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Sulfated hyaluronan and chondroitin sulfate derivatives interact differently with human transforming growth factor-β1 (TGF-β1)

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ABSTRACT

This study demonstrates that the modification of hyaluronan (hyaluronic acid; Hya) and chondroitin sulfate (CS) with sulfate groups leads to different binding affinities for recombinant human transforming growth factor-β1 (TGF-β1) for comparable average degrees of sulfation (DS). In general, Hya derivates showed higher binding strength than CS derivatives. In either case, a higher degree of sulfation leads to a stronger interaction. The high-sulfated hyaluronan sHya3 (average DS ≈ 3) exhibited the tightest interaction with TGF-β1, as determined by surface plasmon resonance and enzyme-linked immunosorbent assay. The binding strength was significantly weakened by carboxymethylation. Unmodified Hya and low-sulfated, native CS showed weak or no binding affinity. The interaction characteristics of the different sulfated glycosaminoglycans are promising for incorporation into bioengineered coatings of biomaterials to modulate growth factor binding in medical applications.

1. Introduction

Transforming growth factor-β1 (TGF-β1) is the founding member of a superfamily of secreted polypeptides [1]. It includes three different forms of TGF-β, the bone morphogenetic proteins (BMP), the Nodals, the Activins, the anti-Müllerian hormone and other structurally related factors in vertebrates, insects and nematodes [1,2]. They are produced by diverse cell types and reported to regulate cell migration, adhesion, multiplication, differentiation and death [1]. The predominant serum and plasma form is an inactive complex with α-macroglobulin [3,4].

High concentrations of TGF-β1 can be found in platelets [5] and bone [6]. In fact, TGF-β1 is one of the most abundant cytokines in the bone matrix (200 μg kg^{-1}) [7].

TGF-β1 is a disulfide-bonded dimeric protein, synthesized and secreted as a large precursor molecule [8,9]. It is enzymatically cleaved into active TGF-β1 and latency-associated protein (LAP). LAP remains non-covalently linked to active TGF-β1, masking the receptor-binding domain and keeping it inactive. Osteoblasts are unique in producing two latent forms of TGF-β1: a 100 kDa precursor latent complex and another one that also contains a 190 kDa binding protein [10,11]. TGF-β1 is thus deposited in the bone matrix as an inactive, latent complex [7]. Active TGF-β1 is released during bone resorption, possibly owing to the acidic osteoclastic microenvironment [12] or secreted proteases degrading LAP [13]. It then coordinates bone formation by inducing migration of bone mesenchymal stem cells (MSC) [7] as well as recruitment and proliferation of osteoblasts [14–16]. However, the effect of TGF-β1 on bone cell replication is biphasic and depends on both the growth factor concentration and cell density in monolayer culture [14]. Therefore, TGF-β1 functions to couple bone resorption and formation [7] and is a powerful stimulator of bone formation in vivo [11,17]. In MSC and osteoblasts, TGF-β1 is also very important in matrix formation. It stimulates the synthesis of proteoglycans [18] and is the most prominent inducer of procollagen and fibronectin expression [14,19,20].

In bone ECM, the concentration of free TGF-β1 is regulated by its interaction with the proteoglycans biglycan and decorin [21,22]. Via binding, decorin acts as a negative regulator of the growth factor [22]. In biglycan/decorin-deficient mice, the lack of these binding partners resulted in excess of free TGF-β1, causing accelerated apoptosis of bone MSC, decreased numbers of mature osteoblasts and subsequently reduced bone formation [23].

The active 26 kDa dimer is known to also interact with other extracellular matrix components such as fibronectin [24], thrombospondin [25] and type IV collagen [26]. In contrast to decorin, thrombospondin and type IV collagen were shown to maintain the activity of TGF-β1 [25–27].

Furthermore, human TGF-β1 and TGF-β2, but not TGF-β3, bind to heparin and high-sulfated heperan sulfate [28,29]. They potentiate the activity of TGF-β1 via protection from proteolytic degradation [30] and dissociation of the α-macroglobulin/TGF-β1 inactive complex, while having no effect on the activities of TGF-β2 and

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