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IJBCB
The International Journal of Biochemistry & Cell Biology 38 (2006) 1855–1861
www.elsevier.com/locate/biocel

Signaling networks in focus

Perlecan signaling: Helping hedgehog stimulate prostate cancer growth

Sumana Datta [a,*], Michael Pierce [b,1], Milton W. Datta [c,2]

[a] *Department of Biochemistry and Biophysics, Department of Biology, MS 2128, Texas A&M University, College Station, TX 77843-2128, United States*
[b] *University of Georgia Cancer Center, Complex Carbohydrate Research Center, University of Georgia, 315 Riverbend Road, Athens, GA 30602, United States*
[c] *Department of Pathology, Department of Urology, Winship Cancer Institute, Emory University School of Medicine, 1365-B Clifton Road NE, Room B4219, Atlanta, GA 30322, United States*

Received 7 February 2006; received in revised form 24 March 2006; accepted 31 March 2006
Available online 25 April 2006

Abstract

Perlecan, an extracellular matrix proteoglycan, regulates signaling by a variety of growth factors through protein–protein and protein–carbohydrate interactions. Recent evidence demonstrates that Perlecan modulates sonic hedgehog signaling during both development and neoplasia, in particular in prostate cancer. Perlecan directly binds to sonic hedgehog and is required for its signaling. Increased sonic hedgehog signaling due to Perlecan in aggressive and metastatic prostate cancer cells can be attributed to increased Perlecan expression or changes in Perlecan glycan structure. Additional co-localization studies suggest that other tumor types may also have a Perlecan-modulated hedgehog signaling pathway. Inhibitors of Perlecan function at either the protein or glycan level would be ideal drug candidates for anti-cancer therapies.

Keywords: Cancer; Sonic hedgehog; Perlecan; Medicine

1. Introduction

Perlecan, a large (>400 kDa) protein, is part of the extracellular matrix in organisms from worms to humans (Iozzo, 2005). Perlecan's size is further increased by the presence of heparan sulfate sugar chains at its amino terminal end. Together, the protein core and carbohydrate domains create a proteoglycan of 700–800 kDa. Besides being a structural component of the extracellular matrix, Perlecan also plays a role in modulating the signaling of various peptide growth factors through interactions with either its protein core or its sugar chains. Knock-down of Perlecan in multiple tissue culture studies results in decreased binding of growth factors and decreased signaling activity. Complementary genetic studies in mice and flies where Perlecan is lost reveal mutant phenotypes consistent with loss of signaling by multiple growth factors. While initial studies focused on Perlecan's role in development, these studies have been translated into cancer growth and metastasis. For example, in development

* Corresponding author at: Department of Urology, Winship Cancer Institute, Emory University School of Medicine, 1365-B Clifton Road NE, Room B4202, Atlanta, GA 30322, United States. Tel.: +1 404 778 3487/979 862 4641; fax: +1 404 778 3965.
E-mail addresses: sumad@tamu.edu, sdatta2@emory.edu (S. Datta), hawkeye@uga.edu (M. Pierce), mdatta@emory.edu (M.W. Datta).
[1] Tel.: +1 706 542 1702; fax: +1 706 542 1759.
[2] Tel.: +1 404 778 4089; fax: +1 404 778 5016.

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doi:10.1016/j.biocel.2006.03.022

Signaling network facts

- Perlecan modulates several growth factor pathways via its glycan and protein domains.
- Heparan sulfate chains are required for hedgehog signaling.
- Hedgehog signaling is critical for growth and metastasis of advanced prostate cancer.
- Perlecan regulates the level of hedgehog signaling activity.
- Perlecan modulated hedgehog signaling may be found in other tumor types.
- Further insight into Perlecan activity can be found at: http://www.uku.fi/laitokset/anat/PG/perlecan.htm.

