3D printing of composites containing copper-incorporated mesoporous bioactive glass induce different cell responses depending on cell type and donor

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INTRODUCTION: Bioactive glasses are used for dental and orthopaedic applications thanks to their osteoconductivity and bioactive properties. Mesoporous bioactive glasses (MBG) are special type of bioactive glasses with highly ordered channel structure and high specific surface area, which can be loaded with drugs and growth factors, making them suitable as delivery systems. Besides that, their structure can be modified by substitution with bioactive metal ions assessing desired therapeutic effect after release. With that in mind, ions showing antimicrobial effect would be appropriate solution for prevention and treatment of implant-related infections. However, certain ions such as Cu^{2+} can be cytotoxic at concentrations effective against bacteria. Ion release from MBG can be tuned and controlled by integrating MBG in established biomaterial inks. Our aim here was to investigate release of Cu^{2+} from 3D printed composite scaffolds containing MBG and to evaluate effects of release products on human pre-osteoblasts (hOB), primary and immortalized mesenchymal stem cells (hMSC).

EXPERIMENTAL: Calcium in MBG was partially substituted with 5 mol.% Cu^{2+} (5CuMBG) and completely with 15 mol% Cu^{2+} (15CuMBG), following already established protocol [1]. In order to make this particulate material extrudable, we integrated the different MBG variants in already established alginate-methylcellulose blend [2] to prepare composite biomaterial inks containing 2 and 7 wt.% MBG. Scaffolds were produced using extrusion 3D printing, crosslinked with 100 mM $CaCl_2$ and incubated in cell culture medium over 21 days. Ion release profiles were determined and the effect of release products on viability of hOB, primary and immortalized hMSC as well as on differentiation towards osteoblastic cells was investigated.

RESULTS AND DISCUSSION: Full substitution with Cu disturbed channel structure of the MBG, while it was maintained in 5CuMBG. Release of Cu^{2+} from all composite scaffolds was initially high, but it dropped over time. Initially released concentrations from all 15CuMBG-containing composites as well as from the ones containing 7 wt.% of 5CuMBG were highly cytotoxic towards all tested cell types. However, composites containing 2 wt.% of 5CuMBG showed different levels of cytotoxicity towards two different donors of hOB. Viability of both types of hMSC was not affected in the presence of release products of the same type of composite scaffolds, while specific ALP activity of osteogenically differentiated MSC was significantly increased.

CONCLUSIONS: Our findings show that the cytotoxic effect of CuMBG in composite scaffolds depends on cell type and is also donor-specific. Therefore, it seems that CuMBG can play a promising role in future patient-specific therapies.

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