Acta Biomaterialia 8 (2012) 659–666

Contents lists available at SciVerse ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Artificial extracellular matrices composed of collagen I and sulfated hyaluronan with adsorbed transforming growth factor β1 promote collagen synthesis of human mesenchymal stromal cells

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ARTICLE INFO

Article history:
Received 14 June 2011
Received in revised form 14 September 2011
Accepted 18 October 2011
Available online 25 October 2011

Keywords:
Artificial extracellular matrix
Collagen synthesis
Glycosaminoglycans
Mesenchymal stromal cells
Sulfated hyaluronan

ABSTRACT

Sulfated glycosaminoglycans (GAG) are multifunctional components of the extracellular matrix and are involved in the regulation of adhesion, proliferation and differentiation of cells. The effects of GAG are mediated in general by their interactions with cations and water, and in particular by their binding to growth factors. The aim of this study was to generate artificial extracellular matrices (aECM) containing collagen I and hyaluronan sulfate (HyaS), which are capable of adsorbing and releasing transforming growth factor β1 (TGF-β1), and to promote collagen synthesis of cultured human mesenchymal stromal cells (hMSC). For the preparation of aECM, monosulfated Hya (HyaS1) or trisulfated Hya (HyaS3) were used; the natural chondroitin-4-sulfate was used as a control. As applied for the in vitro experiments, the resulting matrices were composed of 93–98% collagen I and 2–7% GAG derivative. Adsorption of TGF-β1 to the aECM and release from the aECM was dependent on the degree of sulfation of hyaluronan. Collagen synthesis of hMSC was promoted only by aECM with adsorbed TGF-β1; the bare aECM had a slightly inhibitory effect on collagen synthesis. The promoting effect did not correlate either to the amount of adsorbed TGF-β1 nor to the release of TGF-β1, indicating that the correct presentation of TGF-β1 to the cells might be critical. The results indicate that sulfated hyaluronan-containing aECM have the potential to control both the adsorption and release of TGF-β1, and thereby promote collagen synthesis of hMSC. Thus, these aECM might be a useful tool for different tissue-engineering applications to enhance bone formation when used for biomaterial coating.

1. Introduction

Hyaluronan and sulfated glycosaminoglycans (GAG) have many functions in the extracellular matrices (ECM) and pericellular space of cells. They are involved in adhesion and migration of cells, in ECM remodeling, wound healing and inflammatory processes [1–3]. Non-sulfated, negatively charged hyaluronan is able to bind enormous amounts of water and to swell, and acts in several tissues as a space holder and immune modulator. Sulfated, negatively charged GAG-like chondroitin sulfate, dermatan sulfate or heparan sulfate are mostly bound to core proteins, forming proteoglycans (PG), and are found in membrane-spanning syndecans and glycosylphosphatidylinositol-anchored glypicans or associated to ECM such as aggrecan, versican, biglycan or decorin. Within the ECM and pericellular space, hyaluronan and GAG/PG are not only structural components; they also underlay a highly dynamic remodeling (sulfation/desulfation, glycosylation/deglycosylation, epimerization), are responsible for extracellular cation homeostasis, support primary cell adhesion, act as co-receptors for many growth factor receptors and thus modulate outside–inside signaling [4–6]. GAG/PG are known to bind different proteins like collagen I, growth factors, chemokines and interleukins. Collagen I provides binding sites for heparan sulfate with a binding constant of about 1 nM; one heparan sulfate proteoglycan can interact with 80–200 collagen I fibrils [7,8]. GAG are important for accumulation and presentation or sequestration of small regulatory proteins, and can build up mediator gradients in the extracellular space [9]. The GAG–protein interaction is characterized by high capacity, but mostly by low affinity and specificity [9]. The interaction depends strongly on the fine structure of GAG (disaccharide units,

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doi:10.1016/j.actbio.2011.10.026