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CEACAM1 Inhibits MMP-9-Mediated Blood-Brain-Barrier Breakdown in a Mouse Model for Ischemic Stroke

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ABSTRACT: *RATIONALE:* Blood-brain-barrier (BBB) breakdown and cerebral edema result from postischemic inflam-mation and contribute to mortality and morbidity after ischemic stroke. A functional role for the carci-noembryonic antigen-related cell adhesion molecule 1 (CEACAM1) in the regulation of reperfusion injury has not yet been demonstrated.
OBJECTIVES: We sought to identify and characterize the relevance of CEACAM1- expressing inflamma-tory cells in BBB breakdown and outcome after ischemic stroke in Ceacam1-/- and wild type (WT) mice. *METHODS AND RESULTS:* Focal ischemia was induced by temporary occlusion of the middle cerebral artery (tMCAO) with a microfilament. Using magnetic resonance imaging (MRI) and Evans blue permea-bility assays, we observed increased stroke volumes, BBB breakdown and edema formation, reduction of cerebral perfusion and brain atrophy in Ceacam1-/- mice. This translated into poor performance in neurological scoring and high post stroke-associated mortality. Elevated neutrophil influx, hyperproduction and release of neutrophil-related matrix metalloproteinase (MMP)-9 in Ceacam1-/- mice were confirmed by immune fluorescence, flow cytometry, zymography and stimulation of neutrophils. Importantly, neutralization of MMP-9 activity in Ceacam1-/- mice was sufficient to alleviate stroke sizes and improve survival to the level of CEACAM1-competent animals. Immune histochemistry of murine and human post-stroke autoptic brains congruently identified abundance of CEACAM1+MMP9+ neutrophils in the ischemic hemispheres.
CONCLUSIONS: CEACAM1 controls MMP-9 secretion by neutrophils in postischemic inflammation at the BBB after stroke. We propose CEACAM1 as an important inhibitory regulator of neutrophil-mediated tissue damage and BBB breakdown in focal cerebral ischemia.

STATEMENT: *This is the first time that a negative regulator for cerebral edema formation after stroke is described. Ischemic stroke is the leading cause of death and permanent disabilities in the industrialized world. One major clinical problem after ischemic stroke is cerebral edema and secondary expansion of cerebral injury. To date, the only immediate clinical intervention to relieve intracranial pressure is by hem-icraniectomy. The underlying mechanisms of edema formation after stroke are only poorly defined. Our study demonstrates a link between the cellular adhesion molecule CEACAM1, and the extent of BBB breakdown. We show that CEACAM1 is a negative regulator of MMP-9 production by neutrophils and therefore protects from metalloproteinase-induced BBB damage. The loss of CEACAM1 results in an increase in cerebral vascular permeability producing larger infarction sizes, increased tissue damage, poor neurological outcome, and higher mortalities. These findings can be reversed by inhibition of MMP-9. Hence, the modulation of CEACAM1-mediated effects offers a new venue for understanding and future interventions in cerebral edema formation after stroke.*

BACKGROUND: This work was performed at the Institute of Clinical Chemistry and the Department of Neurology in the group of Andrea Kristina Horst and Tim Magnus. The experiments were conducted by Peter Ludewig in the group of A.K.H. and T.M. in close collaboration with Jan Sedlacik from the Department of Diagnostic and Interventional Neuroradiology. The focus of the work is set on the mechanism of cerebral edema formation after ischemic stroke. The project was funded by grants to A.K.H. and T.M. (DFG grant HO3312) and the ERA-NET grant (Nanostroke) to T.M.