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Contributions of chondroitin sulfate proteoglycans to neurodevelopment, injury, and cancer

Daniel J Silver[1] and Jerry Silver[2]

Chondroitin sulfate proteoglycans (CSPGs) are a diverse family of extracellular matrix (ECM) molecules that make significant contributions to the patterning and routing of migrating neural cells and extending axons. Three distinct modes of migration mediation result from the relative abundance and positioning of expressed CSPGs, the profile of CSPG receptors expressed by the motile cell types, and the overall way in which the CSPGs integrate into and stabilize the neural ECM. Here we discuss recent findings that help to clarify the molecular mechanisms that underlie these distinct migration-regulating properties as they pertain to neural development, CNS injury, and gliomagenesis.

Addresses

[1] Human Biology Division, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, Mailstop C3-168, Seattle, WA 98109, United States

[2] Department of Neurosciences, Case Western Reserve University, 2109 Adelbert Road Rm E-658, Cleveland, OH 44106, United States

Corresponding author: Silver, Jerry (jxs10@case.edu)

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Introduction

Chondroitin sulfate proteoglycans (CSPGs) are a large and diverse family of extracellular matrix (ECM) molecules. The central nervous system (CNS) enriched CSPGs, referred to collectively as the lectican subfamily, share three key features. The core protein structure of each lectican, which ranges from 97 to >262 kD, begins and ends with a conserved N-terminal (G1) and C-terminal (G3) globular domain linked by a central, CS-GAG anchoring backbone, of variable length, bound to at least one, long-chain chondroitin sulfate glycosaminoglycan (CS-GAG) polysaccharide [1]. By binding hyaluronan and tenascin-R through their G1 and G3 domains, respectively, CSPGs provide one of three major components of the tripartite lattice that forms the CNS ECM [1,2]. While the contribution of CSPGs to the inhibitory nature of certain restricted territories within the embryo as well as the glial scar in the adult has been known for many years (see review by [3]), until recently, a mechanistic explanation of how CSPGs might redirect the advancement of cells or growth cones was lacking. This brief review will describe work that begins to elucidate how CSPGs provide varied biological effects during normal development and after trauma in the adult and, in addition, present some new ideas on how CSPGs orchestrate glioma invasion or the lack thereof.

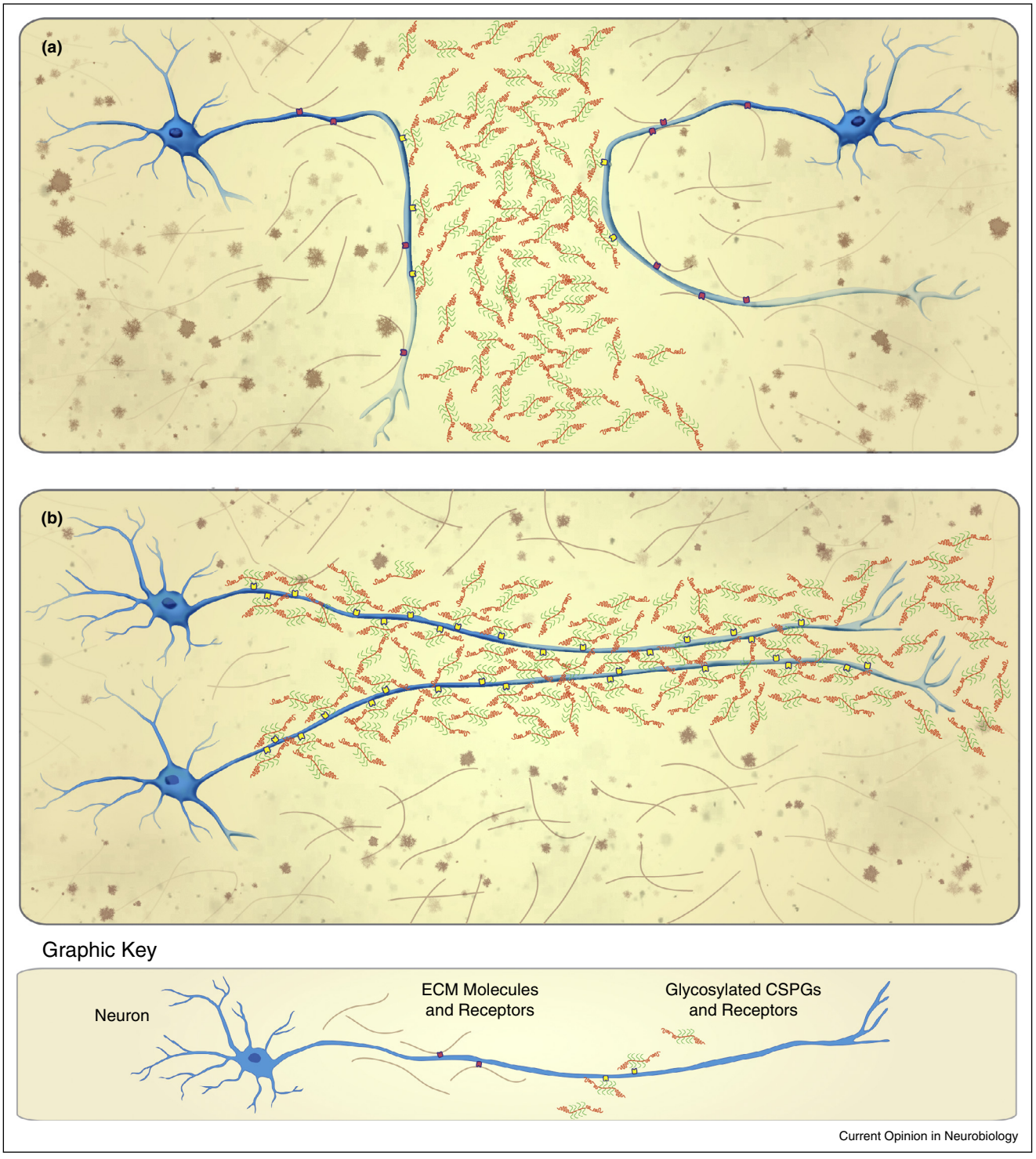
Expression and the role of CSPGs during development

