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Age- related cognitive impairment induced by chronic systemic inflammation is associated with microglia dysfunction

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Ageing is the major risk factor for the development of dementia and neurodegenerative diseases. Clinical and experimental evidence suggests that acute stress, such as major surgery or systemic infection, can contribute to cognitive decline and dementia. The aging process involves, among other things, deficits in pathways of macromolecular degradation (proteasome, autophagy, phagocytosis) and generation of reactive oxygen species (NADPH oxidases, mitochondria), which may impact the accumulation of neurotoxic protein aggregates and oxidative stress. Our hypothesis is that a microglial dysfunction associated with aging (immunosenescence) can determine the accumulation of defective macromolecules and organelles in the CNS, which can be neurotoxic. We developed an animal model to study the effect of chronic low-grade systemic inflammation (CLSI) on cognitive functions of young and aged mice. To produce CLSI we injected Swiss male mice, two- months old (young) or fourteen- months old (aged), with lipopolysaccharide (LPS0, 3 mg/Kg i.p.) once a week for eight weeks. Memory was evaluated with the object recognition test; depressive behavior was evaluated with the forced swimming task sensorimotor gating was evaluated by pre-pulse inhibition (PPI). Microglial activation was evaluated morphologically by immunohistochemistry for Iba-1 and cytokines were quantified by multiplex analysis. Oxidative stress was measured by immunohistochemistry and quantified by western blot through 4-hydroxynonenal immunodetection. Systemic inflammation (blood neutrophils counts) was significantly increased in aged mice after each LPS injection ($P<0.0001$, Two-way ANOVA). Basal plasma IL-6 ($P<0.05$) and brain MCP-1 ($P<0.05$) were significantly higher in the aged mice. However, after CLSI aged mice presented surprisingly lower levels of almost all cytokines measured and distinct microglia morphology as opposed to young mice. Interestingly, only aged mice presented memory impairment and oxidative stress after CLSI. . Our data show that age- dependent memory impairment induced by CLSI is associated with a deregulation in the inflammatory response and increased oxidative stress in brain regions associated to memory. We developed an experimental model with clinical relevance, in which young mice presented significant depressive- like behavior whereas aged mice present memory impairments after CLSI. Our data demonstrate that persistent systemic inflammatory challenge leads to microglial dysfunction and cognitive impairment in older animals, by molecular mechanisms that involve oxidative stress. These data support the hypothesis that the proper function of glial cells is necessary for CNS physiology.

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Antigen-specific cellular therapy for MS patients: Induction of tolerance by autologous myeloid dendritic cells treated with vitamin D3 and loaded with myelin peptides

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Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system. Current treatments for MS patients consist in non-specific immunomodulatory drugs with moderate efficacy and some important associated side effects. In the way to restore the tolerance against myelin peptides that has been lost in MS patients, efforts have been directed to new cell therapy treatment approaches. In this sense, the efficacy of different tolerogenic cells (regulatory monocytes and T cells monocytes, and tolerogenic dendritic cells) have been evaluating for autoimmune diseases such as diabetes, arthritis rheumatoid and MS. In our laboratory, we have generate functionally stable tolerogenic dendritic cells (tolDC) from MS patients by treating monocyte-derived DC with vitamin D3 ($1,25(OH)_2$ D3) and using a cytokine cocktail (TNG-a, IL-1b and PGE2) as maturation stimulus. These tolDC loaded with a pool of seven immune-related myelin peptides induced antigen-specific and stable hyporesponsiveness in autologous myelin-reactive T cels *in vitro*. In addition, *in vivo* efficacy of murine antigen specific-tolDC have also demonstrated in the animal model of MS, the experimental autoimmune encephalomyelitis (EAE) resulting in EAE prevention and transient reduction of clinical signs in mice treated therapeutically. Currently, we are working to initiate in 2016 a phase I clinical trial using myelin peptides-loaded tolDC in MS patients.

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