

ID 00504152/Editorial Board Member

July 18, 2013

Dear Editor,



I would like to thank you for the thorough and instructive review of my manuscript which has further improved it.

Please find enclosed the edited manuscript in Word format (file name: the interplay of adipokines and myokines\_WJEM 4250\_edited.doc).

**Title:** The interplay of adipokines and myokines in cancer pathophysiology: emerging therapeutic implications

**Author:** Maria Dalamaga

**Name of Journal:** *World Journal of Experimental Medicine*

**ESPS Manuscript NO:** 4250

The manuscript has been improved according to all Reviewers' suggestions.

- 1) The format has been updated. **REVISED.**
- 2) Revision has been made according to the Reviewers' suggestions. **REVISED.**

#### **Responses to Reviewer #1**

*This is a very interesting, well written concise review on the interplay between paracrine/endocrine factors of fat and muscle origin, in the context of cancer and cancer-cachexia. I am definitely favorable to its publication, since it would be of interest for a wide audience in both basic and clinical research.*

Thank you for finding this manuscript interesting and well written. Thank you also for your review which further improved the present manuscript.

*I have a few minor issues to point out:*

- 1) *Introduction, line 5: references 1-7 are appropriate, but references to diseases other than cancer (such as those cited in the sentence) are missing.*

I added appropriate references to diseases other than cancer (ref#1-3). **REVISED.**

- 2) § 'Skeletal muscle, main myokines and cancer prevention', line12: 'At the same time, skeletal muscle cells may secrete adipokines such as...?' this concept that adipokines may not be specific of adipose tissue and vice versa is important, and not obvious, and it would be great if it could be stressed elsewhere or put in greater evidence same

Thank you for pointing out this issue which is analyzed on page 7, as suggested. **REVISED.**

3)§, line18-19: *Recent meta-analyses and epidemiological studies...? While it is established that physical activity reduces cancer risk, it is even more striking that physical activity postdiagnosis improves prognosis, rather than exercise habits established before disease (breast and colorectal cancers): indeed physical activity after diagnosis lowers the risk of both cancer-specific and overall mortality. The author could mention this. (possible references: a. Physical activity and survival after breast cancer diagnosis. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. JAMA. 2005 May 25;293(20):2479-86. michelle.holmes@channing.harvard.edu b. Physical activity and survival after colorectal cancer diagnosis. Meyerhardt JA, Giovannucci EL, Holmes MD, Chan AT, Chan JA, Colditz GA, Fuchs CS. J Clin Oncol. 2006 Aug 1;24(22):3527-34. c. Influence of pre- and postdiagnosis physical activity on mortality in breast cancer survivors: the health, eating, activity, and lifestyle study. Irwin ML, Smith AW, McTiernan A, Ballard-Barbash R, Cronin K, Gilliland FD, Baumgartner RN, Baumgartner KB, Bernstein L. J Clin Oncol. 2008 Aug 20;26(24):3958-64. melinda.irwin@yale.edu d. Physical activity and survival after diagnosis of invasive breast cancer. Holick CN, Newcomb PA, Trentham-Dietz A, Titus-Ernstoff L, Bersch AJ, Stampfer MJ, Baron JA, Egan KM, Willett WC. Cancer Epidemiol Biomarkers Prev. 2008 Feb;17(2):379-86. crystal.holick@i3drugsafety.com).*

Again, thank you very much for emphasizing on this particular subject. This has been added along with the suggested references on page 8. **REVISED.**

4)§ *'The interplay of adipokines and myokines...'*, REFS 11-12 following the phrase *'1) an activation of the ATP-dependent. (...) calcineurin and MyoD? would be better replaced by references to original research articles, rather than reviews.*

References to original articles have replaced the review articles as suggested. **REVISED.**

5)same §, following the phrase *'Muscle regeneration may be further...? It is a very interesting point, worth being developed. In agreement with this concept there are evidences that TNF inhibits muscle regeneration in vivo (possible references: a. Tumor necrosis factor-alpha inhibition of skeletal muscle regeneration is mediated by a caspase-dependent stem cell response. Moresi V, Pristerà A, Scicchitano BM, Molinaro M, Teodori L, Sassoon D, Adamo S, Coletti D. Stem Cells. 2008 Apr;26(4):997-1008. b. Tumor necrosis factor-alpha gene transfer induces cachexia and inhibits muscle regeneration. Coletti D, Moresi V, Adamo S, Molinaro M, Sassoon D. Genesis. 2005 Nov;43(3):120-8.)*

This interesting point has been developed on page 11 as proposed by the Reviewer. **REVISED.**

6) finally, a major point is the use of the word 'sarcopenia' to mean 'muscle wasting' or 'muscle atrophy'. The terms are not synonyms, being sarcopenia invariably associated with aging, and they should not be used as such, as recently discussed for instance by Hepple (Muscle atrophy is not always sarcopenia. Hepple RT. J Appl Physiol. 2012 Aug 15;113(4):677-9. doi: 10.1152/jappphysiol.00304.2012. Epub 2012 Apr 19. No abstract available.). The word sarcopenia should be replaced throughout the paper.

The word sarcopenia was replaced throughout the paper, as suggested. **REVISED.**

## Responses to Reviewer #2

*The author has presented an overall review of the current scientific knowledge regarding the interplay of adipokines and myokines in cancer pathophysiology. I think that this article will be of interest to both basic scientists and clinicians in the field of cancer research.*

Thank you for finding this manuscript interesting.

*Typographical:*

1. 'at increased risk from cancer' should be 'at increased risk of cancer' (page 2,3 and 13).

Corrected as suggested. **REVISED.**

2. Define GSK3 (page 7).

GSK3 is now defined. **REVISED.**

3. 'In regard to cancer cachexia' (page 12) should be 'Regarding cancer cachexia'.

This was corrected. **REVISED.**

4. Specifically: 1. Zn- $\alpha$ 2-glycoprotein (ZAG) is a soluble plasma protein not 'the plasma protease' (page 9).

Corrected as suggested. **REVISED.**

5. In addition, ZAG is also an adipokine which is upregulated in tumour-bearing cachectic mice and cancer patients with cachexia, which may contribute to increased lipid mobilization (Bing et al, Proc Natl Acad Sci U S A. 2004;101(8):2500-5. Mracek T et al, Br J Cancer. 2011;104(3):441-7).

This issue has been discussed briefly on page 10 as proposed by the Reviewer. The abovementioned references were added. **REVISED.**

6. The section 'Emerging preventive and therapeutic implications' is somewhat speculative. For example, increased brown fat has beneficial metabolic effects (page 12); is this also the case in reducing the risk of cancer? Although the improved profiles of adipokines and myokines might be attractive for cancer prevention, it will be more convincing if the author could provide some evidence ?

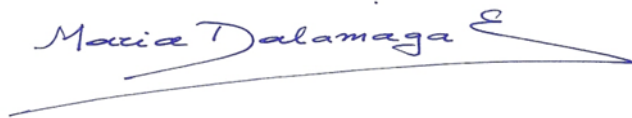
Following the Reviewer's concern, this section is further enriched with more evidence.  
**REVISED.**

### **Responses to Reviewer #3**

*This is a well-written paper, reviewing the most important aspects of adipokines and myokines contribution in cancer cachexia, including modalities and trends in therapeutic anti-cachexia targeting. No comments to be addressed before publication.*

Thank you for finding well-written the present manuscript.

Sincerely yours,

A handwritten signature in blue ink that reads "Maria Dalamaga" followed by a stylized flourish.

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