成熟脳のペリニューロナルＥＣＭの形成と機能について

Formation and role of perineuronal ECMs in the mature brain

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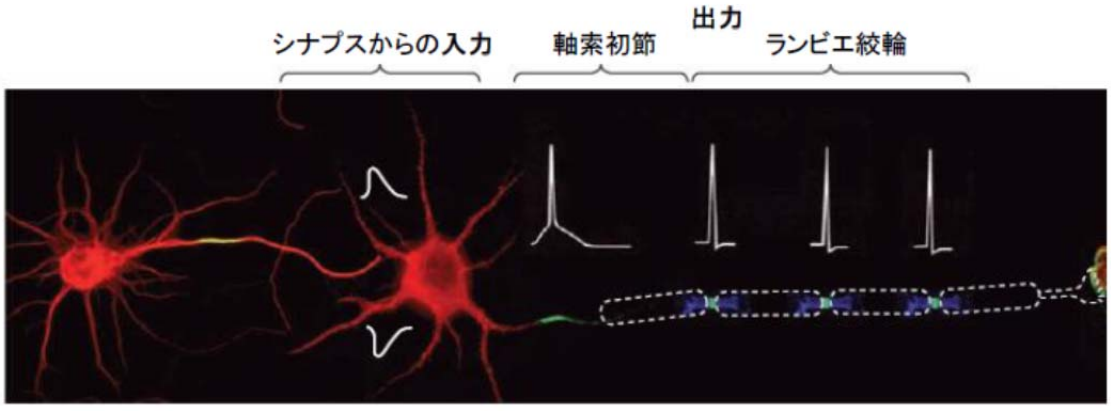
The extracellular matrix (ECM) in the brain is composed of molecules synthesized by neurons and glial cells. During development, ECM plays crucial roles in proliferation, migration and differentiation of neural cells. In the mature brain, ECM undergoes a slow turnover and supports multiple physiological processes. The hyaluronan-based condensed pericellular matrix is formed around some neuronal cell bodies and nodes of Ranvier late in postnatal development around the time either when myelination is finished or when synaptic contacts are stabilized. The lattice-like perineuronal nets (PNNs) that surround cell bodies, proximal dendrites and axon initial segments is formed as synapses stabilize and critical periods for plasticity close. The perinodal matrix and PNN both share common features of molecular organization which includes the backbone hyaluronan, chondroitin sulfate proteoglycans (CSPGs), tenascin-R and link proteins.

At the nodes of Ranvier, excitable axon membranes are exposed directly to the extracellular fluid. Cations are accumulated and depleted in the local extracellular nodal region during action potential propagation. We have previously reported the physiological importance of nodal ECM as ion-diffusion barrier during salutatory conduction. Nodes contain ion channels and cell adhesion molecules (e.g. neurofascin186: NF186) that are linked to the axonal cytoskeleton by the scaffolding proteins ankyrinG (ankG) and beta IV spectrin. ECM brevican binds to NF186. Together with myelin, clustered nodal proteins are responsible for the regeneration and rapid propagation of action potentials. Despite their importance, the molecular mechanisms underlying node formation remain controversial and poorly understood. There are three potential mechanisms to assemble nodes: 1) clustering of NF186 by an ECM, 2) restriction of nodal protein mobility by paranodal axoglial barriers (PJ), and 3) stabilization of Na channels by axonal cytoskeletal scaffold (CS). To test this idea, we generated mice with two of the three mechanisms simultaneously disrupted. Mice with a single disrupted mechanism had mostly normal nodes, but mutants with two disrupted mechanisms showed juvenile lethality, profound motor dysfunction, and significantly reduced Na channel clustering. Our results demonstrate that ECM, paranodal, and axonal cytoskeletal mechanisms ensure robust CNS nodal Na channel clustering. Bral1 link protein function to stabilize nodal ECM components rather than promote their initial assembly.

PNNs play a structural role as well as instructive roles in the control of CNS plasticity and the termination of critical periods. The cartilage link protein Crtl1/Hapln1 was reported to be a trigger for the formation of PNNs in the visual cortex. Bral2/Hapln4 is another link protein that is expressed in PNNs, mainly in the brainstem and cerebellum. To assess the role of Bral2 in PNN formation, we examined the expression of PNN components in targeted mouse mutants lacking Bral2. We show here that Bral2-deficient mice have attenuated PNNs, but the overall levels of chondroitin sulfate proteoglycans, lecticans, are unchanged with the exception of neurocan. Bral2 deficiency markedly affected the localization of brevican in all of the nuclei tested, whereas no effect was seen on aggrecan. Bral2 may have a role in the organization of the PNN, in association with brevican, that is independent of aggrecan binding. There was a heterogenous attenuation of PNN components, including glycosaminoglycans, indicating the elaborate molecular organization of the PNN components. In the current study, we focused on the PNN at the medial nucleus of the trapezoid body (MNTB). Each principal cell of MNTB is contacted by a very large presynaptic glutamatergic terminal, the Calyx of Held. The MNTB is a vital structure of sound localization circuits in the auditory brainstem. We found the dissociated expression of aggrecan and brevican at MNTB, which was correlated with that of Crtl1 and Bral2. We report the formation of PNN in MNTB during critical period to the adulthood. Our results may contribute to understanding the physiological role of proteoglycans on synaptic functions in the auditory system.



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