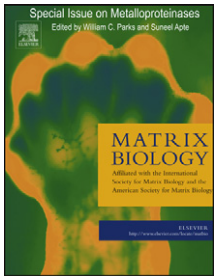
Review



ADAMTS expression and function in central nervous system injury and disorders

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Abstract

The components of the adult extracellular matrix in the central nervous system form a lattice-like structure that is deposited as perineuronal nets, around axon initial segments and as synapse-associated matrix. An abundant component of this matrix is the lecticans, chondroitin sulfate-bearing proteoglycans that are the major substrate for several members of the ADAMTSs (a disintegrin and metalloproteinase with thrombospondin motifs) family. Since lecticans are key regulators of neural plasticity, ADAMTS cleavage of lecticans would likely also contribute to neuroplasticity. Indeed, many studies have examined the neuroplastic contribution of the ADAMTSs to damage and recovery after injury and in central nervous system disease. Much of this data supports a role for the ADAMTSs in recovery and repair following spinal cord injury by stimulating axonal outgrowth after degradation of a glial scar and improving synaptic plasticity following seizure-induced neural damage in the brain. The action of the ADAMTSs in chronic diseases of the central nervous system appears to be more complex and less well-defined. Increasing evidence indicates that lecticans participate in synaptic plasticity in neurodegenerative disease states. It will be interesting to examine how ADAMTS expression and action would affect the progression of these diseases.

Extracellular matrix in the developing and adult CNS

The extracellular matrix (ECM) in the central nervous system (CNS) shares similarities to other tissues, although there are several aspects of nervous system matrix that make it unique [1]. In the CNS there is little collagen or other fibril forming molecules. The extracellular space in the parenchyma is limited to 20% of the total CNS volume [2] and is filled with a lattice-forming structure composed of hyaluronan, glycoproteins including tenascin C/R, and a small family of chondroitin sulfate (CS)-bearing proteoglycans (PGs) termed lecticans [3–5]. The lecticans include CNS-specific brevican and neurocan [6], aggrecan (also highly abundant in cartilage), and versican (found in nearly all tissues including blood vessels and basement membranes) [4,7]. The amino terminus of lecticans binds hyaluronan and the carboxy terminus binds tenascin.

The make-up of the matrix changes significantly during CNS development [8,9] and is quite varied in different regions of the adult CNS. During development, the ECM directly influences neuronal and glial migration and differentiation, neurogenesis, and axonal outgrowth and guidance that are vital for synaptogenesis [10–12]. Compared to the ECM during early development and later developmental "critical periods", adul tECM is located just adjacent to the active zone of many synapses and directly affects synaptic plasticity and stability [3,6]. Additionally in the adult CNS, the ECM forms perineuronal nets (PNNs) around selected neuronal soma where it can influence synapses on the membrane of the cell body [13]. After injury to the CNS, glial scars form that contains robust amounts of ECM

molecules, especially CS-bearing PGs, secreted mainly by activated glia. Although these scars are thought to assist in the isolation of the injured region of the brain, the scar inhibits repair mechanisms [11]. In fact, be it synaptic or neurite plasticity, the role of CS-bearing PGs appears to be negative in every case, but little is known about how the presence and turnover of matrix is regulated. However, it is known that extracellular proteases act selectively on lecticans, other CS-bearing PGs, other matrix proteins, and a small number of non-matrix protein substrates. These proteinase families are called a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTSs) and matrix metalloproteinases (MMPs) [5,14]; tissue plasminogen activator is also capable of cleaving lecticans. Changes in deposits of matrix protein in the CNS involve the action of these proteases. The remainder of this chapter will describe what is known about the expression and activity of ADAMTS glutamyl-endopeptidases

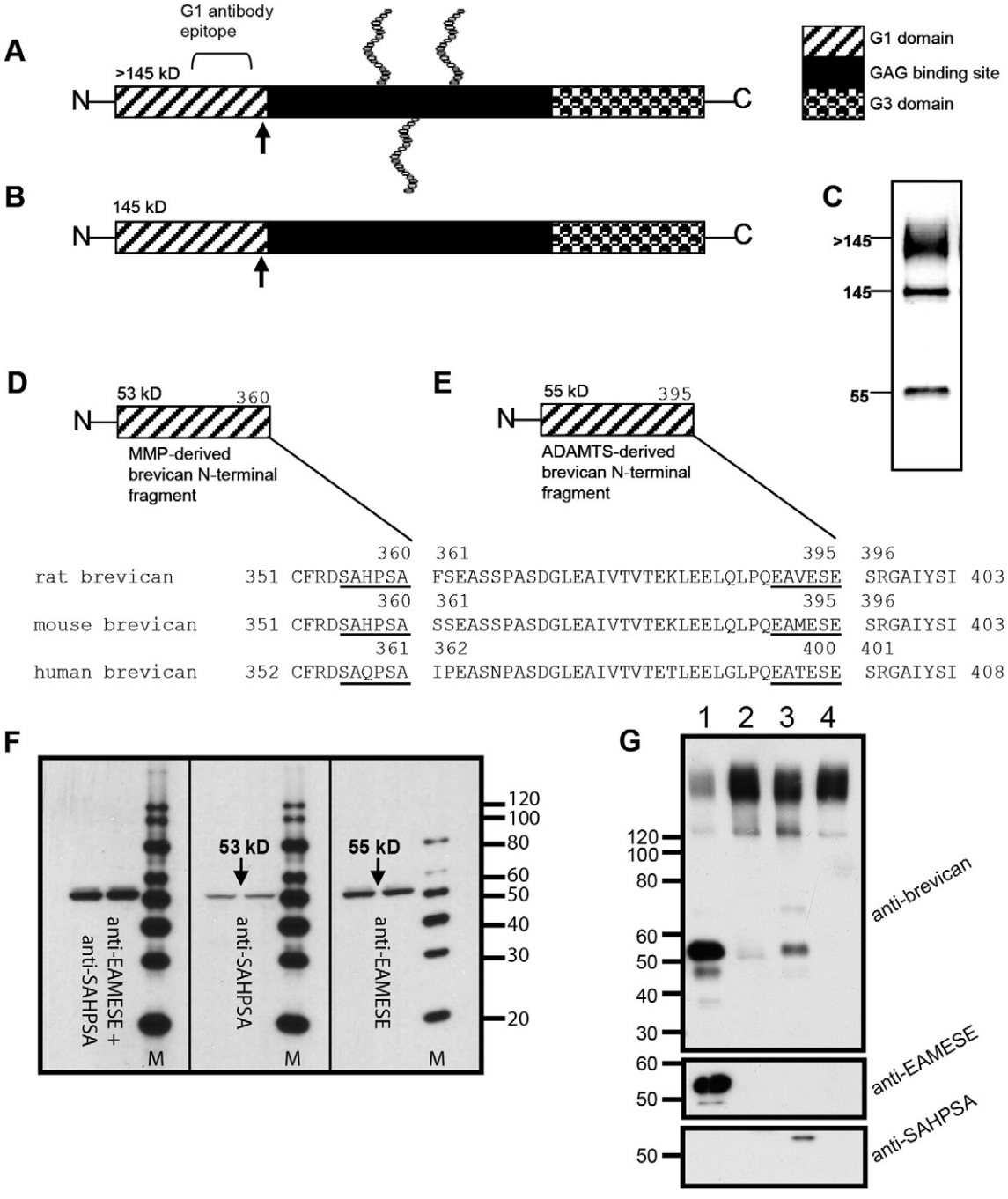

Fig. 1 (*legend on next page*).