Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road,
Wan Chai, Hong Kong, China

ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 5194
Title: Adaptive immune response during HCV infection
Reviewer code: 02450507
Science editor: Wen, Ling-Ling
Date sent for review: 2013-08-21 21:32
Date reviewed: 2013-09-03 16:41

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[Y] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

This article by Larrubia et al. reviews what is presently known about the role of adaptive immune response during HCV infection. The exercise may be useful since it's by now evident that the pathogenic potential of HCV is clearly driven by host immune response. The article is well prepared and makes a pleasant and useful reading for those in the field and may help popularise the subject among those who have not fully known its importance. Information is clearly and concisely described. The number of references could be downsized.

Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road,
Wan Chai, Hong Kong, China

ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 5194
Title: Adaptive immune response during HCV infection
Reviewer code: 02462675
Science editor: Wen, Ling-Ling
Date sent for review: 2013-08-21 21:32
Date reviewed: 2013-09-06 00:58

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[Y] Accept
[Y] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

Journals: World Journal of Gastroenterology Manuscript Number: 5194 Manuscript Title: Adaptive immune response during HCV infection COMMENTS TO AUTHORS: MY SPECIFIC COMMENTS ARE AS FOLLOWS: Title: The title reflects main content of the review. Abstract: Appropriate for the review. But there are some minor changes 1- In the first line, please remove to "affects to" So the new sentence'll be Hepatitis C virus (HCV) infection affects 130-170 million people worldwide. 2- There are direct effects of HCV on hepatocytes leading to hepatic stellate cell activation, fibrosis and cirrhosis. In addition, HCV disturbs the host immune system to establish persistent infection. That means both HCV infection and the host immune system play role in liver damage so could you please change sentence at line 4 to "liver damage and disease progression are driven by both viral and host factors. 3- At line 13 remove to "affects to" So the new sentence'll be "HCV affects effector T cell regulation". Introduction: Appropriate for the review. In Paragraph: 2. General features of Adaptive Immune response: 1- In the first line remove d from and "and advantage" to be "an advantage". 2- In line 7 please rephrase this sentence " To control non-cytopathic viral infections is necessary the activation of the adaptive immune system and especially the cellular immune response" to "To control non-cytopathic viral infections, the activation of the adaptive immune system is necessary especially the cellular immune response" 3- In line 14 write Subsequently instead of Secondly. 4- Abbreviation (Th1, MHC), please write the full name then write the abbreviation between brackets. 5- I prefer to add an illustrative figure to show how Na?ve T cells can express one of two different molecules, CD4 or CD8, on their surface, and are accordingly classified as CD4+ or CD8+ cells. This figure should show how Na?ve CD4+ is stimulated to become helper T (TH) lymphocytes, cells that go on to stimulate B cells or CD8+ cytotoxic T cells directly or

secrete cytokines to fight the pathogen. In contrast, CD8+ are stimulated to become cytotoxic T lymphocytes (CTLs), which directly kill infected cells by apoptosis and emit cytokines to amplify the immune response. In Paragraph 3.1 Humoral Immune Response: 1- I need the author to clarify that during the natural course of HCV infection, a large number of antibodies are produced. The vast majority of antibodies induced have no antiviral activity, either because they are elicited by degraded or incompletely processed proteins released from dying cells or because they are directed against epitopes that do not play any role in the virus entry process “non-neutralizing antibodies”. Only a small proportion of antibodies termed “neutralizing antibodies” are able to target exposed epitopes of the viral structural proteins and neutralize the infectious virus by preventing or controlling viral infection. Actually, during the chronic phase of HCV infection, most HCV infected patients develop high-titer of antibodies. Paradoxically, these antibodies were not able to control HCV infection which may be attributed to the generation of non-neutralizing HCV-specific antibodies that compete with neutralizing Abs and reduce their effectiveness. It was reported in other viral infections that highly immunogenic non-neutralizing epitopes mislead the humoral immune response contributing to viral escape from neutralization. 2- There is a double space before Immune complexes, please remove one space. In Paragraph 3.2.1 Adaptive cellular response during acute HCV infection 1- Abbreviation (CD4, IL2), please write the full name then write the abbreviation between brackets. In Paragraph 3.2.2 Adaptive cellular response during chronic HCV infection 1- Please rephrase this long sentence "There are evidences that demonstrate during chronic HCV infection the appearance of rapid HCV escape mutations [48, 49],

Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road,
Wan Chai, Hong Kong, China

ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 5194
Title: Adaptive immune response during HCV infection
Reviewer code: 00504015
Science editor: Wen, Ling-Ling
Date sent for review: 2013-08-21 21:32
Date reviewed: 2013-09-06 06:09

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

Lurrubia et al. present an interesting review regarding the role of the adaptive immune response in HCV infection. The adaptive immune response against HCV includes antibodies, CD4+ T cells, and CD8+ T cells. A number of reviews have recently been published that tackle this issue, highlighting the general interest for the subject. In this review authors address most of the important aspects regarding HCV infection and the host adaptive immune response. However, in some sections this review tends to be biased as authors avoid confronting contradictory data. As this is a review the reader should be confronted to all the existent data and authors should help him slide through. In no case data should be omitted to give sense to the most accepted, but not solely model to explain how HCV relates to the adaptive immune response. Comments: 1) The use of English should be improved. Some example are: line 2, page 2 "…affects to 130-170….."; line 14, page to "…HCV affects to effector…."; line 16, page 3 "…which is and advantage…."; line 14, page 6 …"is more tend to induce…"; line 15, page 11 "….T cell deletion in…", line 20, page 11 "…Bim activity is contra-regulated…."; line 23, page 6 "…..In table 1 is summarized the…."; line 7, page 15 "…has not been shown a clear HCV….". 2) The review should focus exclusively on HCV thus generalization such as those stated in page 3 should be avoided. For example: "…because this type of viruses behaves as an intracellular parasite……". By definition all viruses are intracellular parasites. 3) Association with what can be seen with viruses from other families should be avoided. This is particularly valid when these comparisons do not necessary contribute to the understanding of the text. For example, line 18 of page 8 "…Like retroviruses, HCV polymerases……" 4) In the section regarding neutralizing antibodies the work of Farci et al (1996). PNAS 93:15394–15399; Pestka et al (2007). PNAS 104:6025–6030; Christie et al. Clin Exp Immunol. 1997;110(1):4–8 and Adams et al (1997),

Pediatr Infect Dis J 16:533–534; Logvinoff et al. PNAS. 2004;101(27):10149–54 ; Dowd et al. Gastroenterology. 2009;136 (7):2377–86 should included (if not) and discussion should be better developed. As this is a review authors should confront and discuss all relevant data. Omission of the data presented in some of these papers seemed inappropriate. 5) When discussing HCV escape from T cell response authors should include and discuses the work of Cox et al. (2005), Hepatology 42:104–112 ; Cox et al. (2005) J Exp Med 201:1741–1752. These studies suggest that selection of viral escape mutations occurred early in acute infection and remained fixed thereafter, indicating that viral escape may indeed be a causative mechanism of CD8+ T cell failure and viral persistence. 6) Authors omit to discuss the relationship between the generation of HCV escape mutants and viral fitness. 7) Authors have failed to discuss in depth the dysfunction of HCV-specific T cell (impaired in cytotoxicity, production of antiviral cytokines, and antigen-triggered proliferation) observed during HCV infection.

Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road,
Wan Chai, Hong Kong, China

ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 5194
Title: Adaptive immune response during HCV infection
Reviewer code: 00504167
Science editor: Wen, Ling-Ling
Date sent for review: 2013-08-21 21:32
Date reviewed: 2013-11-06 17:10

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[Y] Accept
[Y] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

Review, "Adaptive immune response during HCV infection" by Larrubia et al. In this review the authors report on the role of adaptive immune response in controlling HCV infection and the HCV mechanisms to evade this response. The authors refer to recent scientific literature as well as to cornerstone studies performed years ago. Although the picture is quite complex, the authors put their efforts trying to simplify the complex interplay between the virus and the immune system response.However,sometimes the exposition is not very clear.