Neuroinflammation in amyotrophic lateral sclerosis: new targets for the treatment?

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Amyotrophic lateral sclerosis is rapidly progressive neurodegenerative disorder which is characterized by the loss of motor neurons in the spinal cord and brainstem accompanied by degeneration of corticospinal and corticonuclear neurons within the cerebral cortex.
The loss of motor neurons lead to paralysis which progressively involves all the skeletal muscles.
A variety of mechanisms have been investigated in the pathogenesis of ALS. Excitotoxicity took a prominent role in the last decades. At the same time, a detrimental effect of glial cells surrounding motor neurons was postulated. Excitotoxicity and glial cells may be simultaneously involved given the metabolic relationship between astrocytes and motor neurons in regulating the availability of glutamic acid. Besides this, the role of glial cells appears to be more important than a mere buffer for an excess of extracellular glutamate. For instance, it is demonstrated that in the absence of glial cells pure motor neuron cultures carrying a mutation in the SOD1 gene which leads to ALS are not affected by the disease process while this occurs in the presence of glial cells. Specific glia-derived factors were demonstrated to be involved in such a detrimental cell-to-cell communication although the specific role of each molecule remains to be established. The existence of a toxic cell-to-cell communication led to the concept of ALS as a motor neuron disorder characterized by the occurrence of non autonomous cell death in which the disease mechanism is not expressed at the level of isolated motor neurons. Such a concept was extended in recent years to cells other than motor neurons and glia. For instance Martin and co-workers (2007) found that synuclein positive interneurons degenerated more than motor neurons and further studies documented the involvement of multiple cell types from the anterior horn in the pathogenesis of ALS.
The present communication is aimed to disclose the role of abnormal cell to cell communication in sustaining and spreading the molecular mechanisms of cell death. This process is reminiscent of disease transmission in other neurodegenerative disorders featuring a prion-like cell to cell spreading. This is confirmed by prion domains typical of ALS-specific proteins. The role of cell membrane proteins belonging to the immune system as well as the expression of advanced glycation end products (AGE) will be analyzed along with different cell types and glia-derived cytokines.