Author’s response to reviews

Title: Immunity, atherosclerosis and cardiovascular disease

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Author's response to reviews: see over
Stockholm 13th of March 2013

Please find here my answers to Editorial comments and to reviewers which have been helpful in making the paper more clear.

Best regards, Johan Frosteård, Professor of Medicine, Karolinska Institutet, senior consultant and specialist in internal medicine and in rheumatology.

Editorial comments

1. As indicated by the referees, the review would be improved by keeping the focus on targeting inflammation in cardiovascular disease and removing the section on evolution and atherosclerosis.

I have now removed evolutionary discussions and also considerably shortened the somewhat related questions of aging and atherosclerosis. I have focused the remaining aspects in this section on its relevance to immunity and immune senescence in humans. I should also add that the focus very much is immunity in atherosclerosis, where inflammation is a part, but still, the focus is immunity. Further, I should also add that I conciously have kept more focus on human studies than many investigators in the field of atherosclerosis/immunity/inflammation. Even though such models are essential, it is in my opinion still the human studies which should be most in focus, one reason being that the disease studied, CVD, is difficult to mimick in mice.

I would argue not to remove the whole discussion and review around the nature of atherosclerosis, disease or not. I also added two very interesting references, showing signs of MI in an old sample, and also, in a striking study just published in Lancet, that atheroslerosis indeed is present all over the world, including in hunter-gatherers of old times. I have tried to focus these sections much more, to show they are relevant, and also, again, considerably shortened them.

2. Your review could be further improved by the addition of a figure and some tables. I would suggest the following:
   a) a figure depicting how inflammation occurs in atherosclerosis, perhaps with a diagram of a blood vessel?
   b) a table summarizing the potential causes of inflammation in atherosclerosis
   c) a table summarizing the anti-inflammatory treatments, targets, and effect on atherosclerosis.

A figure has now been included depicting inflammation and immune mechanisms in atherosclerosis. I think the new version of the manuscript makes the causes of inflammation in atherosclerosis more clear; further, the figure also describes this. I would therefore suggest a table is not needed. I have added a table summarizing potential anti-inflammatory treatments.

3. The following sections should be included at the end of your manuscript: abbreviations, competing interests, authors' contributions, and acknowledgements.

Abbreviations, competing interests and acknowledgements have been added. Since I am the only author, I suggest author´s contribution is not implicated.

4. Please shorten the abstract to within the 175 word limit

This has now been done

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Reviewers’ report

Reviewer 1.

The proposed review is not sufficiently focused, too many aspects are being addressed. It should rather be orientated towards a limited number of issues. As a consequence, the author takes several ‘shortcuts’ and the general feeling is a lack of in-depth analysis of inflammation and immunity in the context of atherosclerosis. Out-of-focus (or appearing as such) considerations are presented (for instance, effect of aging in human and animal studies) without a clear link with what is supposed to be central to the review: the interaction of inflammation, immunity and atherosclerosis.

I have now removed evolutionary discussions and also considerably shortened the somewhat related questions of aging and atherosclerosis and also made more clear the connection to immunity and immunosenescence. I have focused the remaining aspects in this section on the relevance to immunity and immune senescence in humans. I should also add that the focus very much is immunity in atherosclerosis, where inflammation is a part. Further, I should also add that I consciously have kept more focus on human studies than many investigators in the field of atherosclerosis/immunity/inflammation. Even though such models are essential, it is in my opinion still the human studies which should be most in focus, one reason being that the disease caused by atherosclerosis complications, CVD, is difficult to mimick in mice. I would argue not to remove the whole discussion and review around the nature of atherosclerosis, disease or not. I have tried to focus these sections much more, to show they are relevant, and also, again, considerably shortened them.

Major Compulsory Revisions

1/ The impact of inflammation/immunity is presented as it was contributing equally to atherogenesis and plaque complication and no clear definition is given to these terms: what is inflammation as compared to immunity? I have added a clearer discussion of inflammation and immunity, p 2. I have also differentiated more clearly between atherogenesis and plaque complications, p 2.

2/ While the contribution of immune effectors is clearly demonstrated in atherogenesis in experimental models of hypercholesterolemic animals (especially in mice), it is much less clear for human early lesions, even though many reviews repeat this statement. Again, the contribution of immune effectors in the genesis of plaque should be split from their effects on plaque complications.
I have now made more clear the difference between atherogenesis and plaque rupture/CVD more clear, p 2 and elsewhere.

3/ Immune modulation strategies are presented as anti-inflammatory treatments. The target of the immune response and the effector mechanisms triggered will define whether the immune modulation will result in reduction or exacerbation of inflammation: detoxification of oxLDL by anti-oxLDL antibodies is beneficial and reduces plaque inflammation; targeting HSP-expressing stressed endothelial cells is pro-inflammatory and pro-atherogenic. These two immune modulation cannot be considered as anti-inflammatory. Indeed, the author should consider splitting the immune modulation strategies that have been used to understand the pathophysiology and those that are being tested as therapeutic options.

I agree that there is a difference between immune modulation and anti-inflammatory
treatment, but on the other hand, what is the point with immune modulation if it does not reduce inflammation. I have now made the points more clear, and also amended the discussion on HSP, p 15. I therefore think the changes are in line with those suggested by the reviewer.

4/ New immuno-pathophysiological mechanisms of atherosclerosis currently discussed in the field are not presented by the author: adventitial immune response, local and systemic B cell response, intraplaque hemorrhage and neovascularization of the vessel wall, crossroads between metabolic and inflammatory pathways…There are many new existing findings linking inflammation, immunity and plaque progression that could be presented in such a review.

I agree with this, and have now added a section, p 9, where these issues are discussed.

5/ There are (too) many misspellings in this ms.
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests.
I have now tried to improve the language
Major Compulsory Revisions
Section of “Immune modulatory therapy”, last paragraph
The list of references on HSP immunization is not complete. HSP immunization has been recently reported to reduce atherosclerosis in animal models. Here are few examples --
Given the athero-promotion effect of HSP immunization reported in the earlier literature (ref 51 in the manuscript), a short discussion of the discrepant reports on the effect of HSP immunization on atherosclerosis would be helpful.

I have now changed the manuscript according to the suggestions, which I agree with.

Minor Essential Revisions
1. Section of “oxidized LDL and related compounds”, 1st sentence – “Present at an early stage is low density lipoprotein (oxLDL) ...” Should be .....(LDL).
2. Section of “oxidized LDL and related compounds”, 12th sentence -- :…(PC) as an important epitope (PC)”. Delete second (PC).
3. Section title of “autoantibodies against phospholipid-related epitopes” – delete “autoantibodies against”. The phospholipid-related epitopes are the potential cause of inflammation, not autoantibodies.

I have now made these changes as suggested

Discretionary revisions
The section of “Is atherosclerosis a disease or a part of normal aging – or both?” is interesting, especially from evolutionary point-of-view. However the author can consider shortening this section. It would be more informative if the author can present his view (or answer) to the question.

I have now shortened this section and made my own conclusions clearer.

Quality of written English: acceptable
Statistical review: The manuscript does not need to be seen by a statistician.
Declaration of competing interests: no conflict of interest
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.