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## **RESTAURATION OF AGE RELATED MOTOR IMPAIRMENT: ROLE OF IGF-1 BASED GENE THERAPY AND MICROGLIAL ACTIVATION**

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Microglial cells play an important role in healthy and diseased brain removing apoptotic neurons (Perry et al., 1985; Ashwell, 1990; Calderó et al., 2009; Sierra et al., 2010), establishing transient connections with neuronal synapses (Wake et al., 2009) and producing neurotrophic factors that modulate neurogenesis during embryogenesis and adulthood (Ueno et al., 2013; Xia et al., 2015). These cells are essential for ensuring neuroprotection in the normal and pathological condition of central nervous system as they are an important sources of neurotrophic factors. It has been described that aging reduces the ability of microglia to provide neuroprotection (Streit and Xue, 2014; Floden and Combs, 2011; Harry, 2013, Orre et al., 2014, Suh et al., 2013).

Microglia-mediated neuroprotection has been described in the nervous system (Polazzi and Contestabile, 2002; Lai and Todd, 2008). Several studies have shown that, after axotomy of the motor axons of the facial nerve, the injured neurons regenerate when activated microglial cells are present (reviewed in Raivich, 2002), being the activation of microglia crucial for the regeneration to happen. Moreover, transplantation studies showing that engraftment of cultured microglial cells into the injured spinal cord promotes neurite growth into such microglial grafts (Rabchevsky and Streit, 1997) support this idea that microglial neuroinflammation is a vital component of the regenerative process. Previous studies of our group described that intracerebroventricular (ICV) Insulin-like growth factor-I (IGF-1) gene therapy induced a significant improvement in motor performance in aged rats (Sanchez et al., 2008, Nishida et al., 2011). Several works report that IGF-1 stimulates microglia proliferation (O'Donnell et al., 2002). We propose that restorative effects of IGF-1 in motor skills could be mediated by glial cells.

In the current study we implemented ICV IGF-1 gene therapy in very old rats (28 months) and assessed the motor performance pre and 17-days after surgery. Glial immunoreactivity in striatum was evaluated by Iba1 and GFAP markers.

### **Results**

As we previously reported, IGF-1 restored motor coordination and forelimb grip strength in aged rats (Sanchez et al., 2008). We found that microglia immunoreactivity (Iba-1+) was significantly increased for at least 17 days after treatment with IGF-1 ( $X_{m-senil-IGF-1}=556.2\pm30.50$  vs  $X_{m-senil-DsRed}=359.9\pm18.08$ ;  $p<0.001$ ), astrocytes (GFAP+) showed not changes.

Our results identify a novel function of microglia in the maintenance of motor performance and suggest an original approach for reversing age-associated motor and exploratory performance recorded in rats.

### **Palabras claves**

Aging  
Microglia  
IGF-1s.