Peripheral macrophages as a promising target to modulate ALS disease progression

Acronym: PeriMAC

Principal Investigator: Christian Lobsiger

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Duration: 3 years

Summary of the research project

Microglia/macrophages are implicated in disease progression in ALS mice. As the majority of ALS patients are of sporadic etiology, targeting the symptomatic disease phase could serve the entire ALS population. By manipulating the monocyte/macrophage/microglia lineage as a whole, several groups including ours, have shown that these cells impacted motor neuron survival. However, so far, none of these studies has specifically assessed the potential contribution of macrophages at the periphery along motor nerves, on their own, (independent of microglia in the spinal cord), to ALS.

As the spinal cord motor neuron’s biggest part, its axon, lays in the periphery and macrophage activation in the peripheral nerves precedes motor neurone degeneration, we therefore hypothesize that modulating macrophages at the periphery could impact motor neuron survival.

Macrophages are progressively activated in sciatic nerves of hSOD1^G93A^ ALS mice. Sciatic nerves of control (B6) or hSOD1^G93A^ mice at different disease stages were stained with a cocktail of anti-macrophage antibodies [anti-CD68, -CD11b, -F4/80]. Graphs represent the surface occupied by the combined immunostaining showing that already at onset macrophage activation occurs and increases during disease.

Aim 1. We will analyze how peripheral macrophages along motor axons respond to progressive motor neuron degeneration over the disease course in ALS mice. We will define pathways unique to reactive peripheral nerve macrophages and potentially distinct from reacting microglia in the
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spinal cord. For this, peripheral macrophages will be isolated from ALS mouse nerves at different disease stages and their response profiles (RNAseq) compared to microglia in the spinal cord. This will reveal promising new candidates to modulate disease course.

**Aim 2.** We will identify the peripheral nerve macrophage candidate genes that are independent of ALS causing mutations but only dependent on the response to progressive motor neuron degeneration, thus, more relevant for sporadic ALS. For this, we expand on Aim-1 by using an ALS model with macrophages/microglia not expressing mutant SOD1 (Cre/Lox approach), but still reacting to ALS linked motor neuron degeneration.

**Aim 3.** We will validate promising candidates for their capacity to ameliorate ALS disease progression using peripheral macrophage cell-replacement (Bulsulfan/bone marrow transplant) in ALS mice. This will validate our candidates as peripheral macrophage pathways contributing to ALS disease progression.

**Aim 4.** We will confront the candidates from mice with human ALS tissues and monocyte/macrophage cells, to reveal potential new biomarkers and therapeutic targets.

This project could identify new pathways in peripheral macrophages to target motor neurons from the periphery and slow disease progression.

**Christian Lobsiger** is INSERM Researcher, Assistant Professor in the Lab of Dr. S. Boillee “ALS Causes and Mechanisms of Motor Neuron Degeneration” at ICM, Paris

**Relevant research articles for this project are:**