STUDYING GLYCOSAMINOGLYCAN DERIVATIVE/PROTEIN INTERACTION - PREREQUISITE FOR THE DESIGN OF FUNCTIONAL BIOMATERIALS

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Introduction

Numerous biological processes (tissue formation, remodelling and healing) are strongly influenced by the cellular microenvironment [1]. Glycosaminoglycans (GAGs) are important components of the native extracellular matrix (ECM) able to interact with biological mediator proteins [2,3]. They can be chemically functionalized and thereby modified in their interaction profiles [4]. Thus, they can be considered as promising candidates for the design of functional biomaterials to control healing processes in particular in health-compromised patients.

Materials and Methods

GAG derivatives based on hyaluronic acid (HA) and chondroitin sulfate (CS) are characterized in their interaction properties with mediator proteins (MMP-1, MMP-2, TIMP-3, TGF-β1, OPG, and sclerostin) using surface plasmon resonance (SPR; BiacoreT100), receptor binding studies, immunochemical methods and molecular modelling. The biological property profiles of selected GAG derivatives, either alone or being a component of collagen type I-based artificial ECM (aECM) are studied in vitro with cells relevant for healing processes in bone and skin (human mesenchymal stromal cells (hMSC), osteoblasts, osteoclasts, osteocytes, fibroblasts).

Results and Discussion

Biophysical studies show that the interaction profiles between mediator proteins and GAGs are strongly influenced by (i) sulphation degree, (ii) sulphation pattern, and (iii) composition and structure of the carbohydrate backbone. Hyaluronan (HA) derivatives demonstrate typically a higher binding strength in their interaction with biological mediators than chondroitin sulphate for a comparable sulfation degree [5]. Furthermore sulphated GAG derivatives alter the interaction profile of mediator proteins with their cell receptors or solute native interaction partners. FIG. 1 shows this exemplarily for a system comprising the immobilized TGF-receptor II being in interaction with TGF-β1, a GAG derivative, and the TGF-receptor I.
These results are in line with biological effects on cells relevant for wound healing processes. This is valid for solute GAGs as well as those incorporated in collagen-based aECMs. Prominent effects are (i) a tailored degradation behaviour of the native ECM under the influence of MMPs and TIMP-3, (ii) anti-inflammatory, immunomodulatory properties towards macrophages/dendritic cells [6], (iii) enhanced osteogenic differentiation of human mesenchymal stromal cells, (iv) altered differentiation of fibroblasts to myofibroblasts, (v) reduced osteoclast activity [7] and (vi) improved osseointegration of dental implants in minipigs [8].

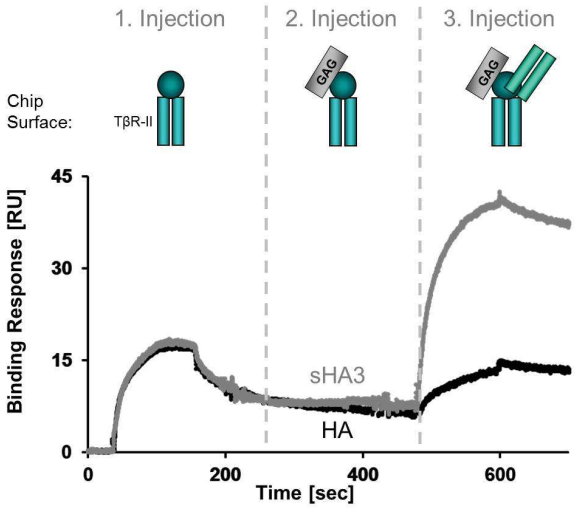

FIG. 1. SPR response curves for the sequential interaction of immobilized TGF-receptor II with solute TGF-β1 (green circle), followed by solute GAG and TGF-receptor I. GAGs: native HA in comparison to sulfated HA (sHA3) with a sulfation degree of 3.

Conclusions

The findings of our consortium Transregio 67 contribute to an improved understanding of structure-function relationships of GAG derivatives in their interaction with mediator proteins and cells. This will enable the design of bioinspired, functional biomaterials to selectively control and promote bone and skin regeneration.

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