Reviewer's report

Title: Age-dependent defective TGF-beta1 signaling in patients undergoing coronary artery bypass grafting.

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Reviewer: Junsuke Igarashi

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Editorial Team
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Attached please find my comments to the authors on the manuscript MS:1426406098104018. I recommend the editors to handle this paper as "Major Compulsory Revisions".

The authors raised an interesting hypothesis that aging alters TGFbeta1 production by cardiovascular cells. They utilized human vascular smooth muscle cells derived from varying ages of population, and were able to show that cells derived from aged men secrete markedly lower TGFbeta1 into the culture medium. Although this finding is important, I would argue that these studies lack mechanistic insights how aging attenuates TGFbeta1. I propose the authors to perform several additional experiments (below), which can be carried out without too much technical difficulties.

I thank the Editorial Team for providing me an opportunity to review this potentially important paper. I look forward to having a chance to read the revised manuscript.

Sincerely yours,
Junsuke Igarashi

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Redondo et al. asked an interesting question whether or not aging alters TGFbeta1 production by cardiovascular cells. They obtained human VSMC from varyingly aged populations, and were able to demonstrate that cells derived from older men secrete markedly lower amounts of the TGFbeta1 protein into the culture medium than those from the younger. They also demonstrate that IMA samples derived from older patients yield lower degrees of p27 protein expression, which they believe to be a surrogate marker of TGFbeta1 signaling. The manuscript is well focused and nicely presented. Although these results are certainly interesting, this reviewer has felt that some additional experiments, by providing mechanistic insights to their current observations, would greatly enhance the significance of this study.

Major comment

Molecular mechanisms whereby aging is associated with lower degrees of TGFbeta1 production and p27 expression remain unexplored. This reviewer proposes authors to perform at least following two sets of experiments.

1) protein/mRNA analysis within the VSMC culture.

Using VSMC cultures derived from aging patients, authors can perform immunoblot/qRT-PCR to analyze TGFbeta1 transcript expression within the cells. This will allow the authors top dissect at which level TGFbeta1 production/secretion is perturbed in aged men-derived VSMC.

2) Smad regulation.

The authors focused on p27 as marker of TGFbeta1 signal in their IMA experiments. p27 can be also regulated, however, by a number of other cellular stimuli. The principal signal transducing module of TGFbeta1 receptor system are the Smad proteins, which undergo phosphorylation at specific residues when the receptors are liganded by the TGFbeta1. I would therefore propose that the authors reprobe membranes of IMA experiments (for example the one in the Fig 2A) for phosphorylated as well as total of Smad2/3 proteins.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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