Microglia / macrophages contribution to motor neuron degeneration in ALS models

Call for projects 2009
Grant: 275 000 €
Project Duration: 3 years

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Updated results December 2012

During the course of motor neuron degeneration other cells in the spinal cord react to the disease and become activated. Microglial cells, the macrophages of the central nervous system are reacting particularly fast to any kind of injury of the nervous system including in response to the progressive motor neuron death taking place in ALS.

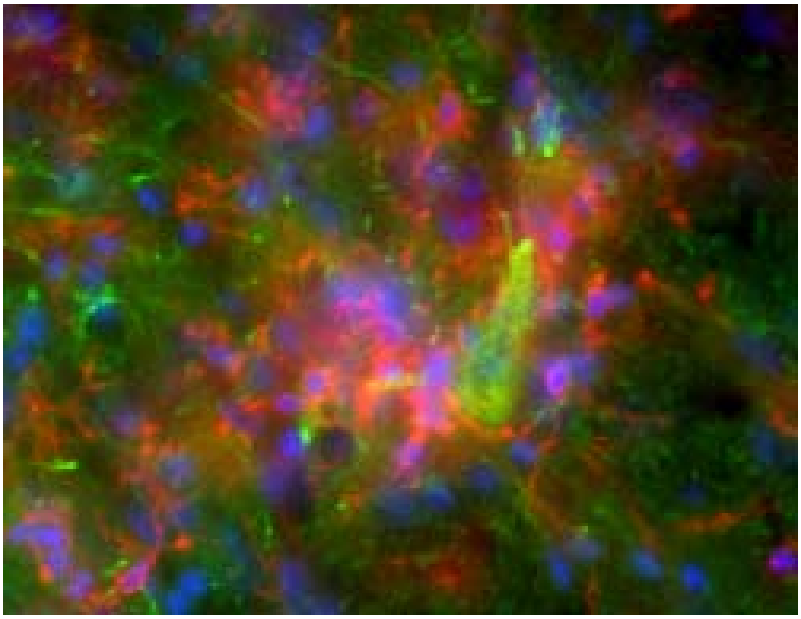
Previous work has shown that microglial cells/ macrophages were implicated in the progression of the disease in ALS animal models. Since acting on the progression of the disease could benefit the majority of ALS cases including sporadic cases that can only be diagnosed when the symptoms are installed, we believe that the microglial cell/ macrophage component could be a relevant target for therapy. Our interest is therefore to study the communication between motor neurons and microglial cells/ macrophages through three different aspects in order to be able to slow down disease progression.

The first aspect concerns the factors produced by motor neurons and that can act directly on microglial cells. Identifying these factors and showing their potential to activate (rendering toxic) or attract microglial cells would unravel new candidate pathways to target to prevent microglial cell deleterious action towards motor neurons. We identified one such factor, a member of the large family of the chemokines. This chemokine is released by motoneurones and attracts microglial cells. Therefore our next step is now to block this receptor to analyze the consequences on microglial activation, motor neuron degeneration and ALS mouse survival.

The second part of our project is focused on the factors expressed and released by microglial cells that can be directly toxic towards motor neurons. We identified a specific pathway that influences the progression of the disease in ALS mice.

Finally, as microglial cells are the macrophages of the nervous system and participate in motor neuron degeneration, we also wanted to study the participation of the other macrophages, at the periphery. Indeed, when motor neurons degenerate, macrophages in the peripheral nerve (e.g. the sciatic nerve) are activated and show increased numbers in ALS mice. As macrophages at the periphery would be easier to reach than microglial cells in the spinal cord, our goal is to define if the macrophages at the periphery are playing an active role during the progression of the disease - which would make them a promising novel potential therapeutic target. We developed a protocol to reach macrophages at the periphery leaving microglial cells (in the spinal cord) unaffected in order to ascertain that our results will reflect the action of peripheral macrophages only. This strategy has

first been evaluated in control mice and we are now using it in ALS mice to unravel whether macrophages at the periphery are also active participants to motor neuron degeneration and can be used to slow down ALS disease progression.



A motor neuron (in green) surrounded by activated microglia cells (in red) in a lumbar spinal cord section of an ALS mouse. The cell nuclei are stained in blue. Picture from Pinar Mesci (PhD student in the team).

STUDY OF THE PATHOLOGICAL NEURO-IMMUNE INTERACTIONS BETWEEN THE MACROPHAGES/MICROGLIAL CELLS AND THE AFFECTED MOTOR NEURONS IN ANIMAL MODELS OF ALS

S. Boillée, France
Grant : 275 000 €

In ALS, the motor neurons in the spinal cord that innervate the muscle are the cells that degenerate which leads to the progressive paralysis of the patients and ultimate death 1 to 5 years in mean after the diagnosis.

However, other cells surrounding the motor neurons are also implicated in their degeneration especially the microglial cells, macrophages (immune cells) of the central nervous system. We have previously shown that microglia/ macrophages participated to the symptomatic phase of the disease and since most of the ALS patients are sporadic and therefore diagnosed after the appearance of the symptoms, finding pathways implicated in the progression of the disease could help finding targets to slow down motor neuron degeneration.

