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Regulation of CNS plasticity and regeneration by chondroitin sulfate proteoglycans

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The limited degree of plasticity and regeneration in the adult central nervous system (CNS) of mammals is reflected in failure to regrow neurites (axons and dendrites) after the injury, which causes a major medical problem in traumas of the brain and the spinal cord. The extracellular matrix (ECM) of the central nervous system and its chondroitin sulfate proteoglycans (CSPGs) are currently regarded as major inhibitory regulators of plasticity and regeneration. Based on the recent findings of the group, the current ECM concept should be revised; the role of the CSPG-rich matrix can be reversed from inhibition to activation of regeneration, depending on factors present in the extracellular space. According to this paradigm shift, the juvenile plasticity and regeneration enhancing property can be restored in the adult CNS using the CSPG-binding protein HB-GAM (heparin-binding growth-associated molecule; also designated as pleiotrophin) that is highly expressed in the juvenile CNS but is essentially lost upon adulthood. We suggest a model according to which HB-GAM links chondroitin sulfate (CS) side chains of matrix CSPGs to neuron surface heparan sulfate (HS) chains of glypican-2 that acts as a cell surface receptor in neurite growth. Our results using injury models in mice support the suggested mechanism, and show that HB-GAM injected into injured cerebral cortex accumulates to the area of CSPG-rich scar and enhances regeneration of dendrites. In a spinal cord injury model, HB-GAM enhances regrowth of axons through the injury sites.

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