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Chondroitin sulphate proteoglycans (CSPGs), consisting of core proteins linked to one or more chondroitin sulphate (CS) chains, are major extracellular matrix (ECM) components of the central nervous system (CNS). Multi-functionality of CSPGs can be explained by the diversity in structure of CS chains that undergo dynamic changes during development and under pathological conditions. CSPGs, together with other ECM components, form mesh-like structures called perineuronal nets around a subset of neurons. Enzymatic digestion or genetic manipulation of CSPGs reactivates neural plasticity through specific interaction of CS chains with its binding partners in a manner that depends on the structure of the CS chain.

Keywords: axon regeneration/chondroitin sulphate proteoglycan/critical period plasticity/glycosaminoglycan/perineuronal net.

Abbreviations: BDNF, brain-derived neurotrophic factor; ChGn-1, chondroitin GalNAc transferase-1; CNS, central nervous system; C4ST, chondroitin 4-O-sulfotransferase; C6ST, chondroitin 6-O-sulfotransferase; CS, chondroitin sulphate; CSPGs, chondroitin sulphate proteoglycans; ECM, extracellular matrix; GABA, γ-aminobutyric acid; GalNAc4S-6ST, GalNAc 4-sulphate 6-O-sulfotransferase; HS, heparan sulphate; HSPGs, heparan sulphate proteoglycans; LAR, leukocyte common antigen-related phosphatase; Narp, neuronal activity-regulated pentraxin; PGs, proteoglycans; PNNs, perineuronal nets; PV cells, parvalbumin-expressing inhibitory neurons; RPTPσ, receptor protein tyrosine phosphatase sigma; Sema3A, semaphorin3A; Sema5A, semaphorin5A; UST, uronyl 2-O-sulfotransferase; WFA, Wisteria floribunda agglutinin.

Chondroitin sulphate (CS), a class of sulphated glycosaminoglycan chains, is covalently linked to core proteins in the form of proteoglycans (PGs). The tremendous structural variation of chondroitin sulphate proteoglycans (CSPGs) arises from differences in the number and length of CS chains per core protein and the arrangement of sulphated sugar units along the CS chains (1, 2). CSPGs are found on the cell surface and in the extracellular matrix (ECM) of various tissues, where they play important roles in complex biological events such as cytokinesis (3, 4), maintenance of pluripotency (5), chondrogenesis (6–8), myogenesis (9), osteogenesis (10) and so on. In the central nervous system (CNS), CSPGs are known to act as major inhibitors of the structural and functional plasticity of neural circuits (11). Digestion of CSPGs with a bacterial enzyme called chondroitinase ABC, which degrades CS chains, enhances synaptic plasticity in the adult brain and improves axon regeneration after spinal cord injury, offering a novel therapeutic strategy for CNS diseases and injuries (12, 13). However, the mechanism by which CSPGs restrict plasticity remained unknown until recent studies showing that CSPGs, at least partially, exert their function through specific interaction of CS chains with its binding partners in a manner that depends on the sulphation patterns of CS chains. In this review, we focus on recent progress in understanding the multiple functions of CSPGs during brain development and CNS injury.

