Review

A current view of perlecan in physiology and pathology: A mosaic of functions

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http://dx.doi.org/10.1016/j.matbio.2016.09.003

Abstract

Perlecan, a large basement membrane heparan sulfate proteoglycan, is expressed in a wide array of tissues where it regulates diverse cellular processes including bone formation, inflammation, cardiac development, and angiogenesis. Here we provide a contemporary review germane to the biology of perlecan encompassing its genetic regulation as well as an analysis of its modular protein structure as it pertains to function. As perlecan signaling from the extracellular matrix converges on master regulators of autophagy, including AMPK and mTOR, via a specific interaction with vascular endothelial growth factor receptor 2, we specifically focus on the mechanism of action of perlecan in autophagy and angiogenesis and contrast the role of endorepellin, the C-terminal fragment of perlecan, in these cellular and morphogenic events.

Introduction

Proteoglycans, ubiquitous residents of the extracellular matrix, participate in a range of both structural and signaling roles in order to maintain cellular homeostasis [1]. Proteoglycans participate in the genesis and maintenance of the extracellular milieu, the complex meshwork of proteins comprising multicellular organisms [2,3]. An example of proteoglycan versatility comes in the form of perlecan, an immense heparan sulfate proteoglycan primarily localized to basement membranes and pericellular spaces [4–9]. The modular structure of perlecan enables homeostatic regulation within a vast array of cellular processes including cell adhesion [10,11], endocytosis [12], bone and cartilage formation [13–16], lipid metabolism [17], peripheral node assembly [18], inflammation and wound healing [19,20], thrombosis [21], cancer angiogenesis [9,11,22–33], cardiovascular development [34], and autophagy [35,36]. Given the gargantuan structure and multitude of functions of perlecan, it is no surprise that its gene, *HSPG2*, is similarly large and transcriptionally controlled by complex promoter interactions.

In this review, we will provide a current analysis of the biology of perlecan focusing on its genetic regulation and protein structure as well as its functional role in physiological processes. In particular, we will examine the dichotomy between perlecan and its C-terminal fragment, endorepellin, in coordinating angiogenesis and autophagy as well as provide commentary on the emerging paradigm regarding the connection between these two vital cellular pathways.

Form follows function: Overview of the perlecan gene and protein structure

Perlecan is one of the largest proteoglycans discovered, possessing a protein core of approximately 500 kDa that can be modified by the addition of N-terminal heparan sulfate (HS) side chains, measuring ~65 kDa each [37]. The protein core is divided into several unique structural regions, each imparting distinct biofunctional diversity to perlecan [1,38]. The complexity and sheer size of the core protein is rivaled only by the modular nature [39] and tight regulation of the gene encoding this key proteoglycan. Here, we will discuss the genetics of perlecan as well as analyze the structure of each intra-protein domain and ascribed functions (Fig.1). A more extensive description of the role of specific

