Heparan Sulfate-Modifying Enzymes: Intriguing Players in Cancer Progression

Fabio Henrique Brasil da Costa1,2, Mary C Farach-Carson1,2,3 and Daniel D Carson1,4*

1Biosciences Department, Rice University, Houston, USA
2Department of Diagnostic and Biomedical Sciences, The University of Texas Health Science Center School of Dentistry, Houston, USA
3Department of Bioengineering, Rice University, Houston, USA
4Department of Genetics, The University of Texas MD Anderson Cancer Center, Houston, USA

*Corresponding Author: Daniel D Carson, Biosciences Department, Rice University, Houston, 77005, USA; Tel: 713-348-3347; E-mail: dcarson@rice.edu

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Heparan sulfate (HS) is a sulfated glycosaminoglycan that is deposited in human tissue matrices at specialized sites [1,2]. HS interacts with diverse extracellular matrix (ECM) components with HS binding sites, including inflammatory cytokines, and heparin-binding growth factors (HBGFs) [3,4]. Within the ECM and in the cell surface glyocalyx, HS-proteoglycans (HSPGs) act as reservoirs for cytokines and HBGFs, and as cofactors for surface receptors where they stabilize active signaling complexes [5–7]. The bioavailability and activity of HBGFs stored on HSPGs are primarily regulated by HS-modifying enzymes that act on HSPGs, such as perlecan, the syndecans and the glypicans [8,9]. Therefore, HSPGs and their enzymic modifiers are crucial for tissue homeostasis, both in normal biology, as in development and wound healing, and in pathological processes such as fibrosis and cancer biology [1,10,11]. To date, studies have identified three key extracellular enzymes that modulate HS function and growth factor signaling: tissue heparanase (HPSE) and the extracellular endosulfatases SULF1 and SULF2. HPSE is an endoglycosidase that cleaves HS chains yielding diffusible HS fragments [12] that often still retain bound growth factors (Fig. 1A). HS-bound growth factors can subsequently bind to surface receptors to form HS-HBGF-receptor ternary complexes (Fig. 1B) [12]. Like HPSE, SULFs are secreted but, for the most part, stay peripherally associated with the cell surface through the interaction with HSPGs in the glyocalyx, primarily syndecans and glypicans [13,14]. Enzymatic activity of SULFs involves selectively removing 6-O-sulfate groups from HS polymers (Figure 1A) [14,15]. Because many HBGFs require 6-O-sulfate for high-affinity binding to HSPGs or surface coreceptors [3,15,16], SULFs release HBGFs in a form free from HS chains. Freed HBGFs can bind subsequently to cognate cell receptors to form signaling complexes, or they may rebind to distant unmodified HSPGs that retain 6-O-sulfate. Therefore, both HPSE and SULFs are crucial enzymes that define activation parameters of HS-independent signaling networks in both positive and negative ways that often are context-dependent [17,18].

Better understood than the SULFs, HPSE generally is regarded as a tumor promoter. Cleavage of HS by HPSE releases and increases the availability of HBGFs, including vascular endothelial growth factors, hepatocyte growth factors [19–22] and fibroblast growth factors [23–26], thereby improving their access to their cell surface receptors and enabling downstream growth signaling. Consequently, HPSE can stimulate pro-tumorigenic processes including neoangiogenesis, tumor cell proliferation and invasion, inhibition of apoptosis, and metastasis, all among the well-accepted hallmarks of cancer [27,28]. Because of the intricacies from potential outcomes of SULF activity, predicting their impact on complex microenvironments, a priori, such as tumors, is more complicated. Numerous studies have implicated the SULFs as significant players involved in critical aspects of cancer progression, including proliferation, invasion and metastasis [1,15]. The expression of these intriguing enzymes is abnormal in many carcinoma cells, yet no consensus conclusion has been made as to whether they support or inhibit general cancer progression. Some of this confusion may be attributed to differences in regulation of gene expression between SULF1 and SULF2. For example, tumor necrosis factor α (TNFa) [29] and Wilm’s tumor transcriptional factor [30] stimulate SULF1 expression to a greater extent than SULF2. In contrast, SULF2, but not SULF1, is a p53 target [31]. A comparison of potential transcription factor binding sites (TFBS) in the SULF1 and SULF2 promoter regions in silico revealed that ~50% of TFBS were not shared between these two genes [32]. Therefore, dysregulated transcriptional programs and different transcriptional targeting in SULF genes both in cancer cells and cells in the tumor microenvironment may partially explain some of the apparently contradicting data concerning SULF functions in tumorigenesis.

