Author's response to reviews

Title: Changed adipocytokine concentrations in colorectal tumor patients and morbidly obese patients compared to healthy controls

Authors:

Andreas Hillenbrand (Andreas.Hillenbrand@uniklinik-ulm.de)
Juliane Fassler (Andreas.Hillenbrand@uniklinik-ulm.de)
Nadine Huber (Nadine.Huber@uniklinik-ulm.de)
Pengfei Xu (Pengfei.Xu@uniklinik-ulm.de)
Doris Henne-Bruns (Doris.Henne-Bruns@uniklinik-ulm.de)
Markus Templin (Templin@nmi.de)
Hubert Schrezenmeier (H.Schrezenmeier@blutspende.de)
Anna M Wolf (Anna-Maria.Wolf@uniklinik-ulm.de)
Uwe Knippschild (Uwe.Knippschild@uniklinik-ulm.de)

Version: 3 Date: 19 September 2012

Author's response to reviews: see over
Dear Dr. Keku,

Thank you very much for your e-mail dated August 30th, 2012 regarding our manuscript no. 1912167671706131 titled "Changed adipocytokine concentrations in colorectal tumor patients and morbidly obese patients compared to healthy controls". First of all we would like to thank the reviewers for their careful reading and their highly appreciated comments. We list, below, our responses to the issues raised on a point-by-point basis. These are in the format where I present the reviewer’s comments (verbatim) in italics and follow each point with our response in plain text. Actions taken are highlighted in bold.

We have modified the manuscript according to the reviewers’ recommendations.

Please do not hesitate to contact me in case of any questions arising. Thank you very much indeed for your efforts.

Yours sincerely,
Andreas Hillenbrand
General:

The final version of the manuscript was again proofread by a professional editor/native speaker. Please find enclosed the corresponding certificate.

Reviewer 1

Major Compulsory Revisions:

1. Please change throughout the manuscript "adipose tissue derived hormones" to "adipose tissue expressed hormones". The reason for this change is that leptin, resistin, and adiponectin are strongly expressed in adipose tissue but are also expressed in other tissues. Thus, the plasma concentrations originate only partly from adipose tissue.

   This is a good point. We now have changed the term “adipose tissue derived hormones” to “adipose tissue expressed hormones”.

2. I’m not convinced that your data support your conclusions at the end of pages 5 and 15 that adipocyte derived hormones and proinflammatory cytokines/chemokines contribute to colorectal tumorigenesis. The reason is that the more adipose tissue specific leptin and adiponectin differ in concentrations between CRC and MO patients, while the proinflammatory cytokines/chemokines are similar. In my view, your data indicate that MO and CRC have both chronic low-grade inflammation as part of their etiology.

   We agree on the point the reviewer has raised. We have now changed the sentence. Initial: “Our data underline that changes in the secretion of white adipose tissue derived hormones increase the risk for CRC tumorigenesis and tumor progression.”

   Changed into (p 5, last paragraph / p 15): “Our data indicate that MO and CRC both have chronic low-grade inflammation as part of their etiology.”

3. I strongly discourage you to state at the end of page 5 that "white adipose tissue derived hormones increase the risk for CRC tumorigenesis and tumor progression". Your data indicate similarities in the cytokine/chemokine profile of CRC and MO patients but you do not have any data that would provide even association between obesity and CRC or even more causality. I would recommend "Our results suggest that both MO and CRC have low-grade inflammation as part of their etiology”

   This initial statement is, of course, speculative. In the new version, this statement is changed as suggested.
Initial (p5, p 15): “White adipose tissue derived hormones increase the risk for CRC tumorigenesis and tumor progression.”
This sentence has been changed to: “Our data indicate that MO and CRC both have chronic low-grade inflammation as part of their etiology.”

4. Page 12 second last line: Please change to "Adiponectin may be a molecular marker for obesity and CRC, but...
This sentence has been changed to (p11): “Adiponectin may be a molecular marker for obesity and CRC …”.

5. Page 13 line 5: Please change to "however, we report, as do other [34, 35], no association between plasma adiponectin concentrations and CRC."
This sentence has been changed according to the reviewer’s suggestion.