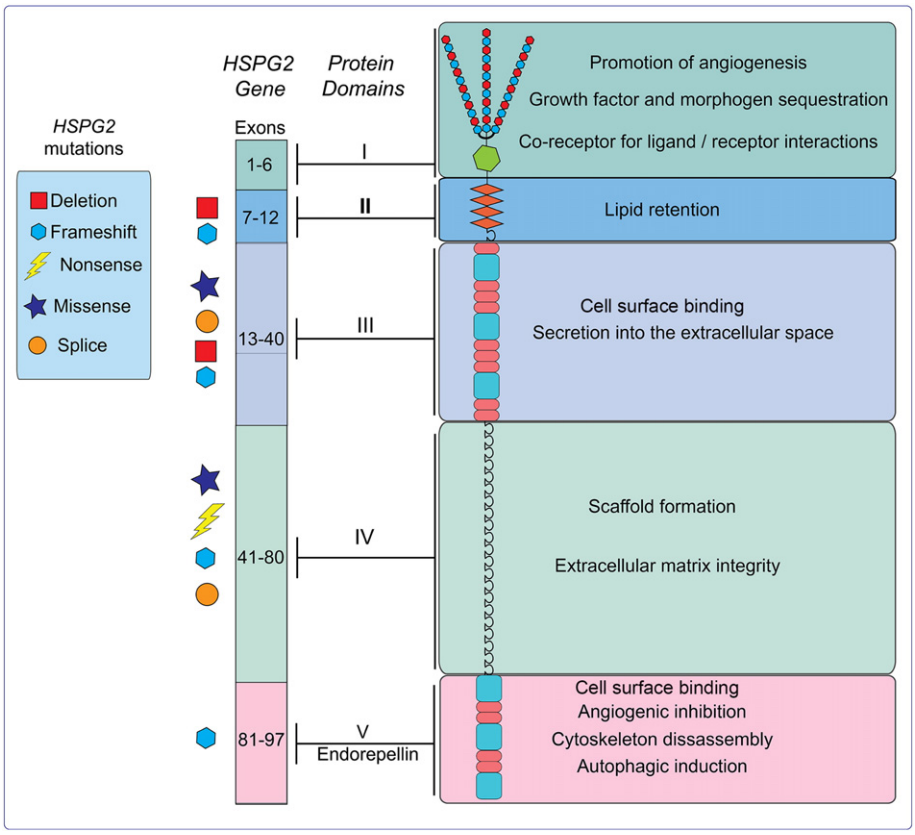

Fig. 1. Graphical representation of the human perlecan gene, *HSPG2*, and protein. Reported disease-causing mutations in the gene are symbolically depicted to the left of the exons. Individual domains of the protein are highlighted and grouped with their corresponding functions.

perlecan protein modules in angiogenesis and autophagy will be considered later.

Genomic organization and transcriptional regulation of perlecan

The gene encoding perlecan, *HSPG2*, spans over 120 Kb and encompasses 97 exons [39,40] and is highly conserved across species [41]. The genomic DNA is organized in a modular fashion, with specific exons corresponding to distinct protein domains conventionally found in other basement membrane constituents (Fig. 1). Further, this exonic organization is evolutionarily conserved for the corresponding regions seen in homologous *HSPG2* genes [40], suggesting a common ancestor arising from gene duplication and exon shuffling. Structurally, *HSPG2* is one of a subset of so-called TATA-less driven-genes and is seemingly regulated by a variety of housekeeping transcription factors (e.g. Sp1 and ETF) while also being responsive to growth factor-controlled gene induction. This response is evidenced by *HSPG2* transcriptional activation downstream of canonical TGF-β signaling via direct binding of nuclear factor-1 to its promoter [42] and transcriptional suppression mediated by IFN-γ [43]. Moreover, transcriptional activation by NFκB enhances *HSPG2* gene expression in the desmoplastic prostate cancer microenvironment [44]. Due to this regulatory circuit, perlecan is considered an early response gene. Additionally, consistent with the lack of a traditional TATA-box, the perlecan promoter harbors multiple transcriptional start sites scattered over an 80-bp region of genomic DNA [40].

Complementing the transcriptional complexity mentioned above, the perlecan pre-mRNA is subject to alternative splicing, as splice variants occur in the HMC-1 human mast cell line [19]. Interestingly, these shorter perlecan isoforms encode biologically active endorepellin [20], an effective anti-angiogenic and pro-autophagic proteolytic cleavage product.

This complex regulatory scheme underscores the dynamic expression profile for perlecan in various tissues throughout development [15,45–48] and in several pathological processes [29]. These areas include vascularized and non-vascularized regions as well as the connective tissue stroma [38,49]. This expression pattern leads to several downstream functional consequences. For example, as it is found ubiquitously within a diverse population of basement membranes [8,50], perlecan aids in the formation and maintenance of polarized epithelial cells, chiefly