

SYNTHETIC MORPHOGENS AND PRO-MORPHOGENS FOR TISSUE REGENERATION

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INTRODUCTION: The regeneration of tissues damaged by either trauma or disease depends on the control of inflammatory and tissue cell activity by biochemical signalling and extracellular matrix bioligands. Semi-dendrimers (SD) are highly and 3D ordered, hyperbranched polymers forming nanostructures with tuneable physico-chemical properties. Recently, SD have been investigated as a possible way to expose bioligands for specific cell receptors as well as to present the cells with growth factors and peptidic growth factor analogues [1]. Aim of the presentation is to provide examples of biofunctionalisation of poly(ϵ -lysine) (PL) SD semidendrimers to obtain biocompetent, nanostructured systems (BSD) and their ability to interact with biochemical and cellular components with a role in tissue regeneration control.

METHODS: PL BSD assembly was performed by conventional peptide solid-phase method. Tenta Gel NH₂ resin (Iris Biotech, Germany) presenting a rink amide linker (Iris Biotech) to allow the late cleavage of the synthesised BSD. BSD synthesis was initiated by grafting to the linker a core amino acid or peptides. Three branching generations were obtained the synthesis was with a specific biocompetent amino acid or peptide. BSD were characterised by HPLC, gravimetric method and mass spectroscopy (MS). BSD were grafted onto biomaterials and optical waveguide lightmode spectroscopy (OWLS) sensor chip surfaces and tested for their ability to induce, biomineralization, molecular interactions with growth factors and drugs as well as control of cell adhesion and activity.

RESULTS: Various BSD were synthesised at a hundred milligram scale; their synthesis being proven to be reproducible by HPLC and MS and always higher than 60%. BSD exposing phosphoserine functionalities were able to induce surface biomineralization upon incubation in simulated body fluids and to encourage osteoblast adhesion and differentiation. Similarly, the contractile phenotype of smooth muscle cells was preserved by the combination of the nanotextured BSD surface, while their proliferative phenotype was inhibited by the controlled release of nitric oxide donors. In a different example, BSD presenting functional groups able to bind growth factors (e.g. VEGF) were synthesised in the view of controlling angiogenesis in cartilage and bone.

The BSD ability to respond to cell stimuli was achieved by synthesising BSD bearing in their structure elastin-like domain undergoing cyclic temperature transition at body temperature. Various types of cells such as osteoblasts and endothelial cells underwent a significantly more ordered organization of their cytoskeleton and of key cell receptors. The BSD substrate also improved cell proliferation over 72 h and cell differentiation over a period of time of 14 days.

DISCUSSION & CONCLUSIONS: BSD led to very specific interactions with cells and biochemical components relevant to the regeneration of different tissues in different clinically-reflective models. The flexible and scaled up synthesis, their degree of purity and tuneable interactions with bioactive molecules and cells highlight the potential of these nanostructured biomaterials to be used as synthetic morphogens and pro-morphogens in tissue regeneration.

REFERENCES: ¹ A.W. Lloyd, G.W.J. Oliver, G. Standen, M. Santin, S. T. Meikle. Surface functionalisation of biomaterials WO2008068531

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