ANSWERING REVIEWERS

Dear Editor,

Please find enclosed the edited manuscript in word format (file name: 20399-Review.doc).

Title: Intimal pericytes as the second line of immune defence in atherosclerosis

Author: Ekaterina A Ivanova, Yuri V Bobryshev, Alexander N Orekhov

Name of Journal: *World Journal of Cardiology*

ESPS Manuscript NO: 20399

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated.

2 Revision has been made according to the suggestions of the reviewer:

With respect to Reviewer 1:
In this manuscript Ivanova et al review the current literature concerning the immune-inflammatory processes in the pathogenesis of atherosclerosis, with a focus on the role of parasite-like cells as the second line of immune defense. The review is of interest and underscores the importance of immune/inflammatory responses in disease development. However, it has certain shortcomings that need to be addressed. 1. The first that should be mentioned, but was not used as an assessment criterion, is the language. The manuscript will benefit from editing by a native English speaker. Wording and verb corrections need special attention. Overall, it needs improvement in English. 2. The manuscript provides an extensive review of the current literature, which is good. However, it will certainly benefit from an integration of all these valuable findings in order to be less descriptive. For instance, a hypothesis of how the immune-inflammatory processes are involved in the development, can this be controlled or managed, how really all these immune/inflammatory cells and mediators interact...etc. would be helpful. 3. The title of the manuscript puts the focus on the role of parasite-like cells, however the manuscript as presented does clearly describe or propose this role or propose. The reader at the end of the manuscript as presented can reach neither a conclusion nor a definition of such role. This need to be addressed. 4. The authors may include a schematic model that would help the understanding of how immune-inflammatory processes and pericyte-like cells may contribute to artherosclerosis.

Response:
We wish to thank Reviewer 1 for the positive consideration of our work and for the valuable comments.
We have responded to the comments as follows:
1) The revised manuscript has been checked by a native English speaker, as suggested. Furthermore, we now provide an English language professional certificate, as recommended.

2) The integration of all the findings of our study is provided in the Discussion section in which we discuss the mechanisms responsible for immune-inflammatory processes in atherosclerosis.
3) The revised manuscript clearly shows that it focuses on the role of pericyte-like cells in the development of atherosclerotic lesions. This is also reflected in the title of the manuscript.
4) Fig 1 of the manuscript provides a scheme that indicates the location of pericyte-like cells in the arterial wall, whereas Fig. 2 and 3 show the functional predisposition of pericyte-like cells in atherogenesis.

In Respect to Reviewer 2:
Immune-inflammatory processes in the pathogenesis of atherosclerosis: Focus on the role of pericyte-like cells as the second line of immune defence in the arterial intima By Ivanova et al. In this manuscript, authors review the role of pericyte-like cells as the second line of immune defense in the arterial intima in atherosclerosis. In addition to presenting suggestions on the role of pericyte-like cells in the atherosclerosis and innate immunity, the author also reviewed atherosclerosis and cellular composition in macrovascular intima. The paper title and abstract are both appropriate. Although the authors provide an overview of atherosclerosis, the detailed discussion of the involvement of perivascular cells in atherosclerotic events was not been achieved. 1) Although the authors discussed what is known about perivascular cells so far, the paper needs a narrow explanation of the nature of perivascular cells. For example, instead of discussing maturity and pluripotency, it is more appropriate to draw the attention of the reader to a specific type of cell that contains specific markers (such as NGS1). 2) The nomenclature of the cells provided by the authors is not consistent. While they, most of the time, refer to the cells as pericytes, in other instants they are called pericytes-like satellite cells. 3) The review is lacking in terms of figures and tables that will help to present the overall idea the authors want to convey. 4) Appropriate referencing is important and is an indicator of scientific integrity and of extreme importance for review articles. Referencing information in this paper lacking, for example three paragraphs (page 4-5) are not referenced. This must be addressed throughout the manuscript. Finally, this paper presents an important topic on the cellular biology in atherosclerosis. The title is excellent. And the review covers all aspects in the pathological events of atherosclerosis. Overall, It can be considered to be a step toward understanding the involvement of cells from different niches in the pathology observed in atherosclerosis, which does not have cell specific therapeutic target yet. Although, we have some comments and suggestions, these will not decrease the impact of the paper.

Response:
We wish to thank Reviewer 2 for the positive consideration of our work and for the valuable comments.
We have responded to the comments as follows:
1) In our work we indicated that intimal stellate cells expressing smooth muscle alpha-actin co-expressed antigen 3G5 antigen and 2A7 antigen, which are known to be specific for pericytes. Commonly used markers for pericytes also include platelet-derived growth factor receptor β (PDGFRβ), CD146, anminopeptidases A and N (CD13), endoglin, neuron-glial 2 (NG2), non-muscle myosin, desmin, vimentin and nestin, but most of these markers are shared with VSMCs and/or dependent on pericyte maturity or activation state. Definitely, further studies are required in order to analyse the spectrum of the expression of alpha-actin smooth muscle(+)/3G5 antigen(+) stellate-shaped cells.
2) We completely agree with Reviewer 2 that "pericytes-like satellite cells" is not a histological term that would properly describe a specific cell type. However, because of the peculiarities of the distribution of smooth muscle alpha-actin(+)/3G5 antigen(+) stellate-shaped cells (namely -

in some distance from endothelial cells) and because of lack of our knowledge about the spectrum of the expression of pericyte-associated markers in the arterial wall, we prefer to avoid at this stage the identification of smooth muscle alpha-actin(+)/3G5 antigen (+) stellate-shaped cells as true pericytes. Obviously, further studies are necessary to verify this hypothesis. This opinion is reflected in our manuscript.
3) Indeed, the manuscript does not contain table(s), but the authors feel to be impractical to summarize the existing data into a table(s), especially as the topic of research is very narrow and currently available data is still too fragmented.
4) The referencing issue has been addressed during the revision, as recommended. In particular, references in three paragraphs on page 4-5 have been indicated.

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Cardiology*.