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Bio-inspired hybrid materials with smart functionalities for regenerative medicine

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The recent years are experiencing new regenerative approaches for the healing of diseased tissues and organs, with the aim to recover the original functionality and reduce the healthcare costs and the patient's pain. In this view regenerative medicine has to proceed hand in hand with advances in Materials Science aiming to develop new smart, stimuli-responsive bio-devices. In fact, to trigger the correct cascade of biological events that lead to tissue regeneration, cells need to be exposed to an adequate array of chemical-physical, structural and morphological signals whose presentation follows precise spatial and temporal patterns. This requires the establishment of suitable strategies in designing scaffolds for the regeneration of a specific tissue so as to reproduce such signals and provide cells with information compelling them to express specific phenotypes. The formation of human hard tissues is governed by self-assembling and organization of collagen molecules in a complex 3-D structure, which acts as a template for simultaneous mineralization with nanocrystalline, ionically substituted apatite. Since a decade, the reproduction of the biomimetic conditions of bone synthesis allowed to settle a biomineralization process generating hybrid constructs where the mineral phase is nucleated upon guidance by the chemical features and physical confinement imposed by the self-assembling/self-organizing polymeric matrix, so that the mineral phase has physical, chemical and ultra-structural resemblance with mineral bone. The possibility of tailoring the mineralization extent also enabled the synthesis of graded constructs mimicking the different areas of multifunctional articular regions (i.e. subchondral bone, mineralized cartilage and hyaline cartilage). The high mimicry of the hybrid scaffolds with natural tissues is the source of their high regenerative ability. In fact the chemico-physical and morphological features of the scaffold trigger the cascade of events leading to tissue regeneration, which starts from cell colonization and subsequent differentiation. Quantitative macroscopic and histological score evaluations showed that this novel osteochondral scaffold is safe and easy to use, and may represent a suitable matrix to direct and coordinate the process of bone and hyaline-like cartilage regeneration. Very recently a new superparamagnetic, bioactive and bioresorbable apatite was developed through controlled substitution of $Ca2+$ ions with $Fe2+/3+$ ions, with specific Fe/Ca and $Fe2+/Fe3+$ ratios. Pinning on this recent development, it will be illustrated how bio-hybrid bone- and osteochondral-mimicking devices with intrinsic superparamagnetic properties can be obtained nucleating Fe-HA on assembling Collagen fibers. Such devices can increasingly assist the osteogenic and angiogenic capacity during the remodeling process under the influence of a static magnetic field. In addition the novel non-toxic, bioactive and completely bioresorbable Fe-HA can be also prepared as nanoparticles .This study realized an innovative *in vitro* 3D cell culture model that relies on magnetically controlling cell migration, growth factor/drug delivery and hyperthermia effect using novel FeHA MNPs. Cells can be moved after their magnetization, in a well localized area of the biomaterial. The proposed method will have a great impact in tissue engineering and nanomedicine, filling the gap between the standard two-dimensional cell studies and the *in vivo* environment. This new 3D model will allow to precisely predict cell behavior, tissue regeneration, reducing the number of animals necessary for *in vivo* experiments as required by the principles of the 3Rs (Replacement, Refinement and Reduction).

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