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Review

Chondroitin sulphate proteoglycans: Extracellular matrix proteins that regulate immunity of the central nervous system

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ABSTRACT

The extracellular matrix (ECM) is a complex network of scaffolding molecules that also plays an important role in cell signalling, migration and tissue structure. In the central nervous system (CNS), the ECM is integral to the efficient development/guidance and survival of neurons and axons. However, changes in distribution of the ECM in the CNS may significantly enhance pathology in CNS disease or following injury. One group of ECM proteins that is important for CNS homeostasis is the chondroitin sulphate proteoglycans (CSPGs). Up-regulation of these molecules has been demonstrated to be both desirable and detrimental following CNS injury. Taking cues from arthritis, where there is a strong anti-CSPG immune response, there is evidence that suggests that CSPGs may influence immunity during CNS pathological conditions. This review focuses on the role of CSPGs in CNS pathologies as well as in immunity, both from a viewpoint of how they may inhibit repair and exacerbate damage in the CNS, and how they are involved in activation and function of peripheral immune cells, particularly in multiple sclerosis. Lastly, we address how CSPGs may be manipulated to improve disease outcomes.

Contents

1. The extracellular matrix: the glue that holds the CNS together

The central nervous system (CNS) is a specialised cellular system that provides the body with the signals vital for life. Neurons are supported by a cellular network that includes astrocytes, microglia and oligodendrocytes which function, respectively, to maintain synapses and blood brain barrier integrity, perform immune surveillance, and ensheath axons with myelin. Exterior to and between these cells is the extracellular matrix (ECM) which constitutes approximately 20% of total brain volume [1]. The ECM is integral for the structure and organisation of the CNS as well as for binding and presenting proteins such as cytokines, chemokines and growth factors to cells [2–6]. The ECM is therefore not only critical for the development and daily

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maintenance of the CNS, but it is also involved in the initiation and progression of CNS pathology.

The major components of the CNS ECM include hyaluronan, tenascins, laminins, collagen, fibronectin, link proteins and proteoglycans such as the chondroitin sulphate-, dermatan sulphate- and heparan sulphate-proteoglycans. These components form a specialised mesh network that differs depending on the specific location in the CNS. For example, the basement membranes that are associated with blood vessels and help support the blood–brain barrier are rich in collagen, fibronectin and laminins [7] whilst the equally dense perineuronal nets around the soma of some neurons, and which are integral for maintaining synaptic plasticity [8], contain hyaluronan, tenascin-R, link proteins, and high levels of chondroitin sulphate proteoglycans (CSPGs) [9,10]. The neural interstitial matrix, which is diffusely dispersed between cellular structures and is rich in CSPGs and hyaluronan, contains most of the ECM components that are found in the CNS [11].

While the ECM is integral for everyday function of the mature CNS, alterations in ECM component expression often occur following CNS pathology such as gliomas, spinal cord injury, and inflammatory diseases such as multiple sclerosis (MS) [12–18]. Up-regulation of several proteins, particularly CSPGs, results in the generation of a 'barrier' to neuroregeneration [12–16]. In this review we focus on the role that CSPGs play in immunity of the diseased/injured CNS, particularly the putative autoimmune condition of the CNS, MS. We also take guides from an autoimmune condition in the periphery, arthritis, on the possible impact that CSPGs may have on cells of the immune system once they reach the CNS.

2. CSPG biology

The molecular characteristics of CSPGs have been extensively reviewed elsewhere [10,13,18–23]. In brief, CSPGs consist of a large protein core which is covalently attached to glycosaminoglycan (GAG) chains via a linking region (Fig. 1). The GAG chains are made up of repeating chondroitin sulphate (CS) disaccharide subunits linked to form varying lengths and are thought to mediate many of the binding interactions between CSPGs and other proteins. There are several submembers of CSPGs as determined by their protein core including aggrecan, brevican, versican, neurocan, NG2, and phosphacan (Fig. 1A) [24–26]. NG2 consists of a transmembrane region and can therefore be extracellular or membrane bound (on the surface of oligodendrocyte precursor cells (OPCs) in the CNS [27]), whereas the other proteoglycans are generally secreted into the ECM [24–26]. Each of the core proteins has different lengths and numbers of GAG chains attached, and the GAG chains themselves can have varying chondroitin sulphate sulphation patterns (Fig. 1B). In some cases, CSPG core proteins can bind hyaluronan and/or tenascin proteins [10,28], therefore aiding in the organisation of the ECM. Furthermore, CSPG core proteins can also be covalently bound to not only chondroitin sulphate GAG chains, but also dermatan sulphate GAG chains thereby increasing functional diversity within the proteoglycan family [29].