During CNS development, glycosylated CSPGs are highly expressed in specific locations and were first thought to serve only as molecular barriers, blocking cells or axons from moving across the boundary between two adjacent, emerging structures (Figure 1A). For example, CSPGs repel axons from extending across the roof plate of the spinal cord [4,5•], the midline of the rhombencephalon and mesencephalon [6,7], the periphery of the developing retina [8,9], certain portions of the optic chiasm and distal optic tract [10,11] and the posterior somite [12]. A second mode of CSPG-mediated migration was then discovered within the subventricular germinal centers of the embryonic and adult brain. This ''addictive'' growth constrained movement to pathways that were spatially defined by the uniform and robust expression of glycosylated CSPGs [13–16]. Unlike classic, chemoattractive guidance, which involves forward movement up an increasing gradient of attractant, the addictive growth observed within the ventricular zones, the subplate of the developing forebrain [17•], and the raphe [18], restricted cellular movement and process extension within specific, spatially defined highways of CSPGs (Figure 1B). Thus, two distinct cell migratory behaviors are associated with CSPGs during development: (1) turning away from a zone of CSPG production, and also (2) a type of ''addictive'' growth constrained within CSPG containing territories (Figure 1). What is the mechanism that allows for such diverse motile behaviors during interactions with the same family of molecules?

For years it was posited that CSPGs exert their effects through relatively nonspecific mechanisms such as substrate occlusion [19], or presentation of negative charge [20]. This view has evolved considerably with the discovery of several receptors that directly bind sulfated glycosaminoglycan moieties [21•,22•,23••].

The receptor protein tyrosine phosphatase sigma (PTPRs, or PTPσ) was the first receptor identified with the ability to both bind CS-GAGs and convey a signal for

Figure 1



CSPGs mediate the distinct migratory behaviors of turning and addiction. (A) Extending axons and migrating neuroblasts are re-directed, or ''turned'' away from developmentally regulated proteoglycan boundaries when their receptor profiles favor adhesion to the non-addictive ECM molecules (*i.e.* laminin and fibronectin) adjacent to these CSPG-rich barriers. (B) In contrast, migrating neuroblasts and extending axons may become ''addicted'' to moving within CSPG-rich tracts through preferential expression of CSPG-receptors.

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