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# ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Cardiology
**ESPS manuscript NO:** 27900
**Title:** Endothelial progenitor cells: exploring the pleiotropic effects of statins

## COMMENTS TO AUTHORS

well done

## Author comments

The authors would like to thank the reviewer for their kind comments.

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## COMMENTS TO AUTHORS

The review discusses endothelial progenitor cells in vascular repair and pleiotropic effects of statins in cardiovascular diseases. I have minor comments on it as following: 1. Please rewrite the abstract according to journal format for review manuscript. 2. Please correct "…either presence of absence of…" as "…either presence or absence of…" in Page 5, line 5. 3. Please clarify 3 markers in the sentence "Studies have identified 3 markers associated with early functional EPCs including CD133, CD34, and the vascular endothelial growth factor receptor-2 (VEGRF2) also known as kinase insert domain receptor (KDR), Fik-1 or CD309" in page 5. Are "kinase insert domain receptor (KDR), Fik-1 and CD309 in VEGRF2 family as one marker? If so, may put them in brackets. 4. Regarding several proposed intracellular signaling mechanisms for pleiotropic effects of statin therapy, it is better to give subtitle for each mechanism.

## Author's response

Thank you for your comments.

We have now rewritten the abstract according to the journal format

We have now corrected the error as;" . . . . denoting either presence or absence of a particular CD. . . . "

We have changed to the following "Studies have identified 3 markers associated with early functional EPCs including CD133, CD34, and the vascular endothelial growth factor receptor-2 (VEGFR-2) also known as *kinase insert domain receptor* (KDR, *Flk-1* or *CD309)* [7, 31]."

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## COMMENTS TO AUTHORS

This review article is timely and comprehensive. 1) A figure (or two) depicting the molecular/signaling mechanisms described in the text would be very helpful to the reader and an important addition to improve the manuscript. 2) What about the effects of statins on GPCR signaling/function in EPCs? Is there anything reported in the literature about this? The authors have covered exclusively and extensively RTKs and cytokine receptors in these cells; for some reason however, they seem to have ignored GPCRs altogether.

## Author's response

Thank you for your comments.

We have now added a section on GPCR within the text as follows;

G PROTEINS AND G PROTEIN-COUPLED RECEPTORS

G protein-coupled receptors (GPCR) are comprised of seven trans-membrane domain proteins and are a super family consisting of a large and diverse number of proteins encoded by approximately 5% of human genes [179]. There have been a number of classification systems proposed the most recent "GRAFS" (Glutamate, Rhodopsin, Adhesion, Frizzled/Taste2 and Secretin) [180]. In mammals there are five main families [181]. GPCRs have an integral role in transfer of extracellular stimuli to within the cell by conformational changes in transmembrane domain structure. [182-185] They regulate physiological responses to a myriad of endogenous ligands including amines, glycoproteins, peptides and lipids. Therefore, not surprisingly that GPCRs have been implicated in

regulation of cellular maintenance, differentiation, proliferation and migration of various stem cells. [186-188] [189].

GPCRs modulate activity of intracellular signaling via G proteins. There are currently four known G protein subfamilies each able to potentiate a number of drown stream effectors triggering a number of signaling pathways. [182] These include activation of Rho associated kinases (ROCK) [190, 191], activation or inhibition of cyclic AMP production [192] and Phosphoinositide 3-kinases (PI3Ks) and therefore modulate the PI3K/Akt pathway [193, 194]. The aforementioned have been implicated in EPC proliferation and function as described above.

GPCRs have evoked great interest as a possible target for novel drug therapy[195] as an estimated 50% of all currently prescribed drugs target only a small proportion of GPCRs [196]. They are also becoming increasingly recognised as having a major role in stem cell signaling [197].

The role of GPCR in regulation and function of EPCs and the effect of statin therapy remains yet to be elucidated however current evidence suggests that they may have a pivotal role.

Please find a diagram entitled;

Simplified diagram illustrating the positive and negative effects on EPC proliferation, mobilisation and longevity together with proposed mechanisms of action of statin therapy

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