Structure of CS Chain

CS chains, linear polysaccharides consisting of repeating disaccharide units ([4GlcAβ1-3GalNAcβ1-]n), are linked to serine residues in core proteins via the so-called glycosaminoglycan-protein linkage region, GlcAβ1-3Galβ1-3Galβ1-4Xylβ1-O-Ser (Fig. 1A). It should be noted that another class of glycosaminoglycan chain, heparan sulphate (HS), that consists of repeating disaccharide units ([4GlcAβ1-4GlcNAcβ1-]n) is also built on the same tetrasaccharide linkage region. Assembly of a CS chain is triggered when the first GalNAc residue is transferred in a β1,4-linkage to the non-reducing terminal GlcA residue in the tetrasaccharide linkage region (Fig. 1B). In contrast, transfer of a GlcNAc residue in α1,4-linkage to the GlcA residue initiates the synthesis of a HS chain on the tetrasaccharide linkage region. Therefore, the addition of the first GalNAc or GlcNAc is the bifurcation point in the biosynthesis of glycosaminoglycan chains. The initiation and elongation of CS chains are catalysed by a combination of six homologous glycosyltransferases (14–24). Among them, chondroitin GalNAc transferase-1 (ChGn-1) is responsible for the transfer of the first GalNAc residue (16, 17). In cartilage, which contains large amounts of CS, CS production is reduced
by approximately half in ChGn-1-deficient mice, which exhibit skeletal dysplasias (7, 8). However, a considerable amount of CS can still be synthesized even in the absence of ChGn-1, suggesting the presence of redundant synthetic pathways, in which other enzymes catalyse initiation. Elongation of CS chains is achieved by the alternate transfer of GlcA and GalNAc, which is catalysed by chondroitin polymerases composed of multiple combinations of chondroitin synthase-1, -2, -3 and chondroitin polymerizing factor (1) (Fig. 1C). Chondroitin sulfotransferases then sequentially modify the chondroitin backbone with sulphate at positions 4 and 6 of the GalNAc residues and position 2 of the GlcA residues (Fig. 1D). In the first step, a non-sulphated O unit (GlcA-GalNAc) is modified by either chondroitin 4-O-sulfotransferase (C4ST) or chondroitin 6-O-sulfotransferase (C6ST), resulting in the formation of the A unit [GlcA-GalNAc(4-O-sulphate)] or C unit [GlcA-GalNAc(6-O-sulphate)], respectively (25–30). As these two enzymes compete for the same acceptor substrate, and the sulphation pathway is split into two pathways: 4-O-sulphation and 6-O-sulphation. Subsequently, a small portion of A units are converted to E units [GlcA-GalNAc(4,6-O-disulphate)] by GalNAc 4-sulphate 6-O-sulfotransferase (GalNAc4S-6ST), which catalyses 6-O-sulphation of GalNAc(4-O-sulphate) (31). On the other hand, some C-units are converted to D units [GlcA(2-O-sulphate)-GalNAc(6-O-sulphate)] by uronyl 2-O-sulfotransferase (UST), which catalyses 2-O-sulphation of GlcA (32). The arrangement of these sulphated units along with the CS chains creates sulphation codes that may convey the functional information carried by CSPGs. Composition of each sulphated unit is spatio-temporally regulated during brain development, where they play critical roles in neural plasticity, as discussed in the subsequent section.

There is no comparable understanding of how sulphation codes might be introduced into the CS chains due to their non-template-driven biosynthetic pathways.
processes within the Golgi apparatus. However, a recent study revealed that a CS chain on a CSPG called bikunin has a defined sequence, which is characterized by the presence of a 4-O-sulphated domain near the reducing end and a non-sulphated domain at the non-reducing end (33), suggesting an unidentified mechanism for generation of sulphation codes.

It is believed that the CS breakdown occurs predominantly in lysosome by the actions of a combination of several glycosidase and sulphatase (34). However, it has been recently shown that some of hyaluronidase family enzymes that were originally reported to degrade hyaluronan, a glycosaminoglycan chain consisting of a repeating disaccharide units \([-4\text{GlcA}\beta1-3\text{GlcNAC}1-\text{Glc}1]\), have activity towards not only hyaluronan but also CS (9, 34). Interestingly, among them, hyaluronidase-4 is a CS-specific enzyme with no hyaluronidase activity and presumed to be expressed as a glycosylphosphatidylinositol-anchored protein on the cell surface, raising a possibility for degradation and/or remodeling of CS chains in the extracellular space.

