SYNTHETIC PHOSPHOSERINE-TETHERED HYPERBRANCHED PEPTIDES AS BIOMIMETIC COATINGS FOR MEDICAL IMPLANTS

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Introduction

In orthopedic as well as in oral and maxillofacial surgery there is an increasing demand for a faster osseointegration of implants. To improve the mechanical anchorage and biological-chemical bond between the implant and the surrounding bone, the state-of-the-art increasingly focus on technological innovation of surface treatments at nano-, micro- and macro-scale. While dental implant design, thread pattern and pitch distances are mechanical implant features related to the macro design, surface nanostructuring and biofunctionalization are approaches aiming to enhance biological reactivity through biomimicking topography and biocue presentation. The present study for the first time analyses the in vivo osseointegrative potential of the phosphoserine-tethered dendron coating applied to dental titanium implants.

Materials and methods

Titanium alloy fixtures (diameter 4.1 mm, length 9 mm) underwent the following surface treatments: (i) a sandblasting and etching (SE); (ii) a macro-porous additive manufacturing (AM) achieved by Direct Metal Laser Sintering (DMLS). The AM implants had a solid core, a macroporous shell 500 µm in thickness, and a solid thread over the porous shell thus limiting the exposed porosity present in between the threads. The interthreads length was 1.5 mm. Porosity was designed according to gyroid geometry thus having a geometrically ordered and repeated unit spatial cell consisting in a knot with three arms departing with 120° of angular distance; (iii) Phosphoserine modified dendron coating prepared as described by Meikle et al. . Altogether four different groups were analysed: Sandblasted and etched implants (SE), porous additive manufactured implants (AM), SE with additional dendron functionalisation (SE-PSD) and AM with additional dendron functionalisation (AM-PSD).

Results and discussion

After 2 and 8 weeks the bone-to-implant contact (BIC) total values of SE implants (43.7±12.2%;53.3±9.0%) and SE-PSD (46.7±4.5%;61.7±4.9%) as well as AM implants (20.49±5.1%;43.9±9.7%) and AM-PSD implants (19.7±3.5%;48.3±15.6%) showed no statistically significant differences. For SE-PSD and AM-PSD a separate analysis of only the cancellous BIC demonstrated a statistically significant difference after 2 weeks and 8 weeks. Biomechanical findings proved the overall trend of an increased stability of the porous implants after 8 weeks.

Conclusions

The functionalisation of the implant surface by phosphoserine-tethered dendron increases trabecular bone formation at the interface of metal implants supporting the role played by the implant topography in osseointegration

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BIOMATERIAL-BASED REGENERATIVE MEDICINE: CHALLENGES & OPPORTUNITIES

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Abstract

For the author there are three major challenges in Regenerative Medicine (RegMed), namely to develop strategies which are translatable, materials which are functional and methods which are predictive. New strategies in RegMed depend on a concerted interdisciplinary effort between the exact and engineering sciences on the one side and the life sciences on the other. As cells synthesize and reside in an extracellular matrix (ECM), which they remodel, a main focus of biomaterial research is the development of injectable, bioresorbable hydrogels containing biological signals which could be released by tissue responses. These interactive materials will certainly increase in importance in the future. However, a major challenge is how to combine them, for example, in composites with load-bearing capacity relevant for human applications. Where synthetic materials such as metals are still essential, as in orthopaedics and traumatology, there is the possibility of adding such responsive materials as coatings to the bulk material. The use of decellularized matrix is also part of the bioinspired approach to developing biomaterials.

In the life sciences great effort is being invested in understanding the so-called „regenerative niche", which differs from tissue to tissue. Great progress made in stem cell biology has opened up new vistas on the possibility to target

a regenerative niche. Cell-cell and cell-matrix interactions remain a central element of this activity. One of the paradigm shifts we need to master is the step from what is usual even in complex cell biological models, namely the use of purely physiological conditions, to a more realistic situation as would be found in the clinical setting. Thus, we need to understand regeneration in hostile environments, which include post-trauma, cancer and multimorbidity. This will be discussed with examples from the author's own research.

One of the important in vitro methods to investigate the mechanisms involved in regeneration is the use of coculture systems with relevant human cells, usually on tissue culture plastic and, as knowledge progresses, on more complex 3D biomaterial scaffolds. As major limiting factors in bone regeneration are the speed and extent of vascularization, we have established human osteoblast (pOB)-endothelial cell (EC) cocultures to study cellular crosstalk and its possible use for translational strategies [1,2].

Concerning the background, if two cell populations, that is, human pOB and human dermal microvascular EC (HDMEC), are seeded as cell suspensions on an open porous biomaterial scaffold, such as can be made from microfibres of the silk protein fibroin, the two cell types will interact in such a way that lumen-containing, capillary-like structures (CLS) will form as a vascular network [3]. Further molecular studies on the cellular crosstalk revealed that the EC induce an upregulation of growth factor and matrix production in pOB, such as VEGF and collagen type I resp. The EC then respond to these signals by promoting the angiogenic phenotype [4,5].

