Contribution of Metabolic Dysfunction to Amyotrophic Lateral Sclerosis Pathogenesis

Call for projects 2009
Grant: 240 000 €
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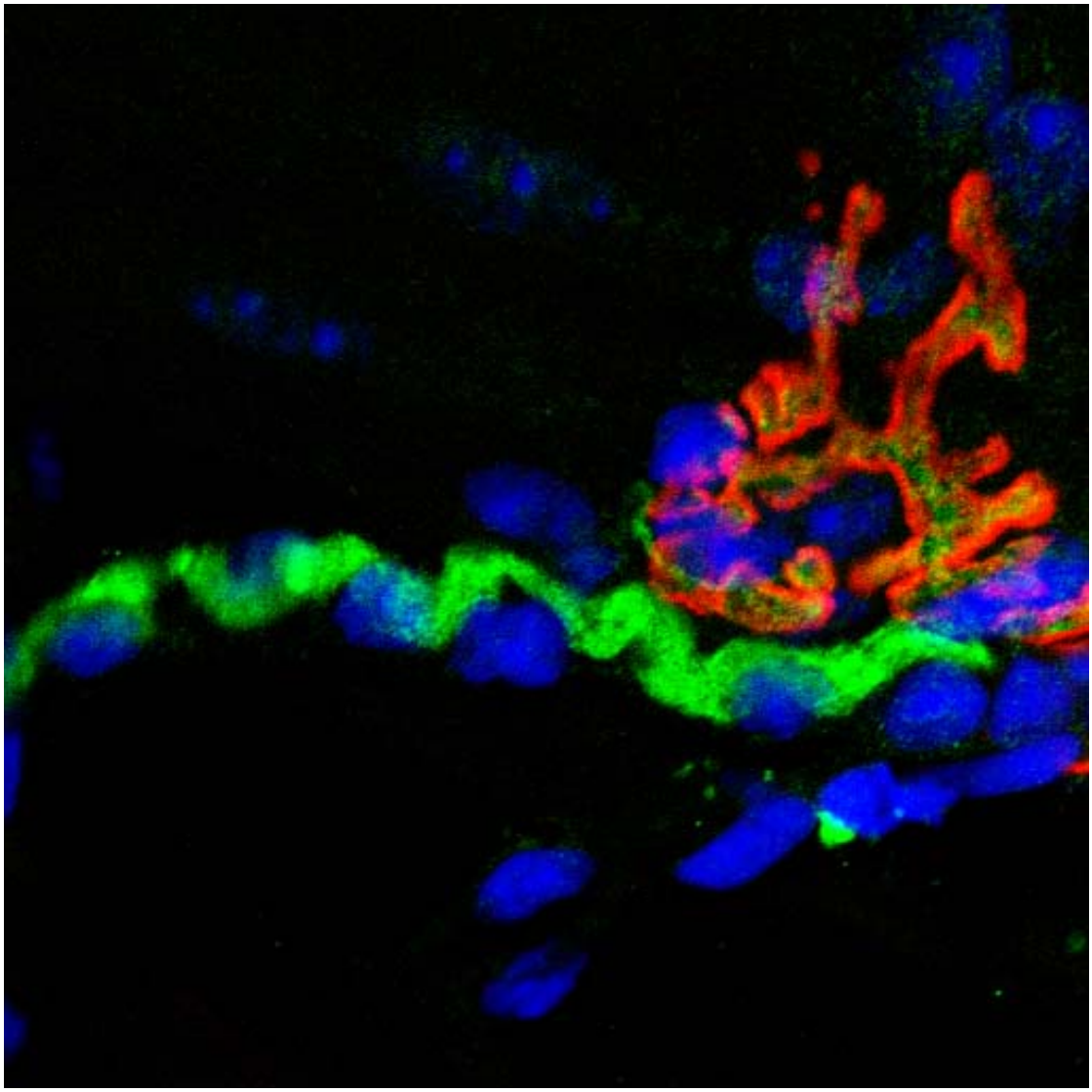
There is evidence that clinical manifestation of the motor symptoms in ALS is preceded by metabolic disturbances at the body level, such as increased oxygen consumption and diminished lipid content. In this study, we focused on the role of muscle stearoyl-coenzyme-A desaturase-1 (SCD1), a key enzyme involved in the production of monounsaturated fatty acids which, in turn, are the substrate for the synthesis of several classes of lipids necessary for living cells. Since mice lacking SCD1 show metabolic alterations similar to those observed in ALS, we investigate the effects of loss of SCD1 on the motor function in ALS.

