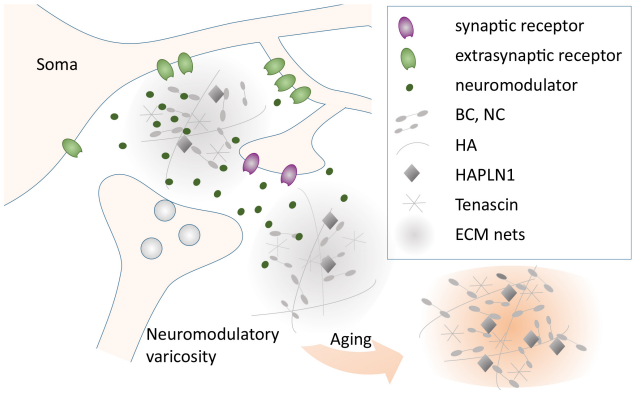
TP8: The perisynaptic extracellular matrix (ECM) of the aging brain: impact of enriched environment and neuromodulation on ECM composition and cognitive performance (Eckart D. Gundelfinger & Constanze I. Seidenbecher)


About 20-25% of brain volume is occupied by ECM. The composition and integrity of the brain's ECM regulate tissue diffusion properties and are essential determinants of neural plasticity, e.g. via regulating volume transmission of neuromodulators. Developmental changes in brain plasticity after the 'critical period' coincide with massive reformation of ECM structures (reviewed in Gundelfinger et al., 2010). In the aging brain, ECM levels have been associated with changes in age-dependent cognitive decline (Vegh et al., 2014). Brain synapses are wrapped by ECM deposits consisting of hyaluronan (HA)-based proteoglycan networks of glial and neuronal origin (Faissner et al., 2010). Hyaluronidase treatment leads to increased short-term plasticity by changing AMPA receptor surface mobility (Frischknecht et al., 2009). ECM structures organize functional compartments on the extracellular side of neural membranes, which are important for structural and functional types of plasticity (Dityatev et al., 2010). Moreover, perineuronal and perisynaptic ECM nets contribute to homeostasis and affect plasticity also via insulating and stabilizing synaptic contacts and acting as diffusion corridors for transmitters and neuromodulators and as low affinity receptors trapping neurotrophic factors. Synaptic plasticity (Brakebusch et al., 2002) as well as drug conditioning (Lubbers et al., 2016) are affected by proteoglycan deficiency in *brevican* (BC) mutant mice. Also, homeostatic forms of plasticity go along with reorganization of brain ECM via selective proteolytic cleavage (Valenzuela et al., 2014). During normal aging, extracellular space diffusivity changes in correlation with learning abilities. We found that double-KO mice for the ECM proteins neurocan (NC) and BC show better remote memory and little if any aging-related changes in apparent diffusion coefficient and fractional anisotropy. Deposits of NC, BC, Tenascins and HAPLN1 are increased in the aging hippocampus (Vegh et al., 2014a,b). Various studies revealed that environmental enrichment (EE), which is known to lead to better cognitive performance in aging, affects ECM structure and BC expression in the rodent forebrain (e.g. Favuzzi et al., 2017).

Hypotheses: We hypothesize that age-dependent changes in ECM composition contribute to cognitive decline. BC and NC deficiency in mouse mutants is supposed to affect aging-related cognitive decline. EE improves cognitive abilities during aging via modulating the ECM. Aims:

1. To provide a comprehensive catalogue of aging-related changes in composition and structure of the peri-synaptic ECM related to cognitive performance in our mutants
2. To determine how EE affects ECM composition in wild-type (WT) and ECM-mutant mice with phenotypes in learning and memory.
3. To study first *in vitro* how cholinergic modulation, e.g. via biperiden, affects matrix integrity and composition
4. To study effects of modulatory pharmacology on ECM aging in NC and BC mutant mice.



Integrity and composition of the ECM undergo age-related changes, which will affect volume transmission of neuromodulators like ACh or dopamine. ECM alterations are postulated to affect the accessibility of nearby receptors. In addition, surface mobility of receptors might be altered.

Collaborations: **TP1/9** Dieterich (synaptic ECM proteostasis; astrocytic contribution to ECM), **TP2/10** Stork (behavioral experiments, physiology), **TP5** Dunay (effect of neuroinflammation on aging ECM), **TP6** Dityatev (ECM neuron-glia interaction), **TP7** Schreiber/Dityatev (ECM in cerebral small vessel disease); **TP10** Stork **TP13** Ullsperger (Neuromodulation).

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