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Review

Syndecans in wound healing, inflammation and vascular biology

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Abstract

Syndecans are heparan sulphate proteoglycans consisting of a type I transmembrane core protein modified by heparan sulphate and sometimes chondroitin sulphate chains. They are major proteoglycans of many organs including the vasculature, along with glypicans and matrix proteoglycans. Heparan sulphate chains have potential to interact with a wide array of ligands, including many growth factors, cytokines, chemokines and extracellular matrix molecules relevant to growth regulation in vascular repair, hypoxia, angiogenesis and immune cell function. This is consistent with the phenotypes of syndecan knock-out mice, which while viable and fertile, show deficits in tissue repair. Furthermore, there are potentially important changes in syndecan distribution and function described in a variety of human vascular diseases. The purpose of this review is to describe syndecan structure and function, consider the role of syndecan core proteins in transmembrane signalling and also their roles as co-receptors with other major classes of cell surface molecules. Current debates include potential redundancy between syndecan family members, the significance of multiple heparan sulphate interactions, regulation of the cytoskeleton and cell behaviour and the switch between promoter and inhibitor of important cell functions, resulting from protease-mediated shedding of syndecan ectodomains.

Keywords: Syndecans; Heparan sulfate; Vasculature; Wound healing; Inflammation

Contents

Abbreviations: Aβ, amyloid β protein; AD, Alzheimer's disease; AT-III, antithrombin-III; CAA, cerebral amyloid angiopathy; CS, chondroitin sulphate; EB, embryoid body; ECM, extracellular matrix; EGF, epidermal growth factor; ES cells, embryonic stem cells; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; GAG, glycosaminoglycan chains; GlcA, glucuronic acid; GlcNAc, *N*-acetylglucosamine; GlcNAcT-I, 1,4-*N*-acetylhexosaminyl transferase; GPI, glycosylphosphatidylinositol; HB-GAM, heparin-binding growth associated molecule; HepII, heparin-binding domain; HS, heparan sulphate; HS6ST2, 6-*O*-sulphotransferase-2; HSPGs, heparan sulphate proteoglycans; HUVECs, human umbilical vein endothelial cells; IdoA, iduronic acid; IL-1β, interleukin-1β; IL-8, interleukin-8; LPS, lipopolysaccharide; MI, myocardial infarction; MMP, matrix metalloproteinase; NDST, *N*-deacetylase/*N*-sulphotransferase; NFTs, neurofibrillary tangles; NMR, nuclear magnetic resonance; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; PDGF, platelet derived growth factor; PIP_2, phosphatidylinositol (4,5) bisphosphate; PKC, protein kinase C; RFPECs, rat fat pad endothelial cells; SPs, senile plaques; TGF-β, transforming growth factor-β; TIMP-3, tissue inhibitor of metalloproteinase-3; TNF-α, tumour necrosis factor-α; TSP-1, thrombospondin-1; VEGF, vascular endothelial growth factor.

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1. Introduction

Syndecans are heparan sulphate proteoglycans (HSPGs) consisting of a core protein modified by heparan sulphate (HS) chains. They represent a major class of HSPGs in the vasculature, along with glypicans and matrix HSPGs. While syndecans are type I membrane proteoglycans, glypicans are bound to the membrane by a glycosylphosphatidylinositol (GPI) anchor and the matrix HSPGs including perlecan, agrin and type XVIII collagen are not membrane bound but are enriched in vascular basement membranes. The glypicans and matrix HSPGs have been the subject of recent reviews (Bezakova & Ruegg, 2003; De Cat & David, 2001; Häcker, Nybakken, & Perrimon, 2005; Iozzo, 2005; Jiang & Couchman, 2003; Song & Filmus, 2002). Syndecans-1, −2 and −4 have been purified from vascular sources (Kojima, Shworak, & Rosenberg, 1992; Mertens, Cassiman, Van den Berghe, Vermylen, & David, 1992), while syndecan-3 has been purified from neonatal rat brain (Chernousov & Carey, 1993). However, all syndecan family members have been identified in cells of the vasculature (Cizmeci-Smith, Langan, Youkey, Showalter, & Carey, 1997; Fears, Gladson, & Woods, 2006; Ishiguro et al., 2000; Li, Brown, Laham, Volk, & Simons, 1997). Syndecan expression shows temporal and spatial specificity but virtually all nucleated cells express one or more family members. Syndecan-1 is the major syndecan of epithelial cells including vascular endothelium (Cizmeci-Smith et al., 1997; Elenius et al., 1991; Gallo, Kim, Kokenyesi, Adzick, & Bernfield, 1996; Kojima et al., 1992), syndecan-2 is present mostly in mesenchymal, neuronal and smooth muscle cells (Cizmeci-Smith et al., 1997; Pierce, Lyon, Hampson, Cowling, & Gallagher, 1992), syndecan-3 is the major syndecan of the nervous system (Chernousov & Carey, 1993; Hienola, Tumova, Kulesskiy, & Rauvala, 2006), while syndecan-4 is ubiquitously expressed but at lower levels than the other syndecans (Tkachenko, Rhodes, & Simons, 2005; Yoneda & Couchman, 2003). The four mammalian syndecans are derived from a single ancestral invertebrate syndecan, where a vasculature is either absent or an open system. Indeed, invertebrate syndecan is implicated in the regulation of neural migration and axon guidance (Johnson et al., 2004; Rawson et al., 2005; Rhiner, Gysi, Fröhli, Hengartner, & Hajnal, 2005). Additionally, Drosophila syndecan is also detected at cellularisation, while at later stages it is present in the lymph glands and gut epithelium (Bellin et al., 2003; Spring, Paine-Saunders, Hynes, &