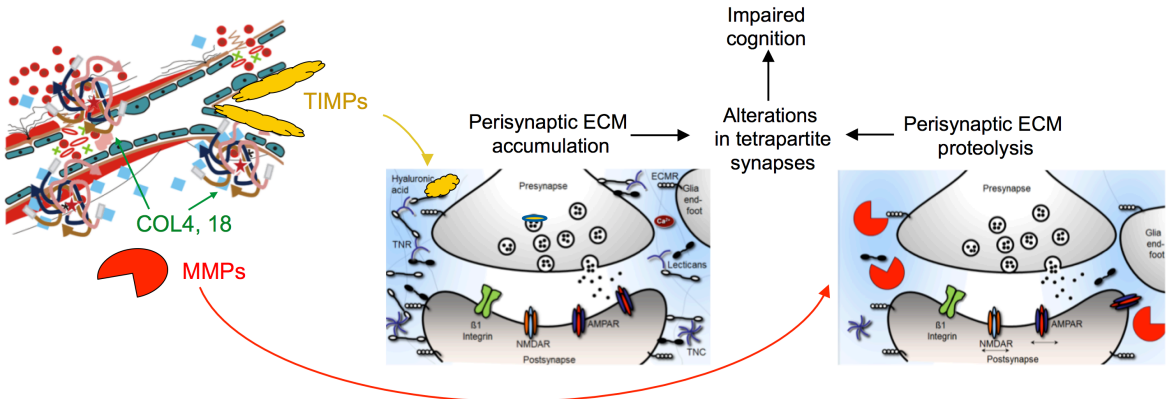
TP7: Targeting perisynaptic ECM mediated synaptic dysfunction in cerebral small vessel disease (Stefanie Schreiber & Alexander Dityatev)


Cerebral small vessel disease (CSVD) is responsible for about a fifth of all strokes worldwide and contributes to up to 45% of dementias. Establishment of efficient prevention and therapy remains challenging, as CSVD results from a complex interplay between environmental and genetic factors, suggesting that CSVD has to be considered as a continuous disorder where sporadic and familial CSVD variants converge on a common pathogenic pathway such as dysregulation of the extracellular matrix (ECM) of the neurovascular unit (NVU) (Joutel et al., 2015). The exact mechanisms of ECM remodeling and how the latter contributes to tissue alterations (e.g. white matter lesions), impaired synaptic plasticity and related cognition/behavior, however, remain unknown. Collagen type XVIII (COL18)-related (familial) disease is caused by COL18A1 mutations resulting in (i) basement membrane (BM) integrity loss, (ii) overall small vessel wall abnormalities, (iii) NVU changes, (iv) altered ECM function and tissue homeostasis, probably affecting synaptogenesis. Collagen XVIII further interacts and accumulates together with misfolded proteins such as β-amyloid (Aβ) possibly impeding Aβ clearance (Heljasvaara et al., 2017). In familial CSVD there are further BM/vascular deposits of TIMP-3, a tissue inhibitor of ADAMTS metalloproteinases involved in the remodeling of neural ECM (Monet-Lepretre et al., 2013). Strikingly, animal models of sporadic CSVD likewise demonstrate collagen and TIMP-3 accumulations within the vascular BM (**Figure**) occurring together with blood-brain barrier (BBB) breakdown, BM thickening and NVU changes (Schreiber et al., 2012; Held et al., 2017). Increased TIMP-3 concentrations are also found in human CSVD, especially in those variants characterized by vascular Aβ deposits suggesting there to be some common mechanisms. Thus, we expect sporadic and familial CSVD to be related to dysregulation of ECM modulating molecules (that is TIMP-3), e.g. as a result of abnormal protein deposits, resulting in distinct downstream pathologies of perisynaptic ECM enriched in ADAMTS substrates (e.g. lecticans). This may interfere with dendritic spine formation, synaptic plasticity, cell excitability, and learning and memory (Dityatev et al., 2010). Impairment of neuroplasticity and cognitive functions can thereby be abrogated by enzymatic attenuation of neural ECM with chondroitinase ABC (Yang et al., 2015). In conclusion, COL18 and TIMP-3 dysregulation/deposits driving perisynaptic ECM remodeling should thus serve as an excellent target mechanism cross-linking age, arterial hypertension, genetics, and cognitive impairment in CSVD.

Hypothesis: We hypothesize that familial and sporadic CSVD are related to ECM remodeling resulting from the interplay between environmental factors and genetics and that these ECM alterations interfere with homeostatic maintenance, synaptic plasticity, cognition and behavior. Targeting ECM modulating enzymes/molecules will have the potential to alter perisynaptic ECM downstream pathologies leading to new therapeutic strategies in CSVD. We define the following Aims:

1. To understand the impact of environmental factors (age, arterial hypertension) and genetics on ECM remodeling in CSVD.
2. To understand the impact of ECM remodeling and ECM modulating enzymes on synaptic plasticity, cognition and behavior in CSVD.

3. To target ECM modulating enzymes/molecules to improve synaptic function and slow down cognitive decline in CSVD.



CSVD is related to ECM remodeling, impairment of synaptic plasticity and cognition. Small vessel wall damage and associated BM/vascular deposits of pathological proteins (TIMPs, COL18) result in the (i) dysregulation of ECM modulating enzymes (e.g., matrix metalloproteinases [MMPs]) and (ii) perisynaptic ECM alterations affecting ECM homeostasis, synaptic plasticity and cognition.

Collaborations: **TP9** Dieterich (ECM-dependent signaling through mechanoreceptors), **TP3** Kreutz (synaptic proteomics and signaling), **TP8** Gundelfinger/Seidenbecher (imaging of perisynaptic ECM and other synaptic components).

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