Review

The function of heparan sulfate during branching morphogenesis

Vaishali N. Patel, Dallas L. Pineda and Matthew P. Hoffman

Matrix and Morphogenesis Section, *National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD 20892, United States*

Correspondence to Matthew P. Hoffman: *mhoffman@mail.nih.gov*
http://dx.doi.org/10.1016/j.matbio.2016.09.004

Abstract

Branching morphogenesis is a fundamental process in the development of diverse epithelial organs such as the lung, kidney, liver, pancreas, prostate, salivary, lacrimal and mammary glands. A unifying theme during organogenesis is the importance of epithelial cell interactions with the extracellular matrix (ECM) and growth factors (GFs). The diverse developmental mechanisms giving rise to these epithelial organs involve many organ-specific GFs, but a unifying paradigm during organogenesis is the regulation of GF activity by heparan sulfates (HS) on the cell surface and in the ECM. This primarily involves the interactions of GFs with the sulfated side-chains of HS proteoglycans. HS is one of the most diverse biopolymers and modulates GF binding and signaling at the cell surface and in the ECM of all tissues. Here, we review what is known about how HS regulates branching morphogenesis of epithelial organs with emphasis on the developing salivary gland, which is a classic model to investigate epithelial-ECM interactions. We also address the structure, biosynthesis, turnover and function of HS during organogenesis. Understanding the regulatory mechanisms that control HS dynamics may aid in the development of therapeutic interventions for diseases and novel strategies for tissue engineering and regenerative medicine.

Published by Elsevier B.V.

Introduction to branching morphogenesis and extracellular matrix (ECM)

Many organs, including the lung, kidney, liver, pancreas, prostate, salivary, lacrimal and mammary glands are formed during embryonic development by the process of branching morphogenesis. Iterative rounds of epithelial branching, driven by the expansion and maintenance of pools of stem and progenitor cells, establish the branched architecture (Fig. 1A). This is required to increase the internal surface area for the particular organ function, whether it is gas exchange, filtration, waste excretion or fluid secretion. The main cellular mechanisms involved in branching morphogenesis include cell proliferation, differentiation, migration, and apoptosis. In addition, there are reciprocal interactions among the epithelial stem and progenitor pools and their niche that include the surrounding ECM and a variety of cell types including mesenchymal, neuronal, immune, lymphatic and endothelial cells [1]. The ECM is critical during branching morphogenesis for not only providing structural integrity, but for controlling communication among cell populations by the HS binding secreted growth factors, morphogens, cytokines and other mediators of development [2]. For the purposes of this review we will refer to all of these factors simply as growth factors (GFs). The ECM is produced by the mesenchymal cells in the tissue surrounding the developing organ and by the epithelial cells themselves [3]. ECM is composed of several distinct families of molecules such as laminins, collagens, and fibronectin, and their role in branching morphogenesis has previously been reviewed elsewhere [2,4].

The functions of heparan sulfate (HS) in ECM

The basement membrane (BM), a specialized ECM structure that epithelial cells adhere to, is composed primarily of collagen IV, laminin isoforms, nidogen, and HS proteoglycans, including perlecan [5]. An important function of the negatively charged

