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Microglia react distinctively during inflammation

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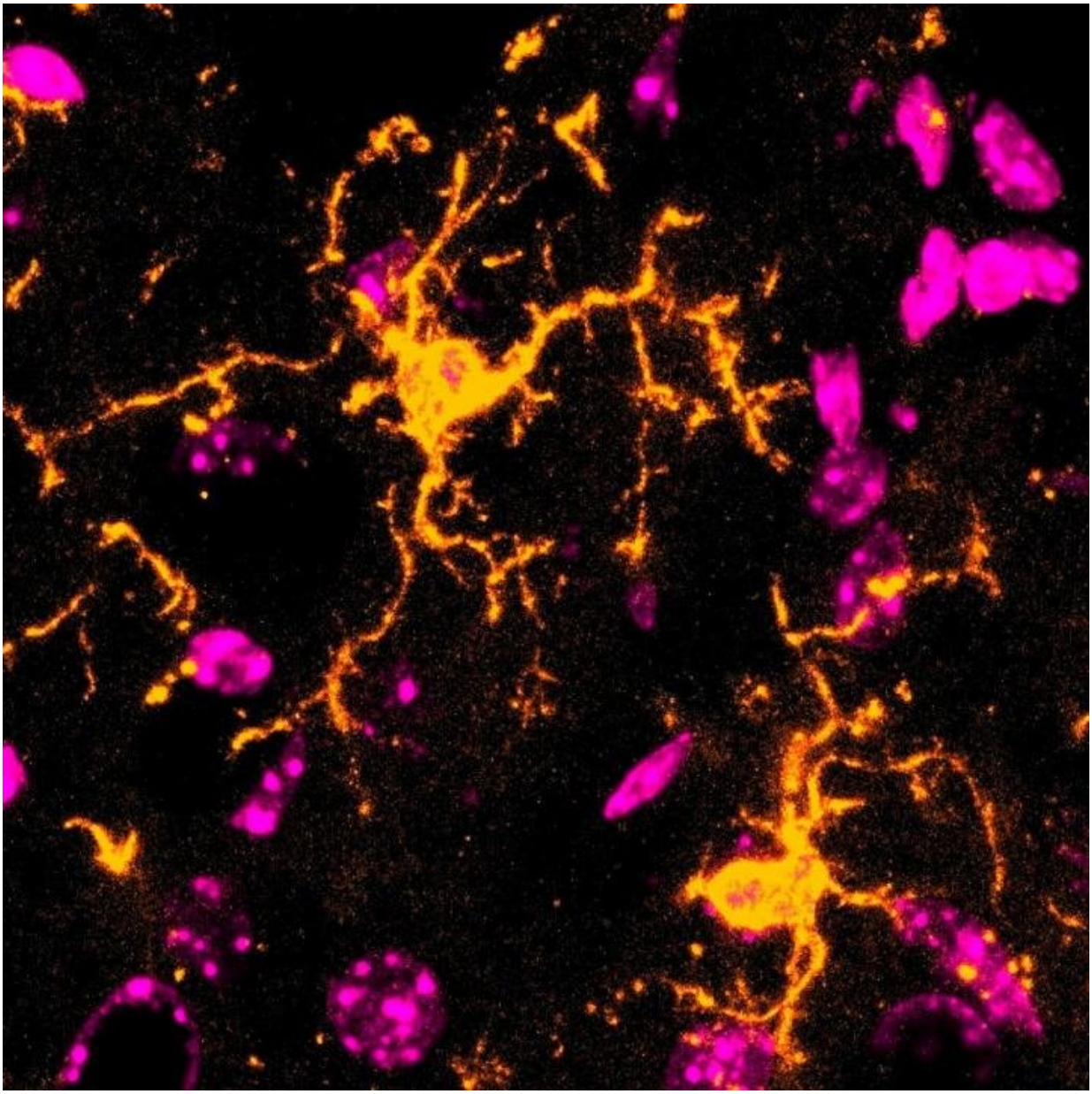

Confocal picture of microglia stained with macrophage-specific marker (IBA) shown in yellow. Cell nuclei are shown in pink (Hoechst). Credit: LIH

The NorLux Neuro-Oncology Laboratory at LIH's Department of Oncology conducts research on brain diseases, with a special emphasis on glioma biology, drug resistance and systems approaches. Within this research unit, Dr. Alessandro Michelucci focuses on the role of glial cells and inflammatory responses. Jointly with team member Dr. Carole Sousa and collaborating research groups from LIH and the University of Luxembourg, the team published their findings in the November 2018 issue of *EMBO Reports*in an article titled "Single-cell transcriptomics reveals distinct inflammation-induced microglia signatures."

Studying the effect of inflammation

The brain is a unique organ with its own tailored immune cells and mechanisms, distinct from those of the rest of the body. The central nervous system (CNS) contains specialized parenchymal-resident phagocytes, microglia, that survey and modulate the neural environment and respond to infections, toxins or contaminants, thereby promoting neuronal health and ensuring normal brain function. Microglia can sense homeostatic perturbations and coordinate immune responses between the periphery and the CNS. Dysfunctional microglia have been observed in chronic neurological disorders such as Alzheimer's disease, Parkinson's disease, multiple sclerosis and brain cancer, and are thought to worsen their outcome.

The activity of microglia during acute neuro-inflammatory processes as those caused by infection remains largely elusive. Acute inflammation represents the early phase of what could result in chronic inflammation and/or neurodegenerative processes. Therefore, microglial responses at

this very early phase of perturbation should provide important insights into the cells' role and adaptive capacities. The aim of the present study was to uncover the heterogeneity of microglial responses under early acute inflammatory conditions to elucidate potential beneficial signatures of subpopulations that could contribute to resolving inflammation and avoiding to enter into a chronic phase causing disease.

To study the cells' activation, the researchers from LIH isolated microglia from mice injected with lipopolysaccharide (LPS), a bacterial component mimicking an acute infection and triggering inflammation signals in the brain. The use of this model combined with modern single-cell sequencing and multicolor flow cytometry allowed for an in-depth profiling of microglia activation at the transcriptomics level.

Distinct inflammation-induced signatures revealed

The researchers observed a marked global downregulation of the typical microglial homeostatic signature and simultaneously an up-regulation of genes classically activated by inflammation. "When investigating further and comparing to published data, we could show that under acute systemic inflammation, microglia presented a highly activated state that is clearly distinct from neurodegenerative disease-associated profiles," says Dr. Sousa, who performed most of the experimental work.

Importantly, the researchers also noticed unforeseen heterogeneity among the activated cells. They hypothesized that a subset of reactive microglia may be less sensitive to the inflammatory stimulus caused by LPS or partly recovered from the activated state.

"Our findings reveal that microglia responses in inflammatory conditions are heterogeneous and clearly distinct from the responses described in the context of neurodegenerative diseases," says Dr. Michelucci, who initiated and led the project. "We hope that these results obtained from

single-cell transcriptomic profiling of microglia under inflammatory conditions will contribute to the establishment of new resources that will clarify the specific responses to brain disorders. This should boost the development of novel therapeutic strategies against CNS diseases with an immunological component."

More information: Carole Sousa et al, Single-cell transcriptomics reveals distinct inflammation-induced microglia signatures, *EMBO reports* (2018). DOI: 10.15252/embr.201846171

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