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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 7509
Title: Involvement of heat shock proteins in gluten-sensitive enteropathy
Reviewer code: 00001391
Science editor: Qi, Yuan
Date sent for review: 2013-11-22 19:39
Date reviewed: 2013-12-03 18:21

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	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

The major point is: increase expression of HSP is a biomarker or simply a consequence of the immunotoxic agression of gluten in CD or predisposition to CD patients. I think you have to focus on this point. 1 Abstract: there is no relation, at the present time, between new possible CD treatment and HSP. So delete or precise in the abstract The review is not "recent". I think it is the "present" review. 2 Page 4 Anti-gluten is "anti gliadine" antibodies? 3 Page 5. Can you precise "nutritionnal" stress/ors? 4 Page 6 Can you precise type of tissue for HSP family especially if intestine is involved 5 Page 12 I thnink it is not necessary to have details concerning IBD, a very different pathology to my view 6 What kind of therapeutic modulation can you speculate with HSP and how in CD?

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 7509
Title: Involvement of heat shock proteins in gluten-sensitive enteropathy
Reviewer code: 00187623
Science editor: Qi, Yuan
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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	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

The conclusion is exceptional in its summarization of the practical aspects of the topic. The current use of the Heat Shock Proteins might be discussed a bit more. Nevertheless, I see this as a good resource for investigators looking at this topic. I would suggest accepting the article with the following changes: On page 2: The incidence of CD continued to increase worldwide in the past decade however most cases still remains undiagnosed-- this should read "still remain undiagnosed" On page 3: — including inflammatory bowel disease (IBD), allergy or asthma — beside of genetic predisposition environmental factors has a crucial impact. "this needs revision - unclear" In conclusions, consider elaborating further or more specifically regarding the potential benefits of evaluating the proteins.

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
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Title: Involvement of heat shock proteins in gluten-sensitive enteropathy
Reviewer code: 00002649
Science editor: Qi, Yuan
Date sent for review: 2013-11-22 19:39
Date reviewed: 2013-12-31 02:46

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[Y] Accept
[Y] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[Y] 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

MS 7509. Involvement of heat shock proteins in gluten-sensitive enteropathy

1. In Figure 1, authors summarize the key processes during the pathogenesis of CD. They do not label gliadin. They also indicate in the text that gliadin peptides can directly activate TLRs on macrophages and DCs, which leads to the upregulation of proinflammatory cytokiens and chemokines, which is not shown in Figure 1. TLR's are also not shown. These should be added to Figure1. Is TG the same thing as TTG?

2. On page 8, Inflammation and HSPs, the first sentence should be deleted because CD is not the topic of the section. Also, the authors summarize that HPS60 stimulates DCs more rapidly than LPS; and HSP-peptide complexes bind to TLR2 and 4 on the surface of APC and activate the T cell pathways leading to enhanced expression of proinflammatory cytokines. On the other hand, HSP60 resolves inflammation by up-regulation of Tregs. These findings seems opposite -- how do the authors explain this?

3. The authors state on p. 9 "HSP60 has been shown to be a novel mitochondrial permeability transition regulator.." Could they give a little bit more detail on this? How does HSP60 regulate mitochondrial permeability and apoptosis?

4. On page 11, lines 7-10, the authors promote the concept that activation of TLR signaling produces pro-inflammatory cytokines and inflammation with further disruption of barrier function. However, HSP70 activates TLR2 and TLR4 which "can contribute to the maintenance of intestinal barrier function by preserving the integrity of the tight junction proteins..."?

5. The summary gives some evidence that HSP induction may be used to treat CD. This paragraph should be expanded. Injury in animals produced by NSAIDs, dextran sulfate colitis, and

bisphosphonate induced cell injury are prevented by the HSP inducer geranylgeranylacetone. Do the authors postulate that such drugs or vaccines will eventually replace the gluten-free diet?

Minor comments:

1. The authors use "pathomechanism" throughout. I am not familiar with this word. Do they mean "pathophysiology" or "pathogenesis" or "disease mechanism"?
2. INTRODUCTION:

-Ninety-five percent should be spelled out when it is the first word of the sentence.

-Second paragraph, second sentence: "asthma – a genetic predisposition combined with environmental factors leading to disease manifestation."

-Under "Effect of stress…" would replace "beneficial" with "compensatory."

-"homeostasis and ensuring survival."

-(such as heat, toxins, radiation, infection, mechanical force, and metabolic disturbances."

3. Page 4: Would delete "therefore exerting an immunomodulatory activity."
4. Page 4: "Reaching the epithelial cells, gluten enhances IL-15…" should be placed after reference 16 because it is the initial event before gluten residues reach the lamina propria.
5. What is meant by "organisatory"--?should it be deleted?
6. Top of p. 6, first sentence, would include intestinal and colonic epithelium.
7. Page 7, would reverse the 1st sentence to say "Several environmental and chemical agents inducing oxidative stress may lead to enhanced ROS…"
8. Second para under Oxidative stress: Wischmeyer and Chang also showed in vivo that induction of hsp (by glutamine feeding) preserved intestinal epithelial cells. So there are studies in vitro (cited) and in vivo.
9. Page 8, under Inflammation and HSP's: the conclusion sentence can be part of the paragraph above.
10. Page 9: I would change the topic from Mucosal Damage and HSPs to Intestinal Epithelial Integrity and HSPs.
11. Page 10: All grammar issues, because the section is critical. First sentence "not surprising, in part owing to the lack of experimental models which makes it challenging to identify the complex pathophysiology of CD."

HSP are present throughout the GI tract; however, there are…

In contrast, small intestinal expression of HSPs is normally negligible, but under stress, HSP25 and HSP70 are markedly increased.

The applied gluten free diet reduced clinical sx and also the level of intestinal HSP72, but its expression remained elevated…

"We also demonstrated that the most abundant expression of HSP72 was in villus enterocytes and immune cells of the LP…"

12. Page 11: Would delete "there are only a few data available—because this might irritate some investigators, e.g. Chang E et al. "Previously, Yang et al found that heat stress increased protein transport… What is meant by protein transport?

13. "strengthened by Cario et al (98), who reported that…"
14. Suggest: "Other HSPs such as HSP65 and small MW HSPs (<30KD) were also suggested to contribute to the pathophysiology of CD."
15. Would not state "excluded for the disease" even though this was published. The authors I think mean "without CD based on a normal biopsy."
16. Page 11, bottom: What is meant by "slow" and "fast"?
17. IS IBD spelled out the first time?
18. Would delete "good" bacteria or say "beneficial"
19. Table 2. The authors need to put a statement in the MS such as "Table 2, below, summarizes…"

In this table, I think the T84 cell studies should be deleted because CD is not part of those reports.
Also, "excluded from having the disease" rather than "excluded for…"

20. SUMMARY: "In this review, we summarize the main…"

"chaperones" sp.
Needs a comma after CD in the first paragraph and after factor in the second.
The second and 3rd paragraphs can be combined.