4:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Thank you very much to let me have an opportunity to read this comprehensive review on the multiple pathogenic roles of HEV-ORF3.

Manuscript is well written and preparation.

Response: We thank reviewer for this comment.