

03472394 Conclusion: Minor revision

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

This is a comprehensive review. Authors analyzed the great databases of scientific literature. But they don't present the data in a clear form of figures and tables. Authors described the data from scientific literature. Authors describe the main factors affecting stem cell behavior, proliferation and differentiation. Authors propose a complex multiple combination of many factors that control the fate of MSCs. But they didn't mention some important factors. For example, the effect of biomaterials used in tissue engineering on MSCs growth and differentiation, e.g. the effect of mechanical properties of scaffolds on MSCs growth and differentiation, as well as the effect of the biomechanics of extracellular matrix on MSCs fate. Authors are really sure that mesenchymal stem cells are pluripotent cells? The tables, graphs or any other figures are absent. The manuscript doesn't contain any numerical data. The number of references is 132 from 1986 to this year with the majority of them for last 5 years. It's great for the review. The manuscript well organized and presented. The style and language are OK. Authors prepared their manuscript according to manuscript type and the appropriate category: a Review.

Authors: We thank the Reviewer for his comments that have improved our manuscript. We revised the manuscript according with his suggestions, mentioning factors as biopolymers and scaffold implicated in regulation of stem cell fate: "Synthetic scaffolds and biopolymers are incorporated in stem cell cultures, to induce their growth, miming the stem cell niche <sup>[60]</sup>. Biomaterials provide a physical environment controlling cell functions. The interaction of stem cells with these surfaces modulates multiple processes such as cell migration, proliferation and differentiation, as well as the extracellular matrix deposition (ECM), providing dynamic signaling able to regulate cell behavior <sup>[61,62]</sup>". Moreover, we inserted two images, relative to epigenetic regulation of stem cells and bioactive molecules that modulate cell differentiation.

02929791 Conclusion: Minor revision

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

This review article is focused on understanding stem cell behavior, proliferation and pluripotency, and stem cell applications. This manuscript is very interesting. Comment 1: There are minor grammatical and language errors. Comment 2: To summarize "Epigenetic regulation of self-renewal and pluripotency" and "Bioactive molecules in orchestrating cell differentiation", two separate graphical images should be clearly depicted. Comment 3: Other epigenetic regulator of stem cells should be explained. For example: DNA methylation and demethylation, chromatin remodeling, and micro RNAs.

Authors:

We thank the Reviewer for his comments that have improved our manuscript. We revised the manuscript according with reviewer suggestions, mentioning factors as DNA methylation and chromatin remodeling involved in stem cell regulation: "DNA methylation plays a key role in maintaining the undifferentiated state in stem cells by silencing the differentiation genes, being also implicated in somatic cell reprogramming <sup>[38,39]</sup>. All these classes of enzymes promote changes in chromatin structure, exerting a crucial role in regulating the balance between pluripotency and differentiation <sup>[40]</sup>". We have also mentioned the role of miRNAs in stem cell fate and cell reprogramming, highlighting their use in treatment of several diseases: "MicroRNAs (miRNAs), a

small non-coding RNAs, have been discovered as regulators of different signaling pathways, as stem cell pluripotency and somatic cell reprogramming <sup>[41]</sup>. The modulation of cell differentiation by miRNAs can be used in order to treat various diseases, including myocardial infarction, neurodegenerative and muscle diseases <sup>[42]</sup>”.

As suggested, we inserted two images, relative to epigenetic regulation of stem cells and bioactive molecules that modulate cell differentiation and revised all text to correct grammatical errors.