Inspired by nature

Bio-inspired artificial scaffolds and the quest to replicate biology

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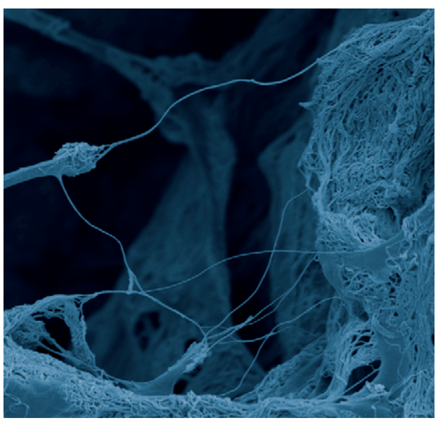
Research on scaffolds that mimic the three-dimensional organization of physiological tissues is of fundamental importance for treatments in regenerative medicine that aim to reconstruct lost or damaged tissue. In the case of osteochondral regeneration, the scaffolds must reproduce the complex physico-chemical features of the articular cartilage and of the underlying subchondral bone, from the macro- to nano-scale and provide the right environment for cellular activity, favouring cell colonization, and assuring the appropriate communication between cells and the material. To date, various porous bioactive substitutes have been developed, with good biocompatibility and bioresorbability, for the repair of osteochondral lesions. Still, most of these are not yet able to satisfy all the conditions for clinical implementation[1]. This is mainly because these substitutes have been unable to reproduce all of the required cartilage and bone tissue characteristics.

Bone tissue is composed of hydroxyapatite (HA) nanocrystals, grown on collagen fibers, morphologically and structurally organized up to the molecular scale. It is thus able to exchange suitable physical, chemical, and morphological information with the extracellular matrix that drives cells towards the formation of new bone. The bone substitutes currently used in clinical practice do not exhibit such self-organized complexity, lacking the relevant features of biomimesis that allow proper regenerative behaviour and which are necessary in a biomimetic bio-hybrid composite. At the same time, the loading of cells onto scaffolds is a critical step in developing self-sustained scaffolds for *in situ* implantation, and a proper equilibrium must be reached.

Research at the Institute of Science and Technology for Ceramics, National Research Council, Faenza, Italy, in collaboration with the Rizzoli Orthopaedic Institute, Bologna, Italy, has been focusing on the development of innovative bioinspired and biomimetic materials for bone and osteochondral regeneration. The concept of biomimetics is a crucial factor for the development of new biomaterials for regenerative medicine. Biomimetic properties allow biomaterials to be recognized and accepted by the organism as itself. We have developed collagen-HA nano-composite biomaterials which exploit the self-assembling process of collagen fibers and induce the nucleation of a nanostructured HA mineral phase: similar to what happens during the formation of natural bone.



The biomimetic properties of such materials, prepared through this biologically inspired process, are the result of both the specific chemical composition and the three-dimensional structure of the material. The structural biomimetics are provided by the collagen fibers, which mimic the extracellular matrix of the osteochondral human tissue, and by the low crystallinity of the mineral phase. This phase grows with the crystallographic *ab*-plane perpendicular to the collagen fiber, as is required to increase osteoblast affinity. The chemical biomimetics are obtained through the use of collagen macromolecules, together with HA nanocrystals, which, when nucleated on the organic matrix, undergo the phenomenon of nano-structural confinement that influences its chemical-physical and nano-structural properties. Both conditions must be met for the successful design of 3D scaffolds[2]. These scaffolds can be designed with different compositional gradients varying the HA-collagen ratio[3]. Moreover, magnetic HA can be nucleated into the material, inducing a super-paramagnetic effect which improves fixation in complex articular sites[4]. Bio-functionalization can also be performed to incorporate new bioactive molecules for *in situ* release.

This month's cover image shows human osteoblast-like cells completely embedded within the nanostructure of a bio-inspired collagen-HA scaffold. This 3D bone biomimetic scaffold is composed of type I collagen fibers, biomineralized with HA during fiber self-assembling. This image was acquired through scanning electron microscopy, which allows the analysis of cell-material interactions over a submicron range, with a high depth of field and high resolution. We can see here the complex collagen-HA fibre mesh and how cells take advantage of such a matrix; illustrating the high biocompatibility and osteoconductivity performance of such scaffolds. More interestingly, we can see that cells are capable of adhering to and spreading over single collagen fibres, which imposed directionality, and allows the cells to *dangle on collagen*.

Such an interaction between cells and materials represents the focus of both current bone tissue engineering strategies and biomaterial science.

FURTHER READING

1. Hollister *et al.*, *Biomaterials* (2002) **23**, 4095.
2. Tampieri *et al.*, *Trends Biotechnol* (2011) **29**, 526.
3. Tampieri *et al.*, *Biomaterials* (2008) **29**, 3539.
4. Tampieri *et al.*, *Nanotechnology* (2011) **22**, 015104.