

Specific Comments to Authors: 1. This manuscript describes endothelial progenitor cells in the context of coronary artery disease. The authors have discussed different cell markers and their functions. Although this is an interesting manuscript, the following point should be clarified before its publication.

Answering for reviewer: We have add page and line numbers in our manuscript.

2. The authors have truly mentioned that currently, no specific endothelial marker exists to distinguish EPCs from the rest of endothelial cells, however, recent findings mostly through bioinformatic analysis reported some dissimilarities among ECs. The following article could help you build this section. PMID: 33627177

Answering for reviewer: We have add the point of dissimilarities among ECs page 5-6 and line 98-114 in our manuscript: the angiogenic potential such as BMP2, 4, and ephrinB2 were highly expressed in EPCs; the expression of neuropilin-1 and VEGF-C were significantly up-regulated in EPCs and HUVECs; another genes such as Notch1, MIR21 and PECAM-1 were also differentially expressed in various origin of EPCs. The single-cell RNA sequencing was also showed a interesting result for

US.

3.Regarding the comparison between mature and immature ECs, the authors have to discuss their newly reported immunological differences. It has been shown that, unlike HAECs, EPCs from both cord blood and adult peripheral blood sources are immunosuppressive against T cells and can regulate them. This manuscript lacks immunological discussions. The following articles can help you to cover this domain. PMID: 32546175, PMID: 33397378

Answering for reviewer: We have add page 6-7 and line 122-150 in our manuscript:1)The EPCs have function to suppress T cell proliferation and modulate T cells differentiate into less pro-inflammatory and active phenotypes.2)TNF α boosting interaction with TNFR2 obviously enhanced EPCs immunosuppressive and anti-inflammatory effects.

4.The authors have mentioned that the expression of CD146 was related to endothelial dysfunction. However, they have mentioned another study using CD146 to

capture EPCs on stents. Please discuss the controversial role of this marker and its applications.

Answering for reviewer: We have discussed role of CD146 in page 3-4 and line 63-74 in our manuscript: CD146 expression reflected vascular permeability alterations and was significantly increased accompanied with cell adhesion molecules releasing when endothelial dysfunction was present. A reduction in this permeability is observed in CD146-deficient mice. In addition, CD146 is expressed on the late EPC, which enhanced the angiogenic properties, endothelial function and reduction of neointimal formation of EPCs.

5. The authors do not describe the role of CD31 anywhere in the text.

Answering for reviewer: We have added the role of CD31 in page 14 and line 295-394 in our manuscript: CD31 is a type of vascular cell adhesion and signaling molecule and expressed on the surface of human granulocytes, monocytes and platelets. Animal experiments have illustrated that CD31+ EPCs therapy was enhanced perfusion and reduced apoptosis in the healing myocardium, and more anti-inflammatory cytokine was stimulated in immune responses.

may predicted the less adverse effect,the other experiment on mice observed no abnormal proliferation after EPCs transplantation.