In the adult CNS, all of the major cell types (such as astrocytes, neurons, oligodendrocytes and microglia) are thought to be capable of making CSPGs and aiding in their arrangement in the ECM, particularly in perineuronal nets [30]. Whilst it is clear that CSPGs are critical for guidance of migrating cells within the developing CNS, a basal level of CSPG production is necessary in adulthood to maintain ECM structures in order to afford synapse stabilisation and plasticity as well as correct neural network structure and prevent improper organisation and sprouting of axons [30]. However, CSPG over-production in the CNS can be induced upon inflammatory stimulation, such as that which occurs following spinal cord injury and during MS [12,13,15–17,31] (see Sections 3.1 and 3.3). Astrocytes are thought to be primarily responsible for up-regulation of CSPGs in pathological environments following exposure to cytokines such as IL-1β, TGF-β and EGF [32].

2.1. Methods of altering CSPG function

Several methods have been used to reduce CSPG expression or to degrade existing CSPGs in experimentally induced disease or injury (Table 1). Firstly, synthesis of CSPGs can be reduced by inhibitors that affect the GAG side chains. For example, fluorinated glucosamine analogues prevent the synthesis of chondroitin/heparan sulphate side chains by inhibiting an enzyme important for the elongation of polysaccharide chains [33]. Alternatively, GAG chains are built off of a characteristic xylose sugar in the linker region of the proteoglycan [34] (Fig. 1C), and the use of small xylose-conjugated organic molecules, such as 4-Methylumbelliferyl-beta-D-xylopyranoside (xyloside) reduces GAG synthesis machinery from attaching GAG chains to the CSPG protein core [35,36]. In turn, either of these strategies will reduce the amount of complete CSPGs released into the media [35].

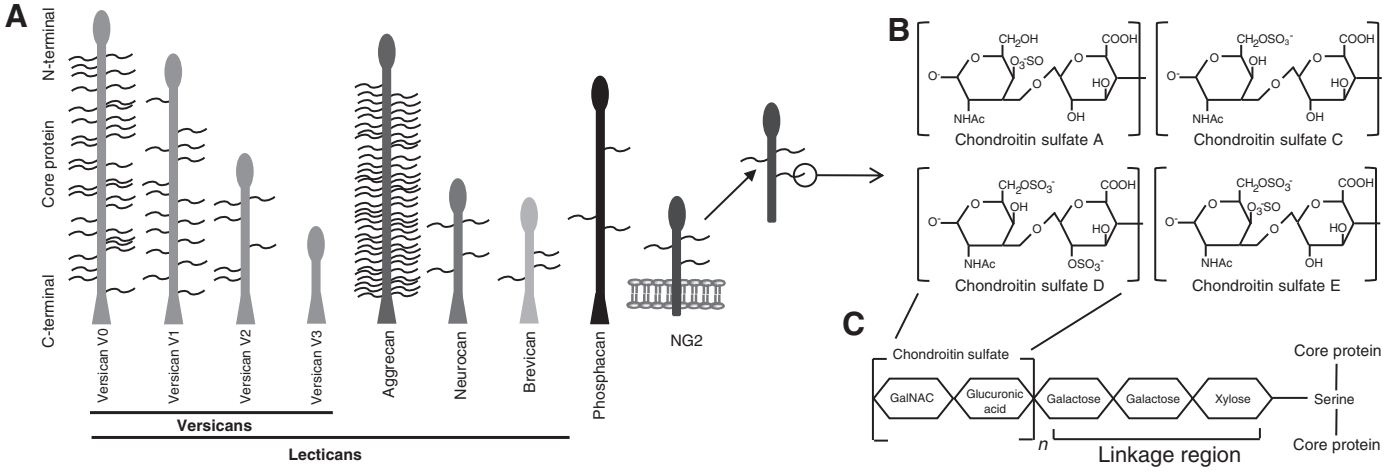

Fig. 1. Schematic diagram of CSPG family members, chondroitin sulphate subunits and the core-protein-GAG linking region. (A) The CSPG family consists of Aggrecan, Versican, Brevican, Neurocan (also known as Lecticans), Phosphacan, and NG2 (which can either be membrane-bound or extracellular). The CSPG core proteins generally contain an amino terminal which binds Hyaluronan and a carboxy terminal which binds tenascin proteins (Adapted from [24–26]). (B) The GAG chains consist of repeating chondroitin sulphate units that are designated CS-A, CS-C, CS-D or CS-E depending on the position of their sulphation (Adapted from [25]). (C) The GAG chains are attached to the core protein via a linking region (Adapted from [26,85]).