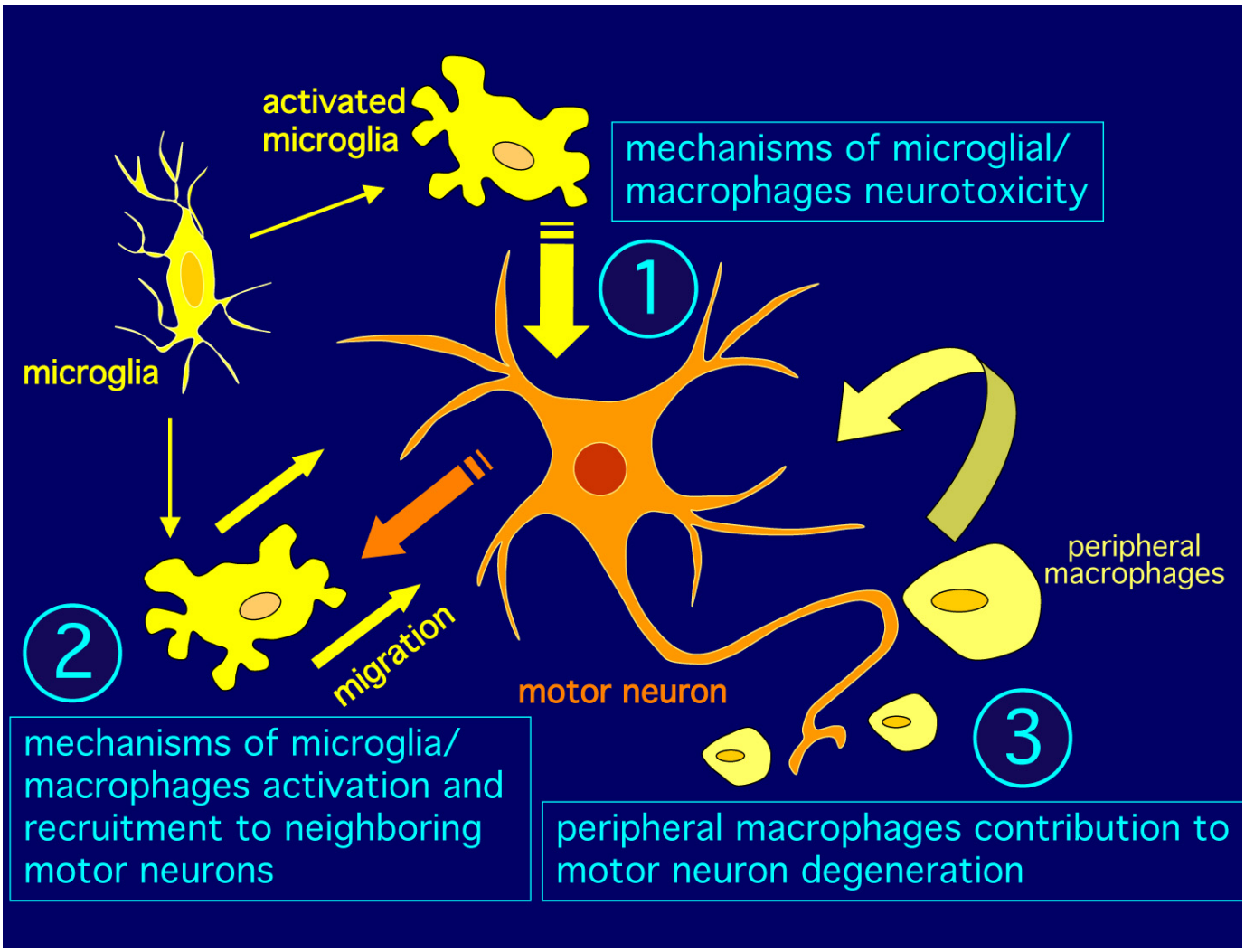
The aim of our project is to find these pathways implicated in the symptomatic phase of the disease by studying the interactions between the microglial cells/ macrophages and the motor neurons through 3 aims. Our first aim will focus on factors released by microglial cells and potentially toxic for motor neurons while our second aim will study factors produced by motor neurons and that can activate and attract microglial cells and render them more toxic, the goal being to block those pathways to increase motor neuron survival.

Our third aim will look at macrophages at the periphery that could be used as an easier accessible target to reach motor neurons.

We anticipate that at the completion of the project we will have contributed to:

1) Identify pathways implicated in motor neuron/ microglia interaction that could open ways to identify new targets for development of therapies for ALS (aims 1 and 2).
2) Find ways to slow the symptomatic phase of the disease relevant to ALS patients (aims 1 to 3).
3) Determine if the peripheral macrophages have a role in ALS linked motor neuron degeneration what could allow targeting motor neurons through the periphery (Aim 3).
As microglial cells are activated both in familial forms of ALS and sporadic cases that re-

present from far the highest number of patients, we hope that finding pathways implicated in microglial/ motor neurons interaction will help identifying new targets for future therapies in ALS.



TEAM

This project will be coordinated by the Principal Investigator (PI), Séverine Boillée that acquired a background in ALS through a post-doctoral stay in the laboratory of Don W Cleveland one of the world leading scientist working on ALS. We are a young team of researchers working at INSERM and University Pierre & Marie Curie (UPMC) whose research focuses exclusively on ALS, recently installed in the Salpetriere Hospital, in Paris, and belonging to the Research Center of the Brain and Spinal Cord Institute (CRICM) dedicated to research on the nervous system.