Bone regeneration - from the first generation of bioinert materials to application of extracellular vesicles (EVs)

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The first generation of biomaterials - bioinert materials was developed with the goal to achieve a suitable combination of physical properties with the minimised toxic and immune response to the foreign body. The second generation of biomaterials - bioactive materials provide cellular reaction such as colonization of osteoblasts, proliferation and differentiation of the cells to form new bone. Third generation biomaterials were designed to stimulate specific cellular responses at molecular level and to activate genes that stimulate regeneration of living tissues. Two alternative routes of repair are now available with the use of these biomaterials: tissue engineering and *in situ* tissue regeneration. A recent trend based on latter approach for reconstruction of bone defects is combination of biocompatible scaffolds with embedded bioactive components such as extracellular vesicles (EVs), derived from mesenchymal stem cells (MSCs), as a “cell-free therapy approach”.
In this presentation, the focus will be on the differences of the osteogenic/osteoinductive properties and cytocompatibility of the first generation of biomaterials such as Ti-based scaffold, and contemporary approach such as the application of extracellular vesicles (EVs) in combination with biomaterials. We compared the 3D-printed Ti6Al4V scaffold and 3D-printed Ti6Al4V scaffold functionalized with ceramic coatings and extracellular vesicles (EVs) derived from stem cells of human exfoliated deciduous teeth (SHED cells) embedded in a collagen hydrogel. Cytocompatibility tests of these biomaterial constructs showed a higher metabolic rate of SHED cells on coated scaffolds compared to uncoated Ti scaffold. Further, the osteogenic potential of EV-loaded scaffolds was tested on autologous SHED cells for 10 day period. The qRT-PCR analysis revealed significant upregulation of RUNX-2 and BMP-2 gene expression compared to non-functionalized Ti6Al4V scaffold indicating the pro-osteogenic effects of the SHED-EV-enriched scaffold. These findings suggest that the integration of SHED-derived EVs within a functionalized Ti scaffold is a promising strategy for enhancing bone regeneration in critical-sized defects.

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