ABSTRACT SUBMISSION

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Osteoinductive material to fine-tune paracrine crosstalk of mesenchymal stem cells with endothelial cells and osteoblasts

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(*PhD defense in 2018 or before the end of 2019".

INTRODUCTION: The capacity to secrete protective and biologically active mediators places MSCs among the most suitable tools for tissue regeneration. Studying mesenchymal stem cell (MSCs) responses to biomaterials provides evidences that their chemical, biophysical and/or mechanical cues have a deep impact on MSCs fate[1]. However, current strategies neglect the effect of materials on MSCs paracrine activities. The present study investigates whether bone-mimetic material (B-MM) could promote MSCs pro-regenerative secretome; especially on the production of angiogenic and osteogenic factors

METHODS: Bone-mimetic material (B-MM) made from inorganic calcium phosphate supplemented with chitosan and hyaluronic acid biopolymers was built-up using an automated spraying device[2]. Human MSCs were seeded in 24 well plates at 24×10^3 cells/cm^2 on UV-decontaminated B-MM and cultured for 21 days. Between 19th and 21st day of culture, MSCs conditioned media (MSCs-CM) were collected, and stored at -80°C. Cytokines, chemokines and growth factors release were quantified by ELISA and their activities were evaluated on human endothelial cells (ECs) and osteoblasts (OBs).

RESULTS & DISCUSSION: MSCs cultured on B-MM, composed of carbonated apatite, chitosan and hyaluronic acid biopolymers for 21 days, showed the formation of bone-*like* nodules. However, bone-*like* nodule arising from MSCs fibroblastic layers occupied only 8 % of cultured area. The secretome analysis showed that B-MM significantly affects the production of soluble mediators required for bone healing and homeostasis. MSCs on B-MM decreased the production of IL-1β, IL-6 and IL-8 inflammatory mediators and increased the release of PGE2, HGF, b-FGF and VEGF angiogenic growth factors, enhancing thus ECs chemotaxis, inducing ECs inflammatory profile, regulating neutrophils recruitment through an up-regulation of ICAM-1 and interestingly promoting ECs osteogenesis properties by up-regulating BMP-2. IL-1β, IL-6, IL-8 and VEGF are reported to mediate, in dose-dependent manner, bone regeneration by promoting pre-osteoblasts proliferation and differentiation[1]. As for OBs cultured in osteogenic media, qRT-PCR experiments showed that MSCs-CMs up-regulate the expression levels of *RUNX2*, *COL1A1* and *ALPL* over the time, however no boosting effect of OBs differentiation was observed as *BGLAP*, late bone specific marker, was not detected.

CONCLUSION: Our data provide, herein, evidences that the indirect crosstalk between MSCs and various cell types involved in bone regeneration might be finely regulated by B-MM.

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[2] Rammal, et al., ACS Appl. Mater. Interfaces 2017, 9, 12791.

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