Critical Period Plasticity in the Visual Cortex

Neural plasticity is the ability of the brain to reorganize neural circuits based on new experiences. Plasticity is most evident during a limited time window in early life, so-called the critical period (35). For example, amblyopia, which causes the loss of visual acuity, is treatable by patching the stronger eye and forcing the brain to use the weaker eye until the critical period for vision had passed. However, this treatment does not work for adult brains, which are no longer plastic, and the weaker eye permanently loses vision (36). The critical period for this phenomenon, called ocular dominance plasticity, is around age 5–8 years for humans and postnatal days 20–30 for mice and has been studied extensively as a model for understanding effects of experience on cortical circuits. It is proposed that the development of molecular ‘brakes’ terminate the critical period in adulthood (37). Several molecules are identified as functional brakes that restrict plasticity through their influence on the balance between excitation and inhibition within local circuits (38–41). The onset and termination of the critical period can be accelerated by prematurely enhancing inhibitory tone by overexpression of brain-derived neurotrophic factor (BDNF) (38). Conversely, the onset of the critical period can be delayed by preventing the maturation of inhibitory neurons by deletion of glutamic acid decarboxylase 65, which encodes the γ-aminobutyric acid (GABA)-synthetic enzyme (39). In the mammalian cortex, GABAergic inhibitory neurons play a great diversity based on their morphological, immunohistochemical and physiological properties (42). Several lines of evidence have demonstrated that a single class of inhibitory neurons, expressing the calcium-binding protein parvalbumin (PV cells), plays an essential role in the control of critical period plasticity (43, 44).

Formation of Perineuronal Nets by CSPGs Terminate the Critical Period

Importantly, CSPGs selectively accumulate around PV cells, forming specialized ECM structures called perineuronal nets (PNNs) that interdigitate with synaptic contacts (45, 46) (Fig. 2A). Formation of PNNs begins during late development and is completed following the critical period. In the visual cortex, condensation of CSPGs into PNNs is dependent on visual experience, as rearing animals in complete darkness prevents this process (47). The critical period for ocular dominance plasticity can also be prolonged by dark rearing, suggesting a relationship between PNN formation and ocular dominance plasticity. In 2002, Pizzorusso et al. (12) demonstrated that digestion of PNNs by chondroitinase ABC treatment reactivates ocular dominance plasticity in adult animals after the critical period has passed. This study also demonstrated that CS moieties of CSPGs are responsible for PNN formation and the control of critical period plasticity.

In PNNs, CSPGs form massive macromolecular complexes with hyaluronan, tenascin-R and the link proteins Crtl1 and Bral2 (Fig. 2A). CSPGs belonging to the lectican family (e.g. aggrecan, versican, neurocan and brevican) are major components of PNNs (45, 46) (Fig. 2). Lectican family members share a common domain structure that consists of an amino-terminal hyaluronan binding domain, a central region that contains covalently bound CS chains and a carboxy-terminal C-type lectin-like domain, which binds to tenascin-R (Fig. 2B). It is proposed that transmembrane hyaluronan synthase, present on the plasma membrane of PV cells, acts as a dock that immobilizes PNNs on the neuronal surface (46). Secreted CSPGs bind to cell surface hyaluronan, and this interaction is stabilized by link proteins. Multimeric forms of tenascin-R may cross-link CSPGs by binding to both the C-terminal domain and CS chains (Fig. 2A).

PNNs can be visualized by the well-established marker Wisteria floribunda agglutinin (WFA), a lectin that is presumed to recognize CS moieties on CSPGs (48). Primary cultured neurons from aggrecan-deficient mice apparently lack staining for WFA, indicating that aggrecan is essential for PNN formation and that WFA recognizes CS chains carried by aggrecan (49). Because of the neonatal lethality of aggrecan-deficient mice, the precise function of aggrecan during critical period plasticity is unclear (50). In contrast, mice deficient for other lectican family members have largely normal PNNs (51–53). Tenascin-R-deficient mice display abnormal aggregation of CSPGs into PNNs, supporting the above-mentioned model for PNN formation (54). These mice also show reduced hippocampal long-term potentiation and an abnormal balance between excitatory and inhibitory transmission (55). The binding between CSPGs and hyaluronan is stabilized by link proteins. Expression of Crtl1 in the visual cortex is regulated by visual experience, as dark rearing reduces its expression in PV cells (56). Mice lacking Crtl1 have attenuated PNN formation and...
retain ocular dominance plasticity in adulthood (56) (Fig. 2C). Mice deficient for another link protein, Bral2, also show attenuated PNN formation (57).