The following additional approaches have been adopted to study CLS formation: use of early embryonic signals, such as sonic hedgehog (shh), to accelerate both osteo- and angiogenesis [6,7], use of intermittent hypoxia, but not constant hypoxia, to promote vascular sprout formation, and study of possible stimulatory roles for macrophages in the bone regenerative niche [8]. How this is investigated in coculture models will be discussed in the context of future developments. Naturally, all phenomena from in vitro studies require proof of concept in relevant in vivo models, as only this approach can lead to a translational perspective. Thus, we were able to demonstrate that these in vitro pre-formed vessels can rapidly become inosculated, that is, incorporated into the pre-existing microcirculation of host tissue in a subcutaneous implantation model [9]. The major role of the osteoblasts as a natural „drug delivery system" was shown by the fact that host vascular response can be stimulated by these cells even in the absence of a pre-cultivation with endothelial cells [10].

A further aspect offering a promising perspective for the future is NanoMedicine, which uses advances in nanotechnology for medical applications. For reasons of time this will not be addressed in the context of the presentation.

In conclusion, biomaterials, especially so-called responsive biomaterials, are an essential element of modern regenerative medicine, and must be accompanied by state of the art life sciences, from cell and molecular biology to good clinical practice. To achieve this the multidisciplinary approach is a conditio sine qua non.

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References

[1] Kirkpatrick CJ, Fuchs S, Hermanns MI, Peters K, Unger RE. Cell culture methods of higher complexity in tissue engineering and regenerative medicine. Biomaterials 2007; 28: 5193-5198
[2] Kirkpatrick CJ, Fuchs S, Unger RE. Co-culture systems for vascularization - learning from Nature. Adv Drug Deliv Rev 2011; 63: 291-299
[3] Unger RE, Sartoris A, Peters K, Motta A, Migliaresi C, Kunkel M, Bulnheim U, Rychly J, Kirkpatrick CJ. Tissue-like self-assembly in co-cultures of endothelial cells and osteoblasts and the formation of microcapillary-like structures on three-dimensional porous biomaterials. Biomaterials 2007; 28: 3965-3976
[4] Santos MI, Pashkuleva I, Alves CM, Gomes ME, Fuchs S, Unger RE, Reis RL, Kirkpatrick CJ. Surface-modified 3D starch -based scaffold for improved endothelialization for bone tissue engineering. J Mater Chem 2009; 19: 4091-4101
[5] Santos MI, Unger RE, Sousa RA, Reis RL, Kirkpatrick CJ. Crosstalk between osteoblasts and endothelial cells co-cultured on a polycaprolactone-starch scaffold and the in vitro development of vascularization. Biomaterials 2009; 30: 4407-4415
[6] Dohle E, Fuchs S, Kolbe M, Hofmann A, Schmidt H, Kirkpatrick CJ. Sonic hedgehog promotes angiogenesis and osteogenesis in a co-culture system consisting of primary osteoblasts and outgrowth endothelial cells. Tissue Engineering Part A 2010; 16: 1235-1246
[7] Dohle E, Fuchs S, Kolbe M, Hofmann A, Schmidt H, Kirkpatrick CJ. Comparative study assessing effects of sonic hedgehog and VEGF in a human co-culture model for bone vascularization strategies. E Cells & Mater J 2011; 21: 144-156
[8] Dohle E, Bischoff I, Böse T, Marsano A, Banfi A, Unger RE, Kirkpatrick CJ. Macrophage-mediated angiogenic activation of outgrowth endothelial cells in co-culture with primary osteoblasts. E Cells & Mater J 2014; 27:149-164
[9] Fuchs S, Ghanaati S, Orth C, Barbeck M, Kolbe M, Hofmann A, Eblenkamp M, Gomes M, Reis RL, Kirkpatrick CJ. Outgrowth endothelial cells from human peripheral blood contribute to in vivo vascularization of bone tissue engineered constructs based on starch polycaprolactone scaffolds. Biomaterials 2009; 30: 526-534
[10] Ghanaati S, Unger RE, Webber MJ, Barbeck M, Orth C, Kirkpatrick JA, Booms P, Motta A, Migliaresi C, Sader RA, Kirkpatrick CJ. Scaffold vascularization in vivo driven by primary human osteoblasts in concert with host inflammatory cells. Biomaterials 2011; 32: 8150-8160

NANOFIBROUS MEMBRANE WITH FIBRIN AND COLLAGEN STRUCTURES AS CARRIERS FOR SKIN CELLS

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