Chapter 10
Amyotrophic Lateral Sclerosis Involving Gliopathy:
Insights Into the Underlying Mechanisms

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ABSTRACT

Amyotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative disease, causing death within two to five years following diagnosis. ALS is a disease characterized by motor neuron degeneration and destruction of the neuromuscular junction (NMJ). To date, numerous genetic mutations have been associated with ALS, but the mutation in the gene coding for superoxide dismutase (SOD1) has been the most extensively studied. Nevertheless, studies carried out on rodent models and ALS patients have shown that damage to glial cells contributes directly to the development and progression of the disease. However, few studies have focused on the properties of glial cells in ALS. The accumulation of knowledge on the active role and pathological mechanisms of each glial type in the disease must be carefully applied to better understand the ALS pathophysiology, but also for the development of targeted therapy for glial cells. Therefore, in this chapter the authors aimed to compile the most recent information on how each type of glial cell contributes to the development of ALS.

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1. INTRODUCTION

Amyotrophic lateral sclerosis is a fatal neurodegenerative disease for which, unfortunately, there is currently no effective treatment. The disease is characterized by progressive motor neuron death, primarily affecting motor neurons in the cortex, brain stem, and spinal cord (Viader, 2023). The result is a loss of voluntary motor function, although sphincter control and oculomotricity remain unaffected. In the typical form, the motor deficit is associated with cramps, fasciculations, amyotrophy, and pyramidal syndrome. Affected patients do not all present the same symptoms, the same temporality of onset or the same order, nor the same speed of aggravation (Fonollosa and Tourlet, 2023). 10% of ALS cases are hereditary, while the remainders are considered sporadic and the cause has yet to be discovered. 20% of hereditary cases of ALS are caused by mutations in the gene coding for superoxide dismutase 1 (SOD1) (Rosen et al; 1993; Pasinelli and Brown, 2006). In its unmutated form, the enzyme encoded by this gene neutralizes cell-damaging oxygenated free radicals. Mutations in SOD1 found in ALS patients lead to a change in the structure of the enzyme, which then becomes toxic (Inserm, 2017).

Mitochondria also appear to play a role in the disease. These small cell-specific energy centers malfunction in the motor neurons of SOD1-deficient mice, leading to a reduction in the amount of energy produced. Motor neurons (MNs) then develop alternative survival strategies, such as the production of energy from fatty acids, which leads to the synthesis of ketone bodies toxic in large quantities, or cholesterol. Moreover, some patients exhibit hypermetabolism, i.e. increased use of glucose or fatty acids by the body, which can generate significant weight loss and worsen their prognosis (Inserm, 2017).

Despite the specific loss of MNs in ALS, the results of several studies suggest that non-neuronal cells contribute significantly to the disease, particularly glial cells. Expression of the mutated SOD1 gene in MNs had an impact on the development and early progression of the disease, while expression of the SOD1 gene in central nervous system (CNS) glial cells affected the development and progression of the disease. Indeed, studies conducted in animal models of ALS have highlighted a chronic inflammatory state in which astrocytes, microglial cells, and macrophages present in the motor neuron environment play a deleterious role and participate in disease progression (Clement et al; 2003; Arbour, 2016). These mechanisms could therefore constitute a therapeutic target. In this chapter, we will discuss more data implicating glial cells in ALS pathology.

2. THE INVOLVEMENT OF ASTROCYTES IN THE PATHOGENESIS OF ALS

Astrocytes form the main glial cell population of the nervous system (Chneiweiss, 2002). They play a critical role in CNS development and physiology, being involved in many relevant aspects of neuronal function, such as neuronal trophic support, differentiation, and neuronal survival (Araque et al; 1999). A strong glial reaction has been observed which generally surrounds the upper and lower motor neurons in ALS patients (Kushner et al; 1991; Schipper, 1998). The presence of activated astrocytes has been confirmed in tissue from patients with ALS brain and spinal cord (Philips and Rothstein, 2014). Astrocyte activation becomes increasingly prominent in advanced stages of the disease (Keller et al; 2009). All these observations have led to the study of the potential role of astrocytes in the pathogenesis and progression of ALS, which involves different mechanisms that can lead to the loss of homeostatic functions or the acquisition of toxic functions.