THE ROLE OF THE COMPLEMENT SYSTEM IN ISCHEMIC STROKE AND NEURAL PLASTICITY

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ABSTRACT

Evidence from experimental animal studies suggests that complement activation in the brain is a "double-edged sword" as it exerts beneficial or detrimental effects depending on the context. Here, we assessed whether complement activation in the systemic circulation could be a predictive biomarker of functional outcome after stroke. Further, we studied the role of the complement system in brain plasticity and recovery after ischemic stroke.

We found that acute and delayed phase plasma levels of C3 and C3a differ substantially among patients suffering from ischemic stroke of different etiology, and the association of plasma C3 and C3a levels with case/control status and with functional outcome is ischemic stroke subtype-dependent. In large vessel disease and cardioembolic stroke patients, C3 levels at 3-month follow up were associated with an unfavorable functional outcome at both 3 months and 2 years after stroke. However, in cardioembolic stroke patients moderate increase in plasma C3a/C3 ratio predicted favorable outcome after 2 years (Paper I and II). Furthermore, two single nucleotide polymorphisms (SNPs) in the *C3* gene were found to be associated with ischemic stroke independently of traditional risk factors and one of these SNPs was associated with cryptogenic stroke (Paper III). Also, two SNPs were associated with plasma C3a or C3 levels independently of age, sex and case/control status. Taken together, the role of the complement system in ischemic stroke is strongly dependent on stroke etiology.

We have also found that C3a overexpression in mice increased, whereas C3a receptor (C3aR) deficiency decreased the number of post-stroke-born neurons in the peri-infarct cortex without affecting the infarct size. Furthermore, the density of presynaptic puncta and GAP43-positive axonal growth cones in the cortex surrounding the infarct were lower in the C3aR-deficient compared to control mice, while in the C3a-overexpressing mice post-stroke axonal plasticity response was increased. Mice lacking C3aR showed a more pronounced sensorimotor functional deficit as assessed by behavioral testing (Paper IV). These results indicate that C3aR signaling should be considered as a target when designing therapeutic strategies to improve functional recovery after ischemic stroke.

To study complement-related neural plasticity in a non-pathological context, we performed electrophysiological recordings in the CA1 region of live hippocampal slices of young mice lacking C3 and control mice. We found that the C3-deficient mice had a decreased neurotransmitter release probability but dendritic spine density, and frequency and amplitude of miniature excitatory postsynaptic potentials were comparable in both groups of mice. Behavioral testing using the IntelliCage platform revealed that the C3-deficient mice performed better in the place and reversal learning tasks (Paper V). These findings may have implications for the management of disorders involving synapse elimination, such as Alzheimer's diseases, autism or multiple sclerosis.

Keywords: ischemic stroke, complement system, neurogenesis, synaptic plasticity, hippocampus, learning and memory, functional outcome

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II. **Stokowska, A**, Olsson, S, Holmegaard, L, Jood, K, Blomstrand, C, Jern, C, Pekna, M. Cardioembolic and small vessel disease stroke show differences in associations between systemic C3 levels and outcome. *PLoS One. 2013; 8(8): e72133.*

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IV. **Stokowska, A**, Atkins, AL, Barnum, SR, Wetsel, RA, Dragunow, M, Pekna, M. Receptor for complement peptide C3a stimulates neural plasticity after experimental brain ischemia. In manuscript.

V. Perez-Alcazar, M, Daborg, J, **Stokowska, A**, Wasling, P, Björefeldt, A, Kalm, M, Zetterberg, H, Carlström, K, Blomgren, K, Clementson Ekdahl, C, Hanse, E, Pekna, M. Altered cognitive performance and synaptic function in the hippocampus of mice lacking C3. Submitted.

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