UKE Paper of the Month November 2020

Characterization of brain-derived extracellular vesicles reveals changes in cellular origin after stroke and enrichment of the prion protein with a potential role in cellular uptake

Santra Brenna, Hermann C. Altmeppen, Behnam Mohammadi, Björn Rissiek, Florence Schlink, Peter Ludewig, Christoph Krisp, Hartmut Schlüter, Antonio Virgilio Failla, Carola Schneider, Markus Glatzel, Berta Puig* and Tim Magnus*

* joint senior authorship

J Extracell Vesicles. 2020 Aug 27;9(1):1809065.doi: 10.1080/20013078.2020.1809065.

ABSTRACT:
Extracellular vesicles (EVs) are important means of intercellular communication and a potent tool for regenerative therapy. In ischaemic stroke, transient blockage of a brain artery leads to a lack of glucose and oxygen in the affected brain tissue, provoking neuronal death by necrosis in the core of the ischaemic region. The fate of neurons in the surrounding penumbra region depends on the stimuli, including EVs, received during the following hours. A detailed characterization of such stimuli is crucial not only for understanding stroke pathophysiology but also for new therapeutic interventions. In the present study, we characterize the EVs in mouse brain under physiological conditions and 24 h after induction of transient ischaemia in mice. We show that, in steady-state conditions, microglia are the main source of small EVs (sEVs), whereas after ischaemia the main sEV population originates from astrocytes. Brain sEVs presented high amounts of the prion protein (PrP), which were further increased after stroke. Moreover, EVs were enriched in a proteolytically truncated PrP fragment (PrP-C1). Because of similarities between PrP-C1 and certain viral surface proteins, we studied the cellular uptake of brain-derived sEVs from mice lacking (PrP-KO) or expressing PrP (WT). We show that PrP-KO-sEVs are taken up significantly faster and more efficiently than WT-EVs by primary neurons. Furthermore, microglia and astrocytes engulf PrP-KO-sEVs more readily than WT-sEVs. Our results provide novel information on the relative contribution of brain cell types to the sEV pool in murine brain and indicate that increased release of sEVs by astrocytes together with elevated levels of PrP in sEVs may play a role in intercellular communication at early stages after stroke. In addition, amounts of PrP (and probably PrP-C1) in brain sEVs seem to contribute to regulating their cellular uptake.

STATEMENT:
EVs constitute a new and exponentially growing research field. The understanding of EVs for cell to cell communication mechanisms is essential in the understanding of cell communication as a whole. Moreover, EVs can also be used as therapeutics due to their unique capabilities to shuttle their contents into cells or, as biomarkers in acute and chronic diseases. This is the first study analysing EVs from brains of mice that have undergone experimental stroke. We unveiled the EV protein composition and their cellular origin, which allows for a deeper understanding of brain cell interactions in the acute phase of stroke. Moreover, it also sheds light on the not yet understood mechanism of EVs uptake by recipient cells, proposing the prion protein as an important player.

BACKGROUND:
This work was performed at the Experimental Research in Stroke and Inflammation (ERSI) laboratory, Department of Neurology headed by Tim Magnus (UKE), in close collaboration with the Institute of Neuropathology (UKE), the Institute of Clinical Chemistry and Laboratory Medicine (UKE), the UKE Microscopy Imaging Facility and the Heinrich Pette Institute. It is part

of the PhD thesis of Santra Brenna, under the supervision of PD Dr. Berta Puig. This work was supported by the “Werner Otto Stiftung” (BP, HCA), the “Hermann und Lily Schilling Stiftung” (TM), and the DFG: SFB 1328 (TM), FOR 2879 (TM, PL), GRK1459 (BM, MG); Alzheimer Forschung Initiative (AFI), and CJD Foundation, Inc. (HCA).