A review of studies focusing on SULFs and published in the past twenty years reveals contrasting expression levels and opposing effects on tumor growth depending on the type of cancer and the surrounding microenvironment. For instance, an analysis of SULF1/SULF2 in various cancer cell lines suggested a mostly tumor-suppressing role of SULFs [33]. In contrast, other researchers demonstrated that high SULF1 or SULF2 levels correlate with poor prognosis in a wide range of tumor types [34]. Additionally, contrary to SULF2, SULF1 can exert a tumor suppressor effect in cancers, including myeloma, ovarian,
head and neck, breast, liver, and pancreatic [33,35–39] cancers, despite being upregulated in others [40]. The paradox of how SULFs, sharing essentially identical target specificity, have different biological functions remains an open research question. In seeking to reconcile these observations, an essential point to consider is the signaling context. Most of the studies mentioned above solely focused on the cancer compartment, where cultured cells respond to artificially supplied HBGFs. However, there is overwhelming evidence that associated “bystander” stromal cells play a vital role in the regulation of tumor growth [41–13]. Cancers with reduced expression of HPSE or the SULFs still may be impacted by the actions of these enzymes in scenarios where they are being produced by cancer-associated fibroblasts (CAFs) and/or tumor-associated macrophages (TAMs). In recent years, the role of immune cells in cancer progression has gained increased attention. TAMs stand out as a major cell population in the tumor stroma [44] where they can, together with CAFs, modulate the expression of matrix remodeling enzymes, HSPGs, and HBGFs via pro- and anti-inflammatory cytokines [45–48] (Fig. 1D).

Also part of the signaling context controlling cell behavior are the specific ligands and their binding preferences to various HS modifications, spatial distribution of the enzymes themselves, cellular composition of the microenvironment, and the combination of HBGFs and cytokines present. Examples of such variations include whether: 1) ligands require HS fragments as cofactors for ternary complex signaling (Fig. 1B); 2) desulfation results in HBGF release or disruption of cofactor potential; 3) the enzymes are more abundant at the cell surface or in the ECM (Fig. 1C); 4) a robust reactive stroma response supporting cancer progression is present. While SULFs have been shown to suppress signaling at the cell surface through disruption of coreceptor functions, their release of HBGFs from fibroblasts in a desmoplastic stroma might favor growth. To date, studies exploring the influence of these different aspects of the signaling context are scarce, primarily from a lack of in vitro model systems that can reproduce the convoluted tumor microenvironment. Recent improvements in bioengineered cancer tissues are changing this, and new insights are on the horizon. While several HPSE inhibitors have reached and/or are currently undergoing clinical trials [49,50], no drug targeting the SULFs specifically has reached the clinic. Given the diverse nature of SULF expression and opposing activity in different contexts, as discussed above, targeting SULFs for cancer therapy is a complex endeavor. A key concern relates to the consequences of potentiating or inhibiting SULF activity. While silencing SULFs can lead to anti-tumor effects in some cancers, in others where they act as tumor suppressors, SULF inhibition could enhance tumorigenicity.
significant amount of pre-clinical work is needed to understand the full repertoire of pro- and anti-tumor activities of the SULFs such that SULF-based therapies can be designed with confidence. Nonetheless, the undeniable involvement of HPSE and SULFs in regulating cancer progression makes these enzymes attractive both as therapeutic targets and prognostic indicators of tumor progression.

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