Author’s response to reviews

Title: Does LDL-cholesterol Induce Inflammation? If So, Does It Matter? Current Insights and Future Perspectives for Novel Therapies

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Also see attached word document

Response letter incorporation peer review


Ruurt A. Jukema, Tarek A.N. Ahmed, Jean-Claude Tardif

First we would like thank both reviewers for their feedback. We consider their comments helpful and have incorporated them throughout the text as advised. Please find below a point by point discussion.

Peer review by Roland Klingeberg

Thank you for your worthwhile comments, we have adapted the text accordingly:

• Be consistent throughout ms writing "IL-1β"
  o Page 3 ln 20: IL-1B  IL-1β
  o Page 4 ln 28 : IL-1B  IL-1β
  o Page 5 ln 26 + 28: 2x IL-1B  IL-1β
  o Page 8 ln 2 + 10: IL-1B  IL-1β
Peer review by Norbert Gerdes

Thank you for your worthwhile comments, we have adapted the text accordingly:

This is an interesting opinion piece summarized by Jukema et al. The authors provide a comprehensive overview of the "lipid hypothesis" of cardiovascular disease and summarize established and novel therapeutic strategies to combat hyperlipidemia. They continue to introduce the "immune concept" of atherosclerosis before combining and connecting both and describing hypercholesterolemia/hyperlipidemia as the main propagators of vascular immune reactions.

The opinion is very well-balanced. It should be mentioned, however, that the entire process of atherosclerosis and vascular dysfunction is not only based, as so often suggested, on local vascular inflammatory response but is rather a consequence also of a continuing systemic chronic hyper-inflamed state. Overall, the manuscript addresses an important and clinically relevant topic that has gained a lot of attention recently. The article is well-structured and logically connected.

Feedback:

• The entire process of atherosclerosis and vascular dysfunction is not only based, as so often suggested, on local vascular inflammatory response but is rather a consequence also of a continuing systemic chronic hyper-inflamed state.

- Added pg 5 ln 4-6: Note should be taken that the inflammatory component of atherosclerosis is a chronic hyper-inflamed systemic response rather than a local vascular dysfunction.
The title is very attention-catching. That is good. However, the reader is looking for clear answers to these defined questions. Yet, those are given neither in the conclusions of the abstract nor the main text.

- Added to abstract pg 2 ln 1 “LDL-C induces inflammation”
- Added to conclusion pg 15 ln 3: “LDL-C induces inflammation”

The paragraph referring to references 36 and 37 is somewhat out of focus and could be omitted without great loss.

- The request of the editor was to provide a wide scope with regard to inflammasome activation, therefore our preference would be to keep this paragraph. Needless to say that if the editor prefers to have this removed we will adapt the article (and abstract)

- In the same paragraph: Is the ASSAIL-MI trial investigating STE-MI. If understood correctly, the previous study (ref 51) already investigated acute MI?

- Pg 12 ln 28/39 we agree that this not clearly enough written down. We rewrote the text and changed acute myocardical infarction to STEMI. In the previous paragraph we outlined the role and clinical importance of IL-6. In this paragraph we discuss that blocking IL-6 in a NSTEMI works and that it is being investigated whether there are also positive effects of blocking IL-6 in STEMI.

- When the authors refer to tocilizumab (p12) they should mention that this is a IL-6R antagonizing antibody.

- Added pg 12 ln 25: a IL-6R antagonizing antibody

- When referring to co-stimulatory molecules as further interesting targets the relevant original publication should be mentioned.

- Inserted new ref 56 and moved relevant ref 57 (ref 56 in previous version) forward

- The text requires some proof reading. For example, use of singular and plural should be controlled.

- Pg 4 ln 21: lipoproteine corrected to lipoprotein

- Pg 4 ln 30/31: "Both innate and adaptive immune systems corrected” to “Both the innate and adaptive immune system”

- Pg 5 ln 20: low density lipoprotein-C corrected to LDL-C

- Pg 5 ln 23: added s and made new sentence

- Pg 6 ln 11: modulates corrected to modulate

- Pg 6 ln 21: support corrected to supports
• Check the sentence p7, line 33.

• It was not fully clear to us to what sentence is referred hereto exactly, but we have checked p 7/8 and have reworded some sentences.

• Spelling of IL-1b should be controlled and adhere to uniform standard.

• Page 3 ln 20: IL-1B  IL-1β

• Page 4 ln 28: IL-1B  IL-1β

• Page 5 ln 26 + 28: 2x IL-1B  IL-1β

• Page 8 ln 2 + 10:IL-1B  IL-1β

• Page 17 ln 3: IL-1B  IL-1β