Heterogeneity of Astrocytes and Microglia in Neurodegenerative Diseases

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The two major reactive cell types of the central nervous system with regulatory functions, astrocytes and microglia, comprise several phenotypes with functional diversity. When producing inflammatory mediators they are termed A1 and M1, respectively, and as A2 and M2 if generating immunoregulatory mediators. Neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS) and Alzheimer´s disease (AD) have been associated to neuroinflammation. Reactive astrocytes and astrogliosis show increased expression of glial fibrillary acidic protein (GFAP); however, GFAP is not always expressed in reactive and non-reactive astrocytes. Complementary markers, i.e. connexin-43 (Cx43), S100B, glutamate transporters (GLT-1 and GLAST) and vimentin, should be used for characterization. Cortical astrocytes isolated from SOD1G93A mice pups, an ALS model, that present accumulation of mutated SOD1 have high proliferative potential, decreased levels of GFAP, GLAST and GLT-1, but high content of S100B, Cx43 and vimentin. Such profile was observed in cortical samples from the symptomatic mice. Dysfunctional astrocytes evidenced low expression of microRNA(miR)-146a, a regulator of inflammation and proliferation, and neurotoxic potential towards wild type and SOD1G93A transfected motor neurons, reason why should be consider for target-driven therapies for ALS.

M1-polarized microglia by lipopolysaccharide showed amoeboid morphology, decreased migration, enhanced phagocytosis and proliferation, elevated iNOS and MHC-II expression, decreased arginase-1 and Fizz1 (M2 markers), and inflammasome complex activation. When microglia was aged in culture (Caldeira et al. Front Cell Neurosci 2014) we observed reduced migration and phagocytic abilities, enhanced miR-146a expression and high senescence-associated-beta galactosidase activity, altogether indicating a switch from reactive to non-responsive microglia. Furthermore, treatment of microglia with amyloid-beta peptide, a risk factor for AD, induced a dysfunctional senescent phenotype with a faulty amyloid-beta clearance. Thus, recovery of responsive microglia may constitute a therapeutic strategy for AD.

Collectively, the existence of heterogenous astrocytes and microglia phenotypes may explain anti-inflammatory therapeutic failure in ALS and AD patients.

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