Biochemical analysis suggests that even in the adult brain most CS chains are diffusely present or loosely associated in the ECM, and only 1.3% of total CS chains are tightly associated with PNNs (58). PNN-associated CS chains are rich in O, C, D and E units when compared with water-soluble CS chains (58). Deletion of Crtl1 causes abnormal PNN formation without affecting diffuse CS chains, demonstrating the indispensability of PNN-associated CS chains for the closure of the critical period. CS chains that are diffusely present around synapses may restrict dendritic spine dynamics, as discussed in the subsequent section.

The components of PNNs are produced either by PV cells themselves or by neighbouring glial cells (59). However, the contribution of glial cells seems to be unnecessary for the development of PNNs, because PNNs are formed in dissociated neuronal culture in the absence of glial cells (60). Primary neurons from mutant mice lacking four ECM components (brevican, neurocan, tenascin-R and tenascin-C) show a reduced number of PNNs around PV cells and impaired synapse formation (61). This phenotype cannot be rescued with co-cultured astrocytes prepared from wild-type mice.
Sulphation Patterns of CS Chains Modulate PNN Formation and Critical Period Plasticity

Intracortical injection of chondroitinase ABC not only digests CS moieties but also releases core proteins from the cell surface, which results in PNN disruption and suggests the involvement of CS chains in the process of PNN formation. During postnatal development of mouse brain, the proportion of 6-O-sulphation gradually decreases, whereas that of 4-O-sulphation progressively increases, which results in an increase in the 4S/6S ratio (62, 63). Notably, transgenic mice overexpressing C6ST-1, which retain a low 4S/6S ratio, have a reduced number of WFA-positive conventional PNNs. Additionally, a subpopulation of PV cells is surrounded by 6-O-sulphation-enriched PNNs that are not colocalized with WFA-positive PNNs (63). In contrast to WFA-positive PNNs that display a meshwork structure tightly encasing synaptic contacts, 6-O-sulphation-enriched PNNs show a diffusely spread and less condensed morphology. This demonstrates that developmental changes in sulphation patterns of CS chains are required for normal formation of PNNs. The interaction between CSPGs with other PNN components, such as tenascin-R, may depend on sulphation patterns of CS chains. Importantly, C6ST-1 transgenic mice retain juvenile-like ocular dominance plasticity in adulthood (Fig. 2C). Overexpression of C6ST-1 prevents the maturation of electrophysiological properties of PV cells and reduces the inhibitory effects of PV cells (63).

Molecular Mechanisms for Regulating Neural Plasticity by CS Chains

CS chains may inhibit plasticity by acting as a physical barrier that prevents rearrangement of synaptic connections. Chondroitinase ABC digestion releases neuronal activity-regulated intracellular components to regulate PV-cell function. Semaphorin 3A (Sema3A), a chemorepulsive axon guidance protein, may be one such molecule. Sema3A is localized to WFA-positive PNNs surrounding PV cells and is removed by chondroitinase ABC treatment (70, 71). Sema3A directly interacts with CS-E, and this interaction is inhibited by antibodies against CS-E. Although it remains unclear whether Sema3A interaction with PNNs via CS-E is involved in critical period plasticity, Sema3A may restrict plasticity by acting as an inhibitory cue for synapse formation. PNNs may also regulate plasticity by facilitating trans-synaptic transport of neuronal activity-regulated pentraxin (Narp), which is pre-synaptically secreted, binds to AMPA receptors at post-synaptic sites on PV cells and regulates synaptic plasticity (72). Disruption of PNNs with chondroitinase ABC prevents accumulation of Narp on PV cells. Additionally, Narp-deficient mice show decreased excitatory synapse density on PV cells and abnormal ocular dominance plasticity (73).