Perlecan has been implicated in hedgehog signaling and neural stem cell division in the embryonic brain (Park et al., 2003). We noted an association between Perlecan and genetic mapping studies for families with high rates of brain and prostate cancers (Datta et al., 2006). Our subsequent studies demonstrated Perlecan's role in the growth and metastasis of human prostate cancer cells. These studies linked Perlecan's roles in development to subsequent functions in neoplasia. Similar links are being encountered with Perlecan, other growth factors, and different cancers.

2. Functions

Perlecan has a long history of affecting signaling by molecules ranging from integrins to the fibroblast growth factors (FGFs). Some molecules, such as FGF7, bind to the protein core of Perlecan (Mongiat et al., 2000), while others such as FGF2 bind to the heparin sulfate chains (Aviezer et al., 1994) (Fig. 1). The FGF2–Perlecan complex binds with high affinity to the FGF receptor, resulting in more sensitive growth factor

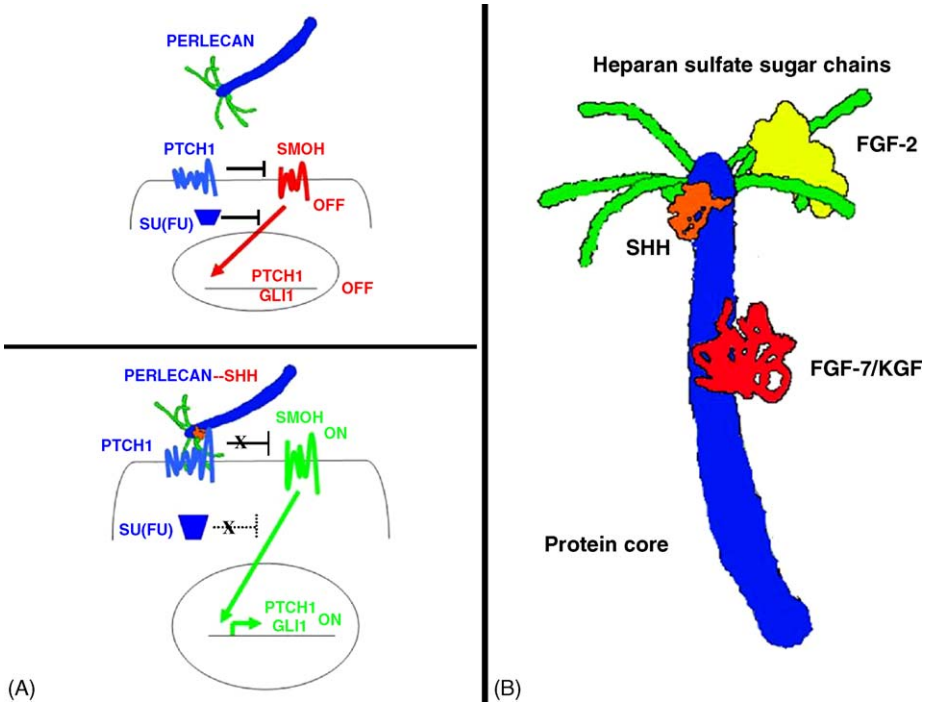

Fig. 1. Hedgehog signaling, Perlecan structure and growth factor binding. (A) A simplified representation of the hedgehog pathway indicating a proposed role for Perlecan as an extracellular co-receptor for hedgehog. PTCH1 = Patched1, the sonic hedgehog receptor. SMOH1 = Smoothened1, a cell surface protein. SU(FU) = Suppressor of fused, an intracellular inhibitor of sonic hedgehog signaling. PTCH1 and GLI1 are sonic hedgehog response genes, their transcription is activated by hedgehog signaling. (B) Perlecan is composed of a protein core and heparan sulfate sugar structures attached at the amino terminus. Growth factors bind to Perlecan through its protein core (fibroblast growth factor-7/keratinocyte growth factor, FGF-7/KGF), heparan sulfate sugars (basic fibroblast growth factor, FGF-2), or both (sonic hedgehog, SHH).