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Brain-infiltrating CD4+ T cells exacerbate microglial reactivity and promote neuronal death after experimental subarachnoid hemorrhage

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Background. Subarachnoid hemorrhage (SAH) is a common consequence observed in cases of moderate and severe traumatic brain injury leading to an increase of morbidity and mortality. SAH triggers sustained neuroinflammation, including immune cell recruitment and activation. T-cells, in particular, are known to promote secondary brain injury after ischemic stroke; however, their role in SAH remains unclear. This study evaluated T-cell recruitment and pathological contribution in a clinically relevant mouse SAH model.

Materials and methods. Adult wild-type (WT) and CD3 knockout (KO, T-cell-depleted) mice underwent pre-chiasmatic cistern blood injection to induce SAH or sham procedure. At 7 days post-injury (dpi), brains were collected for neuroinflammatory gene expression (Nanostring® transcriptomic analysis and RT-PCR) and histology. Additionally, three SAH patient cohorts were evaluated for T-cell levels in blood and CSF at 2, 5, and 10 dpi.

Results. Transcriptomic profiling revealed a major involvement of T-cells and microglia after SAH. Histology showed CD3+ T-cell infiltration, predominantly CD4+ (80%), in brain parenchyma, meninges and choroid plexus in SAH WT mice ($p<0.01$ vs sham). Similarly, in human patients, a progressive CD4+ T-cell increase was reported in CSF ($p<0.05$ 10d vs 2d), supporting clinical relevance of experimental observations. In SAH WT mice, neuronal death ($p<0.01$ vs sham) and microglial activation ($p<0.001$ vs sham) were observed in the same area of T-cell infiltration and hippocampus. In contrast, CD3-KO mice displayed widely reduced microglial activation, evaluated by Iba1 stained area, with key pro-inflammatory microglial genes that were upregulated in SAH WT mice ($p<0.01$ vs sham) remained unaltered in CD3-KO mice after SAH. Importantly, CD3-KO mice also preserved hippocampal neuronal viability and showed reduced microglial reactivity after SAH.

Conclusions. These findings indicate T-cells as key modulators of neuroinflammation and secondary injury evolution, by driving microglial pro-inflammatory activation and promoting neuronal death after SAH.