Dear editor,

We thank for you and reviewers' insightful and valuable comments, and give us the opportunity to submit a revised version of the manuscript. We have indicated the changes with red font in the revised version, and included a "clean" version of the revised manuscript. Point-by-point responses to reviewers' comments are listed below.

Response to reviewers' comments

Reviewer #1

This review article is based on review of very important topic address the processes involved in blood vessels formation. The efforts from the authors are well appreciated; however, there are some limitations in this manuscript.

Comments

In the section **Biomechanical stress for vascular injury and repair** Name the receptors of ECs which are responsible for mechanical signal transduction. Similarly, author mentioned about mechanosensors but didn't specified these, it is recommended to include the name and role of each sensor.

Response: We appreciate a lot for your excellent comment. We read the section **Biomechanical stress for vascular injury and repair** again**.** In the section, we firstly describe the mechanical characters of two types of blood flow, then we recommend a variety of mechanosensors, and defines and details of each sensor under different mechanical stress in the next two sections.

There are three types of laminar flow: steady, pulsatile and oscillatory flows; the steady laminar flow does not occur in arteries, while the pulsatile and oscillatory ones are unsteady.

Endothelial cells possess a variety of receptors to sense the altered flow and then transmit the mechanical signals through mechanosensitive signaling pathways to activate a series of signaling cascades and cell events. Several potential mechanosensors, including ion channels, cell surface or cytoplasmic receptors, integrins, kinases, and extracellular matrix components have been well determined [31, 32].

Comments

In figure 1, paracrine factors are mentioned, it will be better to add the name of paracrine factors which responsible angiogenesis, also can add factors which attract stem cells at the site of injury.

Response: Thanks for your suggestions. We have added the name of paracrine factors in figure legend, which responsible for either vascular regeneration or stem cells' recruitment. Besides, the description of these paracrine factors and its function is mentioned in the section **Stem cells for vascular repair** (third paragraph, line 3-10).

At the beginning of vessel repair, a part of EPCs directly incorporate into vessel intima, differentiate into endothelial cells with active angiogenesis, while the other part of EPCs display a proliferative potential[18]. The mechanism of EPCs promoting the angiogenesis varies a lot, including the direct formation of neovessels and the production of paracrine signals such as VEGF, stromal cell-derived factors (SDF), and platelet-derived growth factor (PDGF), which further activate the proliferation and vascular repair of endothelial cells [19]; this process depends on the recognizing of the markers on cells surface. These findings suggest that vascular repair is probably induced by the interaction between stem cells and the certain microenvironment of injured vessels such as the biomechanical stresses.

Figure 1: Then these stem cells move to the sites of lesion, differentiate into EPs, product of paracrine signals such as VEGF, PDGF, and SCDF; these actions take part in the vessel regeneration.

Comments

In the section **The response of stem cells to strain stress,** The first two paragraphs are irrelevant to vascular injury. It will be better to replace them with relevant materials.

Response: Thanks for your kind comments; we have moved the two paragraphs and replaced them with informative sentences to make the logics much clearer in this section.

The response of stem cells to strain stress

The vascular wall is subject to cyclic stretch of about 100-150kPa, which is generated by the pulsatile blood pressure[72]. The excessive and pathological mechanical stretch which occurs during hypertension is harmful as these high magnitude strain stress perturbs the vascular tone and causes improper cellular response of vascular wall, leading to

cardiovascular diseases[29].

Venous bypass grafting is one of the most commonly used surgery for atherosclerosis patients; the insertion of a grafted vein into the arterial system probably exposes the vascular wall to the new hemodynamic environment, which has been considered to be a critical stimulus for vascular remodeling[72]. Cyclic strain stress generated after venous bypass grafting have been reported to regulate and change the functions of VSMCs such as excessive proliferation, differentiation and apoptosis[73]. The cyclic strain is able to ensure the smooth muscle cells within the wall maintaining an active and contractile status[73]; several membrane proteins or compounds have been found to be mechano-sensitive to stretch, consisting of integrins, G-proteins, receptor tyrosine kinases(RTKs) and ion channels[74]. The overall signaling pathway was described in **Figure 5**.

Comments

The final summary of the review is very board, it is recommended to focus only on the mechanical factors responsible for the vascular regeneration.

Response: Thank you very much for valuable suggestions. We have rewritten the whole section according to your suggestions.

In this review, we firstly discussed the responses of stem cells to biomechanical stress and the underlying mechanisms, and then elaborated the role of stem cells in vascular repair. As the direct stimuli of vessel walls, mechanical forces play a crucial role in vascular injury and repair which can directly activate the mechanosensing molecules. Mechanosensors of stem cells such as integrins, ion channels, GPCRs, RTKs, and VEGFR are able to sense the mechanical stresses and then involve in the cytoskeleton rearrangement and finally the regeneration of endothelium. Manipulation of stem cells' mechanosensors should be beneficial for vascular repair in clinics and the development of new therapeutic strategies. Therefore, identification of the mechanosensors and a full understanding of the molecular mechanism are essential to design

effective treatments.

Many authors have proposed that increasing the number of stem cells is necessary to achieve sufficient vascular recovery and regeneration; hence, the safe and effective strategies to obtain enough number of stem cells which maintain the mechanical sensing potential are still a major challenge for the basic scientists and surgeons. Stem cells represent a promising tool for mechanical stresses sensing in the vasculature, but the methods to activate the resident and circulating stem cell and the underlying mechanisms for vascular repair remain unclear. The deep understanding of how the stem cells response to the mechanical forces should open a new dimension for the treatment of vascular disease, and enhance the clinical translation of stem cell-based strategy.

Reviewer #2

This review article focuses mainly on the studies have shown the promising role of stem cells in vascular repair using in vitro and in vivo experimental settings were compiled (between 1999 and 2019). Approximately 19 review papers (best match 7) have been published about this subject area (https://www.ncbi.nlm.nih.gov/pubmed/?term=mechanical+forces+stem+cells+vascular). The most recent of these was published in 2017.

The review article provides a comprehensive overview of recent advances about the effect of mechanical forces on vascular regeneration by stem cells and has a good bibliography (with external reference linking if possible).

The review paper provides a balanced view of recent studies in the subject area and makes a valuable contribution to this field.

The review manuscript cites appropriately important references and is coherently organized and systematically presented. The diagrams are appropriately illustrative of the paper contents.

I hereby declare, on behalf of myself, that I accept this review manuscript can be published in World Journal of Stem Cells.

PROOFS: The following proofs are made by adding the page and line numbers to **"46891-Manuscript File.docx"** file.

Page 12, line 10 "**….stablilise**", should be changed as "**…. stabilise**".

Page 14, line 7 " **….nelucear**", should be changed as "**…. nuclear**".

Page 20, line 5 "**….signaling**", should be changed as "**….signalling**".

Response: Thank you for your positive comments and the attentions to details. We have made the necessary revisions accordingly in the text.