6. Page 15 line 3: Please speculate why PAI-1 was proportionally more elevated in MO patients and MCP-1 was proportionally more elevated in CRC patients.
The following sentences have been added:
This could be explained by the fact that PAI-1 is not only produced by the visceral adipose tissue (increased in morbidly obese) but also by steatotic liver tissue in morbidly obese patients [Mertens et al., SeminVasc Med 2005; Alessi et al., ArteriosclerThrombVascBiol 2003]. Monocyte chemotactic protein-1 is produced by cancer cells and multiple different host cells within the tumor microenvironment and serves as one of the key mediators of interactions between tumor and host cells [Zhang J et al. ProgMolBiolTransl Sci. 2010].

7. Page 15 after line 4: Please speculate why cytokine/chemokines/PAI have a similar profile in MO and CRC patients, while the profile for MO and CRC patients differ for the adipokines leptin and adiponectin
The following sentence has been added:
Similar cytokine/chemokines/PAI-1 profile in MO and CRC patients reflects the obesity and tumor associated chronic inflammation. However, the specific influence of adipokines on tumor development and progression is still not fully understood and has to be addressed.

8. Page 15 last two sentences: Please remove the last two sentence because you reiterate the same in the conclusion section.
The last two sentences on p 15 have been removed.
9. Page 16 line 4 to 6: Please remove "provided a reliable adipokine profile in three different groups (CRC patients, MO patients and healthy BD as control group) and". You did not test the reliability of the adipokine profile.

This phrase has been removed.

**Minor Essential Revisions:**

1. Please revise throughout the manuscript: Sentences are not started with an abbreviation.

All sentences now start with whole words. The only exception is the following sentence (p 7): “R indicates the correlation coefficient.”

2. Please revise throughout the manuscript: A paragraph should consist of at least two sentences.

All paragraphs consist now of at least two sentences.

3. Page 7 first sentence: Please change to "Fasting blood sample from MO and CRC patients were collected preoperatively at 7 AM."

4. Page 7 line 11: Please change "antibody -coupled" to "antibody-coupled".

5. Page 8 line 9: Please change to "declared at p < 0.05". I think "p < 0.005" was a mistake.

6. Page 9 line 1: Please change "are" to "were".

7. Page 9 line 8: Please change "difference" to "differences".

8. Page 11: Please change to "are comparable in MO and CRC patient. In contrast, PAI-1 was higher in MO than CRC patients, and MCP-1 was higher in CRC than MO patients."

9. Page 12 line 8: Please change "are" to "were".

10. Page 12 last sentence: Please change "diminished" to "decreased".

Thank you for pointing that out. Points 3 to 10 are changed in the manuscript according to the reviewer's suggestions.

11. Throughout the manuscript: Please avoid using hyphenations for insertions.

Wherever possible, hyphenations for insertions have been removed and mostly replaced by commas.
Reviewer 2

1. Page 8: “statistical significance was declared at p < 0.005…” I assume the authors mean 0.05?
We apologize for the mistake. We have now changed “p<0.005” to “p<0.05”.

2. The authors still present mean BMI and a comparison by sex in the Methods section. I agree with them that there are different ways to present results/data, but I still believe that these are actual results of their study and better suited in the Results section (a short paragraph on baseline characteristics of the study participants).

A short paragraph on baseline characteristics of the participants has been included into the result section.

3. New version: “In patients suffering from colon cancer, there was no correlation of resistin levels with tumor size based T-staging and tumor grading.” Maybe better “with tumor sized based ON T-staging...”? We have changed the sentence as suggested.

4. New version: “In patients suffering from colon cancer, there was no correlation of resistin levels with tumor size based T-staging and tumor grading.” The authors may shortly want to add this to the strengths/limitations paragraph. We have added this statement now to the strengths/limitations paragraph.

5. Comment #5 of reviewer 1: The authors state that “As proposed by our statistic division, the case numbers are too small to receive significant results after adjustment for age and gender.” The authors should at least shortly acknowledge this in the text.

We have addressed this point and acknowledged it in the text. The following sentence was added on p12: “However, no significant results after adjustment for age and gender could be observed by multivariate logistic regression due to the small number of cases.”

6. The problem of missing BMI in the BD group is still not appropriately addressed in the strength/limitations section.
The problem of missing BMI in the BD group is now appropriately addressed in the strength/limitations section.