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MICRO-BLEEDs

MICROglia as modulators of brain BLEEDs

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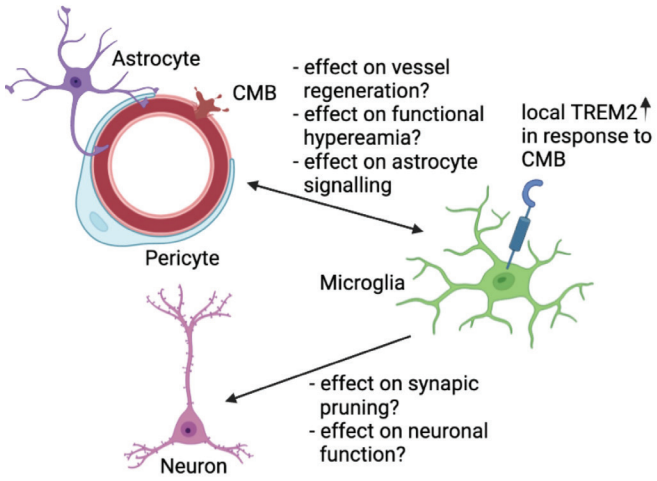
Cerebral microbleeds (CMBs) are small chronic brain bleedings which are caused by pathological fragility of the small blood vessels of the brain. They can be observed in individuals with stroke and cognitive impairment and in apparently healthy elderly individuals. Because of their small size, CMBs usually do not cause any acute symptoms, but insidiously, they trigger delayed and persistent nerve cell death and long-term problems such as memory decline and dementia. The mechanisms at the basis of this brain tissue damage are currently unclear. Hence, there is an unmet need to identify the molecular pathways contributing to brain damage after CMBs, and to test the potential of modulating these pathways as a new therapeutic approach. Importantly, CMBs lead to a local activation of the brain's resident immune cells, called microglia. In general, microglia can have a protective or deleterious role for the brain, with the microglial gene TREM2 representing a main switch controlling these opposing functions. However, whether and how microglia and TREM2 are involved in the damage imposed by CMBs is still unknown. Our MICRO-BLEEDs consortium will gather an interdisciplinary group of clinicians and researchers internationally recognized in the field of cerebral small-vessel diseases as well as the normal function of brain cells including microglia and TREM2. The team will exploit advanced technologies to define the role of microglia and TREM2 in brain tissue damage occurring in mouse models of CMBs. We will specifically investigate how TREM2 activation controls microglial function, and how this may lead to changes in the function of blood vessels, synapses and different brain cell types. Importantly, we will also test whether antibodies that modulate the activity of TREM2 can be harnessed to ameliorate the damage caused by CMBs, with the final goal to identify novel targets for CMB prevention and treatment that can be moved forward into clinical trials.



Highlighted Methods

WP I

Role of TREM2 in the microglial response to CMBs

- Lead PIs: P1 & P4 in collaboration with all partners
- Use of TREM2-KO mouse to investigate microglial-, monocytes and perivascular fibroblasts changes in CMBs
- Use of TREM2-KO to investigate long-term vessel fate and BBB integrity

Highlighted Methods:
- In vivo 2-Photon imaging
- Imaging mass cytometry
- RNAscope in situ hybridization
- Immunohistochemistry

WP II

Effects of TREM2 on BBB patency, vascular function and the multicellular functional response to CMBs

- Lead PIs: P3 & P2 in collaboration with all partners
- Use of TREM2-KO mouse to investigate impact on astroglial and neuronal calcium activity and BBB integrity.
- Use of TREM2-KO to analyse pericytes and smooth muscle cells response in CMBs

Highlighted Methods:
- In vivo 2-Photon imaging
- Wide field and 2-Photon calcium imaging
- Neurovascular in vitro model

WP III

Modulation of synaptic pruning, refinement and network activity after CMBs by TREM2

- Lead PIs: P4 & P3 in collaboration with all partners
- Use of TREM2-KO to analyse neuronal and synaptic damage
- Analysis of synaptic pruning by microglia in relation to CMBs
- Correlation to data from imaging mass cytometry

Highlighted Methods:
- In vivo 2-Photon imaging
- imaging mass cytometry
- In vivo 2-photon STED microscopy
- Immunohistochemistry