A multicentric approach to monocyte alterations in ALS

Acronym: MultiMono

Principal Investigator: Jochen Weishaupt

Grant: 190 000€

Duration: two years

Summary of the research project

This study aims to replicate the results obtained through the innate Target project, selected during the 2013 Call for projects.

Professor Jochen Weishaupt is a researcher and a physician in the department of Neurology, University of Ulm, therefore he can lead a research program oriented directly to the patient.

One common feature in all ALS cases, including familial and sporadic patients as well as animal models of the disease, is a massive neuroinflammatory reaction. However, increasing evidence suggests an involvement of both, the central nervous system specific and peripheral branches of the innate immune system. Monocytes are a central constituent of the peripheral innate immune system. They are dividable into two major subpopulations, the "classical" CD14++CD16- monocytes and the "non-classical" CD14+CD16++ monocytes subtypes. "Classical" monocytes are highly plastic and, upon recruitment to inflamed tissue, modify their phenotype according to the requirements of the specific microenvironment. They can differentiate into macrophages or dendritic cells and are involved in tissue maintenance, pathogen clearance and induction of adaptive immune responses. "Non-classical" monocytes are thought to patrol along blood vessels and to be involved in tissue homeostasis and local regeneration.

Results of the study was published in Acta Neuropathologica in September 2016.

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ORIGINAL PAPER

Peripheral monocytes are functionally altered and invade the CNS in ALS patients

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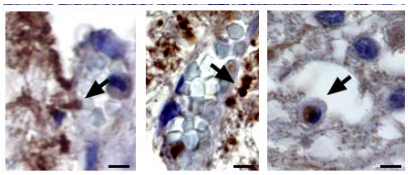
It shows that peripheral monocytes are deregulated regarding subtype composition. In addition, they observed ALS-associated alterations in phagocytic function, adherence properties and gene expression. Moreover, CNS infiltration of monocytes was increased in ALS patients, pointing to the possibility that CNS invading monocytes may have a modifying role in the context of ALS pathogenesis, at least in the early phase of the disease. Further suggesting that monocytes may be a causal player in the pathogenic ALS cascade was the finding that the monocyte subtype composition was already altered in still healthy individuals who carried a known, highly penetrant ALS disease mutation (pre-manifest mutation carriers). Monocytes may thus be causally involved in the development of ALS.



Monocytes (arrows) invading spinal cord

Those recently published observations were obtained in a monocentric setting, and consequently a multi-centric validation study is warranted.

This new study aims to replicate and extend previously described ALS-associated alterations of peripheral, i.e. circulating monocytes as part of the innate immune system in ALS that could represent a part of the pathogenic cascade and/or turn out to be valuable biomarker candidates in ALS. Three centers will be involved with a total of 270 analyses: 60 ALS patients / 60 matched controls / 45 pre-symptomatic ALS mutation carriers / 45 controls of samples / 60 patients with another neurological disorder.

The two other centers are the department of Neurology at the University of Leuven, Prof. Philip Van Damme will be the co-investigator, and the department of Neurology at La Pitié-Salpêtrière, Dr. François Salachas will be the 2nd co-investigator in collaboration with Séverine Boillée at ICM.

Research laboratory : from left to right :
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