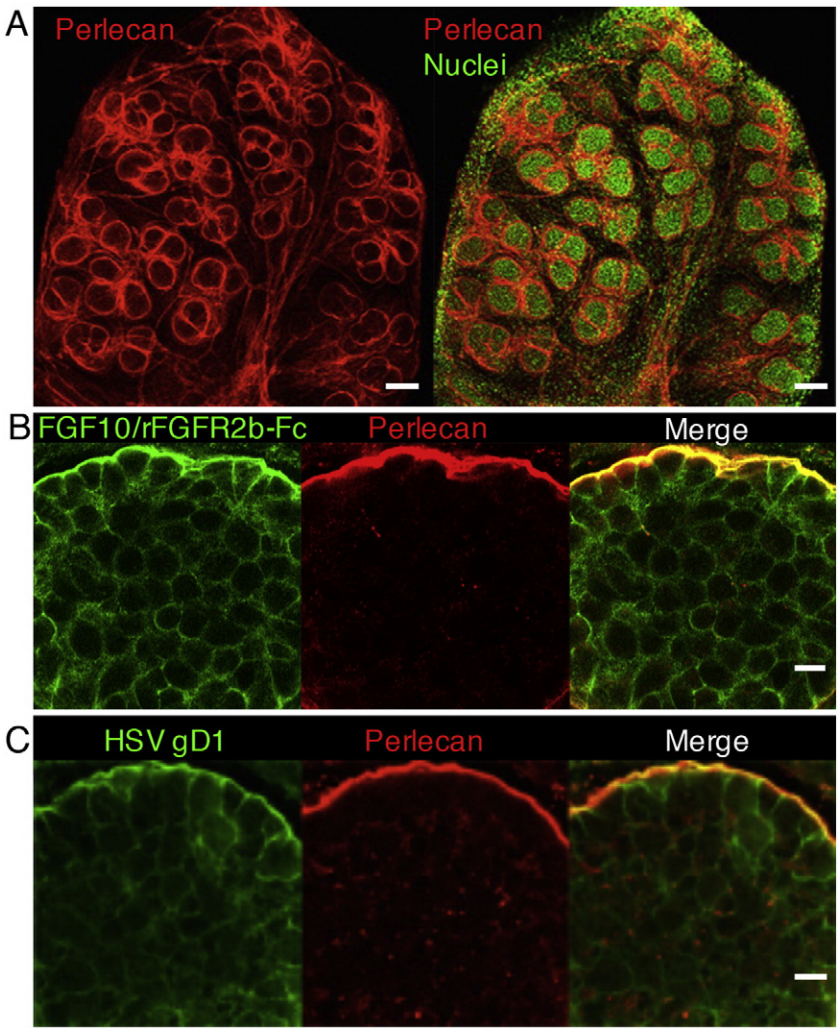

Fig. 1. The BM separates epithelial cells from mesenchyme during SMG branching morphogenesis and contains HS that binds growth factors and viral receptors. (A) Whole-mount staining of E14 SMG showing perlecan staining the BM (red) surrounding the branching epithelium, and nuclei (green). Images are 10 μm confocal projections. Scale bar: 100 μm. (B) Higher magnification of the SMG endbud shows that FGF10/rFGFR2b-Fc (Ligand and carbohydrate engagement (LACE) assay, green) binds the endogenous HS at the epithelial cell surface and colocalizes with perlecan (red) in BM. Images are single confocal sections. Scale bar: 10 μm. (C) The endbud HS also binds the viral receptor HSV-1 gD285 protein (green) at the epithelial cell surface and colocalizes with perlecan (red) in BM. Images are single 2 μm confocal sections. Scale bar: 10 μm.

HS in the ECM and BM is to bind and concentrate GFs and thus act as a reservoir for GFs [6]. HS is a co-receptor to facilitate signaling complex formation between GFs and their receptors or oligomerization of these receptor complexes. The endogenous HS of any tissue can be tested for its ability to bind growth factor and receptor complexes using the ligand and carbohydrate engagement (LACE) assay [7]. As shown in Fig. 1B, both cell–cell and cell-BM HS binds the FGF10/recombinant FGFR2b-Fc complex. HS is also bound by viral receptors for entry into cells, the herpes simplex virus uses the gD1 protein receptor to bind a 3-*O*-sulfated epitope of HS on the cell surface and in the BM [8] (Fig. 1C). HS also functions by binding, and storing GFs and then releasing them in a controlled manner [9]. HS can generate GF and morphogen gradients through affinity based localization of HS binding components [10]. Binding of a GF to HS can enhance its binding and signaling through its receptor, regulate GF activity due to HS cleavage and release of HS fragments, inhibit its function by sequestering it from its receptor, or protect the GF from proteolytic cleavage [2,11]. The HS in the ECM can selectively bind to GFs and, as a consequence, help determine the binding specificity between ligands and

Download English Version:

https://daneshyari.com/en/article/5528537

Download Persian Version:

https://daneshyari.com/article/5528537

Daneshyari.com