Glial dysfunction in the pathogenesis of neuropsychiatric disorders: beyond inflammation, toward the development of novel therapies

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In the last decade, the neuron-centric vision of neuropsychiatric disorders has undergone considerable changes. Indeed, it is now clear that the non-neuronal cells could be involved in the pathogenesis and progression of many diseases due to their important and active roles exerted in the brain physiological and pathological conditions. Glial cells are non-excitable cells of the central nervous system. These cells belong to a highly heterogeneous population responsible for the control the brain homeostasis. It is now well accepted that glia allow neurons to functioning.

Recent evidence assigns to astrocyte dysfunctions a critical role in aging and in several neurodegenerative diseases, including Alzheimer's disease (AD). In fact, several brain injuries, including Aβ deposition, modify astrocyte physiological functioning and they acquire a reactive phenotype. Activation of these cells is fundamentally a protective response aimed at removing injurious stimuli. However, uncontrolled and prolonged activation goes beyond physiological control, and detrimental effects override the beneficial ones. In this condition, astrocytes foster neuroinflammatory response, accounting for the synthesis of different cytokines and pro-inflammatory mediators, as well as they lose many of their physiological functions, contributing to the exacerbation of the damage. Therefore these cells should not be considered simple co-stars in the drama of neuropsychiatric disorders, including AD.

Given the complex heterogeneity of pathological changes occurring in AD, any therapeutic effort absolutely requires a multi-targeted approach, since attempts addressing only a single event may result ineffective. In this context, molecules able to counteract glial over-activation, as well as to blunt neuroinflammatory processes could be promising tools to develop new, and hopefully most efficacious, AD treatment. Here we show the last results of our studies in rodent models of AD, supporting the possibility that glial cells could be considered a promising target for future AD therapies.

These data suggest novel strategies that hopefully could have the potential not just to alleviate the symptoms but also to modify disease progression.