CS Chains in Memory Formation and CNS Diseases

PNN formation is not restricted to the visual cortex and can be found in many brain regions. In the amygdala, a brain region involved in emotional behaviour, PNNs appear to play roles in the consolidation of traumatic memories, as fear memories can be erased by injection of chondroitinase ABC (74). Similarly, this treatment also facilitates the erasing of drug addiction memories (75). Both Ctrl1-deficient mice and chondroitinase ABC-treated wild-type mice show an enhanced long-term object recognition memory in the perirhinal cortex (76). Disruption of PNNs by injecting hyaluronidase in the auditory cortex enhances cognitive flexibility in reversal learning (77). In the aged brain, PNNs may play a critical role in neuroprotection against oxidative stress. The
polyanionic nature of glycosaminoglycan chains can help reduce local oxidative potential by scavenging redox-active iron. In fact, neurons surrounded by PNNs are better protected against iron-induced neurodegeneration than neurons lacking PNNs (78). Degradation of PNNs by chondroitinase ABC renders PV cells more susceptible to oxidative stress (79). Thus, PNNs can potentially act as an antioxidant to protect neurons from the toxicity of amyloid fibrils in Alzheimer’s disease. Neurons encased by PNNs are shown to be less frequently affected by neurofibrillary degeneration in the brains of Alzheimer's disease patients (80). PNNs may also be involved in some psychological disorders, such as schizophrenia, because the number of PNNs is reportedly reduced in patients with schizophrenia (81). It should be noted that in the brains of schizophrenia patients, PNN-like WFA-reactivity of neurons is decreased, whereas WFA-labelled astrocytes are markedly increased (82), raising the possibility that the imbalanced production of CS between neurons and astrocytes contributes to the emergence of schizophrenia.

CS Chains in Axon Regeneration after CNS Injury

Following CNS injury, such as spinal cord injury, functional recovery is mainly limited by the formation of a glial scar, due to the inability of damaged axons to regenerate beyond the glial scar. The glial scar is composed of reactive astrocytes, which produce molecules inhibitory toward axon growth, including CSPGs (11). Removal of CS chains by chondroitinase ABC reportedly improves axon regeneration and functional recovery after spinal cord injury (13). In contrast, another type of glycosaminoglycan, HS, has the opposite effect on neurons, whereby HS promotes axon growth and acts as an attractive guidance cue (82–84). Intracortical injection of glypican, a membrane-bound HS proteoglycan (HSPG), promotes neurite extension and improves behavioural outcomes from experimental stroke in rats (82). Semaphorin5A (Sema5A) is a bifunctional guidance cue exerting both attractive and inhibitory effects on developing axons (83). The thrombospondin repeats of Sema5A bind to both HS and CS. HSPGs on the neuronal surface are required for Sema5A-mediated attraction, whereas CSPGs convert Sema5A from an attractive to an inhibitory guidance cue.