We found that SCD1 is decreased in muscle of ALS mice. Also we observed that the absence of SCD1 is not detrimental per se but increase the number of muscle fibers with a higher metabolic oxidative potential and the expression of genes that maintain the healthiness of the neuromuscular junction. Interestingly, a decrease of SCD1 by genetic or phamacological means, accelerated the recovery of motor function after a sciatic nerve lesion. Thus, SCD1 appears to enhance the regenerative capacity of the neuromuscular axis.

We are now testing whether similar abnormalities of lipid metabolism are present in patients suffering from ALS. For this purpose, we have collected blood samples in a series of ALS patients. We will determine the activity of SCD1 but also other enzymatic activities involved in the metabolism of fatty acids in this population and will compare them to those obtained from a population of unaffected subjects. In parallel, we will measure the expression of SCD1 and other fatty acid metabolism enzymes in muscle biopsies obtained from patients with ALS.



The microphotograph shows a healthy neuromuscular junction in the muscle of a mouse lacking SCD1, as visualized by an immunofluorescent approach. The axon of the motor neuron appears in green, whereas the muscle structure that receives the neuronal input appears in red. Muscle nuclei are in blue.

CONTRIBUTION OF METABOLIC DYSFUNCTION TO AMYOTROPHIC LATERAL SCLEROSIS PATHOGENESIS

JP. Loeffler and PF. Pradat, France
Grant : € 240 000

ALS was classically considered as caused exclusively by diseased motor neurons subsequently leading to muscular atrophy. From this perspective, that progressive immobilization occurred concomitantly with systemic changes, such as increased energy expenditure, appeared a priori paradoxical.. Growing evidence indicates, however, that ALS, both in man and related animal models, can no longer be considered as a disease solely affecting motor neurons, as admitted previously, but rather as a disease with multiple facets whose ultimate consequence is the selective loss of motor neurons.

Our laboratory was pioneering in this field by showing clear-cut abnormalities in peripheral lipid metabolism that occur before the onset of motor impairment in animal models of the disease, and are also observed in patients with ALS. Our previous work has identified a number of modifications in the management of energy needs in the body that precede the clinical manifestations of the motor symptoms. In consequence, muscles become a central player in the pathological process, because they are primary consumers of energy and many of the metabolic alterations we found in the course of ALS occur in this tissue. We hypothesize that these metabolic alterations contribute to the initiation and progression of the disease, and propose in this work to decipher in detail (that is, at the molecular level) the mechanisms underlying such modifications.

By connecting the fields of energy metabolism and neurobiology, we will thus pave the way for innovative therapeutic strategies to fight against this devastating disease.

TEAM

Dr. Jean-Philippe Loeffler is the head of an Inserm laboratory (Signalisations Moléculaires et Neurodégénérescence, U692, Strasbourg, Fance) internationally recognized in the field of ALS, as attested by numerous articles in high-rank peer-reviewed journals, patents and invitations to meetings on ALS research.

Dr. Pierre-François Pradat is a leader physician in the Centre référent for ALS at the Pitié¬Salpétrière Hospital (Paris, France), which handles several hundreds of French ALS patients, and forms part of the European ALS network for the collection and management of samples. Dr. Pradat' s implication in ALS research is documented by numerous articles in high-rank peer-reviewed journals, several of these being published in collaboration with Dr. Loeffler' s team.