

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 73047

Title: Hepatitis B core-related antigen: Are we near a treatment endpoint?

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04092306

Position: Peer Reviewer

Academic degree: PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: India

Manuscript submission date: 2021-11-07

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-11-07 17:00

Reviewer performed review: 2021-11-08 10:23

Review time: 17 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript lacks of the reference section; please add the references, so that the revision process could be properly performed. As specific comment, the authors stated that HBcrAg may not be an ideal marker in HBeAg negative CHB patients. Several studies support its use in these patients; see PMID: 33525443 and 33465257. In addition, given the low analytical sensitivity, I have some concerns on its possible usefulness in patients/subjects with occult HBV infection. In a recent manuscript, authors observed HBcrAg values below 2.0 log in HBsAg-negative/anti-HBc-positive liver donors irrespectively from the presence or absence of intrahepatic HBV cccDNA (PMID: 29621551)

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 73047

Title: Hepatitis B core-related antigen: Are we near a treatment endpoint?

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03646974

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Chief Doctor, Chief Physician

Reviewer's Country/Territory: China

Author's Country/Territory: India

Manuscript submission date: 2021-11-07

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-11-08 13:39

Reviewer performed review: 2021-11-09 13:50

Review time: 1 Day

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

I read this letter carefully, but I don't understand the author's true thoughts. In the life cycle of HBV, cccDNA combines with histones to form HBV minichromosomes. They play two roles, one part is stored in the nucleus of liver cells, and the other part is transcribed into pregenomic RNA and mRNA. Therefore, I cannot understand the connection between cccDNA and HBcrAg. Reading the first paragraph, I do not agree with the author's conclusion, 'even on antiviral treatment, HBcrAg can reflect cccDNA activity in hepatocytes'. On the contrary, my conclusion is that HBcrAg can not reflect cccDNA activity in hepatocytes. In addition, in the last paragraph of the letter, the author also believes that HBcrAg, as a marker, has three critical defects. Suggestion: re-submission after revising manuscript.

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 73047

Title: Hepatitis B core-related antigen: Are we near a treatment endpoint?

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03538156

Position: Editorial Board

Academic degree: PhD

Professional title: Associate Professor, Chief Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: India

Manuscript submission date: 2021-11-07

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-11-08 05:11

Reviewer performed review: 2021-11-10 02:41

Review time: 1 Day and 21 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
<https://www.wjgnet.com>

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

As a promising novel serum marker, HBcrAg has been increasingly paid attention to. The author discussed the origin, composition, clinical significance and so on, and put forward some problems that need to be discussed in the original paper, for example, different treatment schemes (NAs and PegIFN) may cause bias in results and analysis. At last, author pointed out many issues about HBcrAg. I agree to publish this manuscript.

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 73047

Title: Hepatitis B core-related antigen: Are we near a treatment endpoint?

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00070760

Position: Peer Reviewer

Academic degree: MD

Professional title: Full Professor

Reviewer's Country/Territory: China

Author's Country/Territory: India

Manuscript submission date: 2021-11-07

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-11-07 19:34

Reviewer performed review: 2021-11-14 09:56

Review time: 6 Days and 14 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This review evaluates the research value of the manuscript for HBcrAg and presents issues such as low detectable rates in clinical practice, possible not an ideal marker in patients with negative HBeAg CHB, and can be found in 40% patient with HBsAg seroclearance, and so on. Which are very objective and informative, and I really agree with these points. On my opinion, It is still controversial for HBcrAg as a potential serological markers of chronic hepatitis B infection and activity. It may be of more predictive value if the subjects are limited to certain specific population, such as HBeAg-positive patients.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 73047

Title: Hepatitis B core-related antigen: Are we near a treatment endpoint?

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03646974

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Chief Doctor, Chief Physician

Reviewer's Country/Territory: China

Author's Country/Territory: India

Manuscript submission date: 2021-11-07

Reviewer chosen by: Jing-Jie Wang

Reviewer accepted review: 2022-01-05 13:42

Reviewer performed review: 2022-01-05 14:15

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

I still disagree with the author's answer, The intrahepatic cccDNA transcribes into pregenomic RNA and precore mRNA. Then precore mRNA further is translate into HBcrAg (HBeAg, HBcAg and p22cr Ag). Therefore, HBcrAg indirectly reflects precore mRNA, how can it reflect cccDNA.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 73047

Title: Hepatitis B core-related antigen: Are we near a treatment endpoint?

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04092306

Position: Peer Reviewer

Academic degree: PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: India

Manuscript submission date: 2021-11-07

Reviewer chosen by: Jing-Jie Wang

Reviewer accepted review: 2022-01-05 13:00

Reviewer performed review: 2022-01-06 11:54

Review time: 22 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The authors improved the manuscript according to the comments raised. I suggest to add in line 16, that "HBcrAg can reflect cccDNA quantity and activity in hepatocytes" (PMID: 32008810 and PMID: 30529504). Furthermore, please check reference numbers in the References section.