As described earlier, both CS and HS are synthesized on the common glycosaminoglycan-protein linkage region. ChGn-1 triggers CS synthesis by transferring the first GalNAc residue, whereas the initiation and elongation of HS are mediated by glycosyltransferases belonging to EXT family (85). Recently, it has been found that ChGn-1-deficient mice show an excellent recovery from spinal cord injury (84). Behavioural recovery of ChGn-1-deficient mice is greater than wild-type mice treated with chondroitinase ABC. Although the amount of CS is reduced by only 30% in the spinal cord of ChGn-1-deficient mice, these mice show better axon regeneration and smaller glial scars compared with chondroitinase ABC-treated wild-type mice. Surprisingly, the amount of HS chains is 20-fold higher at the injury site of ChGn-1-deficient mice than of wild-type mice. The increased amount of HS does not occur in chondroitinase ABC-treated wild-type mice. Enzymatic digestion of HS chains reduces the degree of functional recovery in ChGn-1-deficient mice, indicating that up-regulation of HS levels is responsible for the superior recovery and axon regeneration in these mice. In the injury sites, ChGn-1-deficient mice show elevated expression of EXT1 and EXT2 that form a hetero-oligomeric complex catalysing elongation of HS chains (85). Another EXT family member enzyme, EXT2, is also highly up-regulated in ChGn-1-deficient mice. EXT2 suppresses both CS and HS biosynthesis in a manner dependent on the phosphorylation status of the common glycosaminoglycan-protein linkage region and is proposed to be essential for proteoglycan quality control (86). Therefore, the up-regulated expression of EXT2 may optimize the balance of CS and HS production for axon regeneration.

These opposing effects of CS and HS chains on axon regeneration are at least partially explained by the function of the receptor protein tyrosine phosphatase sigma (RPTPs), which is a common receptor for CS and HS chains (87, 88). Binding of HS chains to RPTPs induces oligomerization of the receptor and may elicit intracellular signalling for axon growth (88). Conversely, CS chains cannot induce oligomerization, compete with HS chains and inhibit axon growth. After spinal cord injury, RPTP-deficient mice show an enhanced ability for axonal regeneration. RPTPs are a member of the type IIa receptor protein tyrosine phosphatase family, and another member, leukocyte common antigen-related phosphatase (LAR), is also identified as a receptor for CSPGs (89). Binding of CSPGs to LAR inactivates the Akt and activates the RhoA signal pathways, and ultimately inhibits axonal growth. Recently, two Nogo receptor family members, NgR1 and NgR3, were also shown to be receptors of CS chains that mediate CSPG-induced inhibition (90). It is currently unclear whether these CS receptors recognize specific sulphation patterns. In this regard, it should be noted that C6ST-1 and C6ST-2 6-O-sulphation are preferentially up-regulated after CNS injury, and C6ST-1-deficient mice show decreased ability for axon regeneration as compared with wild-type mice (91, 92).

Notably, certain CS preparations, such as CS-E, show facilitatory, rather than inhibitory, effects on axon growth (2). This indicates that CS chains can either inhibit or promote axon growth depending on sulphation patterns, suggesting the existence of a novel type of receptor that mediates the neuritogenic effects of CS-E. Contactin-1, a glycosylphosphatidylinositol-anchored cell adhesion molecule of the immunoglobulin superfamily, has been identified as a specific receptor for CS-E (93). Binding of CS-E to contactin-1 induces intracellular downstream signalling and leads to axon growth. In addition, CS-E acts as a coreceptor and/or reservoir for neuritogenic factors, such
as midkine and BDNF, and stimulates neurite outgrowth (2).

Conclusions

In the CNS, CSPGs are known to act as non-specific physical barriers to axonal regeneration and neural plasticity. However, recent studies have shown that CSPGs can actively modulate neural plasticity through specific interaction of CS chains with its binding partners. Diversity in structure of CS chains can explain diverse function of CSPGs. Secreted molecules such as Otx2 and Sema3A require specific CS sulphation pattern in PNNs to exert their function. In the injury sites, CS chains can either inhibit or promote axon regeneration via binding to its inhibitory receptors such as RPTPα or facilitatory receptor such as contactin-1. Dysregulation of PNNs also has been implicated in some psychological disorders and Alzheimer’s disease. Therefore, future studies focusing on sulphation pattern-dependent receptors and their downstream signalling are required to elucidate the multiple functions of CSPGs and may shed light on novel therapeutic strategies for alleviating CNS injuries and disorders.

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Conflict of Interest

None declared.

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