Redox regulation of monocyte migration across the blood-brain barrier

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Migration of monocytes from the cerebral vasculature into the brain parenchyma is a critical step in the development of new lesions during multiple sclerosis (MS). To enter the central nervous system, monocytes have to cross the blood-brain barrier (BBB), which mainly consists of specialised endothelial cells and their tight junction complexes. Transendothelial migration of monocytes requires the active participation of brain endothelial cells (BEC); they need to rearrange their cytoskeleton and tight junctions. Previously it was shown by our group that reactive oxygen species (ROS) are essential for the migration of monocytes and that superoxide is the pertinent ROS that affects the integrity of the endothelial cell layer.
Since superoxide is necessary for monocyte migration we investigated whether a ROS-scavenger, lipoic acid (LA), could inhibit migration of monocytes across the blood-brain barrier. LA is a naturally occurring antioxidant, which acts via several mechanisms, including metal chelation, regeneration of endogenous antioxidants and direct ROS-scavenging. *In vitro,* LA decreased migration of a monocytic cell line across a monolayer of BEC. Using life cell imaging techniques we now have quantitatively assessed that ROS are produced within minutes upon interaction of monocytes with endothelium, subsequently inducing changes in the cytoskeleton. These cytoskeletal changes could be prevented by LA.
In vivo, LA prevented the development of clinical signs and cellular infiltration into the CNS in the animal model of MS, acute Experimental Allergic Encephalomyelitis (EAE), in a dose-dependent manner. Monocytes isolated from LA animals revealed an impaired migration across a monolayer of BEC compared to monocytes isolated from vehicle treated animals.
Together, these results indicate that oxygen radicals are essential for monocyte-migration *in vitro* as well as *in vivo*. ROS-scavengers like LA may be tools to prevent monocyte migration across the BBB and may therefore be potential candidates for the treatmet of MS.

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Oral presentation, session 35