A single combination dose of natalizumab (aVLA4) and odulimomab (aLFA1) prevents fatal cerebral herniation in a rodent model of hemorrhagic stroke

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Introduction: Immune response to cerebrovascular injury at the capillary level

Cerebral edema and hemorrhagic transformation are associated with worse prognosis in patients with cerebrovascular injury. The mechanism of edema formation is driven by osmotic gradients and vascular permeability. Several studies have attempted to inhibit parts of the diapedesis pathway to prevent post stroke injury with variable results. We hypothesized that identifying and inhibiting the dominant mechanism of myeloid cell invasion would effectively mitigate edema formation. We targeted VLA4 and LFA1 that are integrins found on leukocytes and play key role in cell extravasation through interaction with VCAM-1 and ICAM-1, respectively.
Methods

• We created a model of cerebrovascular injury using a combination of ultrasound and intravenously injected microbubbles.

• We used multiparameter flowcytometry, two-photon laser scanning microscopy, immunohistochemistry and qPCR to map the immune landscape and assess endothelium activation.

• We evaluated the effect of neutrophil depletion, monocyte depletion, inflammatory monocyte depletion and diapedesis inhibition on edema formation and survival.
Flowcytometric analysis and intravital microscopy demonstrated rapid invasion of various myelomonocytic cells within 1 hour after injury and persistence of these cell populations up to 6 days after injury.
Depletion of myelomonocytic cells using anti-Gr-1 antibody prevented cerebral edema development and, while injured naïve mice die within 2 days, anti-GR-1 treated mice all survived. Depletion of only inflammatory monocytes, using CCR2 ko mice, or only neutrophils, using anti-Ly6G antibody, did not significantly decrease edema or improve survival.
Treatment with anti-LFA1/VLA4 after injury effectively inhibited myeloid cell penetration, in the tumor and peritumor area.

Administration up to 6 h after injury resulted in a decrease in cerebral edema and promoted survival.

Treatment with either only aLFA1 or only aVLA4 antibodies alone (not combined) was not effective at preventing fatal edema formation. This is explained by the intervessel and intersample variability of ICAM-1 (LFA-1 ligand) and VCAM-1 (VLA-4 ligand) on the endothelium of injured vessels.
Discussion/ Summary

We show that cerebral edema following cerebrovascular injury is primarily mediated by active invasion of monocytes and neutrophils. Depletion of these cells prior to injury completely prevented fatal cerebral edema.

A single dose of αLFA1/αVLA4 antibody within 6 hours after injury can prevent fatal cerebral edema and constitutes a promising treatment for edema following ischemic stroke or intracerebral hemorrhage.